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New Aspects in Phosphorus Chemistry II

Volume Editor: Jean-Pierre Majoral

With contributions by
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T. D. Nixon, R. Streubel, J. G. Verkade, M. Yoshifuji

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Preface

The first volume of Topics in Current Chemistry (volume 220), dedicated to New Aspects in Phosphorus Chemistry was very attractive for a large number of readers. This success encouraged us to continue our efforts in presenting all the facets of modern phosphorus chemistry. What makes phosphorus so attractive that chemists have a natural tendency to use it? Virtually every chemist can take profit of the properties of such an element. Applications in different fields have already been realized or are under current investigation. A few of these applications and properties covering some aspects of catalysis, organometallic chemistry, polymer chemistry, biophosphates or carbonylphosphonate chemistry, use of white phosphorus etc... have been presented in the first volume.

The interdisciplinary „input" of phosphorus chemistry can be found also in biological and material sciences and has stimulated chemistry as a whole.

In view of the fascinating potential of phosphorus compounds, it is of substantial interest to develop a deeper understanding and presentation of their chemistry. In this volume leading scientists present modern research trends in seven comprehensive reviews providing a deep insight into the specific subjects.

The first contribution concerns exceedingly strong nonionic phosphorus bases (J. Verkade), namely pro-azaphosphatranes and related species which become broadly useful in organic synthesis methodology as stoichiometric bases and as catalysts. Some of these derivatives are now commercially available.

The second chapter highlights the past, present and future of the asymmetric phospho-aldol reaction, one of the most powerful method to control the stereochemistry at the alpha-carbon of alpha-functionalized phosphonic systems (T.P. Kee and T.D. Nixon). Attention focused for the future to the design of new catalysts, improved processing and to medicinal chemistry and disease targets.

The preparation and properties of phosphanylidene carbenoids, a class of inherently unstable low coordinated phosphorus compounds are then described by M. Yoshifuji and S. Ito. The kinetic stabilization method reported by the authors, allows them to develop a rich chemistry leading to phosphaethenes, phosphaalkynes, heavier heteroallenic compounds, stable biradical derivatives etc...

There are still many efforts to create new versatile building blocks in chemistry in general and in phosphorus chemistry in particular. Transient nitrilium phosphanylid complexes, new 1,3-dipole systems, can be regarded as powerful reagents: their preparation, the theoretical aspects of their formation and their

synthetic potential in organophosphorus chemistry is overviewed by R. Streubel in chapter 4.

Dendrimers, perfectly branched, highly symmetrical tree-like macromolecules have evolved from curiosity to an important trend in current chemistry. The contribution of J.P Majoral and A.M. Caminade focuses on phosphorus-containing dendrimers, aiming at a comprehensive summary of the state of the art of the field. The first really promising applications of these giant molecules in different fields – biology, material science, catalysis – are reviewed in chapter 5.

The aim of the review written by M. Mikolajczyk and P. Balczewski is to collect and discuss works concerning the use of phosphonates in the preparation of biologically active or natural products. Some recent developments of this important field of research are mentioned in chapter 6.

The last chapter concerns the chemistry of triphosphabenzenes and valence isomers reviewed by H. Heydt. The remarkable versatile reactivity of 1,3,5 triphosphinines through a fruitful and smart organophosphorus chemistry and leading to a large variety of new phosphorus heterocycles is presented.

I hope that this new collection of reviews demonstrates the attractiveness and the enormous potential of phosphorus chemistry and will help chemists to further develop this stimulating and still lively field of challenging research.

Toulouse, September 2002 Jean-Pierre Majoral

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New Aspects in Phosphorous Chemistry I

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$P(RNCH_2CH_2)_3N$: Very Strong Non-Ionic Bases Useful in Organic Synthesis

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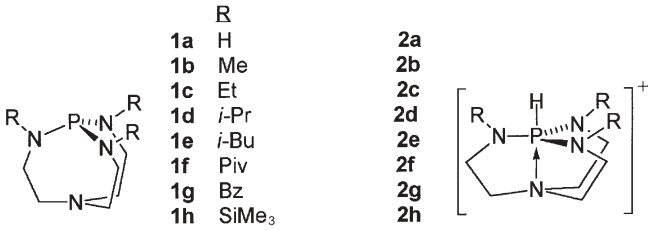
Bases of the title type (pro-azaphosphatranes) are very strong (pK_a ca. 32 in acetonitrile). After briefly reviewing recent uses of popular nitrogen-containing bases of various types, the synthesis, unusual structural features and unique chemical characteristics of pro-azaphosphatranes and some of their derivatives are described. Recent advances in utilizing pro-azaphosphatranes as stoichiometric reagents and as catalysts in a wide variety of useful organic transformations are then summarized. In their role as catalysts, pro-azaphosphatranes are seen not only to act as deprotonation agents, but also to activate for further reaction of carbon and silicon in several substrates possessing such atoms.

Keywords. Pro-Azaphosphatranes, Transannulation, Catalysis, Basicity, Nitrogen bases

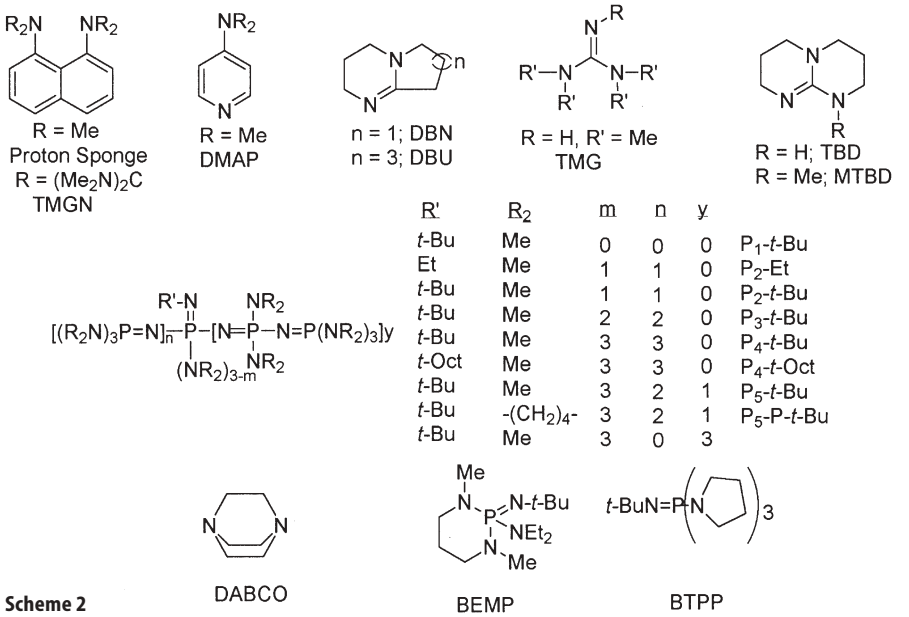
Topics in Current Chemistry, Vol. 223

1 Introduction

Strong non-ionic bases are highly advantageous as stoichiometric reagents and as catalysts in synthetic organic chemistry owing to side reactions that frequently occur when ionic bases such as LDA or alkali metal alkoxides are employed. A second reason that non-ionic bases are frequently more useful in these applications is that such bases are often more soluble in less polar organic solvents, particularly at low temperatures. Thirdly, non-ionic bases can provide reactive naked or tightly associated deprotonated substrate anions that are stabilized by the relatively large, poorly solvated cations formed by the protonated base. In such cations, extensive positive charge delocalization can occur. Prior to our work on pro-azaphosphatranes of type **1** (Scheme 1), the very strong non-ionic bases utilized for organic transformations were largely confined to the nitrogenous bases shown below (Scheme 2).



Scheme 1



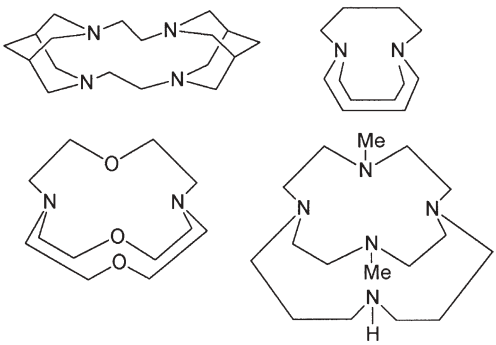
Scheme 2

2
Uses of Strong Nonionic Nitrogen Bases

2.1
Amines

One of the earliest strong non-ionic bases to make its appearance was Proton Sponge and its derivatives [1] and these systems have been reviewed [2]. More recently Proton Sponge has been used in the palladium-catalyzed arylation of 2,3-dihydrofuran [3], and it also catalyzes Knoevenagel condensations of substrates possessing activated methylene groups [4].

Recently the synthesis of the macrocyclic tetramine below (Scheme 3) was reported [5]. The encrypted nitrogens are very basic (pK_a, 24.9 in MeCN) and it was observed that chloroform is dehydrohalogenated in its presence to give dichlorocarbene. Because this new cryptand and related cage structures shown below (such as the diamine [6], the commercially available diamine triether [7] and the pentamine [8], Scheme 3) have thus far not experienced significant application in organic methodology, they will not be further treated herein.



Scheme 3

2.2
Imines

Reviews on catalytic uses of DMAP and other 4-(dialkylamino)pyridines have appeared [9]. These bases are very efficient reagents for acylations, alkylations, silylations, phosphorylations, condensations, and transesterifications [10]. More recent applications of DMAP as a catalyst include a parallel synthesis of benzyl purine derivatives [11] and it has been employed as a base in the asymmetric synthesis of an amino acid via an auxiliary [12]. Uses of DMAP tethered to solid supports (of which one such example is commercially available) have been reviewed [10, 13]. Such a system has recently been employed to synthesize multiple oligonucleotides linked end to end in tandem [14].

2.3 Amidines

Uses of bases of this type, such as DBU and DBN have been reviewed [15] and more recently they have been used as stoichiometric bases in the synthesis of 2*H*-isoindoles [16], biaryl thioethers [17], phthalocyanines [18] and the related macrocyclic compounds [18], 2,4-dioxo-1,2,3,4-tetrahydroquinazolines [19], dihydro alanine-containing peptides [20] and {[pyrazolylmethyl)amino]-propyl}azepinones and -pyrrolidinones [21]. Chiral DBU/DBN-related molecules have also been synthesized which were found to be useful as catalysts in an asymmetric Michael reaction [22].

2.4 Guanidines

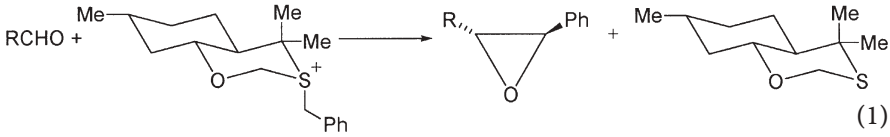
These bases have in recent years been utilized as stoichiometric bases in Wittig reactions [23], in Horner-Wadsworth olefinations [23] and in the synthesis of etioporphyrin from protoporphyrin [24]. Guanidines are useful as catalysts in, for example, the selective synthesis of monoglycerides [25], enone epoxidation [26], and Michael addition of azoles with α,β-unsaturated nitriles and esters [27]. A review of the use of modified guanidines as chiral auxiliaries in stoichiometric and catalytic asymmetric synthesis has very recently appeared [28].

The use of guanidine bases mounted on various supports has gained increased attention in recent years and has been reviewed [29]. Guanidine salts mounted on silica are useful in hindered ester synthesis, acyl chloride formation, and in the deprotection of acetals [29c]. Solid-supported guanidines (of which one is commercially available) are effective for carrying out an array of organic transformations, as for example, the catalysis of aldol [30], transesterification [29a, 29b, 31], Michael addition [32], Robinson annulation [32b], Knoevenagel [32b, 33] and nucleophilic epoxidation [32b] reactions, and also monoglyceride synthesis [33]. They also catalyze the direct introduction of CO_2 into acetylenic amines to form 5-methylene-1,3-oxazolidin-2-ones [32b]. Solid-supported guanidines are bases for the regioselective synthesis of 1-acyl-phosphatidylcholines [34], for the high throughput synthesis of an aryl triflate [35] and a nonaflate [35], and for the synthesis of esters [36], alkylated active methylene compounds [36] and aryl ethers from phenols in the presence of organic halides [37]. Interestingly, the aldol addition of acetone to benzaldehyde using *N*,*N*′,*N*″-tricyclohexylguanidine trapped in zeolite Y as the catalyst gave 4-phenyl-4-hydroxybutan-2-one as the principal product, whereas in the homogeneous system, 4-phenyl-3-buten-2-one was formed via a condensation reaction [38].

2.5 Phosphazenes

These highly interesting compounds have also become useful in a variety of organic transformations, as has been described in reviews [39], and several of

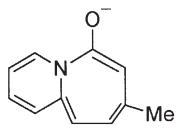
these bases are commercially available. Phosphazene bases used stoichiometrically have been reported for a considerable number of reactions. Thus, they deprotonate sulfones (forming anions that are able to react with electrophiles such as alkyl halides [40], ethyl acrylate [40], and aldehydes [40, 41]. They can be used to prepare biaryl thioethers from aryl iodides and arenethiols [17], and also 2*H*-isoindoles [16]. Three-membered ring sulfones (episulfones) undergo substitution in the presence of P_4-*t*-Bu and electrophiles to give either substituted episulfones or the corresponding alkenes subsequent to loss of SO_2 [42]. Phosphazene bases have very recently been demonstrated to deprotonate cyanoacetates in syntheses of pyrrole esters which in turn are employed in making porphyrins [43], and also in the synthesis of mono- and difluoroalanines via deprotonation of the activated methylene of diethyl *N*-acetylaminomalonate [44]. Deprotonation of the chiral sulfonium salt shown in Eq. (1) with P_2-Et in the presence of aldehydes gives *trans*-epoxides displaying high (96.8 to 99.8 %) enantiomeric purities [45]. In the presence of P_4-*t*-Bu, cyclosporin A is regiospecifically alkylated at the NH of Val-5 with reactive bromides[46], and oligopeptides can be protected by *N*-peralkylation with benzyl or allyl bromide [47].



(1)

Polymer-supported phosphazene bases (of which one example is commercially available) can be used to deprotonate a phenol group for allylation in the generation of an intermediate during an efficient synthesis of the natural product carpanone [48]. Such a system was also employed for a dehydration step in the synthesis of 1,3,4-oxadiazoles [49].

Using a phosphazene base, an optically active benzylsulfonium salt in the presence of ethyl acrylate provided an aryl-C moiety for the *trans*-2-arylcyclopropanecarboxylate that is formed in 98 – 100 % ee, while in the presence of acrolein, *trans*-2-aryl vinyl epoxide was the major product [50]. In contrast to the action of LDA on a pyrido[1,2-*a*]azepinone, P_5-*t*-Bu transforms this starting material to the enolate shown in Scheme 4 [51].



Scheme 4

Reactions catalyzed by phosphazenes have also been described. The catalytic enantioselective alkylation of the amino acid intermediate $Ph_2C{=}NCH_2CO_2$-*t*-Bu by alkyl halides was reported to occur efficiently in the presence of BEMP or BTTP [52], and such bases catalyze Michael additions in non-aqueous [53] and aqueous media [54]. Methyl [55] and butyl [56] methacrylates are anionically polymerized using a phosphazene base as an initiator in the presence of an ester that is apparently deprotonated in the process. Functioning as promoters in the

presence of alkyllithiums as initiators, phosphazene bases facilitate the synthesis of polybutadiene-poly(ethylene glycol) and polyisobutylene-poly(ethylene glycol) block copolymers [57], and also the polymerization of cyclosiloxanes [58]. In the polymerization of ethylene oxide initiated by *n*-BuLi, P$_4$-*t*-Bu is reported to serve as a cryptand for the lithium ion [59]. Isomerizations and rearrangements are also catalyzed by phosphazene bases. Thus, the isomerization of vinyl sulfones to allyl sulfones [60], the [3,3] sigmatropic oxy-Cope rearrangement of 1,5-hexadiene-3-ol [61], and the rearrangement of unactivated *N*-alkyl-*O*-benzoyl hydroxamic acid derivatives to 2-benzoyloxy amides are mediated by phosphazene bases [62]. BEMP has been reported to catalyze the reaction of carbon dioxide with acetylenic amines to afford 5-methylene-1,3-oxazolidin-2-ones [63].

3
Pro-Azaphosphatrane Bases

Having had a long-standing interest in the metal ligation properties of bicyclic phosphorus ligands [64], it occurred to us that cylindrical pro-azaphosphatrane ligands of type **1** might function as donors suitable for the formation of linear polymers containing metal moieties ligated by a bridgehead pnictogen atom from each of two pro-azaphosphatrane ligands. Although tertiary amines are relatively poor metal ligands compared with ammonia, due to steric hindrance [65], it was believed at the time that the "tied back" nature of the bridgehead nitrogen in pro-azaphosphatranes would allow such molecules to behave more like DABCO, which does form a variety of metal complexes [65, 66]. However, this goal was not achieved, owing to an unusual structural feature of pro-azaphosphatranes [67] (described in Sect. 3.2) which contributes to their tendency to transannulate.

3.1
Synthesis

Pro-azaphosphatranes **1** derive their name [68] from the fact that they are precursors to azaphosphatranes **2** when they become protonated. Their preparations are summarized in Scheme 5 and it may be noted that **1b**, **1d** and **1e** are now available from Aldrich Chemical Co. Owing to its ready oligomerization, we have not been able to isolate **1a**, although it can be formed in situ and converted to isolable derivatives such as its corresponding azaphosphatrane cation **2a** [68, 74]. The same is true for the prophosphatrane **3** which can, however, be isolated as salts of the phosphatrane cation **4** (Fig. 1) [68, 74]. It may be mentioned in this respect that **5** has been isolated and structured by X-ray means [75], but, cation **6** was too unstable for isolation by other investigators [75].

It was found early on in our research that the direct reaction of P(NMe$_2$)$_3$ with a tetramine was inefficient but that ClP(NMe$_2$)$_2$ reacted readily to form the intermediate cation chloride [**2**]Cl [68]. Thus all but one of the preparations of the pro-azaphosphatranes of type **1** (the exception being **1h**) are best carried out using ClP(NMe$_2$)$_2$ followed by deprotonation of the cation with KO-*t*-Bu. Cations

$P(NMe_2)_3 + (H_2NCH_2CH_2)_3N + HOSO_2CF_3 \longrightarrow$ [**2a**]O_3SCF_3 $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1a**[72]

$ClP(NMe_2)_3 + (H_2NCH_2CH_2)_3N \longrightarrow$ [**2a**]Cl $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1a**[68,69,72]

$ClP(NMe_2)_3 + (MeHNCH_2CH_2)_3N \longrightarrow$ [**2b**]Cl $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1b**[69,70,72]

$ClP(NEt_2)_2 + (EtHNCH_2CH_2)_3N \longrightarrow$ [**2c**]Cl $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1c**[67a]

$ClP(NEt_2)_2$ or $ClP(NMe_2)_2 + (i\text{-}PrHNCH_2CH_2)_3N \longrightarrow$ [**2d**]Cl $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1d**[67a]

$ClP(NMe_2)_2 + (i\text{-}BuHNCH_2CH_2)_3N \longrightarrow$ [**2e**]Cl $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1e**[71]

$ClP(NMe_2)_2 + (PivHNCH_2CH_2)_3N \longrightarrow$ [**2f**]Cl $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1f**[71]

$ClP(NMe_2)_2 + (BzHNCH_2CH_2)_3N \longrightarrow$ [**2g**]Cl $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1g**[72]

$ClP(NMe_2)_2 + ((S,S,S)\text{-}PhHMeCHNCH_2CH_2)_3N \longrightarrow$ [**2i**]Cl $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1i**[73]

[**2a**]O_3SCF_3 $\xrightarrow{3\text{ equiv }n\text{-BuLi}}$ [**2j**]O_3SCF_3 $\xrightarrow{3\text{ equiv }ClSiMe_3}$ [**2h**]Cl $\xrightarrow{KO\text{-}t\text{-}Bu}$ **1h**[67b]

Scheme 5

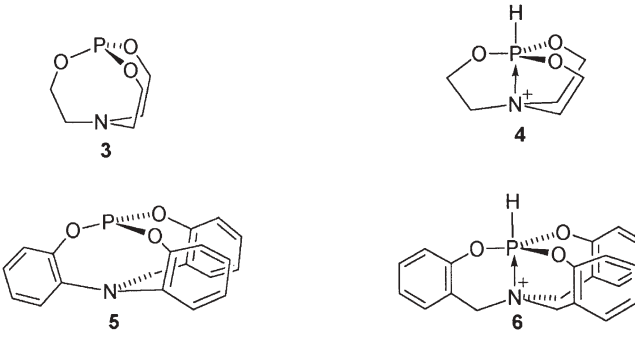
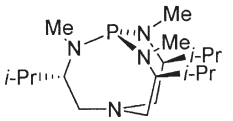


Fig. 1

of type **2** as the triflate salt can be made by reacting $P(NMe_2)_3$ with a corresponding tetramine in the presence of triflic acid, as for example, for the formation of **2a** in Scheme 1 [72]. Deprotonation of cations of type **2** can also be effected with *n*-BuLi as in the case of the conversion of **2b** to **1b** [69]. Interestingly, the three NH protons can be selectively removed from cation **1a** with *n*-BuLi to give **2j** whose lithiums can be replaced with three Me_3Si groups to afford [**2h**]Cl as the intermediate to **1h** (Scheme 1). The base **1j** has not yet been obtained in pure form. Most of the tetramines in this Scheme are derived from commercially available *tris*-aminoethylamine ("tren") by condensation with the appropriate aldehyde or ketone followed by sodium borohydride reduction. The exceptions



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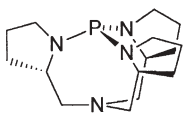
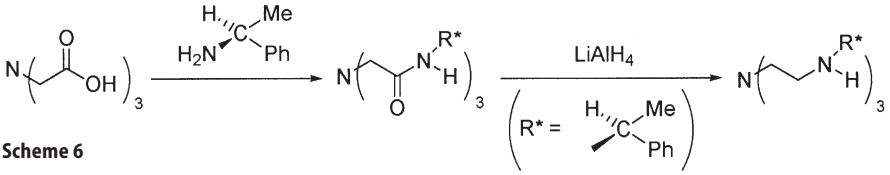


8

Fig. 2

are (MeHNCH$_2$CH$_2$)$_3$N and [(S,S,S)-PhHMeCHNCH$_2$CH$_2$]$_3$N. The former is synthesized by condensing tren with ethyl chlorocarbonate followed by LAH reduction [70], whereas the latter tetramine is afforded via Scheme 6 [73]. The synthesis of **7** [76, 77] and of **8** (Fig. 2) [78] (further examples of chiral pro-azaphosphatranes) have been recently reported by others.



Scheme 6

3.2 Structural Features

In contrast to the aforementioned amines, imines, amidines, guanidines, and phosphazenes, bases of type **1**, unexpectedly, are protonated at phosphorus rather than at one of the nitrogens. We have attributed phosphorus protonation of **1** to the electron-enriching effect on phosphorus of the accompanying transannulation in these compounds to give their corresponding very robust cations **2** [68, 74]. Stabilization of these cations is further enhanced by the formation of three five-membered rings that "chelate" the phosphorus, and the delocalization of the positive charge as suggested in the resonance structures below (Fig. 3) [68, 74]. Thus the pro-azaphosphatrane bridgehead nitrogen is sterically forced to adopt a higher-energy transition state structure in which this strain is relieved when protonation occurs, forming a trigonal bipyramidal phosphorus that is chelated with three five-membered rings. As a result, the bridgehead nitrogen adopts a more pyramidal conformation.

Evidence for strain in the eight-membered rings of molecules of type **1** (which is probably augmented by the van der Waals interactions among the methylene protons adjacent to the bridgehead nitrogen [68, 74]) is the aforementioned observation that **1a** oligomerizes via ring opening. Such instability to

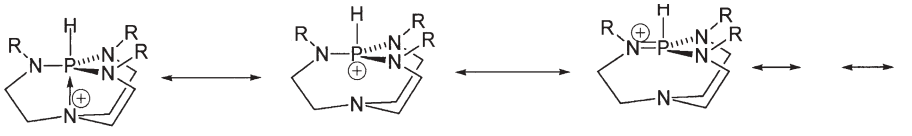


Fig. 3

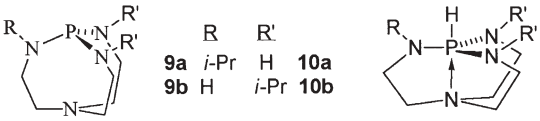
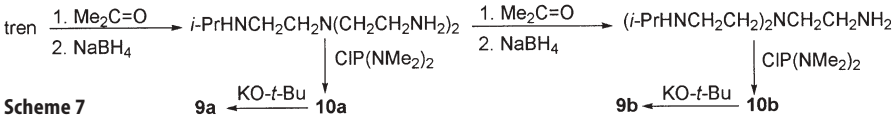


Fig. 4

oligomerization is also apparent in **9a** [71] and **9b** (Fig. 4) [79] which have been synthesized via the pathways depicted in Scheme 7. Thus **9b** can be isolated in pure form and is reasonably stable whereas **9a** is only observable by ^{31}P-NMR spectroscopy, although both compounds are easily isolated in pure form as their protonated cations **10b** and **10a**, respectively. Substituents on all of the secondary amine nitrogens in stable **1b – i** apparently effectively inhibit oligomerization.

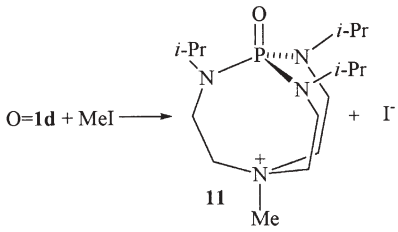


Scheme 7

The question regarding the possibility of a transannular interaction in **1** and **9** is an interesting one. Molecular structure determinations of **1d** [67a] and **1h** [67b] by X-ray crystallography reveal that their respective bridgehead-bridgehead distances [3.293(2) and 3.360(7) Å], average NPN angles [103.24(7)° and 103.3(2)°] and average CNC angles [119.6(2)° and 119.3(5)°] are quite comparable. Thus any changes in stereoelectronic effects of the substituents appear to have a minimal effect on the overall geometry of the core cage framework of **1**. The bridgehead-bridgehead distances in **1d** and **1h** are about 2 % shorter than the sum of the van der Waals radii of 3.35 Å, but this shortening has been concluded from a theoretical analysis to be too insignificant for transannular interaction [80]. It was also shown from a theoretical analysis of the electron density distribution in the transannular bond in structures of azaphosphatranes (wherein this distance is very close to 2.00 Å in cations **2a** [69], **2b** [81], **2d** [67a], **2e** [71], **2f** [71] and **2h** [67b]) that a weak but well-defined transannular bond exists. This 2.00 Å distance represents only a ca 40 % shortening over the van der Waals radius of 3.35 Å and it is considerably longer than the approximately 1.6 Å for a covalent P-N bond.

It is interesting that the bridgehead nitrogen of the oxide of **1d** (O=**1d**) can be quaternized[82] [Eq. (2)] thus elongating the interbridgehead distance in cation **11** to 3.56 Å, which is 6 % longer than the sum of the van der Waals radii. Noteworthy is the non-tetrahedral angle of about 114° for the H_2C-N-CH_2 bond angles at the bridgehead nitrogen whose relatively large size could be associated with the van der Waals interactions among the hydrogens on the adjacent methylene carbons. There is, however, a substantial twist along the C_3 axis that does not allow easy racemization of the cage, thus giving rise to AB NMR patterns for the methylene protons of this cation. The bridgehead-bridgehead distance in the parent O=**1d** structure is expected to be similar to that in the anal-

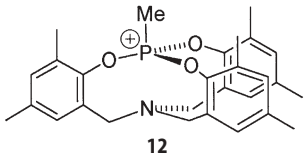
ogous derivative O=**1b** [3.137(3) Å] [83]. Making this reasonable assumption, the elongation of this distance from O=**1d** to **11** is ca 0.4 Å.



(2)

The interpretation of He I and He II photoelectron spectra of **1b** and **1d** using ab initio calculations [84] is that their first ionization energies (6.61 and 6.41 eV, respectively) are among the lowest ever reported for phosphorus compounds. Geometry optimization of the ionic states of the parent pro-azaphosphatranes revealed that there are two minima on the potential energy surface at different P-N$_{ax}$ distances, representing two bond-stretch isomers. The structure with the longer distance (3.3 Å) is similar to that of the neutral molecule while the one with the shorter length (2.07 Å) is as much as 1 eV lower in energy than the other. This greater stability and shorter bridgehead-bridgehead distance is characteristic of azaphosphatranes in which a transannular bond (albeit a weak one [80]) exists. Moreover, the adiabatic ionization energy for the transannulated bond stretch isomer is concluded to be lower, in agreement with the strong basicity of pro-azaphosphatranes.

The optimum ring size for stabilizing phosphatrane structures of type **2** is not obvious since such systems to date have been constructed only with two-carbon aliphatic linkages. As was mentioned earlier, the trioxaphosphatrane **6** has been reported, but it is unstable to isolation [75] (in contrast to its precursor **5** [75]) suggesting that the benzo bridges confer considerable ring strain on transannulated **6**. This ring strain was mitigated by expansion of the ring with a methylene group in each bridge, as was recently reported by others for the phosphonium salt **12** (Fig. 5) [85]. An X-ray crystallographic investigation revealed, however, that the transannular distance [2.81(2) Å] is too large to consider the presence of significant transannulation [85]. This is not surprising in view of the observation that its analogue **13** (Fig. 5) was found to possess a similar interbridgehead distance of 2.771(4) Å [86] which is only 17 % shorter than the sum of the relevant van der Waals radii. Interestingly, the structure of cation **13** does feature an upwardly protruding bridgehead nitrogen and enlarged NPN bond angles, both of which are suggestive of some transannular interaction.



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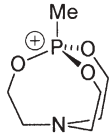
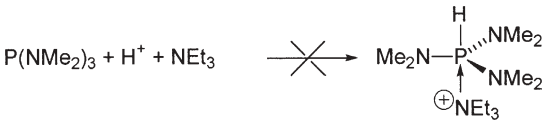


13

Fig. 5

Partial transannulation of a pro-azaphosphatrane to form a quasi-azaphosphatrane can occur to varying degrees, as is illustrated in Fig. 6. We associate the versatility of compounds of type **1** as catalysts for useful organic transformations with the flexibility of the transannular interaction in these cage-like molecules. This distance progresses gradually from about 3.30 down to 2.00 Å, depending on the nature of the axial Z substituent [68]. This distance varies quite monotonically with the NPN angle at the phosphorus bridgehead, which gradually opens from about 104° in the untransannulated pro-azaphosphatrane structures to 120° in fully transannulated trigonal bipyramidal azaphosphatranes. The nearly linear (99 % confidence interval) response of the bridgehead NPN bond angles to intensifying transannulation could arise from a lower reorganization energy associated with rehybridization of the phosphorus compared with other atoms in the bridges connecting the bridgehead atoms. The stepwise formation of the transannular bond depicted in Fig. 6 could reflect increasing strain and decreasing entropy associated with forming these five-membered rings in azaphosphatranes, which counterbalance the electron-withdrawing ability of the Z substituent. In this regard, our attempts to carry out the reaction shown in Eq. (3) (wherein ring strain is absent) have failed and only $HNEt_3^+$ was observed to form [87]. This reaction (wherein three molecules must condense to one) would appear to require a greater entropy decrease than transannulation of **1**, which is an intramolecular process.



(3)

Another structural feature of **1** that favors transannulation is the already virtual planarity of the bridgehead nitrogen. A conformational change in the cage upon deprotonating protonated **7** results in substantial steric repulsions according to density functional calculations carried out in other laboratories, and this effect is believed to account for the weak acidity of this cation [77].

The top row of Z substituents in the plot in Fig. 6 implies that full transannulation can be realized by a sterically sizable ("cationic") group [$Ph_2P(O)O$] as well as polarizing ("cationic") atoms that form reasonably strong to very robust bonds to phosphorus (H, 78; Cl, 79; F, 119 kcal mole^{-1} [88]). The role of decreasing electronegativity can also be seen in weakening and lengthening of the transannular interaction in the series Z = CF_2Br, CF_2H, CH_3; Z = HPhN, H_2N; and Z = O, S. It is interesting to observe in Fig. 6 that the presence of a positive charge seems to be a prevalent but not a necessary condition for full transannulation. Thus a neutral Z substituent [$(NC)_2C=C(CN)_2$] is a more polarizing group (perhaps owing to a zwitterionic contribution [89]) than the next three "cationic" species below it in Fig. 6.

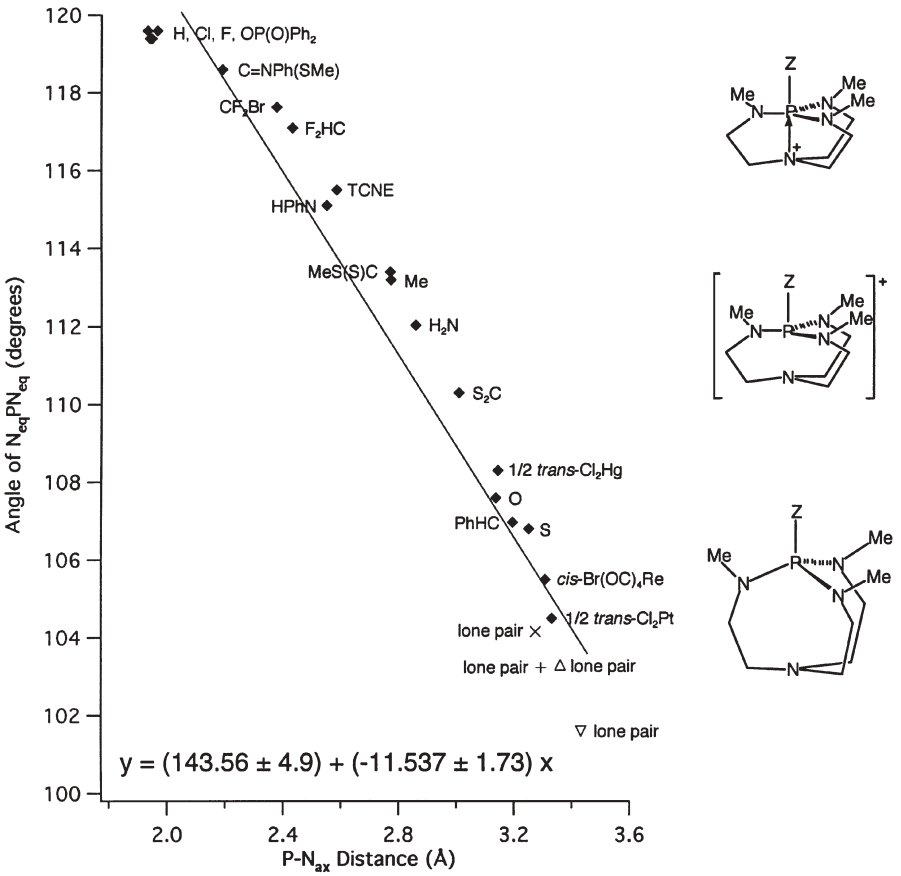


Fig. 6. Plot of the transannular distance versus the average bridgehead N-P-N bond angle for a series of pro-azaphosphatranes, quasi-azaphosphatranes, and azaphosphatranes. The different markers for Z = lone pair denote data for the following substituents on the nitrogens adjacent to phosphorus: Me (♦), Me_3Si (∇), i-Pr (+) and (S,S,S)-PhHMeC (×). Crystals suitable for X-ray data were obtainable for these pro-azaphosphatranes but not for P(MeNCH$_2$CH$_2$)$_3$N

3.3
Basicity/Nucleophilicity of Pro- and Quasi-Azaphosphatranes with Reactive Z Groups

The influence of the cage structure in reactions of pro- or quasi-phosphatranes wherein Z is a reactive substituent is now illustrated with several examples. Semi-stabilized ylides of the type Z = PhHC and the acyclic analogue HPhC = P(NMe$_2$)$_3$ are interesting to compare in the Wittig reaction [90]. Although semi-stabilized ylides typically yield mixtures of *Z* and *E* isomers, reactions of the ylide in Fig. 6 wherein Z = PhHC with aldehydes give alkenes in high yield with quantitative *E* selectivity, in contrast to the corresponding ylide made with acyclic phosphines including the aminophosphine HPhC = P(NMe$_2$)$_3$ [90a]. This *E* selectivity was maintained for Z = HPhC despite changes in the metal ion of the ionic base used to deprotonate the bicyclic ylide, temperature, and solvent

polarity. This stereoselectivity of Z = PhHC in the Wittig reaction was rationalized on the basis of the peculiar stereoelectronic properties of the bicyclic ylide. As was shown by others, the acyclic ylide $HPhC=P(NMe_2)_3$ is very basic with a pK_a in THF between those of **2b** and protonated P_4-*t*-Bu [90b]. $HPhC=P(NMe_2)_3$ was also shown to be capable of deprotonating a variety of amide NH and $O=CCH_2$ functionalities. By reacting $P(NMe_2)_3$ with a Merrifield resin followed by deprotonation, polymer-$PhC=P(NMe_2)_3$ was formed which also was effective in the aforementioned deprotonations [90b]. When $Z=CS_2$, a sulfur is alkylated by MeI to give Z = MeS(S)C in which the transannular distance decreases substantially compared with the starting compound [86] (Fig. 6).

Although Z = O is not significantly transannulated (Fig. 6), several Lewis acids acting on the oxygen lead to transannulation according to the upfield ^{31}P-NMR chemical shifts observed for the bridgehead phosphorus [91]. Thus the negative shifts for $Z=Ph_2P(O)O$ (– 22.60 ppm), Ph(Cl)P(O)O (– 31.51), 1/2PhP(O)O (– 11.08), Cl_2MeSiO (– 38.01), and Cl_3SiO (– 39.67 ppm) are all consistent with substantial transannular interaction in these cations. When the compound in which Z = O was protonated with non-aqueous HCl, no compound could be isolated. Oddly, $O=P(NMe_2)_3$ was easily isolated as its hydrochloride salt and its X-ray structure unexpectedly revealed an O-H bond distance (1.005(5) Å [91]) which is within experimental error of that in water.

When Z = O (Fig. 6) condensation of aryl and alkyl isocyanates to carbodiimides is effectively catalyzed and it is a much stronger catalyst in this reaction than the monocyclic analogue $Me_2N(O)P[NMeCH_2]_2$ or the acyclic analogue $OP(NMe_2)_3$ [92]. Thus, when Z = O, the phosphoryl oxygen facilitates transannulation that enhances its nucleophilicity; a process that is precluded in the monocyclic and acyclic analogues. The analogue, in which Z = S, is almost as active in the same catalytic transformation. Noteworthy here is the observation, however, that the Z = S compound is transformed to the Z = O derivative presumably with the formation of OCS [92].

In contrast to the pro-azaphosphatrane in which Z = O, Z = PhN catalytically trimerizes a variety of isocyanates to isocyanurates [92]. Its activity in this reaction is only somewhat less than that reported earlier by us for **1b** (see Sect. 3.5.5.2) [93]. It should be noted from Fig. 6 that the pro-azaphosphatrane cation wherein Z = PhN has been protonated (i.e., Z = HPhN) is quite transannulated. From qualitative equilibrium measurements in acetonitrile, we have ascertained that DBU is a stronger base than the pro-azaphosphatrane wherein Z = PhN, which is in turn a stronger base than $PhN=P(NMe_2)_3$ [94]. On the other hand, such experiments in the same solvent also showed that the Z = MeN derivative is a stronger base than $PhN=P(NMe_2)_3$, which in turn is a stronger base by a factor of 1500 than DBU [39b]. As suggested by others, the basicity increase from the acyclic analogues to the corresponding pro-azaphosphatrane imides induced by transannulation may correspond to only a few pK_a units, however [95].

The related imidophosphorane wherein $Z=PhCH_2N$, and its acyclic analogue $PhCH_2N=P(NMe_2)_3$, are very efficient catalysts for the protective acylation of alcohols in the presence of enol esters [96]. Acid-labile groups (such as acetal and epoxide) survive and groups such as TBS and disulfide [which undergo

cleavage in the presence of Ac_2O and the Lewis acid $Sc(OTf)_3$] are (among others) also unaffected. Because secondary alcohols do not react under our conditions, our methodology is attractive for the selective acylation of primary alcohols. Polymer versions of $Z{=}PhCH_2N$ and $PhCH_2N{=}P(NMe_2)_3$ were also effective in these reactions [96].

The protonated species in Fig. 6 wherein $Z = H_2N$ is apparently partially transannulated, in contrast to what would be expected for $Z = HN$ [97]. The acyclic $H_2N{=}P(NMe_2)_3^+$ cation, structured as the acetate salt by others, also revealed an ionic structure, with an ion pair being formed via a bifurcated 3-center hydrogen bond [$NH(\cdots O)_2$] from a proton on the imido nitrogen to both oxygens of an acetate ion [98].

In competitive deprotonation experiments in KO-*t*-Bu/DMSO, the relative proton acidities of cations **1a**, **1b**, and **1g** were estimated from ^{31}P-NMR equilibrium measurements to be between 27 and 30 [72]. More recently, the pK_a values of **2b**, **2d**, **2e**, **2f**, and **10a** were measured in acetonitrile and they are listed in Table 1 along with values for other non-ionic bases for comparison. Although bases **1** are about ten orders of magnitude weaker in basicity than P_4-*t*-Bu or P_5-*t*-Bu in acetonitrile, they are ten to twenty orders of magnitude stronger than nitrogen bases in this solvent. It should also be recalled that, unlike phosphazene bases, pro-azaphosphatranes protonate at the phosphorus rather than at one of the two types of nitrogens in these molecules.

Table 1. pK_a values for conjugate acids of various non-ionic bases

Acid	pK_a	Reference
P_5-*t*-Bu	45 – 46	[39a]
P_4-*t*-Bu	42.6	[39a]
P_3-*t*-Bu	38.6	[39a]
P_2-*t*-Bu	33.5	[99]
P_1-*t*-Bu	26.9	[39a]
1b	32.90	[100]
1d	33.63	[100]
1e	33.53	[100]
1f	32.84	[100]
9a	34.49	[71]
BEMP	27.58	[39a]
DBU	24.32	[39a]
TMGN	25.1	[2c]
TBD	25.96	[39a]
MTBD	25.43	[39a]
DBN	23.79	[39a]
TMG	23.3	[39a]
Et_3N	18.5	[101]
Proton Sponge	18.18	[39a]
DMAP	17.74	[95]
pyridine	12.33	[39a]
P(*t*-Bu)$_3$	17.0	[102]
$PMePh_2$	9.6	[102]
PPh_3	8.0	[102]

Table 1 also reveals that pro-azaphosphatranes are about fifteen to twenty-five orders of magnitude more basic than phosphines (which also protonate at phosphorus). It is interesting here that the conjugate acid of the bicyclic diphosphine 1,5-diphosphabicyclo[3.3.3]undecane possesses a pK_a in acetonitrile (17.9) comparable to that of $P(t\text{-Bu})_3$ (Table 1) and that the pK_a values rise markedly for increasingly larger bicyclic analogues: 1,6-diphosphabicyclo[4.3.3]dodecane (22.5) and 1,6-diphosphabicyclo[4.4.3]tridecane (27.8) as was reported by others [103]. The phosphorus geometry in these compounds is quite flat and the possible contribution of this effect as well as the influence of intrabridgehead bonding has been discussed [103].

It has been suggested that protonated phosphazene bases are good counterions for anions of acids, owing to bulkiness of the cation and also to delocalization of the positive charge over the framework of the relatively large cation [104]. Indeed, NMR evidence has been presented for the conclusion that methyl phenylacetate enolate generated with P_4-*t*-Bu was naked or tightly associated, depending on small changes in solvent composition [105]. Moreover, phosphazenium fluorides are potent sources of naked nucleophilic fluoride ions for mediating alkylation of alkyl halides by allyltrimethylsilane and for mediating base-catalyzed dehydrohalogenation of 1-alkyl halides [106]. As will be seen from the nature of the reactions described in Sects. 3.4 and 3.5, azaphosphatrane cations of type **2** are also capable of producing naked or tightly associated species.

3.4
Applications of Pro-Azaphosphatranes in Stoichiometric Reactions

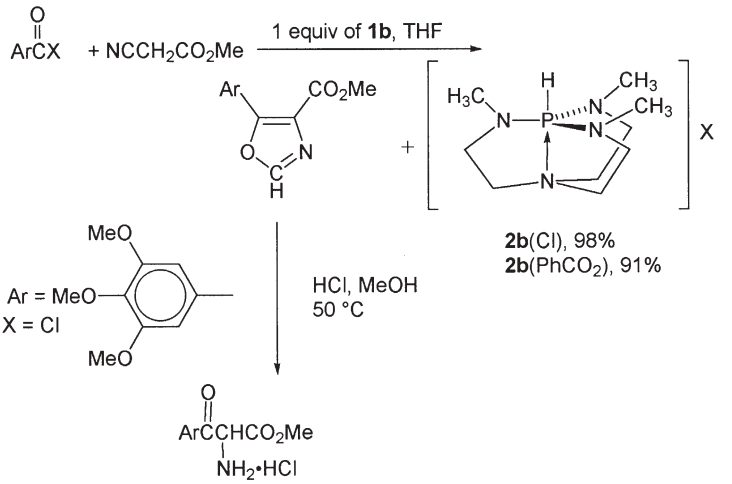
This section is introduced with the interesting report in a patent that the thermal stability of *N,N*-dinitramide salts $\{M^+[N(NO_2)]^-\}$ in which M^+ is a nitrogen-containing cation, is improved by mixing the salt with small amounts of a base of type **1** [107]. *N,N*-Dinitramide salts are used as explosives and as rocket propellant oxidizers.

3.4.1
Reactions in which a CH Deprotonation Occurs

3.4.1.1
Synthesis of Oxazoles and α-C-Acyl Amino Acid Esters

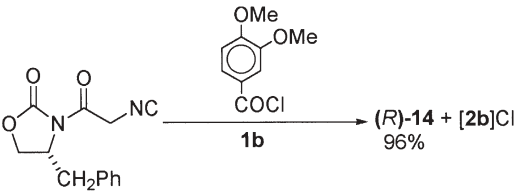
Oxazoles are intermediates to pharmaceutically interesting *α-C*-acyl amino acids which in turn are useful intermediates in the synthesis of *β*-hydroxyamino acids [108]. Base **1b** provides a marked improvement in the yields of oxazoles (Scheme 8) [108] whose synthesis typically requires a large excess of NEt_3 or DBU and long reactions times.

Another advantage of the use of **1b** over DBU is that the **2b** salts produced are easily separated from the product in high yield by filtration for subsequent recovery of the free base [108].



Scheme 8

Base **1b** was also employed to create an oxazole ring in the synthesis of strongly fluorescent (*R*)-**14** (shown in Scheme 9) which we made from the chiral auxiliary-bearing isocyanide (*R*)-**15** (which we also synthesized for the first time) [109]. Also synthesized was (*S*)-**14** by an analogous route. Optically active fluorescent materials with high quantum yields and/or strong circular dichroism signals are rare, but they are important standards in fluorescence-detected circular dichroism for on-column capillary electrophoresis. (*R*)-**14** and (*S*)-**14** were determined to have high fluorescence quantum yields (0.99 in EtOH) [109].

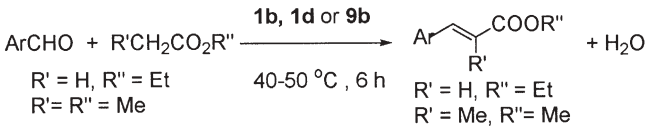


Scheme 9

3.4.1.2 Direct Synthesis of E-α,β-Unsaturated Esters

α,β-Unsaturated esters are formed as the sole products with excellent *E* stereoselectivity upon reacting ethyl acetate or methyl propionate with a variety of aromatic aldehydes in the presence of **1b**, **1d**, or **9b** at 40 to 50 °C for 2 to 6 hours in isobutyronitrile [Eq. (4)] [110]. Commonly employed methods for the preparation of *E*-*α,β*-unsaturated esters are the Wittig reaction and its modifications devised by Horner (although disadvantages are the need for the preparation of intermediates and the lack of the production of a single isomer), Peterson, and Julia-Lithgoe olefinations (which generally require elevated temperatures and/or generally fail to induce good stereoselectivity in the preparation of *tri*-substituted *α,β*-unsaturated esters), the Perkin reaction (which gives low to

modest product yields of α,β-unsaturated acids even at elevated temperatures) and reactions involving a variety of organometallic compounds and transition metal complexes (which have several drawbacks, the chief of which is their toxicity). The synthesis we describe here is not as successful for the preparation of α,β-unsaturated ketones. Preliminary experiments [71] indicate that catalyst **1e** is about as effective in this reaction as **1d** in a *stoichiometric* synthesis of *E*-α,β-unsaturated esters.

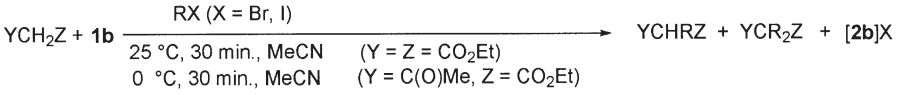


(4)

3.4.1.3
Selective Monoalkylation of Active-Methylene Compounds

Monoalkylated products of substrates such as malonic esters, β-diketones and β-keto esters are highly useful because of their ready conversion to the corresponding ketenes or esters and they also function as starting materials for the preparation of α,β-unsaturated ketones and esters [111]. A frequent difficulty encountered in attempts to monoalkylate such substrates is concurrent formation of a second *C*-alkylated side product, *O*-alkylated systems and, in some instances, condensation products. Among the approaches to overcome these difficulties has been the use of DBU as a base [111]. However, yields are moderate, reaction times are relatively long, and dialkylation of the carbon as well as *O*-alkylation occurs.

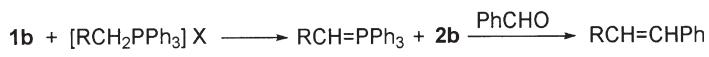
Using **1b**, however, symmetrical active methylene compounds can be selectively monoalkylated under mild conditions and the yields are high (85 to 98 %) with 100 % conversion of the starting material and no detectable amounts of dialkylated products (Scheme 10) [111]. Although the unsymmetrical active methylene compound in this scheme does leave unreacted starting material and also gives rise to dialkylated product, respectable yields of monoalkylated products were obtained (59 to 88 %).



Scheme 10

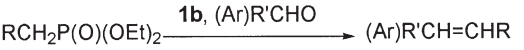
3.4.1.4
Ylide Generation for Synthesis of Wittig and Wittig-Horner Products

Pro-azaphosphatrane **1b** is an efficient base for converting $[RCH_2PPh_3]X$ and $RCH_2P(O)(OEt)_2$ to their corresponding ylides and anions, respectively, in situ under mild conditions [Scheme 11 and Eq. (5)] [112]. The olefins were produced in 70 to 92 % yields. Our test substrate for the Wittig reactions was benzaldehyde and the stereochemistry of the reaction product obtained with **1b** was the same



Scheme 11

as that normally observed for the three classes of phosphonium ylides we generated (i.e., stabilized ylides gave the *E*, non-stabilized afforded *Z*, and semistabilized ylides provided a mixture of *Z* and *E*-alkenes). The Wittig-Horner reaction of phosphonates with aldehydes led to *E*-alkenes with high selectivity.

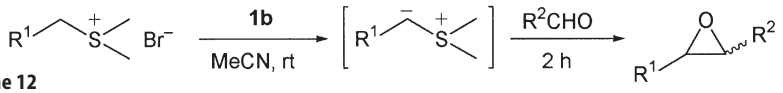


(5)

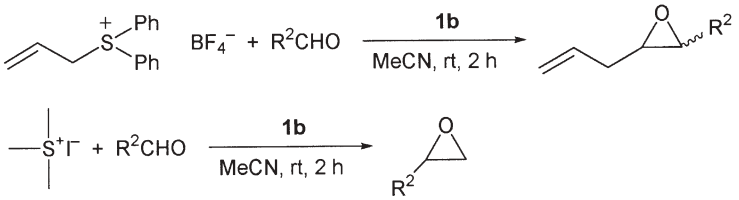
3.4.1.5
Generation of Non-Stable and Somewhat Stable Sulfur Ylides

Sulfur ylides are useful as nucleophilic alkylidene transfer agents in reactions with electron-deficient functional groups, forming epoxides with carbonyls, and either undergoing carbonyl addition with epoxide formation or conjugate addition with cyclopropanation with Michael acceptors, depending on the structure of the Michael acceptor [113].

Base **1b** readily generates somewhat stable and non-stable ylides in acetonitrile, which are then captured by aromatic aldehydes to give oxiranes, generally in 70 to 96 % yields (Schemes 12 and 13, respectively) without evidence of sigmatropic rearrangement (as is sometimes seen with the use of *n*-BuLi) [113].



Scheme 12



Scheme 13

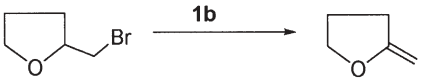
3.4.2
Elimination of HX

3.4.2.1
Dehydrohalogenation of HC-CHX Substrates

The title transformation is a well-known one that has been applied to the synthesis of a variety of compounds including prostaglandins, vitamin A, and polyenes. Because typical organic bases such as Et_3N, DMAP, pyridine, and quinoline are often unsatisfactory for such reactions, DBN and DBU have been employed

[114] owing to their non-nucleophilic nature and greater basicity. However, dehydrohalogenations with these bases often require heating and excess reagent, and yields are often not high.

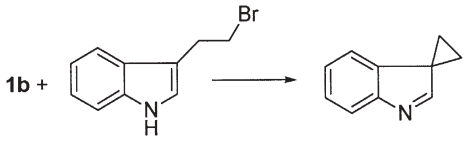
In the presence of only 1.1 equiv. of **1b** at room temperature or at 0 °C, primary alkyl halides form the corresponding phosphonium salts, whereas secondary and tertiary halides, and also primary halides activated by an electronegative β-substituent, undergo elimination to form olefins in 85 to 98 % yields [115, 116]. Elimination from the secondary and tertiary halides appears to be exclusively *trans*, and to our knowledge, these are the only reports of such a highly stereospecific action of a phosphorus base on a substrate that is not sterically restricted from forming one of the olefin isomers. A comparison of the efficacy of **1b** versus DBU in these reactions under the same conditions revealed that the yields using **1b** exceeded those with DBU by moderate to very substantial margins. In this regard, the substrate in Eq. (6), which possesses an electron donating group β to the halogen, provides an 85 % yield of product (albeit after prolonged reaction) whereas no product could be obtained with DBU.



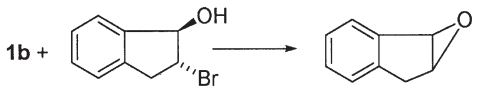
(6)

3.4.2.2
Cyclizations via Dehydrohalogenation

In the presence of **1b**, the reactions in Eqs. (7) and (8) proceed in high yields (90 to 98 %) in acetonitrile at room temperature [116]. In both cases the yields were higher than conversions with DBU under the same conditions. It is interesting in reaction (7) that the exclusive product is the cyclopropane derivative and no evidence of the olefin is observed.



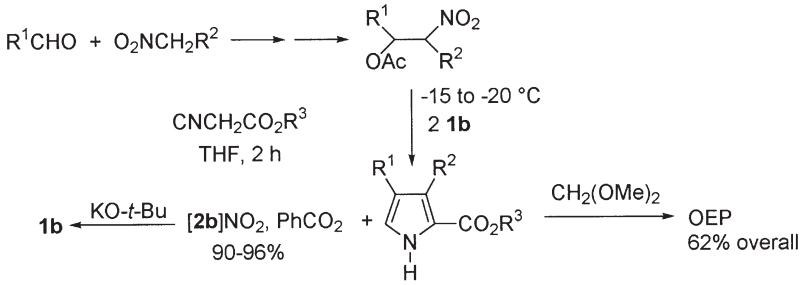
(7)



(8)

3.4.2.3
Elimination of HOAc in the Synthesis of α-(Alkoxycarbonyl)-pyrroles

Pyrrole derivatives are important intermediates in the synthesis of bioactive porphyrins [108]. Octaethylporphyrin (OEP), for example, is widely used for biological modeling studies because of its high symmetry, relatively good solubility, and stability. Pyrrole derivatives are also important intermediates for the synthesis of bile pigments, drugs and agrochemicals.

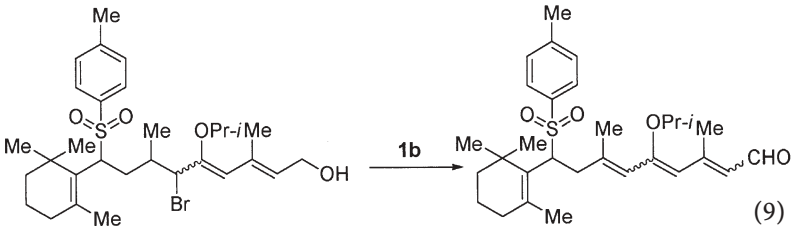


Scheme 14

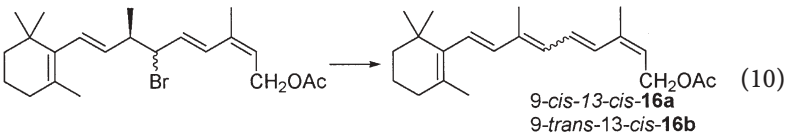
Summarized in Scheme 14 is a "one-pot" strategy we developed for the synthesis of α-(alkoxycarbonyl)-pyrroles, which was then applied to the synthesis of OEP in 62% overall yield [108]. This yield is a substantial improvement over those normally achieved by other methods (22 to 45%). The third step in this scheme is usually carried out with DBU or guanidine at elevated temperatures, which leads to undesirable side products.

3.4.2.4
Elimination in the Synthesis of Vitamin A

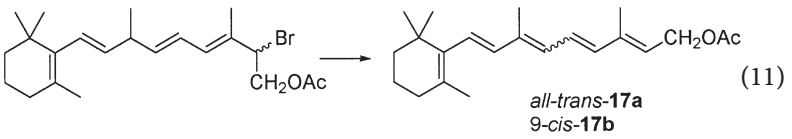
Base **1b** has recently been used in the synthesis of vitamin A [117]. Thus the product in Eq. (9) was reported in a patent [117a] and those in Eqs. (10) and (11) were described in recent work from our laboratories [117b]. Although **1b** was found to be less effective than DBN or DBU in removing HBr from the mixture of vitamin A intermediates shown in Eqs. (10) and (11) when the dehydrohalogenation was carried out in refluxing benzene, **1b** was faster than DBN or DBU in acetonitrile.



(9)



(10)



(11)

3.4.3
Removal of Sulfur from Organosulfur Compounds

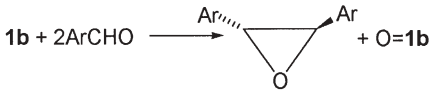
The desulfurization of organosulfur compounds with trivalent organophosphorus compounds has been studied for more than four decades [118]. A variety of such reagents has been used to convert disulfides to monosulfides, trisulfides to disulfides or monosulfides, β-keto sulfides to ketones, and sulfenimides to amines. They have also been used to remove sulfur from thioethers, thiols, and organometallic dithiocarboxylates, and oxygen from sulfones.

We found that **1b** stoichiometrically converts trisulfides at room temperature primarily to disulfides along with monosulfides as minor products [118]. With a higher concentration of **1b**, further desulfurization of trisulfides could be effected to give monosulfides in good to high yields at room temperature or up to 110 °C over periods ranging from 3 to 65 hours. Propylene sulfide was found to give exclusively propylene at room temperature, and somewhat unexpectedly, $S{=}PPh_3$ was desulfurized in moderate yield, although $S{=}P(NMe_2)_3$ and $S{=}P(n\text{-}Bu)_3$ were resistant to this process. The acyclic analogues $P(NMe_2)_3$ and $P(NEt_2)_3$ were considerably less effective in these reactions; an observation that may be attributable to the possibility for transannulation in **1b** during the desulfuriztion process. It may be mentioned here that sulfur as H_2S is efficiently removed from crude oil by a variety of scavengers, including DBU which removes it as the [HDBU]SH salt [119].

3.4.4
Removal of an Oxygen Atom from Aldehydes to form Epoxides

Epoxides are important starting materials in organic synthesis [120]. Although the most frequently used method to generate them is to oxidize olefins with peroxides, this method is not always applicable to epoxides with sensitive structural features. For converting aryl aldehydes possessing electron-withdrawing groups to the corresponding epoxides, $P(NMe_2)_3$ has been used as a reagent that often leads to high product yields. Moreover, this transformation tolerates sensitive functional groups that oxidative methods do not. Although *trans*-epoxides are always major products with $P(NMe_2)_3$, stereoselectivity is usually poor since *cis/trans* ratios between 2.6/1 and 1.1/1 are generally realized, depending on the substrate.

The use of **1b**, however, offers a facile, efficient and highly selective strategy for the synthesis of *trans*-epoxides from aryl aldehydes bearing electron withdrawing groups [Eq. (12)] [120]. It is interesting that pro-azaphosphatrane **1d** did not facilitate this reaction, probably owing to its greater steric bulk.



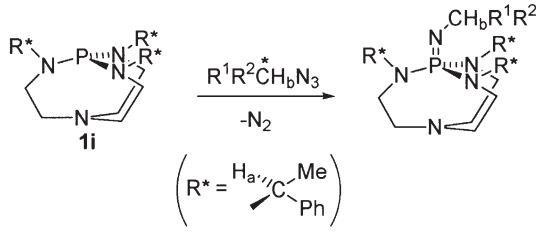
(12)

3.4.5
Removal of Nitrogen from Azides

3.4.5.1
A New Chiral ^{31}P- and ^{1}H-NMR Tagging Reagent for ee Analysis of Chiral Azides

Chiral azides are important starting materials for the synthesis of amines that are used as ligands, chiral auxiliaries, pharmaceutical intermediates, and building blocks for the asymmetric synthesis of natural products [121]. Although amines can be made in several ways, the azide reduction method is often employed because it is facile and well documented in the literature. Hence, numerous methods have been developed to synthesize azides in enantiomeric forms. While a variety of approaches can be taken to establish the enantiomeric purity of chiral compounds, ^{31}P-NMR spectroscopic analysis is very popular because of the attractive features of this nucleus. Although several derivatizing agents have been developed for such analyses of chiral alcohols, amines, and thiols, no derivatizing agent has been reported for the direct determination of ee values of chiral azides by ^{31}P- or ^{1}H-NMR spectroscopy.

We found that the C_3 chiral pro-azaphosphatrane **1i** is an excellent tagging agent for the direct determination of enantiomeric excesses of chiral azides using both ^{31}P- and ^{1}H-NMR spectroscopy [121]. Thus the reaction in Eq. (13) is carried out in an NMR tube at 50 °C for 2 hours, followed by NMR spectroscopic analysis. The excellent separations of the ^{31}P-NMR chemical shifts (ca 1 ppm) allowed the ratios of the diastereomeric imidophosphorane derivatives to be easily measured and these ratios were very close to the expected values for commercially purchased racemic and chirally pure compounds as well as various mixtures of two enantiomers. These ratios were also in good agreement with those measured by ^{1}H-NMR spectroscopic integration of the proton H_b shifts in the tagged product [see Eq. (13)].



(13)

It is of interest that the commercially available chiral phosphoramide shown in Fig. 7, when employed in comparison reactions, afforded no observable diastereomeric differentiation either by ^{31}P- or ^{1}H-NMR spectroscopy [121]. This result may be rationalized on the fact that the monocyclic reagent has only two chiral centers while **1i** possesses three. Moreover, the chiral centers in **1i** are held rigidly in place, thus perhaps providing an enhanced chiral phosphorus environment.

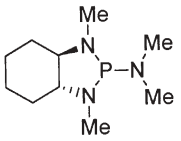


Fig. 7

3.4.5.2
Benzene from a Novel Cyclohexane Derivative

Although the aromatization of cyclohexane derivatives at elevated temperatures (90 °C and above) is well known, this process has apparently not been reported to occur at room temperature [122]. While the synthesis of benzene about to be described using the precursor shown in Fig. 8 is quite impractical, it readily takes place at room temperature and it proceeds by a novel pathway that also produces interesting side products [122]. The triazido precursor shown is remarkably thermally stable to decomposition to the corresponding trisimidophosphorane even at 100 °C under vacuum for 10 hours [122]. This stability was attributed to the well known contribution of steric hindrance and phosphine basicity to the stability of such Staudinger intermediates. In the presence of weak acids such as benzoic acid, however, the triazidophosphorane exothermically decomposes with the evolution of nitrogen gas to afford a 56 % yield of benzene. The low yield of benzene observed in our reaction stems from the observation of the intermediates shown (Fig. 9) in their mass spectra.

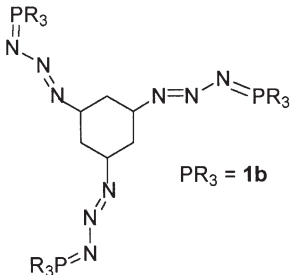


Fig. 8

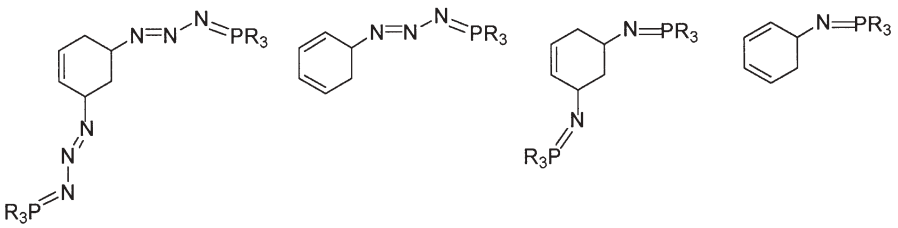


Fig. 9

3.5
Uses of Pro-Azaphosphatranes in Catalytic Reactions

3.5.1
Reactions in which C-H Deprotonation Occurs

3.5.1.1
Promotion of the Nitroaldol (Henry) Reaction

β-Nitroalkanols are important and versatile intermediates in the synthesis of nitroalkenes, 2-amino alcohols, and α-nitroketones [123]. 2-Amino alcohols are of particular significance in the synthesis of biologically important compounds such as epinephrine and anthracycline antibiotics, while α-nitroketones are valuable intermediates in the synthesis of several natural products. β-Nitroalkanols are also important because of their properties as fungicides and because of their utility as intermediates in the synthesis of amino sugars and several antibiotics. Classical as well as more recently developed methods for preparing β-alkanols all have drawbacks, among which are base-catalyzed elimination of water, the formation of 1,3-dinitro compounds, and low yields with ketones.

Bases **1b**, **1d**, and **9b** catalyze the nitroaldol reaction with ketones and aldehydes at room temperature in the presence of $MgSO_4$ in generally superior yields [Eq. (14)] [123]. Moreover, ketone self-condensation was not problematic under our conditions. In a comparison of the effectiveness of **1d** with **1e** and **1f** in these reactions, **1e** and **1f** were more efficacious [71].

$$\underset{\substack{\text{aldehyde}\\ \text{or ketone}}}{R_2CO} + 2CH_3NO_2 \xrightarrow[-\,[\mathbf{2b}],\,[\mathbf{2d}]\text{ or }[\mathbf{10b}]CH_2NO_2]{\mathbf{1b},\ \mathbf{1d}\text{ or }\mathbf{9b}} \underset{\displaystyle OH}{\overset{\displaystyle |}{R_2CCH_2NO_2}} \qquad (14)$$

3.5.1.2
Synthesis of β-Hydroxy Nitriles

The title compounds are useful intermediates in organic synthesis as, for example, for making 1,3-amino alcohols [124]. β-Hydroxy nitriles can be made by a variety of methods, most of which suffer one or more of the following disadvantages: poor to moderate yields, toxicity of a catalyst or solvent, fire or explosion hazard, lengthy reactions times, multistep syntheses and low temperatures.

Pro-azaphosphatranes **1b**, **1d**, and **9b** catalyze the reaction of aldehydes with acetonitrile to give the title compounds in very good to excellent yields [124]. In a comparison of the efficacy of **1e** with **1d** in several cases, **1e** was more effective but **1f** was quite inactive [71]. Aldehydes taking part in this reaction form secondary alcohols which are less sterically hindered and can be more easily deprotonated, thus leading to α,β-unsaturated nitriles. Primary aldehydes, however, undergo aldol condensation.

Contrary to our observation with **9b**, **1b** does not produce substantial quantities of the corresponding undesired α,β-unsaturated nitrile and gives higher

yields of the corresponding β-hydroxy nitrile. When **1b** was used as the catalyst for the reaction of benzaldehyde with benzyl cyanide instead of with acetonitrile, the corresponding undesired α,β-unsaturated nitrile was formed quantitatively. However, the desired β-hydroxy nitrile was achieved in 99% yield by carrying out the reaction at –78 °C in THF, quenching the intermediate alkoxide with TMSCl followed by methanolysis to afford the desired product.

3.5.1.3
Direct Synthesis of α,β-Unsaturated Nitriles

The direct conversion of carbonyl compounds in the presence of nitriles to the title compounds (i.e., without isolating and dehydrating the intermediate β-hydroxy nitrile) is of considerable economic interest since such nitriles serve as versatile intermediates in the synthesis of a variety of products such as perfumes, sex pheromones, vitamin A, and pigments [125]. Classical methods leading directly to the title compounds generally employ sodium ethoxide or methoxide or other ionic bases as the catalyst. Bothersome side reactions realized in such reactions include self-condensation of the nitrile, aldol condensation of the carbonyl (in the case of an enolizable aldehyde or ketone), the Cannizzaro reaction (for aromatic aldehydes and aliphatic aldehydes with no α-hydrogen) and retroreaction of the β-hydroxy nitrile intermediate. Hence α,β-unsaturated nitriles are generally obtained from aliphatic aldehydes by a Wittig-Horner approach. Compatibility of base-sensitive functional groups is poor in classical routes.

An indirect approach to α,β-unsaturated nitriles involves the condensation of a carbonyl compound with acetonitrile using strong ionic bases such as *n*-BuLi, giving the β-hydroxy nitrile, which is then isolated and thermally dehydrated in the presence of a strong acid. The aforementioned strategies, in addition to several others that could be mentioned [125], are less convenient and less versatile (for reasons mentioned in connection with the classical methods) than the one we now describe.

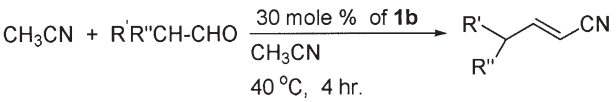
The direct synthesis of α,β-unsaturated nitriles occurs in high yields at 40 to 50 °C from aldehydes and acetonitrile or benzyl cyanide in the presence of catalytic amounts of **1b** or **9b** [125]. These reactions take place in both polar protic and non-polar aprotic solvents. Pro-azaphosphatrane **9b**, which is a stronger base than **1b**, efficiently catalyzes the condensation/dehydration of aromatic aldehydes and tertiary aliphatic aldehydes. The use of **9b** in these reactions gave rise to products with unusually high *E/Z* ratios. With either **1b** or **9b**, aliphatic aldehydes gave aldol products, and secondary aldehydes led to novel Michael addition products which are described in the next section. Ketones do not condense with either benzyl cyanide or acetonitrile under our conditions.

3.5.1.4
α,β-Dimerization of α,β-Unsaturated Nitriles

Processes that lead to olefin dimers are of interest because such products are useful for making copolymers [126]. Although a variety of reactions is known

for the conversion of α,β-unsaturated nitriles to glutaronitriles, yields are low to modest and/or the reactions are not of broad scope.

In the presence of **1b** or **9b**, acetonitrile reacts with a variety of secondary aldehydes to give α,β-dimers of the corresponding α,β-unsaturated nitriles [126]. We observed no β,β-dimer product and only the α-carbon of the delocalized anion adds in Michael fashion to a second molecule of the unsaturated nitrile. Thus secondary aldehydes are assumed to form the corresponding α,β-unsaturated nitriles Eq. (15) which are subsequently deprotonated by the non-ionic base to form an allylic anion that can then undergo Michael addition to a second molecule of the α,β-unsaturated nitrile.

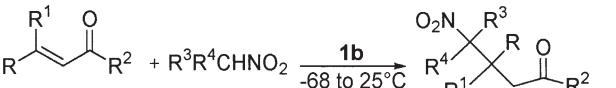


(15)

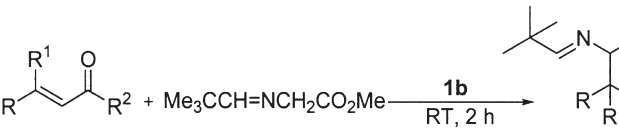
3.5.1.5
Michael Addition of Nitroalkanes and Schiff's Bases of α-Amino Esters

Michael addition is one of the most efficient and effective routes to C-C bond formation[127]. This reaction is widely applied in organic synthesis and several new versions of it have been introduced recently. The commonly employed anionic alkyl synthons for Michael addition are those derived from nitroalkanes, ethyl cyanocarboxylates, and malonates, and their limitations have been largely overcome by newer methodologies. However, the newer approaches are by no means devoid of drawbacks such as long reaction times, modest product yields in many cases, and the requirement for excess nitroalkane. Michael addition reactions of Schiff's bases have long been known to constitute a convenient method for functionalizing α-amino esters at the α position and the ratio of Michael addition to cycloaddition product has been found to depend upon the metal ion employed to chelate the enolate produced upon deprotonation (see below).

We have shown that 1,4-addition of higher nitroalkanes and Schiff's bases of α-amino esters to α,β-unsaturated substrates produces the corresponding products in moderate to excellent yields when carried out at – 63 to 70 °C in the presence of catalytic amounts of **1b**, **1d**, or **1e** in isobutyronitrile Eqs. (16) and (17) [127].



(16)



(17)

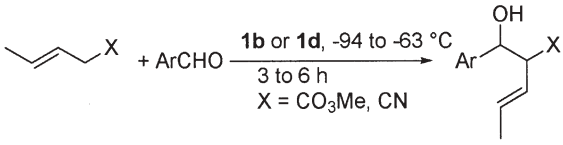
We found that Michael addition of nitroalkanes had limited success with nitromethane owing to its nitroaldol reaction with the products formed from methyl vinyl ketone and cyclohexenone, for example. (It may be noted in this regard that although the product obtained in the reaction of methyl vinyl ketone with nitromethane was achieved in 78% yield [127], a recent report [128] described a 98% yield by employing the less basic catalyst TBD at a higher temperature 0°C). However, 2-nitropropane and nitrocyclohexane were much better candidates for pro-azaphosphatrane-catalyzed reactions for which DBU and TMG typically require longer reaction times and afford only poor to modest product yields [127].

While base-catalyzed Michael additions of Schiff's bases of the type $Me_3CCH=NCH_2CO_2Me$ are known to be catalyzed by NEt_3 and DBU [129], the ratio of Michael adduct to cycloaddition product formed in the reaction depended on the presence of lithium ion [130]. By contrast, the pro-azaphosphatrane bases induce a clean Michael addition of the imine with various α,β-unsaturated compounds in the absence of lithium ion [127].

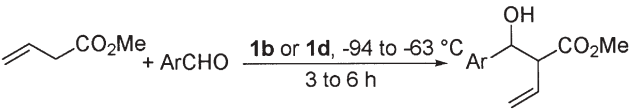
3.5.1.6
1,2-Addition Reactions of Activated Synthons

The formation of C-C bonds is of great utility in organic synthesis and among the transformations that effect the formation of such linkages are aldol condensations, the Henry reaction, Knoevenagel condensations, and the Baylis-Hillman reaction, each of which (except the Baylis-Hillman reaction) occur through the addition of anions derived from compounds bearing an activating (electron-withdrawing) group and/or a halogen [131]. Stabilized allylic anions, which have also been employed to construct C-C bonds, commonly give rise to α- and γ-alkylation since the resonance forms of this ion place the negative charge in both the α and γ positions.

Pro-azaphosphatranes **1b** or **1d** catalyze the reaction of activated allylic compounds with aromatic aldehydes to produce either a Baylis-Hillman product or a β,γ-unsaturated 1,2-addition product, depending on the type of allylic compound employed [131]. As seen in Eqs. (18) and (19), the activated allylic compounds shown react efficiently with aromatic aldehydes in the presence of 20 to 40 mole percent of **1b** or **1d** to give exclusively α-addition products. Such products are useful intermediates for the synthesis of substituted tetrahydrofurans through base-promoted electrophilic cyclizations. To our knowledge there have been only a few reports in which allylic cyanides and esters of the type used here have been utilized in 1,2-addition to aldehydes [131]. In those reports, an ionic base was used, γ addition was observed, or a mixture of α- and γ-addition products were obtained. The latter two observations contrast ours in which exclusive α-addition occurred.

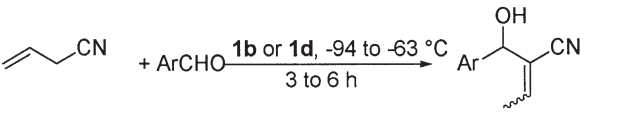


(18)



(19)

Allyl cyanide on the other hand, Eq. (20), results in an allylic transposition affording only the Baylis-Hillman product. The Baylis-Hillman reaction has long been of interest. Generally, high pressure is required to induce such a reaction and an amine such as DABCO as well as lengthy reaction times (1 – 4 weeks) are usually required [131]. The transformation shown in Eq. (20) advantageously affords this product under very mild conditions and in very short reaction times compared with both older as well as more recent literature approaches. Furthermore, this reaction is successful with aromatic aldehydes that have generally led to unreliable results under typical Baylis-Hillman conditions.

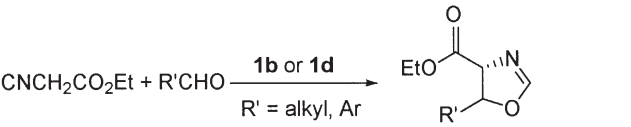


(20)

3.5.1.7 Diastereoselective Synthesis of Oxazolines

Oxazolines are versatile intermediates in the synthesis of β-substituted serines which are of significant importance because of their utility in the synthesis of various antibiotics [132]. Thus, the serine moiety constitutes the primary core structure of antibiotics, such as hypeptin and leucinostatin. Ethyl isocyanoacetate, a synthon for the formation of oxazolines, is relatively acidic and can be deprotonated by a variety of bases for coupling with aldehydes to afford oxazolines. However, the lack of diastereoselectivity of such reactions has rendered this synthetic route of limited use and as a result, alternate routes to the β-hydroxy-α-amino acids have been developed which, however, are also not entirely satisfactory.

In isobutyronitrile, pro-azaphosphatranes **1b** or **1d** are catalysts for the synthesis of oxazoline alkyl carboxylates in good to excellent yields. Moreover, these reactions proceed with greater than 95 : 5 diastereoselectivity for the *trans* isomer Eq. (21) [132]. The oxazoline ethyl carboxylate derived from *para*-methylsulfonylbenzaldehyde, which we synthesized in 97 % yield, is of significance because an analogous oxazoline has previously been used as an intermediate in the synthesis of the broad spectrum antibiotics thiamphenicol and florfenicol. Aliphatic aldehydes gave complex mixtures consisting of the desired compounds, Knoevenagel products and other species that were not identified.

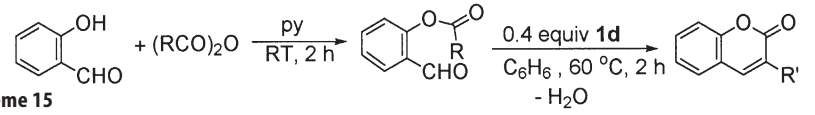


(21)

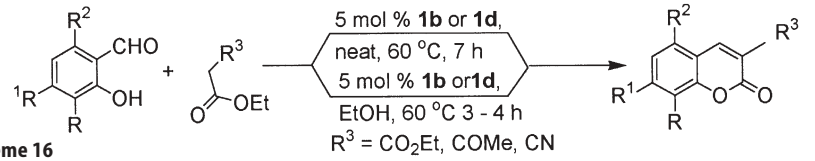
3.5.1.8
Synthesis of 3-Substituted Coumarins

This important class of compounds has been prepared by flash vacuum pyrolysis in an attempt to circumvent the variable yields and inconvenient work-ups encountered in Wittig olefination-cyclizations, and more recently, a rhodium-catalyzed process was introduced that produces a mixture of coumarins and benzofurans in variable yields [133].

The promotion by **1d** of the direct condensation of aromatic aldehydes and methyl propionate to form a trisubstituted *E*-methyl acrylate as the sole product (as described in Sect- 3.4.1.2) was extended with the use of **1b** and **1d** in an intramolecular synthesis of coumarins [133]. The required salicylaldehyde 2-carboxylates were prepared according to the literature as shown in step one of Scheme 15. The crude intermediates were then used in an intramolecular olefination using **1d** as a promoter. Although the isolated yields of the coumarins synthesized by our approach are not superior to those reported in the literature, our methodology represents a more simple and convenient alternative to pyrolysis or Wittig olefination-cyclization. However, by employing either a solvent-free reaction or by using ethanol as the solvent, a catalytic reaction occurred in the presence of 5 mol % of **1b** or **1d** to afford the desired coumarins as the only products in high yields (Scheme 16).



Scheme 15



Scheme 16

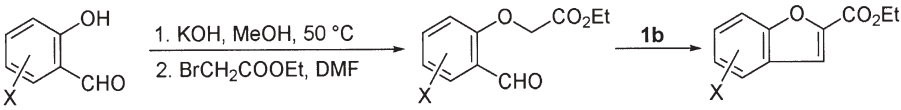
While our product yields (80 to 95%) are not generally superior to those reported in the literature, they are competitive. Moreover, the mild conditions and the shorter reaction times in our methodology constitute a more practical alternate route to coumarins.

3.5.1.9
Synthesis of Substituted Benzofuran-2-Ethyl Carboxylates

The benzofuran moiety is encountered in the synthesis of fluorogenic reagents, central nervous system depressants, bacteriostatic agents, inflammation inhibitors, angiotensin II type I receptor antagonists, antitumor antibiotics, and analgesic agents [134]. Although a variety of methods for the synthesis of 2-(4-substituted phenyl)benzofurans has been developed, the synthesis of benzofuran-2-ethyl carboxylates has been problematic in that either indirect methods are required or [as in the case of a method involving the use of DBU to synthe-

size ethyl 7-methoxy-5-nitrobenzofuran-2-carboxylate from ethyl 2-(6-formyl-2-methoxy-4-nitrophenoxy)acetate] the yield is low (44 %) [135].

Using **1b** as a catalyst in refluxing ethanol, an efficient and direct synthetic route to a variety of functionalized ethyl 2-benzofuran carboxylates in very high yields (80 to 99 %) is provided [134]. To the best of our knowledge this is the first example of the use of a non-ionic base as a catalyst in the synthesis of benzofuran derivatives. Commercially available 2-hydroxyaldehydes were alkylated in 80 – 95 % yield using a modified literature procedure to synthesize the substrates of the type shown in the first step of Scheme 17. The intramolecular aldol cyclization of such substrates, followed by subsequent dehydration of the intermediate hydroxydihydrofuran was achieved using **1b** as a catalyst. The superiority of **1b** over other typically employed bases was also demonstrated. Thus, reaction of the product in the first step of Scheme 16 (X = nothing) in the presence of the indicated catalyst gave the yields of the corresponding benzofuran shown: **1b**, 98 %; DBU, 60 %; DMAP, 0 %; DABCO, 0 %; sodium ethoxide, 0 %; diisopropylethylamine, 0 %.



Scheme 17

3.5.2
Elimination of HX

3.5.2.1
Dehydration of Aldoximes

Although a wide variety of reagents has been reported for this useful transformation, many of these methods present disadvantages [136]. For example, dehydrations with montmorillonite KSF and zeolites require high reaction temperatures or relatively long reaction times. Reagents such as triethylamine/sulfur dioxide and sulfuryl chloride allow rapid and mild dehydration of aldoximes, but the preparation of these reagents is inconvenient, requiring a low temperature. Both Ph_3P/CCl_4 and DBU suffer from limited applicability to the dehydration of aromatic aldoximes. Thus, there is a need for a convenient and broadly applicable methodology for this conversion.

Pro-azaphosphatranes **1b** and **1d** function as mild and generally applicable catalysts for the conversion of both aliphatic and aromatic aldoximes to nitriles in good yield, Eq. (22) [136]. With aliphatic aldoximes the reaction is complete in two hours at room temperature, while the reaction with aromatic aldoximes is achieved in 3 – 4 h at 60 °C. After the reaction, [**2b**]OH and [**2d**]OH are formed. The preferred amount of **1b** is 0.4 equivalent in these reactions. When less catalyst was employed, the reaction was incomplete in the times employed.

$$R{-}CH{=}NOH \xrightarrow[CH_3CN,\ 2\text{-}4\ h,\ 60\ °C]{\textbf{1b}\ \text{or}\ \textbf{1d}} R{-}C{\equiv}N + H_2O \qquad (22)$$

3.5.2.2
Dehydrohalogenation of HC-CX Substrates

The introduction of double bonds into organic systems via the elimination of hydrogen halides is a widely applicable transformation [137] (see also Sect. 3.4.2.1). Dehalogenations have been used as a means for the purification of olefins, for the temporary protection of double bonds, and for generating a new double bond as part of a synthetic sequence[137].

In Sect. 3.4.2.1 the superiority of pro-azaphosphatrane **1b** over DBU as a dehydrohalogenation reagent for primary and secondary alkyl halides was described. Solid **2b**(X), which is produced in these reactions (X = Cl, Br, OTf) can be converted back to **1b** by treatment with NaH, thus allowing for the possibility that neutral **1a**, **1b**, or a polymer-bound form of **1a** (**1k**, Fig. 10) could act as a catalyst in dehydrohalogenations. We showed that, by itself, NaH is not an efficient dehydrohalogenation reagent, but if it could be used effectively, it is considerably less expensive than other bases, such as DBN, DBU, or KO-*t*-Bu. Because **2b**(Cl) is stable to air for months without degradation, it seemed to us that it, as well as **2a**(OTf) and **2k**(OTf), could function as procatalysts for dehydrohalogenations of alkyl halides in the presence of NaH. Indeed, 0.1 equiv of any one of these procatalysts in the presence of excess NaH in CH_3CN is an efficient dehydrohalogenation medium at room temperature.

As was already mentioned in Sects. 3 and 3.1, attempts to isolate **1b** from salts of **2** resulted in an oligomeric product. However, **2a**(OTf) is as effective as **2b**(Cl) for both dehydrohalogenation and debromination, which suggests that intermediate **1a** effects dehydrohalogenation of substrates faster than it forms an oligomer of unknown structure. Pro-azaphosphatrane salt **2k**(OTf) in CH_3CN also effectively allowed dehydrohalogenation, albeit more slowly than **2a**(Cl) and **2b**(OTf). The advantage of the approach with **2k** (in which both the NaH and the procatalyst and catalyst are insoluble) is easy isolation of spectroscopically pure products (ca. 95 %) by filtration.

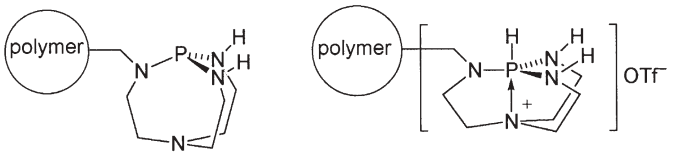


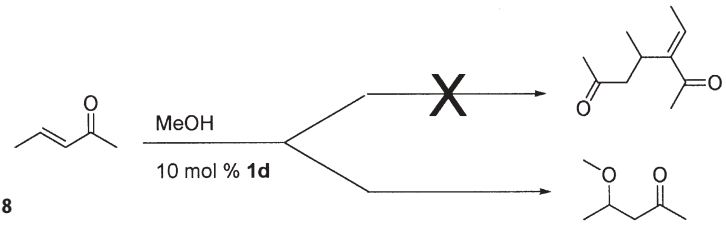
Fig. 10 **1k** **2k**(OTf)

3.5.3
Reactions Involving Deprotonation of Alcohols

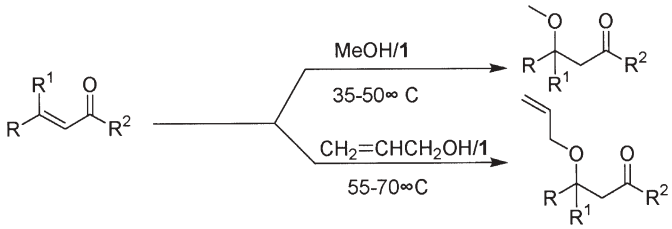
3.5.3.1
Oxa-Michael Addition of Alcohols

Oxa-Michael addition reactions are well known and the protected β-hydroxy carbonyl compounds so produced are of significant importance in organic synthesis [127]. To our knowledge, however, no general reaction has been reported in which β-alkoxy ketones can be prepared via Michael addition. We first detect-

ed a Michael addition reaction promoted by bases of type **1** when we attempted to dimerize (*E*)-3-penten-2-one in the presence of 10 mol % of **1d** in methanol (Scheme 18). Although none of the expected dimer was observed, we were able to isolate 20 – 30 % of the corresponding β-methoxy ketone. Good to excellent yields of hydroalkoxylated products were obtained under the conditions indicated in Scheme 19 using **1b**, **1d**, or **1e** in catalytic amounts [127]. In a comparison of the efficacy of **1e** with **1d** in the presence of allyl alcohol, **1e** was more effective [127]. Although higher alcohols such as *t*-butyl alcohol and 2-propanol resisted addition, allyl alcohol afforded high yields of products using **1d** or **1e**. Hydromethoxylation of α,β-unsaturated esters under our conditions is of limited practical utility because of transesterification.



Scheme 18



Scheme 19

3.5.3.2 Transesterification of Esters and the Acylation and Deacylation of Protected Alcohols

Transesterification is an important transformation in organic synthesis in industrial as well as in academic laboratories [138]. There are many catalysts available for such reactions and the most common procedure is to reflux the ester with a catalytic amount of Ti(O-*i*-Pr)$_4$ in an alcohol solvent. Other catalysts include DBU/LiBr [139] as well as several organometallic compounds [138].

The acyl group is a common protecting group for alcohols that can be incorporated using several methods[138]. The most common acylation method involves the reaction of an alcohol with acetic anhydride in the presence of pyridine. But for some acid- or base-sensitive alcohols, the common procedures do not work very well. Transesterification using vinyl acetate offers an alternate route which is very mild and can be catalyzed by Cp$_2$*Sm•THF, enzymes, and acids.

Deacylation of protected alcohols is an important deprotection reaction [138]. Here, K$_2$CO$_3$/MeOH has been a widely used reagent, and recently DIBAL-H has been shown to effect clean deacetylation. Although the latter reagent is effective, it is pyrophoric.

In all three of the title reactions, substituents such as epoxides, carbamates, acetals, and acetylenes are tolerated under our reaction conditions using pro-azaphosphatrane catalysts [138].

Pro-azaphosphatrane **1b** catalyzes the transesterification of carboxylic acid esters with high selectivity and in excellent yields at 25 °C. The success with simple esters prompted us to turn our attention to amino acid esters, since esters are very useful protecting groups in peptide synthesis. When Boc-Val-Phe-OMe was the substrate and allyl alcohol was chosen as the solvent, the use of **1b** gave a 55:45 mixture of epimers at the phenylalanine residue. By using the more bulky **1d** as a catalyst, however, the product was isolated in 96 % yield with very high diastereomeric purity (98:2). In all cases, yields and selectivities are comparable to those realized with DBU/LiBr in the presence of similar substrates. Catalysts **1b** and **1d** are more efficient, however, because only 10 – 15 mol % is needed whereas the DBU/LiBr system utilizes 50 mol % of DBU and 500 mol % of LiBr [139]. Moreover, our reactions are carried out at room temperature, while other catalysts frequently require refluxing solvent temperatures.

Using vinyl and isopropenyl acetate as acylating agents, primary and secondary alcohols are efficiently protected in very high yields through the catalytic action of **1b** [138].

Base **1b** also catalyzes the deacetylation of protected alcohols under mild conditions in quantitative yields [138]. The reaction with propargyl alcohol is very selective because the reactive acetylene functionality is not affected. In contrast, DIBAL-H is known to react with acetylenes. Secondary and tertiary alcohol acetates also were deacetylated in excellent yields and it is interesting that the latter alcohols do so without undergoing side reactions such as elimination.

In contrast to the strategy to be described in Sect. 3.5.5.1, the aforementioned methodology is not effective for acylating tertiary alcohols, although it is very successful for primary alcohols (including acid sensitive ones) and secondary alcohols.

3.5.4
Deprotonation of Lactam NH

Heating lactams with **1b** as a catalyst gives high molecular weight polyamides [140]. Heating *ε*-caprolactam at 203 °C in the presence of **1b** gives a polymer with a stable melt viscosity [141] and at 270 °C several lactams afford very high molecular weight polymers using either **1b** or one of several phosphazene bases [140]. It is interesting that non-ionic bases with a pK_a greater than about 27 in acetonitrile mimic ionic bases such as an alkali metal hydride, amide, or alkoxide in these anionic polymerizations [140].

3.5.5
Reactions Involving Carbon Activation

3.5.5.1
Acylation of Hindered Alcohols

High-yield acylations of hindered alcohols are of considerable current interest [142]. Older methods for such reactions involve acetic anhydride, acetyl chloride, and the use of *n*-butyllithium in the presence of an acid chloride. More contemporary approaches include catalysts such as DMAP [143], Bu_3P [144], and 4-pyrrolidinopyridine (PPY), with DMAP being the most popular. Although both Bu_3P and DMAP provide good yields of acylated alcohols, these catalysts have disadvantages. For example, Bu_3P has a low flash point and DMAP is fairly toxic.

Base **1b** is an efficient acylation promoter for hindered alcohols; a transformation that easily allows **1b** to be recovered in high yield in a single-step reaction. A comparison of the percent conversion of (±)-menthol, a relatively hindered alcohol, with various acylation catalysts/promoters revealed the following results: Bu_3P (74 %), DMAP (76 %), DBU (<1 %), the phosphazene base P_4-*t*-Bu (49 %), and **1b** (99 %). Only a 10 % molar excess of Ac_2O or Bz_2O is needed in conjunction with **1b** whereas 50 to 100 % molar excesses of these reagents were employed in the presence of DMAP or Bu_3P. Despite the considerably higher basicity of P_4-*t*-Bu compared with **1b**, the former is a much slower promoter for benzoylating (±)-menthol than **1b**, possibly because of the relatively weaker P-C(O) bond in acyl-**1b** intermediate (for which evidence was presented) compared with the N-C(O) bond of the analogous intermediate for P_4-*t*-Bu. It is known that Ac_2O and pyridine react to produce a small amount of *N*-acylated intermediate in an equilibrium reaction [145].

The advantages of using **1b** as an acylation promoter are:

(1) The yields of acylated alcohols are high.
(2) The by-product salts are easily isolated and recycled back to **1b** in moderate to high yields.
(3) Only a slight excess of the acid anhydride is required.
(4) Compound **1a** is commercially available.
(5) Because no acidic (or basic) work-up is required, acid-sensitive alcohols can also be acylated.

3.5.5.2
Trimerization of Isocyanates to Isocyanurates

Triaryl isocyanurates are useful as activators for the continuous anionic polymerization and postpolymerization of ε-caprolactam to nylon-6 possessing a low unreacted monomer content and a highly stable melt viscosity [93]. Although a wide variety of catalysts for the trimerization of aryl isocyanates to triaryl isocyanurates are known, purity of trimerized product (a requirement for nylon of good quality) is problematic and purification results in product

loss. Attempts to increase the yield of trimer frequently require large amounts of catalyst, extended reactions times, and vigorous conditions.

Pro-azaphosphatranes **1b** [93], **1c** [67a], and **1d** [67a] are superior catalysts for the trimerization of isocyanates at room temperature in nearly quantitative yield, with **1d** reacting considerably faster than **1b** which was much faster than **1c**. By contrast, $P(NMe_2)_3$ produces only small yields of the *dimer*, which is an undesirable impurity in activators.

3.5.6
Reactions Involving Activation of Silicon

3.5.6.1
Silylation of Alcohols

Of the functional groups amenable to silylation (e.g., -SH, -COOH, $-NH_2$, and -OH), the hydroxy group has thus far received the most attention because of its presence in many biologically active compounds including prostaglandins, taxols, maytansine, and vitamin D_3. Among the many trialkylsilyl reagents used to protect alcoholic OH groups, *t*-butyldimethylsilyl chloride (TBDMSCl) and *t*-butyldiphenylsilyl chloride (TBDPSCl) have been the most popular [146, 147]. Sterically hindered reagents of this type confer augmented stability on the derivatized substrate over trimethylsilylated analogues. Thus the larger *t*-butyl substituent hinders attack at the silicon atom of the silyl ether, thereby rendering the protected substrate more stable towards hydrolysis in weakly acidic or basic media and towards oxidative and reductive conditions frequently encountered in subsequent synthetic steps. A variety of alcohol silylation methods has been reported; a popular strategy being the reaction of the alcohol with a molar excess of imidazole using dimethylformamide as a solvent. Other methods [147] for synthesizing TBDMS ethers include the reaction of an alcohol with TBDMSCl in the presence of bases such as Et_3N/TMG, Et_3N/DBU, *i*-Pr_2NEt, and Et_3N/DMAP. A problem with TBDMSCl and TBDPSCl has been the difficulty of silylating hindered secondary alcohols, tertiary alcohols, and hindered phenols. Additional disadvantages, often associated with other examples of the wide variety of TBDMSCl silylation methods in the literature, are their inapplicability to substrates bearing acid- or base-sensitive groups and the relatively high base concentrations, long reaction times, and high reaction temperatures required for obtaining high yields of secondary silyl ethers. Hence, more reactive silylating agents, namely, TBDMS perchlorate and TBDMS triflate were developed, which were found to be capable of silylating tertiary and hindered secondary alcohols in high yield [146, 147]. (The perchlorate derivative, however, is explosive, must be handled with great care and is not commercially available.)

A very effective and mild procedure for the silyl protection (using TBDMSCl and TBDPSCl) of a wide variety of OH-containing substrates (including primary, secondary, allylic, propargylic, benzylic, hindered secondary, tertiary, acid-sensitive and base-sensitive alcohols, and also hindered phenols) involves the use of **1b** as the catalyst, Eq. (23). The reactions are carried out in acetonitrile as a solvent from 24 to 40 °C, and on rare occasions in DMF from 24 to 80 °C.

$$\text{ROH} + \text{TBDMSCl/TBDPSCl} \xrightarrow[1.1\text{ eq. } Et_3N]{\text{cat. } \mathbf{1b}} \text{TBDMSOR/TBDPSOR} \qquad (23)$$

The advantages of using **1b** as a silylation catalyst are:

(1) The yields of the silylated alcohols and phenols are high.
(2) Acetonitrile or tetrahydrofuran can be used for the preparation of TBDMS ethers in cases where the use of DMF as a solvent is not desirable or practical.
(3) The catalyst can be recycled in high yields since solid [**2b**]Cl is easily separated from the triethylammonium hydrochloride and the silylated product formed in the reaction.
(4) The catalyst is compatible with a variety of functional groups including aldehydes, esters, nitriles, ketones, lactones, ethers, and methylene-interrupted double bonds.
(5) Catalyst **1b** is commercially available.
(6) Acid- and base-sensitive alcohols can be efficiently silylated by our approach. Similar yields of silylated alcohols can be obtained with or without a solvent.
(7) Catalyst **1b** is superior to DMAP, DBU and TMG in the reaction of TBDPSCl with alcohols in DMF.

TBDMSCl is very effective in the more convenient solvent acetonitrile and under our conditions it is superior to TBDMS triflate for silylating sterically hindered phenols. Minor disadvantages of **1b** are that it cannot be used for alcohol protection with TMSCl (because of an interesting side reaction that is under current investigation) or for the silylation of tertiary alcohols with TBDPSCl.

It is interesting that the chiral pro-azaphosphatrane **8** was found to be ineffective in promoting selective asymmetric silylations [78]. This may be ascribed to the considerable distance in the intermediate of the chiral region from the site of attack on silicon of the alcohol oxygen, which could well be opposite the phosphorus for steric reasons.

3.5.6.2 Desilylation of TBDMS Ethers

A wide variety of Arrhenius acids, Lewis acids, transition metal compounds, and Lewis bases have been used to cleave the Si–O bond in TBDMSOR ethers for parent alcohol regeneration [148]. It does not appear, however, that the use of a non-ionic base in such transformations has been reported.

TBDMS ethers of primary, secondary, and tertiary alcohols and also phenolic TBDMS ethers are desilylated to their corresponding alcohols and phenols, respectively, in DMSO at 80 °C in 68 – 94 % yield in the presence of 0.2 – 0.4 equivalents of **1b** [148]. Using **1d** as the catalyst, 85 – 97 % yields of desilylated alcohols were obtained from TBDMS. Both catalysts were much less effective for the desilylation of TBDPS ethers (22 – 45 % yield) under the same conditions as was used for TBDMS ethers. Desilylations were faster in DMSO than in acetonitrile.

3.5.6.3
Trimethylcyanation of Aldehydes and Ketones

The addition of cyanotrialkylsilanes to carbonyl compounds, and especially the development of catalysts for this transformation continues to attract considerable attention owing to the role of cyanohydrin trialkysilyl ethers and cyanohydrins as versatile intermediates in organic synthesis [149]. A variety of catalysts has been developed for such reactions including Lewis acids, transition metal complexes, 18-crown-6 complexes of alkali metals, tetracyanoethylene, Lewis bases, and alkali earth bases. Trimethylcyanation of ketones using Lewis bases does not seem to have been mentioned in the literature.

Pro-azaphosphatrane **1b** is an effective catalyst for the addition of trimethylsilyl cyanide to aldehydes and ketones under mild conditions, giving rise to cyanohydrins and cyanohydrin silyl ethers, respectively, in moderate to high yields, Eqs. (24) and (25) [149].

$$\mathrm{RCHO + TMSCN \xrightarrow[\text{2. aq HCl/ether}]{\text{1. 1b, 10 mol\%, THF}} \underset{\text{THF}}{\longrightarrow} RCH(OH)CN} \qquad (24)$$

$$\mathrm{R'COR'' + TMSCN \longrightarrow R'C(OTMS)CNR''} \qquad (25)$$

With aldehydes, the corresponding cyanohydrins were observed together with the cyanohydrin silyl ethers. Desilylation (presumably by adventitious water) persisted even when the reaction temperature was decreased to 0 °C. The cyanohydrins were obtained exclusively in high yields by treating the reaction mixture with aqueous HCl, except for aromatic aldehydes bearing electron-withdrawing Cl or CN substituents (which gave low yields of the corresponding cyanohydrins). When optically active **1i** was employed, the cyanohydrin obtained with benzaldehyde was isolated in 95 % yield but no enantioselectivity was observed.

Trimethylcyanation of both aromatic and aliphatic ketones in the presence of **1b** proceeded smoothly at room temperature to give the corresponding cyanohydrin silyl ethers in moderate to high yields. α,β-Unsaturated ketones gave 1,2-addition products regioselectively, and no 1,4-adducts were detected. With 4-*t*-butylcyclohexanone and (–)-menthone, yields were high but diastereoselectivity was poor. With (1*R*)-(+)-camphor, however, the yield was low but diastereoselectivity was excellent.

3.5.6.4
Reduction of Aldehydes and Ketones with Poly(Methylhydrosiloxane)

The reduction of carbonyl compounds by hydrosilylation is one of the most effective methods for the synthesis of alcohols [150]. The reactivity of organosilicon reagents, such as trialkoxysilanes and trihalogenated silanes, in these reactions is enhanced by coordination with Lewis bases such as fluoride or DMF. Upon reaction with diols or aminoalcohols, these reagents can form pentacoor-

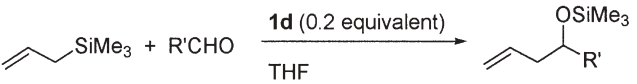
dinate hydrosilicate intermediates that efficiently reduce aldehydes and ketones to the corresponding alcohols. Asymmetric reductions have also been achieved using chiral diols or chiral aminoalcohols, to give optically active alcohols with good to excellent ees. Recently, polymethylhydrosiloxane (PMHS) has been extensively used in the reduction of imines, azides, and esters in the presence of a catalyst. Although aldehydes and ketones can be reduced by PMHS in the presence of fluoride, bis(dibutylacetoxytin), or $ZnCl_2$, the yields are modest or else rather harsh reaction conditions must be employed.

Using **1b** as a catalyst, a variety of aromatic aldehydes was smoothly reduced to the corresponding alcohols in high yields with survival of the aromatic chloro, nitro, cyano, and methoxy substituents [150]. Conjugated as well as isolated double bonds also remained intact during regioselective reduction of the carbonyl groups. Aliphatic aldehydes were reduced to the corresponding alcohols in high yields (92 – 96 % yield in 1 h) even though such aldehydes by themselves undergo aldol condensation in the presence of catalyst **1b**. The analogous reduction of sterically hindered aromatic and aliphatic ketones occurred in 79 – 95 and 64 – 74 % yields, respectively, in 12 h. It was also shown that aldehydes are reduced much more rapidly under our conditions than ketones thus allowing chemoselective reduction of an aldehyde group in the presence of a keto functionality.

3.5.6.5
Allylation of Aromatic Aldehydes with Allyltrimethylsilane

The allylation of carbonyl compounds with allylsilanes under Lewis acidic conditions has been extensively investigated owing to its importance in the formation of C-C bonds in organic synthesis [151]. Recently, the allylation of aldehydes with allylsilanes promoted by Lewis bases has also attracted considerable attention because of the mild reaction conditions and the high regio- and stereoselectivity encountered. Allylsilanes used in these reactions, such as allyltrichlorosilane and allyltrifluorosilane, are easily activated by Lewis bases since the silicon atom bears strong electron-withdrawing groups, thereby facilitating smooth aldehyde allylations. However, we found only one report on the reaction of allyltrimethylsilane with aldehydes in the presence of a Lewis base promoter, namely, fluoride ion, and the use of this base required refluxing THF.

Pro-azaphosphatrane **1d** (20 mol %) acts as a promoter for the allylation of a substantial number of aldehydes in moderate to good yields with allyltrimethylsilane at room temperature or 40 °C, Eq. (26) [151]. Whereas $P(NMe_2)_3$ was ineffective in these reactions as expected, it was somewhat surprising to observe that in contrast to **1d**, **1b** was also inactive and gave complicated reaction mixtures containing only small amount of product. Aldehydes bearing an electron donating group possess lower reactivity under our conditions and gave poor product yields.



(26)

3.6
Conclusions and Outlook

Pro-azaphosphatranes are becoming broadly useful in organic synthesis methodology as stoichiometric bases and as catalysts. In their catalytic applications, pro-azaphosphatranes do not always behave equally well. For example, in preliminary comparisons of the efficacy of **1d** with **1e** in the catalytic formation of β-hydroxy nitriles, nitroaldol reactions, and oxa-Michael reactions, **1e** appears to be more effective [71]. Whereas **1d** is particularly effective for coumarin synthesis, aldehyde allylation, and isocyanate trimerization, **1b** is better than **1d** for converting aldehydes to epoxides. In very recent experiments, catalyst **1e** appears to be most effective ligand in palladium-catalyzed cross-coupling reactions of a variety of types. We plan to examine the efficacy of **1b**, **1d**, and **1e** (all of which are now commercially available from Aldrich) more thoroughly in these and other transformations as well as in the synthesis of molecules of biological interest. Efforts are currently underway to develop recyclable polymeric, mesoporous zeolitic and dendrimeric versions of pro-azaphosphatranes, as well as pro-azaphosphatranes decorated with polyfluorinated alkyl groups for fluorous phase catalysis. The synthesis of specially designed chiral pro-azaphosphatranes may yet prove fruitful in asymmetric synthesis.

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The Asymmetric Phospho-Aldol Reaction. Past, Present and Future

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The phospho-aldol reaction is a well-known and increasingly exploited synthetic process for the construction of phosphorus-carbon bonds. The reaction, essentially a base-catalysed addition reaction between a hydrogen-phosphonate ester and a carbonyl substrate, affords alpha-(α)-functionalised phosphonate esters. Such molecular scaffolds offer considerable scope in medicinal chemistry as the basis for new enzyme inhibitors. Since the 1950s there have been many variants of the basic phospho-aldol reaction published for the stoichiometric synthesis of α-functionalised phosphonates, but most recently attention has shifted to the control of asymmetry in the transformation. It has been shown that the biological properties of α-functionalised phosphonates are influenced by their stereochemistry. This report summarises the developments in asymmetric catalytic variants of the phospho-aldol reaction tracing their evolution from early studies in the 1980s to the current day whilst attempting to suggest future advances within the context of growing applications in biomedical science.

Keywords. Phospho-aldol, Hydrophosphonylation, Asymmetric, Catalysis, Complexes

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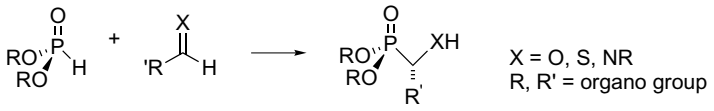
Abbreviations

ATP	Adenosine triphosphate
PA	Phospho-aldol
HIV	Human immunodeficiency virus
EPSP	5-Enolpyruvylshikimate 3-phosphate
PTK	Protein tyrosine kinase
PTP	Protein tyrosine phosphatase
DMHP	Dimethyl *H*-phosphonate
DEHP	Diethyl *H*-phosphonate
SALEN	Chelating Schiff base
SALAN	Chelating reduced Schiff base
α	alpha
γ	gamma
ϱ	Hammett correlation parameter
SALCYEN	Schiff base with diaminocyclohexyl backbone
SALCYAN	Reduced Schiff base with diaminocyclohexyl backbone
Pmp	(Phosphonomethyl)phenylalanine

1 Introduction

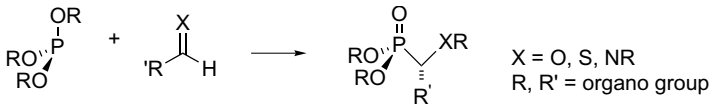
1.1 What is the Phospho-Aldol Reaction (PA)?

The phospho-aldol reaction has been known for many years within the phosphorus-chemistry community, under many names (including the Abramov and Pudovik reactions) and is one of the most valuable and powerful synthetic processes for the construction of phosphorus-carbon bonds [1]. The reaction, illustrated in its usual form, is outlined in Scheme 1a. It involves an addition reaction between a hydrogen-phosphonate ester and a carbonyl substrate to afford an alpha-(α)-functionalised phosphonate ester. Whilst alternative methods or activation have been explored [2], the phospho-aldol reaction is most commonly performed under conditions of base catalysis [3].



Scheme 1a

Since the 1950s there have been many variants of the basic phospho-aldol reaction published for the stoichiometric synthesis of α-functionalised phosphonates. For example, the widely studied Abramov reaction outlined in Scheme 1b (when R = $SiMe_3$, this process can be considered to be a close relative of the Mukaiyama aldol reaction) has been used as a method of building α-functionalised phosphonates both without [4], and more recently with, control over stereochemistry at the α-carbon atom [5].



Scheme 1b

This report summarises the developments in asymmetric catalytic variants of the phospho-aldol reaction tracing their evolution from early studies in the 1980s to the current day whilst attempting to suggest future advances within the context of growing applications in biomedical science.

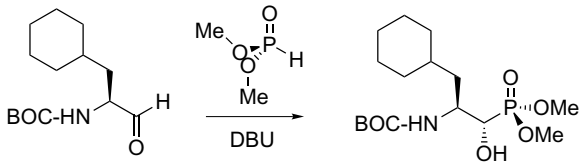
1.2
Why is the Phospho-Aldol Reaction Important?

The products of the phospho-aldol reaction, α-functionalised phosphonate esters such as α-hydroxy- and α-aminophosphonates, find widespread application directly or indirectly as precursors to enzyme inhibitors (such as the enzymes renin [6], thrombin [7], EPSP synthase [8], HIV protease [9] and various classes of PTK and PTPs [10]) and phosphate analogues [11], antibiotics [12], antiviral agents [13], and in nucleotide technology [14]. Within each application stereochemistry of the phosphonate is crucial to eliciting the required properties [15].

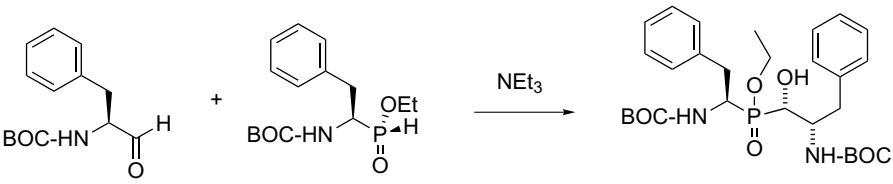
Consequently, chemists must have at their disposal simple, effective, efficient, and stereoselective synthetic methods to construct the necessary frameworks. Development of catalytic asymmetric variants of the phospho-aldol reaction provides, arguably, the most versatile such process for the simultaneous construction of the [P-C] bond and associated α-carbon functionality with control over the stereochemistry at the newly generated alpha-carbon site.

1.3
Stoichiometric Versions – Successes and Limitations

Considerable work has been published on stoichiometric asymmetric routes to α-functionalised phosphonate esters. One of the most commonly exploited methods is the phosphonylation of a chiral aldehyde or imine by a phosphorus(III) ester (Scheme 1b) or a by a hydrogen phosphonate (Scheme 1a). Thus, a team from Bristol-Myers Squibb reported the base-mediated addition of dimethyl *H*-phosphonate (DMHP) to a chiral aldehyde (Scheme 2) as a key step in their synthesis of renin inhibitors [6]. Subsequently, work from the Hoechst AG laboratories in Frankfurt used a related approach to the building of HIV protease inhibitor frameworks (Scheme 3) [9].

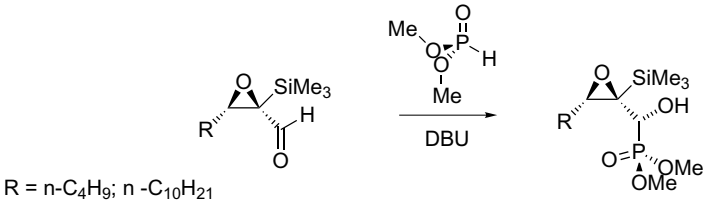


Scheme 2



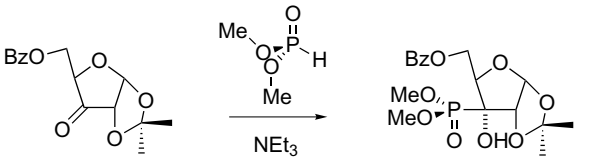
Scheme 3

In related studies, Kabat employed chirality in the carbonyl substrate to control stereochemistry at the newly formed alpha-carbon centre en route to enantiopure γ-hydroxy-β-ketophosphonates (Scheme 4) [16] and the team of Montero et al. used a similar approach to *C*-phosphonosugars (Scheme 5) [17].



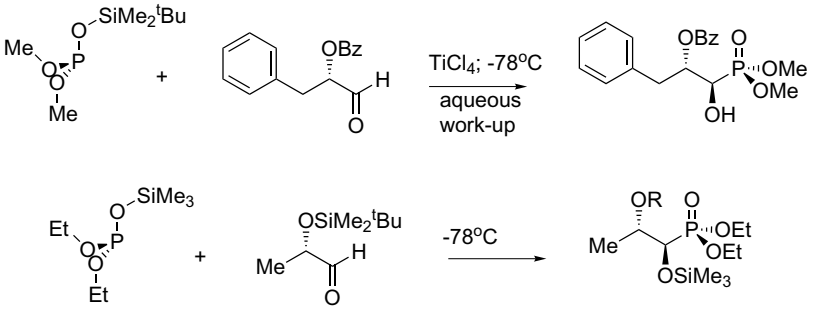
R = n-C_4H_9; n -$C_{10}H_{21}$

Scheme 4



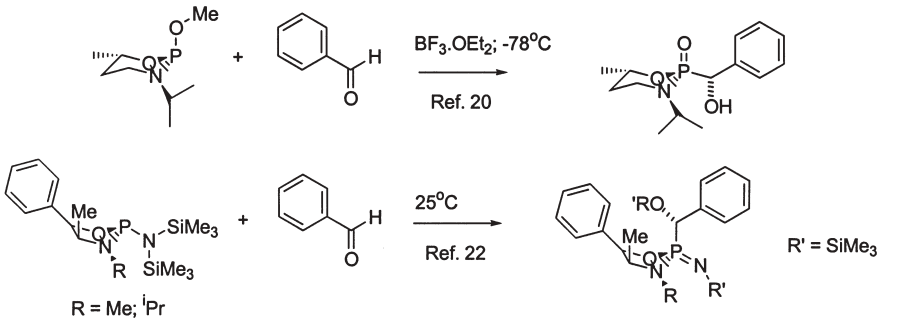
Scheme 5

Asymmetric versions of the phospho-Mukaiyama aldol reaction have also been exploited under conditions of stoichiometric stereocontrol. Thus, the research teams of Shibuya [18] and Spunta [19] independently used stereocontrol within the carbonyl substrate (Scheme 6) whereas the groups of Evans [20], Spilling [21] and Kee [22] preferred to use chiral phosphorus(III) esters (Scheme 7).



Scheme 6

R = $SiMe_2{}^tBu$

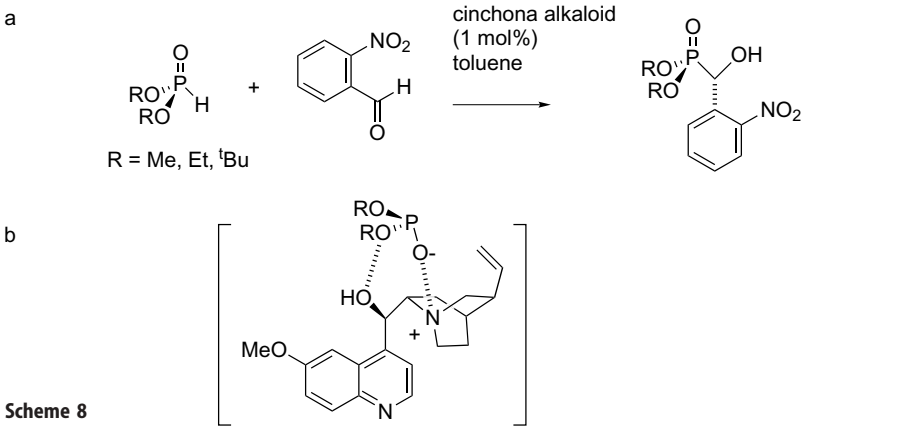


Scheme 7

2
The Catalytic Phospho-Aldol Reaction

2.1
Asymmetric Catalysis Mediated by Non-Metallic Compounds

In 1983, Wynberg and co-workers reported the induction of stereocontrol in the phospho-aldol addition of DMHP to *ortho*-substituted benzaldehydes catalysed by *Cinchona* alkaloids such as quinine (Scheme 8a) [23]. These workers proposed that the inherent (i) chirality of the quinine coupled with (ii) its ability to act as a hydrogen-bond donor, was crucial in bringing together phosphito and carbonyl species within a chiral environment. One possibility is that a chiral ammonium phosphito intermediate (Scheme 8b) might provide such a chiral environment, although the presence of hydrogen-bond acceptor functions in the *ortho* position of the benzaldehyde may also have a role to play in interacting with the quinine. Intriguingly, it was reported that the enantioselectivity in the product phosphonate ester derived from *o*-nitrobenzaldehyde increased from ca. 28 % e.e. when R = Me to >90 % e.e. when R = ^{t}Bu; presumably the result of a steric influence [23].



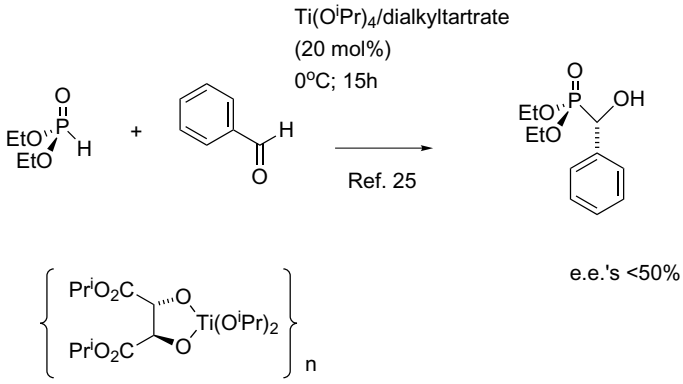
Scheme 8

2.2
Asymmetric Catalysis Mediated by Metallic Compounds

2.2.1
Titanium Complexes

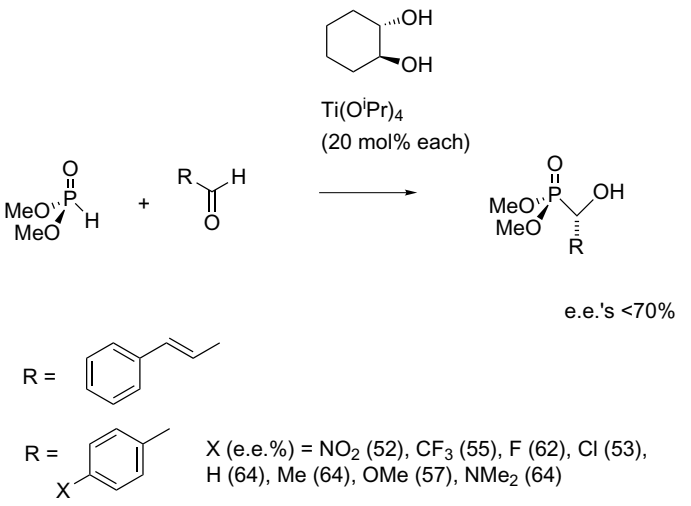
Surprisingly, it took a considerable time for Wynberg and co-workers initial breakthrough to be extended but when that extension did eventually take place in the early 1990s it was to open up the whole field of asymmetric catalytic hydrophosphonylation and the phospho-aldol reaction in particular.

In 1993, Shibuya and co-workers reported the stereoselective addition of DEHP to aldehydes to be catalysed by chiral complexes of titanium, specifically, dialkyl tartrate complexes of titanium that had been used previously with great success by Sharpless in the asymmetric oxidation of allylic alcohols (Scheme 9) [24]. Shibuya described moderate success in controlling enantioselectivities (< 50 % e.e.) with this extremely oxygen- and water-sensitive catalyst system. Rather large (10 – 20 mol %) catalyst loadings were required over a period of 15 h at 0 °C but the potential was definitely there.



Scheme 9

More recently, the group of Spilling in the USA has developed further the use of chiral titanium alkoxo complexes in asymmetric phospho-aldol catalysis [25]. An examination of a range of chiral auxiliary ligands culminated in the finding that *trans*-1,2-cyclohexanediol leads to e.e. values of < 70 % in the addition of DMHP to cinnamaldehyde (Scheme 10). As with the dialkyl tartrate-based systems, catalyst loadings of 20 % were used at temperatures of – 20 °C in diethyl ether and reaction was not compatible with aerobic conditions. Nevertheless, the simplicity of Spilling's modular experimental design whereby the catalytic ingredients are added sequentially, makes the synthetic method both simple and appealing to the synthetic chemist.

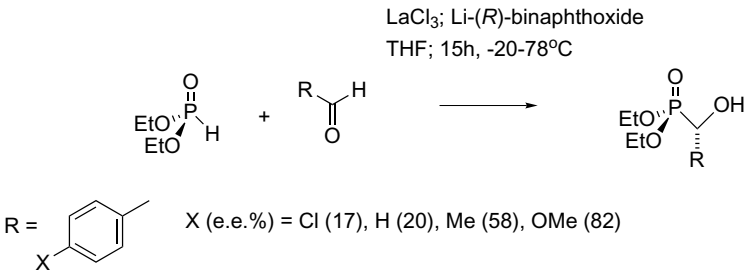


Scheme 10

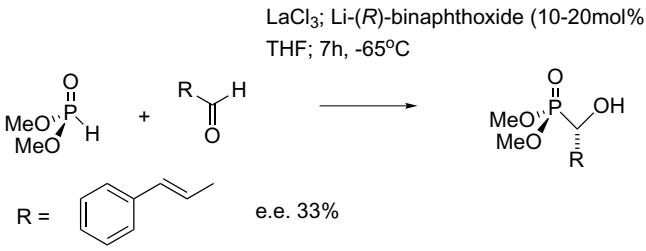
2.2.2
F-Block Complexes

In a companion paper to their work describing catalysis with titanium complexes [26], Shibuya's team reported that complexes of lanthanum, previously prepared and exploited by Shibasaki in related aldol-type reactions, were also capable of catalysing the phospho-aldol reaction between DEHP and various *para*-substituted benzaldehydes and, by using binaphthol as a source of chirality, they revealed higher levels of asymmetric induction (< 79 %) than were achievable via their earlier titanium systems. In addition, the observation that enantioselectivities increased as the electron-donating properties of the *para*-substituent X in benzaldehyde increased, was proposed as effective evidence that binding of the carbonyl substrate to the lanthanum centre was crucial to achieving the highest e.e. values (Scheme 11a). Catalyst loadings were again at the 20 mol % level.

Independently of Shibuya's work, Spilling's team reported comparable results, effective enantioselective phospho-aldol catalysis via lanthanum com-



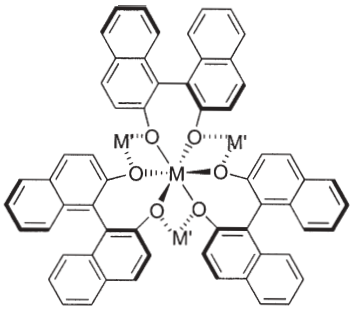
Scheme 11a



Scheme 11b

plexes of binaphthol, focusing on the addition of DMHP to cinnamaldehyde. After 7 h at –65 °C an e.e. of 33 % was achieved [27]. This work flagged up the crucial observation that the relative success of lanthanum-binaphtholato complexes in controlling enantioselectivity was strongly dependent upon the synthetic history of the complex. Again, catalyst loadings were quite high (10–20 mol %) and e.e. values modest but the simplicity of the procedure made optimisation and development inevitable (Scheme 11b). This group also made the observation that product α-hydroxyphosphonate esters tend to crystallise as the racemate, an important fact to bear in mind when attempting measurements of e.e.

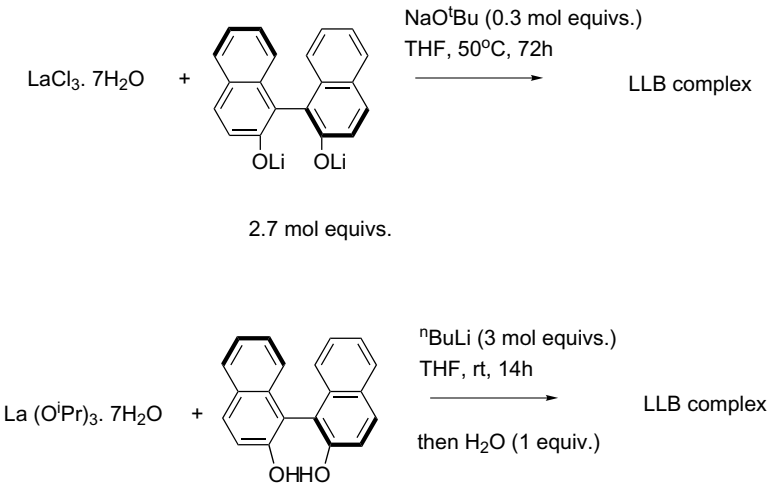
Since these initial publications, the considerable efforts of Shibasaki and co-workers have lead to lanthanide element-binaphtholato complexes as being the most developed and potent of asymmetric phospho-aldol catalysts. From their early work on catalysis in the nitro-aldol reaction [28], Shibasaki and co-workers have published widely and in considerable detail on the use of heterobimetallic catalysis, developing the field to such a degree that enzyme-like comparisons have been made. Much of the success of the Shibasaki team in heterobimetallic catalysis has been reviewed recently [29], the key to which has been the delineation of the solid state structures of the catalytic precursors via single crystal X-ray diffraction studies [30] (Fig. 1) and the development of improved synthetic routes to this class of heterobimetallic system (Scheme 12) which emphasise the important role of added water [31].



M = La, Nd, Pr, Sm, Eu, Yb, Gd
M' = Li, Na, K

LLB = Complex where M = La and M' = Li
LSB = Complex where M = La, M' = Na

Fig. 1



Scheme 12

Table 1

Entry	Aldehyde	Reaction time (h)	Yield (%)	e.e. (%)
1	PhCHO	8	88	79
2	4-$O_2NC_6H_4CHO$	12	85	36
3	4-ClC_6H_4CHO	8	80	63
4	4-MeC_6H_4CHO	7	93	78
5	4-$MeOC_6H_4CHO$	9	83	88
6	4-$(Me_2N)C_6H_4CHO$	12	80	95
7	*E*-PhCH = CHCHO	8	90	84
8	*E*-PhCH = CMeCHO	8	94	–92
9	*E*-$CH_3(CH_2)_2CH$ = CHCHO	8	63	75
10	$CH_3(CH_2)_4CHO$	8	88	61

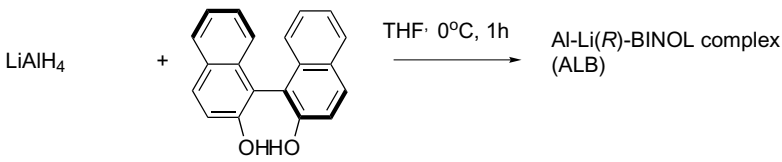
Whilst we discuss some of the more detailed mechanistic aspects of phospho-aldol catalysis via heterobimetallic systems in a later section, it is appropriate to note here the considerable and wide-ranging success that these catalysts have had in phospho-aldol catalysis. Thus, lanthanide heterobimetallics have had considerable success in the synthesis of α-hydroxy- (Table 1) [32] and α-aminophosphonate esters (Table 2) [33].

2.2.3 *Aluminium Complexes*

The work of Shibasaki, Shibuya and Spilling on lanthanide systems has also been extended by Shibasaki and his group to other binaphthol based heterobimetallic systems, notably based not on lanthanides but on aluminium (Scheme 13 and

Table 2. All reactions were performed in the presence of 5 equivs. of DMHP except entries 7 and 8 (1.5 equivs.). A 60 °C, THF; B rt in THF; C rt in THF/toluene (1/7 v/v); D 50 °C in THF/toluene (1/7 %)

Entry	R_2	R_1	Reaction time (h)	Cat (mol %)	Yield (%)	Cond.	e.e. (%)
1	CPh_3	Et	18	LSB (100)	47	A	69
2	$CH(4\text{-}MeOC_6H_4)_2$	*i*-Pr	18	LSB (20)	25	B	55
3	$CH(4\text{-}MeOC_6H_4)_2$	*i*-Pr	18	LPB (20)	27	B	71
4	$CH(4\text{-}MeOC_6H_4)_2$	*i*-Pr	21	LPB (20)	62	C	91
5	$CH(4\text{-}MeOC_6H_4)_2$	*i*-Pr	21	LSB (20)	38	C	49
6	$CH(4\text{-}MeOC_6H_4)_2$	*i*-Pr	21	LPB (20)	46	C	38
7	$CH(4\text{-}MeOC_6H_4)_2$	*i*-Pr	96	LPB (20)	70	C	96
8	$CHPh_2$	*i*-Pr	63	LPB (20)	97	C	97
9	$CHPh_2$	*i*-Pr	143	LPB (5)	82	C	92
10	$CHPh_2$	Me	70	LPB (20)	73	C	75
11	$CHPh_2$	Et	63	LPB (20)	88	C	94
12	$CHPh_2$	C_5H_{11}	63	LPB (20)	57	C	92
13	$CHPh_2$	PhCH = CH	40	GdPB (20)	86	D	66
14	$4\text{-}MeOC_6H_4$	*c*-C_6H_{11}	68	PrPB (20)	75	C	66
15	$4\text{-}MeOC_6H_4$	*c*-C_6H_{11}	89	LPB (20)	71	C	49
16	$CHPh_2$	$C_{12}H_{25}$	84	LPB (20)	50	C	89



Scheme 13

Fig. 2) [34]. These aluminium systems, the most commonly used example being given the acronym ALB for aluminium-lithium-binaphthol, were found to be equally effective for many phospho-aldol transformations as their lanthanide cousins, a little less reactive overall, but especially useful on electron-withdrawing carbonyl substrates (e.g., compare entries 2 and 3 in Table 1 and Table 3).

Building upon this earlier work, Kee and co-workers chose to move away from binaphthol as a chiral framework and explore alternative systems which may permit phospho-aldol catalysis under mild conditions but crucially be compatible with aerobic conditions. Their earliest studies revolved around the well-

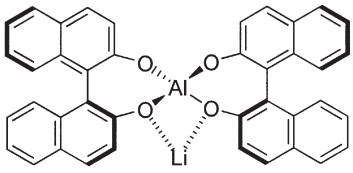


Fig. 2

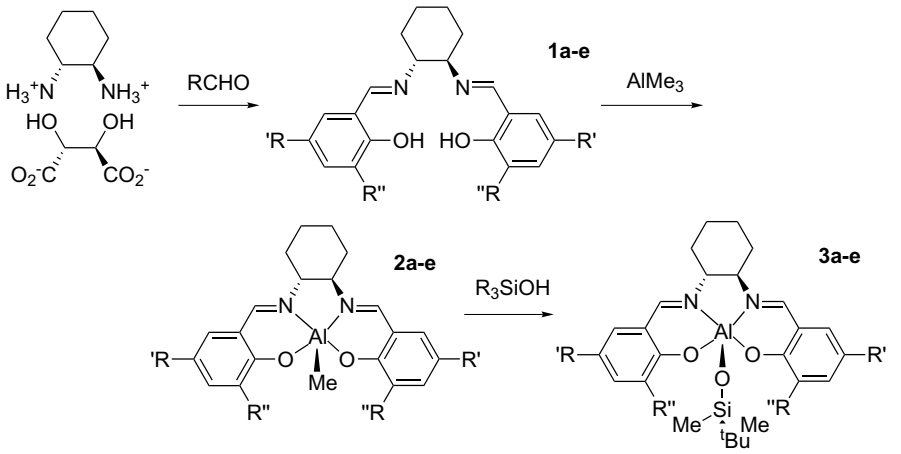
Table 3

Entry	Aldehyde	Reaction time (h)	Yield (%)	e.e. (%)
1	PhCHO	51	95	90
2	4-$O_2NC_6H_4CHO$	40	85	71
3	4-ClC_6H_4CHO	38	80	83
4	4-MeC_6H_4CHO	92	82	86
5	4-$MeOC_6H_4CHO$	115	88	78
6	4-$(Me_2N)C_6H_4CHO$	–	– [a]	–
7	*E*-PhCH = CHCHO	83	85	82
8	*E*-PhCH = CMeCHO	61	47	56
9	*E*-$CH_3(CH_2)_2CH$ = CHCHO	39	53	55
10	$CH_3(CH_2)_4CHO$	41	95	16

[a] No reaction.

used and oft-exploited SALEN class of Schiff base ligand frameworks incorporating the *R,R-trans*-1,2-diaminocyclohexane backbone championed by Jacobsen and others [35]. The Kee group prepared and analysed a range of chiral aluminium SALEN complexes, for which syntheses were straight-forward (Scheme 14) and which were found to catalyse the phospho-aldol reaction under aerobic conditions albeit with modest enantioselectivity (Table 4) [36].

Subsequently, Kee and co-workers recognised the importance of steric and coordination flexibility in the chiral ligand scaffold and have switched their attention more recently to chiral SALAN systems [37], the reduced version of



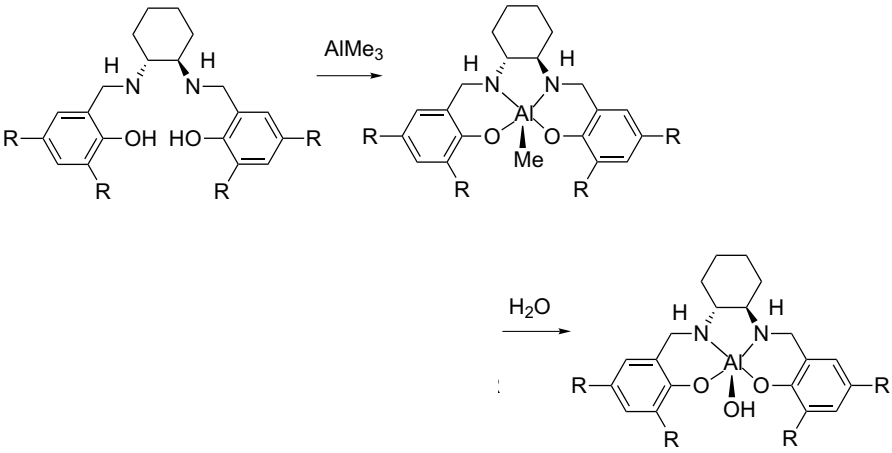
Scheme 14

Table 4

Entry	Aldehyde	e.e. (%)[a]	e.e. (%)[b]	e.e. (%)[c]
1	PhCHO	37	41	45
2	4-$O_2NC_6H_4CHO$	15	10	–
3	4-ClC_6H_4CHO	30	19	–
4	4-MeC_6H_4CHO	44	49	46
5	4-$MeOC_6H_4CHO$	39	46	49
6	4-BrC_6H_4CHO	27	24	21
7	2-ClC_6H_4CHO	12	12	–
8	2-MeC_6H_4CHO	25	20	–
9	2-$MeOC_6H_4CHO$	20	27	–

[a] Reactions performed under dry, inert atmosphere conditions with **2a** as catalyst at 5 mol % in THF.
[b] Reactions performed under aerobic conditions with **2a** as catalyst at 5 mol % in THF.
[c] Reactions performed using **3a** as catalyst at 5 mol % in THF.

their SALEN cousins (Scheme 15) [38]. Phospho-aldol catalysis was to be far more effective with SALAN complex **5** than its SALEN relatives **2** and **3**, with both greater reactivity (note the differences in catalyst loadings between **2, 3**, and **5** in Tables 4 and 5) and greater tolerance to water (Table 5). It is indeed rather surprising that, given the wide exploitation of SALEN ligands, to date there should be such a dearth of published work exploiting chiral SALAN ligands in asymmetric catalysis.



Scheme 15

Table 5. All reactions were performed in air at 298 K unless specified otherwise

Entry	Catalyst load (mol %)	4-XC_6H_4CHO	Solvent	Conv (%)	e.e. (%)
1	45	X = H	THF	100	18
2	20	X = H	THF	100	26
3	10	X = H	THF	100	39
4	5	X = H	THF	100	48 [b]
5	1	X = H	THF	95	59
6	0.5	X = H	THF	74 [c]	58
7	0.2	X = H	THF	54 [d]	52
8	5	X = H	THF [e]	87	50
9	5	X = H	THF [f]	81	52
10	1	X = Br	THF	75	42
11	1	X = Br	THF	85	42
12	1	X = Me	THF	76	57
13	1	X = Me	THF [g]	88	53
14	1	X = OMe	THF	91	47
15	1	X = NO_2	THF	64	18
16	1	X = NMe_2	THF	45	22
17	1	X = Br	CH_2Cll_2	32	40
18	1	X = Me	CH_2Cl_2	8	53
19	1	X = H	C_7H_8	26	42
20	1	X = Br	C_7H_8	60	41
21	1	X = Me	C_7H_8	45	52

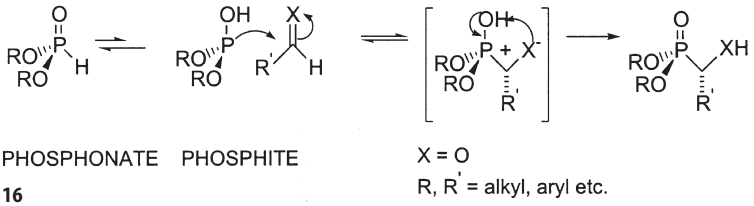
[a] Conversions (Conv) obtained after 4 h. No product other than α-hydroxyphosphate ester was observed.
[b] Yield = 87 % and e.e. = 53 % (*S*) when reaction is performed at 273 K.
[c] After 12 h. All absolute configurations are (*S*).
[d] After 21 h.
[e] With 20 mol % water added.
[f] 100 mol % water added.
[g] In presence of 4 Å molecules sieves.

3
Mechanism of the Catalytic Phospho-Aldol Reaction

3.1
Basic Mechanistic Profile

The phospho-aldol reaction, as the name indicates, is a close relative of the well-known aldol reaction and, as such, is a base-catalysed process.

The basic mechanistic outline is presented in Scheme 16. *H*-Phosphonates exist as two tautomers. Under neutral conditions the equilibrium lies toward the phosphonate tautomer, which is not the reactive form for the phospho-aldol process. The equilibrium must be forced toward the phosphite tautomer, where a lone pair of electrons on phosphorus permit nucleophilic attack at the carbonyl carbon of a suitable substrate. A catalyst is required to



Scheme 16

(i) force the equilibrium toward the active phosphite tautomer,
(ii) bring phosphite and carbonyl substrate together within a chiral environment, and
(iii) permit catalytic turnover through proton transfer.

The most common catalysts are bases since diorgano *H*-phosphonates are protic substances with calculated pK_a values of ca. 14 [39].

We have seen earlier that the first type of chiral catalyst used in the asymmetric phospho-aldol reaction was a chiral organic nitrogen base [23]. Since then, a range of other chiral organic bases has been used but none were found to be an improvement on the *Cinchona* alkaloids [40]. Consequently, the emphasis has changed towards metal complex bases where two principal strategies have been exploited (Fig. 3). In the first instance with bimetallic complexes, one of the metals, either a lanthanide or aluminium, acts as a Lewis acid to bind the carbonyl substrate whilst the second metal, usually an alkali metal in the form of a binaphthoxide, acts to deprotonate the *H*-phosphonate thus generating a nucleophile through which to attack the bound carbonyl substrate (Scheme 17). The situation is slightly different for monometallic systems where the nature of the polar [M-X] bond, where X = oxygen, nitrogen or carbon, allows for carbonyl binding and *H*-phosphonate deprotonation at a single metal centre as outlined in general in Scheme 18. In both scenarios, intermediates are predicted but have yet to be observed directly. Nevertheless, in each case the major issue is controlling stereochemistry (vide infra).

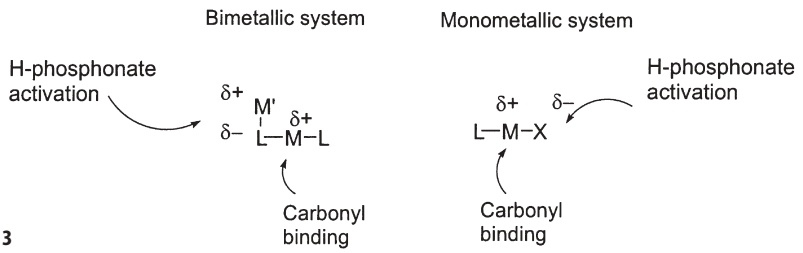
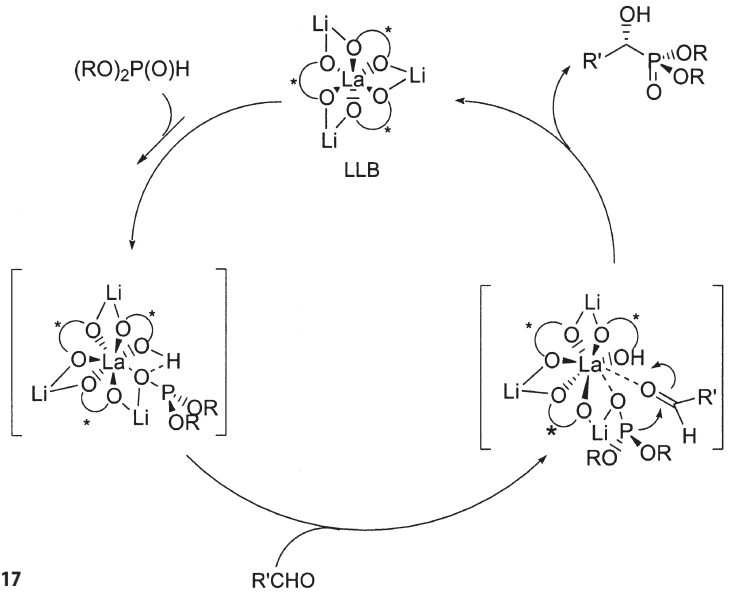
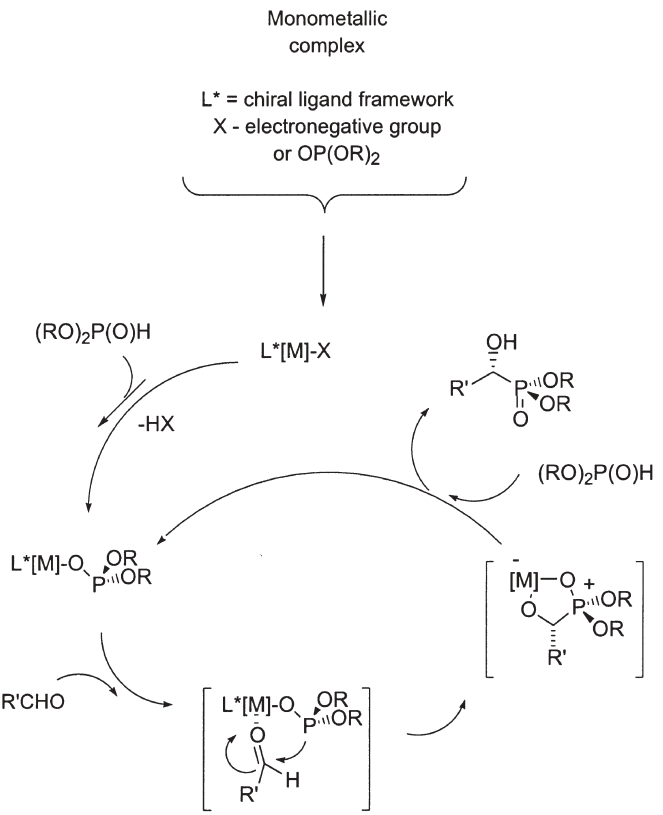


Fig. 3



Scheme 17



Scheme 18

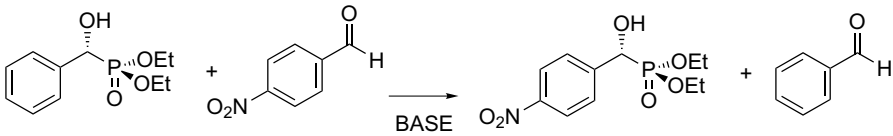
3.2
Kinetic, Structure-Activity and Related Studies

A number of reactivity issues have been addressed by workers in the field based principally around

(a) catalyst structure,
(b) catalyst loadings,
(c) nature of the carbonyl substrate, and
(d) nature of the phosphonate precursor.

We summarise below some of the key findings.

In Sect. 1.2.2.2, we reflected that Shibasaki and his team had managed to isolate and characterise, through single crystal X-ray diffraction, several examples of their heterobimetallic complexes. In each case, the basic frameworks of the complexes are the same with a central six-coordinated (if a lanthanide) or four-coordinated (if aluminium) metal within a naturally asymmetric Δ or Λ geometry. Attached to the binaphthol oxygen atoms in an overall C_{3v} arrangement is an alkali metal ion. Shibasaki and Martens et al. have provided evidence through inhibition studies to suggest that the initial binding and deprotonation of the *H*-phosphonate is the key activity-determining step of reaction (cf. Schemes 17 and 18) [41]. They showed also that the use of cyclic *H*-phosphonate esters provided improvements in the catalyst cyclic [41]. Similarly, Kee and co-workers have indicated a similar finding on the basis of reactivity studies of aromatic and aliphatic *H*-phosphonate esters. The better a complex is at deprotonating an *H*-phosphonate, the more reactive it is in the phospho-aldol reaction. However, there is a need for care over increasing base strength too far since it has also been demonstrated, through carbonyl crossover experiments (Scheme 19), that strong bases (such as basic alumina) can catalyse the reverse reaction, dissociation of hydroxyphosphonate esters into *H*-phosphonates and carbonyls, thus potentially compromising enantioselectivity [42]. Weaker bases such as quinine, however, do not compromise selectivity in this way since they do not catalyse phosphonate decomposition under the same conditions [42].



Scheme 19

Obviously, catalyst structure is the key to determining enantiocontrol in the phospho-aldol reaction. In the lanthanide heterobimetallic systems, backbone chirality within the binaphthol leads to generation of a stereocentre at the metal itself and does so with complete diastereospecificity. This is yet another example of the concept of *chirality transfer*, wherein fixed stereochemistry at one site leads to control over stereochemistry at a more remote site and is one of the most powerful concepts in catalyst design. It is the presence of such a highly

electropositive Lewis acid within a strongly stereoselective environment that permits, it is believed, optimum stereocontrol in the asymmetric phospho-aldol reaction through binding the carbonyl substrate in such a manner that either the *re* or *si* face is selectively attacked by the nucleophilic phosphite reagent.

It is believed that to achieve highest enantioselectivities; a well-defined, structurally rigid asymmetric ligand framework and a strongly Lewis acidic metal to bind the carbonyl substrate are required. It has been shown independently by Shibuya and Kee that enantioselectivities in the phospho-aldol reaction between *H*-phosphonates and *para*-substituted benzaldehydes increase as the electron-donating power of the *para*-substituent increases; both with lanthanum hetero-bimetallic catalysts [26] and with aluminium SALEN systems [36]. In both cases, Hammett correlations between product e.e. and σ_p of the *para*-substituent revealed negative ρ values, consistent with carbonyl binding to the metal being important to achieving the highest e.e. values. The somewhat more negative ρ value obtained for the lanthanum system (–1.30) compared to that of the aluminium SALEN complexes (–0.4) is in line with the lower electronegativity of lanthanum over aluminium (1.10 vs. 1.61 on the Pauling scale) [43].

Shibaski and co-workers have focused very strongly on the binaphthol ligand framework, which they have found to be extremely powerful in this and related catalytic processes. They have been able to manipulate the ligand backbone sterics and electronics to some degree although the synthetic chemistry involved is not trivial [41]. Moreover, there have been some issues over catalyst performance being linked to the synthetic history of the catalyst itself. It was thought possible therefore that complexes could be prepared which possessed

(i) more simple synthesis and ligand tuning,
(ii) complete compatibility towards oxygen and water,
(iii) ability to operate as phospho-aldol catalysts under conditions of ambient temperature and at low (< 1 mol %) catalyst loadings.

Complexes containing the SALEN ligand framework possessed the advantages of simple preparation and handling, stability towards water (to certain and varying degrees) but suffered from rather modest stereocontrol. This was thought to be because most SALEN ligands prefer to bind to a metal so that the donor N_2O_2 platform is close to planar. This in turn makes transfer of chirality from the SALEN backbone to the metal less than straightforward since a metal stereocentre is not possible with a formally planar N_2O_2 platform. At some stage, twisting of the ligand is needed to afford an asymmetric metal centre to bring both phosphite and carbonyl together within a *cis* orientation, similar to those inherently present in binaphthol-based catalysts. Indeed, the results of several single crystal X-ray analyses on SALEN complexes of aluminium suggest that such ligand twisting is possible [35]. However, moving to the chiral SALAN framework makes ligand twisting easier as found with the structure of {[(*R,R*)-SALCYAN]Al(OH)}$_2$ [44]. Intriguingly, even though the backbones of (*R,R*)-SALCYEN and (*R,R*)-SALCYAN ligands have the same absolute chirality, the product phosphonate esters produced is *R* when catalyst has the former ligand and *S* with the latter ligand. An explanation for this is currently being sought [38]. Interestingly, the SALAN complex {[(*R,R*)-SALCYAN]Al(OH)}$_2$ is both air-

and water-stable and permits catalysis to proceed under conditions of room temperature in a beaker in air (with albeit modest stereoselectivity to date; Table 5). Moreover, an observed increase in enantioselectivity as catalyst loading decreases may be evidence for the dimeric starting complex dissociating to afford monomers as the active catalyst carriers. Similar conclusions have been reached by other works in other catalytic systems [45], but are somewhat different to the results reported by Shibasaki on their heterobimetallic binaphthol systems where enantioselectivity is maintained down to low concentrations, even though reactivity is reduced, suggesting that the catalytic species present is the same at all concentrations [41].

4
The Future of the Phospho-Aldol Reaction

4.1
New Catalysts and Improved Processing

It seems that there are several problems still to be tackled including:

(i) Developing a simple, tuneable, modular solution synthesis to highly active catalysts.
(ii) Optimising enantioselectivities, although the binaphthol heterobimetallics are definitely the best available to date.
(iii) Improved processing such as the use of polymer-supported [46], phase transfer [47], fluorous biphasic or aqueous phase aerobic asymmetric systems [48].

There is clearly much still to be done in this field and, equally clearly, since the phospho-aldol reaction is closely related to other, base-catalysed, aldol processes, any catalyst for one may have activity towards another also.

4.2
Medicinal Chemistry and Disease Targets – What can we do with PA Catalysis?

We have already seen in Sect. 1.1.2 some of the broad fields in which chiral alpha-functionalised phosphonate esters can play a role. Indeed, many of the specific applications are medicinal in nature and focus upon the inhibition of enzyme systems. This is not the appropriate place to go into detail on the range of specific enzymes which alpha-functionalised phosphonates are known to inhibit (some key introductory references are given in Sect. 1.1.2). However, we feel it may be useful to flag up one class of enzyme targets which may be especially high profile given the range of disease states and biological functions which are linked to this enzyme class.

Protein tyrosine phosphatases (PTPs) remove phosphate groups from tyrosyl residues in enzyme systems and function in a reversible dynamic equilibrium with protein tyrosine kinases (PTKs) which catalyse the transfer of a γ-phosphate moiety from ATP to tyrosyl residues [49]. The equilibrium set up between

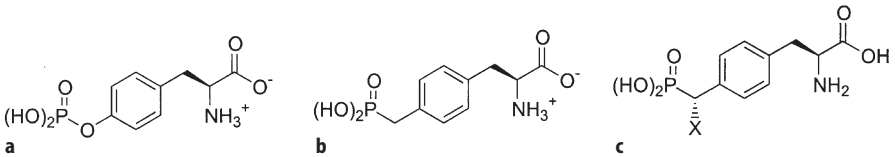


Fig. 4

addition and removal of phosphate groups in this manner is crucial in cellular systems, as it is an integral part of the control mechanism by which cells communicate with each other. An imbalance in this phosphorylation-dephosphorylation equilibrium or malfunction of PTKs or PTPs can lead to diseases such as cancers, diabetes and osteoporosis [50]. Since PTPs and PTKs are essential to effective cellular signalling, any inhibition of this process will have profound effects upon a system. Whilst such effects on a healthy system could be extremely debilitating, an ability to disrupt the cellular signalling pathways of aberrant cells can form the basis of disease control, especially of diseases such as cancer. It has been shown that PTP inhibitors can be used to probe the mechanism of signal transduction and nature of the PTP active site which, in turn, may lead to treatments for some of diseases mentioned above [51].

The [P-O] bond of phosphotyrosine (Fig. 4a) is readily cleaved by PTPs. Replacement of this functionality by a [P-C] bond results in considerably increased enzymic stability and the basis of successful PTP inhibitors (Fig. 4b). (Phosphonomethyl)phenylalanine (Pmp) is a non-hydrolysable mimetic which, if suitably protected, can be incorporated into peptides [52]. The pK_{a2} value of Pmp is higher than that of the parent phosphotyrosyl-phosphate and the ability to form hydrogen bonds is diminished by the introduction of a methylene group in place of the phosphate oxygen. There is also a reduction in the ionisation constant of the phosphonate group of the Pmp. The introduction of fluorine, amino, or hydroxy groups at the alpha-carbon centre permits both modulation of pK_a values and hydrogen bonding which appears to be essential for interaction with the active enzyme site [53]. Since a new stereocentre is created at the alpha-carbon and since stereochemistry at this site is known to influence biological properties [54], clearly there is a need for effective syntheses of alpha-functionalised phosphonic systems where control of stereochemistry at the alpha-carbon can be assured. The phospho-aldol reaction is one of the most powerful methods known for such a purpose.

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Chemistry of Phosphanylidene Carbenoids

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Kinetic stabilization utilizing sterically crowded substituents is very effective to stabilize unstable or unusual chemical species such as multiple bonds of heavier main group elements. Since the first reports were published around 1980 on stable multiple-bonded phosphorus compounds, including phosphaethene (phosphorus-carbon double bond), diphosphene (phosphorus-phosphorus double bond), and phosphaalkyne (phosphorus-carbon triple bond), many types of low-coordinated phosphorus compounds have been isolated. 1-Halo- or 1-pseudohalo-2-phosphaethenyllithium bearing a bulky substituent on the phosphorus atom is a phosphorus analogue of alkylidene carbenoid, being recognized as a phosphanylidene carbenoid, as well as a low-coordinated phosphorus compound. In this article we review the chemistry of phosphanylidene carbenoids in relation to their generation or preparation, structure, and reactions. In analogy with alkylidene carbenoids, phosphanylidene carbenoids can be applied to synthesis of compounds containing multiple bonds of phosphorus. Additionally, this article describes that phosphanylidene carbene (or phosphaisonitrile) differs somewhat from isonitrile in its stability properties.

Keywords. Low-coordinated phosphorus compounds, Phosphanylidene carbenoids, Kinetic stabilization

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Abbreviations

Aa	2,4,6-tri-*t*-pentylphenyl
cod	1,5-cyclooctadiene
Δ	heating
Dbt	2,4-di-*t*-butyl-6-methyphenyl
DBU	diazabicyclo[5.4.0]undec-7-ene
DME (dme)	1,2-dimethoxyethane
DMS	Doering-Moore-Skattebøl
FBW	Fritsch-Buttenberg-Wiechell
hν	photolysis
HF	Hartree-Fock
Mes	2,4,6-trimethylphenyl (mesityl)
Mes*	2,4,6-tri-*t*-butylphenyl
MP	Møller-Plesset
naph	naphthalene
ORTEP	Oak Ridge thermal-ellipsoid plot
r. t.	room temperature
SDQ	single, double, and quadruple
THF (thf)	tetrahydrofuran
Tip	2,4,6-triisopropylphenyl
Tmp	2,2,6,6-tetramethylpiperidino
Tms	trimethylsilyl
Tol	*p*-tolyl (4-methylphenyl)

1 Introduction

It is well-known that multiple bonds involving heavier main group elements are unstable, and thus, some stabilizing techniques are needed to prepare compounds with heavy unsaturated skeletons. Kinetic stabilization utilizing sterically crowded substituents to stabilize a reactive species is a method to obtain such multiple bonding, and many kinds of kinetically stabilized heavy multiple bonds have been derived so far [1]. As for phosphorus compounds, in 1978 Bickelhaupt and coworkers reported the first kinetically stabilized phosphorus-carbon double bond **I** (phosphaethene) [2], and in 1981 Yoshifuji and coworkers reported the first stable phosphorus-phosphorus double bond **II** (diphosphene)

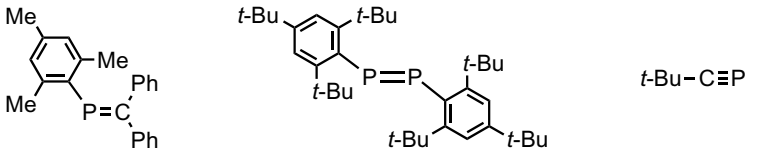


Fig. 1. Fundamental examples of kinetically stabilized low-coordinated phosphorus compounds

[3]. Moreover, Becker and coworkers reported the first stable phosphorus-carbon triple bond (phosphaalkyne) **III** [4]. For research of such low-coordinated phosphorus compounds, bulky substituents such as the 2,4,6-tri-*t*-butylphenyl (abbreviated to the Mes*) group or the *t*-butyl group play an important role in stabilizing unsaturated phosphorus atoms [5] (Fig. 1).

A carbenoid is defined as a species that displays any carbene-like reaction, and in general has a metal atom and a leaving group on the same carbon atom [6]. Alkylidene carbenoid **B** is one such "unsaturated carbene," and its properties have been intensively investigated [6, 7]. 1-Halo-2-(2,4,6-tri-*t*-butylphenyl)-2-phosphaethenyllithium **A** is a low-coordinated phosphorus compound, and is a congener of alkylidene carbenoid **B**. Although previously the chemistry of phosphanylidene carbenoid **A** did not attract much attention, we and other groups have studied this compound to obtain several findings of interest. On the other hand, isocyanide [R–N=C:] is a congener of phosphanylidene carbene [R–P=C:], but the properties are quite different. For example, isocyanides can be isolated, whereas phosphanylidene carbenes have not yet been detected as mentioned in Sect. 4. It seems likely that phosphanylidene carbenoid **A** will display similar aspects to its carbon analogue, alkylidene carbenoid **B**. In this article we review the chemistry of phosphanylidene carbenoid **A** in relation to its generation or preparation, structure, reactions, and applications to the synthesis of low-coordinated phosphorus compounds. Although we focus mainly on lithium carbenoids, we mention another chemical species showing carbenoid aspects. Some of our earlier results are described in a previous account [8]. In addition to phosphanylidene carbenoid **A**, which is a λ^3-phosphorus compound, we also mention phosphoranylidene carbenoid **C** with a λ^5-phosphorus atom (Fig. 2).

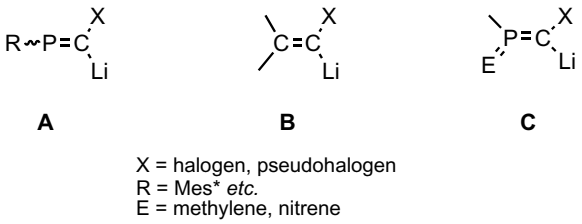


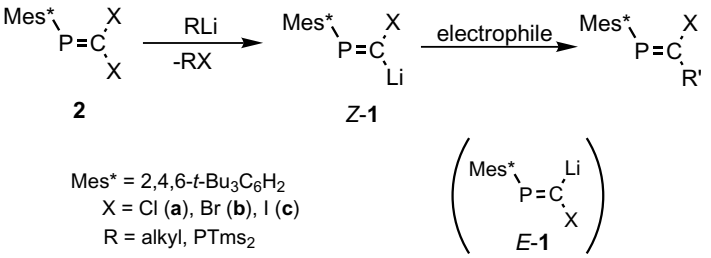
Fig. 2. Unsaturated carbenes

As for nomenclature, although some literature describes the compounds as "phosphavinylidene carbenoid" and so on, we use "phosphanylidene carbenoid" in connection with "alkylidene carbenoid."

2
Preparation or Generation of Phosphanylidene Carbenoids

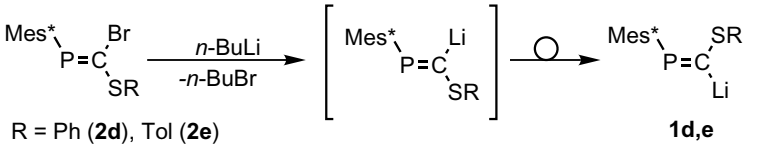
2.1
Halogen-Metal Exchange of 2,2-Dihalo-1-Phosphaethene

The most useful method is halogen-metal exchange of dihalophosphaethenes bearing bulky substituents. At first, Appel and coworkers reported the halogen-metal exchange of 2,2-dihalophosphaethene bearing the Mes* group (**2**) with an alkyllithium reagent to afford the corresponding 1-halo-2-phosphaethenyllithiums **1** [9], and later, Goede and Bickelhaupt established a practical protocol [10]. The lithium phosphanylidene carbenoids **1** thus prepared were allowed to react with a simple electrophile such as a silyl chloride or a carbonyl compound to afford the corresponding multifunctionalized phosphaethenes [9–12]. The regioselectivity of the halogen-metal exchange is high, revealing the exchange of the halogen atom in the *trans* position to the Mes* group to afford *Z*-**1** as the major product [10–12]. Similar regioselectivity is known in the case of alkylidene carbenoids [13]. In addition to alkyllithiums, lithium bis(trimethylsilyl)-phosphide was used for the preparation of phosphanylidene carbenoid **1** [14] (Scheme 1). The lithium phosphanylidene carbenoids **1** were allowed to react with electrophiles to afford the corresponding phosphaethenes as mentioned in Sect. 4.



Scheme 1. Preparation of phosphanylidene carbenoids by halogen-metal exchange

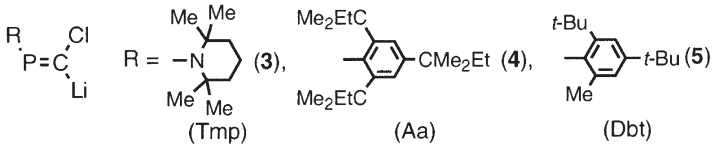
In addition to the halogen derivatives, it is possible to prepare the phosphanylidene pseudohalo-substituted carbenoids **1d,e**, since the sulfanyl group (RS-) can behave as a leaving group to show carbenoid properties [7]. 2-Arylsulfanyl-2-bromo-1-phosphaethenes (**2d,e**) were allowed to react with butyllithium to afford the corresponding carbenoids (**1d,e**). In the course of the halogen-metal exchange, *E*/*Z* isomerization occurs in spite of the steric congestion between the Mes* group and the phenylsulfanyl group (Scheme 2) [15, 16]. We assume a coordination effect of the lone pairs of phosphorus and sulfur on the



Scheme 2. Preparation of sulfanyl-substituted phosphanylidene carbenoids

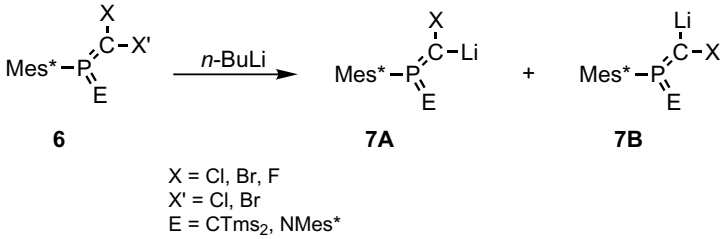
lithium atom for the stability of **1d,e** in the *cis* configuration [15, 17]. Alternatively, the following effects can be considered, such as the stereoelectronic effect between the carbanion (C^-) and σ*-P-C(Mes*) orbitals [18], or the solvation effect on the lithium atom. The *Z*-configured lithium phosphanylidene carbenoids mostly display a dominant stability superior to that of the *E*-isomer, and some aspects of this stability will be discussed in Sects. 3 and 4.

The kinetic stabilizing group of the phosphanylidene carbenoid is not limited to the Mes* group. Besides the Mes* group, other sterically protecting groups such as 2,2,6,6-tetramethylpiperidino (abbreviated to the Tmp) [19], 2,4,6-tri-*t*-pentylphenyl (abbreviated to the Aa) [20], and 2,4-di-*t*-butyl-6-methylphenyl (abbreviated to the Dbt) group [21] can be used to give phosphanylidene carbenoids **3** – **5**, although the yields are not satisfactory (Scheme 3).



Scheme 3. A series of phosphanylidene carbenoids

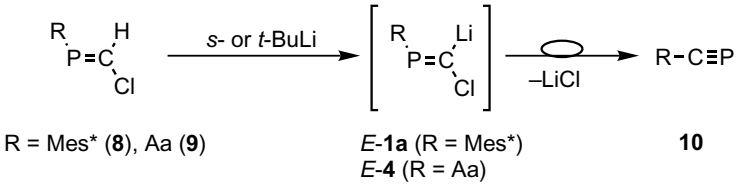
In addition to the λ^3-phosphorus compounds **1**, phosphoranylidene carbenoids **7**, which are λ^5-phosphorus compounds, were synthesized by halogen-metal exchange of the corresponding precursors **6** as mixtures of the geometrical isomers **7A** and **7B** [22 – 24] (Scheme 4).



Scheme 4. Preparation of phosphoranylidene carbenoids

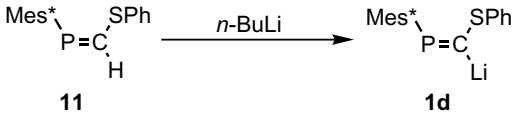
2.2
Proton Abstraction

Proton abstraction with a base is available for preparing phosphanylidene carbenoid. (*E*)-2-Chloro-1-phosphaethenes bearing the Mes* or Aa group (**8**, **9**) were allowed to react with alkyllithium plausibly to afford the corresponding phosphanylidene carbenoids *E*-**1a** or *E*-**4** [20, 25] (Scheme 5). The *E*-configured lithium phosphanylidene carbenoids can be prepared at low temperature, but they are not stable enough to be isolated, resulting in the rearrangement to the phosphaalkyne [R-C≡P (**10**); as mentioned in Sect. 4].



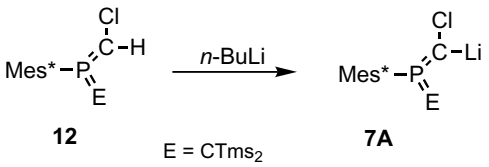
Scheme 5. Phosphanylidene carbenoids generated by proton abstraction

The phenylsulfanyl-substituted phosphaethene **11** was allowed to react with butyllithium to afford the corresponding phosphanylidene carbenoid **1d** through proton abstraction [15] (Scheme 6).



Scheme 6. A sulfanyl-substituted phosphanylidene carbenoid generated by proton abstraction

Phosphoranylidene carbenoid **7A** was also obtained by proton abstraction of the phosphorane **12** [22] (Scheme 7).

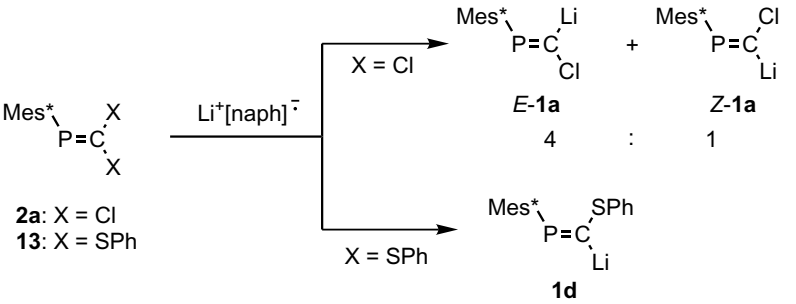


Scheme 7. A phosphoranylidene carbenoid generated by proton abstraction

2.3
Preparation by One-Electron Reducing Reagent

Single-electron reducing reagents are applicable to afford phosphanylidene carbenoids. 2,2-Dichlorophosphaethene (**2a**) was allowed to react with lithium

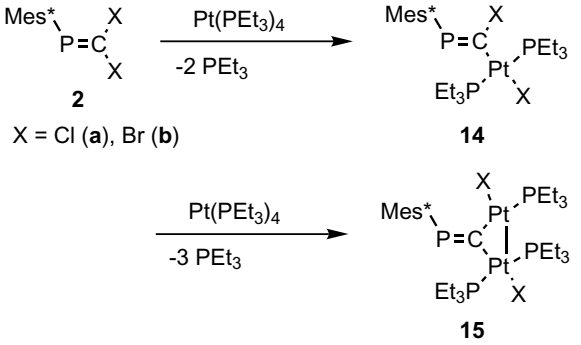
naphthalenide (3 equiv.) to afford the corresponding phosphanylidene carbenoid **1a** although the yield was low (27%). In contrast to the reaction with alkyllithiums, the *E*-configured phosphanylidene carbenoid (*E*-**1a**) was the major product [26]. Additionally, 2,2-bis(phenylsulfanyl)phosphaethene (**13**) was allowed to react with lithium naphthalenide to afford the phosphanylidene carbenoid **1d** with the *Z*-configuration [15] (Scheme 8).



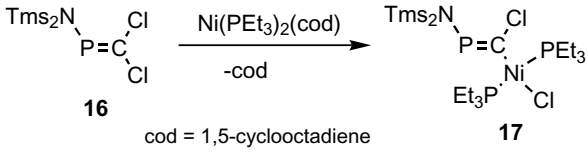
Scheme 8. Preparation of phosphanylidene carbenoids by use of lithium naphthalenide

2.4 Reaction of Dihalophosphaethenes with Low-Valent Transition Metal Complexes

Oxidative addition into the transition-metal center is an important reaction in organometallic chemistry. The Cl-C bond in dichlorophosphaethene is sensitive to this oxidative addition. Thus, the Mes*-substituted 2,2-dihalophosphaethene **2** was allowed to react with tetrakis(triethylphosphine)platinum(0) to afford the corresponding complex **14** to result in the formation of diplatinum complex **15** [27] (Scheme 9). Bis(trimethylsilyl)amino-substituted dichlorophosphaethene **16** was treated with a nickel(0) reagent to afford the corresponding nickel(II) complex **17** [28] (Scheme 10). Complex **14** displays a carbenoid reaction as mentioned in Sect. 4.



Scheme 9. Oxidative addition of dihalophosphaethenes on the platinum(0) center



Scheme 10. Oxidative addition of a dichlorophosphaethenes on the nickel(0) center

3
Structure of Phosphanylidene Carbenoid

In 1999 Niecke and coworkers reported an X-ray determination of the phosphanylidene carbenoid [(*Z*)-Mes*-P=C(Cl){Li(dme)$_2$}] together with spectroscopic and theoretical investigations [29]. Fig. 3 displays an ORTEP drawing of solvated *Z*-**1a** showing a monomeric structure. The structural parameters of *Z*-**1a** in the crystalline state and the observed intermolecular exchange of the lithium ion between different carbanion fragments in solution suggest a low degree of covalency for the C-Li bond, and this was confirmed by natural population analyses and an analysis of the Laplacian of the electron density. A theoretical analysis demonstrated that the structure of *Z*-**1a** is very similar to the carbanion [R-P=C(Cl)]$^-$, and the bonding situation in the phosphanylidene carbenoid *Z*-**1a** is discussed in terms of an isolobal analogy to N_2F_2, which includes the hyperconjugation between the lone pairs and adjacent single bonds. Thus, the carbenoid *Z*-**1a** is more stable than *E*-**1a** with respect to [1,2]-migration as mentioned in Sect. 4. Incidentally, as for alkylidene carbenoids, the isomer for which the lithium atom locates in the less hindered site is more stable, displaying the opposite property to phosphanylidene carbenoids [13, 30].

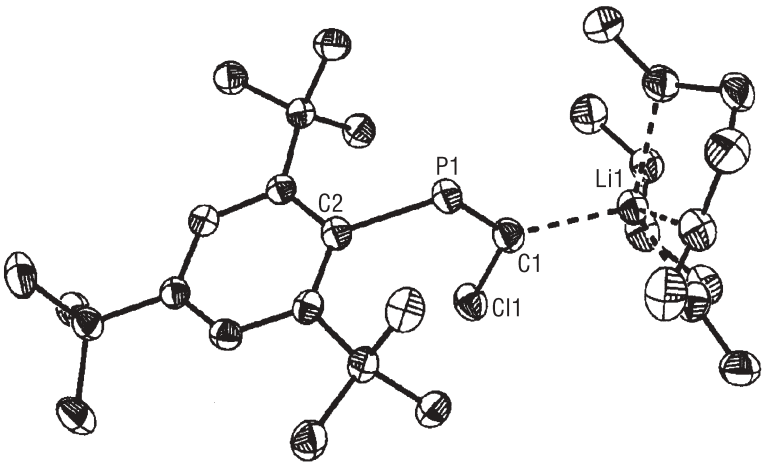


Fig. 3. An ORTEP drawing of the molecular structure of *Z*-**1a** coordinated by two DME molecules in the crystal. Reprinted with permission from ref. [29]. Copyright 1999 the American Chemical Society

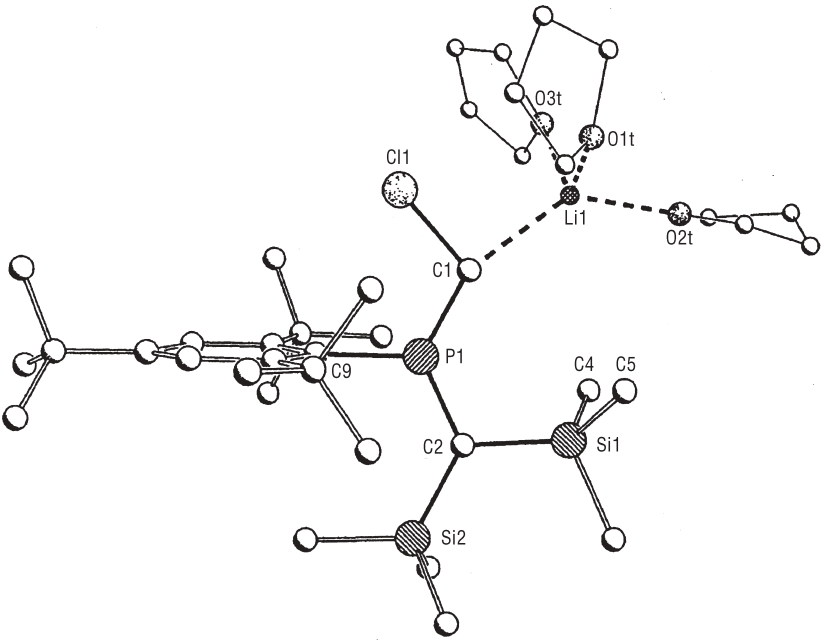


Fig. 4. An ORTEP drawing of the molecular structure of **7A** (E=C(Tms)$_2$; X=Cl) coordinated by three THF molecules in the crystal. Reprinted with permission from ref. [22]. Copyright 1995 Wiley-VCH

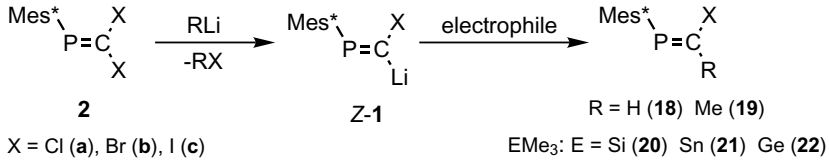
On the other hand, the monomeric structures of phosphoranylidene carbenoids **7A** (as E=CTms$_2$; X=Cl) coordinated by three THF molecules display typical features of carbenoids. As displayed in Fig. 4, it is possible to recognize elongated C-X bonds and distorted carbon bond angles (narrow P=C-X and wide P=C-Li angles) in **7A** [22, 24, 31]. These structural properties can be interpreted by the bonding situation as a contact ion pair between a carbanion and a solvated metal cation [32], and are corroborated by NMR studies. Compound **7A** displays a carbenoid reactivity as indicated by the cyclization to afford the 1*H*-diphosphirene through the elimination of LiCl, whereas the corresponding isomer **7B** does not, indicating similar differences in stability and carbenoid aspects between the geometrical isomers [22, 24].

4
Reactivity of Phosphanylidene Carbenoids

4.1
Nucleophilic Reactions and Transmetallations

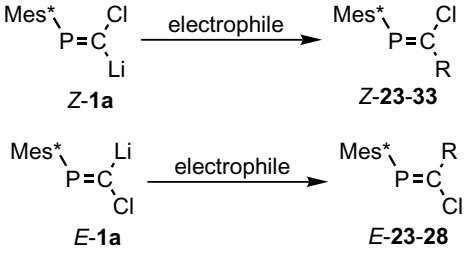
It is quite reasonable that lithium phosphanylidene carbenoids have nucleophilic properties to react with electrophiles. At first, Appel and coworkers reported the reactions of *Z*-**1a** and *Z*-**1b** with methanol, iodomethane, chloro-

trimethylsilane, and chlorotrimethylstannane to afford the corresponding substituted phosphaethenes **18 – 21** [9]. Similarly, Bickelhaupt and coworker reported the reactions of iodo-substituted phosphanylidene carbenoid *Z*-**1c** to give phosphaethenes **18c**- **21c** as well as the germa-substituted phosphaethene **22c** [10] (Scheme 11).



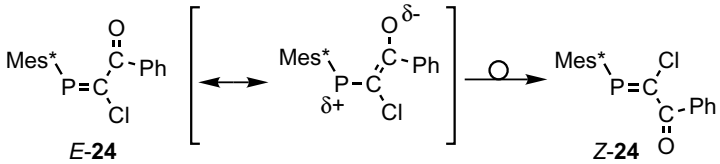
Scheme 11. Nucleophilic reactions of phosphanylidene carbenoids

Carbonyl compounds are typical electrophiles. We and Bickelhaupt and coworkers independently reported the reactions of *Z*-**1a** with carbonyl compounds to give the corresponding multifunctionalized phosphaethenes **23 – 33** with the *Z*-configuration [11, 12, 33]. The spectroscopic data of products containing the >C=O moiety indicate the strong polarization within the P=C-C=O skeleton [11, 12], whereas the structural elucidation for *Z*-**24** and *Z*-**25** did not reveal clear-cut evidence for the conjugation [12]. Similarly, compound *E*-**1a** was allowed to react with electrophiles to afford the corresponding *E*-configured phosphaethenes **23 – 28** [11] (Scheme 12, Table 1).



Scheme 12. Preparation of multifunctionalized phosphaethenes

We found a remarkable effect of conjugation within the P=C-C=O moiety by the facile isomerization of *E*-configured phosphaethene *E*-**24**. That is, although the formation of phosphaethene *E*-**24** was observed, it isomerized to *Z*-**24** during the work-up procedure. Therefore, we propose the effect of conjugation as mentioned in Scheme 13 to enable the facile isomerization [11].



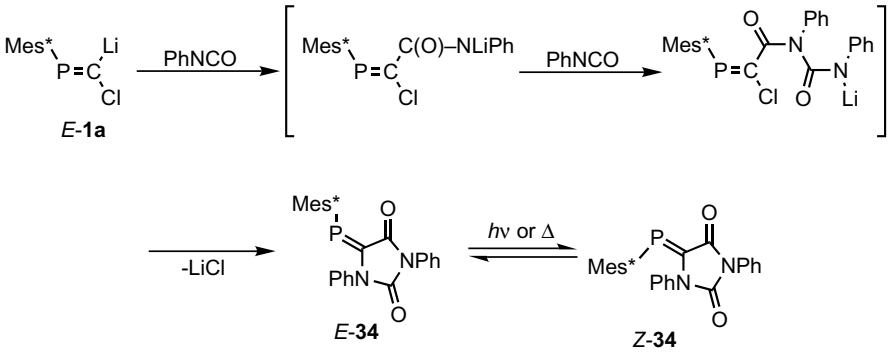
Scheme 13. An *E*/*Z* isomerization of phosphaethene promoted by the carbonyl group

Table 1. Reactions of **1a** with carbonyl compounds

Compound	Electrophile	R	Ref.
23	$ClCO_2Et$	$-CO_2Et$ [a]	[11, 12]
24	PhCOCl	–C(O)Ph [a]	[11, 12]
25	*t*-BuCOCl	–C(O)*t*-Bu [a]	[11, 12]
26	PhNCO	–C(O)NHPh [a]	[11]
27	PhCHO	–CH(OH)Ph [a]	[11, 33]
28	[–$(CH_2)_5$–]C=O	–C(OH)[–$(CH2)_5$–] [a]	[11]
29	Ph_2C=O	–C(OH)Ph_2	[33]
30	(*E*)-MeCH=CHCHO	–CH(OH)–CH=CHMe	[33]
31	Ph(Me)C=O	–C(OH)PhMe	[33]
32	MeCOCl	–C(O)Me	[33]
33	CO_2	$-CO_2Li$	[12]

[a] Both *Z*- and *E*-isomers were obtained [11].

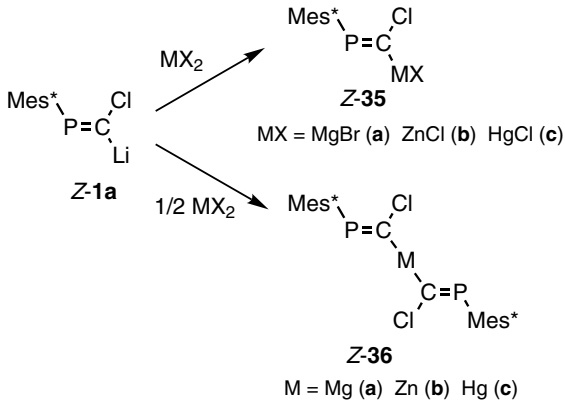
Lithium phosphanylidene carbenoid can react with a number of electrophiles, and an example is described in Scheme 14. The *E*-configured phosphanylidene carbenoid *E*-**1a** was allowed to react with phenyl isocyanate to afford the corresponding amide *E*-**26** but the yield was low. The major product was a hydantoin compound possessing an *exo* P=C bond (*E*-**34**). Compound *E*-**34** isomerized to an *E*/*Z* mixture by irradiation or heating, and *Z*-**34** was analyzed by X-ray crystallography to establish the hydantoin skeleton [11, 34].



Scheme 14. Preparation of a heterocyclic compound possessing an *exo* P=C bond

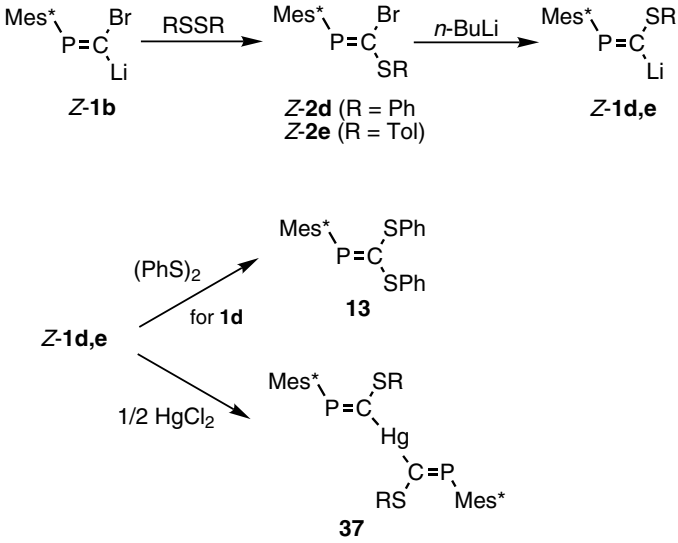
Lithium phosphanylidene carbenoid *Z*-**1a** was transmetallated by group 12 metals to give the corresponding phosphanylidene carbenoids *Z*-**35** or *Z*-**36.** The magnesium congener *Z*-**35a** was utilized for the nucleophilic reaction with acetophenone or acetyl chloride, in which it was easily deprotonated by *Z*-**1a**, to afford the corresponding product *Z*-**31** or *Z*-**32** [33] (Scheme 15).

Bromo-substituted phosphanylidene carbenoid *Z*-**1b** was allowed to react with diaryl disulfides to afford the corresponding phosphaethenes **2d** and **2e** as precursors for further phosphanylidene carbenoids **1d,e**. Moreover, **1d** was



Scheme 15. Transmetallation reactions of phosphanylidene carbenoids with the group 12 metals

allowed to react with a disulfide or a mercury(II) salt to afford the corresponding products **13** or **37** [16] (Scheme 16). The structure of **37** (R=Ph) was unambiguously determined by X-ray crystallography as an example of a stable organometallic compound containing the P=C skeleton [16] (Fig. 5). Compared to the structure of *Z*-**1a** as mentioned in Sect. 3, the P=C bond length and the angles around the P=C carbon atoms of **37** are similar, whereas the bond angles around phosphorus are different.



Scheme 16. Preparation and reactions of sulfanyl-substituted phosphanylidene carbenoids

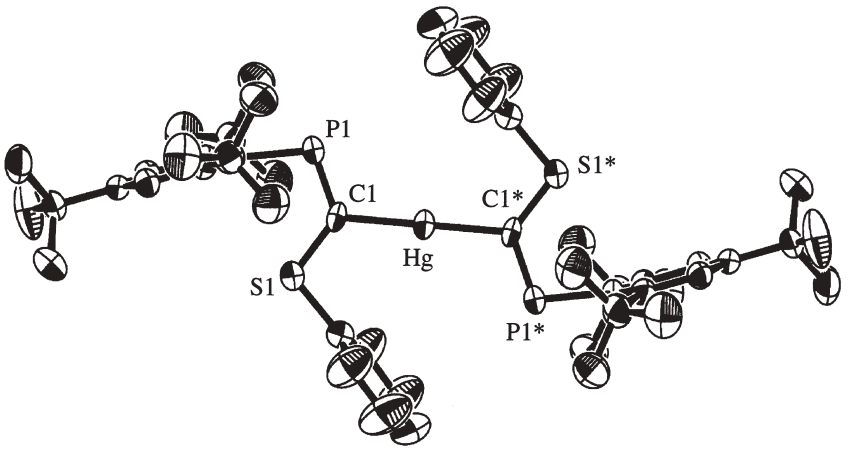
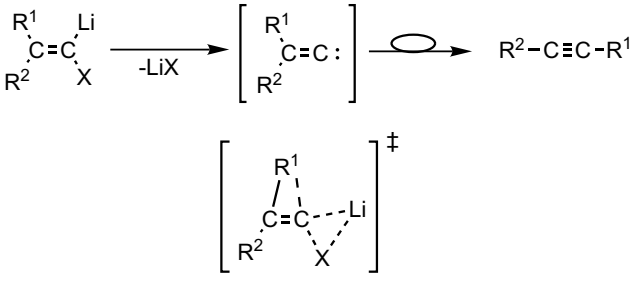


Fig. 5. An ORTEP drawing of the molecular structure of **37** (R=Ph). Reprinted with permission from ref. [16]. Copyright 2000 the Chemical Society of Japan

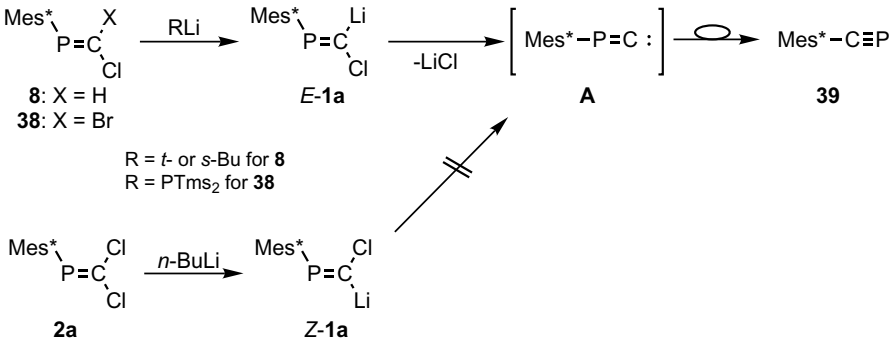
4.2 [1,2]-Rearrangement

As for alkylidene carbenoids, in 1894, Fritsch, Buttenberg and Wiechell reported a synthetic method to alkynes by [1,2]-migration (the FBW-rearrangement) of a substituent by the reaction of 2,2-diaryl-1-chloroethylene and sodium ethoxide [35]. This FBW-rearrangement reaction occurs in the case of lithium alkylidene carbenoids while including a regioselective rearrangement of the substituent in the *trans* position of the leaving group [6]. This rearrangement occurs in the cases of aryl- or cyclopropyl-substituted olefins. The same reaction pattern takes place in the case of phosphanylidene carbenoids. From the regioselectivity and the effect of substituents to operate the migration, a transition state for the rearrangement has been suggested to take up a three-membered ring structure without the complete elimination of LiX, although an alkylidene carbene is formally shown [6, 7] (Scheme 17).



Scheme 17. The Fritsch-Buttenberg-Wiechell (FBW) rearrangement

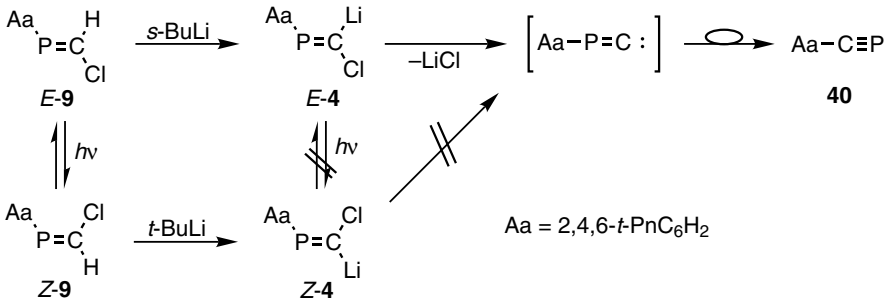
When (*E*)-1-chloro-2-(2,4,6-tri-*t*-butylphenyl)-1-phosphaethenyllithium, *E*-**1a**, prepared from 1-chlorophosphaethene **8** and *s*- or *t*-butyllithium or 1-bromo-1-chloro-2-phosphaethene **38** and lithium bis(trimethylsilyl)phosphide, was heated in THF, the reaction afforded phosphaalkyne **39** through the phosphanylidene carbene or "phosphaisonitrile" (**A**) generated by a [1,2]-rearrangement together with elimination of the lithium chloride. The *Z*-isomer (*Z*-**1a**) does not undergo the [1,2]-rearrangement reaction (Scheme 18) [14, 20, 25].



Scheme 18. [1,2]-rearrangement of a phosphanylidene carbenoid bearing the Mes* group affording the phosphaalkyne

In contrast to isonitrile, the phosphanylidene carbene species [Mes*-P=C:] could not be detected due to its instability. Theoretical investigations have indicated that phosphanylidene carbene (phosphaisonitrile) [H-P=C:] is less stable than phosphaalkyne (phosphanitrile) [H-C≡P] by 84.0 (83.9) kcal mol^{-1} at the MP4SDQ/6–31G**//HF/6–31G** (MP4/6–31G**//HF/6–31G**) level, and there is no energy barrier through the rearrangement reaction [36].

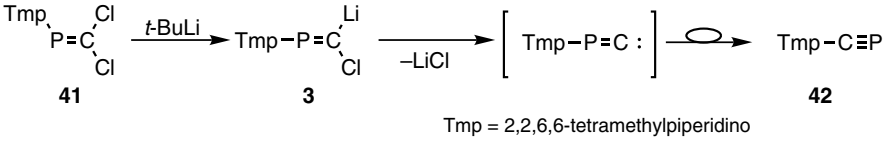
The [1,2]-rearrangement to afford phosphaalkyne was reported in the case of phosphanylidene carbenoid bearing the Aa group. (*E*)-Chlorophosphaethene *E*-**9** was allowed to react with *s*-butyllithium to afford *E*-**4** which gave the corresponding phosphaalkyne **40.** Phosphaalkyne **40** was not obtained in the reaction with any alkyllithium but was formed with *s*-butyllithium. Similar to Scheme 18,



Scheme 19. [1,2]-Rearrangement of a phosphanylidene carbenoid bearing the Aa group

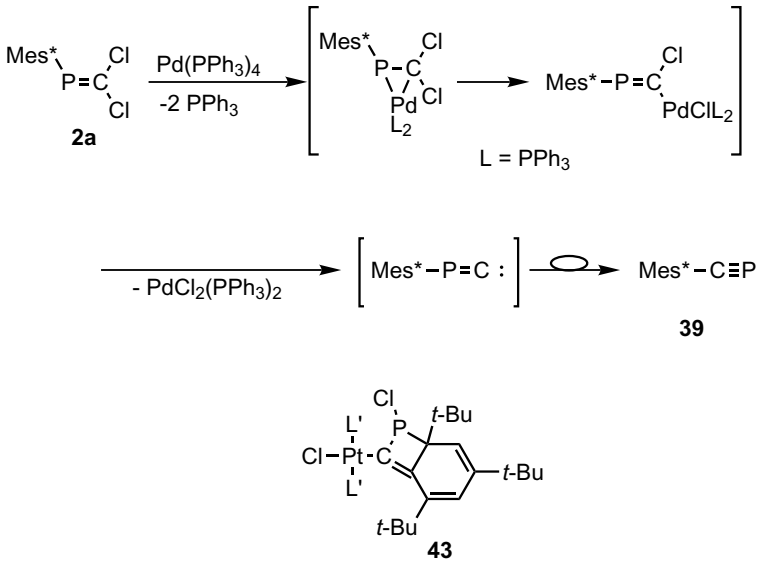
the *Z*-isomer (*Z*-**9**) did not afford **40.** An attempt to prepare *E*-**4** from *Z*-**4** by irradiation with light failed although phosphaethene **9** was easily isomerized under similar conditions [20] (Scheme 19).

The Tmp-substituted dichlorophosphaethene **41** was allowed to react with *t*-butyllithium to afford the phosphaalkyne **42** through the formation of the phosphanylidene carbenoid **3**; however, the yield was low (Scheme 20) [19].



Scheme 20. [1,2]-Rearrangement of a phosphanylidene carbenoid bearing the bulky amino group

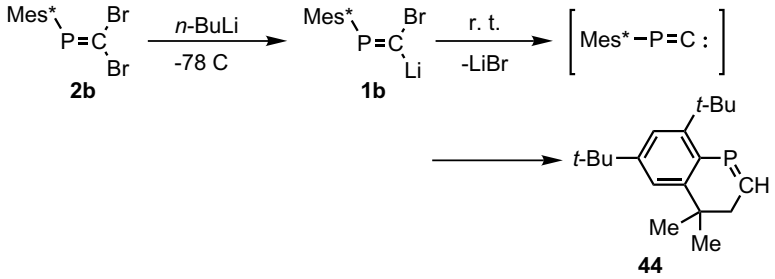
Transition-metal induced [1,2]-rearrangement is also available to obtain phosphaalkyne **39**. Dichlorophosphaethene **2a** was allowed to react with an equivalent amount of tetrakis(triphenylphosphine)palladium(0) to afford phosphaalkyne **39** through intermediates (Scheme 21) [37]. The rearrangement process takes place in the reaction of dibromophosphaethene **2b** with a small amount (0.2 equiv.) of dibromobis(triphenylphosphine)nickel(II) in the presence of zinc and tetraethylammonium iodide through the generation of a nickel(0) intermediate [38]. Complex **43** was isolated in the reaction of **2a** and tetrakis(triethylphosphine)platinum(0) which could afford phosphaalkyne **39** [27, 28, 39].



Scheme 21. Preparation of the phosphaalkyne derivative by a transition-metal induced [1,2]-rearrangement

4.3
C-H Insertion

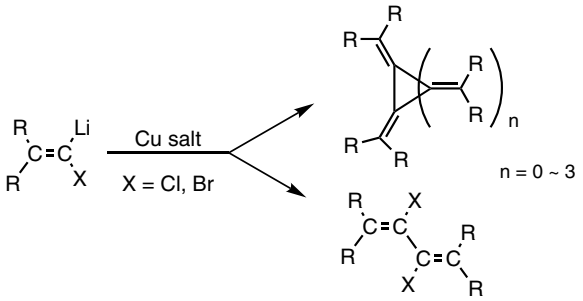
The C-H insertion reaction is a typical carbene or carbenoid reactivity [40]. Indeed, intramolecular C-H insertions were known in the case of alkylidene carbenoids (alkenylidenes) [41], and are applicable to organic synthesis [42]. On the other hand, phosphanylidene carbenoid, which is a congener of alkylidene carbenoid, also demonstrates intramolecular C-H insertion. Dibromophosphaethene **2b** was allowed to react with *n*-butyllithium to afford the cyclized compound **44** through an intramolecular C-H insertion without [1,2]-rearrangement (Scheme 22) [43]. The higher leaving ability of the bromide ion than that of the chloride ion might be responsible for the difference in reactivity. From an absorption spectrum of **44**, we found some interactions between the P=C group and the aromatic ring [43].



Scheme 22. An intramolecular C-H insertion of a phosphanylidene carbenoid

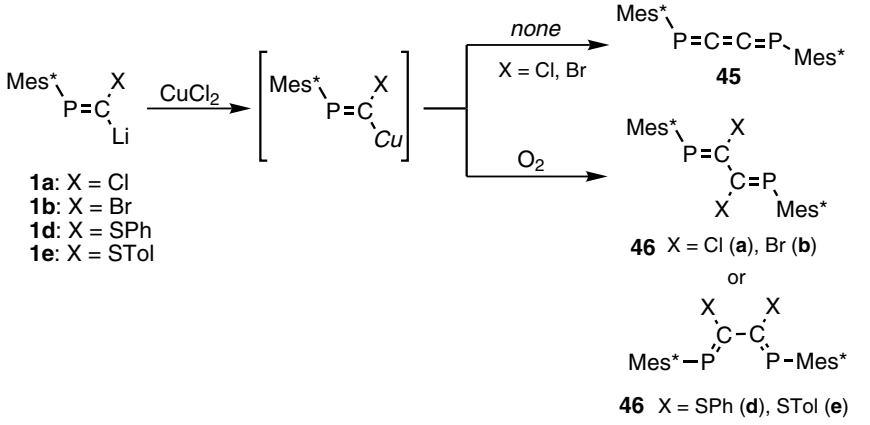
4.4
Coupling Reaction through Transmetallation with Copper

The oxidative coupling reaction of organolithium reagents with copper compounds is still a powerful method for organic synthesis. As for alkylidene carbenoids, the copper-mediated coupling reaction affords the corresponding cumulene derivatives [6, 44] as well as the radialene compounds [45]. It is possible to obtain a homocoupled product without elimination of the leaving group on the carbenoid center to give the corresponding buta-1,3-dienes (Scheme 23) [44].



Scheme 23. Copper-mediated coupling reactions of alkylidene carbenoids

The copper-mediated coupling of phosphanylidene carbenoids was also examined. Phosphanylidene carbenoid **1a** was allowed to react with copper salts to afford 1,4-diphosphabutatriene **45** through the organocopper intermediates [46]. The same coupling reaction occurs in the case of the bromo-derivative **1b** [47]. Previously 1,4-diphosphabutatriene **45** was prepared by an alternative method, that is, the reaction of the bulky ethynylphosphine [Mes*P(H)C≡CTms] [48] or the modified Doering-Moore-Skattebøl (DMS) method utilizing dichlorocarbene [49]. Compared to the previous methods for the preparation of **45**, the copper-mediated coupling reactions of **1** is simpler and more convenient. On the other hand, if **1a** was treated with copper salt and oxygen, 2,3-dichloro-1,4-diphosphabuta-1,3-diene **46** was obtained as a homo-coupled product of the phosphanylidene carbenoid without elimination of the chlorine atoms [46]. Although the reaction mechanism is still unclear, an organocopper intermediate might be considered, and this intermediate is oxidized to afford the coupled product with the organic counterparts involving halogens. The structures of diphosphabutadienes **46a** and **46b** were unambiguously determined by X-ray crystallography to reveal their planar *s-trans* conformations [46, 50]. In addition to halogen-substituted phosphanylidene carbenoids **1a,b**, arylsulfanyl-substituted phosphanylidene carbenoids **1d,e** were coupled to afford **46d,e** by a similar method as mentioned above. In contrast to the halogen derivatives, compounds **46d,e** take up the twisted *s-cis* (*gauche*) conformation (Scheme 24) [15, 16].

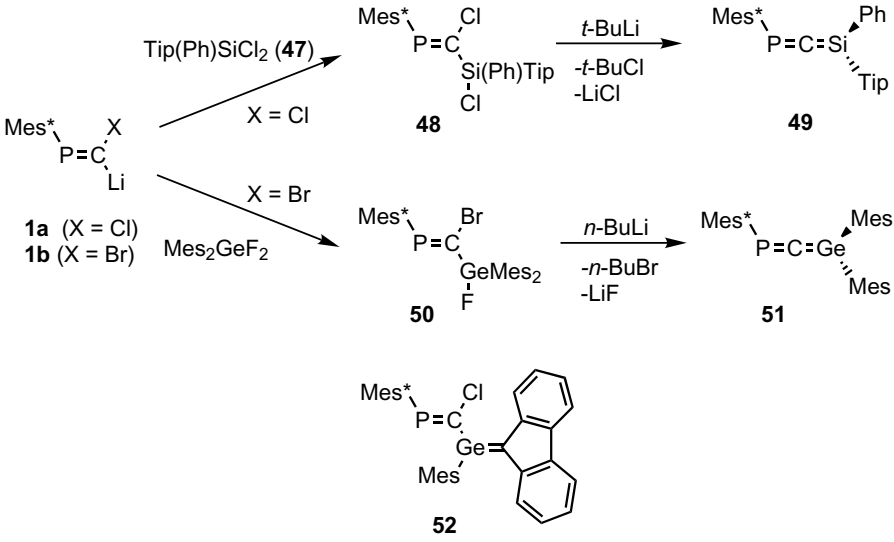


Scheme 24. Copper-mediated coupling reactions of phosphanylidene carbenoids

4.5
Utilization of Phosphanylidene Carbenoids as a Material for Heteroallenes

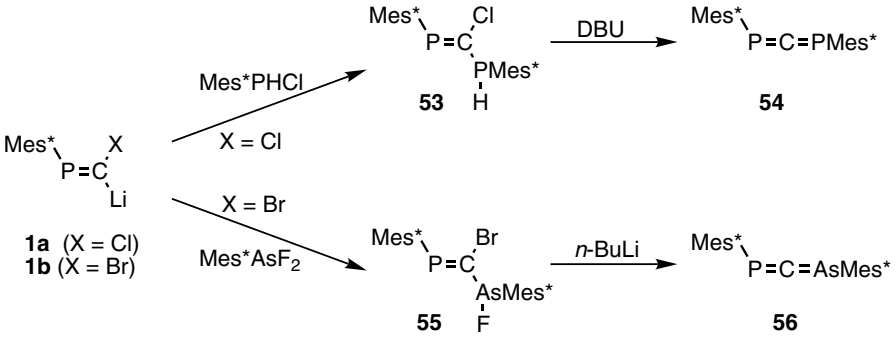
Lithium phosphanylidene carbenoid **1** is a starting material for synthesis of heavy heteroallenes such as -P=C=E (E=Si<, Ge<, P-, As-) [51]. Lithium carbenoid **1a** was allowed to react with diarylsilyl dichloride **47** to afford the corresponding adduct **48**, which gave 1,3-phosphasilaallene **49** on the reaction with *t*-butyllithium. Phosphasilaallene **49** is observed below 0 °C in the ^{31}P-NMR

spectrum [52]. A similar method was applied to the synthesis of 1,3-germaphosphaallene **51** from **1b** and diarylgermyl difluoride via **50**, which is more labile than the silicon congener **48** [53]. A transient 3-germa-1-phosphabuta-1,3-diene (**52**) was prepared in a similar manner (Scheme 25) [54].



Scheme 25. Preparation of a 1,3-phosphasilaallene and a 1,3-germaphosphaallene

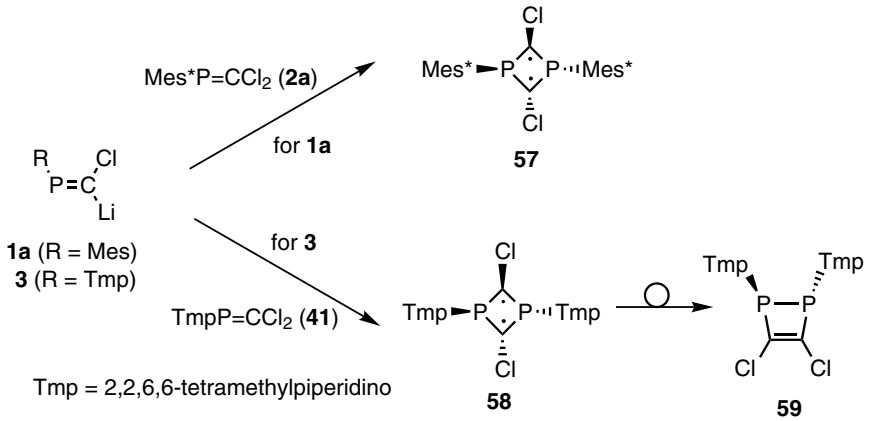
1,3-Diphosphaallene **54** and 1,3-arsaphosphaallene **56** were prepared from phosphanylidene carbenoid **1** and the corresponding halogen-containing phosphine and arsine, respectively (Scheme 26) [55, 56].



Scheme 26. Preparation of a 1,3-diphosphaallene and a 1,3-arsaphosphaallene

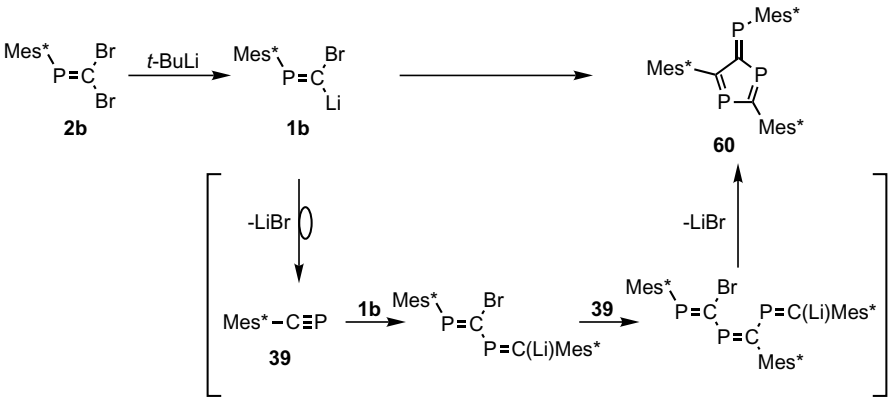
4.6 Miscellaneous Reactions

Recently, a certain number of intriguing organophosphorus compounds have been synthesized by employing "phosphorus tricks" [57]. Lithium phosphanylidene carbenoid was utilized as starting reagent for the synthesis of such compounds. Lithium phosphanylidene carbenoid **1** was allowed to react with 2,2-dihalophosphaethene **2** to afford 1,3-diphosphacyclobutane-2,4-diyl **57** which is a stable singlet biradical species. Neither the diphosphabicyclobutane derivative nor the diphosphabutadiene derivative could be obtained according to the Woodward-Hoffmann rule, which forbids the possible intermediate for the rearrangement [58]. On the contrary, a phosphanylidene carbenoid bearing the Tmp group (**3**) was formally reacted with phosphaethene **41** to afford the intermediate diphosphacyclobutane derivative **58**, leading to 3,4-diphosphacyclobutene **59** [59] (Scheme 27).



Scheme 27. Preparation of 1,3-diphosphacyclobutane-2,4-diyls

As mentioned above, phosphanylidene carbenoid is a novel synthon for organophosphorus compounds, and we found a quite attractive reaction, that is, a formal trimerization of phosphanylidene carbenoids involving the [1,2]-rearrangement reaction for phosphaalkyne. Dibromophosphaethene **2b** was allowed to react with *t*-butyllithium to afford 1,3,6-triphosphafulvene **60**. The reaction mechanism would involve the formation of phosphaalkyne **39** which reacts with a half-equivalent amount of **1b**, and then final annelation leads to **60**. As there was no obvious improvement of the yield, phosphaalkyne **39** was allowed to react with **1b** to afford **60**. We considered the formation of intermediate 1,3-diphosphabutadiene and 1,3,5-triphosphahexatriene species, indicating a possibility for preparing the phosphorus congeners of oligo- or polyacetylenes. The structure of triphosphafulvene **60** was determined after **60** was complexed with the $W(CO)_5$ moiety on the phosphorus atom at the 3 position (Scheme 28) [60]. It should be noted that the reported δ_P value for the phosphorus at the 6-position in **60** [δ_P 313.8] and that for the corresponding carbonyl-



Scheme 28. Preparation of a 1,3,6-triphosphafulvene

tungsten complex **61** [δ_P 318.7] should read δ_P 401.9 and δ_P 397.1, respectively [60]. Triphosphafulvene **60** is one of the isomers of triphosphabenzene which has been intensively studied [61, 62]. Nevertheless, 1,3,6-triphosphafulvene was not considered as an isomer of phosphabenzene until now [63]. As for the properties of **60**, a theoretical investigation indicates a predominant stability of 1,3,5-triphosphabenzene relative to 1,3,6-triphosphafulvene; in other words, the three Mes* groups in **60** would play an important role in stabilizing the 1,3,6-triphosphafulvene skeleton [60].

5 Conclusion

Phosphanylidene carbenoids belong in the category of low-coordinated phosphorus compounds that are inherently unstable. The kinetic stabilization method enabled us not only to prepare low-coordinated compounds, but also to operate the lithiation reaction to generate lithium phosphanylidene carbenoids, such as **1** as well as **7**, without decomposition of the P=C skeleton. The experimental and theoretical structural elucidation of *Z*-configured lithium phosphanylidene carbenoid (*Z*-**1a**) describes it as a tightly bonded ion pair whose carbenic center behaves predominantly as a cryptcarbanion, and the hyperconjugation between the lone pairs and adjacent single bonds explains the higher stability than that of the *E*-isomer. In contrast to *Z*-**1a**, the monomeric structures of phosphoranylidene carbenoids **7A** display typical features of carbenoids as shown in the case of alkylidene carbenoid. Lithium phosphanylidene carbenoids are promising nucleophilic reagents to afford various types of phosphaethenes including multifunctionalized, heterocyclic, or organometallic compounds. The [1,2]-rearrangement (the FBW-rearrangement) reaction is a typical carbenoid reaction to afford P≡C bonded compounds, the phosphaalkynes, displaying regioselectivity. Unlike isocyanide, phosphanylidene carbene [R – P=C:] (phosphaisonitrile) cannot be detected due to its instability.

The C-H insertion reaction of phosphanylidene carbenoid is also found as a typical carbenoid reaction. The copper-mediated oxidative coupling reactions are powerful synthetic tools to construct some conjugated systems with the P=C skeleton, which are operated by treatment of oxygen. Lithium phosphanylidene carbenoids are applicable to synthesize the heavier heteroallenic compounds and stable biradical compounds. Moreover, an intriguing trimerization of phosphanylidene carbenoids is used to give the triphosphafulvene as an isomer of triphosphabenzene, which will lead to a novel organic chemistry. Indeed, the mentioned low-coordinated phosphorus compounds may well be applied to the synthesis of novel materials [5, 64, 65].

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Transient Nitrilium Phosphanylid Complexes – New Versatile Building Blocks in Phosphorus Chemistry

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This review shows preparative and theoretical aspects of the formation of transient nitrilium phosphanylid complexes (NPCs) and highlights their synthetic potential in organophosphorus chemistry with special emphasis on unsaturated five-membered N,P-heterocycles. According to mechanistic investigations NPCs are, most often, formed via terminal [1,1]-addition of electrophilic terminal phosphanediyl complexes with carbonitriles. Although theoretical investigations on NPCs show that the HOMO and LUMO are mainly concentrated at the metal center, they react like common organic 1,3-dipole systems. Experimental investigations on the regioselectivity of NPCs towards terminal alkynes, nitriles and phosphaalkynes (a ≡ b) show a strong preference for the formation of the sterically least hindered products. Furthermore, the five-membered ring formation proceeds with retention of configuration at the carbon centers in the case of stereochemically defined alkenes (a = b); nevertheless, some products undergo subsequent epimerization reactions.

Keywords. Azaphospholes, Azaphosphirenes, 1,3-Dipoles, Heterophospholenes, Nitrilium Phosphanylid Complexes

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Abbreviations

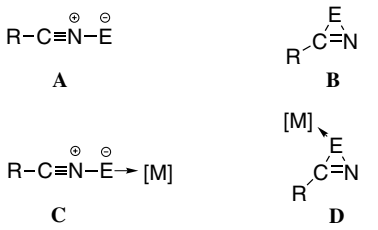
1-ad	1-adamantyl
t-Bu	*tert*-butyl
dr	diastereomer ratio
Et	ethyl
h	hour(s)
Me	methyl
min	minute(s)
Ph	phenyl
i-Pr	isopropyl
rt	room temperature
TCNE	tetracyanoethylene

1 Scope and Time Frame

The aim of the present work is to show preparative and theoretical aspects of the formation of transient nitrilium phosphanylid complexes, a novel 1,3-dipole system, and to highlight their synthetic potential in organophosphorus chemistry with special emphasis on unsaturated five-membered N,P-heterocycles. This review covers the literature until November 2001.

2 Introduction

There is long-standing interest in formation, structure, bonding, and use of 1,3-dipoles in heterocyclic chemistry [1]. Among 1,3-dipoles, nitrilium betaines **A** such as nitrile ylids (E = CR_2) [2], nitrile imines (E = NR) [3], and nitrile oxides (E = O) [4] (Scheme 1) are of interest because of their versatile use in the synthesis of the important unsaturated five-membered nitrogen heterocyclic systems: azoles, diazoles, and oxazoles [1]. It is remarkable that from all cyclic isomers of **A** exclusively 2*H*-azirenes **B** (E = CR_2) have an extensively developed chemistry [5]. In contrast, 1*H*-diazirenes (E = NR) [6] and/or oxazirenes (E = O) [7] are still among the *hardest-to-achieve* aims in heterocyclic chemistry and their extremely low thermal stabilities were attributed to intrinsic destabilizing electronic effects and discussed in terms of anti-aromaticity [8, 9]. In contrast to these classes of compounds, almost nothing is known about related nitrilium



Scheme 1. Nitrilium betaines **A**, their cyclic isomers **B** and complexes thereof **C** and **D** (R = ubiquitous organic substituents; [M] = metal complex fragment)

betaines and three-membered heterocycles having the C,N,E connectivity, in which E represents an organoelement fragment having a third row element such as silicon, phosphorus, or sulfur (**A**, **B**: E = SiR_2, PR, S); exclusively for the latter was some evidence provided for their existence in matrices at low temperatures [10]. Although, no stable derivatives of nitrile sulfides **A** (or thiazirenes **B**, E = S) are known, a rich 1,3-dipolar cycloaddition chemistry was established over the years based on trapping reactions of transiently formed derivatives of **A** (E = S) [11].

Concerning the synthesis of 2*H*-azirenes and so-called heteroazirenes (ring systems with two heteroatoms and a C = N double bond), it is noteworthy that, apart from recently reported examples of [2 + 1] cycloaddition reactions of carbenes to benzonitrile to give 2*H*-azirines [12], no such reactions of either nitrenes, atomic oxygen (or sulfur), or phosphinidenes (phosphanediyls) [13] to nitriles have been reported so far. Very recently, the [2 + 1] cycloaddition reaction of a bulky-substituted silylene derivative with benzonitrile affording the first stable 2*H*-azasilirene (**B**: E = SiR_2) was reported [14]; evidence for transiently formed 2*H*-azasilirenes was given ten years earlier [15].

With respect to ring-opening of three-membered heterocycles of type **B** (E = CR_2, NR), the generation of nitrilium betaines is exclusively established for 2*H*-azirenes. In contrast, transiently formed 1*H*-diazirenes [6a] show other rearrangements (instead of ring-opening to yield nitrile imines) giving 3*H*-diazirenes [16], ring-enlarged heterocycles [16], or carbodiimides [17]. Nonetheless, nitrile imines are accessible via other routes, i. e., through thermolysis of heterocycles such as oxadiazolinones or sydnones [3].

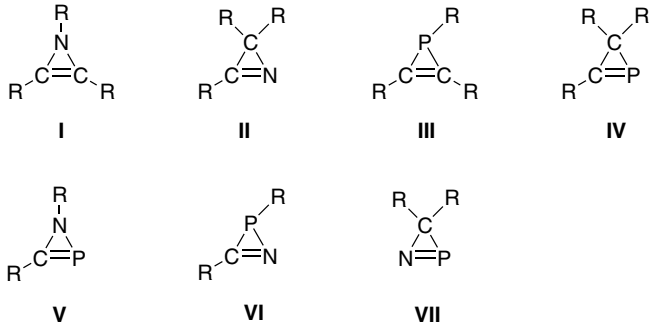
It is remarkable that there were no examples of transition metal-coordinated nitrilium betaines **C** and heteroazirenes **D** until 1997 and 1994, respectively.

3
2*H*-Azaphosphirene Complexes, a *Natural* Starting Point for Nitrilium Phosphanylid Complexes?

The carbon-phosphorus analogy has been extended in different areas of organophosphorus chemistry over the last 40 years – some essential steps and consequences have been described very recently [13b]. Over the years, it became more and more obvious that this analogy is strengthened if the phosphorus

fragment is coordinated to a transition metal. Therefore, the idea that 2*H*-azirene and 2*H*-azaphosphirene complex chemistry could be closely related seems to be obvious. Nevertheless, it should be pointed out again that the ring-opening behavior of all heteroazirenes (cf. Scheme 1) is apparently non-uniform (or unknown in the case of oxazirenes) and nothing is known about their ring-opening if these heterocycles would be coordinated to a transition metal complex fragment.

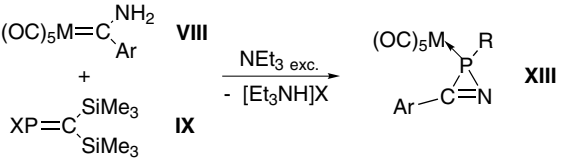
The aim of this chapter is to highlight important aspects concerning synthesis and physical properties of 2*H*-azaphosphirene complexes, especially, because their synthesis does not follow common coordination chemistry methodologies using, e. g., non-coordinated 2*H*-azaphosphirenes. It is interesting to learn that the knowledge about azaphosphirenes **V–VII** [19] is very scarce compared to azirenes **I, II** [5] and phosphirenes **III, IV** [18] (Scheme 2) and that derivatives of 1*H*-azaphosphirenes **V** [20] and 2*H*-azaphosphirenes **VI** [21] have been claimed exclusively as reactive intermediates.



Scheme 2. Three-membered unsaturated heterocycles **I – VII** containing nitrogen and/or phosphorus (R = ubiquitous organic substituents)

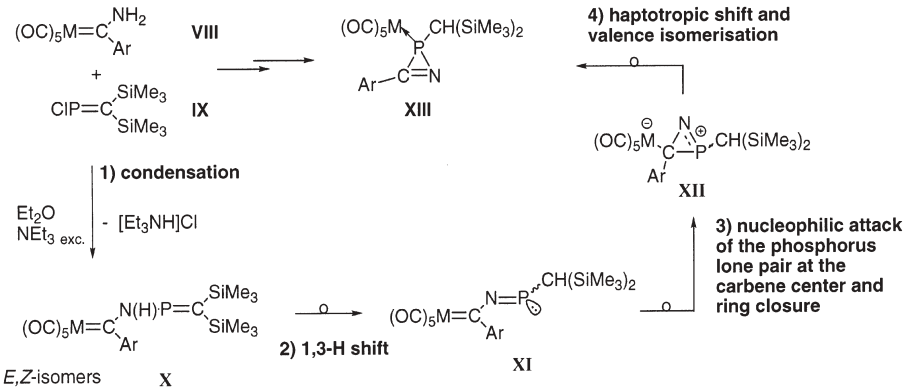
The first route to 2*H*-azaphosphirene complexes **XIII**, published by Streubel et al. in 1994 [22], used a triethylamine-induced condensation-rearrangement cascade starting from amino(aryl)carbene metal complexes **VIII** and [bis-(trimethylsilyl)methylene]halophosphanes **IX** (X = Cl, Br) (Scheme 3); the yields are generally good (50 – 85 %) [19, 23]. Experimental details and scope of this method as well as progress in this field were summarized quite recently [24].

With respect to the following Sections, it is worthwhile to look at the currently discussed mechanism of 2*H*-azaphosphirene complex formation (Scheme 4).



Scheme 3. First route to 2*H*-azaphosphirene complexes **XIII** [22]

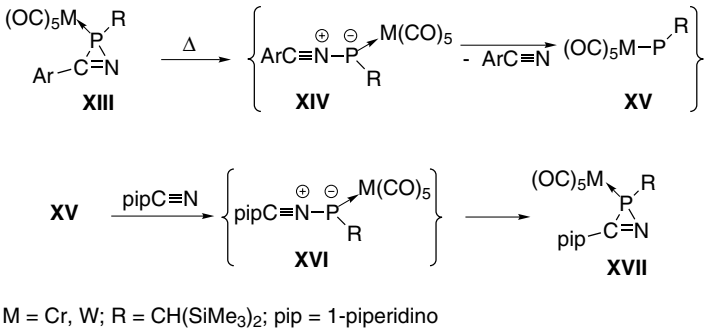
A four-step reaction course was proposed [24], comprising an initial base-induced condensation of **VIII** and **IX** (step **1**), thus leading to *E,Z*-isomers of intermediates **X** having an N-P bond. Then a 1,2-hydrogen shift (step **2**) leads to the formation of the 2-aza-1-phospha-4-metallabutadiene-type system **XI**, which could be trapped and/or observed by ^{31}P-NMR spectroscopy. An intramolecular nucleophilic attack of the phosphorus lone pair at the carbene center furnishes zwitterionic intermediates **XII** (step **3**), thus excluding a direct participation of the metal center in the ring formation. Subsequently, the intermediates **XII** undergo a combined haptotropic rearrangement and valence isomerization to give the 3-aryl-2*H*-azaphosphirene complexes **XIII** as final products (step **4**). A variation of this routes also employs metal carbene complexes **VIII** and organodichlorophosphanes (instead of **IX**) in methylene chloride as solvent and triethylamine as base. This route offers mainly access to 3-phenyl-2*H*-azaphosphirene tungsten complexes, which have various bulky substituents at phosphorus such as pentamethylcyclopentadienyl, triphenylmethyl, and 2,4,6-triisopropylphenyl [24].



Scheme 4. Proposed four-step reaction mechanism of 2*H*-azaphosphirene complex formation [24]

In 1998, Streubel et al. reported a novel access to 2*H*-azaphosphirene complexes using thermal ring cleavage of complexes **XIII** in toluene in the presence of 1-piperidinocarbonitrile, which finally furnished the 3-(1-piperidino)-2*H*-azaphosphirene complexes **XVII** [25]. Although it was originally proposed that the product formation occurred by a [2+1] cycloaddition reaction of the carbonitrile and the electrophilic terminal phosphanediyl complexes **XV**, it now seems to be clear that the reaction course is as depicted in Scheme 5 having the different nitrilium phosphanylid complexes **XIV** and **XVI** as highly reactive intermediates (see also Sect. 5.1).

The following bonding picture for 2*H*-azaphosphirene complexes can be drawn based on the NMR, IR, UV/vis, MS, and X-ray diffraction data [24]: The situation of this N,P-heterocyclic ligand should be described as a resonance hybrid of a three-membered ring system with a covalent bonding (**XIII**) and a



Scheme 5. Intramolecular valence isomerization of nitrilium phosphanylid complexes [25]

π-electron donor-acceptor complex of arylnitrile and the phosphorus atom of the terminal phosphanediyl complex unit (**XIII′**) (Fig. 1) [26].

Ab initio calculations on 2*H*-azaphosphirenes and their pentacarbonylmetal complexes lent further support to this interpretation by showing that the main effect of the metal-coordination onto the ring parameters is a shortening and assimilation of the P,C and P,N bonds (Fig. 2); the endocyclic angles were determined to C-P-N 39.1, P-N-C 67.4, and N-C-P 71.5 [°] (B3LYP/6 – 31 g(d) + ZPE) [27].

Fig. 1. Alternative bonding description of 2*H*-azaphosphirene complexes **XIII** and **XIII′** [26].

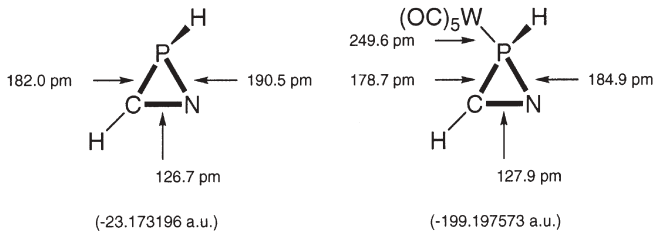


Fig. 2. Calculated geometries of 2*H*-azaphosphirene and their pentacarbonyltungsten complex [27]

4
Ab Initio Calculations of Nitrilium Phosphanylid Complexes

Ab initio calculations on nitrilium phosphanylid derivatives and their corresponding *P*-pentacarbonyl transition metal complexes were carried out at a density functional level utilizing effective core potential basis sets (B3LYP/6 – 31 g(d) + ZPE corrections) [27, 28]. The resulting singlet ground state geome-

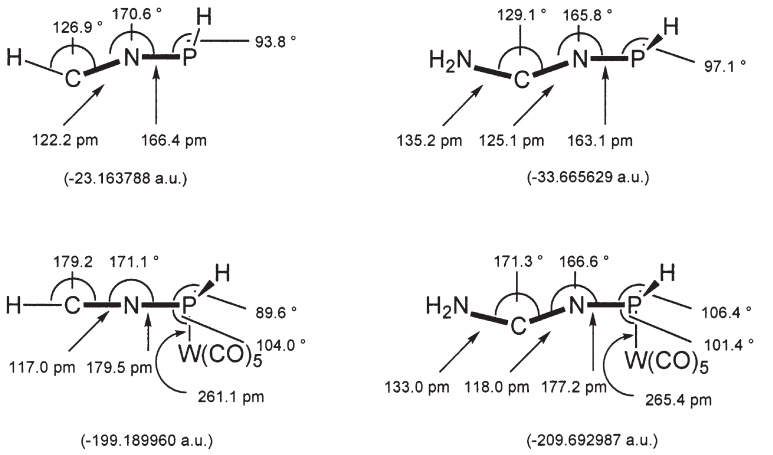


Fig. 3. Singlet ground state geometries of nitrilium phosphanylid derivatives and complexes

tries are depicted in Fig. 3, exclusively for the tungsten complexes. The P,N distances resulting are almost independent on the chosen metal.

The parent compound HCNPH reveals an HCNP unit with an approximately linear geometry. The bonding parameters, i. e., the C,N and N,P distances indicate a combination of a C-N triple bond with an adjacent N-P single bond. The bonding situation is only slightly changed in the corresponding tungsten complex, whereby the N-P distance is significantly lengthened from 170.8 (uncoordinated) to 176.5 pm (coordinated species). The latter change can be rationalized by assuming two competing donor-type contributions into the same vacant orbital at the phosphorus atom of the phosphanediyl complex moiety, i.e., backbonding from the transition metal center and N-donor bonding of the carbonitrile nitrogen [27]. In comparison with the *C*-amino-substituted derivatives the geometry experiences drastic changes [28]. The coordinated and uncoordinated species adopt strongly bent geometries at the carbons atom of the C,N,P-ylid moieties and short C-N bonds to the amino nitrogen atoms. Furthermore, the C,N,P moieties display lengthened C-N bonds and shortened N-P bonds, which altogether point to soft geometries of nitrilium phosphanylids and their complexes, easily to modify by the substitution pattern at the carbon and the phosphorus atoms. The energy balances for the P-complexation of HCNPH and H_2NCNPH by the pentacarbonyltungsten complex fragment turn out to be exothermic with –31.2 and –39.8 kcal/mol, respectively. The energy balances for the alternative reactions HCN (H_2NCN) + $HPW(CO)_5$, the donor-adduct formations at phosphorus (cf. Sect. 5), are also exothermic and result to –11.7 (for HCN) and to –20.3 (H_2NCN) kcal/mol. Especially the latter value clearly demonstrates an enhanced tendency of the aminocarbonitrile to form a donor-adduct – a result that has important synthetic consequences as shown in the next section. There are two more aspects that deserve mention: The first is the possibility of a bis-donor-adduct formation of two carbonitriles and $HPW(CO)_5$ with a trigonal bipyramidal geometry, for which no energy minimum was found [27].

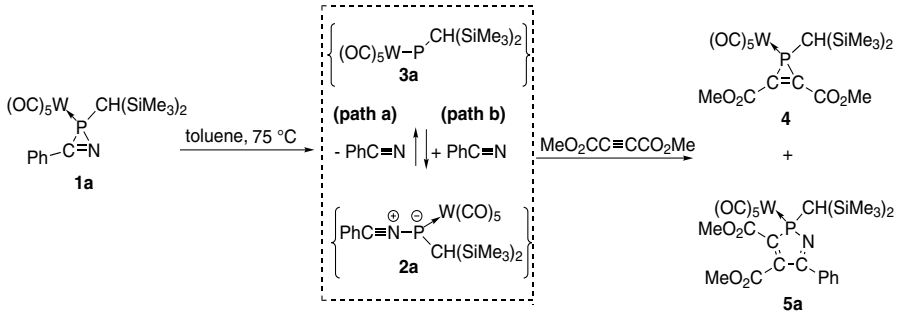
The second aspect is the unexpected result for the electron density distribution in $HCNP(H)W(CO)_5$ and in which both frontier orbitals are mainly concentrated on the metal center [28].

5
Nitrilium Phosphanylid Complexes in Phosphorus Chemistry

5.1
General Preparative Aspects of Formation and Trapping of Transient Nitrilium Phosphanylid Complexes

As already pointed out in Sect. 3 (cf. Scheme 5), thermally induced ring-opening of the 2*H*-azaphosphirene complex **1a** in toluene at 75 °C furnished the nitrilium phosphanylid complex **2a** as transient and highly reactive species. Reaction monitoring (^{31}P-NMR spectroscopy) provided no evidence for **2a**, but a trapping reaction with dimethyl acetylenedicarboxylate (DMAD) was successful, thus forming the 2*H*-1,2-azaphosphole complex **5a** as the minor product [29]. For the formation of the main product, the 1*H*-phosphirene complex **4**, a [2+1] cycloaddition of DMAD with the terminal phosphanediyl complex **3a**, transiently formed by cleavage of the N,P-bond in complex **2a,** was suggested (Scheme 6; hypothetical pathways are enclosed with dotted lines) [30]; benzonitrile was detected by IR spectroscopy. Investigations on the reaction mechanism showed that adding benzonitrile to the reaction mixture significantly increased the amount of the 2*H*-1,2-azaphosphole complex **5a** [29]. Therefore, it was concluded that another reactive intermediate must be involved, which can be generated through reaction of the terminal phosphanediyl complex **3a** with benzonitrile in a terminal [1+1] addition (path b in Scheme 6), thus giving the nitrilium phosphanylid complex **2a** [29].

The same study also showed that adding *para*-substituted benzonitrile derivatives furnished the corresponding 2*H*-1,2-azaphosphole complexes, whereby their amounts significantly depended on the electronic effects of the *para*-substituent whereby electron-donating groups such as methoxy favored and electron-withdrawing groups such as trifluoromethyl disfavored the formation of the 2*H*-1,2-azaphosphole complexes [29]. These observations created the idea of



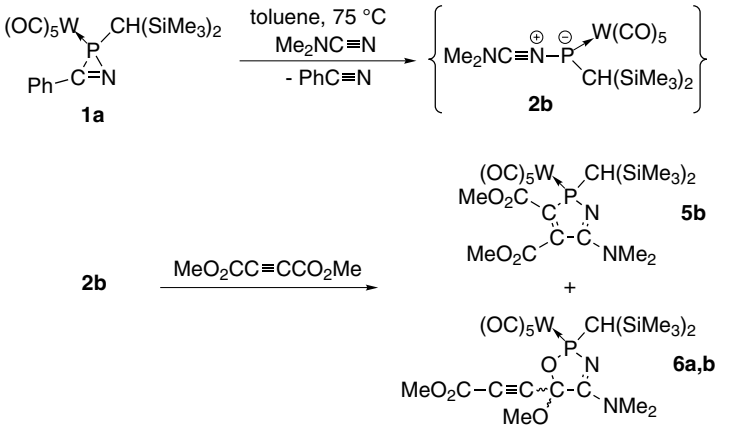
Scheme 6. Formation of nitrilium phosphanylid complexes by terminal [1+1] addition of a terminal phosphanediyl complex to benzonitrile [29]

achieving transylidation reactions of nitrilium phosphanylid complexes by adding differently substituted carbonitriles with better π-donor substituents to the starting materials [31]. Although, in the area of nitrile sulfides, a related observation was made earlier, it had no important synthetic impact [32]. Quite the contrary happened in nitrilium phosphanylid complex chemistry. After having noticed this finding, so-called three-component reactions, employing a 2*H*-azaphosphirene complex, a carbonitrile, and a trapping reagent in 1:2:4 ratio were developed rapidly (in general; for exceptions see following sections). It is very remarkable that this methodology could be also adapted to photochemical reactions [33] and, furthermore, extended by using 7-phosphanorbornadiene complexes under thermal conditions [34] (see Sect. 5.2). The latter development is also remarkable because no reactions of electrophilic terminal phosphanediyl complexes [18b, 27, 35 – 41] had been reported, previously.

5.2
Synthesis of N,P-Heterocyclic Ligands with the P-N=C Structural Moiety via Trapping of Transient Nitrilium Phosphanylid Complexes

5.2.1
2H-1,2-Azaphosphole Complexes

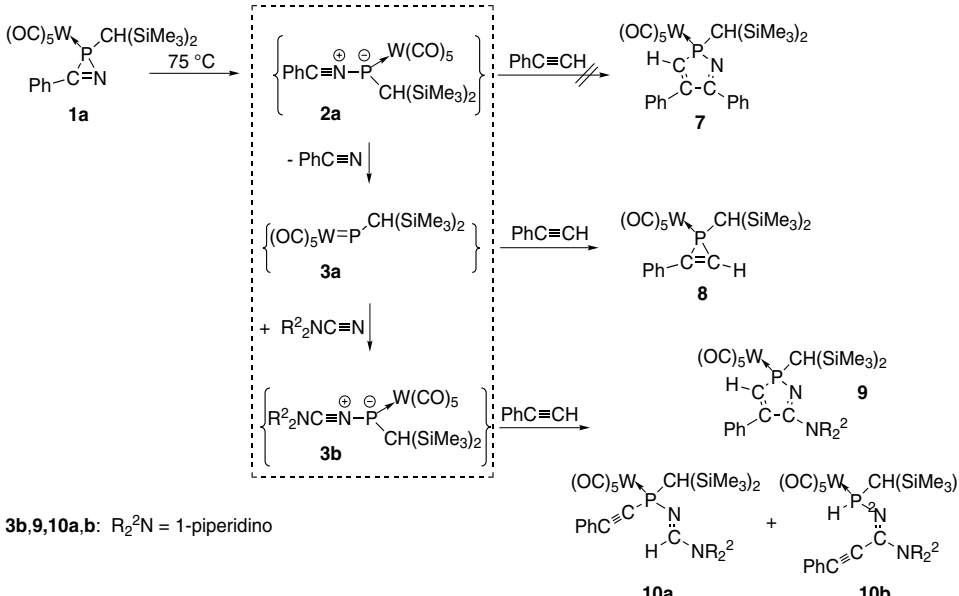
As shortly described in the preceding section, the synthesis of 2*H*-1,2-azaphosphole complexes relies (mainly) on three-component reactions. A good illustration of this methodology, which was first described in 1998 [42], is given by the reaction of 2*H*-azaphosphirene complex **1a** with dimethylcyanamide and DMAD in toluene, which led to the 2*H*-1,2-azaphosphole complex **5b** and the diastereomeric Δ^3-1,3,2-oxazaphospholene complexes **6a,b** (1:1:1 ratio) (Scheme 7). Formation of either the 1*H*-phosphirene complex **4** or the 2*H*-1,2-azaphosphole complex **5a** was not observed [42]. This competing reaction path-



Scheme 7. Example of a three-component reaction using a 2*H*-azaphosphirene complex, dimethylcyanamide and DMAD in toluene [42]

way was exclusively observed in the case of *C*-diorganylamino-substituted nitrilium phosphanylid complexes.

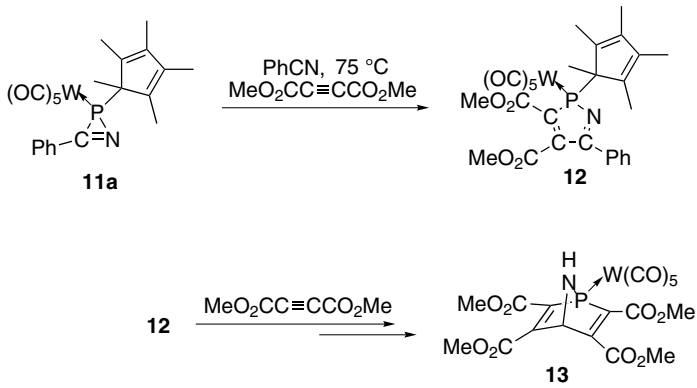
Detailed studies were carried out on reactions of 2*H*-azaphosphirene complexes with respect to the influence of the metal atom, the nitrile substituent, and the alkyne substituents on the product formation and the regiochemistry, whereby mostly complex **1a** was employed [43]. One of the very interesting results with regard to its synthetic usefulness was that even *C*-methyl-substituted nitrilium phosphanylid complexes can be generated and used in 2*H*-1,2-azaphosphole complex synthesis [43]. More recent studies showed that hetarene-substituted carbonitriles such as 2-furanyl, 2-thienyl and 2-(1,5-dimethylpyrryl) derivatives [44] or carbonitriles with P,C- and P,N-ylid substituents [45] can be also employed in generating the corresponding transient nitrilium phosphanylid complexes via 1,1-addition with complex **3a**; in the latter case the three components were used in a 1:1:1 ratio! The *C*-ylid-substituted nitrilium phosphanylid complexes deserve mention because of their high regioselectivities – they yielded exclusively 4-substituted 2*H*-1,2-azaphosphole complexes in reactions with ethyl acetylenedicarboxylate. In other cases, both regioisomers were formed with this trapping reagent, whereby 4-substituted derivatives were always the major isomers [43, 44]. A special outcome was observed when phenylacetylene was employed as solvent and as trapping reagent – in this case a product mixture of complexes **8**, **9**, and **10a, b** (**10a, b** in a 1:1 ratio) was obtained (Scheme 8) [43]; formation of the complex **7** was not observed. Interestingly, complexes **10a, b** seem to be formed by a stereospecific 1,3-addition, which was supported by X-ray crystallography of **10a** [46]. It should be noted that, so far and apart from the reaction shown in Scheme 8, reactions of transient nitrilium



Scheme 8. Thermolysis of complex **1a** in phenylacetylene [43]

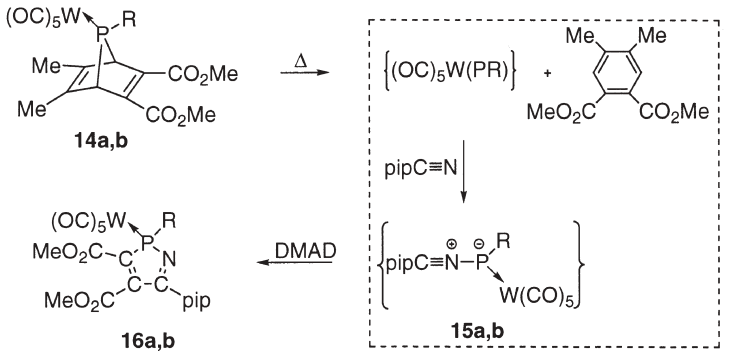
phosphanylid complexes with alkyne derivatives strongly depended on the electronic situation of the latter; exclusively alkynes with low-lying LUMOs showed reactions. Therefore, the reactions were classified as [3 + 2] cycloaddition reactions of 1,3-dipoles, whereby it was concluded that they are directed by a HOMO-dipole LUMO-dipolarophile interaction [43]. Looking at the new theoretical results (cf. Sect. 4) this interpretation of the participating frontier orbitals of the reactants has to be modified to interactions of the HOMO-1 orbitals of the nitrilium phosphanylid complexes with the LUMOs of the trapping reagents.

So far, only very few reactions were reported on the use of 2*H*-azaphosphirene complex **11a** in nitrilium phosphanylid complex chemistry, mainly because of the tendency of *P*-C_5Me_5-substituted derivatives to undergo side reactions [47]. Nevertheless, it seems worthwhile to look at the reaction of **11a** with DMAD, which finally led to the 1-aza-7-phosphanorbornadiene complex **13** via 2*H*-1,2-azaphosphole complex **12** as reactive intermediate (Scheme 9) [48]. Later on, complex **12** was isolated and characterized using a different stoichiometry [49].



Scheme 9. Synthesis of 1-aza-7-phosphanorbornadiene complex **13** via 2*H*-1,2-azaphosphole complex **12** [48]

A real landmark in the generation of transient nitrilium phosphanylid complexes was the discovery that 7-phosphanorbornadiene complexes could be also employed, e. g., the complexes **14a**, **b** in the synthesis of 2*H*-1,2-azaphosphole complexes **16a**, **b** (Scheme 10), thus offering now the possibility to study the reactivity of sterically less encumbered 1,3-dipole species such as **15a**, **b** [34]. Note worthy is the absence of any by-products such as Δ^3-1,3,2-oxazaphospholene complexes (cf. Scheme 7) in these reactions. Even more fascinating are perspectives to use 7-phosphanorbornadiene complexes with *P*-functional substituents in 2*H*-1,2-azaphosphole complex chemistry.

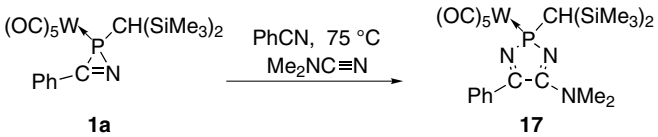


14a-16a: R = Me; **14b-16b**: R = Ph; pip = 1-piperidino

Scheme 10. Selective formation of 2*H*-1,2-azaphosphole complexes using 7-phosphanorbornadiene complexes [34]

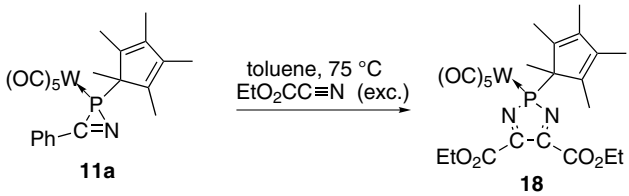
5.2.2
2H-1,3,2-Diazaphosphole Complexes

The first access to 2*H*-1,3,2-diazaphosphole complexes was reported in 1997 by Streubel et al. via reaction of 2*H*-azaphosphirene complex **1a** and dimethylcyanamide in benzonitrile at 75 °C, which led selectively to the 2*H*-1,3,2-diazaphosphole complex **17** (Scheme 11) [50].



Scheme 11. Example of a 2*H*-1,3,2-diazaphosphole complex synthesis via a three-component reaction [50]

Subsequent investigations showed that three-component reaction conditions can be employed in a wide variety of reactions of complex **1a** (and also the chromium and molybdenum complexes **1b** and **1c**, respectively) if the second carbonitrile component was used in excess or, even better, as solvent [25]. This method also provided access to ester-functionalized 2*H*-1,3,2-diazaphosphole complexes such as **18** when complex **11a** was employed (Scheme 12) [51].

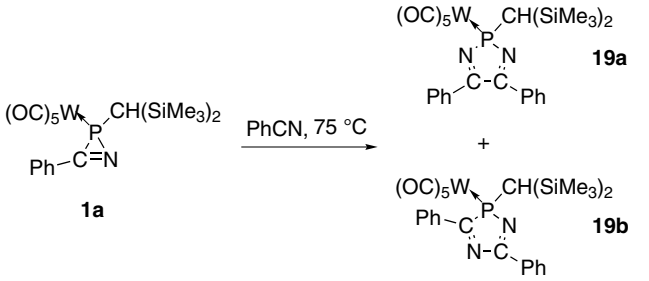


Scheme 12. Synthesis of 5,5′-diester-functionalized 2*H*-1,3,2-diazaphosphole complex **18** [51]

Meanwhile, 7-phosphanorbornadiene complexes can be also employed in the synthesis of 2*H*-1,3,2-diazaphosphole complexes although, in such cases competing reactions were observed, leading also to 2*H*-1,4,2-diazaphosphole complexes [52].

5.2.3
2H-1,4,2-Diazaphosphole Complexes

2*H*-1,4,2-Diazaphosphole complexes were first discovered in thermolytic reactions of 2*H*-azaphosphirene complex **1a** in benzonitrile, whereby both regioisomers, complexes **19a** and **19b**, were formed, the latter as major isomer (Scheme 13) [25].

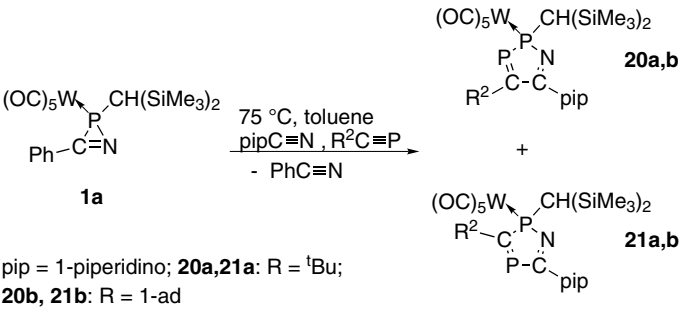


Scheme 13. Example of a 2*H*-1,4,2-diazaphosphole complex synthesis [25]

Apart from photochemical reactions of 2*H*-azaphosphirene complex **1a** with ethyl cyanoformate in *n*-pentane/benzonitrile mixtures at low temperatures, which led selectively to a 2-ester-functionalized 2*H*-1,4,2-diazaphosphole complex [33], the most convenient and versatile routes to 2*H*-1,4,2-diazaphosphole complexes are the TCNE- [53] or ferrocenium salt-catalyzed [54] bond-selective ring-expansion reactions of 2*H*-azaphosphirene complexes at rt.

5.2.4
2H-1,2,3-Azadiphosphole Complexes

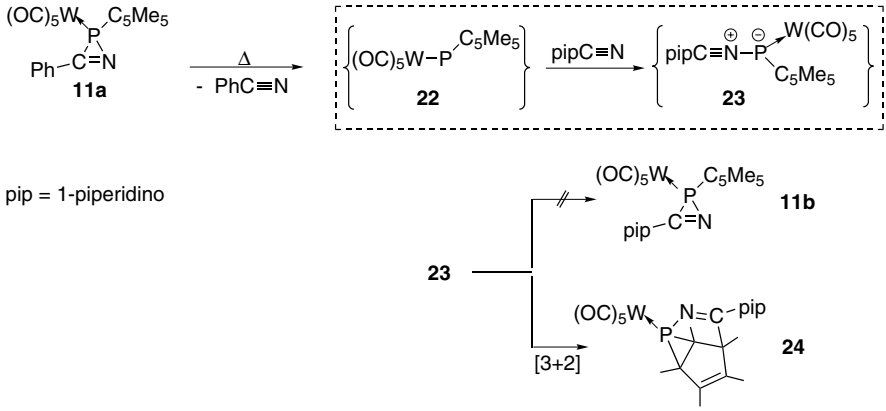
Very recently, the first access to this five-membered unsaturated heterocyclic ring system was provided by thermal reactions of 2*H*-azaphosphirene complex **1a** with 1-piperidinocarbonitrile and *tert*-butyl- or 1-adamantylmethylidynephosphane in toluene, thus yielding the 2*H*-1,2,3-azadiphosphole complexes **20a,b** [55] (Scheme 14). The regioisomeric 2*H*-1,2,4-azadiphosphole complexes **21a,b** were formed also (according to ^{31}P-NMR spectroscopy), but they could not be isolated by column chromatography.



Scheme 14. Synthesis of the first 2*H*-1,2,3-azadiphosphole complexes using transient nitrilium phosphanylid complexes [55]

5.2.5
Δ^4-*1,2-Azaphospholene Complexes*

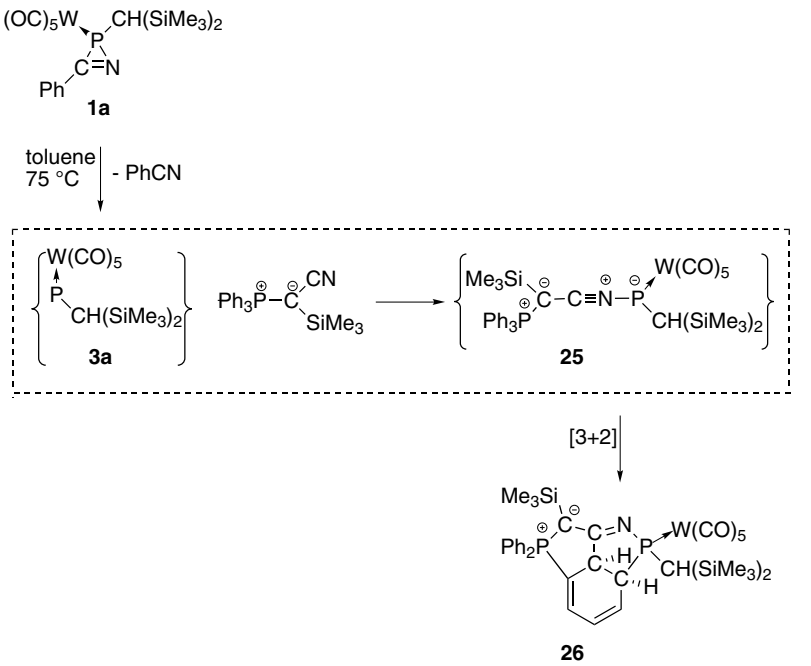
In contrast to the reaction of the terminal phosphanediyl complex **3a** with 1-piperidinocarbonitrile (cf. Scheme 7), the complex $[(OC)_5WPC_5Me_5]$ **22**, thermally generated from complex **11a**, did not furnish the 3-(1-piperidino)-2*H*-azaphosphirene complex **11b** – instead, the polycyclic C,P,N-carbon cage compound **24** was obtained via *intramolecular* [3+2] cycloaddition of **23** (Scheme 15) [51].



Scheme 15. Intramolecular [3+2] cycloaddition reaction of a nitrilium phosphanylid complex to a C-C double-bond [51]

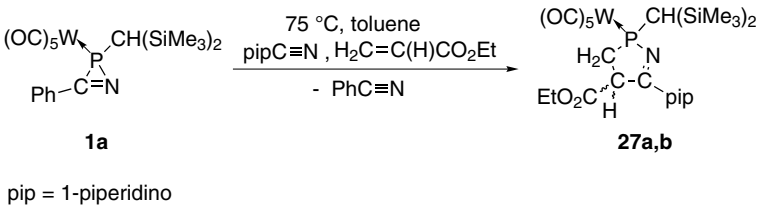
Very recently, another fascinating example of such a reaction of a transient nitrilium phosphanylid complex was found – the intramolecular addition in **25** to a phenyl group of the Wittig-ylid substituent to furnish complex **26** [56] (Scheme 16).

Apart from such *intramolecular* reactions, exclusively electronically activated alkene derivatives such as TCNE [53], maleic anhydride, *E*- and *Z*-ethylenedi-



Scheme 16. Intramolecular [3 + 2] cycloaddition reaction of a nitrilium phosphanylid complex to a phenyl group [56]

nitrile or acryl ethylcarboxylate [46] underwent *intermolecular* [3 + 2] cycloaddition reactions with thermally generated nitrilium phosphanylid complexes to furnish Δ^4-1,2-azaphospholene complexes. For example, complex **1a**, 1-piperidinocarbonitrile, and ethenyl ethylcarboxylate yielded regio selectively the diastereomeric complexes **27a, b** (dr 1.5:1) (Scheme 17) [46]; the constitution of one product was confirmed by X-ray crystallography. With respect to mechanistic considerations, it is important to note that the five-membered ring formation proceeded with retention of configuration at the carbon centers of the employed alkenes, although some products seemed to undergo subsequent epimerization of these carbon centers [46].

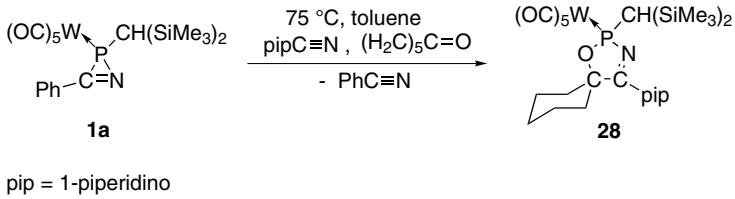


pip = 1-piperidino

Scheme 17. Intermolecular [3 + 2] cycloaddition reaction of a nitrilium phosphanylid complex to a C-C double-bond system [46]

5.2.6
Δ^3-*1,3,2-Oxazaphospholene Complexes*

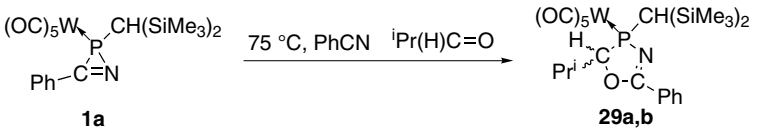
The thermal reaction of 2*H*-azaphosphirene complex **1a** with 1-piperidinocarbonitrile and carbonyl derivatives led regioselectively to Δ^3-1,3,2-oxazaphospholene complexes, e. g., cyclohexanone furnished complex **28** (Scheme 18) [57]. Under the same reaction conditions with phenyl isocyanate selective formation of a Δ^3-1,3,2-oxazaphospholene complex having an *exo*-imino function was observed [58].



Scheme 18. Regioselective formation of Δ^3-1,3,2-oxazaphospholene complex **28** [57]

5.2.7
Δ^2-*1,3,4-Oxazaphospholene Complexes*

More surprising was the observation that the regiochemistry of such reactions seemed to be largely determined by the *C*-substituent of the transiently formed nitrilium phosphanylid complexes. For example, thermal reaction of 2*H*-azaphosphirene complex **1a** with carbonyl derivatives led preferentially to Δ^2-1,3,4-oxazaphospholene complexes, e. g., with isopropyl aldehyde the diastereomeric complexes **29a,b** were obtained regioselectively, whereby and surprisingly the isomer with the isopropyl group and the pentacarbonyltungsten group on the same side of the five-membered ring was largely preferred (Scheme 19) [46].



Scheme 19. Regioselective formation of Δ^2-1,3,4-oxazaphospholene complexes **29a,b** [46]

6
Perspectives

So far, [3 + 2] cycloaddition reactions of transiently formed nitrilium phosphanylid complexes were studied in some depth with regard to mechanistic aspects and synthetic applicability by using the most important π-systems of organic chemistry as trapping reagents. But there are still a lot of other homo- and heterodinuclear π-systems and cumulenes from organic and inorganic

chemistry that remain to be investigated. It is also very fascinating that surprises are still common in this rapidly developing area. Like the reaction shown in Scheme 16 or the very recent finding that a bulky-substituted *P*-chloromethylenephosphane preferentially reacted with *C*-1-piperidino-substitued nitrilium phosphanylid complexes via 1,3-addition of the P-Cl function to the 1,3-dipole system, instead of showing [3 + 2] cycloaddition reactions [59]. It is also very remarkable that three-component reactions of complex **1a**, 1-piperidinocarbonitrile, and a diorganoaminomethylidenephosphane did not react to give the expected azadiphosphole complexes, instead 1*H*-diphosphirene and 1,3,4-triphosphole complexes were formed [60]. In contrast to theoretical predictions [27], this not only provides evidence that methylidenephosphanes can form donor-adducts with electrophilic terminal phosphanediyl complexes but also demonstrates that such adducts can be favored over those of carbonitriles and electrophilic terminal phosphanediyl complexes. Apart from that, the great perspectives and chances of *transient* nitrilium phosphanylid complexes seem to be in the area of *C*-heteroatom-fragment-substituted derivatives.

Finally, there remains the challenge to synthesize a stable nitrilium phosphanylid complex. With regard to the latter, two very recent and exciting results should be mentioned. Reactions of a dinuclear μ^2-phosphanediyltungsten complex with benzonitrile and acetonitrile were reported, in which related donor-adducts, as discussed herein, might have been formed in the first reaction step [61]. Furthermore, syntheses of the first cationic electrophilic terminal phosphanediyl complexes were reported and their reactivity with nucleophiles such as acetonitrile announced [62], but no details were provided on reaction courses and/or products.

Acknowledgements. I am very grateful to all of my coworkers, who helped me in exploring and developing the chemistry of nitrilium phosphanylid complexes. I am also very grateful to Prof. Dr. W.-W. du Mont, the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* for financial support.

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What to do with Phosphorus in Dendrimer Chemistry

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This chapter points out significant advances in the field of phosphorus-containing dendrimers. First attention is focused on recent methods of synthesis of dendrons, dendrimers, and the corresponding linear and hyperbranched polymers. The emphases are associated with the fascinating construction of a variety of surface-block dendrimers, layer-block dendrimers, layered surface-block dendrimers, and dendrons grown within a dendrimer, all these syntheses being possible because of the easy formation of polyfunctionalized monomers and dendrons. Reports dealing with the characterization of these macromolecules using several techniques are considered as well as those describing physical properties of phosphorus-containing dendrimers. Last but not least, the first really promising applications of these giant molecules in different fields – biology, materials science, catalysis – are reviewed.

Keywords. Phosphorus, Dendrimers, Multidendritic macromolecules, Applications in biology and materials science, Catalysis

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Abbreviations

AFM	atomic force microscopy
BET	Brunauer, Emmet and Teller's method
DABCO	1,4-diazabicyclo[2.2.2]octane
DDS	dynamic dielectric spectroscopy
FTIR	Fourier-transform infrared
HSA	human serum albumin
MALDI-TOFMS	matrix-assisted laser desorption ionization time-of-flight mass spectrometry
PEI	poly(ethyleneimine)
PSS	poly(styrenesulfonic acid)
SAXRD	small angle X-ray diffraction
SEC	size exclusion chromatography
SEM	scanning electron microscopy
TEM	transmission electron microscopy
TGA	thermogravimetric analysis
TRIS	tris(hydroxymethyl)aminomethane
TSC	thermostimulated currents
TTF	tetrathiafulvalene
WAXRD	wide angle X-ray diffraction
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction

1 Introduction

Undoubtedly the chemistry of dendrimers represents nowadays a major field of research in molecular, macromolecular, and supramolecular chemistry. The extraordinary diversity of the molecules which can be prepared "à façon", the possibility to tailor exactly a macromolecule for a given application, open some perspectives in "classical" chemistry but also in neighboring sciences such as polymer and material sciences, biology, physics, nanotechnologies, etc.

This explains why more and more research teams are involved in this field. More than 4000 publications concerned with this topic have appeared during the last fifteen years but it can be noted that during the last two years (2000 and 2001) around 1000 papers related to this science were published every year!

Most of these works are concerned with organic dendrimers; a few are devoted to main group element-containing dendrimers. Among the latter silicon and phosphorus-containing dendrimers occupied a place of choice because of the rich diversity of their chemistry.

Historically, the first synthesis of an organic dendrimer was reported in 1978 by Vögtle and co-workers [1] while in a pioneering work Rengan and Engel [2] reported in 1990 the preparation of what they called cascade molecules in which the initiator core and subsequent branch-points are quaternary phosphonium ion sites. Later on the first neutral phosphorus-containing dendrimers possessing either P-N and P-O bonds [3] or P-C bonds [4] were described in 1994. Since that time, synthesis and chemistry of these macromolecules have been blossoming and were reviewed in 1998 [5] and 1999 [6]. Therefore this review will be limited to only the very recent developments of phosphorus dendrimers chemistry. Our focus will be on the synthesis of dendrimers but also of multidendritic macromolecules as well as that of linear and hyperbranched polymers constituted with the same repeating units. Physical properties will be briefly presented while emphasis will be put on the first applications of phosphorus-containing dendrimers.

The synthesis of dendrimers having phosphorus groups located exclusively on the surface will not be discussed here. We will limit our considerations to dendrimers constituted by phosphorus building-blocks at each generation.

2 Synthesis

2.1 Dendrimers

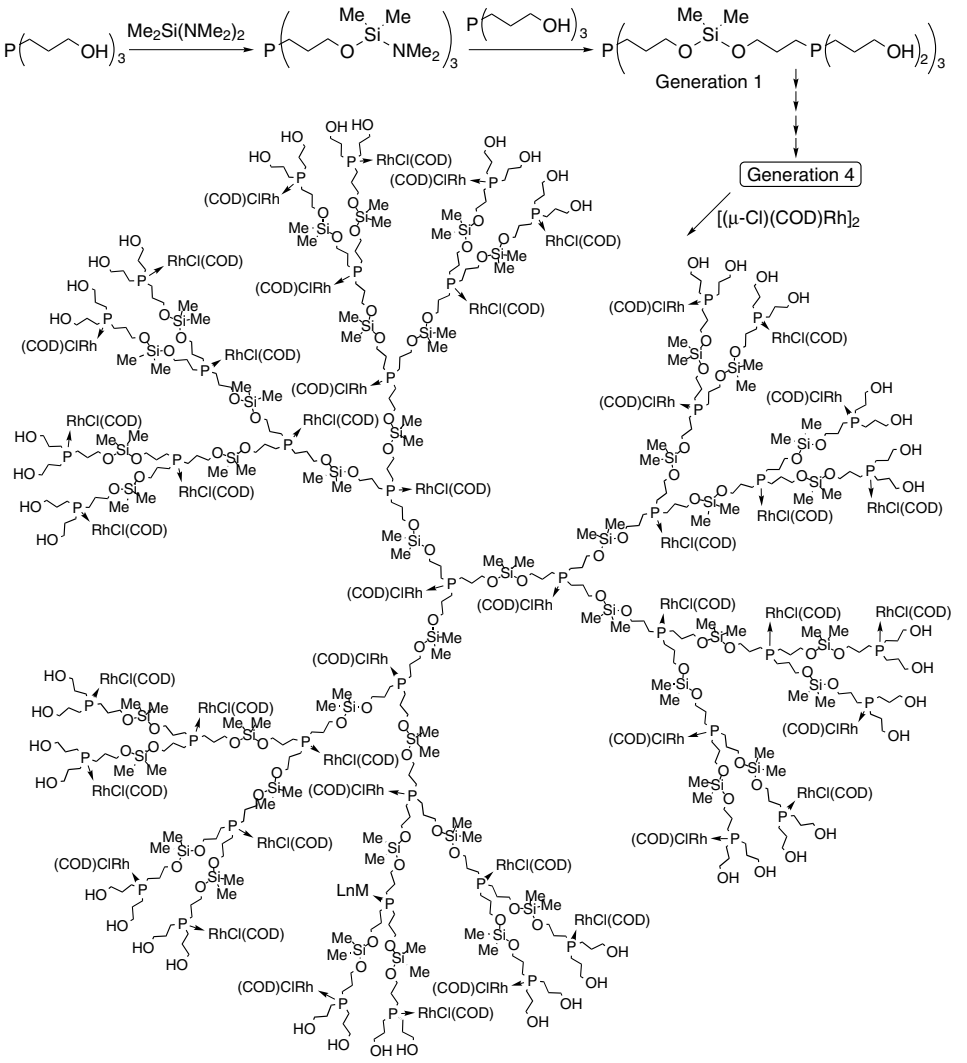
A new divergent synthesis of tribranched phosphorus-containing dendrimers and their metal-containing counterparts was recently proposed [7]. It is based on the acid-base hydrolysis of aminosilanes with derivatives containing OH groups. The preparation involved the reaction of a bifunctionalized silane such

as $(CH_3)_2Si[N(CH_3)_2]_2$ with tri(hydroxypropyl)phosphine $P[(CH_2)_3OH)]_3$ yielding a silylamine adduct in which a dimethylamino group is still linked to each silicon atom. Further addition of three equivalents of $P[(CH_2)_3OH)]_3$ led to the formation of the dendrimer of generation 1 bearing six terminal OH groups. Surprisingly, the expected cross-linking reactions involving OH and NMe_2 groups do not seem to occur here. Reiteration of this sequence of reactions allowed the authors to prepare dendrimers of generations 2, 3 and 4, the last one being constituted with 46 phosphane groups (Scheme 1). These new "silicon, phosphorus"-containing dendrimers were characterized by usual spectroscopic techniques including MALDI-TOF mass spectrometry. This method appears attractive since it offers the possibility to bind a variety of transition metals to the internal and external phosphane groups. This was achieved with Rh(I) complexes using bridge-splitting reactions of the rhodium(I) dimer $[(\mu\text{-Cl})(1,5\text{-}C_8H_{12})Rh]_2$. The organometallic dendrimers can also be prepared directly starting from the complex $Rh(1,5\text{-}C_8H_{12})(Cl)P[(CH_2)_3OH)]_3$ which is reacted further with $(CH_3)_2Si[N(CH_3)_2]_2$. The metalladendrimer of generation 4 with Rh units at the core, within the cascade structure, and on the surface was thus prepared (Scheme 1). It is interesting to note that the rhodium-phosphorus groups from each generation have a chemical shift distinct in ^{31}P-NMR. With the growth of each generation, a new Rh-P doublet emerges, suggesting dendrimer rather than polymer growth.

Rh(I) bound metalladendrimers catalyze the hydrogenation of decene with activities similar to the monomeric adduct, and the catalytic dendrimer can be easily separated and recycled. Such a behavior was also pointed out with other phosphorus-containing dendrimers complexes (Pd and Ru complexes) [cf. Sect. 5.3].

Another divergent synthesis of dendritic polythionophosphates has been accomplished via phosphitylation of propanediol derivatives. Commercially available diethyl phosphoramidous dichloride was reacted with 1,3-propanediol monoacetate (2 equiv.) in the presence of triethylamine (3 equiv.) in anhydrous ether to give the di(3-acetoxypropoxy)-*N,N*-diethylaminophosphine **1** in 75% yield [8]. Such a phosphitylation reagent was then reacted with the triol $(S)P[O(CH_2)_3OH]_3$ in the presence of tetrazole, giving rise to the dendrimer of generation 1 bearing six acetate units on the periphery (Scheme 2). Addition of elemental sulfur afforded the corresponding thiophosphate species. Cleavage of the acetate end groups (large excess of 30 % NH_3/MeOH, 24 h, rt) gave dendritic polyols; reiteration of this sequence of three reactions permits the preparation of dendrimers up to generation 5. In contrast to what it was already observed, ^{31}P-NMR was a useful tool for the characterization of the dendritic compounds only up to the second generation. For the larger dendrimers, the coincidence of chemical shifts of the signals from all the phosphorus atoms present in the molecule was observed.

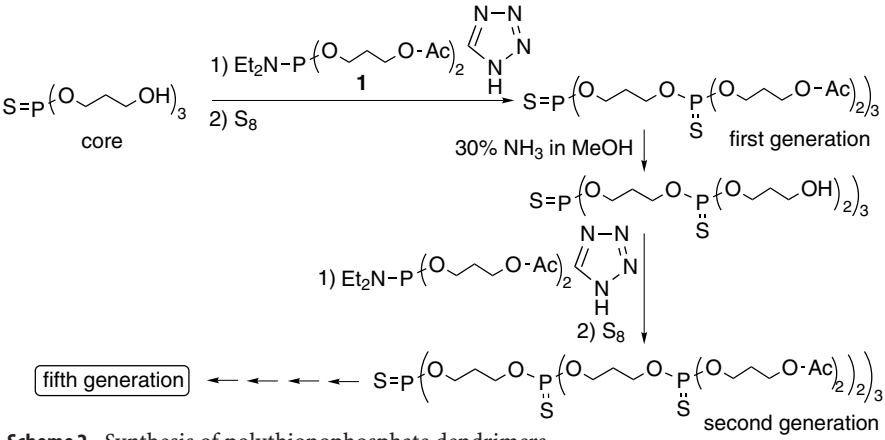
The same strategy was applied to prepare the corresponding P = Se dendrimers [9]. Treatment of the 3rd generation dendrimer incorporating in its backbone 22 P = Se units with *tert*-butylperoxytrimethylsilane resulted in regioselective oxygenation of phosphorus atoms at peripheral branching and extrusion of red selenium. The total conversion of the P = Se units into the cor-



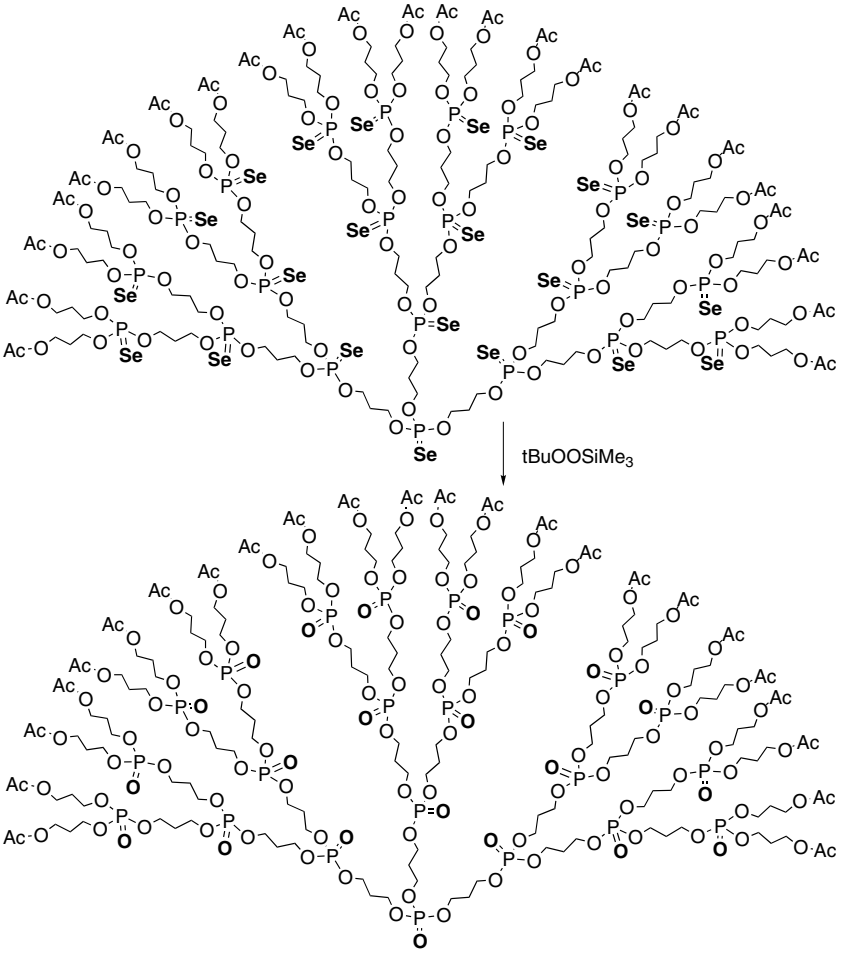
Scheme 1. Synthesis of "silicon, phosphorus"-containing dendrimers

responding P = O groups took place in three days (rt, large excess of the organic peroxide (Scheme 3).

These two new syntheses of phosphorus-containing dendrimers as well as all the previous preparations of dendritic phosphorus macromolecules [2 – 12] involve the reiteration of a sequence of two or even three reactions. Therefore, those methods are more or less tedious due to the large number of steps needed to grow these dendrimers. Consequently there is a need to find faster methods which allow a significant decrease of the number of reactions involved in the process. A method called "orthogonal coupling strategy" [13] consisting in the



Scheme 2. Synthesis of polythionophosphate dendrimers

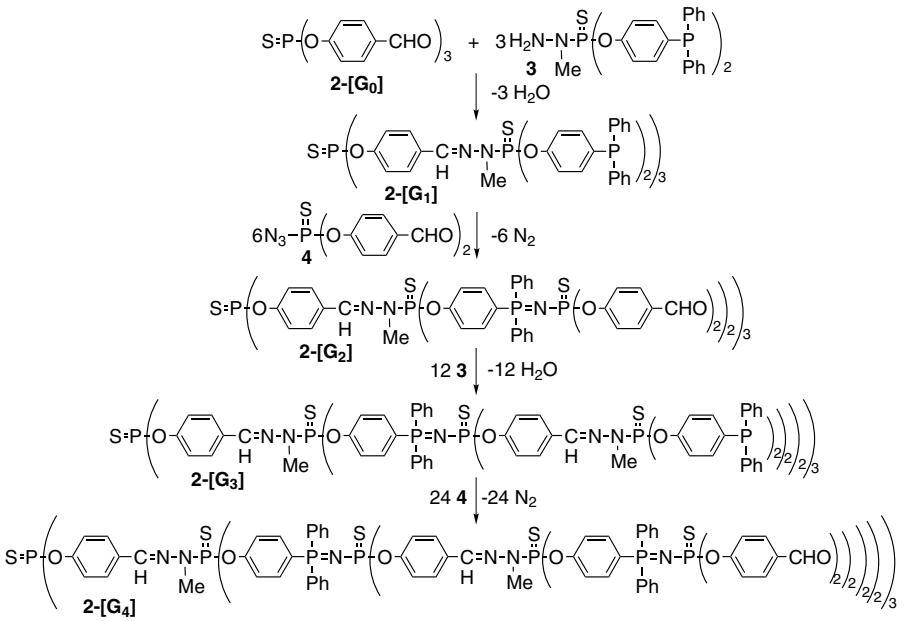


Scheme 3. Conversion of a polyselenophosphate dendrimer in polyphosphate

use of two types of AB_2 units which contain two pairs of complementary coupling functionalities was proposed for the synthesis of purely organic dendrimers. This method implies a set of different and independent protecting groups and generates by-products since one of the two functions (A or B) needs to be activated using another reagent. This method was, however, useful for the convergent synthesis of organic dendrons. The challenge which consists of the preparation and the use of alternatively two pairs of complementary functions able to react spontaneously without any activating agent was never raised till our recent efforts in that sense.

We designated two types of AB_2 monomers, **3**, **4**, one with hydrazine and phosphane functions, the other one with aldehyde and azide functions (Scheme 4). To avoid the reaction between **3**, and **4** to take place – the resulting product would be in that case an hyperbranched polymer – the monomer **3** (3 equiv.) was reacted first with $S=P(OC_6H_4CHO)_3$ **2-[G$_0$]**. Then, the resulting dendrimer of generation 1 with six terminal diphenylphosphane groups **2-[G$_1$]** was heated with 6 equiv. of the azide **4**: a Staudinger reaction occurred and the dendrimer of generation 2 was formed in quantitative yield. Indeed a dendrimer of generation 4 was produced in only fours steps from $S=P(OC_6H_4CHO)_3$ (Scheme 4)! The dendritic macromolecules obtained are layered dendrimers made of O-C_6H_4-Z-P(S) linkages, the difference between two layers being the nature of Z, CH=N-N(Me) or $Ph_2P=N$ groups [14].

What are the advantages of this unprecedented method? First, it allows us to build a generation at each step; second, these sequences of reactions do not require any isolation, since the only by-products are H_2O and N_2. In addition to



Scheme 4. Accelerated synthesis of dendrimers using two types of AB_2 monomers

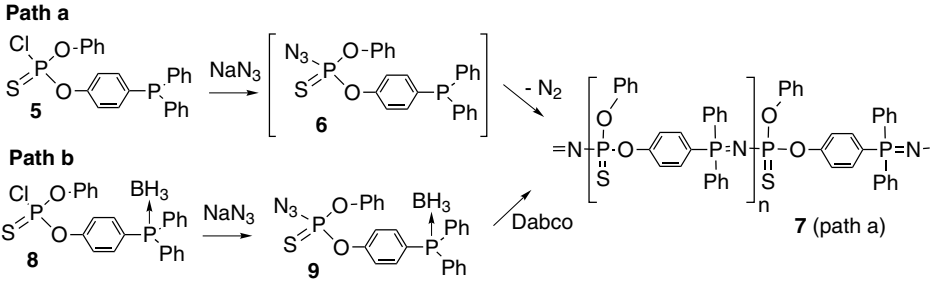
that, the presence of P = N-P = S groups is of the greatest interest since we have already demonstrated their specific reactivity with electrophiles [15] which opens new perspectives for the obtaining of dendritic structures having very original architectures. Last but not least, we carried out with success a one-pot experiment to obtain directly the fourth generation starting from the core (Scheme 4). To the best of our knowledge, this is the first example of the one-pot synthesis of a fourth generation dendrimer obtained rather cleanly. Two aspects of this synthesis require a particular care:

1) a strict control of the stoichiometry is necessary, and
2) it was observed that the condensation step is slower during the one-pot process, therefore it is recommended to concentrate the solution before adding the monomer **3**.

2.2 Linear, Hyperbranched Polymers and Dendrimers Constituted by the Same Repeating Unit

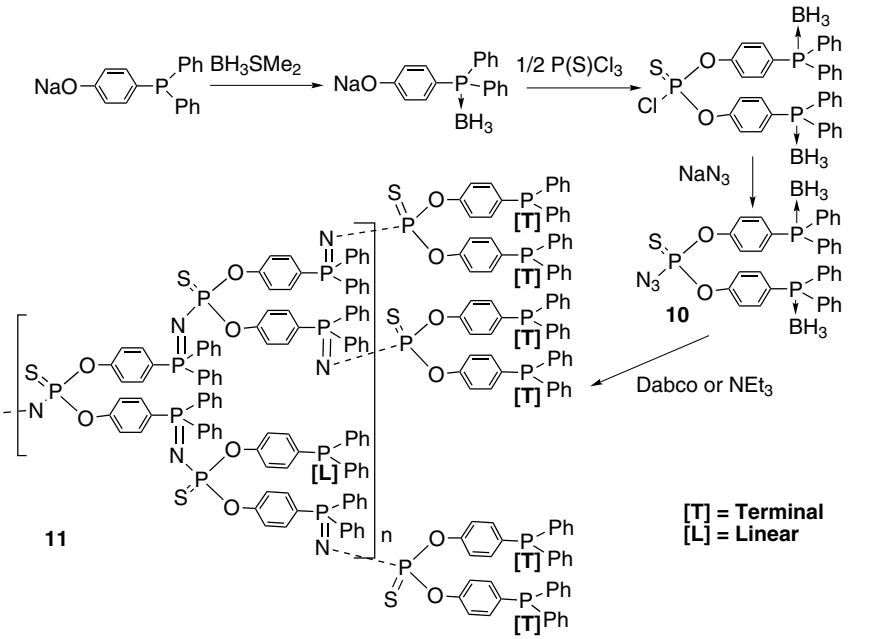
It is well documented that regular dendrimers and hyperbranched polymers exhibit very unique properties as compared with those of their linear analogues [16]. Dendrimers are uniformly branched, three-dimensional structures that are assembled through a regular succession of monomers and branching units. They are characterized by their inability to induce any chain entanglement in their structure, their uniformity in size and their number of terminal functional groups that increases with the number of generations. In contrast to regular dendrimers, hyperbranched macromolecules obtained by the polycondensation of AB_2-type monomers are irregular structures that are not flawless, with numerous unreacted B sites carried by linear units which coexist with dendritic and terminal units. Even though, their characteristic properties mainly depend on their "degree of branching", it is established that these properties resemble those found for regular dendrimers: high solubility, low viscosity, absence of chain entanglement, thermal stability. However, no comparative studies of the behavior exhibited by phosphorus dendrimers, hyperbranched polymers, and linear macromolecules constituted of the same repeating unit was undertaken. Such studies should provide an acute insight into how their molecular features – topology of their building block, polydispersity – affect the structure-property relationship. In order to afford first answers to these interrogations, new series of linear, hyperbranched and dendritic phosphorus polymers were prepared [17].

Two strategies can be followed for the preparation of linear polymers. The first one (Path a, Scheme 5) involves the treatment of the chlorothiophosphane **5** with sodium azide leading to the transient intermediate **6** which undergoes an intermolecular Staudinger reaction with elimination of nitrogen and formation of the polymer **7**. The second one (Path b, Scheme 5) consists in the reaction of **8** with sodium azide leading to the formation of the azide **9**, the last step being the phosphane decomplexation by means of a base like DABCO which affords the transient species **6**, then the polymer **7′**.



Scheme 5. Two ways of synthesis of linear polymers **7** constituted of $[OC_6H_4P(Ph)_2{=}N\text{-}P(S)]$ repeating units

The hyperbranched polymers **11** are synthesized via the one-pot condensation reaction of the predesigned AB_2 monomer **10** that is synthesized as shown in Scheme 6. In order to vary the molecular features of this series of polymers **11**, the nature of the amine used to deprotect the phosphane units (either DABCO or triethylamine was employed) as well as the nature of the solvent (THF or toluene) were varied. The temperature, the initial concentration of monomer **10** to be polymerized and the reaction time were parameters that were also investigated with a view to varying both the molar masses and the degree of branching.

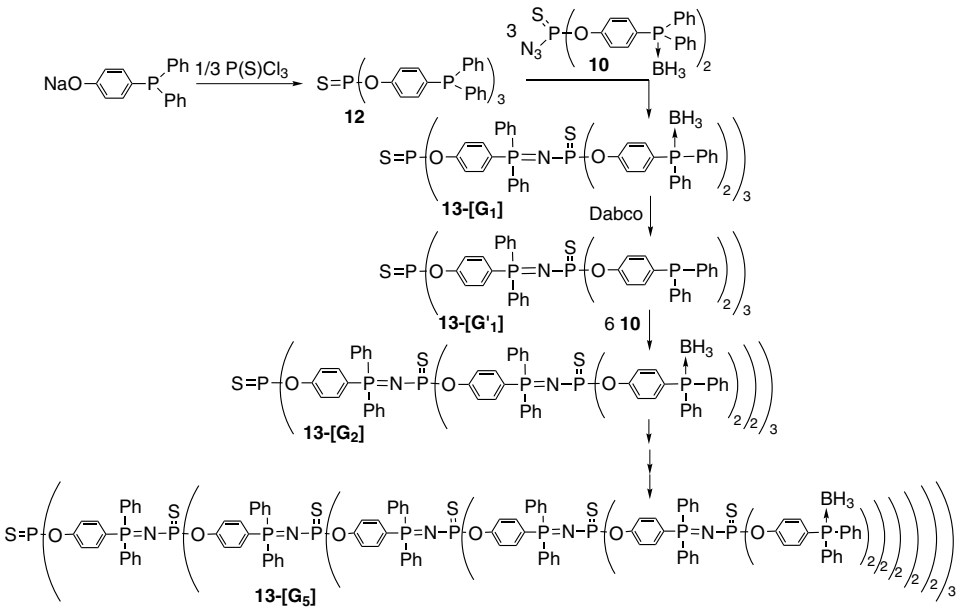


Scheme 6. Synthesis of hyperbranched polymers **11** constituted of $[OC_6H_4P(Ph)_2{=}N\text{-}P(S)]$ repeating units

The synthetic strategy for the synthesis of the dendrimers **13-[G_1]-13-[G_5]**, **13-[G'_1]-13-[G'_4]** involves the reiteration of a sequence of two reactions:

1) a Staudinger type reaction between species carrying free phosphane groups and the azide **10**, the latter bearing complexed phosphane groups,
2) the deprotection of the resulting phosphane-boron adducts with a base like DABCO.

Such a methodology was applied to the preparation of dendrimers up to generation 5 (Scheme 7).

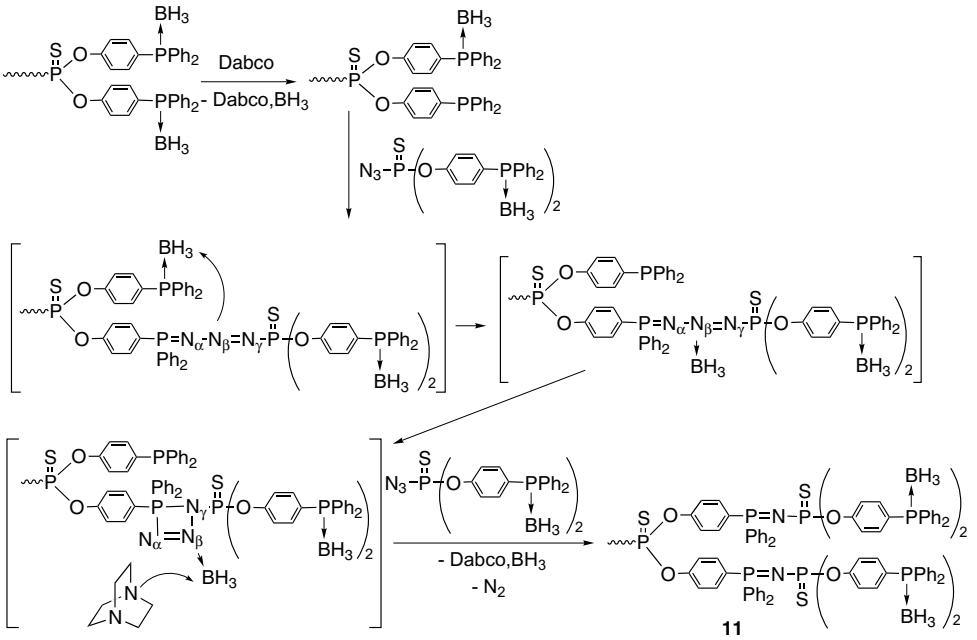


Scheme 7. Synthesis of dendrimers **13-[G_n]** constituted of [$OC_6H_4P(Ph)_2$=N-P(S)] repeating units

Therefore, series of polymers constituted of [$OC_6H_4P(Ph)_2$=N-P(S)] repeating units have been covalently assembled in dendritic, hyperbranched, and linear architectures. Using A-B-type monomers for the preparation of linear chains, AB_2-type reagents for hyperbranched polymers and appropriate building blocks in reiterated reactions for dendrimers, these samples of different topology were obtained through the Staudinger reaction of phosphane groups with azido functions. In the case of the hyperbranched structures, a higher degree of branching (DB = 0.8 – 0.9) than that expected for polycondensations of AB_2 units (DB = 0.5 – 0.6) could be obtained.

To account for the enhanced values obtained in our case, one can assume that the formation in the AB_2 unit of a first P=N linkage can intramolecularly activate the second B group and favors its reaction. Indeed, such a reaction leading to a P=N double bond proceeds by nucleophilic attack of the phosphane on the terminal α nitrogen atom of the azide to afford a linear phosphazide, albeit

scarcely stable, which then dissociates to the iminophosphorane form with elimination of dinitrogen. A few phosphazide complexes were characterized, complexation taking place through α- [18], β- [19], or γ- [20] nitrogen atoms. One can assume that an intramolecular complexation with BH_3 of one of the three nitrogen atoms of the phosphazide unit, probably the less hindered nitrogen atom N_β, takes place with decomplexation and therefore activation of the neighboring phosphino group (Scheme 8).



Scheme 8. Possible mechanism for the synthesis of the hyperbranched polymers **11**

The characterization of these phosphorus-based macromolecular architectures in solution revealed marked differences in their respective behavior. A bell-shaped curve could be established for the intrinsic viscosity [η] of the dendrimers, whereas the [η] of hyperbranched polymers was found to moderately vary with the molar mass. They were shown to depend on both the chemical nature of the repeating units and the terminal functions, as the T_gs of these branched architectures (Fig. 1).

2.3
Dendrons and Multidendritic Macromolecules

The main drawback of dendrimers is, as we have previously shown, their lengthy step-by-step synthesis. A few ways to improve these synthetic pathways have been proposed. The obtaining of a generation using only one step is one of these ways (see above). Another way implies the use of dendrons. The dendrons are

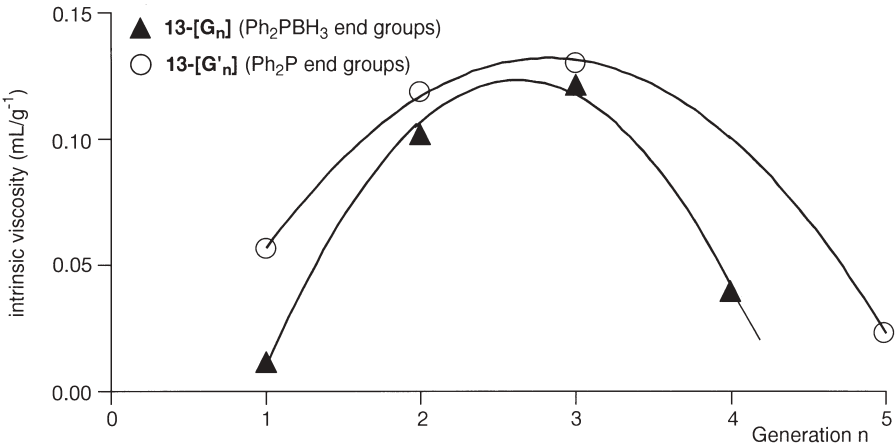


Fig. 1. Bell-shaped curve of the variation of intrinsic viscosity versus generation for dendrimers **13-[G$_n$]** ($Ph_2P \rightarrow BH_3$ end groups) and **13-[G′$_n$]** (Ph_2P end groups)

reminiscent of dendrimers, but in contrast to dendrimers, they possess one reactive function at the level of the core. Most of these dendrons are obtained by a convergent strategy introduced by Fréchet [21] and are prepared in most cases only up to generation 2, 3, or 4 to avoid the steric crowding of the core function. Depending on the type of this function, several dendrons can be associated by their core in a spontaneous self assembly [22], around a metal [23], or by reaction with a multifunctional core [24], which may be a small dendrimer. The grafting of dendrons on a dendrimer allows us to increase dramatically the number of terminal groups of the dendrimer in one step, for instance, from 6 to 96 [25] or from 12 to 288 [26] creating what are called "layer-block" dendrimers [27]. Other types of macromolecular architectures have been obtained mainly using dendrons. "Segment-block" dendrimers are prepared via association of several different types of dendrons while "surface-block" dendrimers are synthesized by grafting dendrons with different end groups together or on a single core [27] (Fig. 2).

The chemistry of phosphorus opens new perspectives in this field and allows, for example, the synthesis of all these special dendritic architectures (layer-

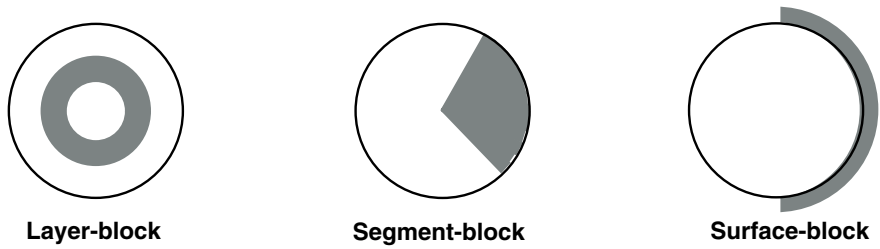
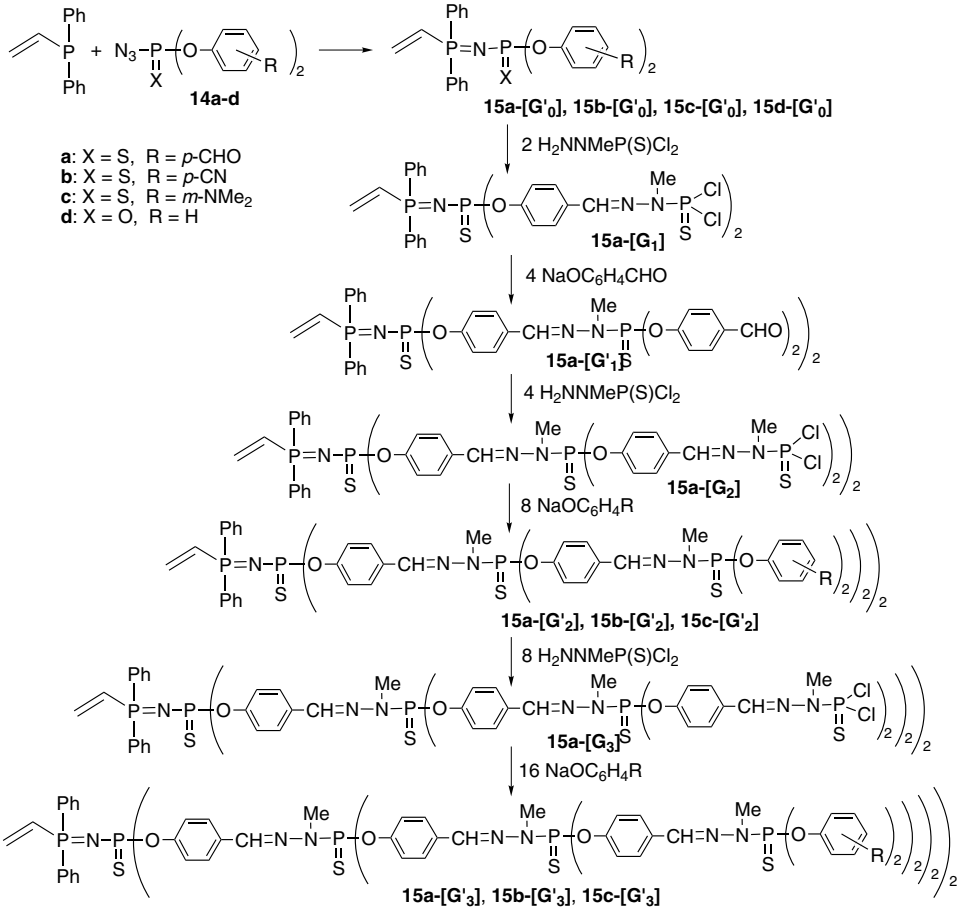


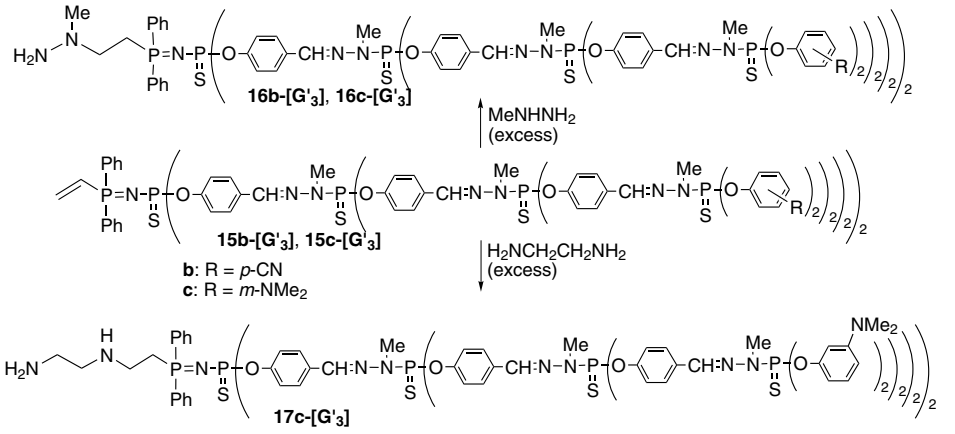
Fig. 2. Schematic drawing of layer-block, segment-block, and surface-block dendrimers

block, surface-block, segment-block dendrimers) using only subtle modifications of a unique dendron in the last step of its synthesis. This will be illustrated hereafter. For this goal we reasoned that the divergent method we used to synthesize phosphorus-containing dendrimers [3, 10a, 10b, 11] could be applied to the synthesis of dendrons. The advantage of the divergent method over the convergent one is that the surface is always very easily functionalized [28]. So the general strategy we applied was to prepare a dendron possessing one function located at the core and several easily reactive functions located on the surface. The function located at the core has to be unreactive when growing the dendron. The function which was placed at the core is an activated vinyl group which should undergo easily Michael-type reactions, Diels-Alder reactions, and so on. The general synthesis of such a dendron is shown in Scheme 9. Several dendrons of generation 3 were prepared with terminal aldehyde, cyano, dimethylamino groups on the surface: all of them possess a vinyl group at the core.

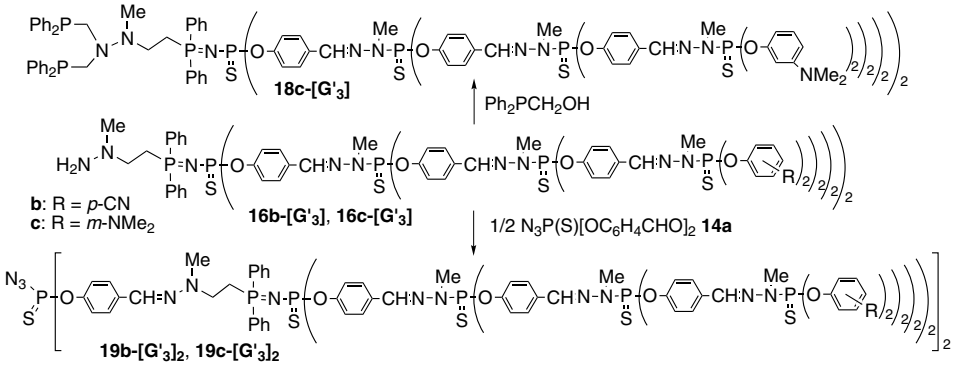


Scheme 9. Synthesis of phosphorus-containing dendrons 15-[G_n]

Regioselective reactions at the core can be performed as shown in Schemes 10 and 11. The Michael addition can be applied to several types of primary and secondary amines as well as to hydrazines. As an example the dendrons **15b**-[**G′**$_3$] or **15c**-[**G′**$_3$] react with an excess of methylhydrazine (200% excess) to give the new dendrons **16b**-[**G′**$_3$] or **16c**-[**G′**$_3$]. Similarly **15c**-[**G′**$_3$] when reacted with a large excess of ethylenediamine (40,000% excess!) affords the dendron **17c**-[**G′**$_3$] (Scheme 10). Two types of condensation reactions have been carried out from **16b**-[**G′**$_3$] or **16c**-[**G′**$_3$]. The condensation of **16c**-[**G′**$_3$] with Ph_2PCH_2OH at 90 °C leads to the formation of a diphosphino-linkage at the core of the new dendron **18c**-[**G′**$_3$] (Scheme 11). The Schiff reaction between two equivalents of **16b**-[**G′**$_3$] or **16c**-[**G′**$_3$] with the dialdehyde $N_3P(S)(OC_6H_4CHO)_2$ induces the association of two dendrons and the formation of **19b**-[**G′**$_3$]$_2$ or **19c**-[**G′**$_3$]$_2$. These last fascinating macromolecules can be viewed as fourth generation layered dendrons made up of two types of layers: one having $S=POC_6H_4CH=NNMeCH_2CH_2PPh_2=N$ linkages, the other one having $S=POC_6H_4CH=NNMe$ linkages repeated three times [29].

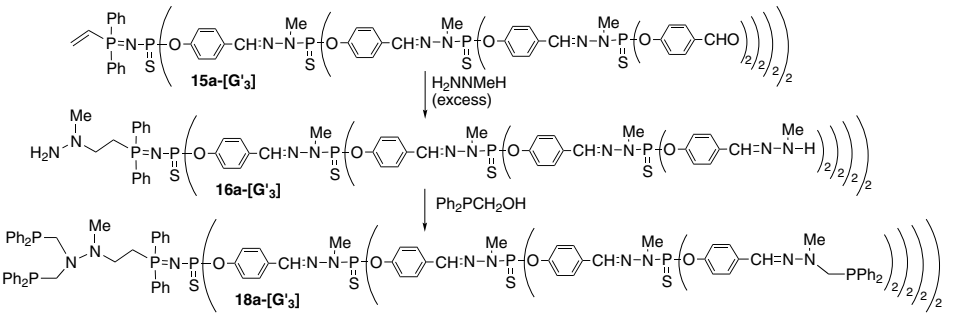


Scheme 10. Michael-type additions at the vinyl core of dendrons



Scheme 11. Reactivity of the hydrazino group located at the core of dendrons

The third generation dendron **15a**-[**G′**$_3$] (R = CHO) is expected to behave in a very special way when reacted with methylhydrazine. Indeed both the vinyl group located at the core and the aldehyde functions grafted on the surface react with methylhydrazine in excess to give **16a**-[**G′**$_3$]. Further reaction of **16a**-[**G′**$_3$] with Ph_2PCH_2OH allows the grafting of a monophosphino group on the surface and a diphosphino group at the core, with the formation of **18a**-[**G′**$_3$] (Scheme 12).



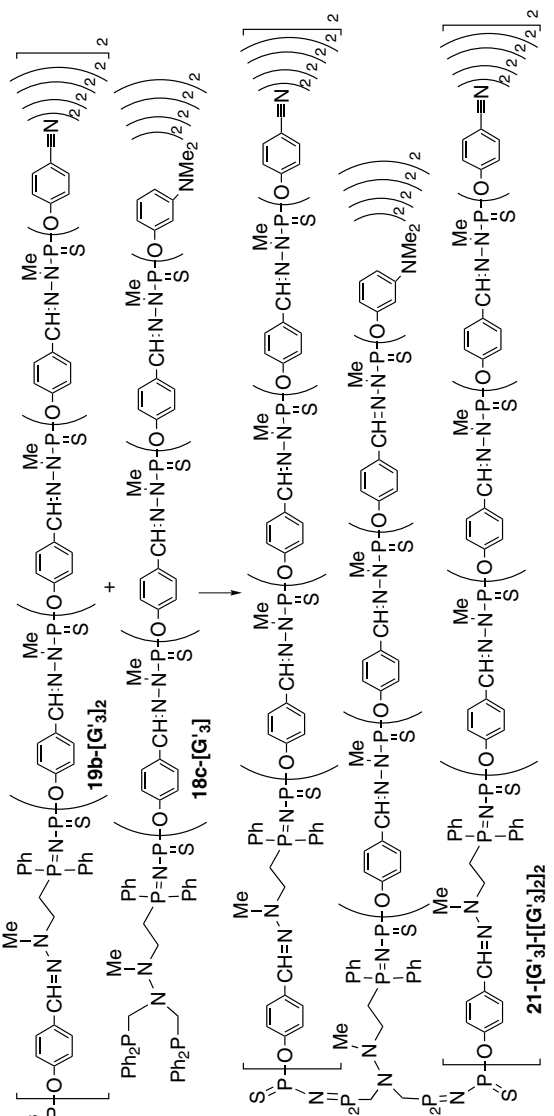
Scheme 12. Reactivity of methylhydrazine both at the core and on the surface of dendron **15a**-[**G′**$_3$]

All these experiments give dendrons possessing either a vinyl, a primary amino, a bisphosphino, or an azido group at the level of the core. Other functional groups can be incorporated [30, 31]. These compounds are useful precursors of multidendritic systems. Various surface-block dendrimers can be prepared from these macromolecules. For instance, a Michael addition between dendron **17c**-[**G′**$_3$] (100 % excess) and dendron **15b**-[**G′**$_3$] at 90 °C induces the formation of dendrimer **20**-[**G′**$_3$]-[**G′**$_3$] (Scheme 13). This dendrimer possesses two different faces: 16 dimethylamino groups on one side, 16 nitrile groups on the other side.

Another type of surface-block dendrimer is obtained when two equivalents of dendron **19b**-[**G′**$_3$]$_2$, having an azide at the core, are associated with one equivalent of dendron **18c**-[**G′**$_3$] having two phosphino groups at the core, via two Staudinger reactions (Scheme 14). It is interesting to note that in ^{31}P-NMR spectroscopy the $Ph_2P=N\text{-}P=S$ linkages formed by these associations are distinguishable from the other $Ph_2P=N\text{-}P=S$ linkages and therefore the reaction can be easily monitored. The resulting macromolecule **21**-[**G′**$_3$]-[[**G′**$_3$]$_2$]$_2$ is both a surface-block and a layer-block dendrimer. Indeed, on the one hand, the internal layers close to the core possess $P=N\text{-}P=S$ linkages, whereas the other internal layers have not and, on the other hand, two types of end groups are located in definite areas of the surface in a 1/4 ratio (16 dimethylamino groups and 64 nitrile groups).

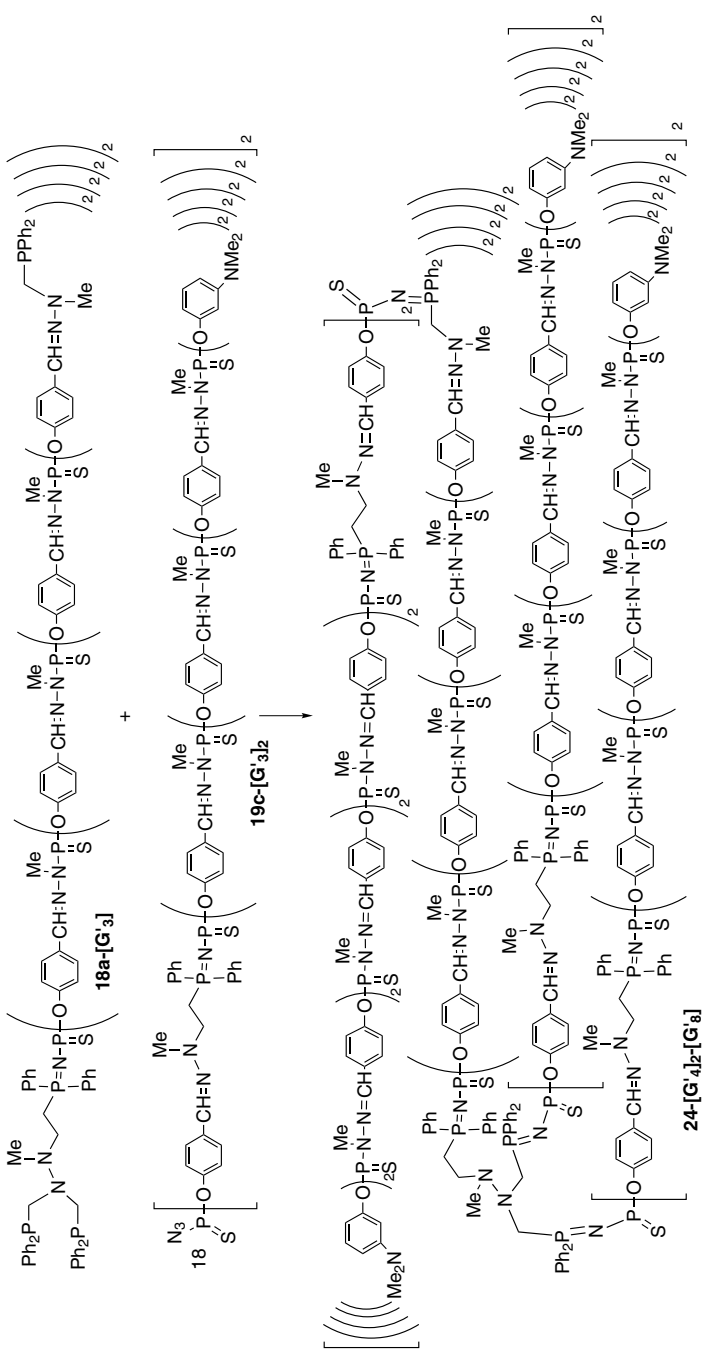
Dendron **19b**-[**G′**$_3$]$_2$ having an azide at the core can also be used to multiply rapidly the number of end groups of a dendrimer possessing phosphino groups at the surface. Indeed the reaction of 24 equivalents of **19b**-[**G′**$_3$]$_2$ with one equiv-

Scheme 13. Coupling of two dendrons giving the unsymmetrical dendrimer **20-[G'$_3$]-[G'$_3$]**



Scheme 14. Synthesis of the surface-block and layer-block dendrimer **21-**[**G′**$_3$]-[[**G′**$_3$]$_2$]$_2$

Scheme 15. One-step synthesis of the eighth generation dendrimer **23**-[**G′**$_8$] from the third generation **22**-[**G′**$_3$]



Scheme 16. Synthesis of the layered segment-block dendrimer **24**-[G'_4]$_{12}$-[G'_8]

alent of the third generation dendrimer **22**-[**G′**$_3$] possessing 24 diphenylphosphino end groups leads in one step to the formation of the eighth generation dendrimer **23**-[**G′**$_8$] possessing 768 nitrile end groups (Scheme 15). **23**-[**G′**$_8$] is a layer-block dendrimer possessing $NCH_2PPh_2=N\text{-}P=S$ linkages at the level of the fourth generation and $NCH_2CH_2PPh_2=N\text{-}P=S$ linkages at the level of the fifth generation, both linkages being absent in the skeleton of the other generations.

The previous examples show that dendrons **19b**-[**G′**$_3$]$_2$ possessing an azide at the core can be grafted to the core of another dendron or to the surface of a dendrimer, provided they bear phosphino groups. Dendron **18a**-[**G′**$_3$] which has phosphino groups both at the level of the core and on the surface was also reacted with **19c**-[**G′**$_3$]$_2$ (Scheme 16). The Staudinger reaction occurs both at the level of the core and on the surface leading to the "unsymmetrical" dendrimer **24**-[**G′**$_4$]$_2$-[**G′**$_8$] incorporating 576 dimethylamino groups on the surface. This compound can be viewed as a kind of layered segment-block dendrimer having two fourth generation dendrons linked to a $(PCH_2)_2NNMe(CH_2)_2P$ trifunctional core (Fig. 3).

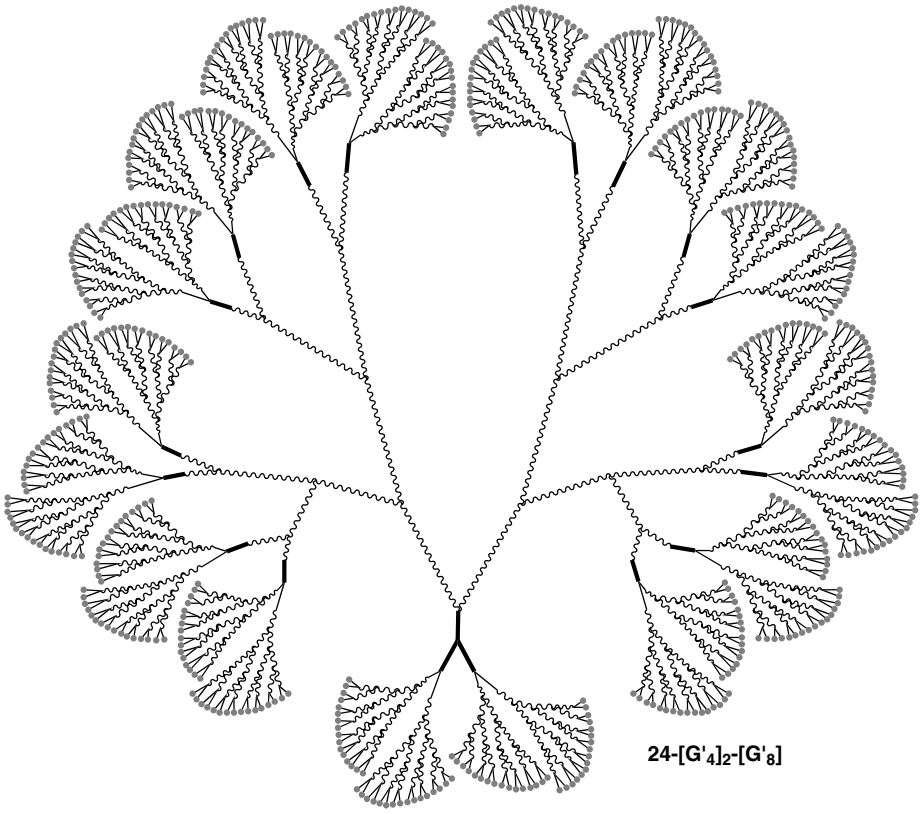
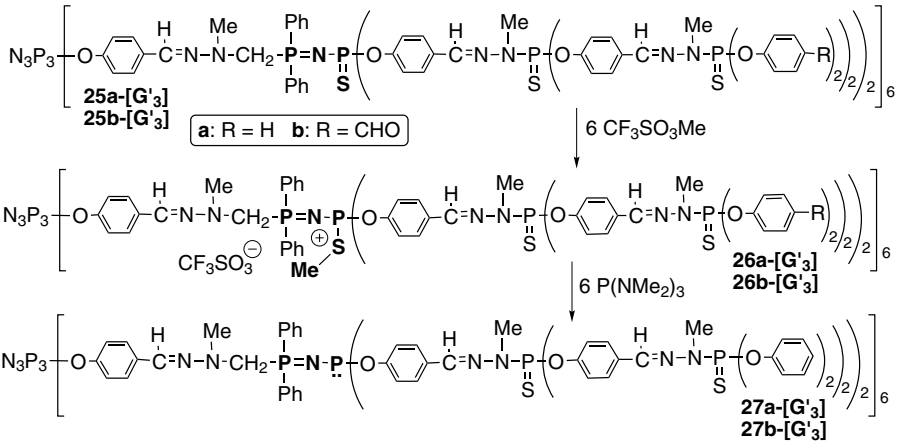


Fig. 3. Schematic drawing of the layered segment-block dendrimer **24**-[**G′**$_4$]$_2$-[**G′**$_8$]

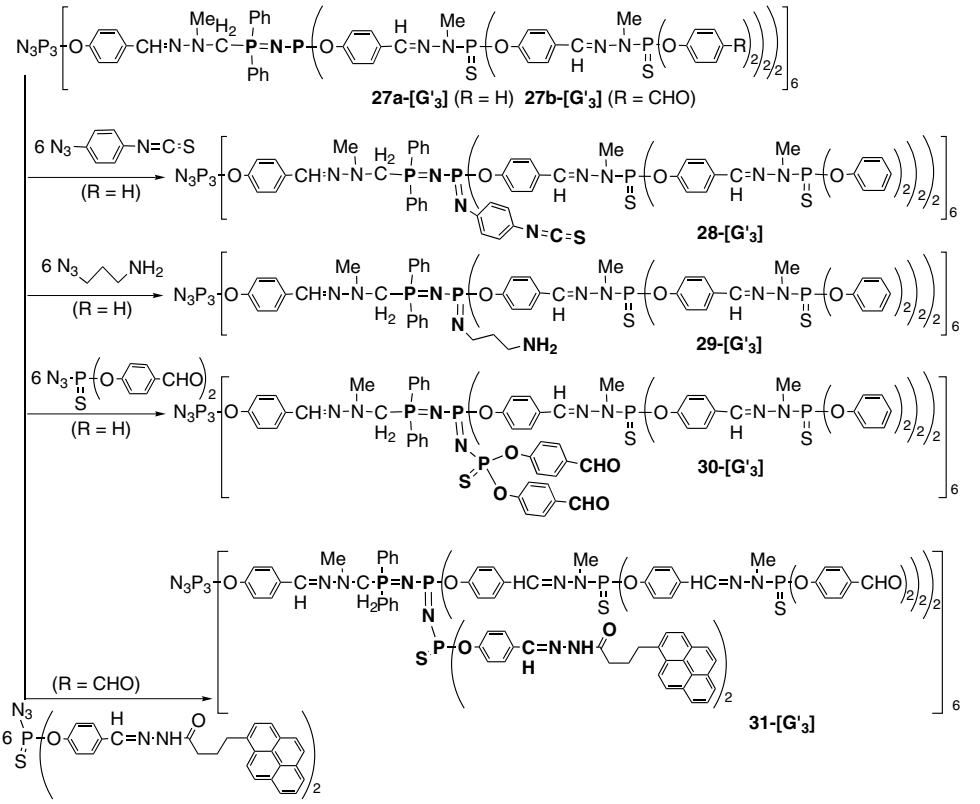
The presence of P=N-P=S linkages within dendrimers [14] allowed us to develop a very original reactivity of the internal layers. Indeed the mesomeric form of these linkages (P^+-N-P-S^-) suggests that they should react with electrophiles such as triflates. Methyl trifluoromethanesulfonate induces the specific alkylation of the sulfur included in the P=N-P=S linkages, whereas the other P=S groups are not alkylated (Scheme 17). The alkylation provokes a



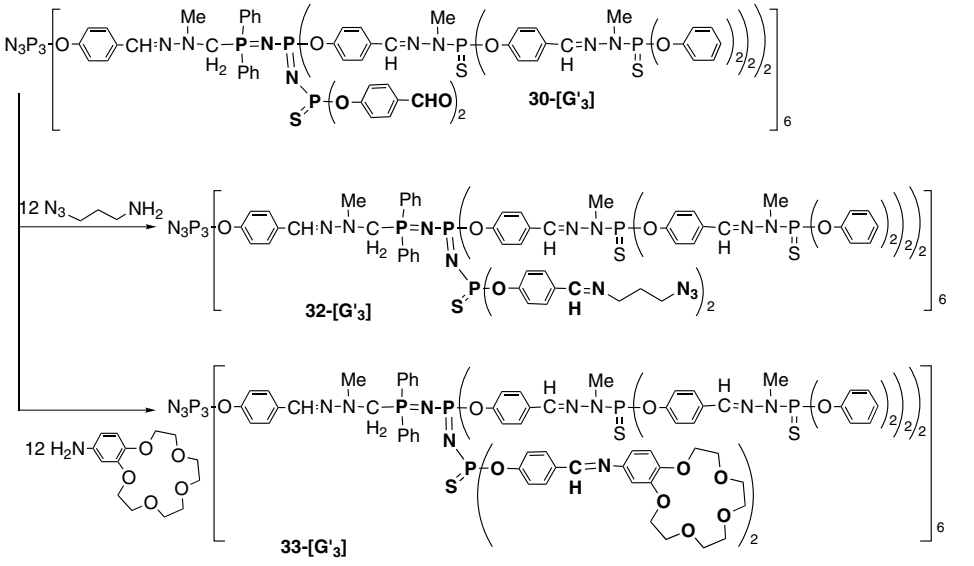
Scheme 17. Specific reactivity of P=N-P=S linkages

weakening of the P-S bonds, which are easily cleaved using nucleophilic phosphanes such as $P(NMe_2)_3$, according to a method previously reported [32]. This reaction induces the formation of tricoordinated phosphorus atoms in the internal layers of dendrimers. These tricoordinated phosphorus atoms are very useful to graft new functional groups within the dendrimers as shown, for example, in Schemes 18 and 19. Incorporation of aldehyde groups within the cascade structure of dendrimers is of special interest since they allow one to link other functional groups within the dendrimer or they allow us to grow new internal branches within the cavities (Schemes 20 and 21). Indeed, six new dendritic wedges emanating from the interior of the main dendrimer can be built (Scheme 22) (Fig. 4) [14a].

Remarkably, it is possible to graft directly in one step, preformed dendritic wedges within a main dendrimer as shown in Scheme 23. This consists on the reaction of the dendron **16b**-[$\mathbf{G'}_2$] bearing a hydrazine group at the core and nitrile groups on the surface with the dendrimer **30**-[$\mathbf{G'}_3$] possessing 12 internal aldehyde groups [31] (Scheme 22).

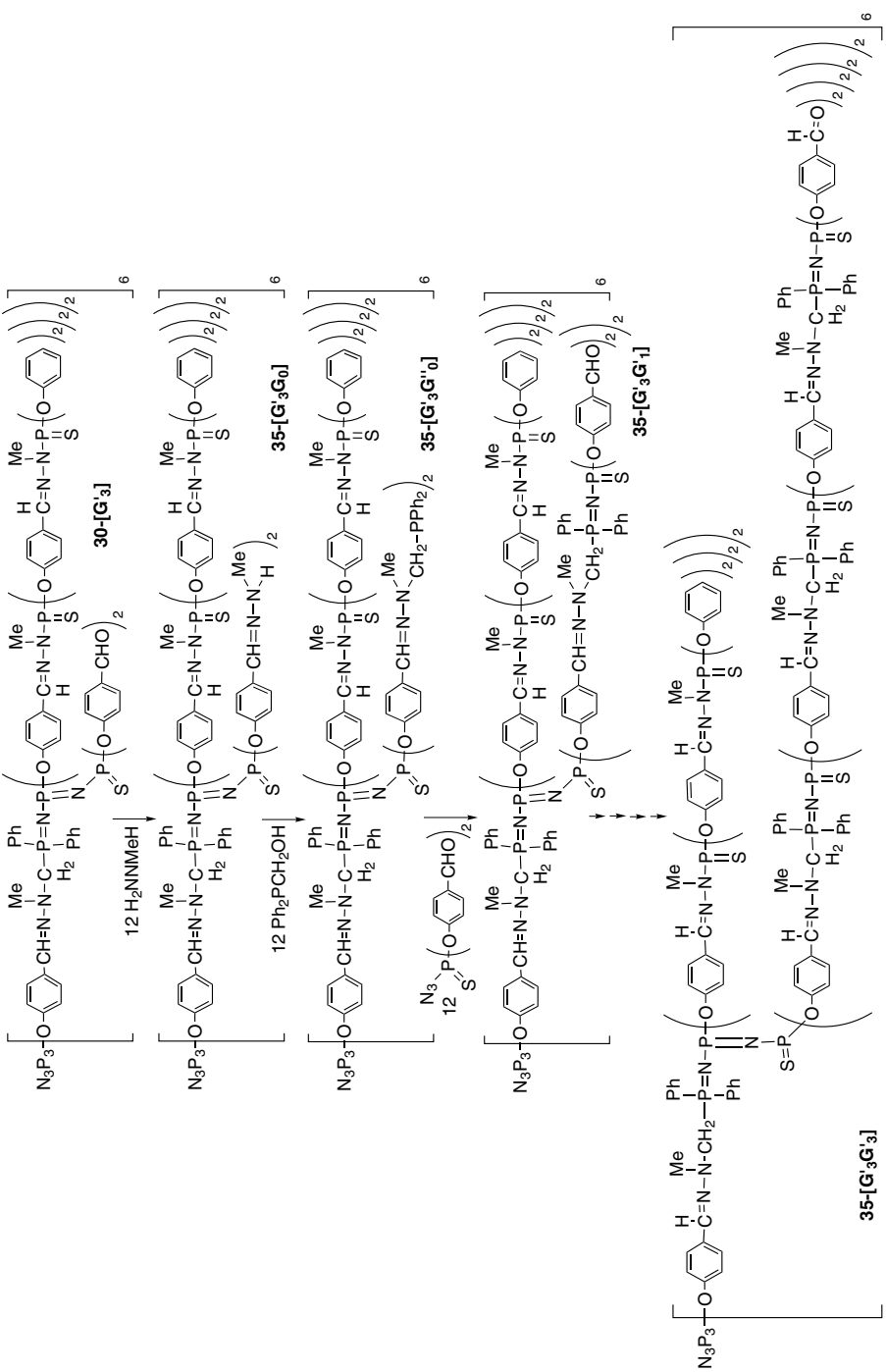


Scheme 18. Specific grafting of various functional groups inside a dendrimer

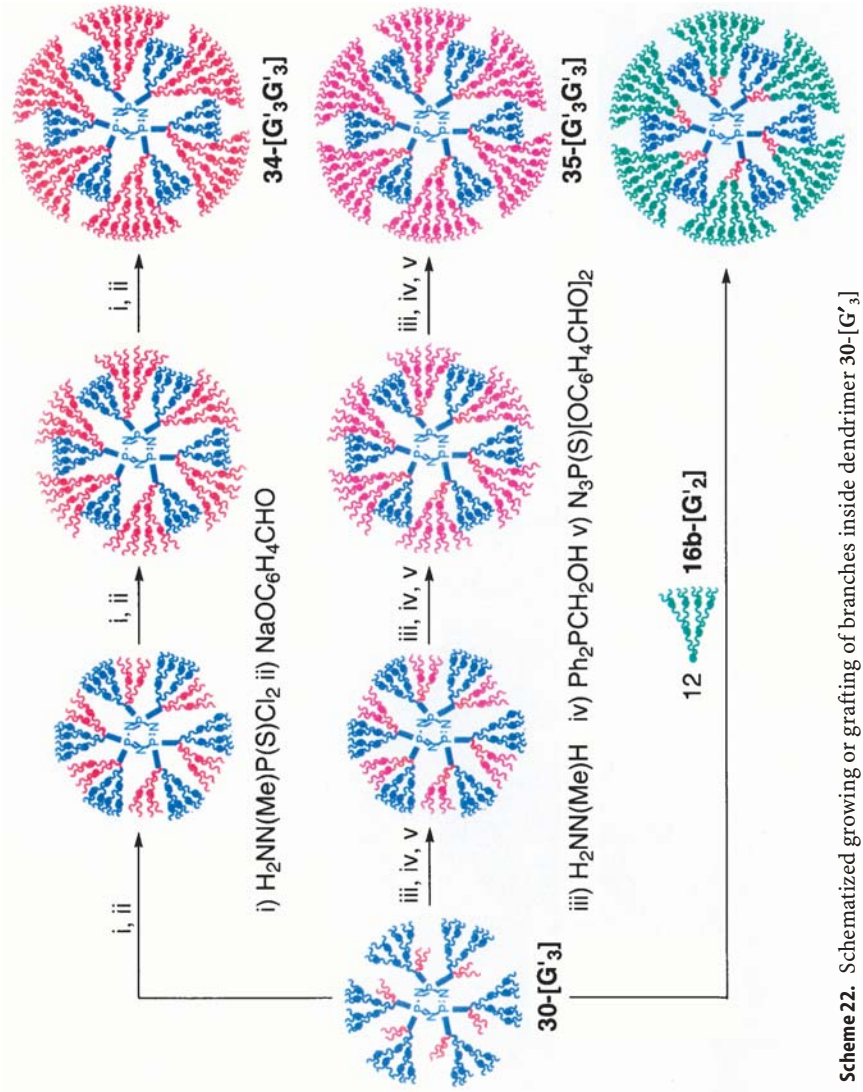


Scheme 19. Reactivity inside a dendrimer

Scheme 20. Growing of new branches inside dendrimer **30-[G'$_3$]** using a two-step process



Scheme 21. Growing of new branches inside dendrimer **30**-[G'_3] using a three step process



Scheme 22. Schematized growing or grafting of branches inside dendrimer **30**-[G'_3]

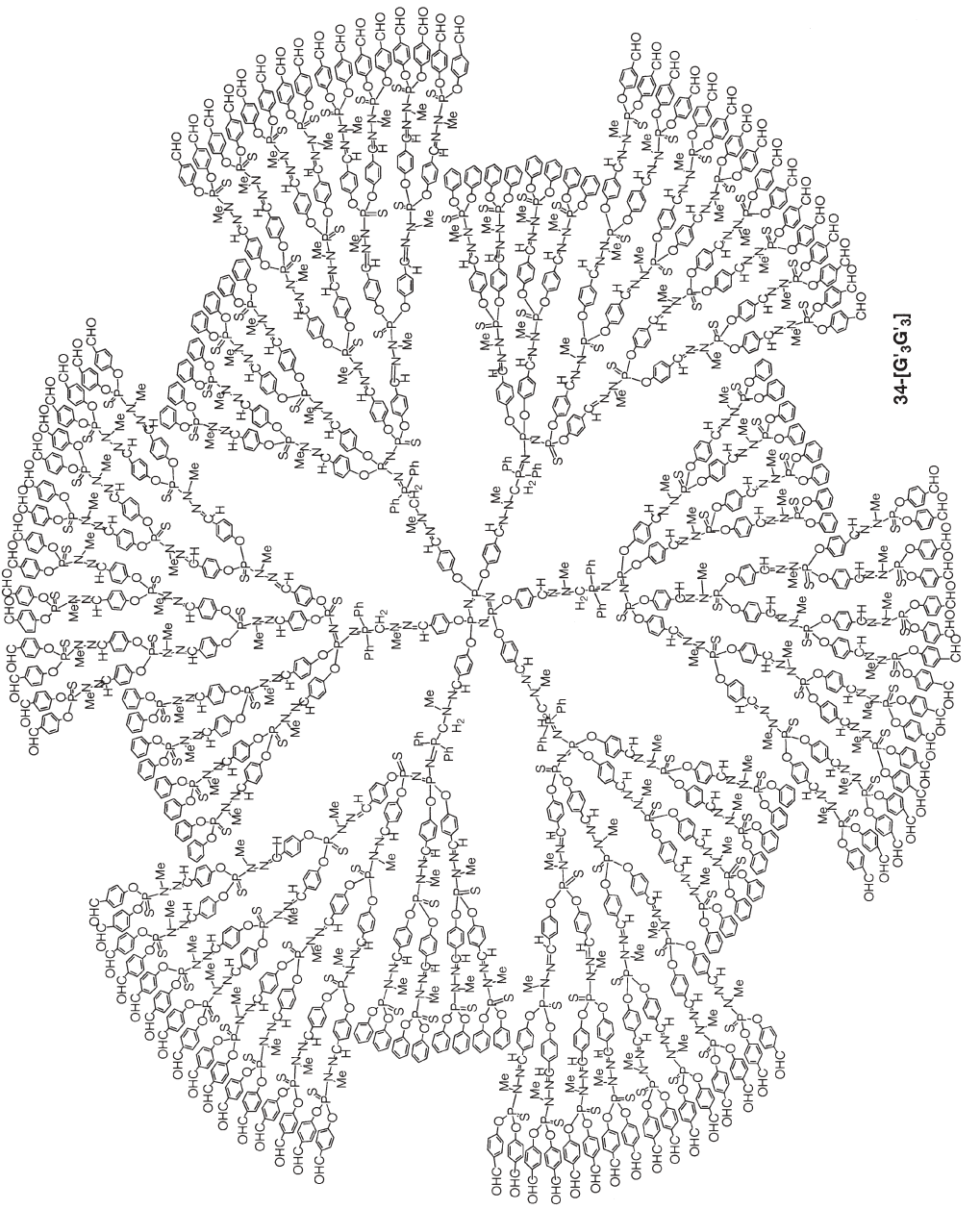


Fig. 4. Chemical structure of dendrimer **34-[G′$_3$G′$_3$]**

Scheme 23. Grafting of branches inside dendrimer **30**-[G'_3]

3 Characterization

3.1 ^{31}P-NMR

As can be expected, ^{31}P-NMR is an extremely useful tool and the method of choice to follow rigorously the construction of dendrimers. Indeed, up to the generation 6 the signal of the phosphorus atom of the core (when SPR_3 is used) or the signal of the three phosphorus atoms of the core (when $N_3P_3R_6$ is used), can be detected; therefore lack of substitution on the surface at one or several of the terminal functional groups, from generation 1 – 6 would be observed. Moreover, as already mentioned above, the Staudinger reaction, which is very often used, allowed the formation of P = N-P = S linkages, that is to say of two doublets in ^{31}P-NMR which are distinguishable from one generation to another (Fig. 5) [14]. Furthermore substitution reactions on the surface generally result in a shielding or deshielding effect (depending on the type of substitution) of the signal due to the phosphorus atoms of the top generation n and a slight deshielding effect for the phosphorus atoms of generation n – 1. It can be emphasized also that the use, alternatively, of P(O) or P(S) units (Fig. 6) during the construction of the dendrimers facilitates the monitoring of the reactions since different "windows" can be used in ^{31}P NMR avoiding overlapping of the different signals [28g].

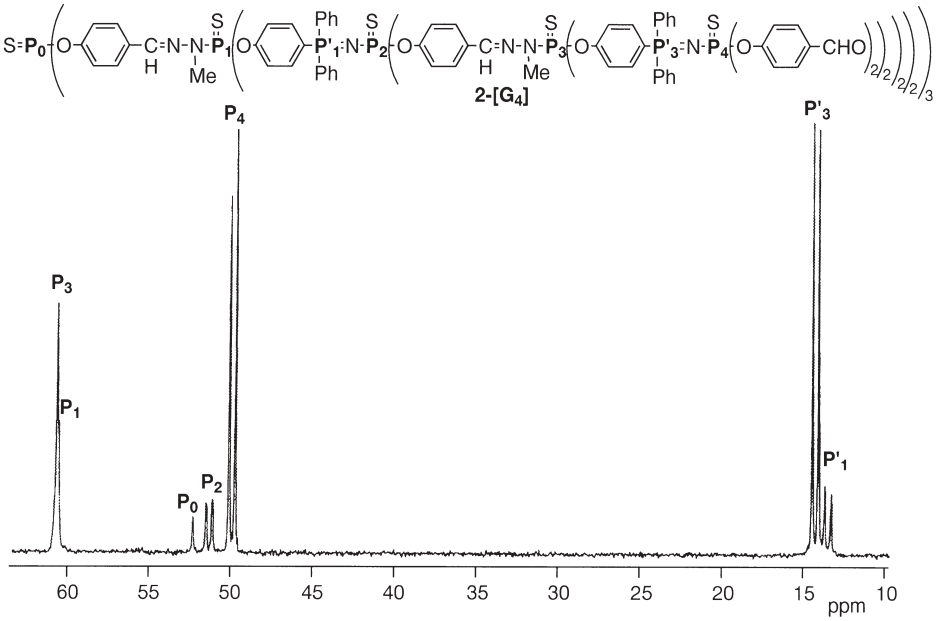


Fig. 5. ^{31}P-NMR spectrum of dendrimer **2-[G_4]**

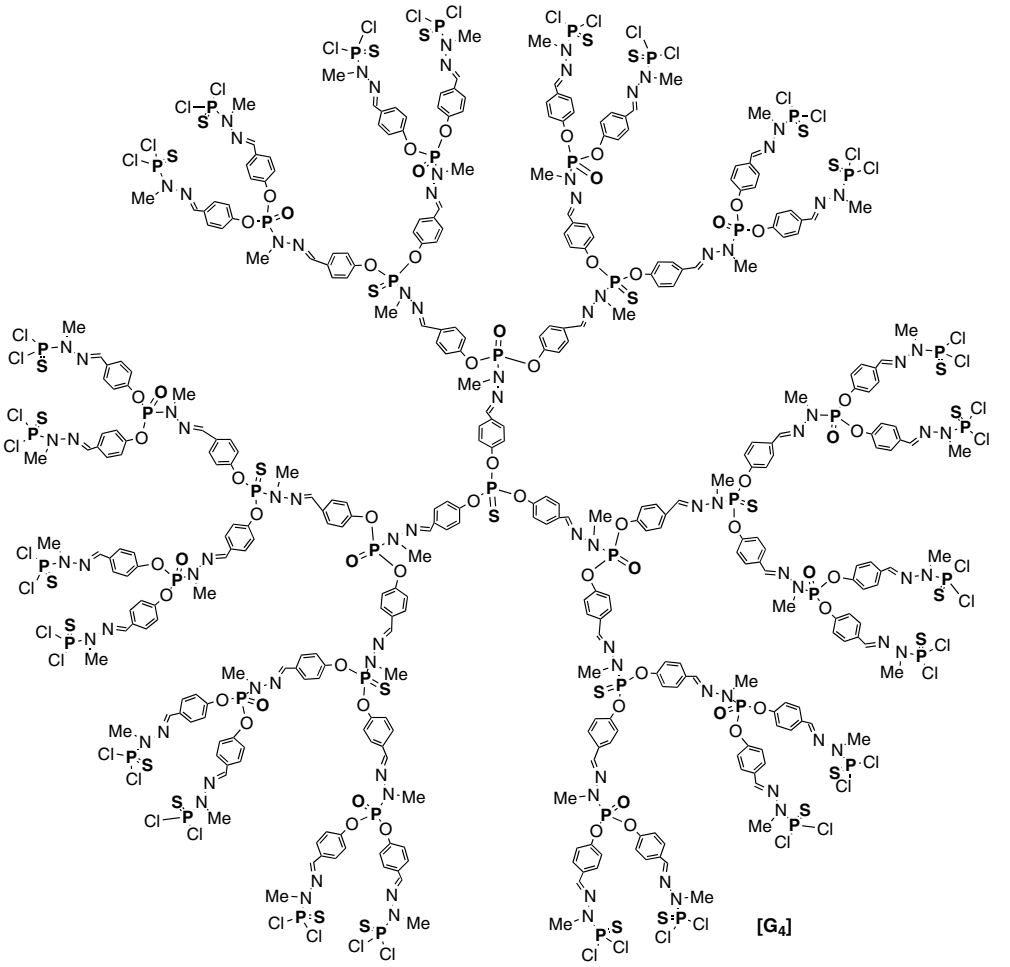


Fig. 6. Chemical structure of a dendrimer having alternatively P(O) and P(S) units

3.2 S.E.C.

The degree of purity of dendrons and dendrimers can be checked by size-exclusion chromatography. As an example, the chromatograms of the dendron **15c**-[**G′**$_3$] show that its dispersity is comparable to or better than that of narrow distribution polystyrene standards (polydispersity $M_w/M_n = 1.03$). Comparison of the SEC trace for **15c**-[**G′**$_3$] and that for **21**-[**G′**$_3$]-[**G′**$_3$]$_2$ indicates that the latter one has a narrow molecular weight distribution. Interestingly, the elimination of the excess of dendron **15c**-[**G′**$_3$] is easily controlled by SEC, as can be seen when comparing Fig. 7 a (**21**-[**G′**$_3$]-[**G′**$_3$]$_2$ partially purified, contaminated by traces of **15c**-[**G′**$_3$]) and Fig. 7 b (**21**-[**G′**$_3$]-[**G′**$_3$]$_2$ purified). Moreover, the retention time of **21**-[**G′**$_3$]-[**G′**$_3$]$_2$ is smaller than that of the dendron, corroborating the increase of

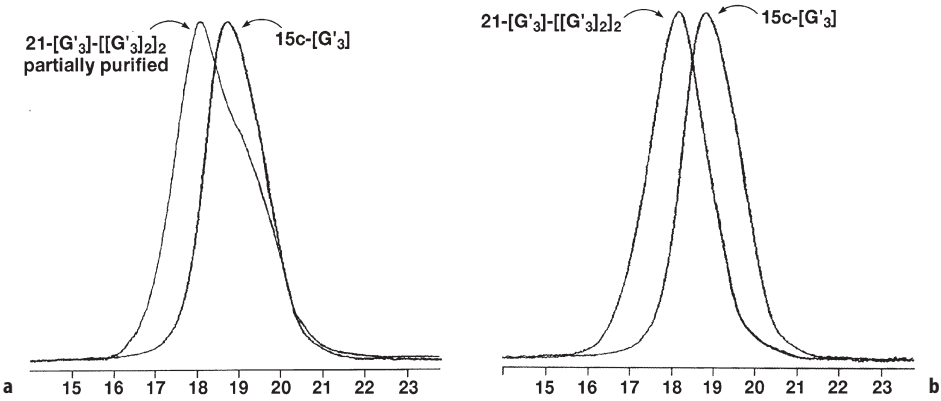


Fig. 7. Size exclusion chromatography traces of dendron **15c**-[G′$_3$] and dendrimer **21**-[G′$_3$]-[[G′$_3$]$_2$]$_2$ (**a**) partially purified; (**b**) purified

the molecular weight. In fact, a plot of log molecular weight versus retention time for the dendrons and dendrimers **15c**-[G′$_3$], **19b**-[G′$_3$]$_2$, **23**-[G′$_8$], **20**-[G′$_3$]-[G′$_3$], **21**-[G′$_3$]-[[G′$_3$]$_2$]$_2$, **24**-[G′$_4$]$_2$-[G′$_8$] gives a relatively straight line (Fig. 8) [29]. In the same conditions, polystyrene standards give another straight line, with a different slope which increasingly deviates from the dendrons and dendrimers plots as molecular weight increases. This tendency was already observed [21] and was attributed to the increase of the density and compactness of dendritic macromolecules as molecular weight increases.

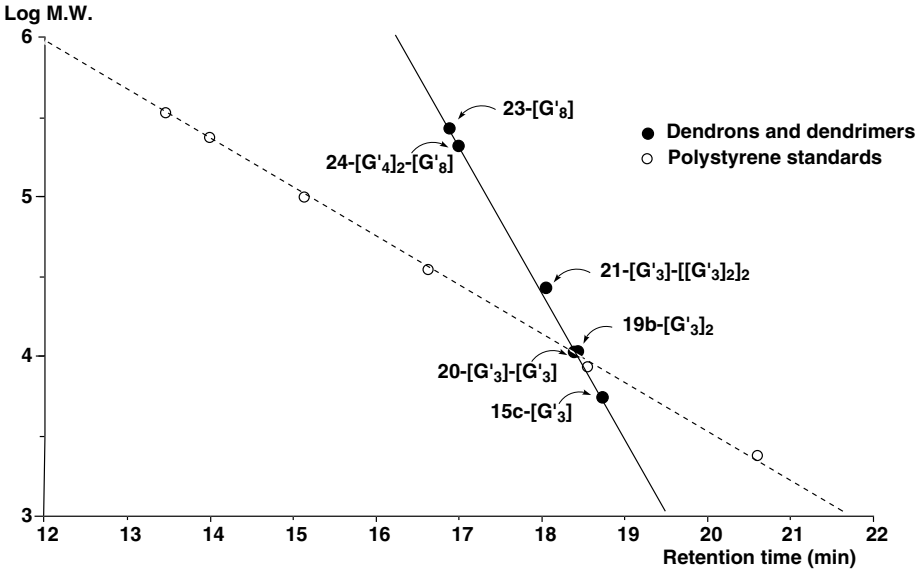


Fig. 8. Plot of retention time (SEC) versus log of molecular weight for various dendrons and dendrimers compared to polystyrene standards

It must be pointed out that the differential scanning calorimetry experiments, for example, for dendrons **15b**-[**G′**$_3$] and **15c**-[**G′**$_3$] which differ only by the nature of the functional group linked to the surface, give a drastic difference: the Tg value is 377 K for **15b**-[**G′**$_3$] (16 CN end groups) and 341 K for **15c**-[**G′**$_3$] (16 NMe_2 end groups). It is interesting to note that the dendrimer constituted of both **15b**-[**G′**$_3$] and **15c**-[**G′**$_3$] has only one Tg with a value intermediate between the values found for these dendrons [29].

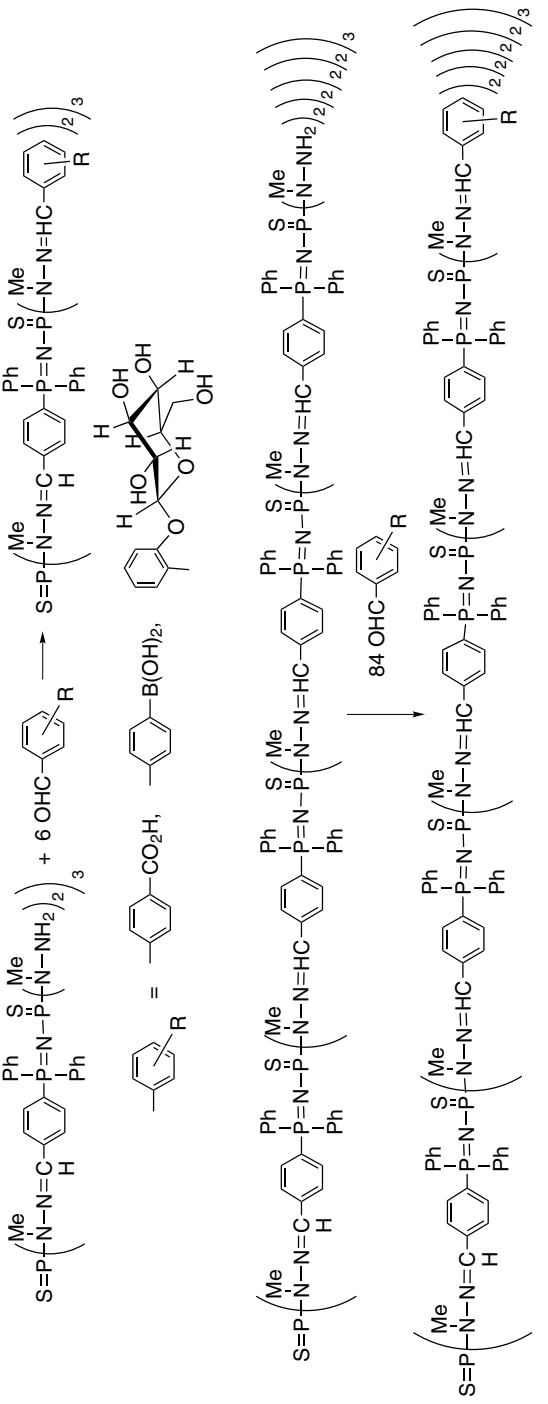
3.3
MALDI-TOF-MS

Neutral phosphorus-containing dendrimers with aldehyde groups at the periphery have been analyzed using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) up to generation four [33]. Although the expected quasi-molecular ion is generally observed, the mass spectral pattern, presence of fragments and adducts related to the original skeleton, is highly relevant to the sample preparation [nature of the matrix: 2,5-dihydroxybenzoic acid (2,5-DHB), 1,8-dihydroxy-9[10*H*]-anthracenone (dithranol), 6-azathiothymine, 2,4,6-trihydroxyacetophenone, 7-hydroxycoumarin or 2-anthramine, and addition of alkali metal salts]. The dithranol matrix with addition of LiI offers milder conditions; however, abundant fragments are still observed for the higher generation dendrimers. Investigation of these effects in connection with SEC, NMR, and MALDI-TOF-MS studies of UV-preirradiated dendrimers allows the assumption to be made that fragmentation occurs in MALDI due to the relatively strong absorption of the dendrimers at 337 nm (wavelength of the laser used). Fragmentations and formation of adducts involve nitrogen-nitrogen bond cleavage, imine metathesis, and reaction of aldehyde groups with internal imino groups. Remarkably the use of infrared laser instead of UV laser dramatically reduces fragmentations [34].

4
Physico-Chemical Properties

4.1
Solubility

The solubility of phosphorus-containing dendrimers strongly depends on the nature of the groups linked on the surface. Therefore, it is really possible to play with the solubility of these macromolecules and to obtain, for example, dendrimers which are soluble in hexane (lipophilic chains grafted on the surface), in perfluorinated solvents [$(CF_2)_7CF_3$ groups linked on the surface] in chloroform, THF (dendrimers decorated with aldehyde groups) and even in water. Several polycationic or polyanionic dendritic macromolecules are hydrosoluble; they incorporate on the surface ammonium or pyridinium moieties, carboxylates or phosphates groups. Water-soluble dendrimers are also obtained when they bear on the surface carbohydrate (helicin) or boronic acid but only after addition of sodium hydride (one equivalent per end group) (Scheme 24) [35].



Scheme 24. Synthesis of water-soluble dendrimers from hydrazine end groups

Taking into account the fact that most of the hydrophilic dendrimers described up to now in the literature have been proposed as tools for various biological applications (e.g., transfection, medical imaging, inhibition of viruses, see below) it is important to have not only water-soluble, but also water-stable compounds. This is the case of most of the phosphorus-containing dendrimers reported in this review, some of them being stable for months and even years in water, demonstrating the very high stability toward hydrolysis of both the internal and external hydrazone units and the whole skeleton of the dendrimer.

4.2 Thermal Stability

Owing to their globular shape and their highly branched architectures, dendrimers are expected to be amorphous. In analogy with their solution properties, the thermal properties of phosphorus-containing dendrimers also depend on the type of their end groups. The thermogravimetric analyses (TGA) of some of these macromolecules (generation 5) are reported in Fig. 9 for illustrative purposes. All kinds of dendrimers were found to be thermally stable up to 250 °C and even up to 400 °C for some of them, irrespective of the generation considered. Therefore, they appear as excellent candidates for a number of applications in materials science (see below).

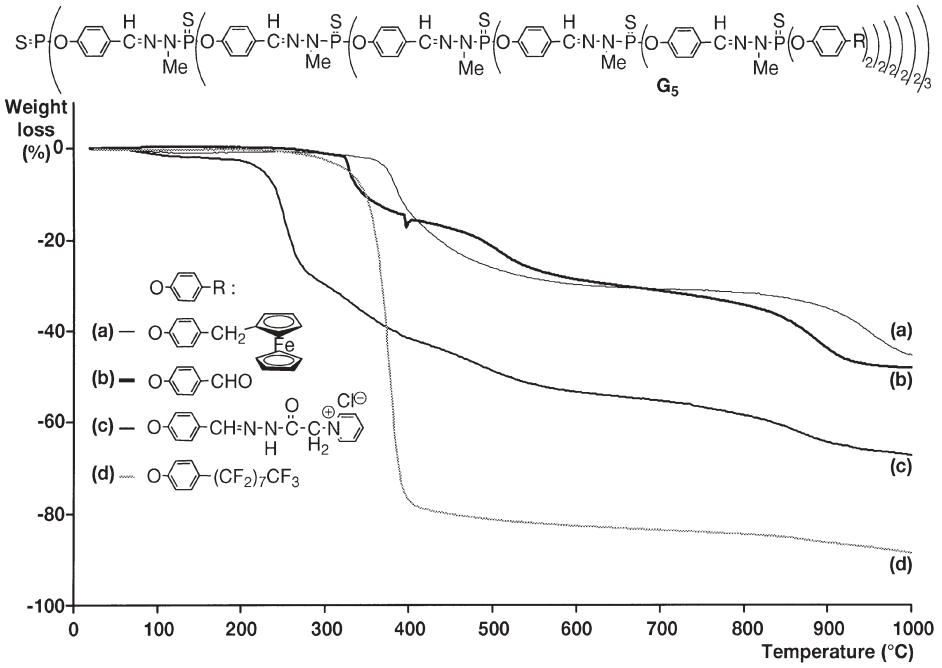


Fig. 9. Thermogravimetric analysis of generation 5 dendrimers variously functionalized on the surface

4.3
Dielectric Spectroscopy Studies

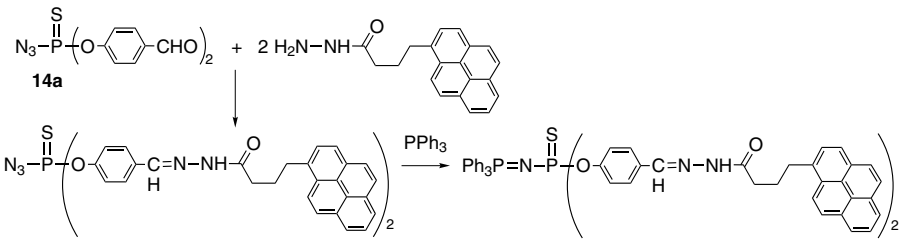
Combined thermostimulated currents (TSC) and dynamic dielectric spectroscopy (DDS) studies allowed us to follow the temperature and frequency dependence of the β relaxation mode of some phosphorus-containing dendrimers bearing terminal aldehyde groups. The dipolar nature of the relaxation modes has been shown [36]. For the "dendrimer" of generation 0, S=P-(O-$C_6H_4CHO)_3$, a narrow relaxation mode is observed: this is consistent with the existence of a single mobile dipolar species, i.e., aldehyde end groups. Those dipolar species interact with P=S dipolar core. The relaxation mode found for the generation 0 exists also for the generations 1 (six terminal CHO groups) and 2 (twelve terminal CHO groups) in the same temperature range. The activation enthalpies remain of the same order of magnitude as for the generation 0. The slight modification of the characteristic parameters has been associated with differences in the interaction with P=S groups. An additional submode is also observed for the dendrimer of generation 2 in the same temperature range: due to its metastability, it might be ascribed to a structural relaxation.

4.4
Vibrational Spectra

IR and Raman spectra studied in conjunction with normal mode calculations provide additional proofs of the structure of phosphorus-containing dendrimers bearing terminal aldehyde groups, up to generation 11. The analysis of the band intensities in the vibrational spectra for generations 0–11 reveals a rather quick saturation and reflects the strong homogeneity of the dendritic macromolecules [37].

4.5
Segmental Mobility

Steady-state fluorescence spectra and decays of excitations of a phosphorus-containing dendrimer labeled with 12 internal (pyrene) labels **31**-[$\mathbf{G'}_3$] and of an iminophosphorane model compound bearing two labels (Scheme 25) dissolved in different solvents revealed that the interior of dendrimers contained, as



Scheme 25. Synthesis of the model compound possessing two pyrene labels

expected, many solvent molecules and movements of internally located pyrene labels were not reduced by interactions with the dendrimer core: formation of ground-state pyrene-pyrene dimers in all investigated species was excluded [38].

4.6 Others

Physical properties of dendrimers having aldehyde end groups were also studied by X-ray photoelectron spectroscopy [39] and dipole moment measurements [10b].

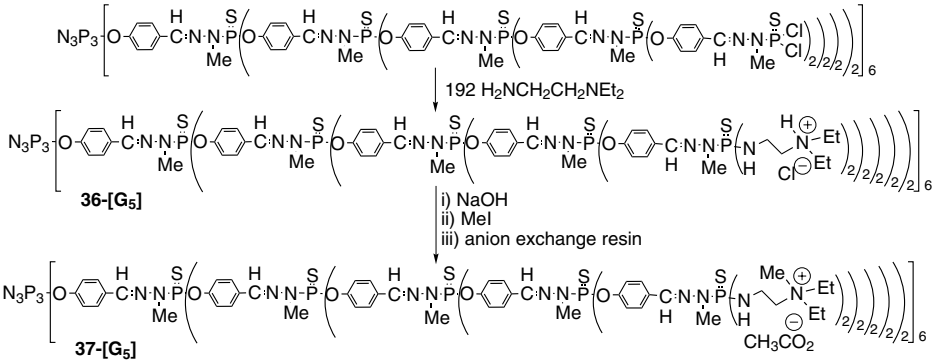
5 Applications

5.1 Biology

Water-soluble dendrimers offer the largest palette of properties and uses in biology.

5.1.1 *Transfection Experiments*

We studied the capacity of dendrimers **36-[G_n]** and **37-[G_n]** (n: generation) (Scheme 26) to mediate the in vitro delivery of nucleic acids (pCMV-luc plasmid, luciferase gene) into mammalian cells (3T3 cells). The property expected in this case is the self-assembly of the cationic dendrimer with the gene bases, which would mediate the penetration of the gene within the cell. The results obtained strongly depend on the type of end groups, even if **36-[G_n]** and **37-[G_n]** differ only by the type of agent used to induce the quaternarization of the terminal amines. Indeed, the methylated forms **37-[G_n]** were found to be rather tox-



Scheme 26. Synthesis of water-soluble dendrimers used for transfection experiments

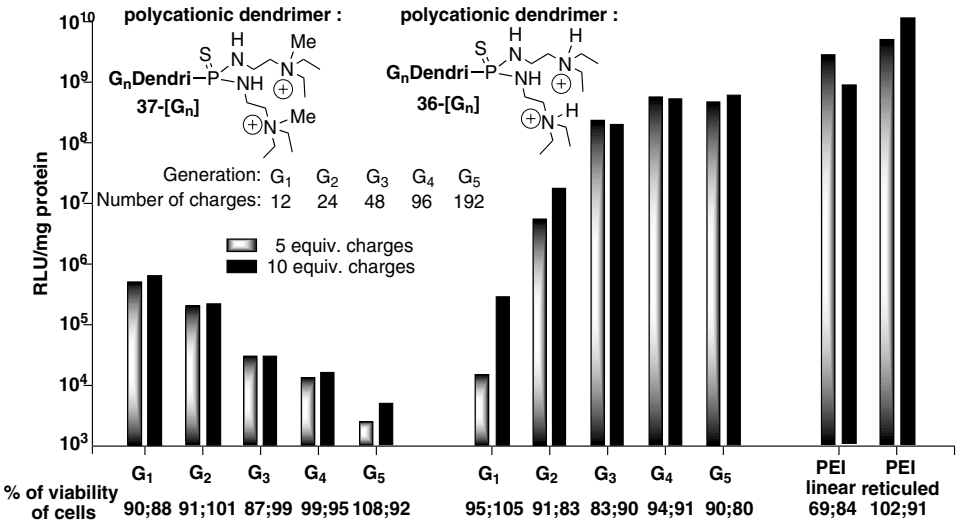


Fig. 10. Transfection experiments performed with dendrimers **36**-[G_n] and **37**-[G_n] in the presence of 10% FCS (serum). NIH 3T3 cell line (murine fibroblast). 2 microg of pCMVLuc/well. Expression stopped 24 h later

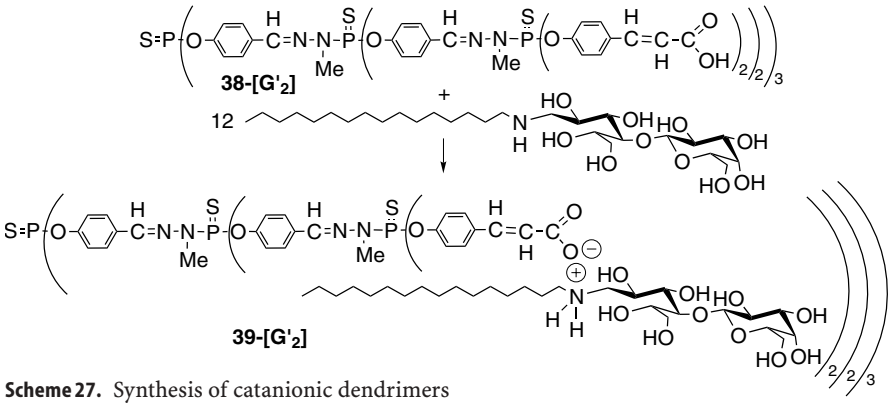
ic and relatively inefficient in transfecting nucleic acids into eukaryotic cells. This phenomenon might be due to the presence of a high and stable positive charge density, which may disrupt the cell membrane, leading to cell death.

In contrast, all protonated dendrimers **36**-[G_n] induce a significant expression of transgene at five equivalents of positive charges per DNA phosphate, better results being obtained in the presence of 10% serum than without serum. Furthermore, the transfection efficiency increased with increasing generation (n) and reached a plateau for generations three to five (Fig. 10).

The difference in efficiency observed between both series of dendrimers is clearly due to the fact that the charge density of series **36**-[G_n] can be modulated by microenvironmental modifications of the pH; this possibility might be a key factor for the release of the luciferase gene within the endosome [40].

5.1.2
Formation of Vesicles

Reaction of dendrimers **38**-[G_2] with L-hexadecylamino-1-deoxylactitol led to the formation of the cationic dendrimers **39**-[G_2] (Scheme 27). A spontaneous supramolecular self-assembly leading to the formation of vesicles was observed by transmission electron microscopy (TEM). It was shown that the size of these vesicles was around 100 nm, and that their shell was constituted by a bilayer (thickness 10 nm) made of two lipophilic layers (thickness 3 nm) separated by a hydrophilic layer. Furthermore, preliminary experiments show that these cationic dendrimers possess an anti-HIV activity in vitro [41].

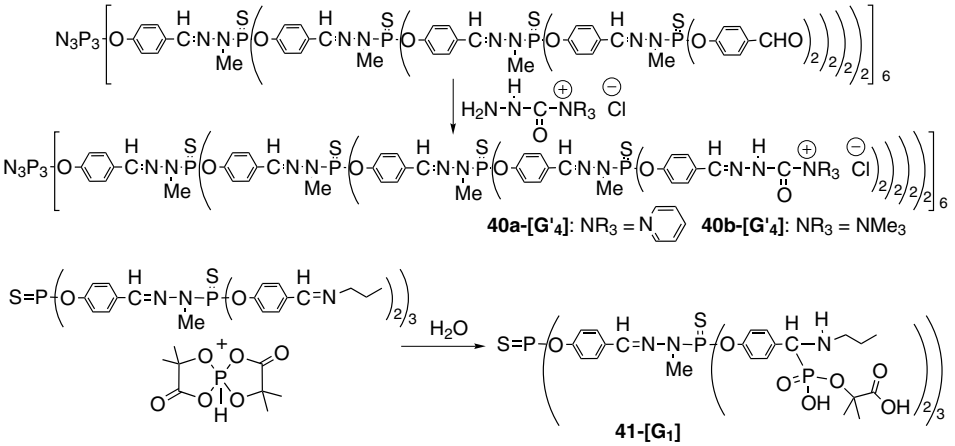


Scheme 27. Synthesis of catanionic dendrimers

5.1.3
Formation of Gels

Dendrimers **40a**-[$\mathbf{G'_n}$] and **40b**-[$\mathbf{G'_n}$] (n = 1 – 4) (Scheme 28) form rigid translucent gels when dissolved and heated in water, even at a relatively low concentration (0.5 % in weight) [42]. Gelation is independent of the generation (from n = 1 to 4) and of the pH (at least from 2 to 10), but strongly depends on the temperature, the concentration, the type of end groups, the nature of the counter ion, and the presence or absence of other substances in the solution. The gels are stable at least for several months at room temperature, they do not flow, and can be even crushed into pieces. Examination of the gel network by freeze-fracture electron microscopy shows that the geometry resembles the one found in gels formed by milk proteins or clay, and suggests that the dendrimers are not covalently bonded, since the dendrimer network is not continuous. This assumption is supported by the reversibility of the gel in organic solvents, particularly in acetonitrile. If the gel is formed in the presence of other hydrosoluble components such as buffer (TRIS), metal salts (Ni, Y, Er acetates), or acids (citric, ascorbic, lactic), these components are integrally incorporated within the gel, and the gelation time is dramatically shortened from several days or weeks to a few hours in some cases. Lyophilization of these gels gives fragile aerogels which have almost retained the size and shape of the initial hydrogels.

A new class of hydrogels is also obtained when a polyanionic dendrimer such as, for example, **41**-[$\mathbf{G_1}$] (Scheme 28) is heated at 60 °C for two days in the presence of Girard P reagents [43].



Scheme 28. Synthesis of water-soluble dendrimers used for the obtaining of hydrogels

5.1.4
Others

Two key applications of phosphorus dendrimers are patented: preparation of DNA chips [44] and use of polycationic phosphorus dendrimers as anti-prions [45].

5.2
Materials Science

We mainly used dendrimers soluble in organic solvents in the field of materials science.

5.2.1
Surface Modification

Dendrimers (aldehyde end groups) were covalently attached to quartz surfaces previously functionalized with NH_2 groups. Characterization of the modified surface by atomic force microscopy (AFM) and X-ray photoelectron spectroscopy (XPS) indicated that the average thickness of the overlayer made of fifth generation dendrimer is 3.7 nm, a value corresponding to the formation of a monolayer. The use of this modified surface for the immobilization of human serum albumin (HSA) from dilute protein solutions induced the formation of clusters composed of at least 50 proteins each. Furthermore, a second layer of dendrimers (having NH_2 end groups) was covalently linked to the first one [46].

The consecutive layer-by-layer adsorption of polyanions and polycations built on glass or silicon wafers first (by chemisorption) with a monolayer of positively charged poly(ethyleneimine) (PEI) was recently reported [47]. Analogous hybrid multilayer architectures were prepared in which polycationic polymers

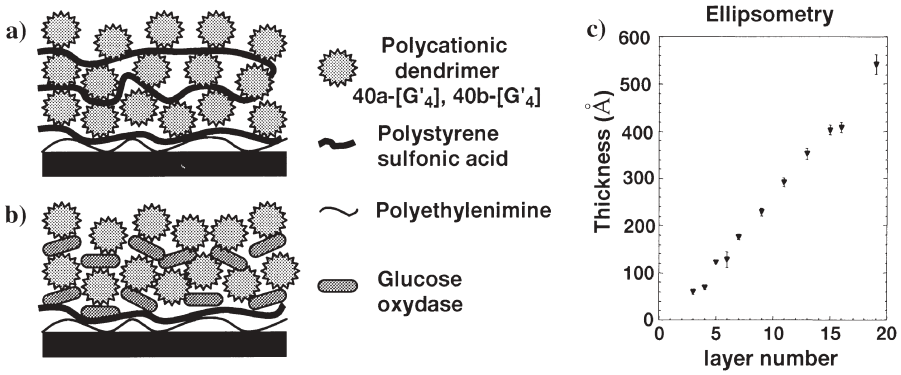
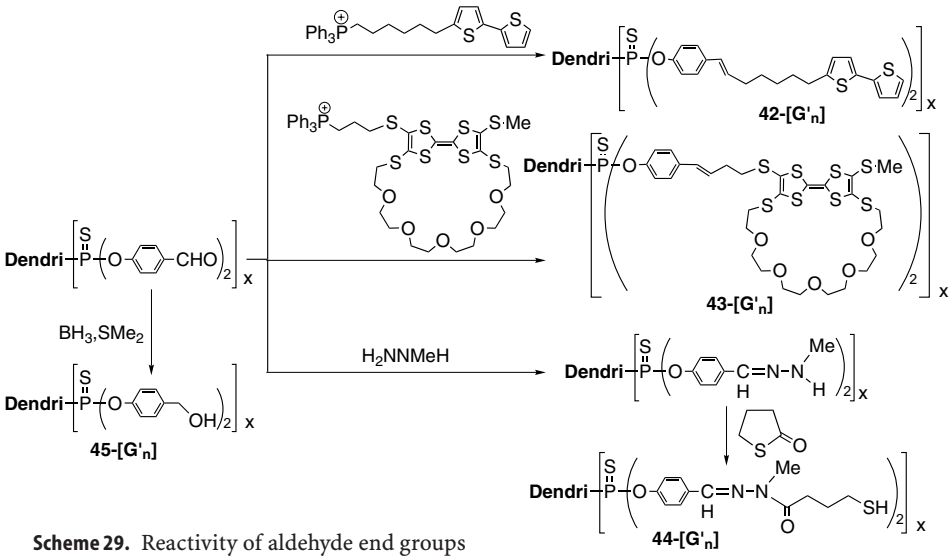


Fig. 11. Hybrid multilayers made of (**a**) polycationic dendrimers and polystyrenesulfonic acid; (**b**) polycationic dendrimers and glucose oxidase; (**c**) thickness of the multilayers obtained in (**a**) depending on the number of layers and measured by ellipsometry

were replaced by polycationic dendrimers of generation 4 with terminal Girard P (**40a**-[**G′**$_4$]) or Girard T (**40b**-[**G′**$_4$]) groups and in which polyanions are either poly(styrenesulfonic acid) (PSS) or glucose oxidase [48]. Linear increases of layer thickness and of maximum absorbance with the number of deposited layers are observed when dendrimers are combined with polyelectrolytes (Fig. 11). Up to fifteen bilayers were prepared. Similarly, combinations of the same polycationic dendrimers with glucose oxidase were investigated. Reactions were done at pH 5. At this pH glucose oxidase has a negative charge of –24 and the enzyme is active for glucose oxidation. A linear increase of layer thickness and of absorbance with the number of deposited double layers are observed. The presence of 1 M sodium salt in glucose oxidase solution is essential to obtain a steady cycle. The thickness associated to glucose oxidase is 30 Å and to dendrimer 14 Å.

Dendrimers were used for the surface modification of electrodes. Phosphorus-containing dendrimers having ferrocene derivatives on the surface are reversibly oxidized upon oxidation and form a blue conducting film on the electrode [28l,m]. On the other hand, the bithiophene derivatives **42**-[**G′**$_n$] (Scheme 29) are irreversibly oxidized to yield a conducting polymer, as shown by the formation of a dark blue film on the anode surface [49]. Interestingly, the aqueous electroactivity of this polythiophene dendrimer film is 100% for the fourth generation, whereas the polythiophene is almost inactive in these conditions. The crown ether-tetrathiafulvalene (TTF) dendrimers **43**-[**G′**$_n$] (Scheme 29) were electrodeposited on a Pt electrode as a consequence of the two step reversible oxidation of the TTF moieties [50]. Scanning electron microscopy (SEM) shows a homogeneous coverage of the whole surface of the Pt electrode by the dendrimer. A remarkable feature of this modified electrode is that it possesses the unique capability to complex and decomplex reversibly Ba^{2+} cations, hence acting as a sensing device.

Dendrimers **44**-[**G′**$_n$] (Scheme 29) allowed a demonstration of both the influence of the number of end groups (the generation) and the density of these groups (same generation but different core, tri- or hexa-functional) on the prop-



Scheme 29. Reactivity of aldehyde end groups

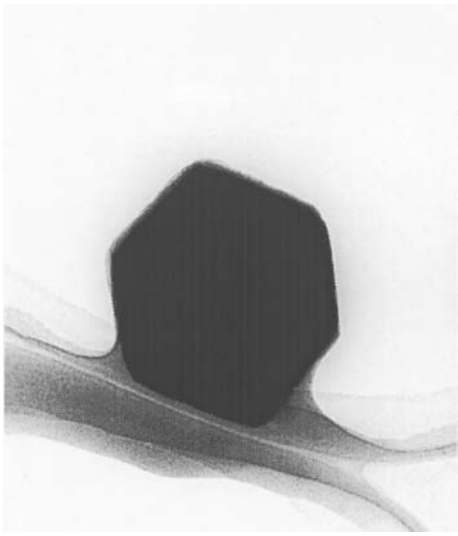


Fig. 12. Transmission electron microscopy photo of a hexagonal crystal of bare Au_{55} protected by dendrimer **44**-[**G′**$_n$]

erties of dendritic molecules. These dendrimers were reacted with the gold cluster $Au_{55}(PPh_3)_{12}Cl_6$ [51]. Whatever the generation was, this reaction resulted in the formation of crystals of bare gold. However, the shape of the crystals was dramatically different. The larger and denser dendrimer (generation 4, 96 thiol end groups emanating from a hexafunctional core) gives well formed hexagonal

microcrystals. The role of the dendrimer is not only to remove the phosphane and chlorine ligands but also to act as an ideal matrix for perfect crystal growth. Transmission electron microscopy (TEM), small- and wide-angle X-ray diffraction (SAXRD and WAXRD) measurements showed that the crystals were made of naked Au_{55} clusters arranged in a distorted cubic lattice. The TME images revealed also the presence of an amorphous shell that envelops the microcrystals. We think that this shell consists of the dendritic material, which acts as a protection for the microcrystals (crystals of naked Au_{55} were unknown up to now) (Fig. 12).

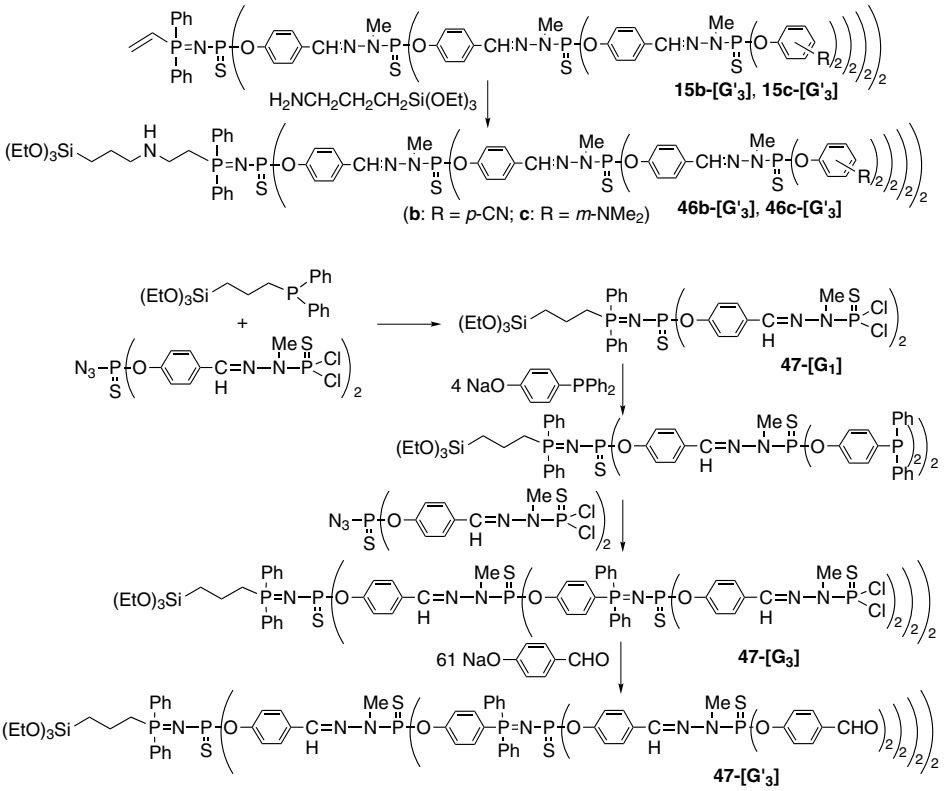
5.2.2 *Hybrid Materials*

We have made new materials incorporating dendritic molecules covalently linked within the material. The strategy based on the assembly of nano-building blocks (ANBB) with well-defined structures should allow the controlled design of new materials. Our first approach consisted in reacting a titanium cluster $[Ti_{16}O_{16}(OEt)_{32}]$ with low generations of dendrimers **38**-$[\mathbf{G'}_n]$ and **45**-$[\mathbf{G'}_n]$ [52]. Meso-structured hybrid materials were obtained in this way, the formation of the hybrid surface consisting in transalcoholysis with the alcohol groups of **45**-$[\mathbf{G'}_n]$, and in bridging carboxylates with the acidic groups of **38**-$[\mathbf{G'}_n]$. Powder XRD indicates in both cases that the dendrimer acts as a spacer, and that a local order is attained.

The elaboration of porous materials by using metal alkoxides [$Ce(O\text{-}i\text{-}Pr)_4$, $Ti(OR)_4$] as inorganic precursors and acid functionalized dendrimers as organic template is also reported [53]. The reactivity of the metal oxide precursors was controlled by using chelation by COOH groups present at the dendrimer surface. This reaction creates anchoring points for the nucleation of a gel phase. The bicontinuous gels resulting after solvent evaporation present a "sponge-like" structure with pore size ranging from 10 nm to 30 nm. The effects of the metal/dendrimer ratio, the sol preparation procedure, and aging conditions were studied by XRD, FTIR, TEM, SEM, and BET.

The dendrons **46**-$[\mathbf{G'}_n]$ and **47**-$[\mathbf{G'}_n]$ allowed us to obtain another type of hybrid material incorporating dendritic structures. The co-hydrolysis and polycondensation of these macromolecules with a defined and varying number of equivalents of tetraethoxysilane (TEOS) was carried out via a sol-gel protocol, giving rise to dendrimer-silica xerogels, in which the dendron is covalently linked by one Si-C bond to the silica [54] (Scheme 30). The nature of the material was determined by solid NMR (^{29}Si, ^{31}P), thermal analyses, and nitrogen adsorption (BET) measurements. Some of these materials were found to be mesoporous with a narrow pore size distribution.

In conclusion, phosphorus-containing dendrimers and dendrons offer a large palette of properties usable in various areas of materials chemistry. Indeed, we have demonstrated that these dendritic macromolecules allow the tailored modification of various surfaces by covalent or ionic interactions. Furthermore, these dendritic macromolecules can be also incorporated within new materials, the dendrimer acting as a template for the formation of the material.



Scheme 30. Synthesis of dendrons usable for the obtaining of silica xerogels

5.3 Catalysis

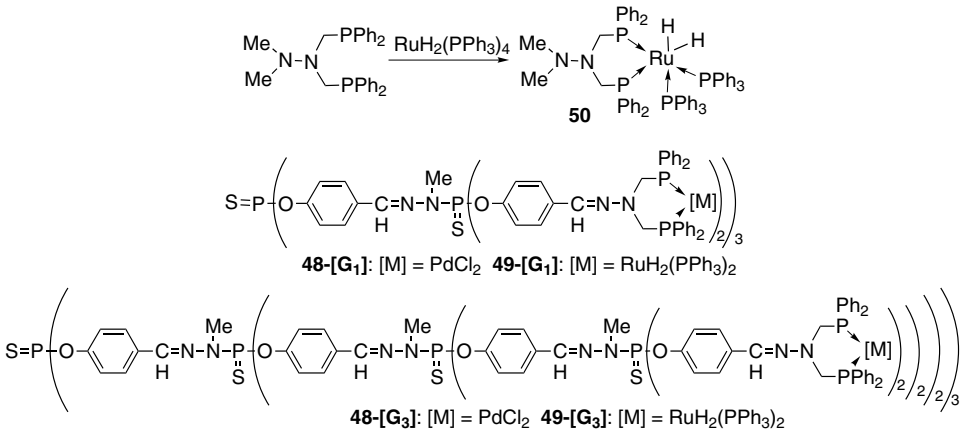
The search for an ideal catalysis that combines advantages of both homogeneous and heterogeneous catalysis is at the center of many investigations. In that sense metalladendrimers are emerging as a promising class of compounds. This interest is due to the properties of dendrimers: high solubility, high concentration of easily accessible active sites, and easy separation by nanofiltration or precipitation. Metalladendrimers can be more active, more selective or more stable than the corresponding monomers. The wide scope of applications of metalladendrimers has been recently reviewed [55, 56]. Practically all experiments using these species have been performed with "organic" dendrimers incorporating phosphorus ligands *only* on the surface or more rarely at the core. As already mentioned in the introduction of this chapter, this review will not cover the synthesis and applications of dendrimers bearing phosphane or diphosphane groups exclusively on the surface.

DuBois et al [4] reported the synthesis of phosphorus-containing dendrimers using a sequential addition of diethyl vinylphosphonate to primary phosphanes

followed by reduction with lithium aluminum hydride. Metallation of these dendrimers containing 12 and 15 phosphorus atoms with $[Pd(CH_3CN)_4](BF_4)_2$, affords complexes exhibiting catalytic activity for electrochemical CO_2 reduction [4]. Rh(I) metalladendrimers (Scheme 1) were also found to be good catalysts for the hydrogenation of decene [7].

We have prepared a variety of metalladendrimers from the reaction of phosphorus-containing dendrimers with various transition metal complexes. Dendritic complexes incorporating metals such as gold [28a, 57], iron [57, 58, 59], tungsten [58, 59], rhodium [59, 60], platinum [60], palladium [61], ruthenium [62], or zirconium [63] were prepared.

Palladium and ruthenium dendritic diphosphane complexes **48**-[G_n] and **49**-[G_n] shown in Scheme 31 were used in three general organic syntheses: cross coupling reactions (Stille coupling), Knoevenagel condensations, and diastereoselective Michael additions [64]. Activity can be compared with that of classical monomer complexes such as, for example, **50** or a more original macrocyclic complex like **51**, and is often higher (Figs. 13 and 14), but in marked contrast with monomer **50**, recycling is possible without significant loss of activity [65].



Scheme 31. Synthesis of dendrimers having organometallic derivatives on the surface, usable for catalysis

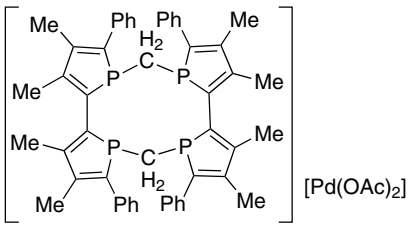


Fig. 13. Monomer **51** used in catalysis

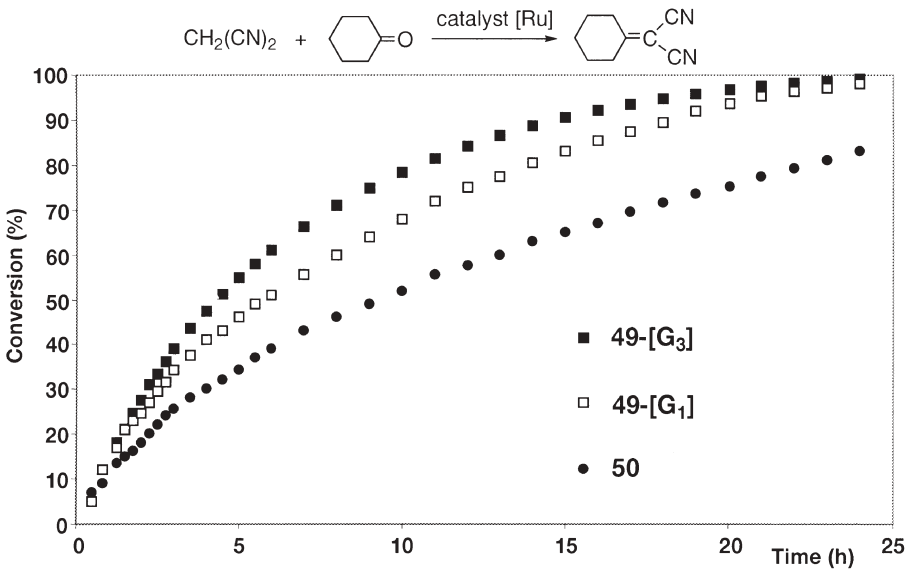
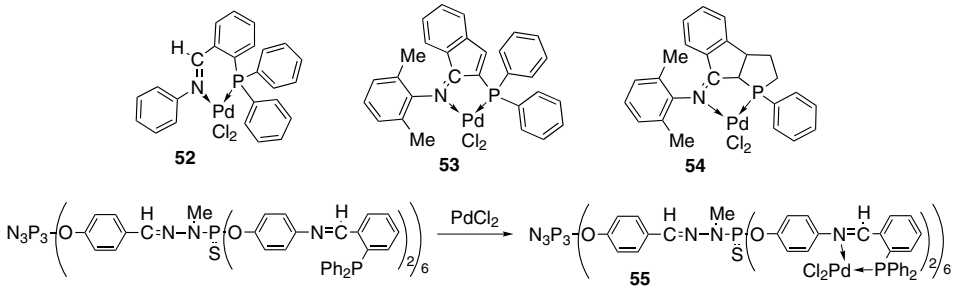


Fig. 14. Plot of the percentage of conversion versus time for various catalysts measured by ^{1}H-NMR for the Knoevenagel condensation

The catalytic performances of phosphorus-containing dendrimers incorporating γ-iminophosphane palladium complexes on the surface have also been compared with that of palladium complexes of a variety of β- and γ-iminophosphanes (Scheme 32) for three different Stille coupling reactions [66]. It clearly appears from these experiments that palladium complexes of the γ-iminophosphane **52** are better catalysts than the complexes formed from bi- or tricyclic β-iminophosphanes **53** or **54**, respectively. The catalytic performances of the metalladendrimers **55** depend on the reagents involved in the investigated Stille coupling reactions: beside the fact that they can be easily recycled, they also allowed improvement of the catalytic activity of γ-iminophosphane palladium complexes in the case of the reaction of iodobenzene with tributylvinyltin. Further investigations concerning the role of steric effect and elec-



Scheme 32. Iminophosphorane complexes usable in catalysis

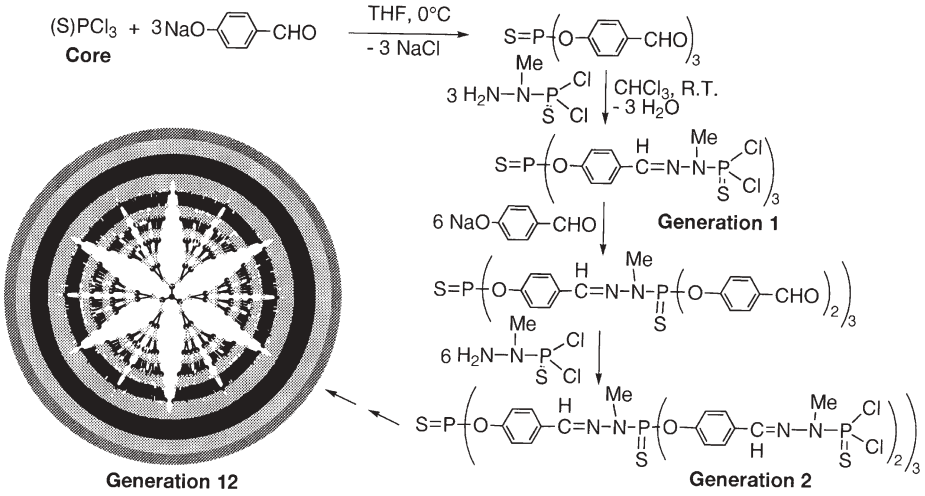
tronic influence of ligands, and the role of the complex inside the dendrimer or on the surface are necessary to understand and explain the behavior of these metalladendrimers.

6 Conclusion

It is clear from this compilation of reports concerning the synthesis and the properties of phosphorus-containing dendrimers that these macromolecules are not just an additional class of dendrimers: they have really their specificity and, as the preliminary results concerning their applications have shown, they are useful tools for many applications from biology to materials science.

The extraordinary versatile behavior of phosphorus makes it possible to put on the market several original ways of synthesis of dendrimers. Indeed a method allowed us several years ago to prepare dendrimers of the highest generation known up to now; this method consists of the reiteration of a sequence of reactions using easily available starting reagents, yields are quantitative and the by-products easy to remove (sodium chloride and water) (Scheme 33). Most of the applications reported in this review concern these dendrimers. Even more promising, a new strategy involving the alternate use of two monomers AB_2 and CD_2 permits us to build each generation using only one step. Remarkably, an unprecedented one-pot multistep procedure leads directly to the synthesis of a dendrimer of generation 4 (by-products: N_2 and water!!).

Therefore, phosphorus-containing dendrimers are easily prepared. Similarly the facile access to dendrons due to the properties of phosphorus reagents allows us to diversify the synthesis of a variety of multidendritic macromole-



Scheme 33. Reiteration of a sequence of two reactions for the synthesis of phosphorus-containing dendrimers

cules. Indeed surface-block dendrimers, layered surface-block dendrimers, layer-block dendrimers can be prepared. The unique regioselective growth of dendrimers into the cavities of a main dendrimer was also proposed.

Last but not least, the synthesis of linear polymers, hyperbranched polymers or dendrimers constituted with the same building blocks was reported. This is one of the very rare examples of such methodology appearing in the literature.

Reactivity of all these phosphorus-containing dendrimers and related species is very high and leads to many new multifunctionalized macromolecules. These giant molecules exhibit very interesting properties, both from a fundamental and applicative viewpoint.

In biology, phosphorus-containing dendrimers – a non-toxic class of dendrimers – offer a broad range of possible applications from DNA transfection agents to DNA chips or as anti-prions, or anti-HIV species.

Hydrogels (thermoreversible or not) represent a promising class of gels able to solve problems concerning drug delivery or encapsulation of active substances. The use of phosphorus-containing dendrimers in materials science is blossoming. They were used in surface modification, multilayers formation, for the formation of nanobuilding assemblies or hybrid inorganic-organic materials, or for construction of the first network of clusters of clusters of naked gold which might have exciting properties in nanoelectronic.

Catalysis is of course a field of research where phosphorus-containing dendrimers should be effective. Preliminary experiments confirm this assumption.

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Phosphonate Chemistry and Reagents in the Synthesis of Biologically Active and Natural Products

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A review on the total syntheses of bioactive compounds and natural products published in the last decade using phosphonate reagents and phosphonate-based methodologies is presented.

Keywords. Phosphonates, Horner-Wittig reaction, Total synthesis, Bioactive compounds, Natural products

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1 Introduction

The last decades have seen the development of many important applications of organophosphorus compounds. There is no doubt that in the field of organic synthesis the Wittig synthesis of alkenes from ylides and carbonyl compounds and its phosphonate version, the so-called PO-olefination, play the most important role [1]. In the latter reaction, named here the Horner-Wittig reaction, α-phosphonate carbanions react with aldehydes and ketones to give olefins and dialkyl phosphate anions. Although this reaction generally gives a preponder-

ance for the *E*-alkene, its regiochemistry can be controlled by the choice of phosphonate derivative. In addition to 2,2,2-trifluoroethoxy group [2], the use of the aryloxy substitutents [3, 4] attached to phosphorus strongly favors formation of the *Z*-alkene. In recent years, the area of asymmetric Horner-Wittig reactions has received increasing attention [5]. The phosphonoacetates, derived from 8-phenylmenthol, were found to be useful chiral Horner-Wittig reagents able to distinguish between enantiotopic carbonyl units in *meso*-dicarbonyl compounds or to resolve racemic aldehydes in a process of kinetic or dynamic kinetic resolution [6–8]. In addition to their use in the Horner-Wittig reaction, α-phosphonate carbanions react with a variety of electrophiles other than carbonyl electrophiles which results in the formation of new carbon-carbon or carbon-heteroatom bonds. These reactions allowed for the synthesis of a large range of new phosphonate structures which have found application in the synthesis of complex natural products or drugs [9]. In contrast to α-phosphonate carbanions, the corresponding, equally important α-phosphonate radicals have received much less attention. Although in the past decade basic studies on this class of reactive intermediates have been reported [10], their synthetic application is in its infancy.

The aim of this chapter is to collect and discuss the use of phosphonates in the synthesis of biologically active or natural products in the last decade. Since in this period, innumerable syntheses of such compounds have been effected with these reagents, we have restricted our discussion to such cases where more extensive use of phosphonates in total syntheses is reported. Therefore, the synthetic approaches to bioactive products, where a single Horner-Wittig or other phosphonate reaction was used, are beyond the scope of this review. Moreover, this article is not intended to provide a comprehensive coverage of the field. It highlights some of the recent developments reported in the literature with the hope to stimulate further research in this area.

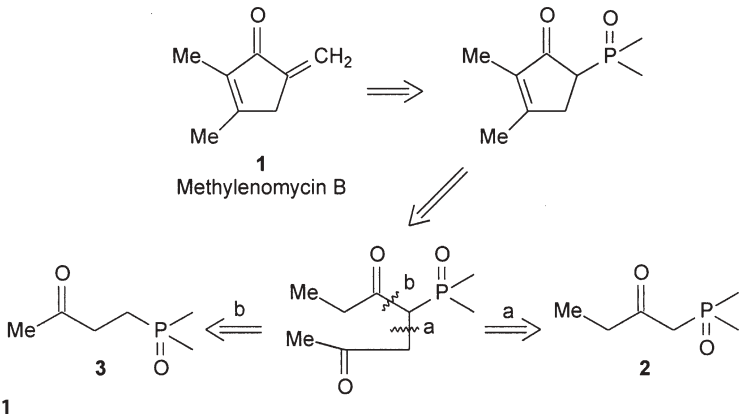
2
Use of Phosphonates in the Synthesis of Biologically Active Cyclopentanones and Cyclopentenones

The 2-cyclopentanone and 2-cyclopentenone structural units are present in a wide range of important natural products such as jasmonoids, cyclopentanoid antibiotics, pentenomycins, prostaglandins, terreins and carbocyclic nucleosides. The broad spectrum of biological activity of this type of compounds has prompted an extensive search for development of new methods for their preparation. Although the structures of these natural products are relatively simple, their synthesis is not trivial because of the low chemical stability of many of these compounds and the specific functionalization of the five-membered ring. The use of phosphonates offers several important advantages in this field. Below is a list of natural products and bioactive molecules, containing the common structural motifs mentioned above, that have been synthesized through the use of phosphonates.

2.1
Synthesis of Methylenomycin B

Methylenomycin B (**1**) isolated from the culture broth of *Streptomyces* species in 1974, is a new antibiotic with inhibitory activity against Gram-positive and Gram-negative bacteria [11 – 13]. Since the first total synthesis [14], which led to the revision of the original structure proposed by Haneishi et al. [11], methylenomycin B (**1**) has attracted considerable attention of many research groups as a synthetic target [15, 16].

Continuing studies on the application of organic phosphorus and sulfur compounds for the synthesis of 1,4-dicarbonyl compounds and functionalized cyclopentenones, Mikolajczyk and Zatorski [17] developed a short and efficient synthesis of methylenomycin B starting from β- and γ-ketophosphonates **2** and **3**. These two reagents were revealed by retrosynthetic analysis shown in Scheme 1.

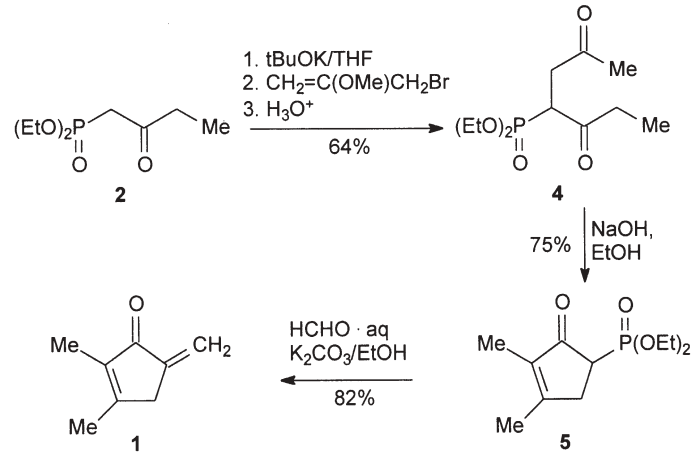


Scheme 1

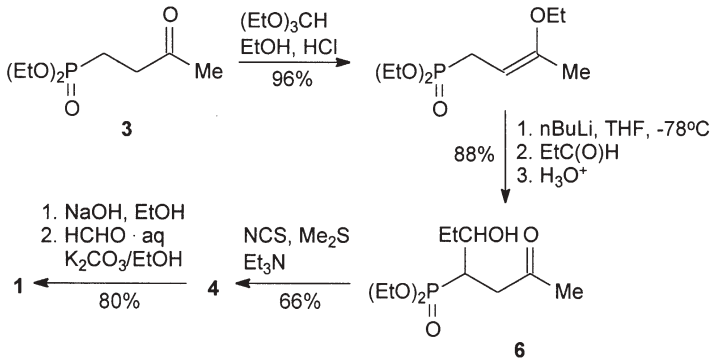
In the first synthetic key step, the β-ketophosphonate **2** was alkylated with 1-bromo-2-methoxyprop-2-ene. Then, the product of monoalkylation was hydrolyzed under acidic conditions to the corresponding phosphorylated 1,4-diketone **4** that was cyclized to the precursor of methylenomycin B, the 5-phosphorylcyclopentenone **5**. The Horner-Wittig reaction of the latter with formaldehyde under very mild conditions completed the synthesis of **1** in 39% overall yield (Scheme 2).

An alternative approach to **1** utilizing γ-ketophosphonate **3** as a substrate turned out to be also efficient. The key steps were addition of *n*-propanal to the phosphonate anion derived from the protected **3** and oxidation of the hydroxy adduct **6** to the diketone **4** (Scheme 3). As a result, methylenomycin B was obtained in five steps and 34% overall yield.

A conceptually different approach to the synthesis of methylenomycin B was developed by Mikolajczyk and Zurawinski [18]. In this case, the construction of the cyclopentenone ring was based on an intramolecular carbenoid cyclization. The four-step synthesis starts from diethyl methanephosphonate **7** which was



Scheme 2

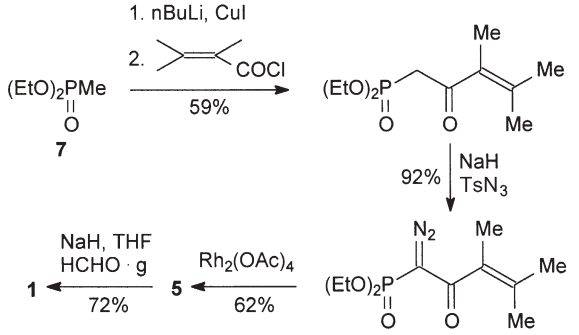


Scheme 3

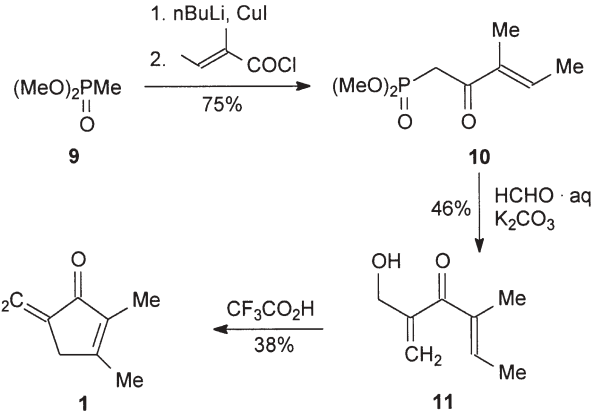
acylated with 2,3-dimethyl-2-butenoyl chloride and then transformed into the corresponding α-diazo-β-ketophosphonate **8**. This key intermediate underwent intramolecular cyclization in the presence of rhodium(II) acetate to afford the well-known 5-phosphorylcyclopentenone **5**. The Horner-Wittig reaction of **5** with formaldehyde completed the synthesis of methylenomycin B (**1**) in 24% overall yield (Scheme 4).

Motoyoshiya et al. in the course of their studies on the Nazarov reaction [19] found a convenient method for the synthesis of **1**, whose substituted cyclopentenone ring with the exocyclic α-methylene group was constructed in one operation [20]. This synthesis began with the acylation of dimethyl methanephosphonate **9** with tigloyl chloride to produce the unsaturated β-ketophosphonate **10** which in the next step was reacted with aqueous formaldehyde to give the dienone **11**. The Nazarov reaction of the latter provided methylenomycin B (**1**) in 12% overall yield (Scheme 5).

Recently, Balczewski [21] reported a formal synthesis of methylenomycin B based on a new free-radical strategy for the synthesis of α-functionalized β-

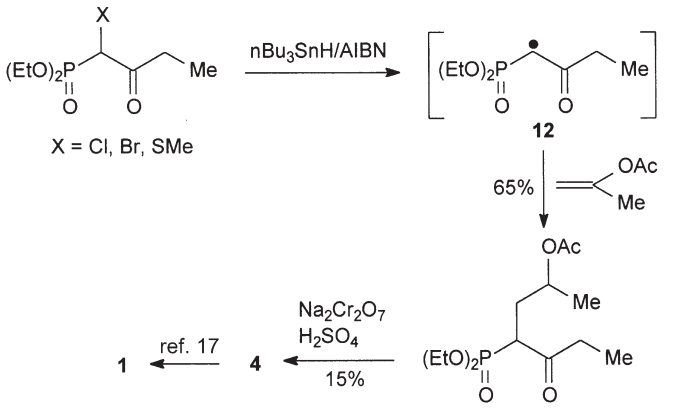


Scheme 4



Scheme 5

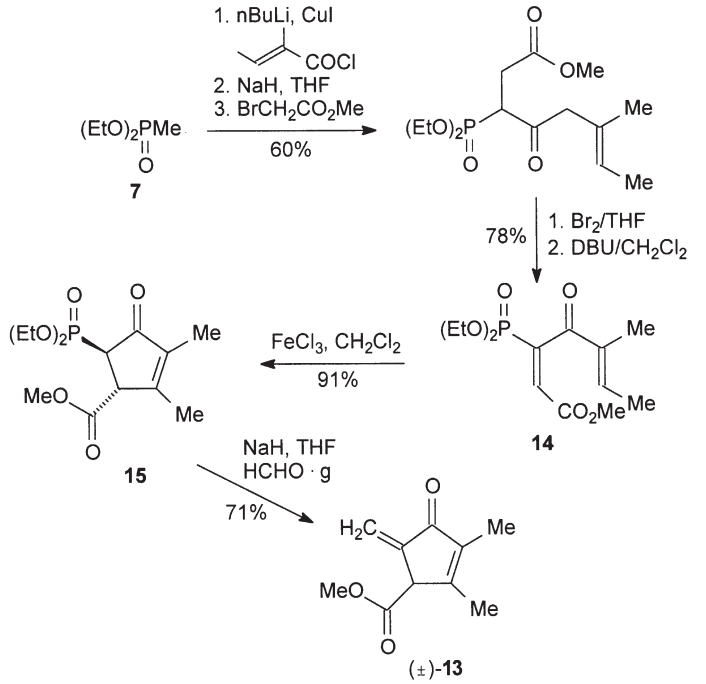
ketophosphonates [22]. The essence of the new concept is the use of α-phosphoryl radical **12** which underwent addition to isopropenyl acetate affording the corresponding adduct. Its oxidation gave **4** – the precursor of methylenomycin B (**1**) (Scheme 6).



Scheme 6

2.2
Synthesis of (±)-Desepoxy-4,5-didehydromethylenomycin A Methyl Ester

The title compound **13** belongs to a family of cyclopentanoid antibiotics and, like methylenomycin B, has shown substantial antibacterial activity. The synthetic route to **13**, devised by Balczewski and Mikolajczyk [22], begins from the phosphonate **7** and involves as a key step the Nazarov cyclization of the dienone **14.** This crucial intermediate was prepared in a simple and efficient way by acylation of the lithium-copper salt of **7** with tiglic acid chloride followed by alkylation of the β-ketophosphonate formed with methyl bromoacetate. A simple bromination-debromination procedure of the resulting α-alkylated β-ketophosphonate gave the desired dienone **14.** Its Nazarov reaction carried out in the presence of iron(III) chloride in methylene chloride at –30 °C gave the cyclopentenone **15** in 91% yield and with the *trans*-situated phosphoryl and methoxycarbonyl groups as the only reaction product. In the last step, the Horner-Wittig reaction of **15** with gaseous formaldehyde allowed the introduction of the exocyclic α-methylene moiety under mild conditions for completion of the synthesis of racemic methyl ester of desepoxy-4,5-didehydromethylenomycin A in 31% overall yield (Scheme 7).

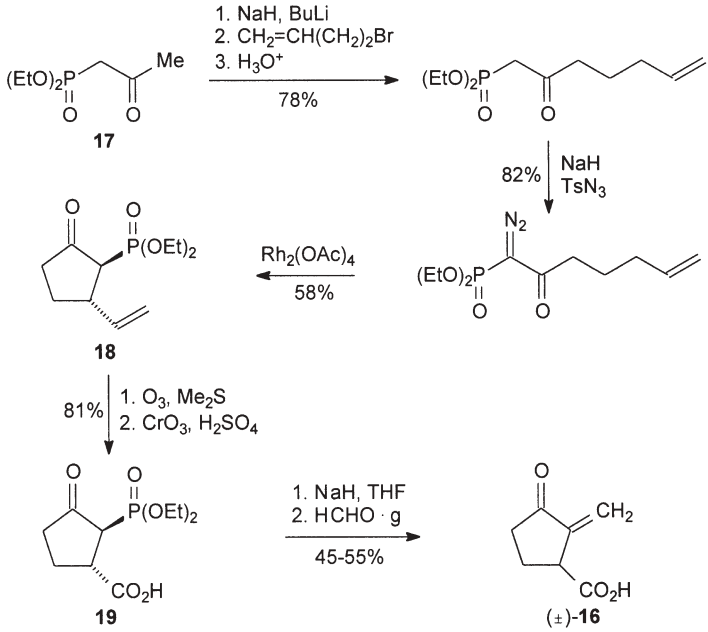


Scheme 7

2.3
Synthesis of Racemic and Optically Active Sarkomycin

Sarkomycin (**16**), a member of the cyclopentanoid class of antibiotics, was first isolated by Umezawa et al. [23] in 1953 and its structure established in 1955 [24]. In contrast to methylenomycins **1** and **13**, sarkomycin is chiral due to the presence of a stereogenic center at the carbon atom 3 of the cyclopentanone ring and the soil microorganisms produce the levorotatory enantiomer having the absolute configuration *R* as correctly assigned by Hill in 1967 [25]. Sarkomycin (**16**) shows not only antibacterial and antiphage properties but also displays antitumor activity [26]. Although sarkomycin (**16**) in one of the simplest antitumor compounds, its total synthesis elicited considerable interest because of a high chemical instability of this deceptively simple structure [27]. As in the case of the synthesis of other cyclopentanoid antibiotics discussed above, the use of phosphonates in the synthesis of sarkomycin turned out to be very advantageous which allowed one to synthesize not only racemic but also the enantiomeric forms of this target. Based on the experience with the synthesis of methylenomycin B (**1**) Mikolajczyk and coworkers [28] decided to utilize the intramolecular carbenoid cyclization for the construction of the suitably substituted cyclopentanone ring. A total synthesis of racemic sarkomycin (**16**) from the readily available diethyl 2-oxopropanephosphonate **17** is shown in Scheme 8 and discussed below.

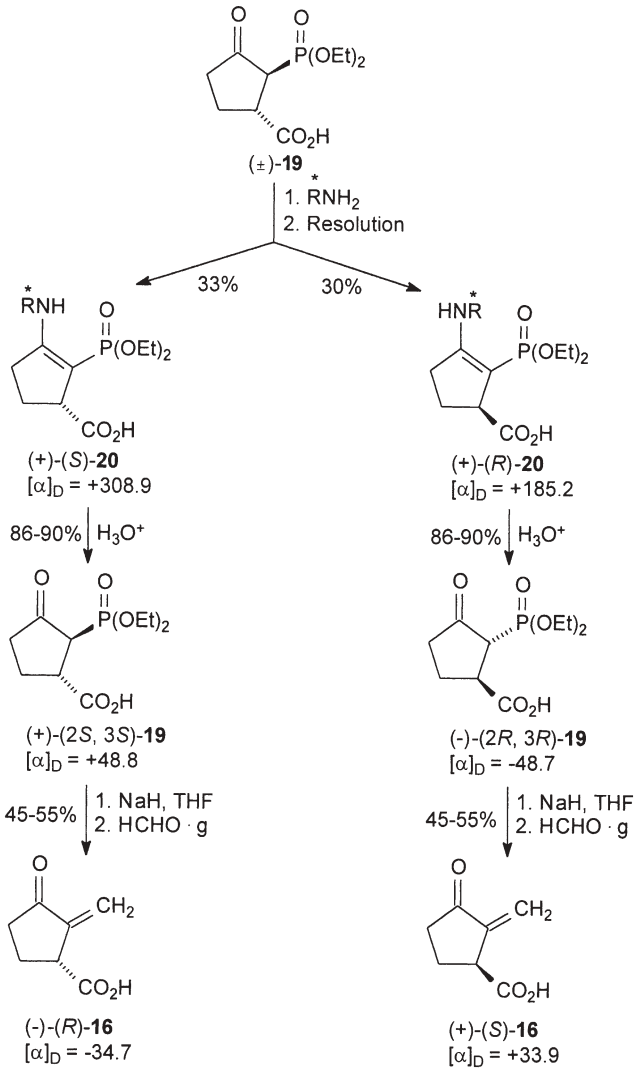
In the first step, the dianion generated from **17** was alkylated with homoallyl bromide to give the corresponding *β*-ketophosphonate which, under typical di-



Scheme 8

azo-transfer reaction conditions, was transformed into the α-diazophosphonate. Decomposition of this intermediate in the presence of rhodium(II) acetate afforded the required 2-phosphoryl-3-vinyl-cyclopentanone **18**. Its conversion into the sarkomycin precursor **19** was effected by ozonolysis of the vinyl moiety and oxidation of the aldehyde formed by the Jones reagent. In the last step, the Horner-Wittig reaction was carried out with gaseous formaldehyde affording (±)-sarkomycin (**16**) in 16% overall yield.

Since the precursor of sarkomycin – the cyclopentanone **19** – is fairly stable and contains the carboxylic group as a resolving handle, its resolution was car-

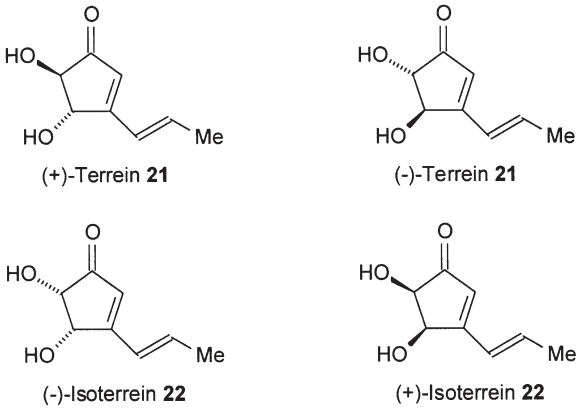


Scheme 9

ried out with (–)-(*S*)-1-(naphthyl)ethylamine. However, in this particular case, instead of the expected diastereomeric salts two diastereomeric enamines **20** were formed which were easily separated by column chromatography. Their hydrolysis gave the enantiomerically pure cyclopentanones **19** from which the sarkomycin enantiomers were obtained for the first time. Scheme 9 shows some details of the resolution of (±)-**19** and synthesis of enantiopure sarkomycins **16**.

2.4 Synthesis of Terreins

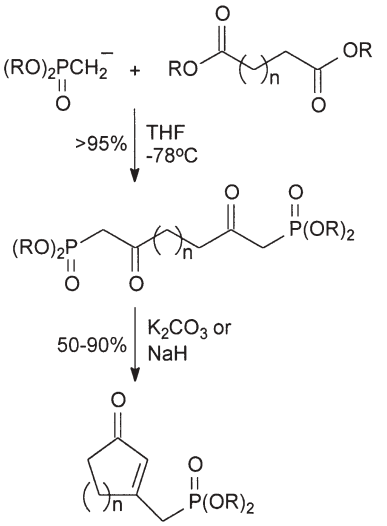
(+)-Terrein (**21**), a metabolite of the mold *Aspergillus terreus*, was first isolated by Raistrick and Smith in 1935 [29]. Its correct structure was established independently by Grove [30] and by Barton and Miller [31]. The latter authors degraded (+)-**21** to a derivative of (+)-tartaric acid and in this way determined the *trans*-configuration of the diol moiety. Barton and Hulshof [33] also described the synthesis of racemic isoterrein **22** which has a *cis*-diol unit. The structures of enantiomeric forms of **21** and **22** are shown below.



Structures 21–22

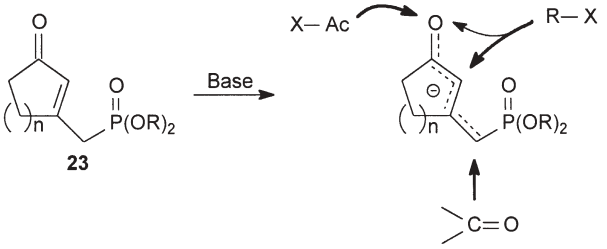
These optically active cyclopentanoids have been synthesized from tartaric acids or their derivatives employing a new phosphonate-based strategy for the construction of substituted cycloalkenones. Therefore, before presenting total syntheses of terreins it is desirable to outline this new strategy because it was used in the synthesis of other bioactive products. It was found [33, 34] that 3-(phosphorylmethyl)-2-cycloalkenones **23** are formed in good yields by intramolecular Horner-Wittig reaction of the corresponding bis-β-ketophosphonates which, in turn, are easily prepared from dicarboxylic acid esters and α-phosphonate carbanions (Scheme 10).

The structure of the cycloalkenones **23** offers many possibilities for further elaboration especially via the anion derived from **23** because its negative charge is distributed among several atoms and electrophiles can react at different sites as schematically shown in Scheme 11.



Scheme 10

23

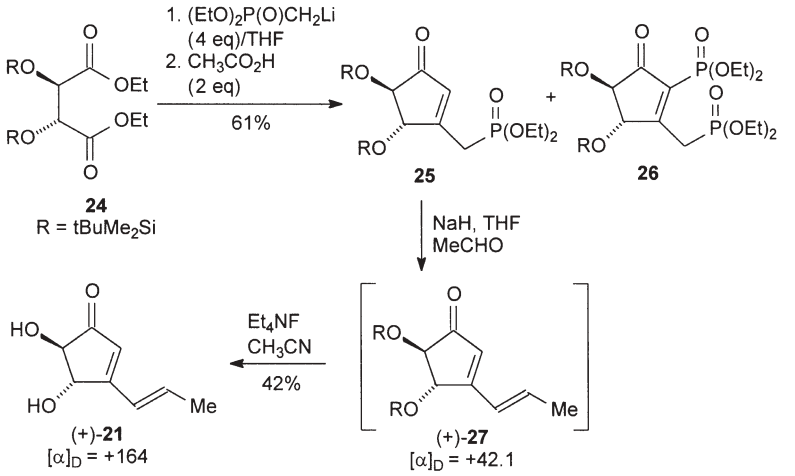


23

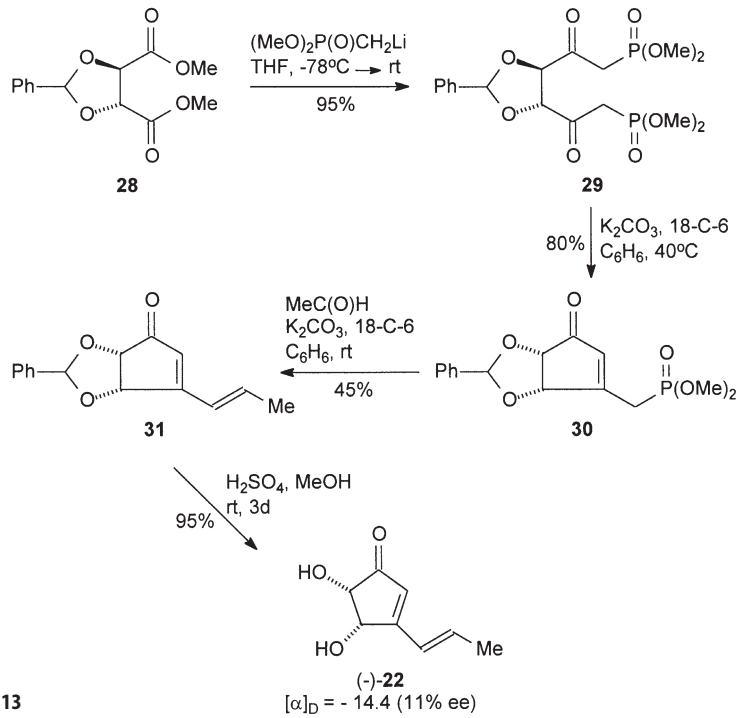
Scheme 11

The ketophosphonate chemistry briefly discussed above indicates that the cycloalkenones **23** can be easily functionalized and, therefore, can serve as synthetic intermediates in the synthesis of bioactive products. Having this in mind, Altenbach and Holzapfel [35] devised an elegant and short synthesis of natural (+)-terrein (**21**) from the protected ethyl ester of (+)-(L)-tartaric acid **24**. Upon reaction of **24** with diethyl lithiomethanephosphonate in the presence of acetic acid under strictly controlled reaction conditions a mixture of two cyclic products **25** and **26** was formed. The first of them, readily separated chromatographically, was the desired product of an intramolecular Horner-Wittig reaction of the transiently formed bis-β-ketophosphonate. Introduction of the unsaturated side chain was achieved via Horner-Wittig reaction with acetaldehyde. Subsequent deprotection of the chiral diol moiety with fluoride ion gave (+)-terrein (**21**) in 26% overall yield (Scheme 12).

However, when the benzylidene protected methyl ester of (+)-tartaric acid **28** was used as a substrate, this methodology resulted in the unexpected formation of (+)-isoterrein (**22**) [36]. Scheme 13 shows this first, serendipitous synthesis of this compound.



Scheme 12

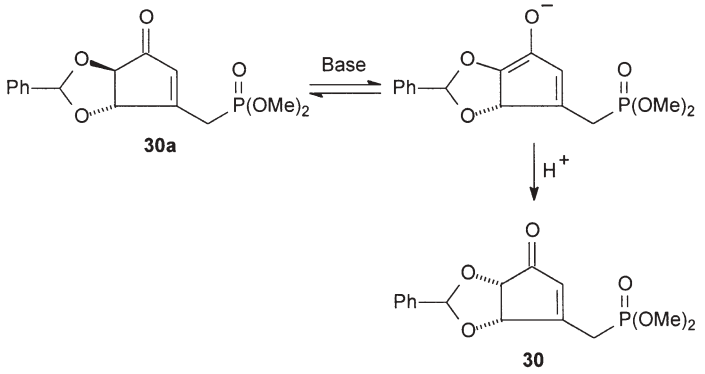


Scheme 13

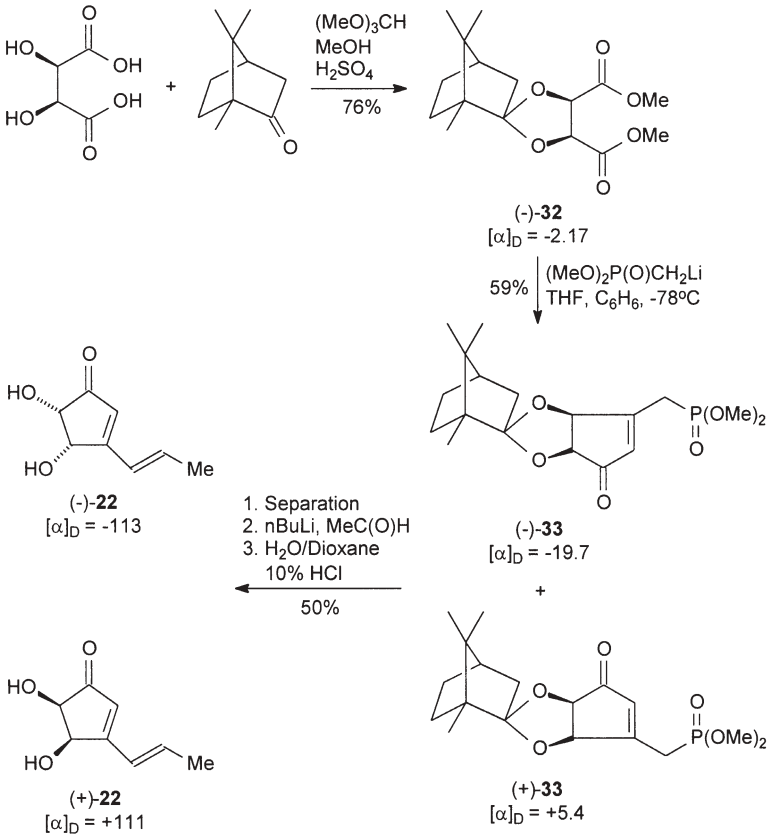
Thus, **28** was treated with dimethyl lithiomethanephosphonate to give the corresponding bis-*β*-ketophosphonate **29**. Base-catalyzed cyclization of **29** afforded the cyclopentenone **30** which was next reacted with acetaldehyde to give the Horner-Wittig olefination product **31**. Deprotection of the diol moiety in **31** gave (–)-isoterrein (**22**). Its optical purity was, however, very low (11%).

Most probably, the cyclopentenone **30a** that should be primarily formed from **29** undergoes isomerization via the enolate anion to give the more stable cyclopentenone **30** with the *cis*-diol moiety (Scheme 14).

To synthesize both enantiopure forms of isoterrein (**22**), Mikolajczyk and coworkers [37] in the first place successfully performed a complete desym-



Scheme 14

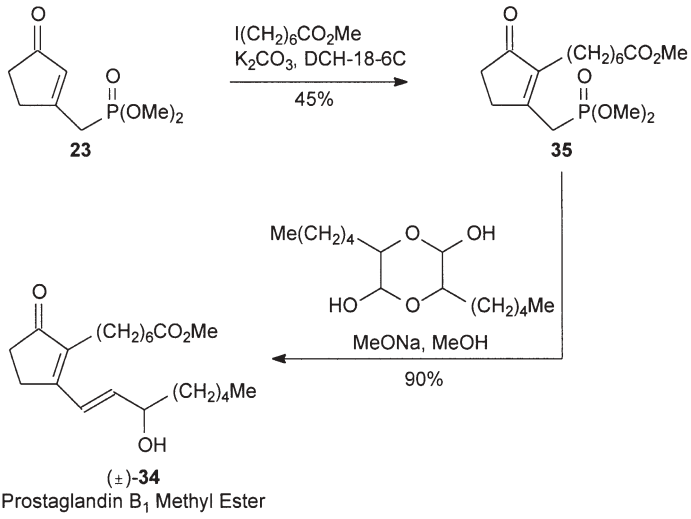


Scheme 15

metrization of optically inactive *meso*-tartaric acid in an acid-catalyzed reaction with (+)-camphor and methyl orthoformate. The single diastereomer **32** formed had the *R* and *S* absolute configurations at the diol carbon atoms as determined by X-ray analysis. This key chiral intermediate was treated with dimethyl lithiomethanephosphonate and yielded two diastereomers of the protected 3-phosphorylmethylcyclopentenone **33**. The Horner-Wittig reaction of the separated diastereomers of **33** with acetaldehyde and subsequent deprotection of the diol moiety in the cyclopentenones formed gave the enantiopure forms of (–)-isoterrein (**22**) and (+)-isoterrein (**22**) as shown in Scheme 15.

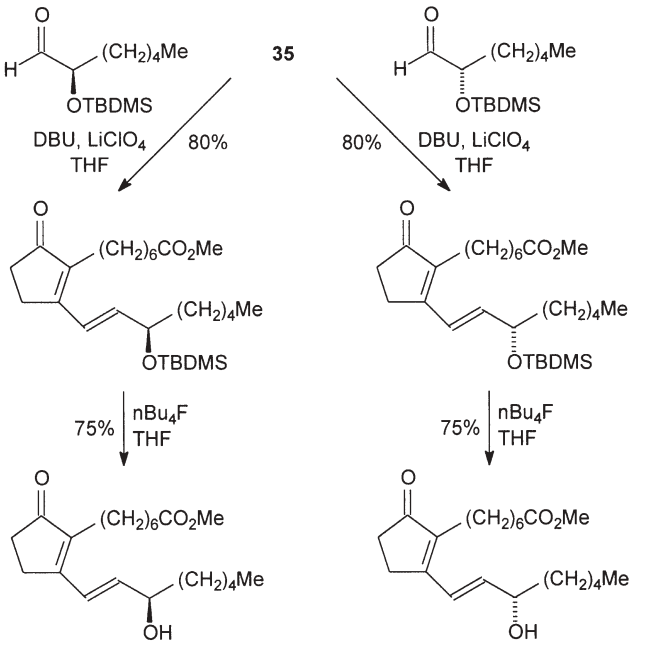
2.5
Synthesis of Racemic and Optically Active Prostaglandin B_1 Methyl Ester

The discovery of prostaglandins, which constitute one of the most exciting groups of highly potent biologically active compounds, has given enormous impetus for the development of methods for the formation of such systems. Therefore it was not surprising that a new methodology for the synthesis of functionalized cyclopentenones based on the reactivity of 3-(phosphorylmethyl)cyclopent-2-enone **23** (n = 1) has been applied for the synthesis of prostaglandin B_1 methyl ester (**34**) [38]. Since the structure of **34** represents a disubstituted cyclopentenone having alkyl and alkenyl substituents at C(2) and C(3), respectively, a simple two-step conversion of **23** into **34** was elaborated which involved regioselective alkylation at C(2) with methyl 7-iodoheptanoate and subsequent Horner-Wittig reaction with the dimer of 2-hydroxyheptanal. Although the alkylation reaction of the anion derived from **23** was not very efficient due to competitive *O*-alkylation, the Horner-Wittig reaction occurred in excellent yield affording the target compound in 42% overall yield [29] (Scheme 16)



Scheme 16

The use of (+)-(*R*)- and (–)-(*S*)-(*tert*-butyldimethylsilyloxy)heptanal for the Horner-Wittig reaction with **35** gave, after deprotection of the hydroxy group, the enantiopure forms of the title compound in 28 % overall yield (Scheme 17).



Scheme 17

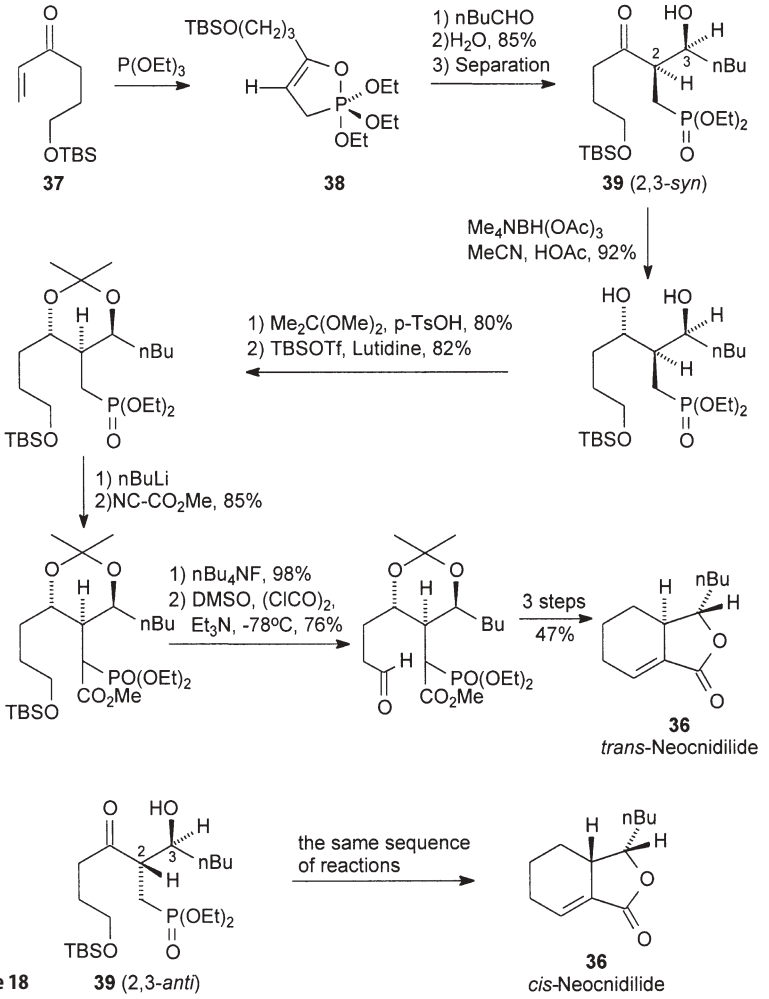
3
Use of Phosphonates in the Synthesis of Biologically Active Lactones

Lactones are commonly encountered compounds produced by both primitive and higher organisms. Their structural diversity is large as exemplified by the mono–, bi-, and tricyclic as well as 5- and 6-membered structures presented here. The biological activity of lactones is often associated with the *exo*- or *endo*-cyclic double bond, as in their cyclopentanone and cyclopentenone analogues discussed earlier. Some syntheses of the lactonic units based on phosphonate chemistry are worth mentioning. However, they will not be presented here in details. For instance, Minami et al. [39] showed a quantitative conversion of the 5-membered α-phosphoryllactones to 6-membered *endo*-α-methylene 3-(2-hydroxyethyl)-coumarins. The pentacovalent oxaphospholene methodology was applied by McClure et al. [40] to a short synthesis of α-(diethoxyphosphorylmethylene)-γ-butyrolactone starting from the requisite oxaphospholene and glyceraldehyde acetonide. β-Diethoxyphosphoryl-γ-butyrolactones, for use as intermediates in the synthesis of β,γ-unsaturated amides, were obtained by Bodalski and coworkers [41] in a coupling of dilithium β-diethoxyphosphoryl-

propionate with aldehydes and ketones. Finally, the increasing interest in modified antisense nucleosides led to the elaboration by Shibuya et al. [42] of a highly diastereoselective (>92% de) synthesis of methylenephosphonate analogues of 2-deoxyribose 3-phosphate.

3.1
Synthesis of *trans*- and *cis*-Neocnidilides

endo-α-Methylene bicyclic lactones – (±)-*trans*- and (±)-*cis*-neocnidilides (**36**) – are major constituents of the volatile oil of most representatives of *Apium graveleues* (Umbelliferae) and inhibit both the growth and the toxin production of mycotoxin-producing fungi. They both were synthesized in racemic forms by McClure and Jung [43] via the route illustrated in Scheme 18 using pentacova-

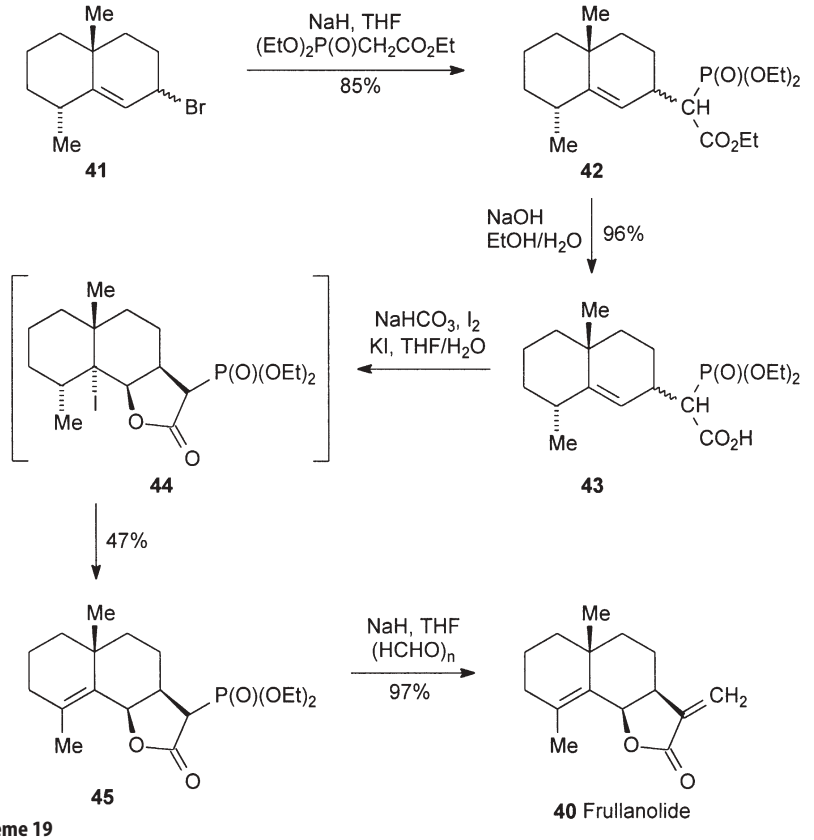


Scheme 18

lent oxaphosphorane chemistry. The starting enone **37** needed for the synthesis of the 1,2λ^5-oxaphospholene **38** was prepared in four steps from 2,3-dihydrofuran. Formation of **38** proceeded by reaction of **37** with neat triethyl phosphite. Condensation of **38** with valeraldehyde followed by hydrolysis produced a separable by HPLC mixture of ketophosphonates **39** in a *syn/anti* ratio 1.78:1. In a sequence of further transformations (methoxycarbonylation with methyl cyanoformate, Swern oxidation, the intramolecular Horner-Wittig olefination reaction, lactonization and Barton's deoxygenation), in which the *syn*-**39** and *anti*-**39** were used independently, (±)-*trans*-neocnidilide (**36**) was obtained from **39** (2,3-*syn*) and (±)-*cis*-neocnidilide (**36**) from **39**-(2,3-*anti*).

3.2
Synthesis of Frullanolide

A new methodology for the synthesis of five-membered *exo*-α-methylene tricyclic lactones was elaborated by Minami at al. [44] and applied to a short synthesis of frullanolide (**40**), an allergenically active α-methylene-γ-butyrolactone sesquiterpene (Scheme 19). In this synthesis, alkylation of the ethyl (diethoxy-

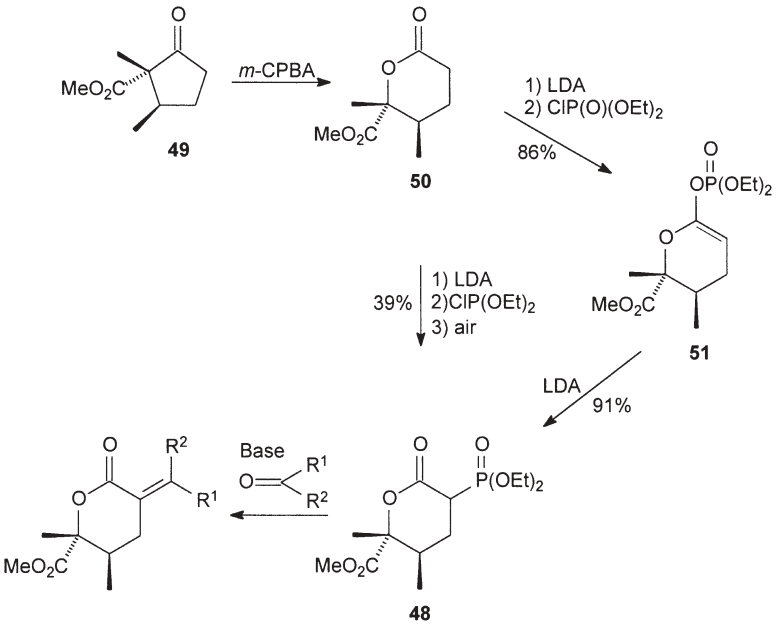


Scheme 19

phosphoryl)acetate carbanion with the cyclic allylic bromide **41** led to a mixture of two diastereomeric ethyl 2-diethoxyphosphoryl-2-(4a,8-dimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-yl)acetates **42**. The mixture was hydrolyzed to give the corresponding 5:3 mixture of the pseudoequatorial acid and its axial isomer **43**. The acid underwent iodolactonization to give α-phosphoryl-γ-lactone **45** which was produced via dehydroiodination of an initially formed iodolactone **44** under the reaction conditions employed. The Horner-Wittig reaction of the α-phosphoryl-γ-lactone **45** with paraformaldehyde gave frullanolide (**40**) in almost quantitative yield.

3.3
Synthesis of Integerrinecic and Senecic Acid Lactones

Two six-membered necic acid lactones: **46** (integerrinecic acid lactone) and **47** (senecic acid lactone) having an *exo*-α-methylene moiety were synthesized by Wiemer et al. [45] in the stereocontrolled Horner-Wittig condensation of the α-phosphonolactone **48** with acetaldehyde (Scheme 20). When KHMDS in acetonitrile was used as a base in this reaction, a 9:1 mixture of *E* and *Z* products was obtained from which the *E*-isomer of integerrinecic acid lactone **46** was isolated in 77% yield. When K_2CO_3/18-crown-6/toluene was employed in a parallel



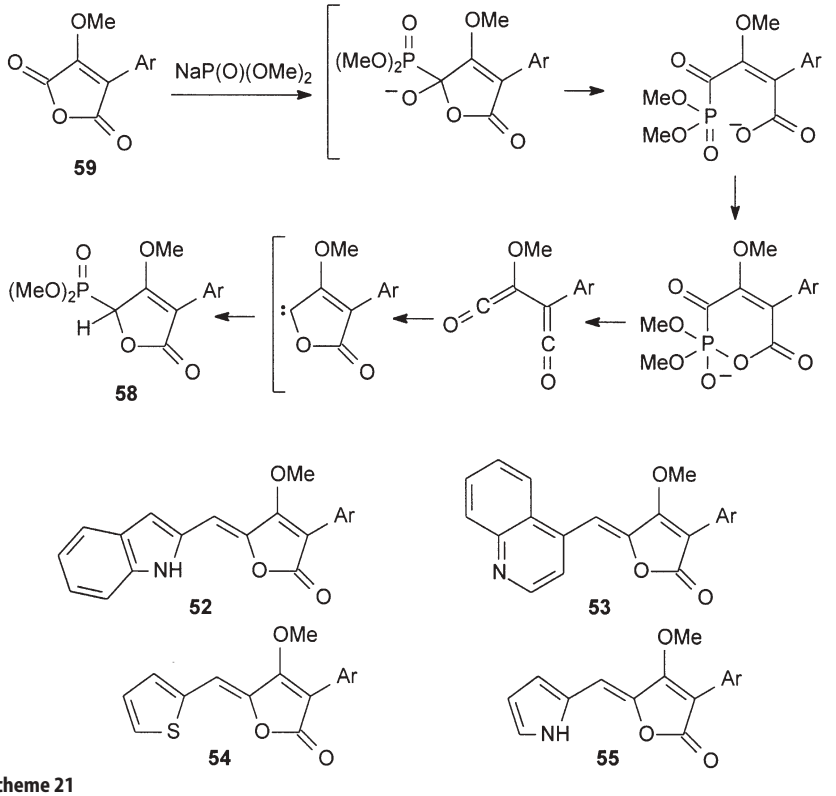
46: R^1 = Me, R^2 = H 77% (DBU, CH_3CN, rt, E/Z = 9:1)
47: R^1 = H, R^2 = Me 46% (K_2CO_3/18-C-6, PhMe, -78ºC, E/Z = 1:1.2)

Scheme 20

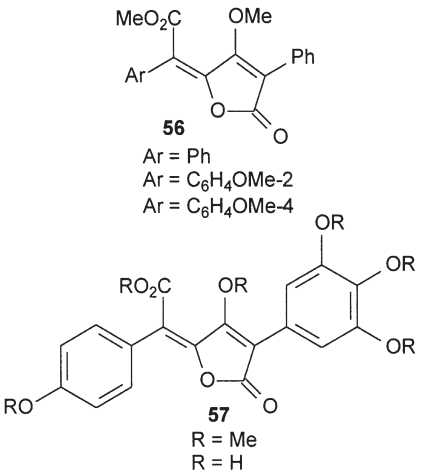
reaction, only slight selectivity for the *Z*-isomer was observed but the methyl ester of senecic acid lactone **47** was obtained in 43 – 46 % yield from the product mixture. The requisite α-phosphonolactone **48** was obtained from the cyclopentanone **49** and the lactone **48** using Wiemer's methods via the corresponding enolates. One of these routes was based upon 1,3-phosphoryl migration in the vinyl phosphate **51** prepared from the lactone enolate of **50** and diethyl phosphorochloridate. The other method employed the reaction of the enolate of **50** with diethyl phosphorochloridite followed by air oxidation.

3.4
Synthesis of Analogues of Pulvinones and Pulvinic Acids

Patenden et al. [46] synthesized heterocyclic analogues of pulvinones **52 – 55** and of permethylated pulvinic acids **56, 57** which were found in higher fungi (Scheme 21). All compounds possessing lactonic structures were synthesized in the Horner-Wittig reaction using the corresponding heteroaryl aldehydes and 4-dimethoxy-phosphorylated lactone **58**. The latter was obtained as the main product in the reaction between substituted maleic anhydrides **59** and sodium dimethyl phosphite via the postulated carbene.



Scheme 21



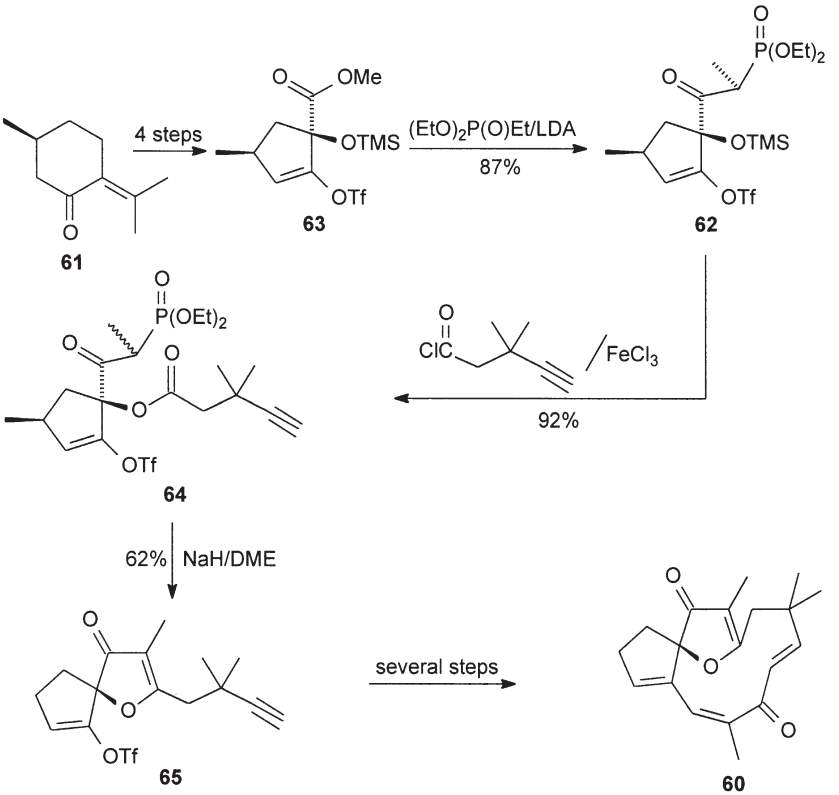
Scheme 21 (continued)

4
Use of Phosphonates in the Synthesis of Biologically Active Macrocycles

The characteristic feature of this group of natural compounds is existence of a macrocycle in which other characteristic subunits like spiro, α,β-unsaturated, polyene, heterocyclic moieties are built in. Due to this structural diversity, total syntheses of macrocycles are complex and difficult. Therefore, research works do not always present full syntheses but approaches to precursors, synthons, model compounds, analogues, etc. Such multistep transformations often include useful, new phosphonate reagents and new methodologies based on them.

4.1
Synthesis of (+)-Jatrophone

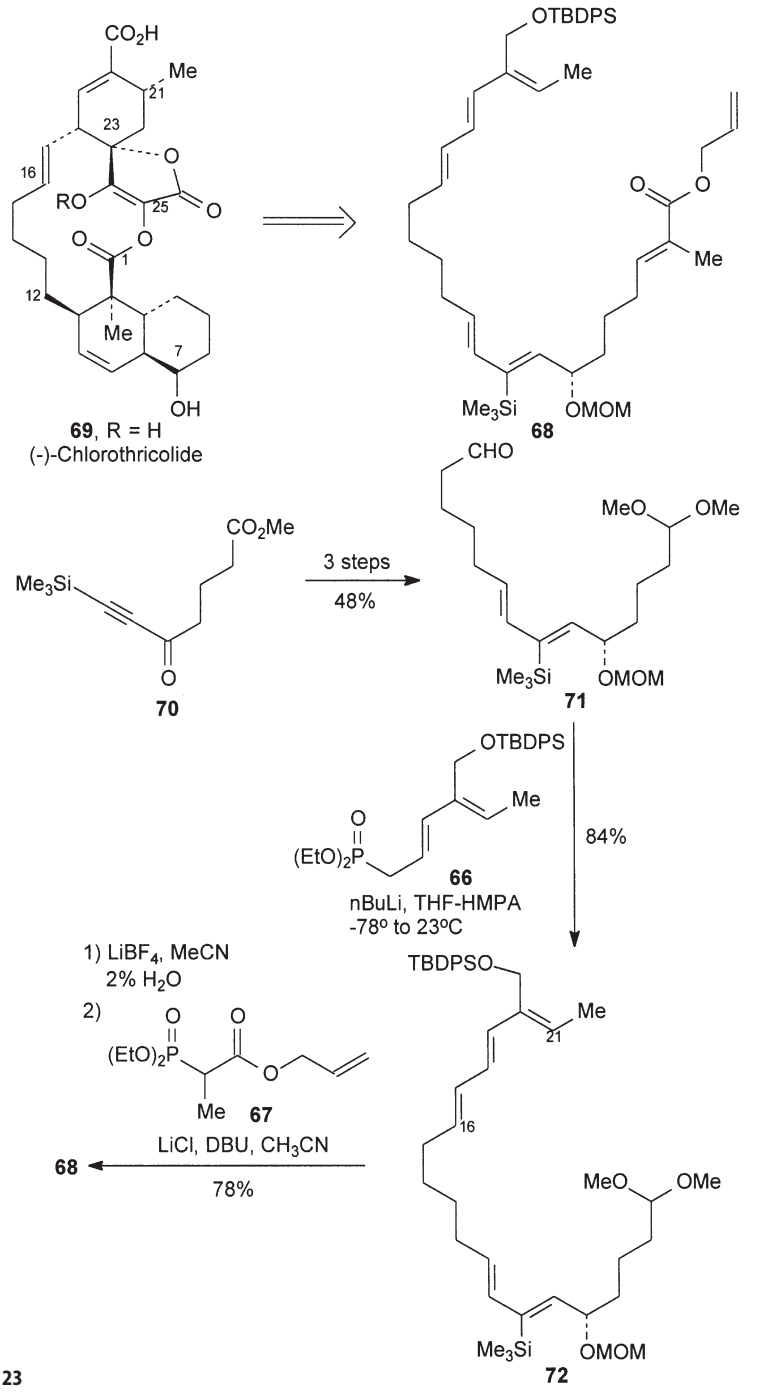
The β-ketophosphonate chemistry was employed by Wiemer and Han [47] to the first total synthesis of optically active (+)-jatrophone (**60**) possessing significant antileukemic activity. This 11-membered macrocyclic diterpenoid was first isolated and characterized by Kupchan et al. [48, 49] in 1970. The convergent synthesis provided the natural enantiomer of **60** in twelve steps from (*R*)-(+)-3-methyladipic acid, easily preparable by oxidation of (*R*)-pulegone (**61**) (Scheme 22). β-Ketophosphonate **62** was obtained in an usual way by condensation of the lithium salt of diethyl ethanephosphonate with the ester **63**. A direct $FeCl_3$-catalyzed acylation of the TMS-protected hydroxy group in **62** by the acetylenic acid chloride was accomplished in the presence of the triflate and β-ketophosphonate moieties and gave **64** in 92% yield. An intramolecular condensation of **64** was best accomplished by treatment with NaH in DME to give its intermediate lithium salt reacting in the Horner-Wittig fashion with the ester function in 62% yield rather than being acylated. Finally, (+)-jatrophone (**60**) was obtained from **65** in twelve steps and 13% overall yield.



Scheme 22

4.2
Synthesis of the (–)-Chlorothricolide Precursor

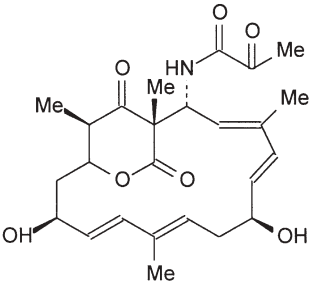
Two different phosphonate reagents **66** and **67** were used in the synthesis of the hexaenoate **68**, a retrosynthetic precursor of (–)-chlorothricolide (**69**) (Scheme 23). Chlorothricolide is the aglycone of the antibiotic chlorothricin, the simplest member of that spirotetronate class of natural products that also includes kijanimicins and tetrocarcins. In the synthesis of **68**, as a part of the first total synthesis of (–)-**69**, Roush and Sciotti [50] started from the acetylenic ketone **70** which was converted in three steps to the aldehyde **71**. The triene unit of **68** was constructed by treatment of **71** with the anion of the dienylic phosphonate **66** giving the C(16)-C(17) olefin **72** in a *trans* configuration. Finally, the C(1)-C(3) unit was introduced by deprotection of the dimethyl acetal in **72** and the Horner-Wittig reaction of the resulting aldehyde with the β-ketophosphonate **67**.


CO2H
Me
21
23
16
RO
25
O
1
12
Me
7
OH
69, R = H
(-)-Chlorothricolide
OTBDPS
Me
Me3Si
OMOM
68
CHO
MeO
OMe
Me3Si
OMOM
71
CO2Me
Me3Si
O
70
3 steps
48%
OTBDPS
Me
(EtO)2P
66
nBuLi, THF-HMPA
-78° to 23°C
84%
TBDPSO
Me
21
16
MeO
OMe
Me3Si
OMOM
72
1) LiBF4, MeCN
2% H2O
2)
(EtO)2P
Me
67
LiCl, DBU, CH3CN
78%
68

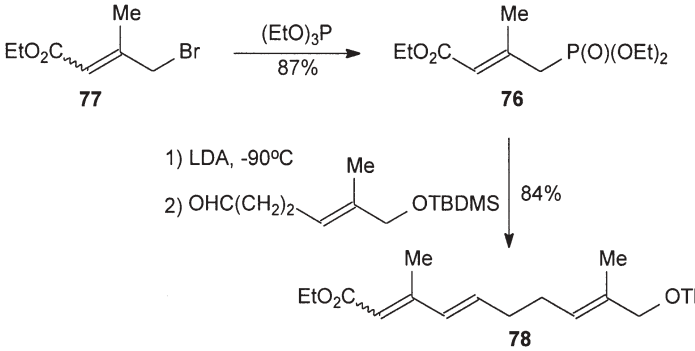
Scheme 23

4.3
Synthesis of the Lankacidin Analogue

The lankacidins, represented by lankacidin C (**73**), are natural products exhibiting both antibacterial and antitumor activity. A multistep, convergent synthesis of the 17-membered carbocycle **74** – a macrocyclic precursor of the lankacidin analogue **75** – involving some interesting phosphorus transformations was devised by Thomas and Mata [51] (Scheme 24). Thus, at the outset a synthesis of the allylic phosphonate **76** was carried out with no isomerization of the double-bond via the Arbuzov reaction using triethyl phosphite and (*E*)-4-bromobutenoate **77**. The Horner-Wittig reaction of the phosphonate **76** with the corresponding aldehyde showed a lack of stereoselectivity due to isomerization of the lithiated phosphonate **76**-Li. However, when the deprotonation of **76** and the addition of the aldehyde were carried out within 1 min at –90 °C, the *E/Z* ratio for **78** could be improved from 50:50 to 93:7. The synthesis of **74** was further continued with *E*-**78** from which an unstable aldehyde **79** was obtained in seven steps. Treatment of the latter with lithiated dimethyl methanephosphonate, afforded a mixture of the epimeric hydroxyphosphonates **80.** After selective removal of the *tert*-butyldimethylsilyl protecting group, oxidation of both hydroxy groups was carried out with tetrapropylammonium perruthenate to



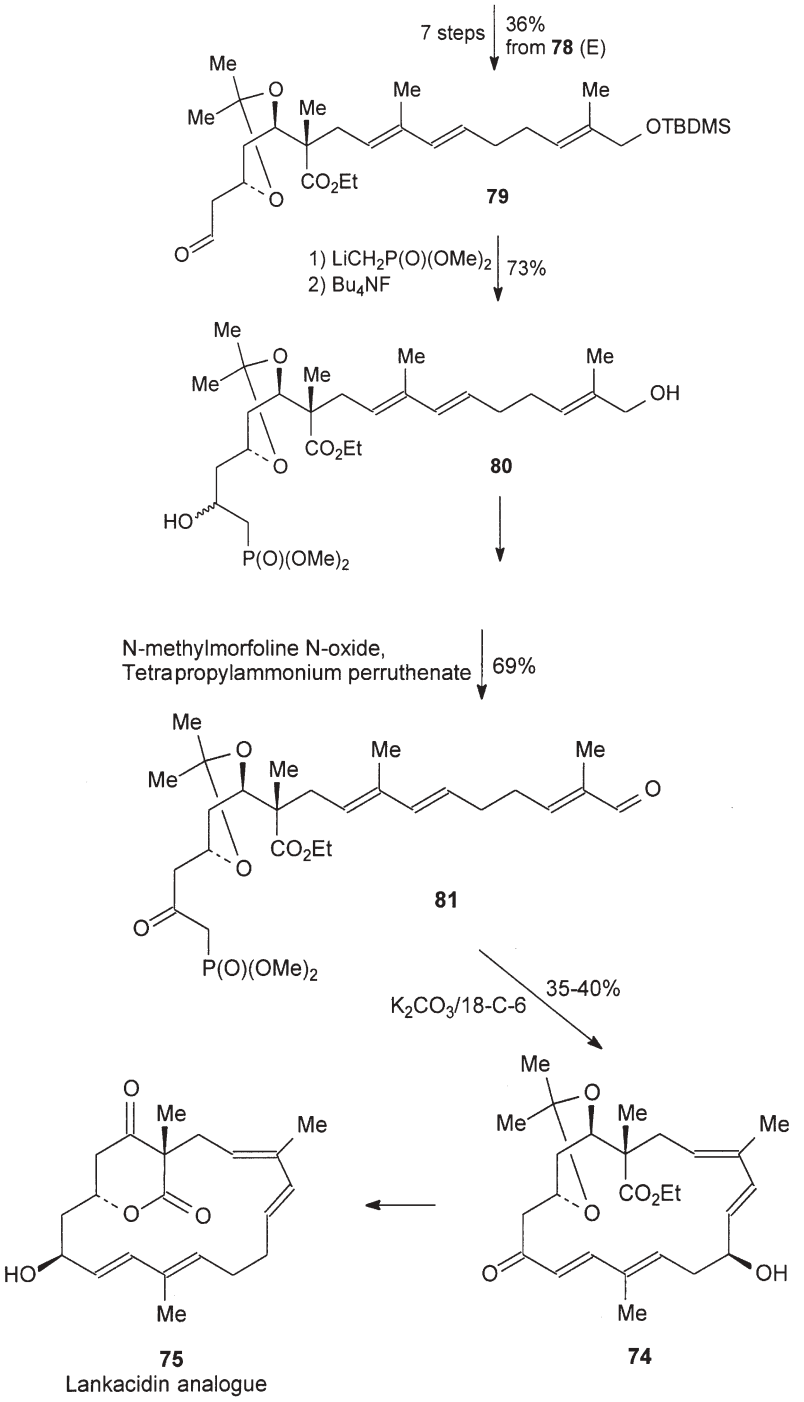
Lankacidin C
73



77 **76**

78
E/Z = 93:7

Scheme 24

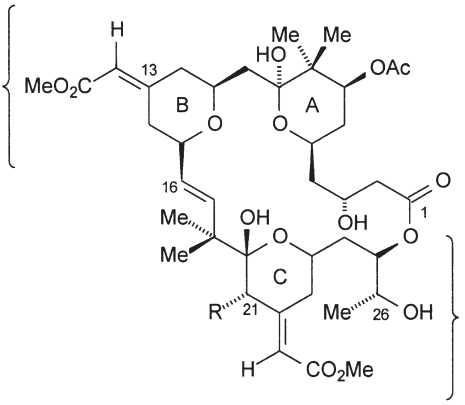


Scheme 24 (continued)

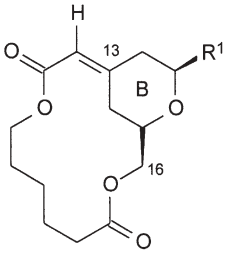
give 16-formyl-2-oxo-phosphonate **81**. Finally, cyclization of the latter to the cycloheptadecatetraenone **74** required heating in toluene at 100°C in the presence of 18-crown-6 and K_2CO_3.

4.4
Synthesis of the Bryostatin 1 Synthon

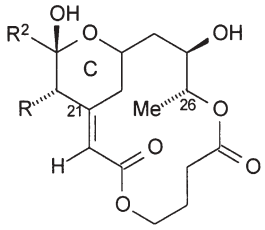
Macrocyclic stereocontrol using a tethered phosphonate reagent was applied by Evans and Carreira [52] to control a remote enoate geometry in bryostatin 1 (**82**) (Scheme 25). This fungal metabolite and eleven additional congeners were isolated as constituents of the bryozoan *Bugula neretina* and found to possess activity against lymphocytic leukemia and ovarian carcinoma. Retrosynthetic analysis of bryostatins 1 (**82**) and 11 revealed two synthons having a similar spatial relationship between C-13/C-21 enoates and C-16/C-26 alcohols. Both the enoates and the alcohols served as anchors for tethered phosphonate reagents and the primary alcohol at C-16 served as an aldehyde pre-



82: Bryostatin 1 R = $O_2C(CH)_4(CH_2)_2Me$
Bryostatin 11 R = H

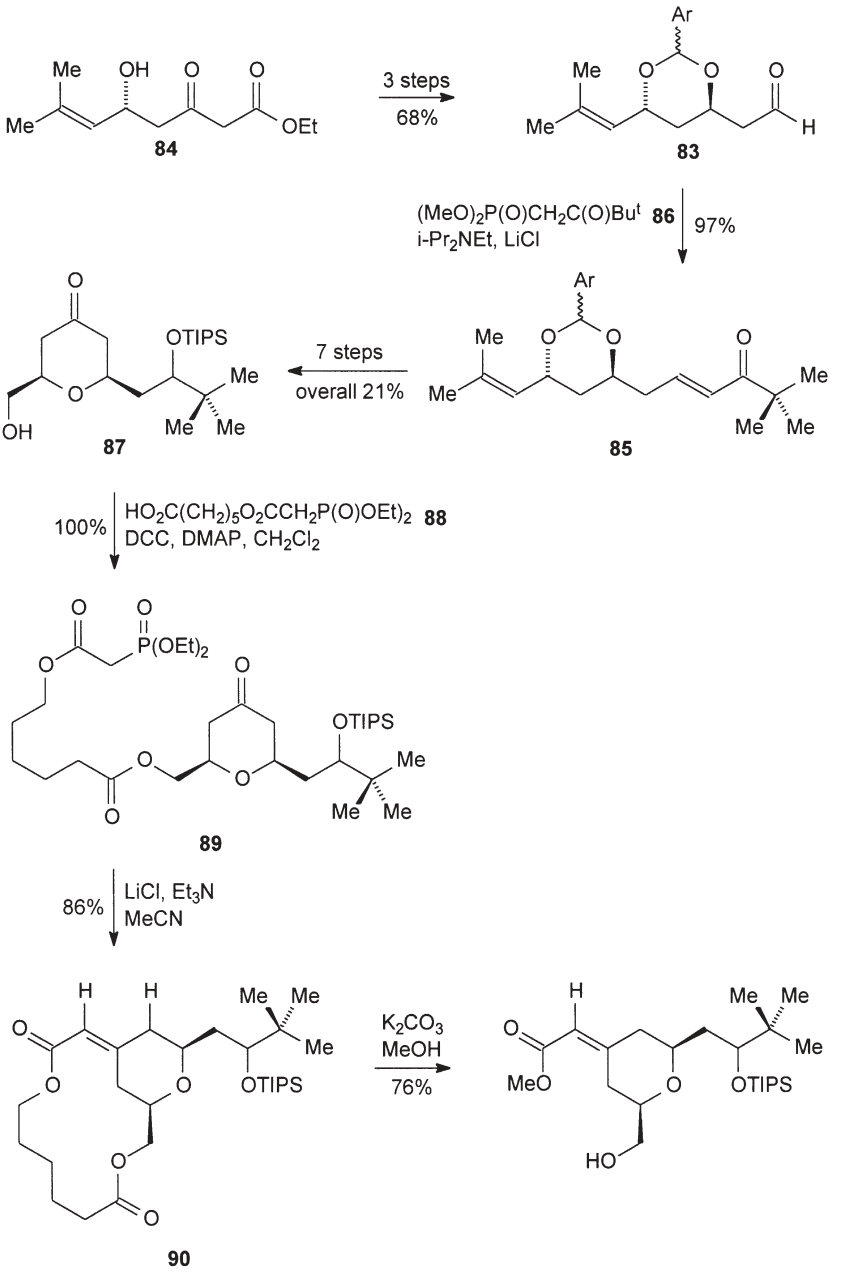


C_{11}-C_{16} Synthon



C_{19}-C_{27} Synthon

Scheme 25



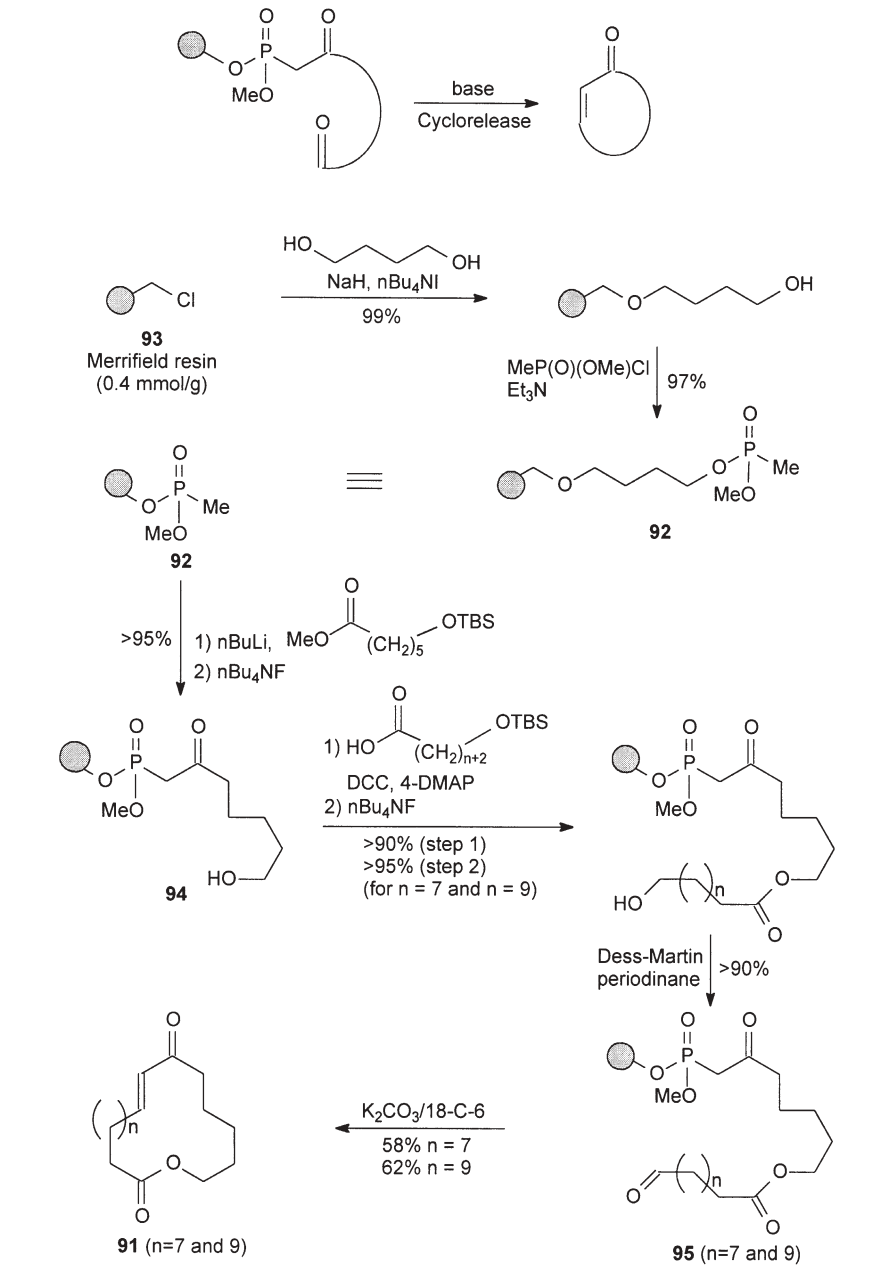
Scheme 25 (continued)

cursor for the C_{11}-C_{16} synthon. In the synthetic approach to the model substrate of this synthon, the aldehyde **83**, obtained from the hydroxyketoester **84** in three steps, was converted to the enone **85** via the Horner-Wittig reaction using the β-ketophosphonate **86**. Starting from the enone **85**, the primary ketoalcohol **87** was obtained in seven steps. Acylation of the latter with the tethered phosphonate **88** provided the macrocyclization precursor **89**. Macrocyclic olefination was achieved by treatment of **89** with LiCl (33 equiv.) and Et_3N (30 equiv.) for 36 h and afforded the desired macrocycle **90** in 86% yield as a single diastereomer. The tether was cleanly removed with K_2CO_3 in methanol to give the product.

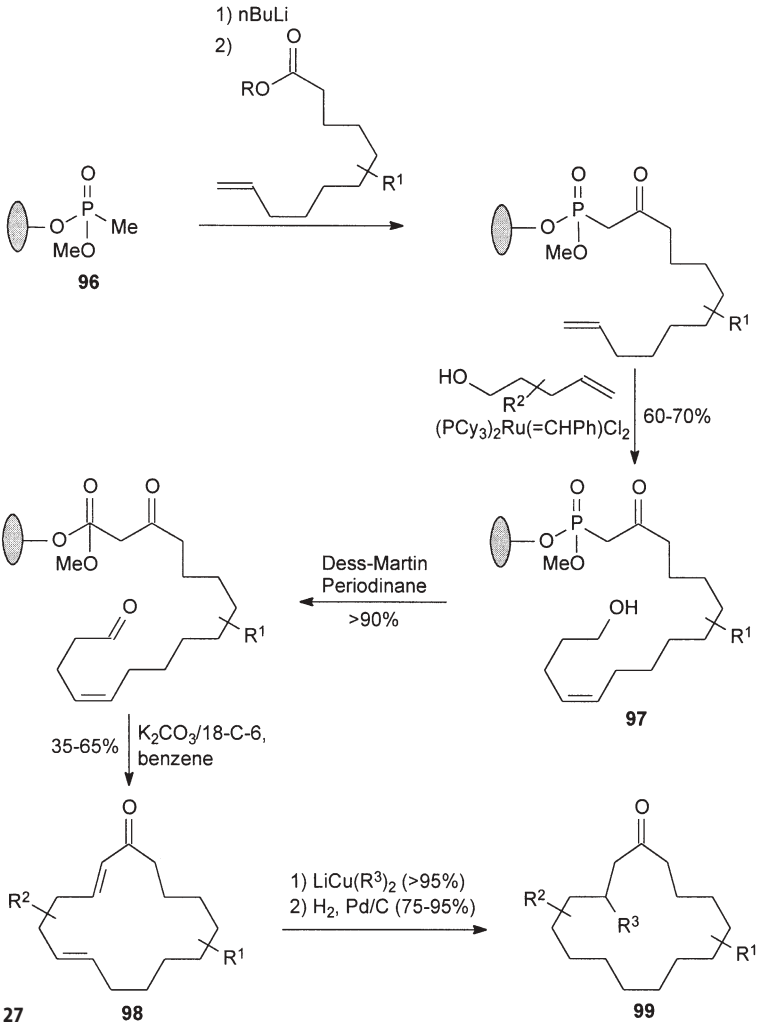
4.5
Solid-Phase Synthesis of Macrocyclic Lactones and a Combinatorial Synthesis of a Muscone Library

An intramolecular Horner-Wittig cyclization of the polymer-bound phosphonates was applied by Nicolaou et al. [53] to the synthesis of 18- and 20-membered macrocyclic lactones **91** (n = 7 and 9). The practical implementation of cyclorelease strategy, presented in Scheme 26, required the polymer-supported phosphonate **92** which was prepared from the Merrifield resin **93**, 1,4-butanediol as a linear spacer, and methyl methanephosphonochloridate. The β-ketophosphonate **94** was obtained in a usual way from the lithium salt of **92** and the corresponding TBS-protected ester, followed by desilylation with *n*-Bu_4NF. Further esterification of the free hydroxy group in **94** with the TBS-protected ω-hydroxy acids (n = 7, n = 9) followed by the desilylation and the Dess-Martin oxidation yielded aldehydes **95**. The macrocycle releases towards **91** were accomplished with K_2CO_3 in the presence of 18-crown-6 as the result of the intramolecular Horner-Wittig reaction.

The same authors demonstrated a solid-phase combinatorial synthesis of a muscone library starting from the monomethyl methanephosphonate **96** bound to the Merrifield resin. The key steps were the synthesis of the β-ketophosphonates **97**, introduction of the aldehyde group, which was necessary for the cyclorelease, and final reduction of double bonds in **98** to the modified muscones **99** (Scheme 27).


base
Cyclorelease
NaH, nBu4NI
99%
93
Merrifield resin
(0.4 mmol/g)
MeP(O)(OMe)Cl
Et3N
97%
92
>95%
1) nBuLi,
2) nBu4NF
OTBS
94
1) HO
DCC, 4-DMAP
2) nBu4NF
>90% (step 1)
>95% (step 2)
(for n = 7 and n = 9)
Dess-Martin
periodinane
>90%
K2CO3/18-C-6
58% n = 7
62% n = 9
91 (n=7 and 9)
95 (n=7 and 9)

Scheme 26



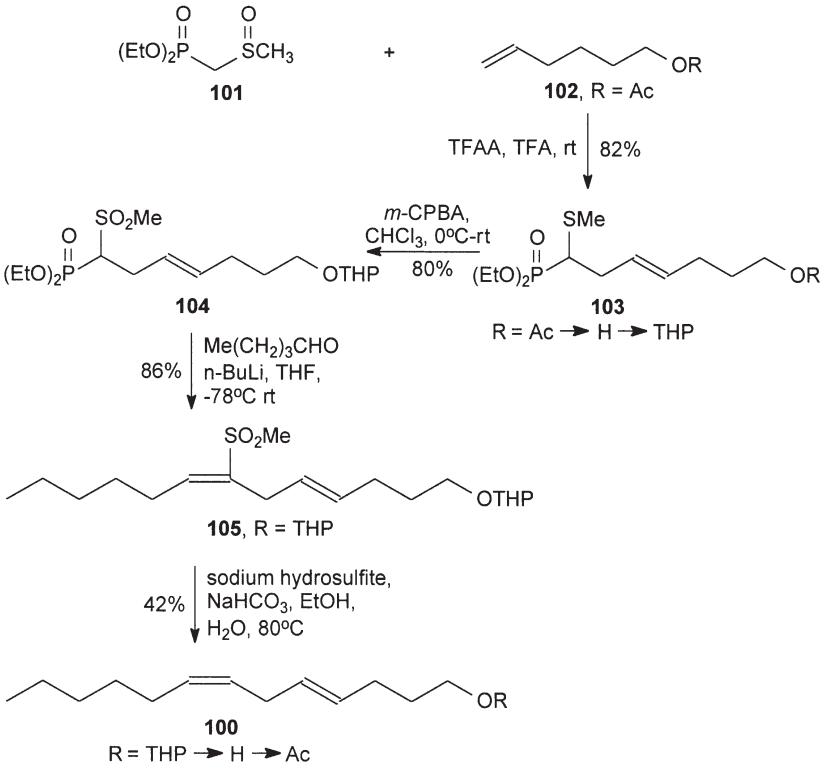
Scheme 27

5
Use of Phosphonates in the Synthesis of Biologically Active Polyenes

This group of natural compounds is also structurally diverse ranging from the simple dienes like a sex pheromone (4*E*,7*Z*)-4,7-tridecadienyl acetate or (±)-*E*,*E*)-coriolic acid through typical polyenes like the all-*trans*-stereomer of ethyl retinoate to the more complex, optically active calyculins A and B. In the total syntheses of polyenes presented below, the structurally complex phosphonate or bisphosphonate reagents were used in the Horner-Wittig olefination reactions solely or in combination with the Suzuki coupling.

5.1
Synthesis of (4*E*,7*Z*)-4,7-Tridecadienyl Acetate (Sex Pheromone)

Dienes, as the simplest polyene systems, are widely encountered in sex pheromones like (4*E*, 7*Z*)-4,7-tridecadienyl acetate (**100**), a component of the sex pheromone of the potato tuberworm moth (*Phthorimaea operculella*). This compund was synthesized by Kim and Park [54] starting from a protected 5-hexen-1-ol and utilizing the chemistry of thio-substituted phosphonates (Scheme 28). Thus, the Pummerer rearrangement of α-phosphoryl sulfoxide **101** with 5-hexenyl acetate **102** afforded 7-acetoxy-1-methylthiohept-3-enyl phosphonate **103** as an *E*/*Z* = 85:15 mixture, being unreactive in the Horner-Wittig reaction, even after OAc deprotection/THP reprotection. However, the reaction of the more reactive α-phosphoryl sulfone **104** with *n*-hexanal successfully led to the required 1,4-diene **105**, as an *E*/*Z* = 70:30 mixture, in 86% yield. The final pheromone **100** was obtained after the desulfonylation of **105** with sodium hydrosulfite and the OTHP → OH → OAc deprotection/reprotection procedures.

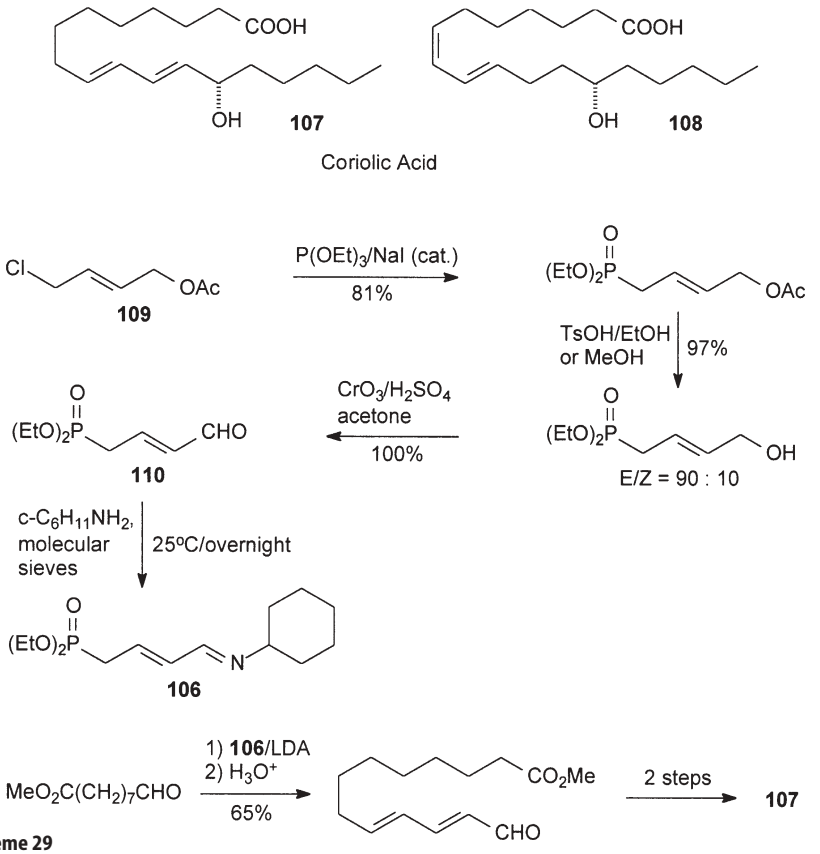


Scheme 28

5.2
Synthesis of (±)-(*E,E*)-Coriolic Acid

The new Horner-Wittig reagent **106** was used to transform carbonyl compounds into 2,4-pentadienals under mild conditions and in good yields. The products were formed predominantly as 2*E*,4*E* isomers with moderate to good stereoselectivity. The reagent **106** was used in the key step of a short synthesis of (±)-13-hydroxy-9(*E*),11(*E*)-octadecadienoic acid (**107**) [(±)-(*E,E*)-coriolic acid] [55] (Scheme 29) which is a double bond isomer of naturally occurring coriolic acid (**108**), isolated from rice (*Oryza sativa* L.). Very recently, it has been demonstrated that both enantiomers of **108**, as well as some analogues of (*S*)-**108**, including (*S*)-**107**, possessed activities against rice blast fungus.

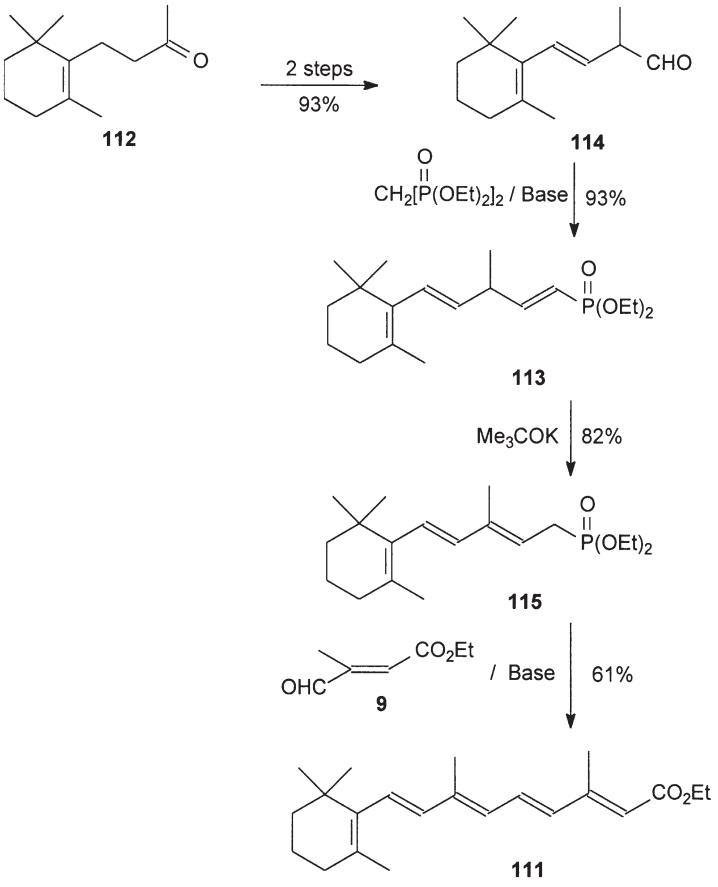
The imine reagent **106** was synthesized in four steps starting from the chloroacetate **109** that was submitted to the Arbuzov reaction. After deprotection of the hydroxy group and Jones oxidation, the resulting aldehyde **110** was condensed with cyclohexylamine.



Scheme 29

5.3
Synthesis of all-*trans* Stereomer of Ethyl Retinoate

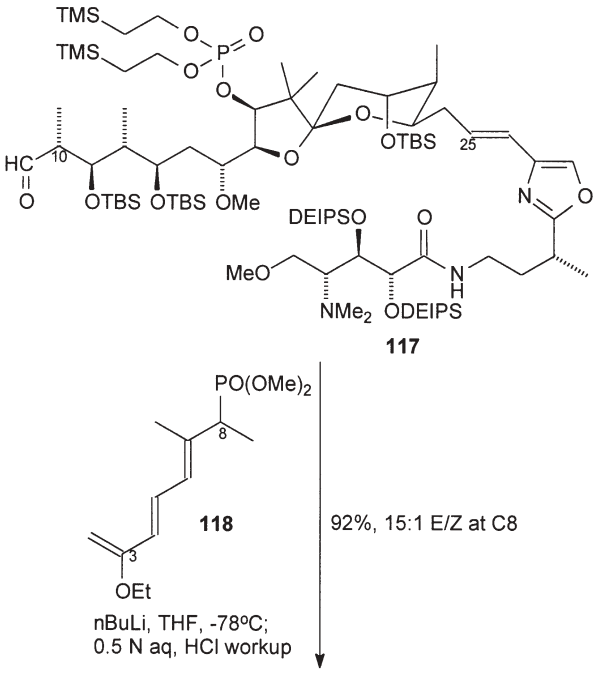
A stereoselective synthesis of all-*trans*-stereomer of ethyl retinoate (**111**) was reported by Babler and Schlidt [56] starting from the easily available *β*-ionone **112** (Scheme 30). The key step of the synthesis was a base-catalyzed isomerization of the vinylphosphonate **113**, which was obtained in the Horner-Wittig reaction of the aldehyde **114** and tetraethyl bisphosphonate, to give the allylic phosphonate **115** as the sole product. The Horner-Wittig reaction of the latter with ethyl *trans*-3-methyl-4-oxo-2-butenoate concluded a facile synthesis of the all-*trans*-polyenic retinoate **111**.



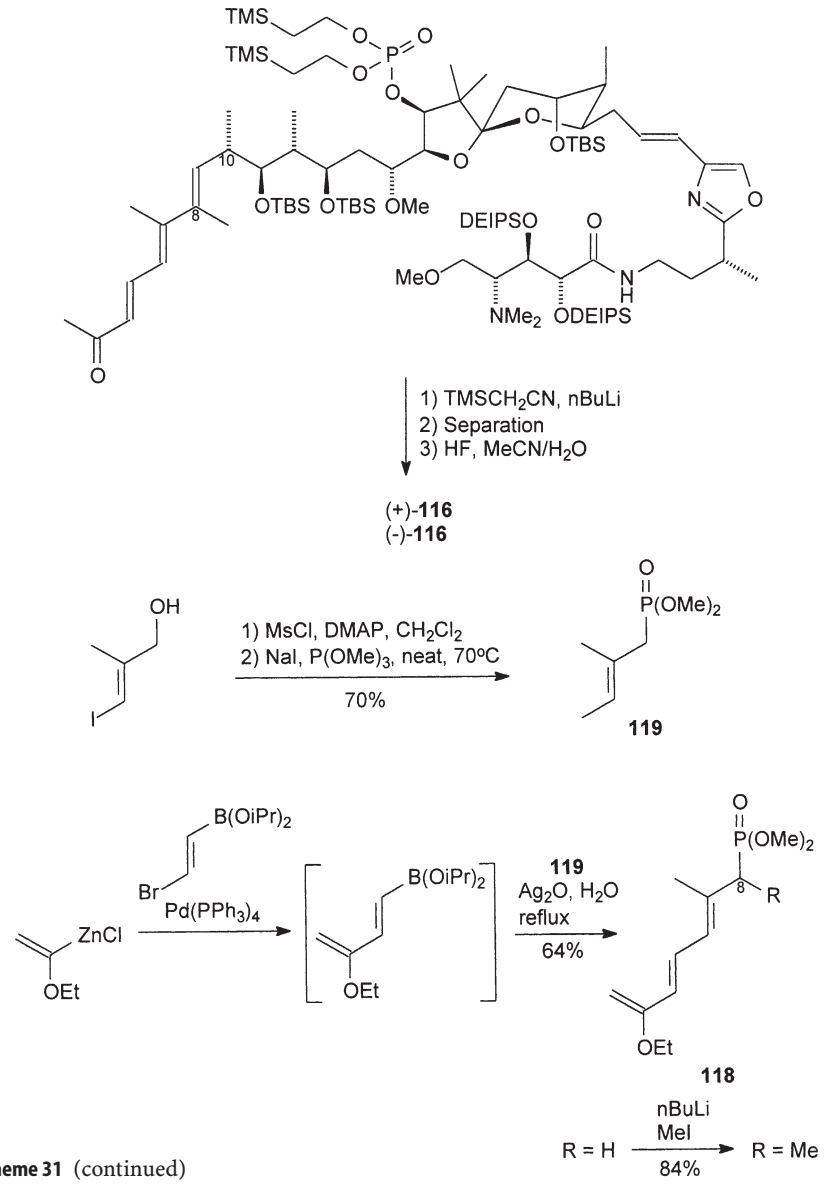
Scheme 30 All-*trans*-ethyl retinoate

5.4
Syntheses of (+)-Calyculin A and (–)-Calyculin B

Smith III et al. [57] described a highly convergent total synthesis of (+)-calyculin A (**116**) and the first total synthesis of (–)-calyculin B (**116**), both belonging to a family of potent, remarkably cell permeable and highly selective serine-threonine phosphatase inhibitors. In this synthesis introduction of the polyene chain at the C-10 position of the fragment **117** was achieved in the Horner-Wittig reaction of the C-9 aldehyde and the metallated phosphonate **118.** As a result, a mixture of regioisomers in a ratio *E/Z* = 15:1 was obtained (Scheme 31). Further steps including the Peterson olefination, the *E/Z* separation and finally the global deprotection completed the calyculin (**116**) synthetic venture in 69% yield for the (+)-**116** and in 84% yield for the (–)-**116** isomers. The key phosphonate **118** was prepared in five steps and 38% overall yield including the Arbuzov reaction leading to the vinyl iodide **119** and the Suzuki coupling of the latter with the corresponding dienylboronate intermediate, the latter reaction being unexpectedly promoted by silver(I) oxide.



Scheme 31



Scheme 31 (continued)

6
Use of Phosphonates in the Synthesis of Biologically Active Polycycles

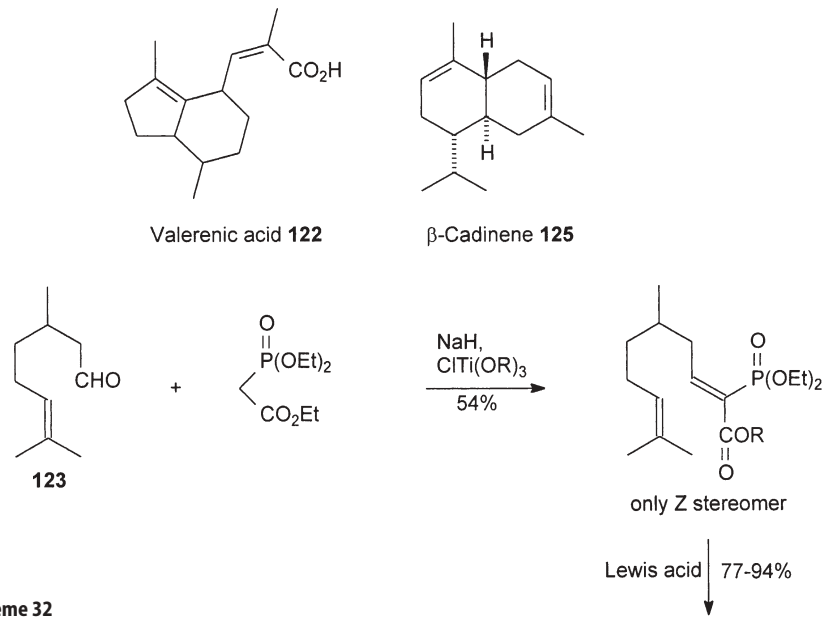
The polycycles, synthesized with the use of phosphonates and discussed below, represent a group of structurally diverse compounds that exhibit a wide spectrum of biological activity. They are antibacterial or spasmolytic agents, pheromones and ingredients of fragrance oils. In this Section syntheses of

both polycarbocycles [cadalene and valerenic acid sesquiterpenoids, (±)-pentalenic acid] and polyheterocycles {[3.3.0]pyrazolidinones, (–)-frontalin} are described.

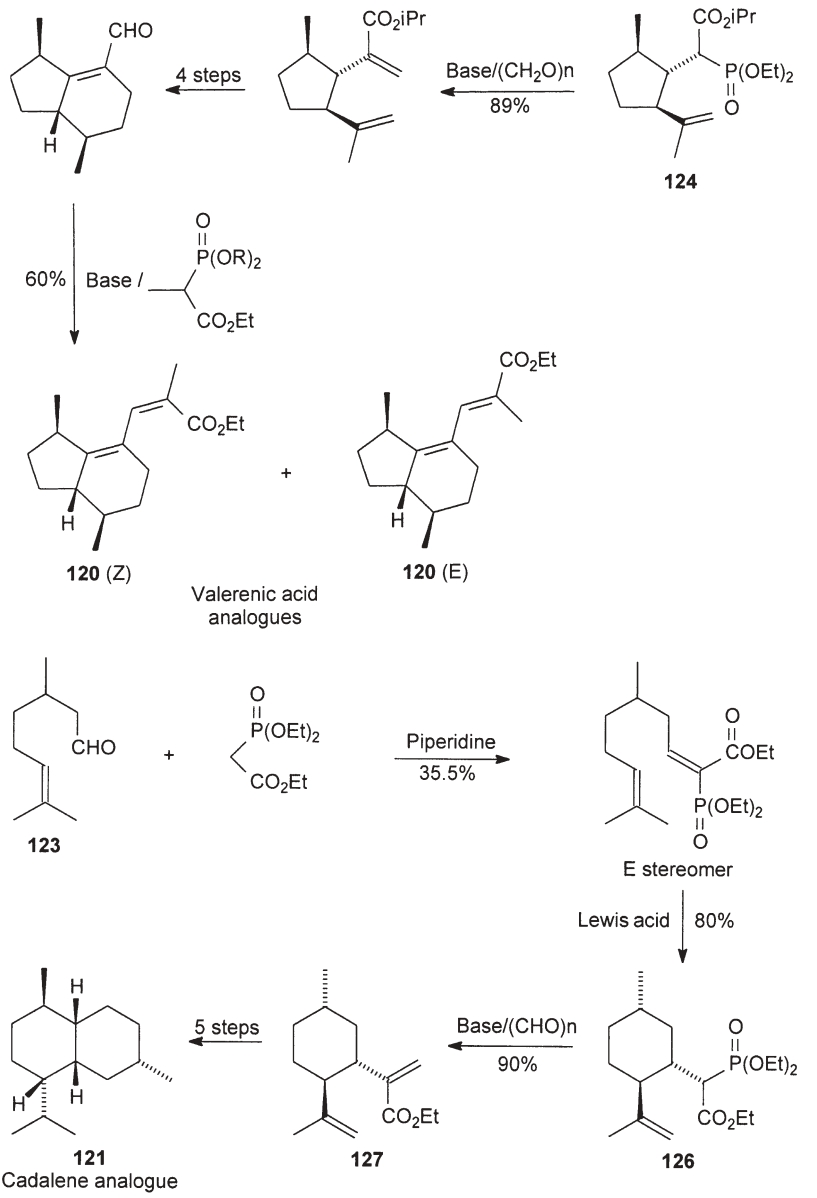
6.1
Synthesis of Valerenic Acid and Cadalene Sesquiterpenoids

Minami et al. [58] developed intramolecular ene reactions of vinylphosphonates and used them for the synthesis of bicyclic compounds, valerenic acid, and the cadalene terpenoids **120** and **121** (Scheme 32). Valerenic acid (**122**), showing spasmolytic effects, was isolated from *Valeriana officinalis* L. roots. A stereoselective synthesis of the valerenic acid analogues (*E/Z*)-**120** started from the Knoevenagel condensation of the aldehyde **123** with triethyl phosphonoacetate and chlorotris(isopropoxy)titanium to give exclusively the corresponding (*Z*)-dienoate in 54% yield. Then, the intramolecular ene reaction of the latter catalyzed by various Lewis acids afforded the corresponding ene product **124** in 77–94% yields. The Horner-Wittig reaction of **124** with paraformaldehyde produced the acrylic acid ester which was converted to the bicyclic aldehyde in four steps. This aldehyde was used, in turn, as a substrate for the Horner-Wittig reaction with the phosphonate anions to give the valerenic acid analogue **120** as a mixture of *E*- and *Z*-isomers. Their ratio was strongly depended on the nature of the phosphonate ester group R (Et, CF_3CH_2). The naturally occurring **122** possesses the (*Z*)-acrylic acid moiety.

The second bicyclic compound synthesized by Minami et al. [58] was the cadalene sesquiterene **121**. The cadalene series of sesquiterpenes, which are rep-



Scheme 32



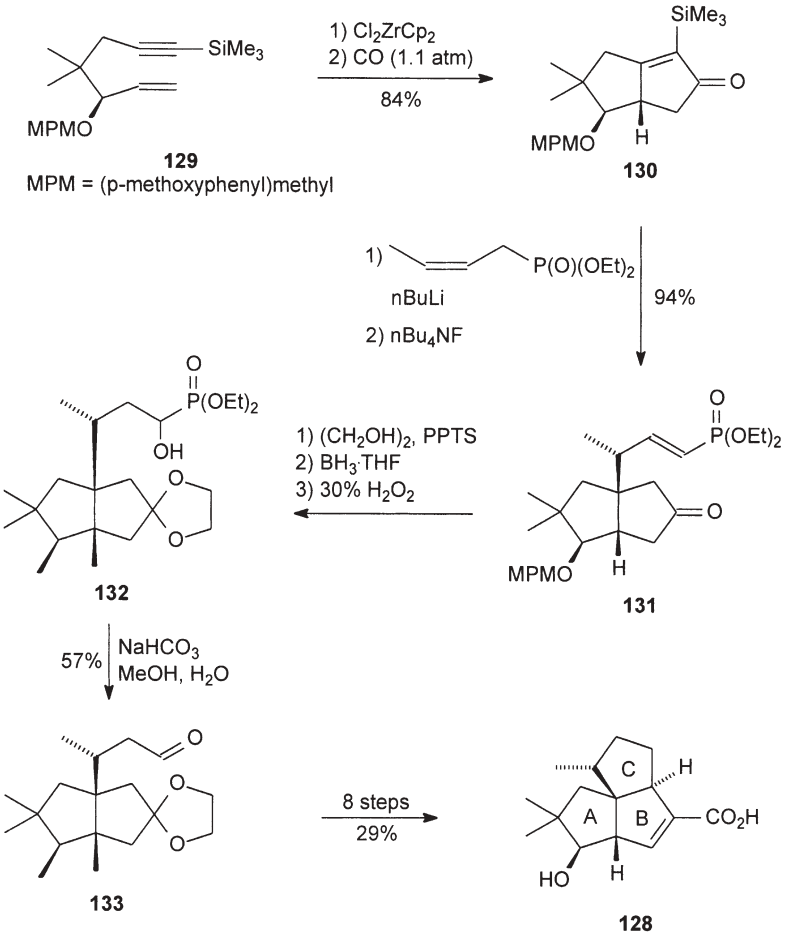
Scheme 32 (continued)

resented by *β*-cadinene (**125**), are isolated from high-boiling hydrocarbon fractions of numerous essential oils of *Mentha piperite, Pinus silvestris, Shorea robusta*, etc. They are used as ingredients of perfumery preparations. The synthesis of **121** started from the Knoevenagel reaction of **123** with triethyl phosphonoacetate using piperidine as a catalyst in ethanol to give an (*E*)-dienoate as

the main reaction product. Treatment of the latter with $EtAlCl_2$ as a Lewis acid afforded exclusively the (2*S**)-diastereomer **126** as the intramolecular ene product. Finally, the acrylic acid ester **127**, prepared in the Horner-Wittig reaction of **126** with paraformaldehyde, was converted in five steps to (1*R**,6*S**)-**121**, a *cis*-fused diastereomer of decahydrocadalenes.

6.2
Synthesis of (±)-Pentalenic Acid

A new concept of highly stereo- and regio-controlled cyclopentaannulation *via* allylphosphonate conjugate addition and application of the hydroboration-oxidation-elimination process was developed by Negishi and Agnel [59] in virtually complete stereo- and regio-controlled synthesis of (±)-pentalenic acid **128** (Scheme 33). Thus, starting from the enyne **129**, in the Zr-promoted bicycliza-

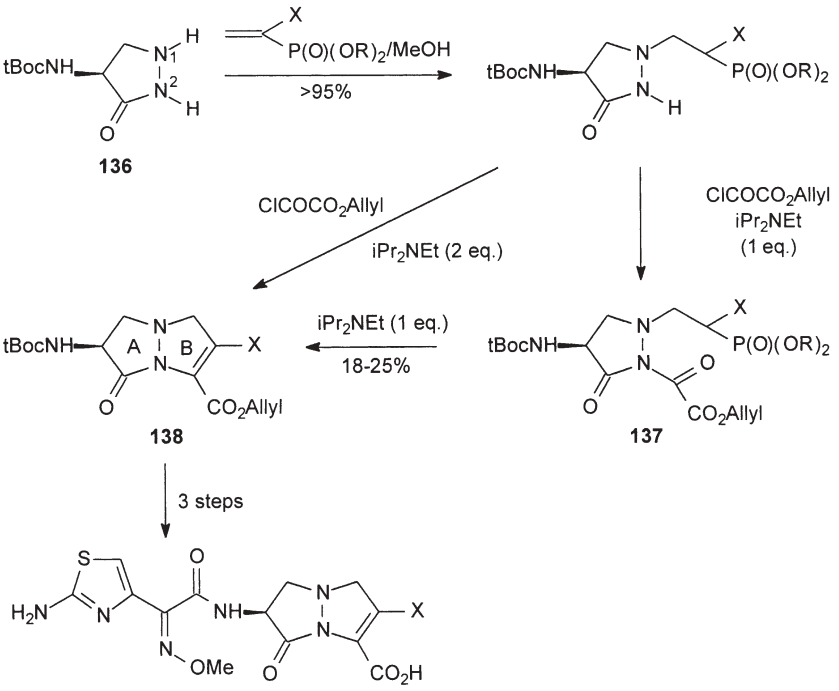


Scheme 33

tion-carbonylation reaction, the bicyclic α,β-unsaturated ketone **130** was produced in >98% diastereoselectivity. After treatment of the latter with the lithio derivative of diethyl (Z)-crotylphosphonate, followed by the desilylation reaction, the phosphonate **131** was obtained in crude form in ≥98% stereomeric purity. Ketalization of **131** and hydroboration with BH_3·THF followed by oxidation with 30% H_2O_2 gave the crude α-hydroxyphosphonate **132.** Formally, as a P,O-hemiacetal, the latter was converted into the aldehyde **133** in the reverse Horner-Wittig reaction upon treatment with $NaHCO_3$ in aqueous methanol. In the final eight non-phosphorus-containing steps, **128** was obtained in 29% yield.

6.3
Synthesis of [3.3.0]Pyrazolidinones

A search for new agents having improved antibacterial activities, especially against organisms resistant to current therapies, led Ternansky and Draheim [60] to the preparation of compounds **134** and **135** (Scheme 34) representing a new class of totally synthetic, antibacterial agents, structurally characterized by the presence of a [3.3.0]pyrazolidinone framework. The new functionality, responsible for inhibition of the cell wall synthesizing enzymes of Gram-nega-



134 X = CN
135 X = SO_2Me

Scheme 34

tive bacteria, can serve as a viable biological surrogate of the beta-lactam functionality common to the penicillins, cephalosphorins, and monobactams.

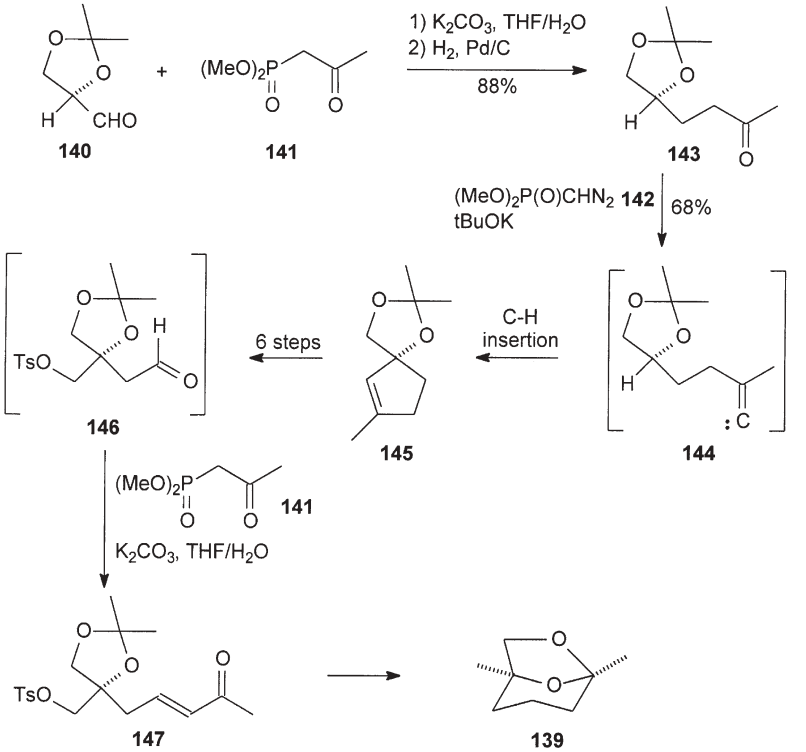
A synthetic route to **134** and **135** comprised:

1) a selective, stepwise functionalization of the pyrazolidinone **136** via alkylation at N-1 with the corresponding vinyl phosphonate, followed by
2) an acylation at N-2 with allyl oxalyl chloride in the presence of *i*-Pr_2NEt and
3) intramolecular Horner-Wittig condensation of the monocycle **137**.

Although the compound **137** could not be isolated in a pure form due to the lability of the glyoxamide group, its isolation was not necessary because addition of a second equivalent of the base caused the desired intramolecular ring closure to **138**. Both compounds **134** and **135**, synthesized in three steps from **138**, exhibited antibacterial activity in vitro, especially compound **134** was active against *Enterobacter cloacae*, which is resistant to many beta-lactam antibiotics.

6.4
Synthesis of (–)-Frontalin

(–)-Frontalin (**139**) is known to be the aggregation pheromone of the southern pine beetle *Dendroctonus frontalis*. The biologically active form of this com-



Scheme 35

pound is the (1*S*,5*R*)-enantiomer (its antipode has been reported to be inactive). Ohira et al. [61] synthesized (–)-frontalin utilizing D-glyceraldehyde **140** and the phosphonates **141** and **142** in three different stages of the synthesis. Thus, **140** was treated with dimethyl 2-oxopropanephosphonate **141** and K_2CO_3 to give, after hydrogenation, the saturated ketone **143**. The Horner-Wittig olefination of the latter, then generation of the alkylidene carbene **144** and subsequent C-H insertion, afforded **145** in 68% yield. The crude aldehyde **146** was then prepared in six steps from **145**. The Horner-Wittig reaction of **146** with **141** afforded the α,β-unsaturated ketone **147**, which was finally converted into (–)-frontalin (**139**) (Scheme 35).

7
Use of Phosphonates in the Synthesis of Biologically Active Steroids

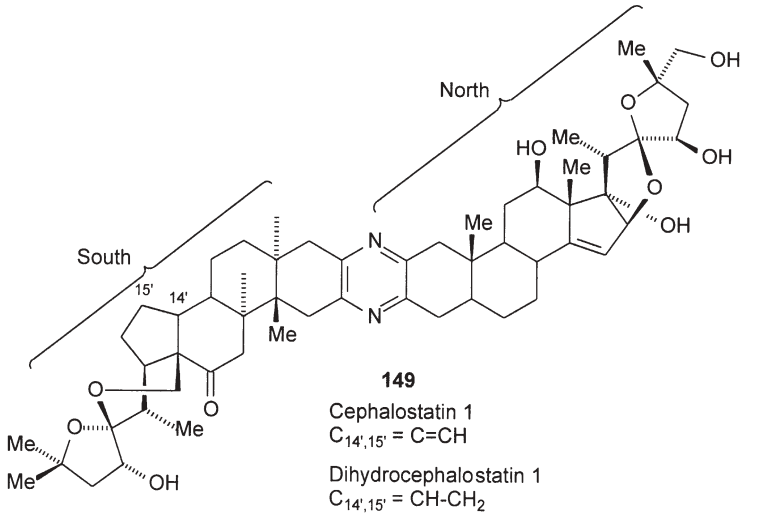
Due to the common occurrence of steroids in Nature, there is not much need to synthesize the steroid skeleton from simple substrates. Therefore, the use of phosphonates in syntheses involving this class of compounds, concerns mostly modifications of the steroid pool, like in the case of the conversion of 17-oxosteroids to 20-ketosteroids and progesterone as well as construction of the "South" steroid subunit of cephalostatin 1 from hecogenin acetate.

7.1
Synthesis of the "South" Hexacyclic Steroid Unit of Cephalostatin 1

The first example of a rhodium(II)-carbenoid insertion reaction into a primary neopentyl alcohol system was demonstrated by Fuchs and Bhandaru [62] in the synthesis of the pentacyclic aldehyde **148** (Scheme 36). This aldehyde was a precursor, suitable for the construction of the C14′/C15′ dihydro derivative of the "South" hexacyclic steroid unit of cephalostatin 1 – **149**, the most potent antineoplastic member of a family of twenty eight trisdecacylic pyrazines. A starting material in the synthesis of the aldehyde **148** was triol **150** obtained from hecogenin acetate **151** in 13% overall yield. The above-mentioned, chemoselective Rh(II)-mediated insertion into a primary neopentyl alcohol system affording the diol **152** followed by the Brown-Jones bis-oxidation gave diketone **153**. Treatment of the resulting 1:1 diastereomeric mixture with NaH effected the intramolecular Horner-Wittig reaction, exclusively utilizing the acetyl carbonyl group to give dihydropyran ester **154** in 86% yield from **152**. The final two-step procedure including reduction and the Swern oxidation generated the desired aldehyde **148**.

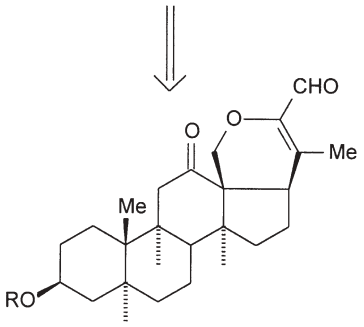
7.2
Synthesis of 20-Ketosteroids and Progesterone

Van Leusen and coworkers [63] demonstrated for the first time that compounds with geminal N and P substitutents attached to the carbon atom behaved like *N,P*-acetals releasing upon hydrolysis carbonyl compounds like other *O,O*-,

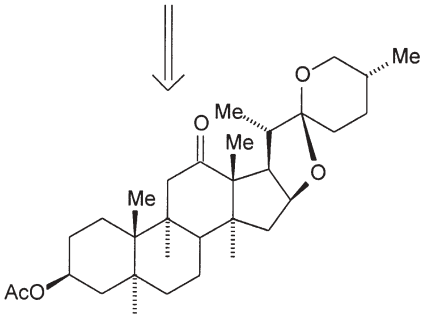


149
Cephalostatin 1
$C_{14',15'}$ = C=CH

Dihydrocephalostatin 1
$C_{14',15'}$ = CH-CH_2

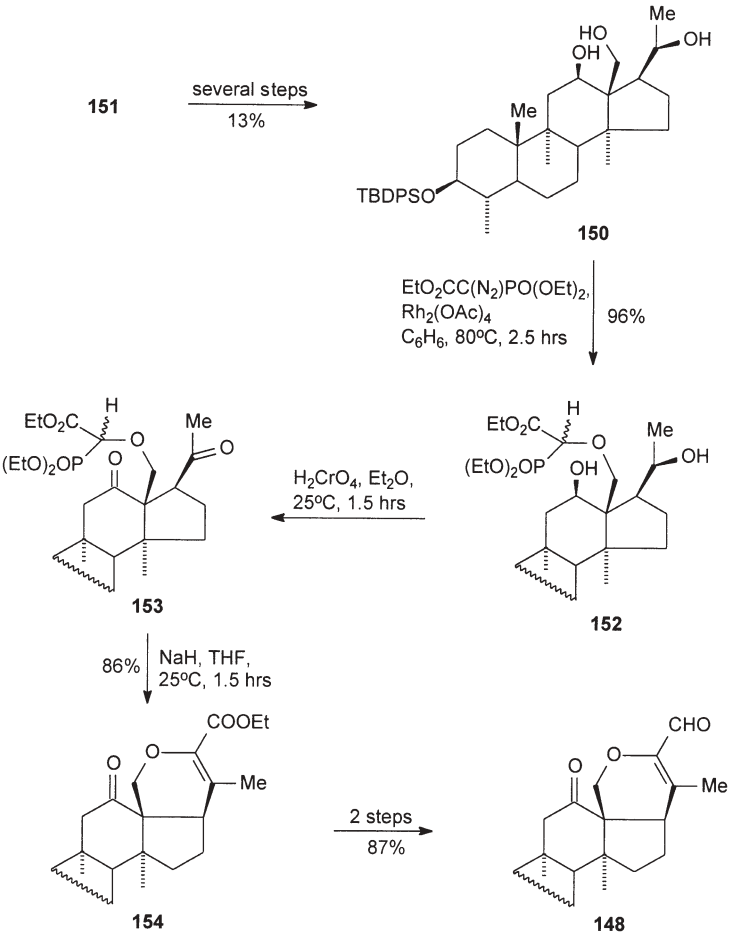


148
Pentacyclic aldehyde



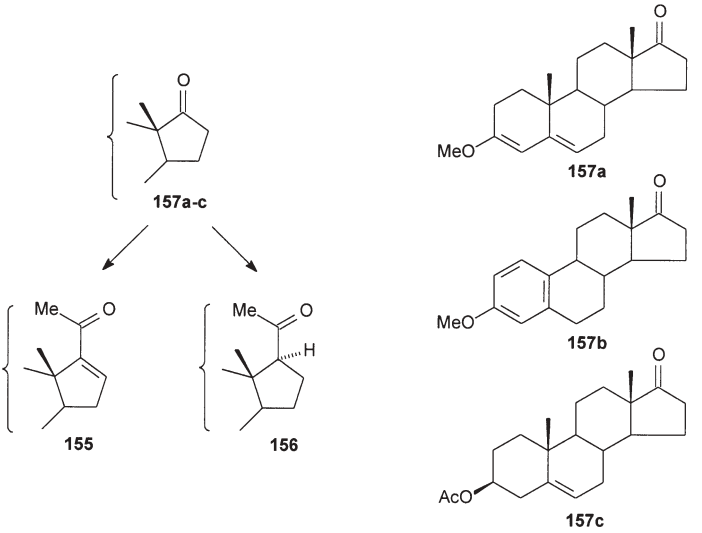
151
Hecogenin Acetate

Scheme 36

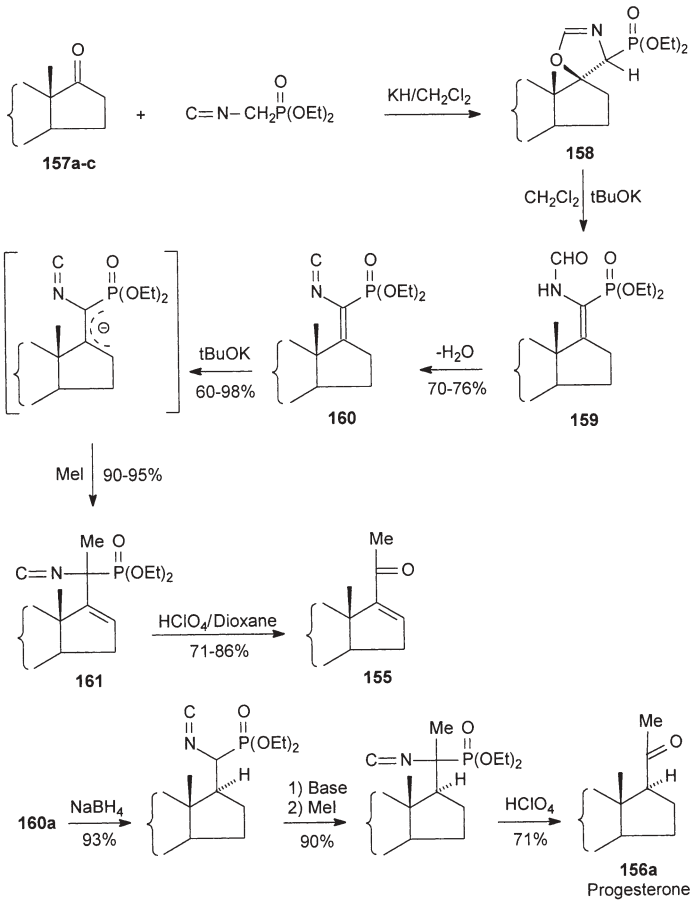


Scheme 36 (continued)

O,S-, *S,S*-, *N,S*-, *N,N*-, and *N,O*-acetals. The new *N,P*-acetals were applied for the synthesis of 20-ketosteroids **155** and **156** starting from 17-oxosteroids **157a–c** and diethyl isocyanomethanephosphonate (Scheme 37 and Scheme 38). In this reaction, the intermediate 2-oxazolines **158** could be obtained. Their subsequent, electrocyclic ring opening was effected with *t*-BuOK to give (*E*)-17-[(diethylphosphono)formamidomethylene]steroids **159** which underwent dehydration of the formamide group to (*E*)-17[(diethylphosphono)isocyanomethylene]steroids **160** in high yields. Both **159** and **160**, which had not been reported previously, are ketene *N,P*-acetals. The latter were easily deprotonated at C-16 and methylated at C-20. The resulting *N,P*-acetals **161** were hydrolyzed under acidic conditions in refluxing dioxane to give the 20-ketosteroids **155**. In a related series, ketene *N,P*-acetals **160** were reduced with $NaBH_4$ prior to methylation at C-20 to give the reduced 20-ketosteroids **156**. In this way, **160a** was converted in 59% yield to progesterone **156a**, obtained as a mixture of C-17 epimers, β/α (6:1).



Scheme 37



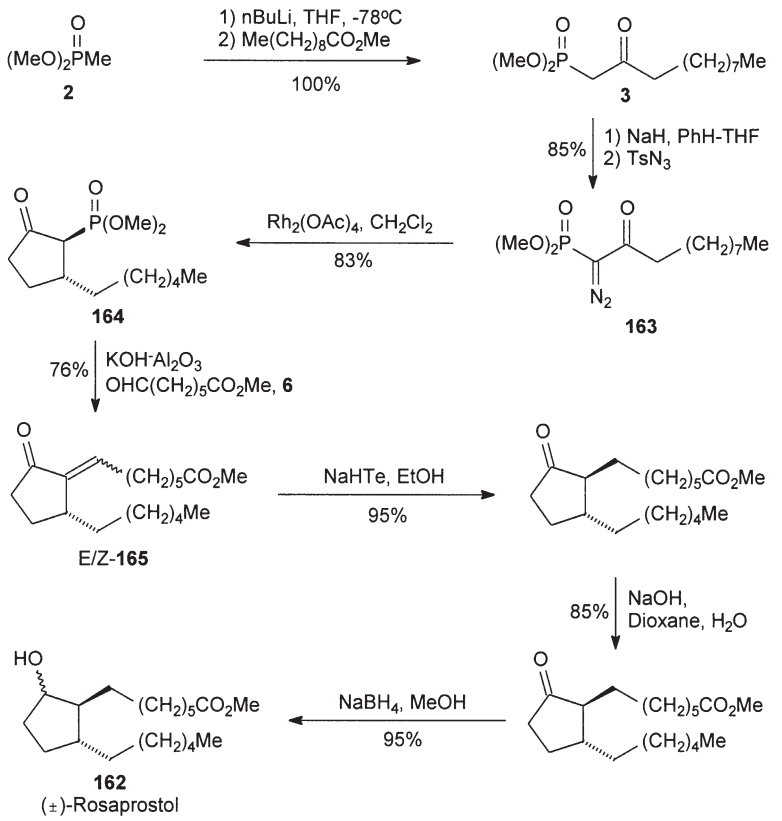
Scheme 38

8
Use of Phosphonates in the Synthesis of Biologically Active Cyclitols

Polyhydroxylated cycloalkanes and cycloalkenes are generally named cyclitols. The use of phosphonates in the synthesis of this class of compounds, is limited in the reviewed literature to only 5- and 6-membered cyclitols with potential biological activity. Therefore, in the present Section, two conceptually different approaches to the synthesis of the simplest cyclitol, i. e., (±)-rosaprostol, showing mainly gastric antisecretory activity, only will be presented.

8.1
Synthesis of (±) Rosaprostol

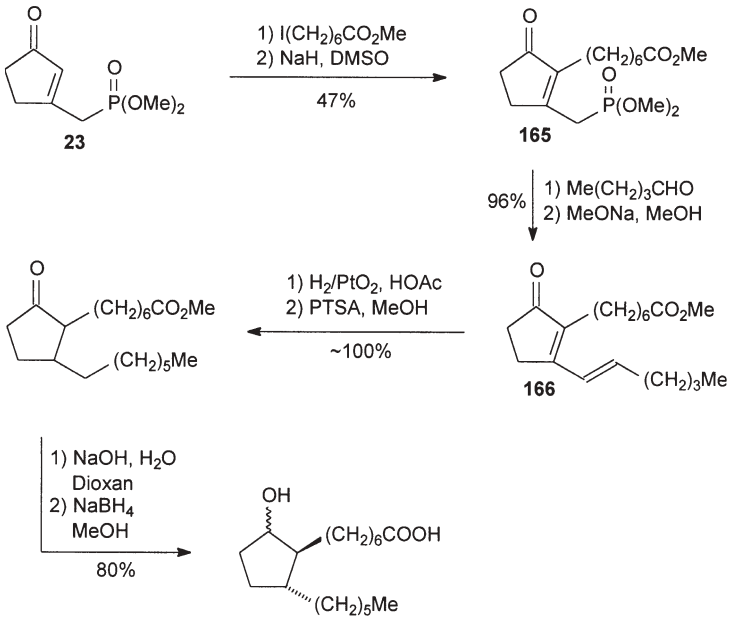
Mikolajczyk and Zurawinski [64] elaborated a total, seven-step synthesis of (±)-rosaprostol (**162**), a trade name for 7-(2-hexyl-5-hydroxycyclopentane)-heptanoic acid, showing gastric antisecretory activity and cytoprotective action common to naturally occurring prostaglandins (Scheme 39). The key steps of



Scheme 39

the synthesis included an intramolecular carbenoid cyclization of dimethyl 1-diazo-2-oxoundecanephosphonate **163** leading to 2-dimethoxyphosphoryl-l-3-hexylcyclopentanone **164** and the Horner-Wittig reaction of the latter with methyl 5-formylpentanecarboxylate employed for the introduction of the methoxycarbonylhexyl moiety at C(2) of the cyclopentanone ring. It is worthy of note that the olefination reaction failed with many commonly used basic systems, however, use of solid Al_2O_3/KOH in benzene afforded a 1.3:1 mixture of the *E* and *Z* olefination products in 76% yield. A necessary, separate reduction of the *exo*-double bond in the obtained enone **165** and the keto group afforded (±)–rosaprostol (**162**) as a 1:1 mixture of *trans-trans* and *trans-cis* stereomers in 42% overall yield.

A shorter five-step synthesis of (±)-rosaprostol was developed by the same research group [65] based on utilization of a new phosphorus reagent, i.e., 3-(dimethoxyphosphorylmethyl)cyclopent-2-enone **23**. As in the case of the prostaglandin B_1 synthesis, alkylation of the anion derived from **23** with methyl 7-iodoheptanoate gave **165** and its Horner-Wittig reaction with *n*-pentanal gave the 2,3-disubstituted cyclopentenone **166**. Further sequential reduction of the two *exo*- and *endo*-double C-C bonds and then the carbonyl group in (±)-**166** followed by the methyl ester hydrolysis completed the synthesis of (±)-rosaprostol (**162**) in 36% overall yield (Scheme 40).



Scheme 40

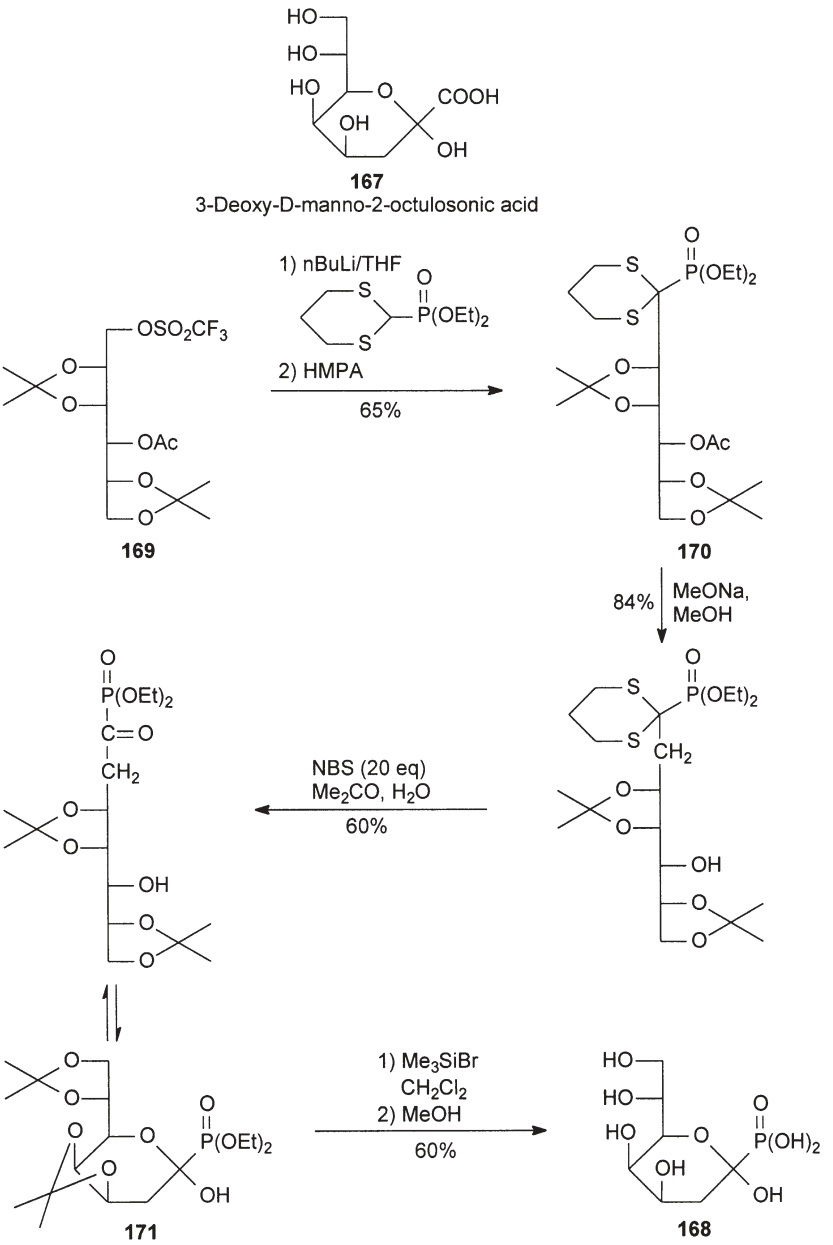
9
Use of Phosphonates in the Synthesis of Biologically Active Carbohydrates

One direction of research in the area of antibacterial drugs was connected with the synthesis of phosphonic analogues of carbohydrates, such as 3-deoxy-D-*manno*-2-octulosonic acid. This was due to the fact that these analogues potentially targeted the biosynthesis of this acid and hence disrupted the outer membrane of all Gram-negative bacteria without affecting mammalian cells.

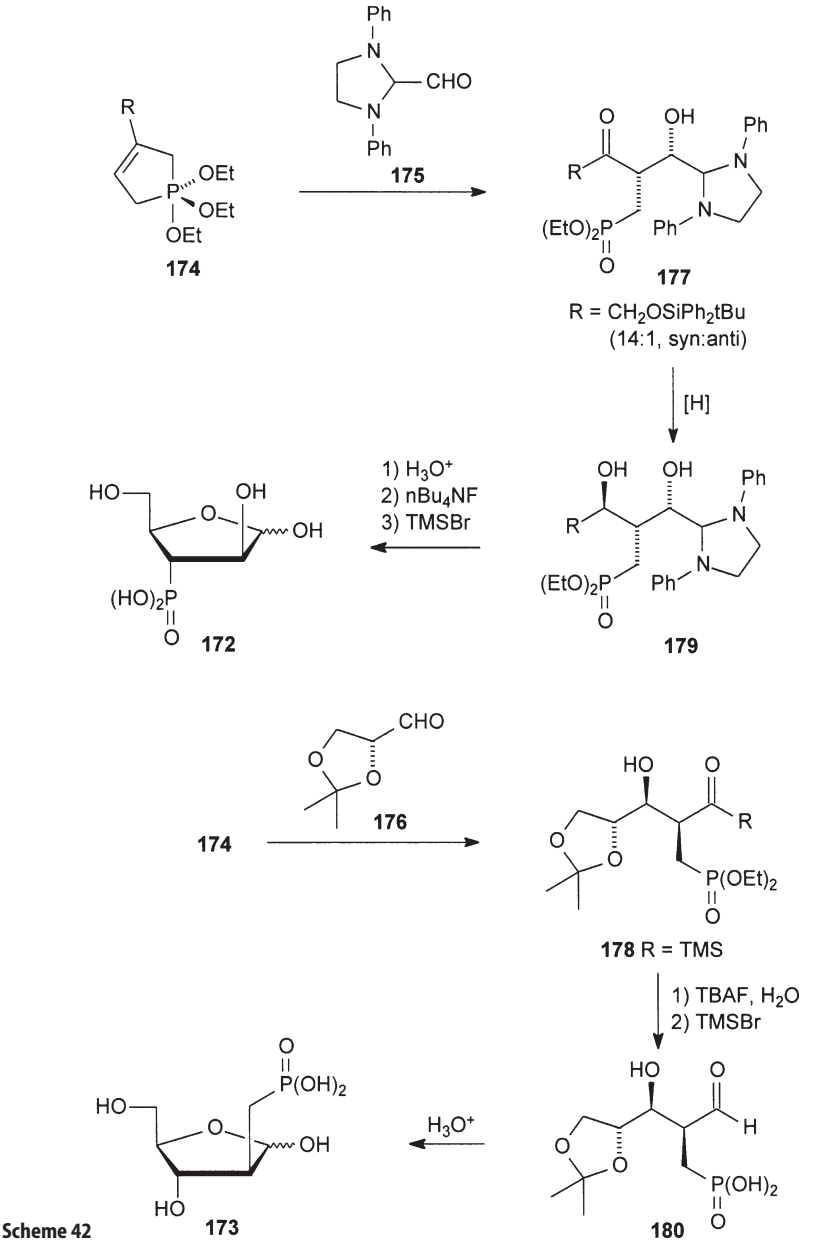
9.1
Synthesis of Analogues of 3-Deoxy-D-*manno*-2-octulosonic Acid

3-Deoxy-D-manno-2-octulosonic acid **167** constitutes the major component of the outer membrane lipopolysaccharides of all Gram-negative bacteria. An interest in the synthesis of analogues of this acid as new antibacterial agents led to the synthesis of a fragile phosphonic acid analogue **168** [66] (Scheme 41). The synthetic approach to this analogue was based on a combination of the carbohydrate chemistry with the chemistry of α-phosphoryl dithioacetals. Thus, condensation of 2,3:5,6-di-D-isopropylidene-D-mannitol triflate **169** with 2-lithio-2-diethoxyphosphoryl-1,3-dithiane gave the adduct **170**, which after selective deprotecting steps afforded finally the phosphonic acid **168**. It is interesting that the acid **168** and the ester **171**, both having hydroxy groups α to the phosphorus atom, were unstable and slowly underwent degradation to the corresponding lactones.

In searching for stable analogues of β-deoxy-*S*-*manno*-2-octulosonic acid **167**, McClure et al. [40] used their pentacovalent oxaphospholene methodology for the synthesis of the 2- and 3-phosphonomethyl derivatives of arabinose **172** and **173**. It was found that the condensations of the oxaphospholene **174** with either aminal **175** or the glyceraldehyde acetonide **176** were highly stereoselective, producing the *syn* aldol products **177** and **178** as major isomers in both cases. Stereoselective reduction of the keto group in **177** followed by hydrolysis of the aminal and acetonide moieties in **179** and **180** led, after cyclizations, to arabinose derivatives **172** and **173**, respectively (Scheme 42).


HO
HO
HO
O
COOH
OH
OH
167
3-Deoxy-D-manno-2-octulosonic acid
1) nBuLi/THF
S
S
O
P(OEt)2
2) HMPA
65%
OSO2CF3
O
O
OAc
O
O
169
S
S
O
P(OEt)2
O
O
OAc
O
O
170
84%
MeONa,
MeOH
NBS (20 eq)
Me2CO, H2O
60%
P(OEt)2
C=O
CH2
OH
171
1) Me3SiBr
CH2Cl2
2) MeOH
60%
HO
HO
HO
O
P(OH)2
OH
OH
168

Scheme 41


Ph
N
CHO
N
Ph
175
R
OEt
P
OEt
OEt
174
O
OH
Ph
R
N
(EtO)2P
Ph
N
O
177
R = CH2OSiPh2tBu
(14:1, syn:anti)
[H]
OH
OH
Ph
R
N
(EtO)2P
Ph
N
O
179
1) H3O+
2) nBu4NF
3) TMSBr
HO
O
OH
OH
(HO)2P
O
172
CHO
O
O
176
174
HO
O
R
O
O
P(OEt)2
O
178 R = TMS
1) TBAF, H2O
2) TMSBr
HO
O
H
O
O
P(OH)2
O
180
H3O+
O
P(OH)2
HO
O
OH
HO
173

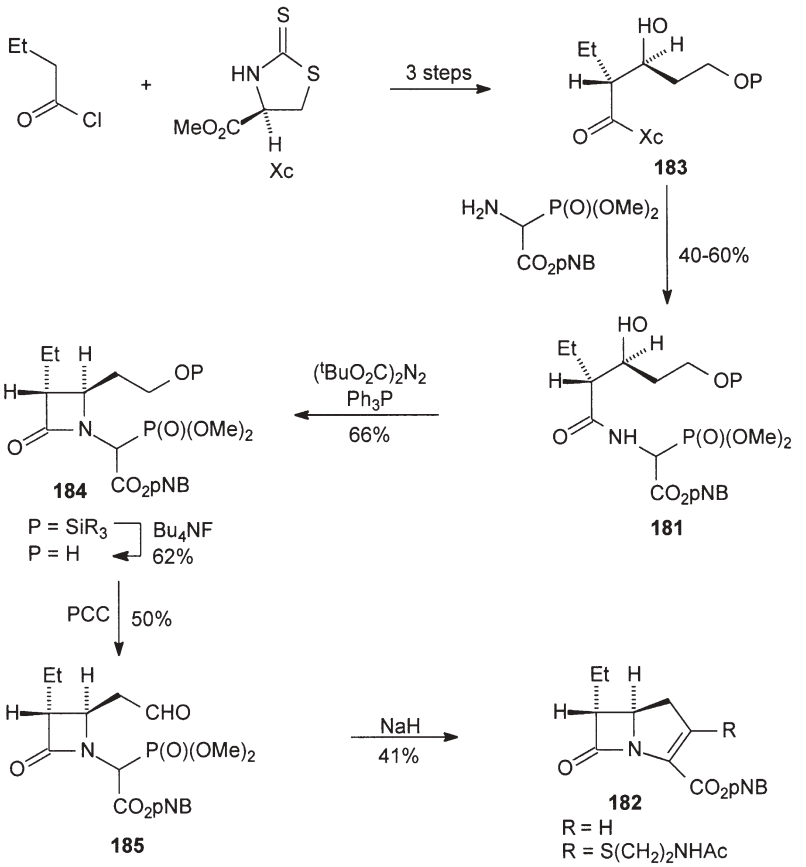
Scheme 42

10
Miscellaneous

The use of phosphonates in the synthesis of representatives of three important classes of biologically active compounds (carbapenems, triquinanes, and cyclitols) will be briefly discussed here.

10.1
Synthesis of the Carbapenem Framework

A double cyclization of the aminophosphonoacetate derived β-hydroxy acids **181** was utilized by Miller et al. [67] in the synthesis of the bicyclic β-lactams **182** as potent antibiotics. The carbon framework for the carbapenems was constructed by an asymmetric aldol condensation utilizing the cysteine-derived thiazolidinethione and subsequent direct coupling of the resulting β-hydroxy acid equivalent **183** with dimethyl aminophosphonoacetate (Scheme 43). Two

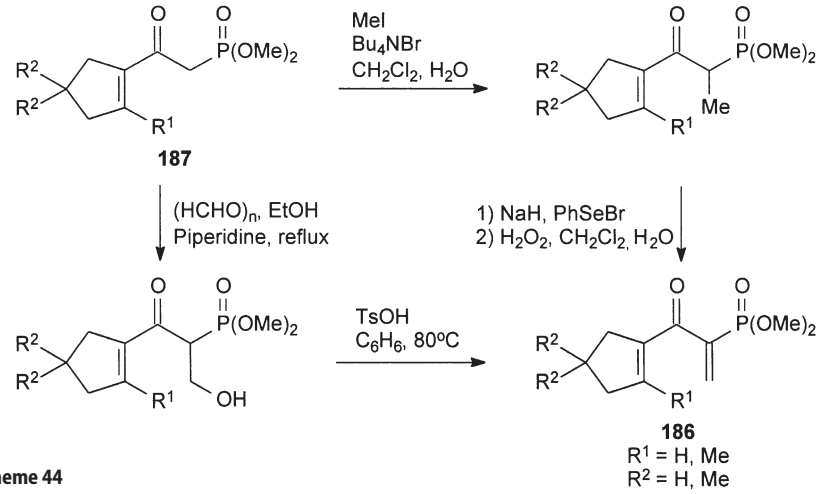


Scheme 43

final cyclization steps involved the Mitsunobu coupling with the di-(*t*-butyl) azodicarboxylate/triphenylphosphine system to give the monocyclic β-lactam **184** and the intramolecular Horner-Wittig reaction of the phosphonoaldehyde **185** leading to the desired carbapenems **182.**

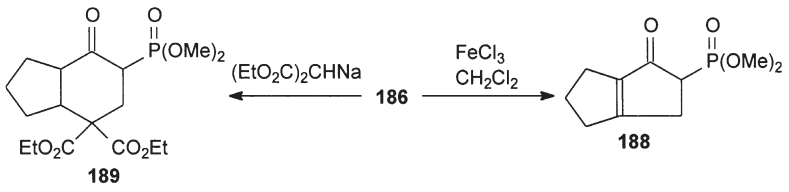
10.2
Synthesis of the Triquinane Ring System

Minami and coworkers [68] developed a very efficient synthesis of 1-(cyclopent-1-enylcarbonyl)vinylphosphonates **186** as versatile cyclopentane annulating reagents. As shown in Scheme 44, these reagents were obtained from 1-(cyclopent-1-enylcarbonyl)methanephosphonates **187** in three steps involving methylation under PTC conditions and a selenylation-deselenylation procedure. An alternative approach to **186** is based on the condensation of **187** with paraformaldehyde.



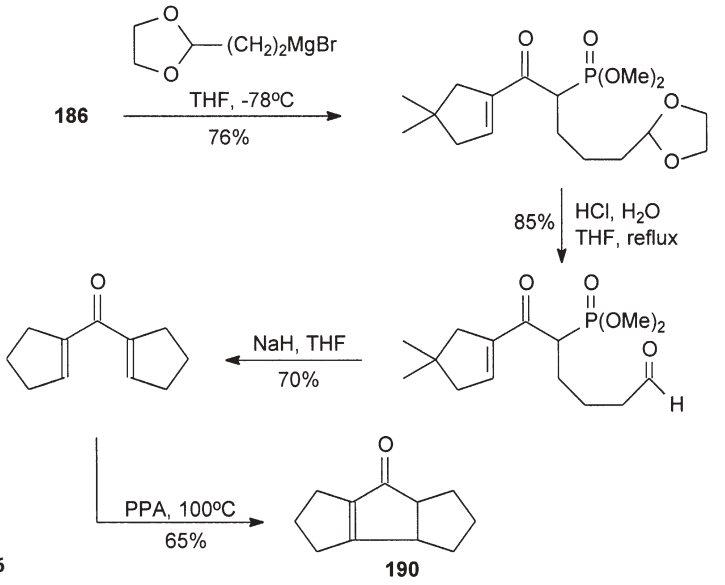
Scheme 44

The Nazarov cyclization of **186** carried out in the presence of $SnCl_4$ or $FeCl_3$ produced in moderate yields (~35%) the corresponding bicyclic compounds **188** (Scheme 45).



Scheme 45

On the other hand, the vinylphosphonate **186** easily underwent the intramolecular double Michael addition of diethyl sodiomalonate to give the bicycle **189**. Moreover, by making use of the β-ketovinylphosphonate moiety in **186** the Japanese group was able to synthesize dicyclopent-1-enyl ketones which, when treated with acid, led to the Nazarov cyclization products **190** having three condensed five-membered rings (Scheme 46).



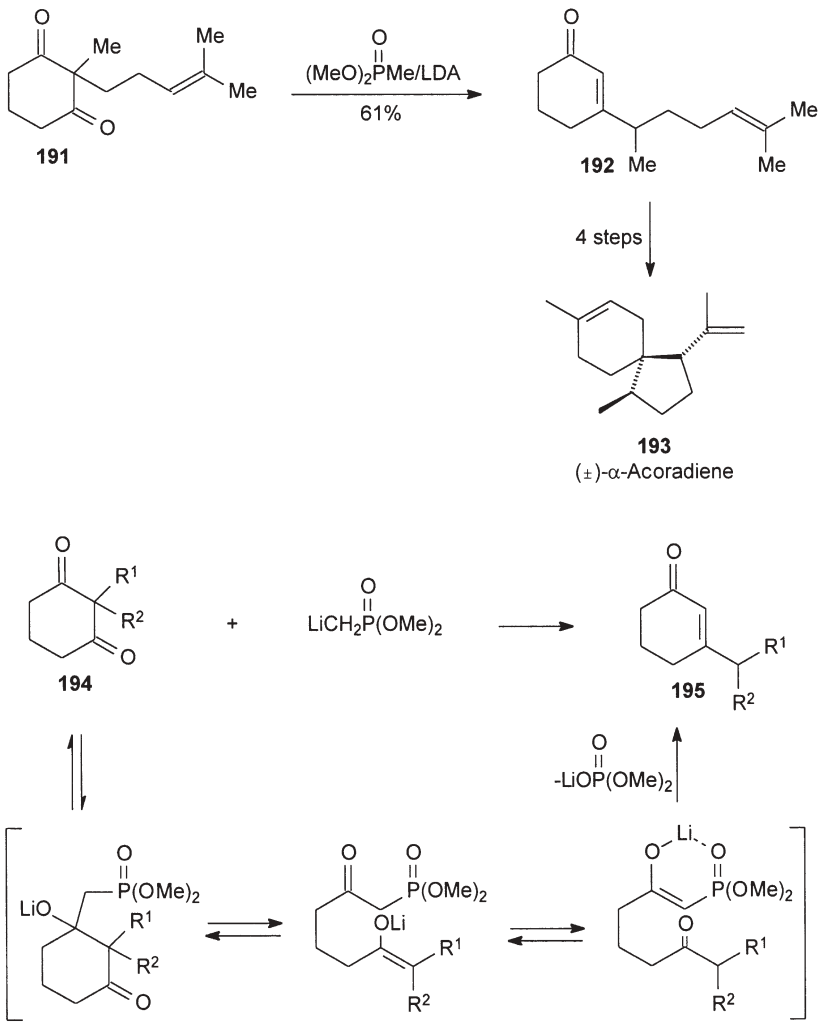
Scheme 46

The synthesis of tricyclo[6.3.0.0^{3,7}]undecenone **190** illustrates this methodology (Scheme 46) which paved the way for the synthesis of naturally occurring diquinane and triquinane terpenoids exhibiting useful antibiotic or antitumor properties.

10.3 Synthesis of the Spirocyclic (±)-α-Acoradiene

A multistep conversion of 2,2-disubstituted 1,3-cyclohexadiones **191** to 3-substituted 2-cyclohexenones **192** mediated by phosphonate anions was applied by Yamamoto and Furuta [69] in a formal synthesis of (±)-α-acoradiene (**193**) (Scheme 47). 3-Substituted 2-cyclohexenones are versatile building blocks for the synthesis of cyclic natural products such as spirocyclic and fused ring sesquiterpenes. These cyclohexenones were easily obtained in a one-pot reaction of **194** with dimethyl methanephosphonate anion in the presence of trimethylsilyl chloride. The new overall reaction is a multistep rearrangement involving

a) attack of the phosphonate anion on a carbonyl group,
b) retroaldol cleavage,



Scheme 47

c) reorganization of the acidic proton, and
d) intramolecular Horner-Wittig reaction to give **195**.

In the synthesis of (±)-acoradiene (**193**), the cyclohexene **192** was prepared in 61% yield and then transformed to the final spirocycle **193** in a four-step reaction sequence.

11 Conclusion

Phosphonates have broad applications in organic synthesis. As we have shown in this review, phosphonate reagents and their diverse reactivity are very useful in the synthesis of biologically active products. Their use as substrates and key intermediates allows the synthesis of very complex structures to be carried out. The phosphonate-based methods compare favorably in terms of brevity and use of simple reagents with the majority of the previously reported syntheses. Another advantage of the use of phosphonates is that the presence of phosphorus in starting materials and intermediates allows the course of each synthetic step to be followed by means of ^{31}P-NMR spectroscopy. While this review presents a small sample of the uses of phosphonates in synthesis, they have been and will continue to be important reagents for synthetic chemists in the future.

Acknowledgement. The financial assistance of the State Committee of Scientific Research (KBN), grant No PBZ 008/T09/98, is highly appreciated. Special gratitude is expressed to all research associates whose name appear in the reference list.

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The Fascinating Chemistry of 1,3,5-Triphosphinines and Valence Isomers [1]

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In contrast to their all-carbon analogues, phosphaalkyne cyclooligomers only became accessible a few years ago. A milestone in the chemistry of the cyclotrimers was the synthesis and structural characterization of the 1,3,5-triphosphinines **11**, obtained by the trimerization of phosphaalkynes in the presence of a vanadium catalyst. This review is focused on the reactivity of these new phosphorus heterocycles.

Keywords. Triphosphinines, Valence isomerization, Phosphaalkynes, Heterophospholes

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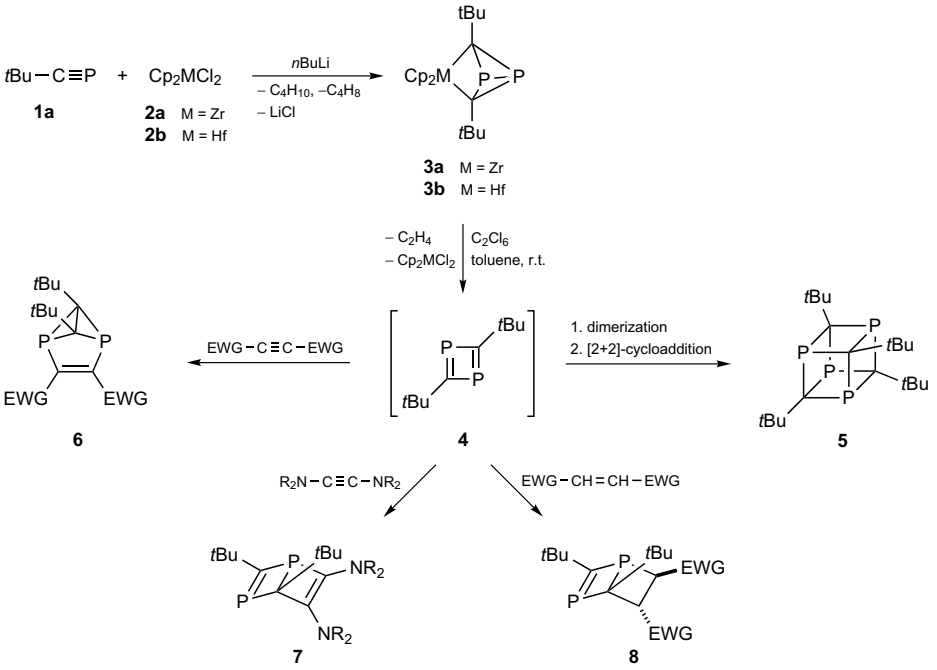
1 Introduction

Cyclooligomerizations of phosphaalkynes are the methods of choice for the construction of phosphorus-containing hetero-, bi-, and polycyclic systems [2]. Although the purely thermal cyclooligomerization provides an access to a series of phosphorus-containing cage compounds in generally modest yields in dependence on the temperature, the transition metal-mediated cyclooligomerization is a considerably more powerful method on account of its higher selectivity and better yields [3–6]. A particularly illustrative example is the cyclodimerization of (2,2-dimethylpropylidyne)phosphane (*tert*-butylphosphaacetylene) **1a** under the influence of metallocene derivatives of zirconium and hafnium, **2a, b**, that leads to dicyclopentadiene complexes with 1,5-diphosphatricyclo[2.1.0.$0^{2,5}$]pentane ligands **3a, b** [7–9].

Under the action of hexachloroethane, the diphosphane ligand can be liberated as the highly reactive 1,3-diphosphete **4**. In the absence of a trapping reagent, the latter dimerizes to furnish derivatives of 1,3,5,7-tetraphosphapentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane (1,3,5,7-tetraphosphacubane) **5** [8–11] or, in the presence of alkynes, valence isomers of 1,3-diphosphinine, namely, 2,5-diphosphatricyclo[3.1.0.$0^{2,6}$]hex-3-enes (diphosphabenzvalenes) **6** or 1,3-diphosphabicyclo[2.2.0]hex-2,5-dienes (diphospha-Dewar-phosphinines) **7**. With acceptor-substituted alkenes as trapping reagents, the corresponding 5,6-dihydrodiphospha-Dewar-phosphinines **8** are obtained [12, 13].

The transition metal-mediated cyclotrimerization of phosphaalkynes could lead to triphosphinines (triphosphabenzenes) if it was possible to remove the transition metal fragment and liberate the cycloalkyne trimer.

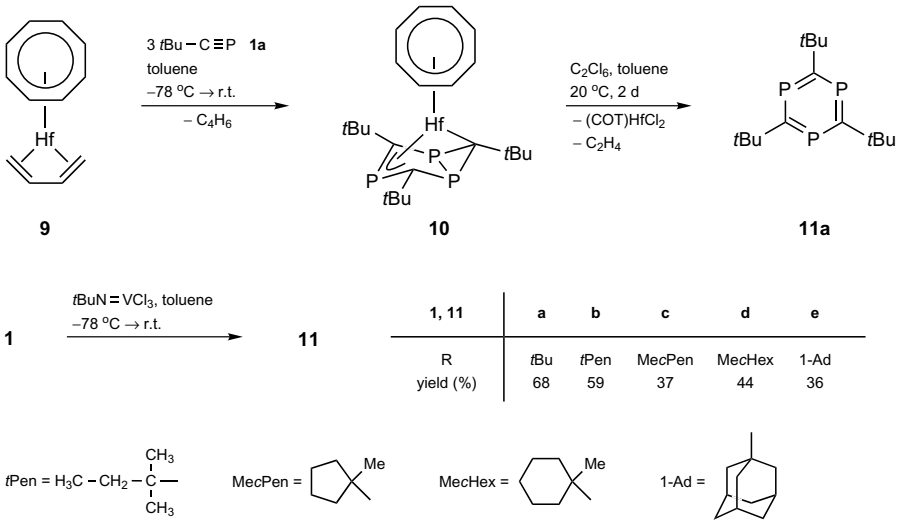


Scheme 1. Cyclodimerization of tert-butylphosphaacetylene (**1a**)

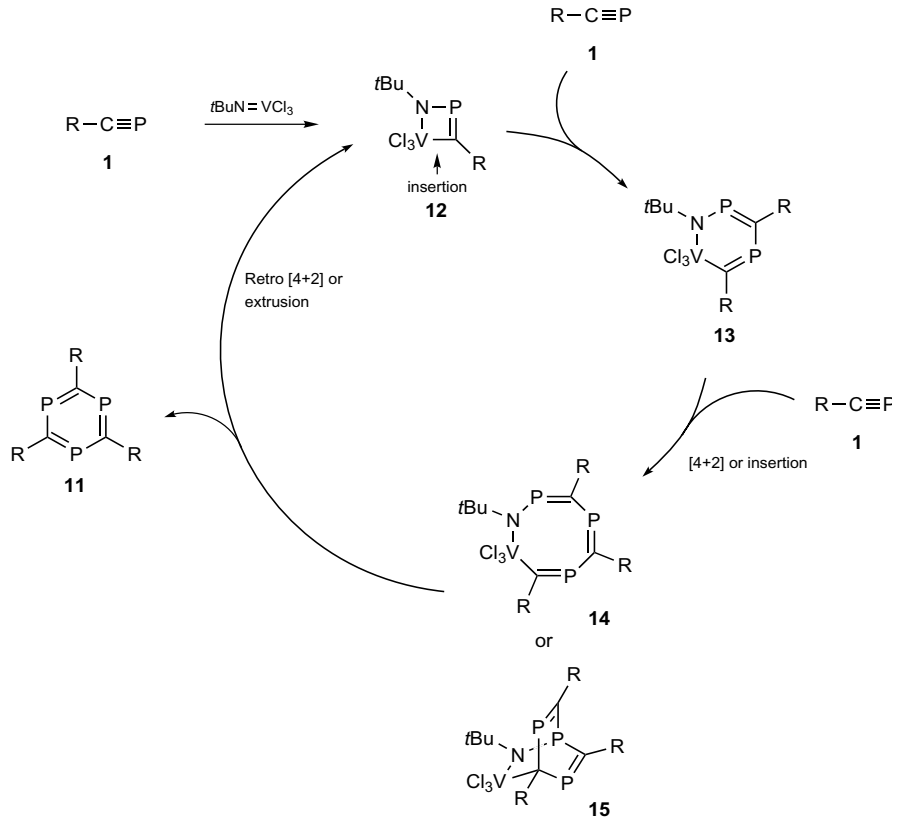
2
Synthesis of 1,3,5-Triphosphinines

The cyclotrimerization of (2,2-dimethylpropylidyne)phosphane (**1a**) in the presence of the (cyclooctatetraene)hafnium complex **9** affords the hafnium complex **10** in 83 % yield; treatment of the latter with hexachloroethane then furnishes 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) through expulsion of the metal fragment [14].

Shortly after the above reaction was reported, the synthesis of 1,3,5-triphosphinines **11** experienced an appreciable simplification, namely the imidovanadium trichloride-initiated trimerization of phosphaalkynes by which, in addition to the *tert*-butyl substituents, other sterically demanding groups can also be attached to the 1,3,5-triphosphinine ring (yields: 36 – 68 %) [15, 16]. As shown in Scheme 3, this cyclotrimerization proceeds catalytically with participation of the 1,4-dihydro-1-aza-2-phospha-4-vanadate **12** as the actual catalytically active species. The vanadium-containing four-membered ring system **12** is formed by a [2 + 2]-cycloaddition of the imidovanadium trichloride with the phosphaalkyne **1**; it can be detected spectroscopically and even isolated. Sequential reactions with three further molecules of the phosphaalkyne result, via the postulated intermediates **13** and **14** or **15**, in the formation of the 1,3,5-triphosphinine



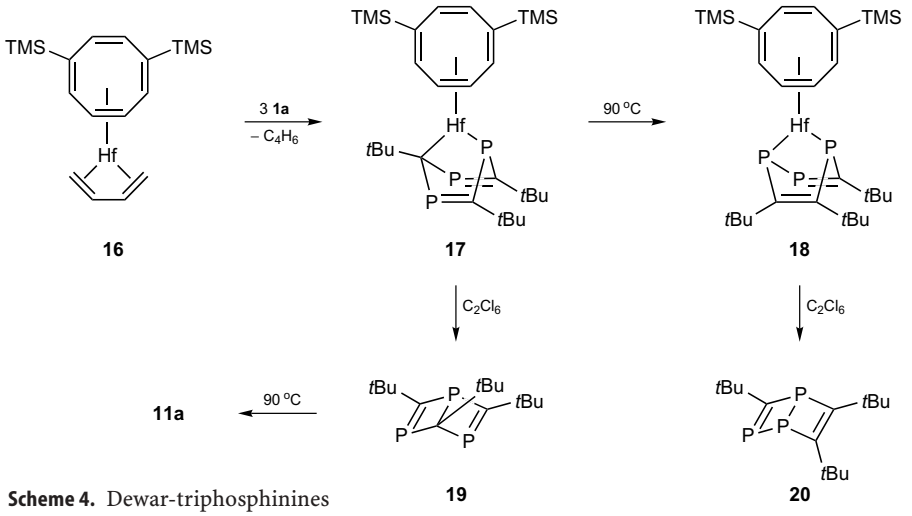
Scheme 2. Cyclotrimerization reactions of phosphaalkynes



Scheme 3. Formation of 1,3,5-triphosphinines by a catalytic process

11 with concomitant liberation of the catalytic species **12.** Although it was demonstrated that this cyclotrimerization occurs, in principle, catalytically the stoichiometric version proved to be better because, on the one hand, insertion of the phosphaalkyne into the nitrogen-vanadium bond of **12** takes place as a competing reaction and thus deactivates the catalytic species [17] and, on the other hand, already formed 1,3,5-triphosphinine reacts further in the presence of a large excess of phosphaalkyne to afford [4 + 2]-cycloadducts that are difficult to separate; see page 240.

When the above-mentioned hafnium complex **9** is modified by the introduction of two trimethylsilyl groups on the cyclooctatetraene ligands (→ **16**), cyclotrimerization with the phosphaalkyne **1a** furnishes the hafnium complex **17** already containing the 1,3,5-triphosphinine skeleton as ligand. Complex **17** undergoes isomerization at 90 °C to complex **18** possessing two coordinated phosphorus atoms. Upon treatment with hexachloroethane, both complexes undergo the known fragmentation reaction to afford the valence isomeric Dewar-triphosphinines **19** and **20**, respectively [18 – 20]. Under thermal conditions (90 °C) **19** undergoes isomerization to the 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**).

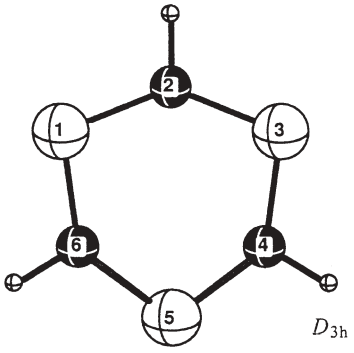


Scheme 4. Dewar-triphosphinines

3
Properties of 1,3,5-Triphosphinines

The 1,3,5-triphosphinines **11a – e** are, with the exception of **11b**, obtained as a yellow oil, isolated as yellow solids that can be stored for unlimited times under an inert gas with exclusion of light.

Ab initio theoretical calculations confirm that the triphosphinines have the lowest energy among the $C_3P_3H_3$ valence isomers [21]. In the series of parent triphosphinines the 1,3,5-isomer has the highest energy. However, when we con-



//MP2(fu)/6-31G*

distances (Å)		angles (°)	
P1-C2	1.736	P1-C2-P3	134.7
		C2-P3-C4	105.3

//x-ray (tris-*t*Bu derivative)[a)]

distances (Å)		angles (°)	
P-C	1.724(5)	P-C-P	130.3(3)
	1.719(4)		130.8(3)
	1.718(4)		130.9(3)
	1.725(5)	C-P-C	109.6(2)
	1.727(4)		109.0(2)
	1.729(5)		109.3(2)

a) Lit. 23

Fig. 1. Optimized geometries (MP4/6-31+G*//MP2(fu)/6-31G*) of 1,3,5-triphosphinine ($C_3H_3P_3$) [21]

sider that as yet only 1,3,5-triphosphinines bearing sterically demanding substituents have been isolated the order should be reversed because in the 1,2,3-triphosphinines three bulky substituents would be directly adjacent in an ecliptic arrangement whereas they are separated by larger distances in the 1,3,5-isomers.

NMR spectroscopic data are indicative of an aromatic character for the 1,3,5-triphosphinines. This is confirmed by homodesmic equations and the NICS value of – 5.8, although these theoretical calculations show that the triphosphinine is less aromatic than benzene, phosphinine, and the diphosphinine isomers [21, 22]. The relatively high reactivity of the triphosphinines is in harmony with this reactivity grading. Photoelectronic studies as well as ab initio calculations reveal the participation of two degenerate HOMO orbitals of the π-type in the reaction behavior while two non-bonding, degenerate molecular orbitals – resulting from the linear combination of the free electron pairs at phosphorus – are of lower energy. The energy difference between the two types of molecular orbital is, however, small although it must be considered that sterically demanding substituents also effect a shielding of the free electron pairs at phosphorus atoms. The degenerate LUMO orbitals are also of the π-type [23, 24].

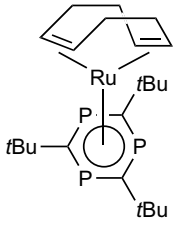
A single crystal X-ray structure determination of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) also provided indications for the aromatic nature of these heterocyclic compounds. The analysis shows a planar, hexagonal basic skeleton with average carbon-phosphorus bond lengths of 1.727 Å, a value lying between those for carbon-phosphorus single and double bonds [14, 23].

4
Reactivity of 1,3,5-Triphosphinines

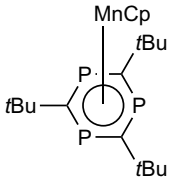
In spite of their aromatic character the 1,3,5-triphosphinines are reactive compounds that participate in numerous interesting reactions; these will be discussed in detail in the following sections.

4.1
Reactivity towards Transition Metals

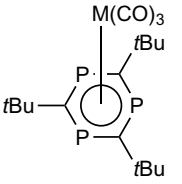
1,3,5-Triphosphinines serve as η^6-ligands for complexes of elements of the 6th, 7th, and 8th groups of the periodic table [25 – 27]. With the exception of the chromium complex **23c**, the preparation of which requires the use of tris(acetonitrile)chromium tricarbonyl [28] or chromium hexacarbonyl [24] at higher temperatures, the complexes **21** – **23b** can be prepared under relatively mild conditions from the corresponding arene complexes. Apparently, the stronger π-back-bonding triphosphinine ligand displaces the weakly η^6-bound arene ligands from the coordination sphere of the metal [24].



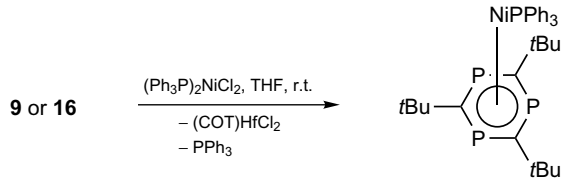
21 81%



22 16%



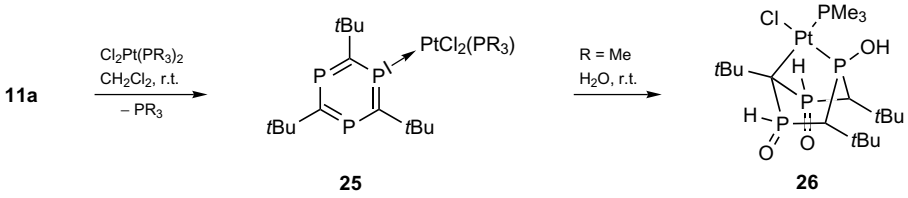
23a M = W 85%
b M = Mo 97%
c M = Cr 65%



24

Scheme 5. η^6-1,3,5-Triphosphinine complexes

The hafnium complexes **9** and **16**, respectively, with their preformed 1,3,5-triphosphinine ligands, are suitable substrates for the preparation of the nickel complex **24** [29]. In addition to the complexes with η^6-coordination, a platinum complex with η^1-coordination is known. Complex **25**, characterized spectroscopically in solution, undergoes hydrolysis with oxidation of the phosphorus atoms of the triphosphinine to afford the η^2-platinum complex **26** possessing a hexahydrotriphosphinine ligand in the boat form as demonstrated by an X-ray crystallographic analysis [30].

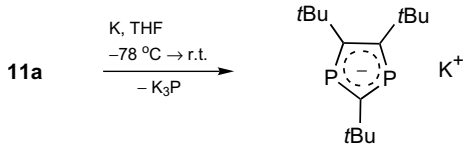


25 26

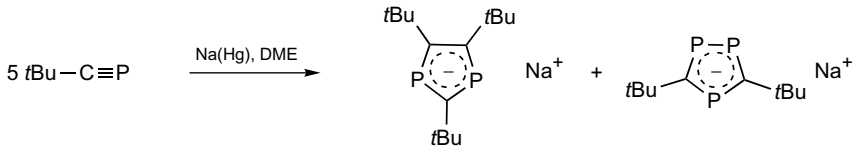
Scheme 6. 2,4,6-Tri-*tert*-butyl-1,3,5-triphosphinine complexes of platinum

4.2
Reactivity towards Alkali Metals

2,4,6-Tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) undergoes an unexpected ring contraction reaction on contact with a potassium mirror [31]. Although the mechanism of this reaction is not known, it apparently profits from the aromaticity of the diphosphacyclopentadienide anion and renders this ligand of interest for metallocenes. The diphospholyl anion **27** (as sodium salt) is obtained together with the 1,2,4-triphosphacyclopentadienide anion **28** in the reduction of *tert*-butylphosphaacetylene (**1a**) with sodium amalgam [32].



27



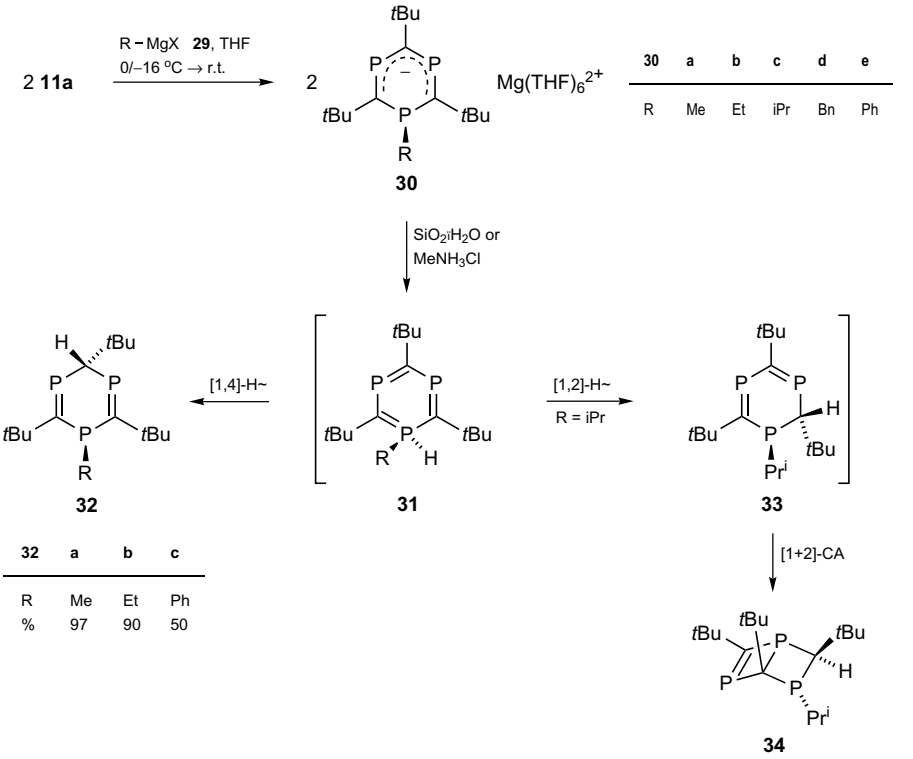
27 37% **28** 42%

Scheme 7. Synthesis of di- and triphospholide anions

4.3
Reactivity of 1,3,5-Triphosphines towards Nucleophilic Reagents

4.3.1
Alkyllithium and Grignard Reagents

2,4,6-Tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) is specifically substituted at one ring phosphorus atom. The thus obtained triphosphacyclohexadienide anions **30** are extremely sensitive to hydrolysis; however, **30a, c,** and **d** can be identified by NMR spectroscopy while **30d** was unambiguously characterized by an X-ray crystal structure analysis [33].



Scheme 8. Reaction of 2,4,6-tri-*tert*-butylphosphinine (**11a**) with Grignard reagents

The $^{31}P\{^1H\}$-NMR spectrum of **30d** contains two signal groups at $\delta = 194$ as a doublet and at $\delta = -60$ as a triplet with a $^2J_{P,P}$ coupling constant of 8.5 Hz, demonstrating the presence of two P/C double bond units and a $\lambda^3\sigma^3$-phosphorus atom. The ring carbon atoms give signals at $\delta = 152$ (C-4) and 137 (C-2, C-6) in the $^{13}C\{^1H\}$-NMR spectrum, thus confirming – with the results of the crystal structure analysis – the absence of covalent interactions between the magnesium cation and the triphosphacyclohexadienide anion (see Fig. 2).

When the salts **30** are not isolated but rather directly hydrolyzed under mild conditions the 1,4-dihydrophosphinines **32** – or in the case of the sterically demanding isopropyl group the dihydro-Dewar-triphosphinine **34** – are obtained [33]. 1,4-Dihydrotriphosphinines of the type **32** are also obtained together with other products on hydrolysis of the hafnium complex **10** [34]. Crystal structure analyses of **32a** and **34** confirmed the structures and revealed the steric arrangement of the substituents shown in Scheme 8. We assume that the hydrolysis proceeds through the common intermediate **31**, formed by protonation of the $\lambda^3\sigma^3$-phosphorus atom; the existence of the latter as the only plausible intermediate has been confirmed by ab initio calculations [35].

When organolithium compounds are employed instead of Grignard reagents, a similar reaction behavior should be observed. Indeed, organolithium compounds do react with 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) at low tem-

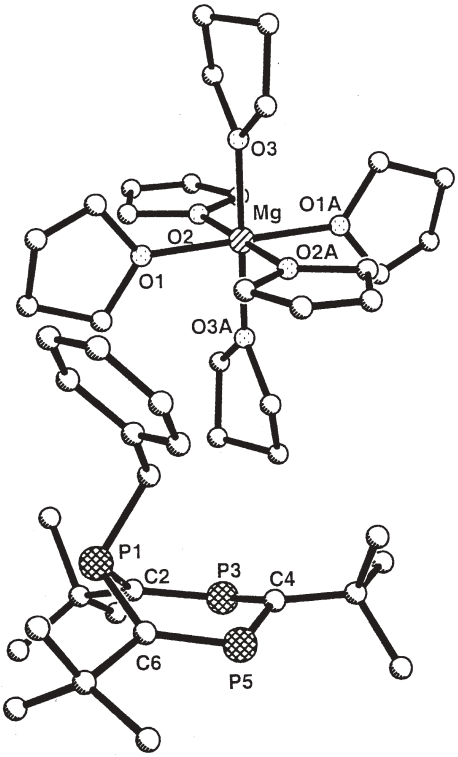
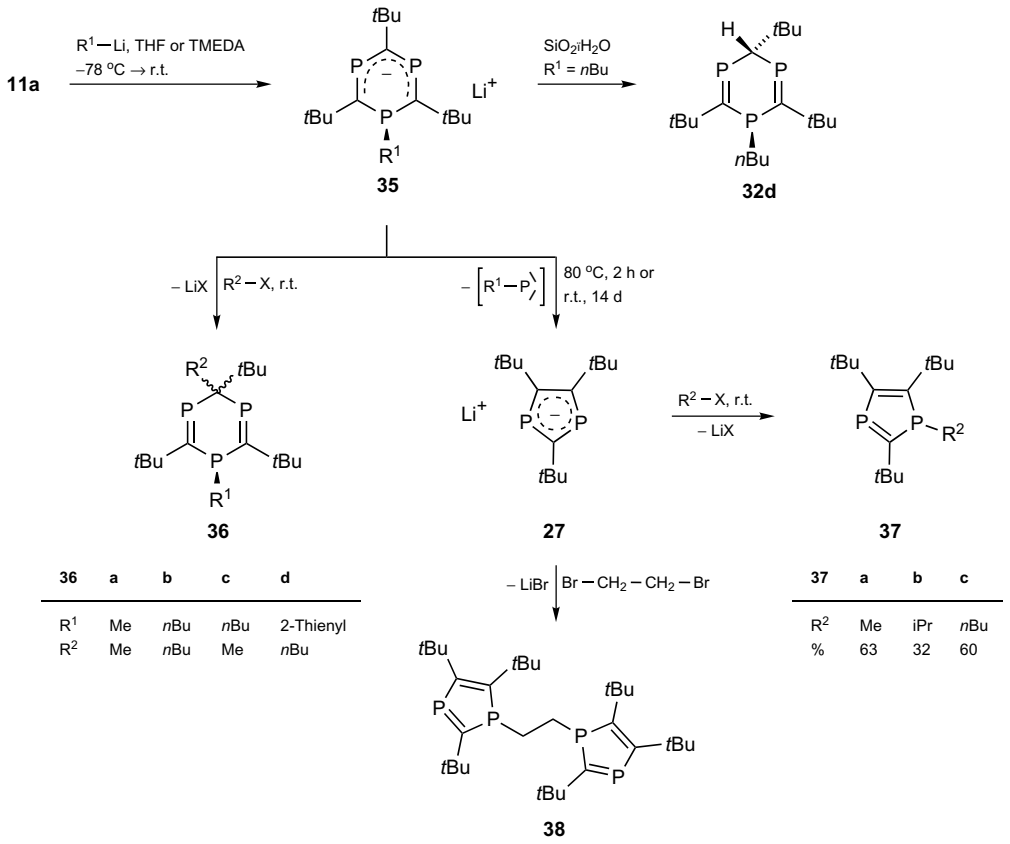


Fig. 2. Molecular structure of magnesium triphosphacyclohexadienide (H atoms are omitted for clarity)

peratures to give the lithium triphosphacyclohexadienides **35** that, on the one hand, undergo hydrolysis as demonstrated for the example of the *n*-butyl derivative which affords the 1-butyl-2,4,6-tri-*tert*-butyl-1,4-dihydro-1,3,5-triphosphinine (**32d**) and, on the other hand, react with alkyl halides to afford the 4,4-dialkyl-1,4-dihydro-1,3,5-triphosphinines **36** [36].

When the salts **35** are allowed to stand in solution at room temperature for several days or are briefly heated to 80 °C a surprising fragmentation takes place: cleavage of a phosphinidene, the fate of which remains unknown, occurs to afford the 1,3-diphosphophosphacyclopentadienide anion **27**, previously described by Nixon, as the lithium salt that can be alkylated to furnish the 1,3-diphospholes **37** in moderate to good yields. Alkylation by 1,2-dihaloalkanes is also possible, as shown by the formation of **38** in the reaction of **27** with 1,2-dibromoethane. Worthy of particular note is the reaction of **11a** with 2-pyridyllithium, leading directly to **27** even at low temperature; the anion **35** (R^1 = 2-pyridyl) cannot be detected in this process [36].



36	a	b	c	d
R^1	Me	*n*Bu	*n*Bu	2-Thienyl
R^2	Me	*n*Bu	Me	*n*Bu

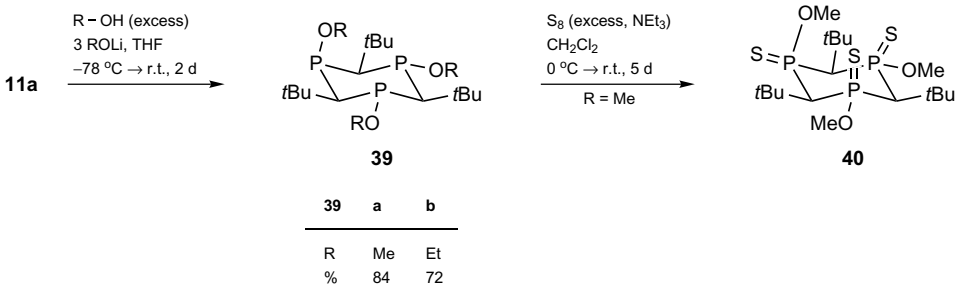
37	a	b	c
R^2	Me	iPr	*n*Bu
%	63	32	60

Scheme 9. Reaction of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine with organolithium reagents

4.3.2
Lithium Alkoxides

When 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) was allowed to react with three equivalents of a lithium alkoxide and an excess of the respective alcohol, a highly regio- and stereospecific, three-fold addition of the alcohol to all three P/C double bonds was observed [37].

The products are the 1,3,5-trialkoxy-2,4,6-tri-*tert*-butyl-1,3,5-triphosphinanes **39a, b**. In an X-ray crystallographic analysis of **39a** the highly distorted chair conformation of the ring skeleton with the *tert*-butyl substituents in equatorial positions is clearly apparent. Two methoxy substituents at P-1 and P-5 occupy approximately equatorial positions while that at P-3 is in an axial position. To examine the reactivity of the new triphosphinanes **39**, we have investigated the reactions of **39a** with sulfur. The reaction proceeds with a coordination increase at all phosphorus atoms to furnish the 1,3,5-triphosphinane trisulfide **40** (74 %) [37].



Scheme 10. Addition of lithium alkoxides to 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**)

4.4
Reactivity of 1,3,5-Triphosphinines in Cycloaddition Reactions

4.4.1
[4 + 1]-Cycloadditions

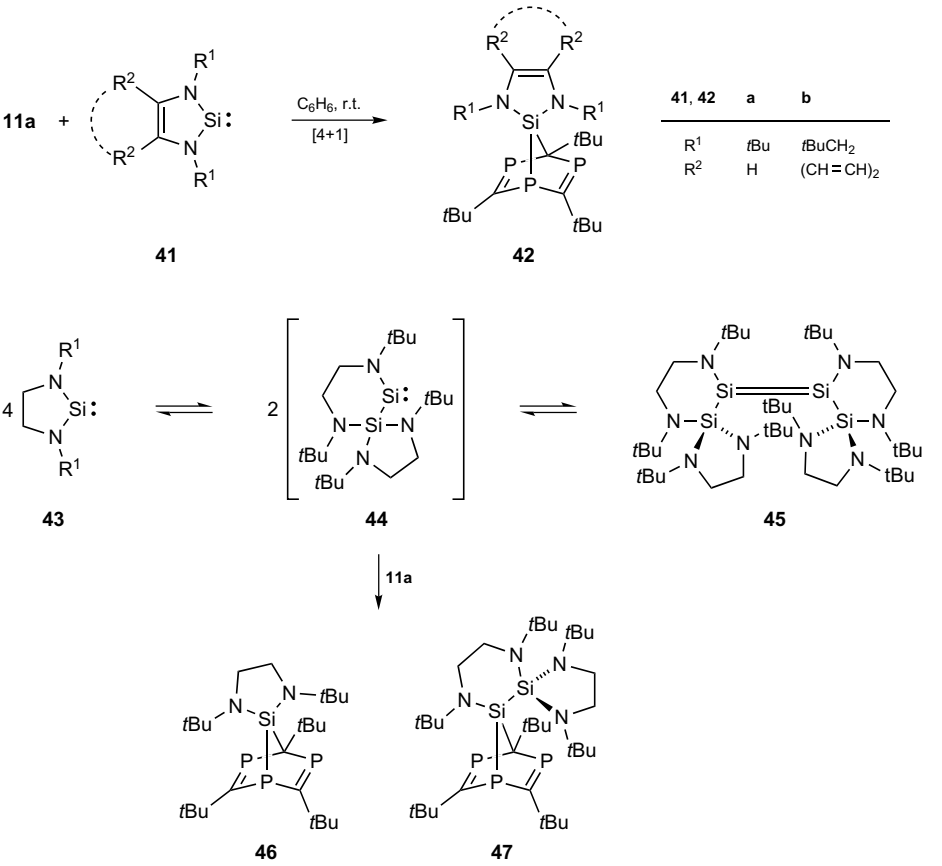
2,4,6-Tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) is a suitable partner for reactions with carbenes and carbene analogues such as silylenes and phosphinidenes. In the majority of the investigated examples [4 + 1]-cycloaddition across the 1,4-position of the 1,3,5-triphosphinine was the predominant reaction process.

4.4.1.1
Reactions with Silylenes and Carbenes

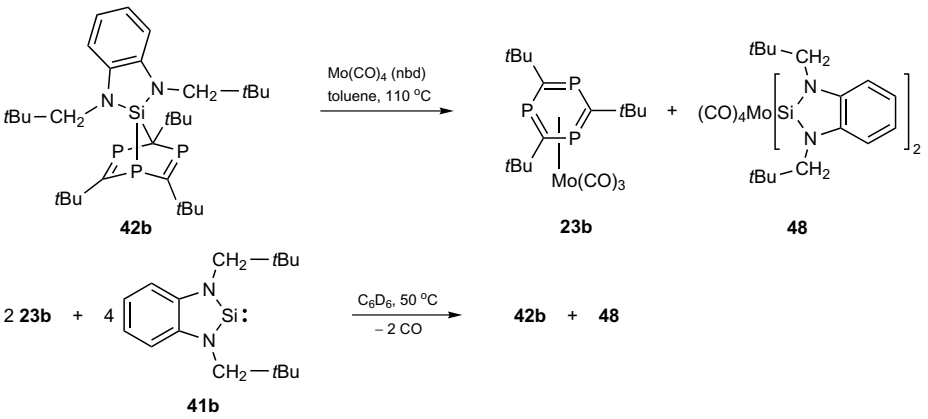
The stable 2,3-dihydro-1,3,2-diazasilylene **41a** [38] or the benzo derivative **41b** [39] reacted smoothly with **11a** in the sense of a [4 + 1]-cycloaddition to afford the compounds **42a** (80 %) and **b** (66 %) respectively, that possess as spiro-linked triphosphasilanorbornadiene skeleton [40, 41].

In comparison to the unsaturated species **41**, the saturated 1,3,2-diazasilylene **43** is less stable [42, 43]. It reacts with itself via insertion into the N/Si bond to afford the dimer **44** that, in its turn, is in equilibrium with the disilene tetramer **45**. The tetramer is a suitable starting material to trap not only **43** but also **44** with 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) in the form of the [4 + 1]-cycloadducts **46** (19 %) and **47** (17 %). It is of interest to note that the [4 + 1]-cycloadditions of 1,3,5-triphosphinines with silylenes are reversible, as shown in Scheme 12.

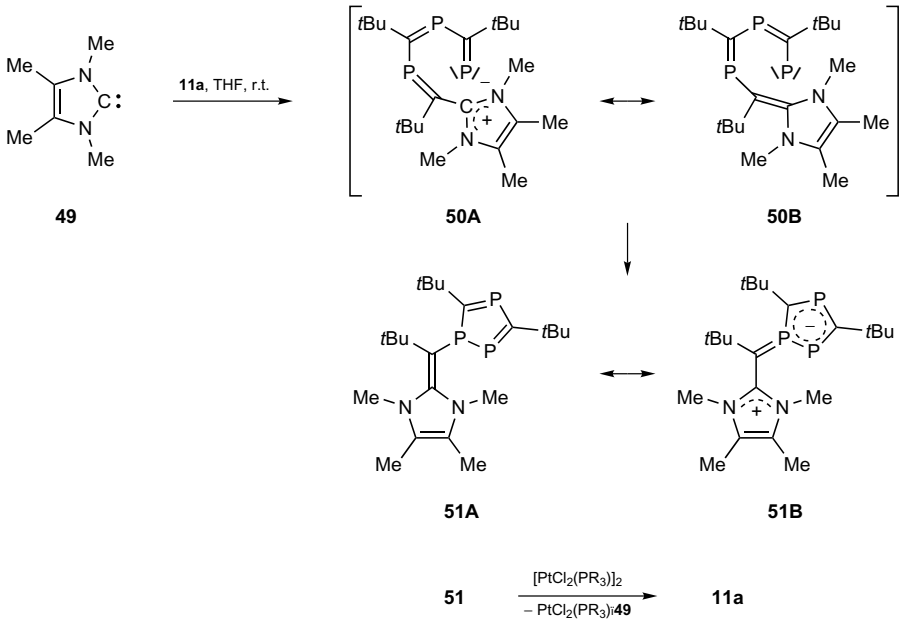
When the cycloadduct **42b** is heated in toluene with a molybdenum tetracarbonyl complex, the already known η^6-triphosphinine complex **23b** [25, 44] is formed together with the disilylenemolybdenum complex **48** that exists as a *cis*/*trans*-mixture. On the other hand, in the presence of an excess of silylene **41b** compound **23b** is transformed into the [4 + 1]-cycloadduct **42b** with compound **48** again being formed as a second product [44]. Attempts to realize [4 + 1]-cycloadditions of 1,3,5-triphosphinines with heavier homologues of the silylenes (Ge, Sn, Pb) have not yet been successful [44]. In addition, carbenes like



Scheme 11. [4 + 1]-Cycloaddition reactions of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) with silylenes



Scheme 12. Reversibility of the [4 + 1]-cycloaddition reaction of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) with silylenes



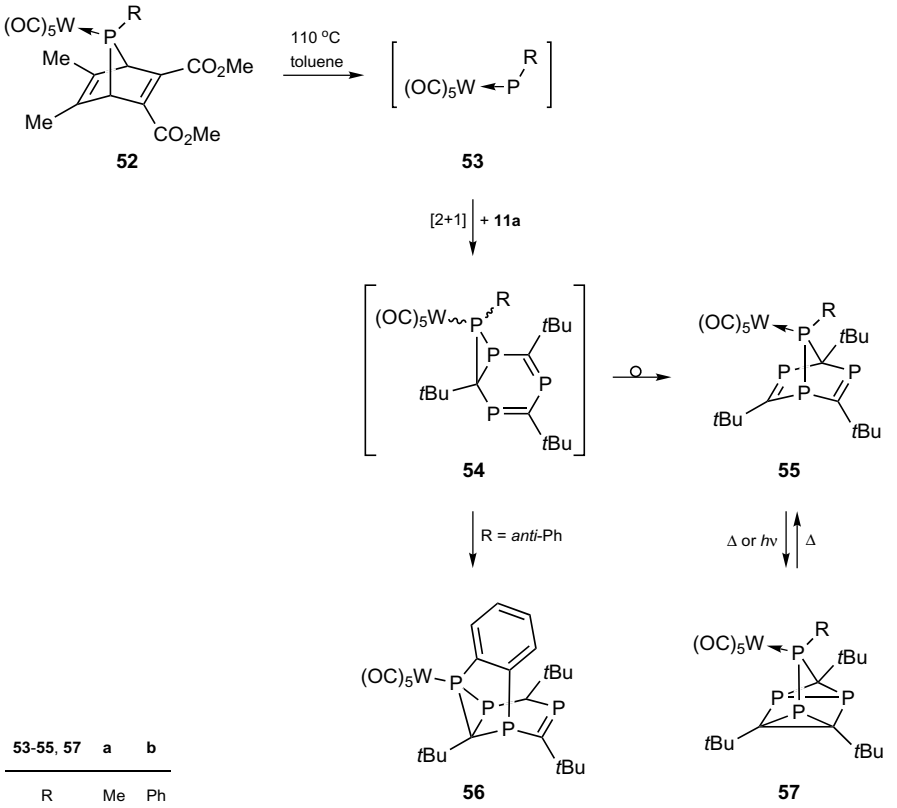
Scheme 13. Reaction of **11a** with a stable „Arduengo"-type carbene

the stable imidazol-2-ylidene [45] do not undergo [4 + 1]-cycloadditions with **11a** but rather initiate an unexpected ring contraction process to furnish a 1,2,4-triphosphole derivative [46].

1,3,4,5-Tetramethylimidazol-2-ylidene (**49**) reacts with 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) to afford the (1,2,4-triphosphol-1-ylmethylene)-imidazole derivative **51**, where one carbon atom of the initial six-membered ring is now present in the exocyclic double bond. The intermediates **50A/B** appear to be reasonable because the reaction is reversible. When **51** is treated with a (bisphosphane)platinum dichloride complex, the latter binds to the carbene increment in **51** and, after a ring expansion step, **11a** is liberated [46]. In this context it should be mentioned that an imidazole derivative analogous to **51** is also formed in the reaction of *tert*-butylphosphaacetylene (**1a**) with a similar nucleophilic carbene such as **49** [47]. X-ray structural analysis of this compound revealed an exactly planar triphosphacyclopentadiene system with a substituent susceptible to mesomerism on the $\lambda^3\sigma^3$-phosphorus atom – and this possibly explains the stability of **51** (formula **51B**) in comparison with the expected [4 + 1]-cycloadduct.

4.4.1.2 Reactions with Phosphinidene Complexes

In contrast to the aminosilylenes and -carbenes in which the nucleophilic character dominates, phosphinidine complexes exhibit a pronounced electrophilic reactivity [48, 49].



Scheme 14. Reactions of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) with phosphinidene complexes

When the phosphinidene complex **53** is generated by thermolysis of the 7-phosphanorbornadiene complex **52** in toluene, tetraphosphanorbornadienes **55**, tetraphosphaquadricyclanes **57**, or the polycylic compound **56** in the form of η^1-tungsten complexes can be isolated in dependence on the substituents on the phosphinidine phosphorus atoms [50, 51]. With a phenyl substituent, compounds **56** (25%) and **57b** (39%) are obtained after a fractional distillation. In contrast, the methylphosphinidene complex **53a** under comparable reaction conditions affords the tetraphosphanorbornadiene **55a** and the tetraphosphaquadricyclane **57a** in a 1:8 molar ratio. The proposed reaction mechanism, supported by ab initio calculations, involves a [2+1]-cycloaddition – it is not yet clear whether this is ionic or pericyclic – between **53** and 1,3,5-triphosphinine at one of the P/C double bonds and, from the thermodynamic point of view, the tetraphosphaquadricyclane **57** represents the compound with the lowest energy. In the case of an *anti*-orientation of the phenyl group at the complexed phosphorus atom, the intermediate **54** undergoes isomerization to **56**; however, it must be emphasized that this reaction is not yet completely understood. In other cases **54** undergoes rearrangement to the tetraphosphanorbornadiene **55**; even so, it can-

not be excluded that **55** is formed by a direct [4 + 1]-cycloaddition between **11a** and the phosphinidene complex. Compound **55b** cannot be detected in the reaction of the phenyl derivative. In this case the [2 + 2]-cycloadditions of the two phosphaalkene units dominate, as is not uncommon for this functional group, and presumably proceed through ionic or radical intermediates [52]. In the case of the methyl derivative **55a** and **57a** exist in a thermal equilibrium. However, complete conversion of **55a** into **57a** can be forced by a photochemical $[\pi^2_s + \pi^2_s]$-cycloaddition that is allowed according to the Woodward-Hoffmann rules.

It should be emphasized that the difference between silylenes and carbenes on the one hand and the phosphinidene complexes on the other hand is due to the nucleophilic or electrophilic, respectively, natures of these species. The former attack the carbon atom of a P/C double bond in the 1,3,5-triphosphinine, whereas the latter should preferentially attack the phosphorus atom.

4.4.2
[3 + 2]-Cycloadditions

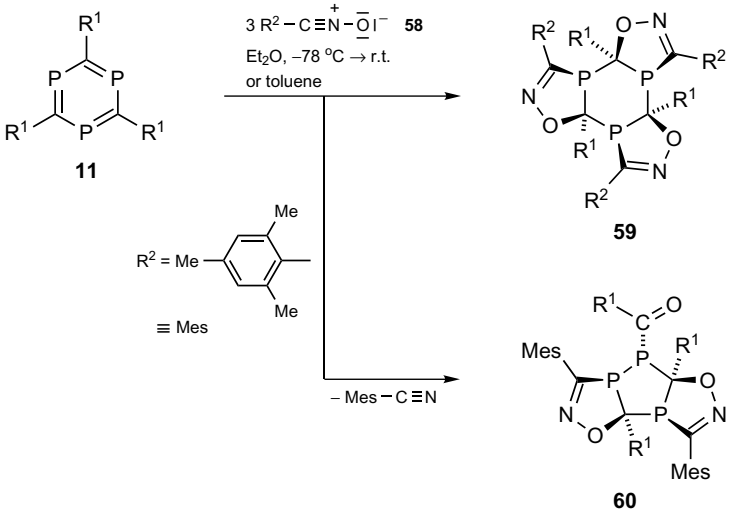
On account of their relatively weakly pronounced aromaticity 1,3,5-triphosphinines should, in principle, be able to act as dipolarophiles in [3 + 2]-cycloaddition reactions. In order to test this assumption, triphosphabenzenes were allowed to react with nitrile oxides and tosyl azides as examples. The latter could also react with the λ^3-phosphorus atom in the hererocyclic ring in the sense of a Staudinger reaction [53].

4.4.2.1
Reactions with Nitrile Oxides

Depending on the substituents R^1 and R^2, reactions of the 1,3,5-triphosphinines **11** with the nitrile oxide **58** in ether or toluene lead either to the trisadducts **59** or proceed with ring contraction from a six- to a five-membered ring to afford the bisadducts **60** with a P-acyl substituent [54].

Benzonitrile oxide **58a** reacts smoothly with **11** to give the trisadduct **59**. When the steric overcrowding in the nitrile oxide is increased by substituting the phenyl group for a mesityl group (**58b**), the formation of trisadducts at all three P/C bonds of the 1,3,5-triphosphinine is no longer possible. The reaction path branches, presumably at the stage of the monocycloadduct, because attack of the second nitrile oxide can occur from the exo- or the endo-side of the monoadduct. When the endo-side is accessible the reaction sequence ends at the tetracyclic species **59**; when this side is shielded exo attack leads to ring contraction, cleavage of mesityl nitrile, and, finally, to formation of product **60**. With methylcyclopentyl and mesityl substituents both reaction paths are equally possible so that an approximately 1 : 1 mixture of **59e/60e** is obtained.

An X-ray crystallographic analysis of **59a** revealed a C_3-symmetrical structure with the central 1,3,5-triphosphinane ring in the chair conformation and the three sterically demanding *tert*-butyl substituents in equatorial positions. The tetracyclic system itself forms a cavity that is open to one side. The crystal structure analysis of **60c** (Fig. 3) unequivocally confirmed the structure of this



58	a	b
R^2	Ph	Mes

59, 60	a	b	c	d	e
R^1	*t*Bu	Mec*P*en	*t*Bu	*t*Pen	Mec*P*en
R^2	Ph	Ph	Mes	Mes	Mes
% **59**	77	72	<1	<1	39
% **60**	–	–	77	65	32

Scheme 15. Reactions of 1,3,5-triphosphinines with nitrile oxides

condensed heterocyclic system; it should be mentioned that the central 1,2,4-triphospholane ring possesses a distorted envelope conformation and that the condensed five-membered rings and the *tert*-butyl substituents have the arrangement shown in the figure [54].

The tetra- or tricyclic systems **59** and **60**, respectively, are themselves suitable starting materials for the preparation of heterophospholes – compounds of increasing interest in the chemistry of low-coordinate phosphorus [55]. As an example, it has been demonstrated with **59a** [54] that heating at 100 °C in toluene results in complete fragmentation to afford the previously known 1,2,4-oxazaphosphole **61a** [56 – 58].

When the tricyclic compounds **60** are subjected to a comparable thermolysis, an initial [3 + 2]-cycloreversion with liberation of mesitylnitrile oxide (**58b**) and formation of the bicyclic species **62** occurs with subsequent decomposition into the oxazaphospholes **61** and the oxadiphospholes **63** as indicated in the scheme. Because oxadiphospholes have as yet only been poorly investigated [59, 60] this synthetic route has potential for exploitation as a specific access to this novel class of heterodiphospholes. Since control experiments have shown that the oxadiphospholes **63** react with mesitylnitrile oxide (**58b**) which prevents their isolation, it seems reasonable to remove the inevitably formed 1,3-dipole by means of a trapping reagent. It is well known that phosphaalkenes of the *Becker* type react with nitrile oxides via cleavage of hexamethyldisiloxane to afford

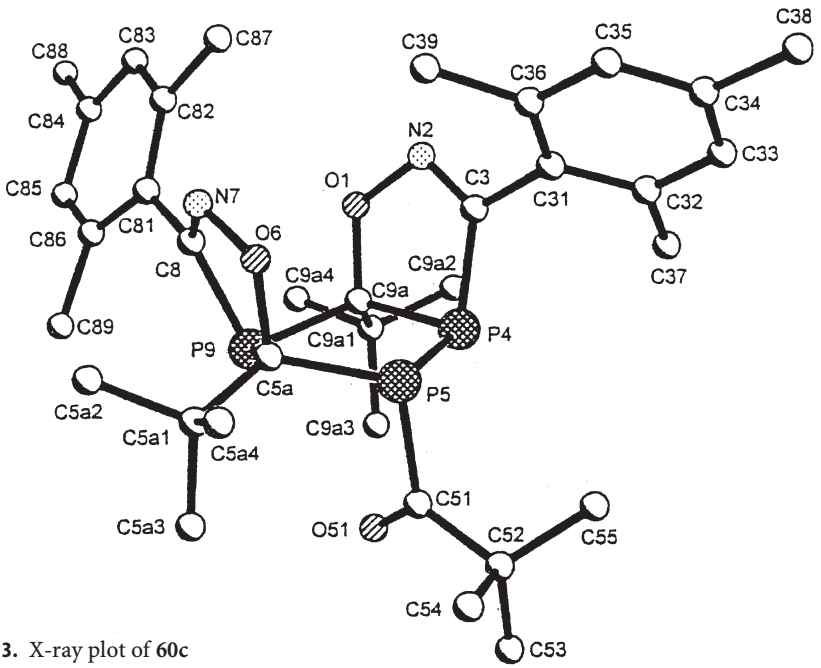
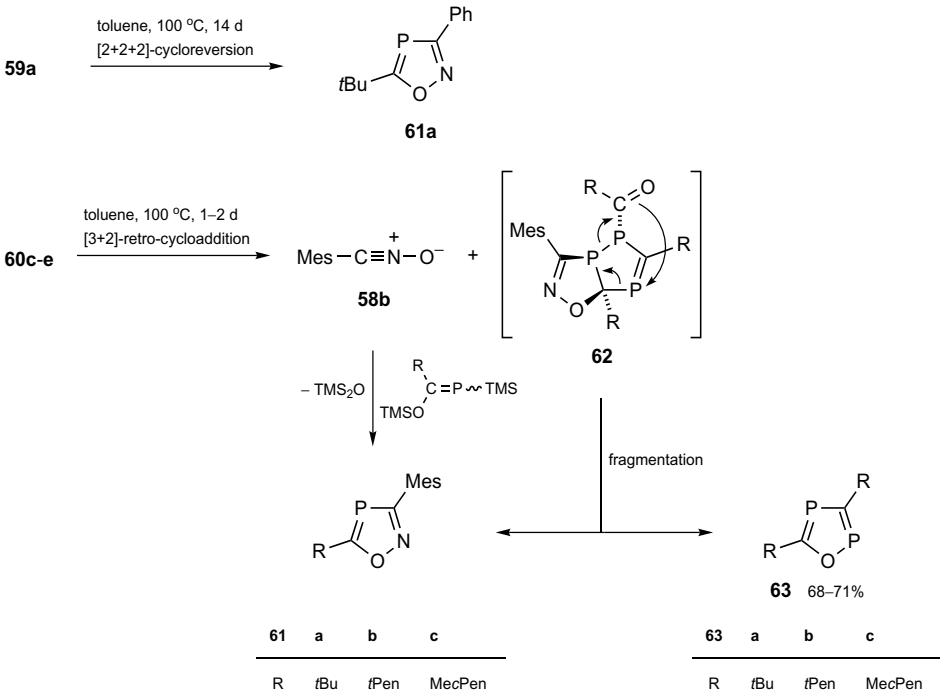
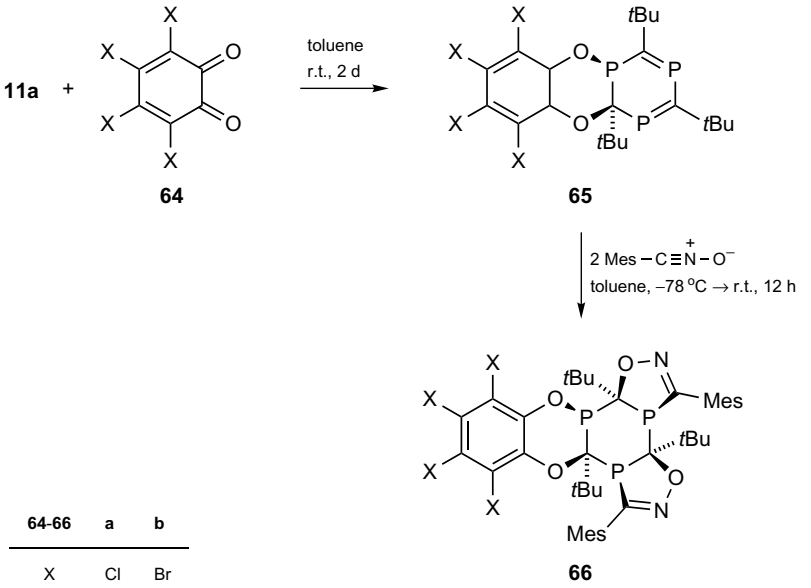


Fig. 3. X-ray plot of **60c**



Scheme 16. Cycloreversion reactions of the tetracyclic (**59**) and tricyclic (**60**) systems

oxazaphospholes of the type **61** [61 – 63]. Thus, when the thermolysis of compounds **60** is performed in the presence of the phosphaalkene corresponding to the compound **60** employed, one can indeed isolate the oxadiphospholes **63** in good yields. It is even possible to carry out the synthesis of **63** as a one-pot process starting with **11**, three equivalents of **58**, and one equivalent of the respective phosphaalkene. As shown for the example of **63a** it is possible to obtain this heterocyclic species in an overall yield of 60 – 65 % [54]. In order to gain further information about the formation of the tetra- and tricyclic systems **59** and **60**, respectively, one of the P/C bonds in **11** was blocked by a [4 + 2]-cycloaddition with the *ortho*-quinone derivative **64** [27, 54].

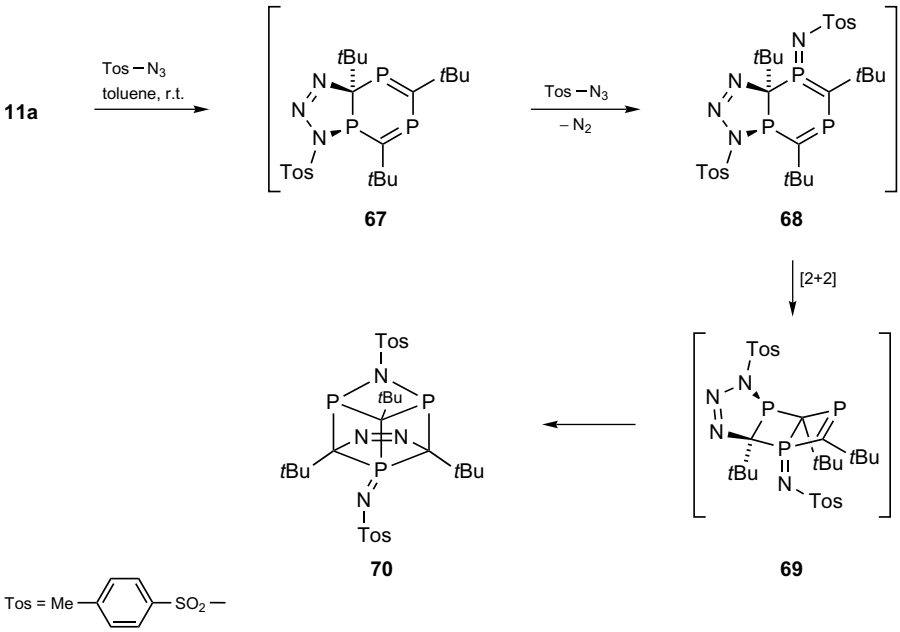


Scheme 17. [3 + 2]-Cycloaddition reactions of the 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine/*ortho*-quinone adducts (**65**) with mesitylnitrile oxide

In this reaction the 1,3,5-triphosphinine **11** acts as a dienophile and not, as in other cases, as a 1,3-diene. The reaction of **65** with two equivalents of mesitylnitrile oxide leads to the tetracyclic product **66** comparable to **59**. A ring contraction, analogous to that in the formation of **60**, was not observed, presumably because the steric demands of the condensed tetrahalocatechol increment are not large enough to force the necessary exo attack [54].

4.4.2.2
Reaction with Tosyl Azide

The reaction of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) with tosyl azide follows an unexpected course.



Scheme 18. Reaction of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) with tosyl azide

The reaction proceeds very slowly (5 weeks at room temperature) to furnish, instead of the expected cycloadduct, the tetracyclic product **70** (78 %), the structure of which was elucidated by X-ray crystallography (Fig. 4) [54].

The C_s-symmetrical structure with a bridging azo unit does not exhibit any remarkable features with regard to bond lengths and angles. The two 1,3-diphosphetane units are planar and folded at 89° to each other.

Although no intermediate products can be detected by spectroscopy during the course of the reaction, the proposed reaction mechanism – that is also supported by ab initio calculations – seems reasonable. It involves at first the expected [3 + 2]-cycloaddition of the azide dipole to one P/C bond of the 1,3,5-triphosphinine. In the intermediate **67** one *tert*-butyl group is twisted out of the ring plane so that the neighboring phosphorus atom is accessible for a Staudinger reaction [53]. Compound **68** contains an iminomethylenephosphorane increment [64] that reacts further as a highly reactive, low-coordinated phosphorus compound by an intramolecular [2 + 2]-cycloaddition to afford **69** that now contains the triphospha-Dewar-phosphinine part of **70.** The driving force for the subsequent rearrangement is probably the loss of the energetically unfavorable P/C double bond.

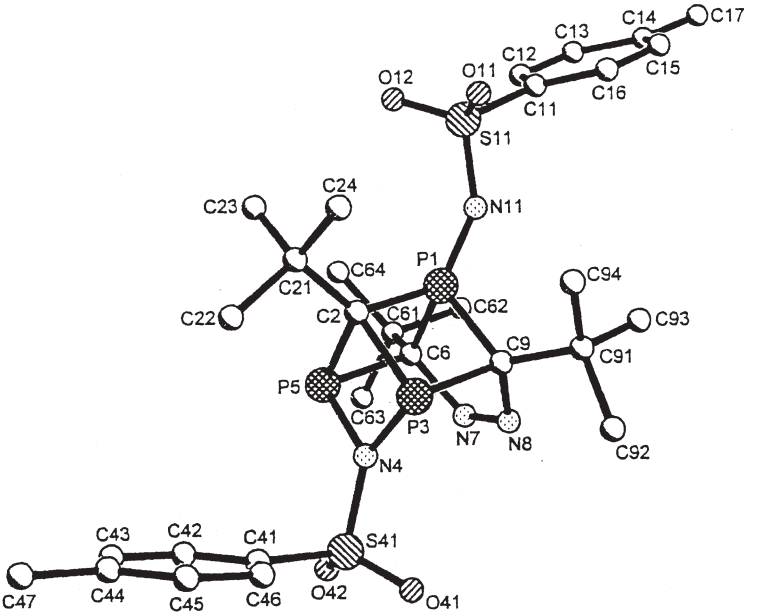


Fig. 4. X-ray structure of **70**

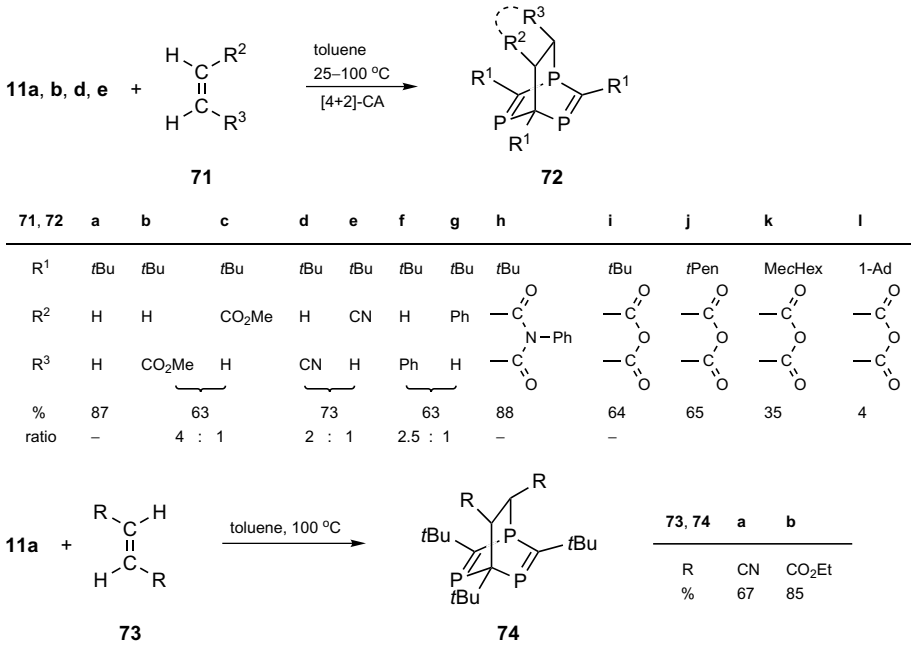
4.4.3 *[4 + 2]-Cycloadditions*

A characteristic feature of arenes is their very low or absent tendency to participate in cycloaddition reactions. Thus, for example, benzene and its methyl derivatives only undergo [4 + 2]-cycloaddition reactions with hexafluorobut-2-yne at above 200 °C to furnish the corresponding barrelenes [65, 66]. Phosphinines, similarly, only react with highly reactive alkynes such as hexafluorobut-2-yne, dicyanoacetylene, or dehydrobenzene at above 100 °C in Diels-Alder reactions to give the corresponding 1-phosphabarrelenes [67, 68]. Hence, it was surprising to find that the 1,3,5-triphosphinines **11** readily entered into [4 + 2]-cycloaddition reactions with a wide range of alkenes and alkynes under very mild conditions.

4.4.3.1 Reactions with Alkenes

When ethylene (**71a**) is bubbled into a toluene solution of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**), a [4 + 2]-cycloaddition reaction occurs to afford the 7,8-dihydro-1,3,5-triphosphabarrelene **72a** [69].

Acceptor-substituted alkenes such as methyl acrylate (**71b** ≡ **71c**) and acrylonitrile (**71d** ≡ **71e**) also react readily at room temperature with **11a** to give the corresponding dihydrobarrelenes **72a – e**, whereas the reaction with styrene (**71f** ≡ **71g**) to furnish **72f, g** requires a large excess of the alkene and higher reac-

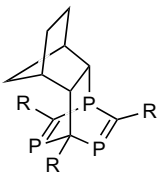


Scheme 19. [4 + 2]-Cycloaddition reactions of 1,3,5-triphosphinines with alkenes

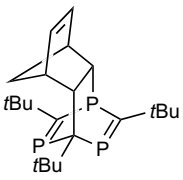
tion temperatures [69]. The possible regioisomers **72b, d, f** and **72c, e, g** that may arise from the reaction with terminal alkenes are found, with formation of the regioisomers **72b, d, f** apparently being favored for electronic reasons. Cyclic disubstituted alkenes such as *N*-phenylmaleimide (**71h**) and maleic anhydride (**71** ≡ **71j** ≡ **71k** ≡ **71l**) also readily undergo [4 + 2]-cycloaddition reactions with **11** to afford the dihydrobarrelenes **72h – k** in good yields. The 1-adamantyl derivative **72l** is an exception [69]. In contrast, open-chain, disubstituted alkenes such as fumaric dinitrile (**73a**) and diethyl fumarate (**73b**) require longer times at 100 °C to form the cycloadducts **74a, b** with 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**). In the reaction of **11a** with diethyl maleate after a total of 18 days, the bicyclic *trans*-compound is the sole product and can be isolated in 81 % yield. Accordingly, it can be assumed that the initially formed *cis*-cycloadduct undergoes complete isomerization to the *trans*-cycloadduct on account of the reversibly of Diels-Alder reactions [69].

Further examples for successfully performed [4 + 2]-cycloaddition reactions of 2,4,6-trialkyl-1,3,5-triphosphinines (**11**) with cyclic and bicyclic alkenes and dienes are depicted in Scheme 20.

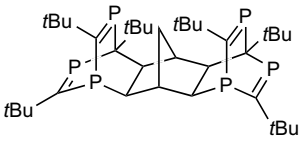
[4 + 2]-Cycloadducts with norbornene (≡ **75a – d**), norbornadiene (≡ **76, 77**), and cyclopentadiene (≡ **79**) were obtained under mild reaction conditions. The reaction of cyclopropene with **11a** is an exception: it reacts even at – 78 °C, but two equivalents of the alkene are required because the initially formed Diels-Alder cycloadduct reacts spontaneously with further cyclopropene in a homo-Diels-Alder reaction to form the cage compound **78** [69].



75

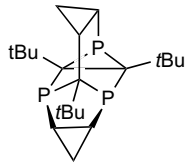


76 23%

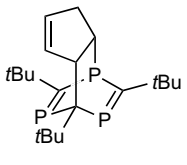


77 (+ isomer)

75	**a**	**b**	**c**	**d**
R	*t*Bu	*t*Pen	Mec*H*ex	1-Ad
%	73	40	64	4



78 83%

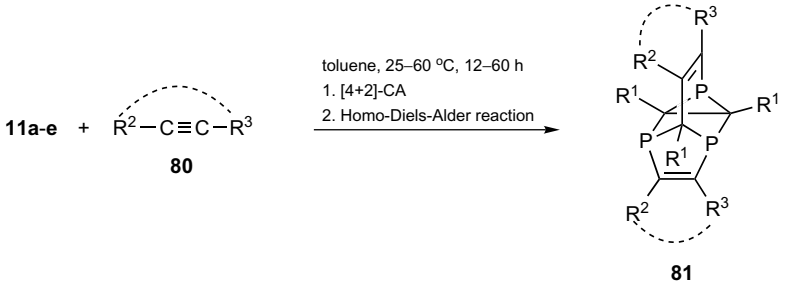


79 47%

Scheme 20. [4 + 2]-Cycloaddition reactions of 1,3,5-triphosphinines **11** with cyclic and bicyclic alkenes and dienes

4.4.3.2 Reaction with Alkynes

A sequence of Diels-Alder and homo-Diels-Alder reaction occurs to furnish the cage compounds **81a – i** when a solution of **11a –e** in toluene is subjected to reaction with alkynes. Suitable alkynes are acetylene itself, phenylacetylene, methyl propynoate, and cyclooctyne [70].

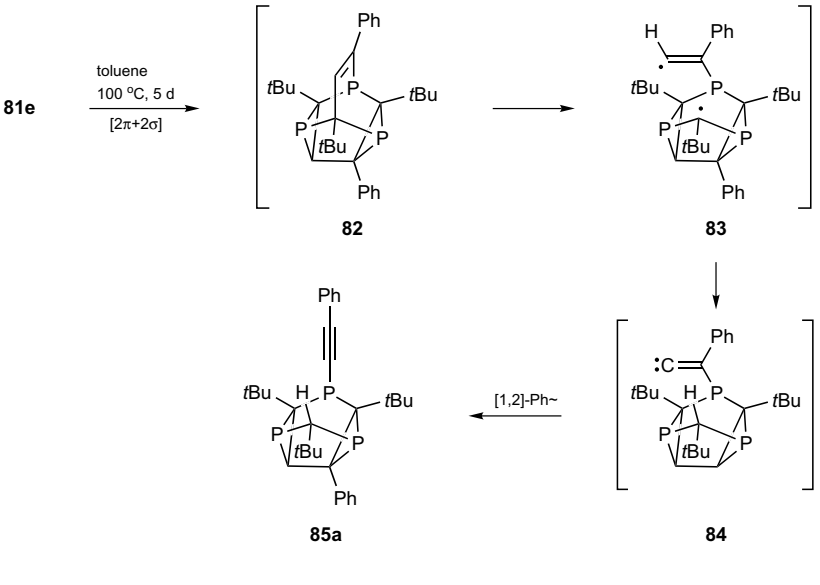


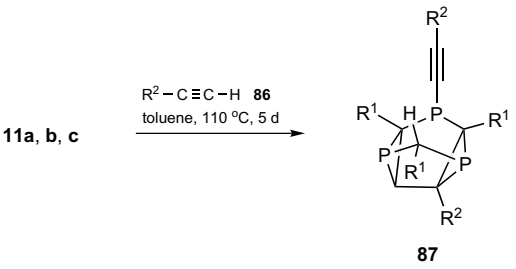
81

80, 81	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
R^1	*t*Bu	*t*Pen	Mec*P*en	Mec*H*ex	*t*Bu	*t*Bu	*t*Pen	Mec*H*ex	*t*Bu
R^2	H	H	H	H	H	H	H	H	$(CH_2)_6$
R^3	H	H	H	H	Ph	CO_2Me	CO_2Me	CO_2Me	
%	70	50	69	53	67	71	60	21	71

Scheme 21. [4 + 2]-Cycloaddition reactions of 1,3,5-triphosphinines with alkynes

It seems that the homo-Diels-Alder reactions proceed markedly more rapidly than the Diels-Alder reactions since the primary [4+2] adducts cannot be detected spectroscopically. Furthermore, it is noteworthy that all 1-alkynes react regiospecifically in the initial [4+2]-cycloaddition process. This addition proceeds in such a way that, independent of the polarity situation of the acetylene, the carbon atom bearing the substituent is positioned in the immediate vicinity of the phosphorus atom of the phosphirane increment. This suggests that steric factors are responsible for the direction of the addition. This is further supported by the observation that **11a** does not participate in cycloaddition reactions with any disubstituted triple bond system, except for cyclooctyne, which possesses the necessary reactivity for a cycloaddition on account for the cisoid-dis-





86, 87	a (= 85a)	b	c	d	e	f	g	h
R^1	*t*Bu	*t*Bu	*t*Bu	*t*Bu	*t*Bu	*t*Bu	*t*Pen	MecHex
R^2	Ph	Mes	p-C_6H_4–OMe	p-C_6H_4–CN	p-C_6H_4–NO_2	*n*Bu	Ph	Ph
%	72	19	68	62	41	23	62	61

Scheme 22. Rearrangement of the tetracyclic compound **81** to the new cage compounds **85** and **87,** respectively

torted substituents at the triple bond and the resultant ring stain. Accordingly, reactions do not occur even under drastic conditions either with electron-rich compounds such as but-2-yne or with electron-poor acetylenedicarboxylates, which are known to react with phosphinine-$W(CO)_5$ complexes [71].

When the cage compound **81e** is heated in toluene for 5 days an interesting skeletal rearrangement occurs [72]. Product of the process is the novel cage compound **85a** containing two phosphirane increments and an alkyne unit bound to a phosphorus atom.

It is in fact not necessary to isolate the cage compound **81** and then allow it to isomerize to **85**; instead heating the 1,3,5-triphosphinines **11a – c** in toluene at 110 °C for 5 days in the presence of phenylacetylene (**86a**) and substituted phenylacetylenes (**86b – e**) results in the direct formation of the tetracyclic compounds **87a – h.** Here again, the use of a terminal alkylacetylene (**86f**) is possible although the yield is poor. The structures of the cage compounds **87** were unequivocally elucidated on the basis of an X-ray crystallographic analysis of the derivative **87d,** the result is shown in Fig. 5.

The crystal structure shows an edge-open, slightly distorted triphosphacuneane skeleton with the alkyne substituent at phosphorus and the opposing *tert*-butyl group pointing away from one another. The bond lengths and angles are within the normal ranges except for the angle describing the position of the triple bond to the phosphorus atom. This has a value of 166.7(4)° and deviates markedly from the ideal value of 180°.

Our mechanistic proposal for the rearrangement of **81** to **85**, supported by deuteration experiments, involves an initial intramolecular [2π + 2σ]-cycload-

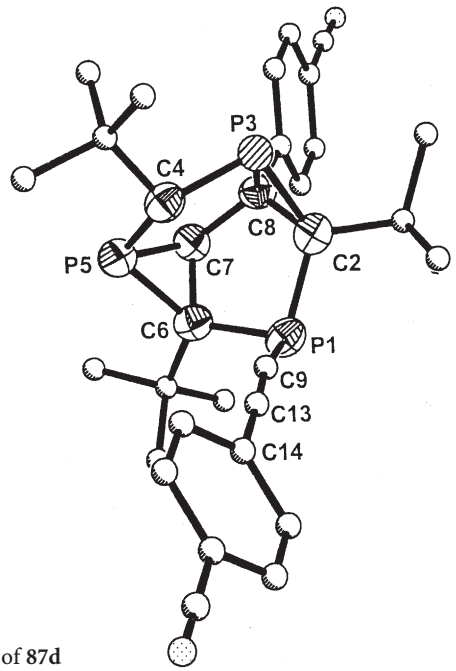
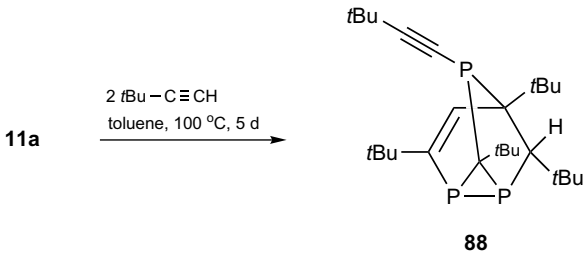


Fig. 5. X-ray structure of **87d**

dition of the three-membered ring with the opposing double bond to form the pentacyclic system **82.** In the all-carbon systems, a cycloaddition of this type has been well investigated for the tricyclo[3.2.1.$0^{2,4}$]oct-6-ene skeleton [73]. The ring strain introduced at the bridging C/C double bond by the cycloaddition leads to bond cleavage in which the diradical **83** transfers the alkenyl hydrogen – or deuterium when 2-deuteriophenylacetylene is used – to the alkyl radical. The intermediate **84** with the alkylidenecarbene increment is stabilized by migration of the phenyl group and formation of the C/C triple bond. Similar reactions of alkylidenecarbenes have been reported [74] and possibly explain why only terminal alkynes bearing substituents capable of easy migration are susceptible to this rearrangement.

The 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) reacts with the sterically highly substituted *tert*-butylacetylene; however, the course of this reaction differs markedly from the previously described conversions [70].



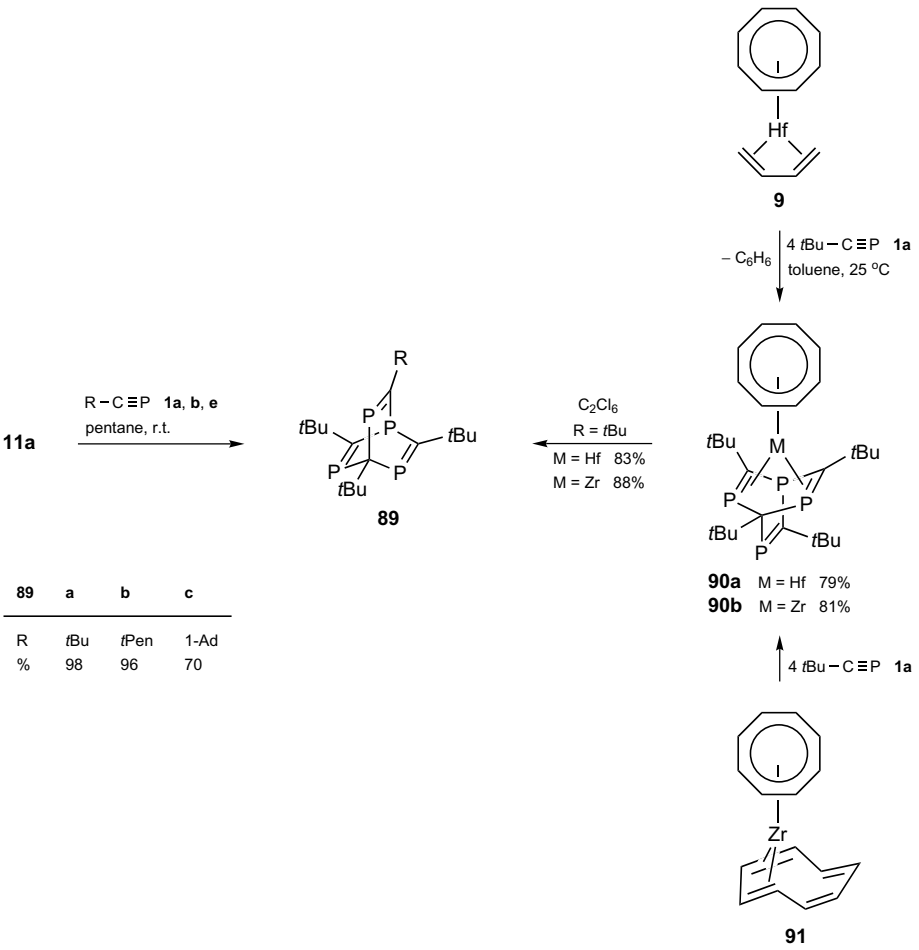
Scheme 23. Reaction of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) with *tert*-butylacetylene

The tricyclic compound **88** is obtained after 5 days. The structure of **88** was elucidated by a X-ray crystallographic analysis. This reveals the tricyclic framework with an endocyclic C/C double bond, an exocyclic C/C triple bond, and a diphosphirane ring as the central structural unit. One conspicuous feature is the lengthened P/P bond distance of 2.221(2) Å, which can be easily explained in terms of the incorporation of the diphosphirane unit in a polycyclic system. At the moment we cannot present a plausible mechanism for the formation of **88** since it has not been possible to detect any intermediates by spectroscopy.

4.4.3.3
Reactions with Phosphaalkynes

[4 + 2]-Cycloadditions of 1,3,5-triphosphinines with kinetically stabilized phosphaalkynes provide an access to the phosphaalkyne tetramer system. Diels-Alder reactions of **11a** with the phosphaalkynes **1a**, **b**, **e** proceed with high selectivity to furnish the tetraphosphabarrelenes (1,3,5,8-tetraphosphabicyclo[2.2.2]octa-2,5,7-trienes) **89** [27, 75].

The tetraphosphabarrelene **89a** is also accessible by an independent route starting from the phosphaalkyne tetramer complex **90** by expulsion of the metal fragment with hexachloroethane [14, 26, 76, 77]. Complex **90a**, in turn, is



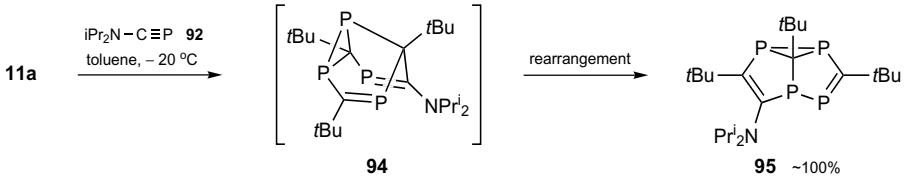
89	a	b	c
R	*t*Bu	*t*Pen	1-Ad
%	98	96	70

Scheme 24. [4 + 2]-Cycloaddition reactions of 1,3,5-triphosphinines with phosphaalkynes

obtained from the reaction of (buta-1,3-diene)(cyclooctatetraene)hafnium with 4 equivalents of *tert*-butylphosphaacetylene (**1a**) via the cyclooctatetraene-phosphaalkyne trimer-hafnium complex **10** (see Scheme 2) [14] or that of bis(cyclooctatetraene)zirconium (**91**), again with 4 equivalents of phosphaalkyne **1a** [76].

The [4 + 2]-cycloaddition of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) with the diisopropylamino-substituted phosphaalkyne **92** follows a completely different pathway. Instead of a tetraphosphabarrelene the tetraphosphasemibullvalene (1,2a,2b,4a-tetraphosphacyclopropa[*cd*]pentalene) **95** is obtained by an as yet unknown mechanism [75].

The tetraphosphasemibullvalene **94** – an isomer of **95** – is considered to be the primary intermediate of the reaction. Ab initio calculations of all possible $(HCP)_4$ isomers reveal that the semibullvalene **95** is of lower energy than a pos-



Scheme 25. [4 + 2]-Cycloaddition of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphinine (**11a**) with the phosphaalkyne **92**

sible tetraphosphacuneane that could be formed from **94** by a [2 + 2]-cycloaddition [11, 78].

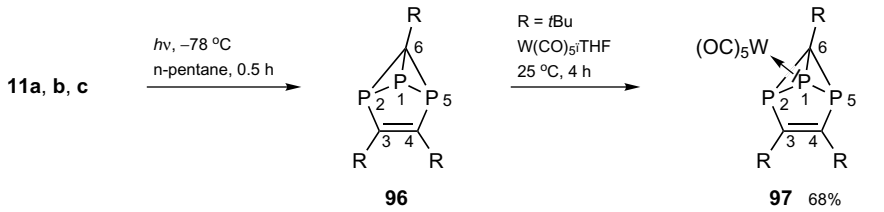
5
Valence Isomers of 1,3,5-Triphosphinines

Of the possible valence isomers of 1,3,5-triphosphinines the Dewar-triphosphinines and the triphosphabenzvalenes are known. The former are obtained by expulsion of the metal fragment in the transition metal-mediated cyclotrimerization of phosphaalkynes (see Scheme 4) and the latter by photolysis of 1,3,5-triphosphinines.

5.1
Synthesis of the Triphosphabenzvalenes

When solutions of the 1,3,5-triphosphinines **11a – c** in pentane at – 78 °C are irradiated a highly selective rearrangement to the 1,2,5-triphosphabenzvalenes (1,2,5-triphosphatricyclo[3.1.0.0^{2,6}]hex-3-enes) **96a – c** occurs [26, 54]. The photolysis must be carried out at low temperature since, otherwise, thermally induced subsequent reactions of the triphosphabenzvalenes will take place.

As mechanism we propose an crossed [2 + 2]-cycloaddition as the initial step leading to the 1,2,4-triphosphabenzvalenes as isomers of **96.** This reaction has also been observed upon irradiation of phosphinines [79] and diphosphinines



96	a	b	c
R	*t*Bu	*t*Pen	Mec*P*en
%	82	84	67

Scheme 26. Photolysis of 1,3,5-triphosphinines **11**

[80, 81] to afford the corresponding valence isomers. There is also a direct analogy to the photolysis of benzene and benzene derivatives affording benzvalenes [82 – 84]. This initial step is followed by an isomerization process, the driving force of which presumably arises from the fact that all phosphorus atoms in **96** possess the favorable $\lambda^3\sigma^3$ configuration.

5.2 Reactivity of the Triphosphabenzvalenes

In order to obtain valid structural data on the novel triphosphabenzvalenes, the bridgehead phosphorus atom P(1) of **96** was subjected to complexation with pentacarbonyl(terahydrofuran)tungsten to afford the η^1-tungsten complex **97** [54]. Coordination of the metal complex to P(2) or P(5) does not occur for steric reasons; this also confirms that P(1) is the most reactive of the three phosphorus atoms.

The geometric parameters for the bond lengths and angles are all in the typical ranges. The P/P single bond lengths of 2.169 and 2.183 Å in the triphosphabicyclobutane roofing unit are in complete harmony with those found for diphosphirane increments [85]. The internal angles at P(1), P(2), P(5) with values between 53.2 and 55.2° are also as expected and somewhat smaller than those at C(6) with values of 71.4 and 71.9°, respectively. The folding angle of 109° between the planes of the two three-membered rings is about 5° smaller than that in the 2,5-diphosphabenzvalene **6** [13, 59] (see Scheme 1).

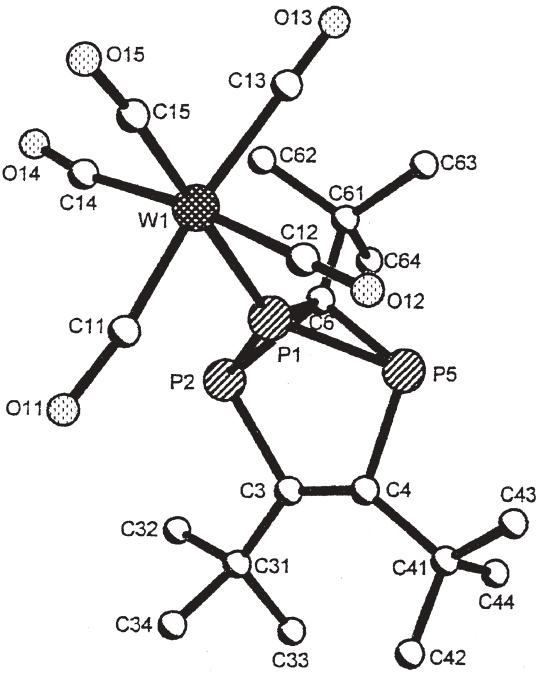
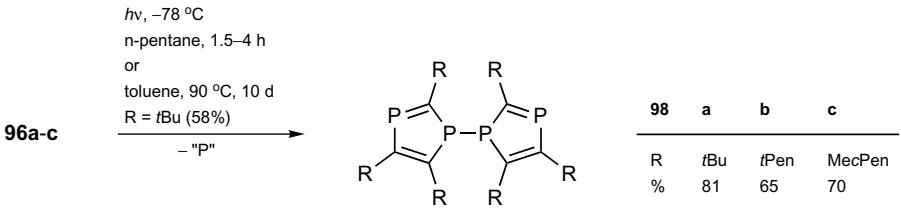


Figure 6. X-ray structure of **97**

As already mentioned, the 1,2,5-triphosphabenzvalenes **96** are not stable thermally and decompose. Also, in the context of the synthesis of **96**, longer exposure of the 1,3,5-triphosphinines **11** to photolysis leads to decomposition of the products **96**. In both cases as well as upon thermolysis of **11a** in toluene, the 1,1'-bi-1,3-diphospholes **98a – c** can be detected spectroscopically or isolated in low yields, respectively [26, 27]. Derivative **98a** has been reported previously and was prepared by an independent route [86, 87]. However, when the 1,2,5-triphosphabenzvalenes **96a – c** are specifically irradiated in pentane at –78 °C the biphospholes **98** are formed with high selectivity in good to very good yields [54]. When the reaction is monitored by ^{31}P-NMR spectroscopy white phosphorus can be detected. Since no other intermediates can be detected on the way from **96** to **98**, any comments about the mechanism are speculative. One possibility is the cleavage of a P/P bond with formation of a 1,6-diphosphabicyclo[3.1.0]hexa-2-ene diradical that spontaneously extrudes phosphorus with dimerization of the remaining 1,3-diphospholyl radical to form **98**. The driving force for the conversion of 1,3,5-triphosphinines to biphospholes is probably associated with the ring strain in the tricyclic skeleton.

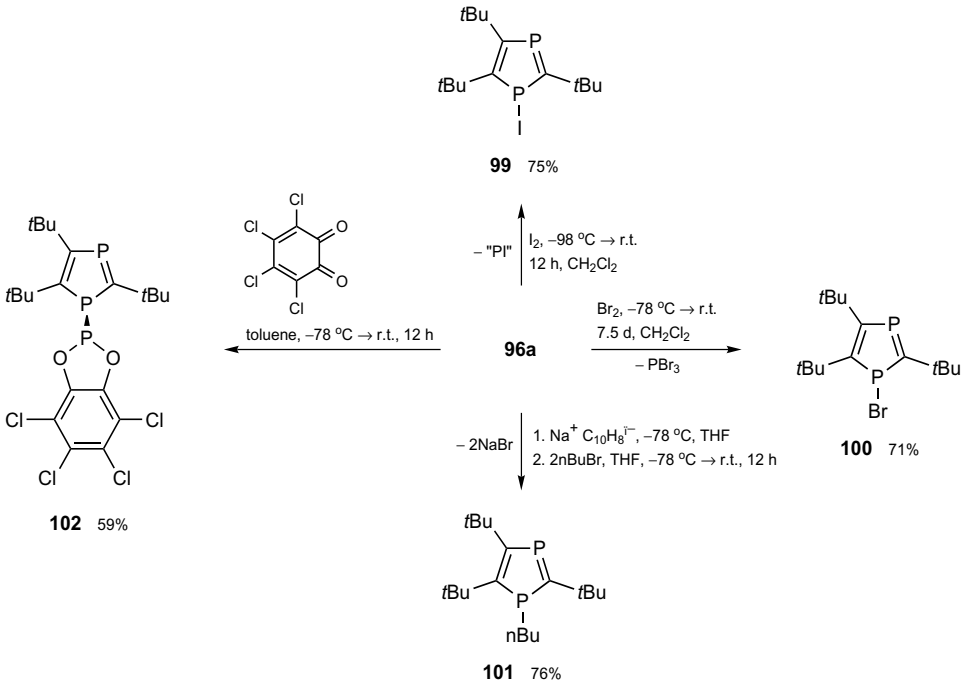


Scheme 27. Synthesis of the biphospholes **98** **98**

Compounds **98** can also be obtained from **96** by thermal processes as demonstrated exemplarily by the synthesis of **98a** from **96a**. However, the reaction times are appreciably longer and the yields lower [54].

The 1,2,5-triphosphabenzvalenes **96** can also be converted specifically to functionalized 1,3-diphospholes, as shown for the example of **96a** in Scheme 28 [54].

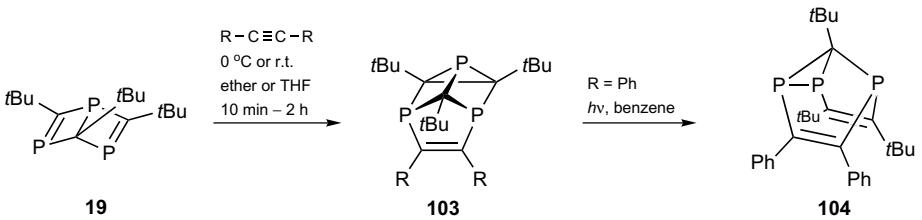
Treatment with the halogens iodine or bromine leads to the formation of the 1-iodo- or 1-bromo-1*H*-1,3-diphospholes **99** or **100**, respectively. In the reaction with bromine, phosphorus tribromide can be detected spectroscopically, it is formed from the phosphorus extruded from the tricyclic skeleton. The cleavage of P(1) from **96a** can also be achieved by a nucleophilic process. When **96a** is treated with sodium naphthalide and subsequently with *n*-butyl bromide as alkylating agent, the 1*H*-1,3-diphosphole **101** is obtained in good yield. The driving force for this reaction is assumed to be the high tendency for formation of the 1,3-diphospholyl anion **27** (see Scheme 7). Finally, the reaction of **96a** with tetrachloro-*ortho*-benzoquinone deserves mention; this also leads to the formation of a 1*H*-1,3-diphosphole derivative, **102**, in which the original phosphorus atom P(1) of the triphosphabenzvalene remains in the molecule as the 1,3,2-benzodioxaphosphole part of the compound [54].



Scheme 28. Reactivity of the 1,2,5-triphosphabenzvalene **96a**

5.3
Reactivity of the Triphospha-Dewar-phosphinines

The 1,3,5-triphospha-Dewar-phosphinines (1,2,5-triphosphabicyclo[2.2.0]-hexa-2,5-diene)s **19** (see Scheme 4) readily participate in homo-Diels-Alder reactions with alkynes. Not only acetylene itself but also diphenylacetylene and acetylenedicarboxylates undergo smooth reactions to furnish the tetracyclic compounds **103** [20, 29, 78, 88].

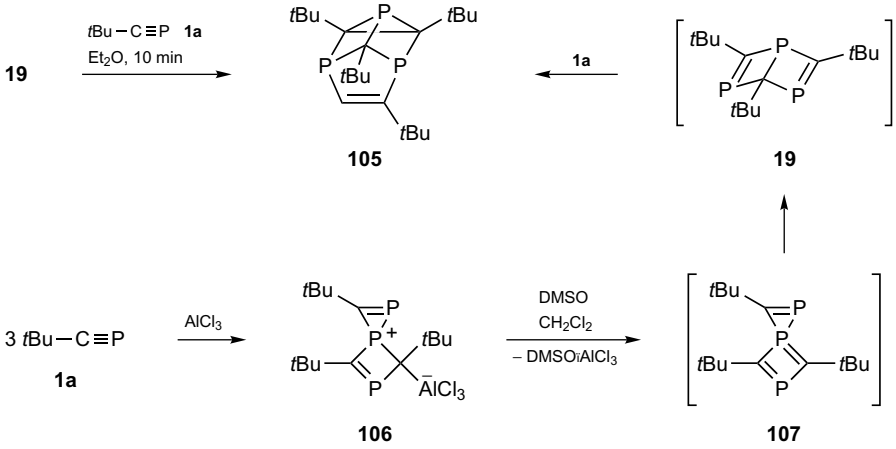


103	a	b	c
R	H	Ph	CO_2Me
% **103**	85	85	82

Scheme 29. Homo-Diels-Alder reactions of 1,3,5-Dewar-triphosphinines

As has been demonstrated for the example of **103b**, these cage compounds can be isomerized photolytically to the triphosphasemibullvalene **104** [88]. Valence isomerizations of this type are well known and have been intensively investigated in the chemistry of phosphorus cage compounds [5, 6, 89].

Phosphaalkynes such as **1a** also readily undergo [2 + 2 + 2]-cycloadditions with the 1,3,5-triphospha-Dewar-phosphinies **19**. Even at 0 °C the reaction of **1a** with **19** is complete within 10 min and furnishes the tetracyclic compound **105** in 96 % yield [20]. The regiochemistry is the same as that of the reaction of **19** with alkynes. Attack at the $\lambda^3\sigma^2$-phosphorus atoms has a more favorable transition state than that at the sp^2 carbon atoms of the 1,4-diene system, as has been deduced from ab initio calculations on parent system [90].



Scheme 30. Homo-Diels-Alder reaction of **19** with phosphaalkyne **1a**

Compound **105** has been prepared by an independent protocol. Phosphaalkyne **1a** undergoes quantitative cyclotrimerization under the influence of a Lewis acid such as $AlCl_3$ to furnish the spirocyclic diphosphirenium betaine **106** [91]. The Lewis acid can be removed by treatment with the weak Lewis base DMSO. The spirocyclic system **107** cannot be isolated since it rearranges rapidly to the 1,3,5-triphospha-Dewar-phosphinine **19** which – again – cannot be isolated under these reaction conditions but is, in turn, trapped by added phosphaalkyne in a homo-Diels-Alder reaction to afford the phosphaalkyne tetramer **105** [92].

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