Chapter 3
Benign Chlorine-Free Approaches to Organophosphorus Compounds

Maria Caporali, Manuel Serrano-Ruiz, and Maurizio Peruzzini

Abstract Organophosphorus compounds have widespread use throughout the world, as agricultural chemicals, medicinal agents, flame retardants, plasticizing and stabilizing agents, selective extractants for metal salts from ores, additives for petroleum products and corrosion inhibitors. Moreover, they are also endowed with metal binding properties, for this reason they have a paramount role in catalysis, being able to direct the activity and selectivity of a metal. Currently, organophosphorus compounds are produced on industrial scale using white phosphorus and chlorine, through an environmentally harmful process which generates equimolar amount of chlorinated waste. In the quest for alternative environmentally benign technology, several routes have been envisaged starting either from elemental phosphorus or from one of its direct low-valent derivative as hypophosphite.

In this contribution, we summarize the latest findings on "green" synthetic approaches towards organophosphorus derivatives. Reactions of elemental phosphorus with organic molecules by means of photochemical irradiation, through a radical mechanism, by electrophilic/nucleophilic addition, mediated by a transition metal or by electrochemical means, will be described. Moreover, a synthetic strategy that uses hypophosphorus acid and its alkali salts as phosphorylating agents towards organic molecules will be as well depicted.

Keywords Elemental phosphorus • Hypophosphite • Organophosphorus • Carbenes • Transition metals • Electrochemistry • Phosphate

3.1 Metal-Mediated Formation of P-C Bond from White Phosphorus

Currently, organophosphorus compounds are produced on industrial scale using white phosphorus as large scale commodity which is first halogenated to phosphorus chloride, PCl_3. In a subsequent step, the chlorine atoms are substituted with

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Scheme 3.1 "Chlorine" route for the bulk production of organophosphorus compounds from white phosphorus

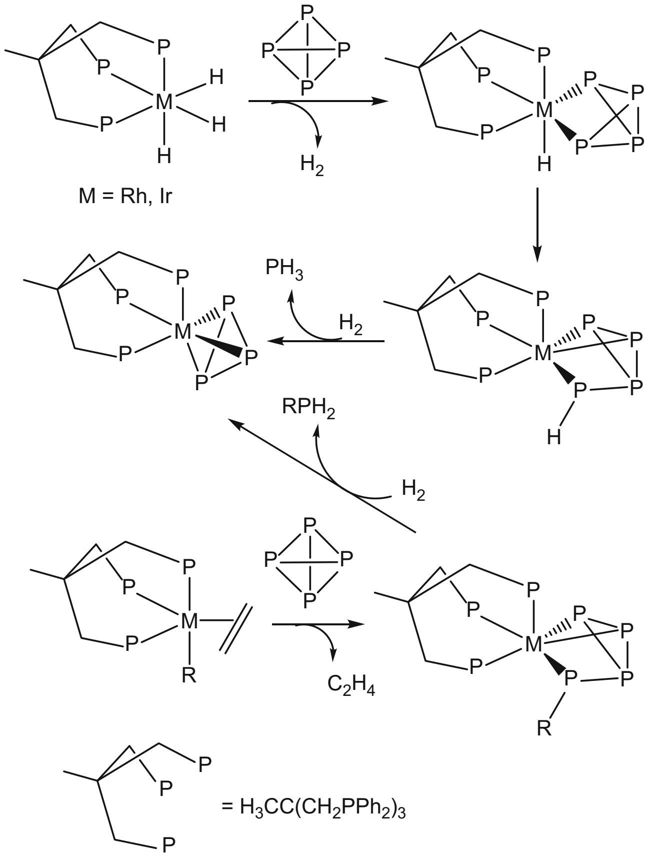
$$\begin{aligned}
1/_4\,P_4 + 6\,Cl_2 &\longrightarrow 4\,PCl_3 \\
PCl_3 + 1/_2\,O_2 &\longrightarrow (O)PCl_3 \\
(O)PCl_3 + 3\,ROH &\longrightarrow (O)P(OR)_3 + 3\,HCl \\
PCl_3 + 3\,RMgBr &\longrightarrow R_3P + 3\,MgBrCl
\end{aligned}$$

organic groups by salt metathesis, generating the desired phosphane R_3P and three molar equivalents of chlorinated waste. On the other hand, reaction of $OPCl_3$ with an alcohol affords the corresponding organic phosphate, $(O)P(OR)_3$, and three times the molar amount of HCl (Scheme 3.1). In other words, the current industrial technology is atom- and energy inefficient and utterly remote from being a sustainable and environmentally benign process. Therefore, the direct and selective processes are needed to avoid the use of chlorine gas, whose production and transportation is highly risk and to circumvent the formation of halogenated intermediates and by-products, which are environmentally harmful and require a high cost to get rid of [1].

Many efforts in academia have been devoted to produce phosphanes, phosphates and phosphites through an alternative route. These compounds are indeed highly valuable in many important industrial fields. Thus, phosphanes as ligand towards a metal center play a key role in catalysis, triorgano phosphates, phosphonates and phosphinates are used as additives to polymers, since are endowed with peculiar properties and can act as plasticizers and flame retardants. Plasticizers play a key role because they increase the flexibility of the polymers and make them easier to process. Additionally, they contribute to lower the glass transition temperature of the polymer, making it more suitable for low temperature applications. Nowadays, the most common plasticizers are phthalates, anyway triorgano phosphates still attract the market in some particular applications thanks to their stability, their rheological properties at low temperature and flame retardants properties. According to the EU legislation [2], halogen-based flame retardants are banned, which is pushing both the academia and the industry to search and develop new materials which behave as efficient flame retardants and do not contain any halogen. Several aryl phosphates fulfill the rule of laws and among them, both triphenyl and tritolyl phosphate are sold commercially as flame retardants, the latter being more common due to its compatibility with PVC.

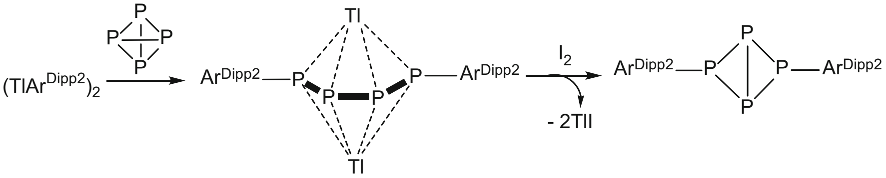
In the quest for alternative ways of the production of organophosphorus compounds, a huge amount of knowledge about P_4 chemistry has been developed in the last decades, though direct functionalization methods are still scarce and applicable mainly on a laboratory scale [2].

One of the most spread approaches is based on the use of a transition metal, either early or late, that can firstly activate white phosphorus through coordination to the metal center, and afterwards the coordinated P_4-moiety is prone to react further with a suitable organic reagent. On this regard, a milestone has been the work by Ginsberg and Lindsell in 1971 [3], who showed for the first time that white phosphorus can bind to a transition metal-ligand system, namely the



Scheme 3.2 Summary of the reactivity of [(triphos)MH_3] (M = Rh, Ir; triphos = MeC(CH_2PPh_2)$_3$) and [(triphos)RhR(C_2H_4)] (R = H, Me, Et, Ph) with P_4

rhodium Wilkinson's complex. Since then, more than 40 years of studies have focused on the key role played by a transition metal, or a main group element or compound, which in principle can carry out the activation and subsequently either aggregation or fragmentation of P_4 to yield a variety of naked Px units ($x \leq 24$) well suited to bind one or more metals. Although subsequent functionalization of the P_4 moiety and liberation reactions from the metal centers are not common due to the strong bond between the metal and the P_4 moiety [4]. In this regard, the Florentine group lead by Peruzzini discovered that rhodium and iridium trihydride complexes bearing as ancillary ligand a tripodal phosphane named triphos (1,1,1-tris(diphenylphosphanylmethyl)ethane) were prone to react with P_4, which upon the displacement of molecular hydrogen was coordinated to the metal center in a di-hapto fashion, see Scheme 3.2. The remaining hydride, being in *cis* position respect to the P_4 moiety, can interact and migrate on the phosphorus moiety, resulting in the formation of a P-H bond. Applying a hydrogen pressure to this



Scheme 3.3 Synthesis of Phosphane derivatives from P_4 and dimeric "dithallene"

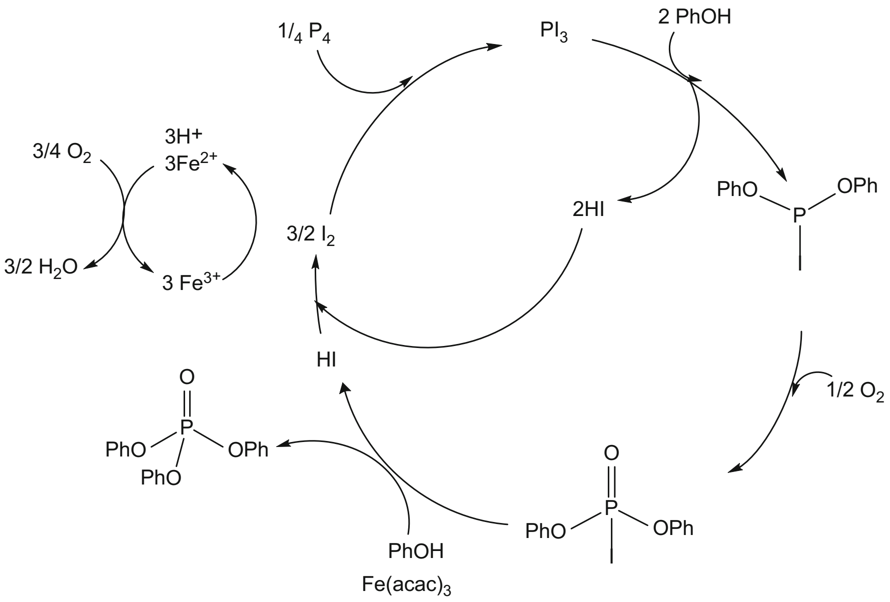
derivative, it is observed formation of PH_3 and the other three P atoms (coming from P_4) forms a highly stable cyclotriphosphorus unit η^3-coordinated to the metal. The latter represents a resting state that does not evolve to an active species able to activate either molecular hydrogen or P_4. Therefore, the reaction of the trihydride metal precursor, P_4, and hydrogen is stoichiometric and cannot be catalytic.

Similarly, the reaction of the ethylene complex [(triphos)RhR(C_2H_4)], R=H, alkyl, aryl, with P_4 in the presence of positive hydrogen pressure gave a stoichiometric amount of the corresponding phosphane RPH_2 and cyclo-triphosphorus rhodium complex [5a–b], see Scheme 3.2.

Another example of a stoichiometric route to access a phosphane derivative starting directly from P_4 in the presence this time of a main group metal was shown by Power in 2005 [5c]. Surprisingly, by reacting the weakly dimerized "dithallene" $[TlAr^{Dipp2}]_2$ ($Ar^{Dipp2} = C_6H_3$-2,6-(C_6H_2-2,6-$i$$Pr_2$)$_2$) with white phosphorus, the tetrahedral structure of the latter was completely disrupted, resulting in an open chain of four P atoms sandwiching the two metal atoms, see Scheme 3.3. Notably, the two aryl groups Ar^{Dipp2} (= C_6H_3-2,6-(C_6H_2-2,6-$i$$Pr_2$)$_2$) were transferred from the metal to the two opposite end of the phosphorus chain. Subsequent mild oxidation with iodine resulted in the quantitative formation of a tetraphosphabicyclobutane derivative, $Aryl_2P_4$, with the elimination of thallium iodide. Later, in Sect. 3.4, we will discuss the formation of tetraphosphabicyclobutane derivative, in the absence of a metal.

Concerning the "chlorine free" production of di- and tri-alkyl phosphates, di- and tri-alkyl phosphites, a remarkable catalytic protocol was developed in the 1990s by Dorfman and Abdreimova [6]. They carried out a mild catalytic oxidative alkoxylation of P_4 dissolved in arene/alcohol solution, using Cu(II) or Fe(III) as catalysts in aerobic conditions, being O_2 necessary as oxidant. Intriguingly, it was observed in the case of copper that the product distribution was strongly influenced by the nature of the ligands. In the presence of copper halides, the main product was alkyl phosphate, while copper sulfate or acetate enhanced the formation of alkyl phosphite. However, these catalytic systems did not work well with phenol or aryl alcohols and lack of narrow selectivity.

A further relevant contribution on this regard comes from Kilian, who recently found out that P_4 can react with phenol in aerobic conditions in the presence of iodine and Fe(acac)$_3$ (acac = acetylacetonate) as catalyst affording quantitative



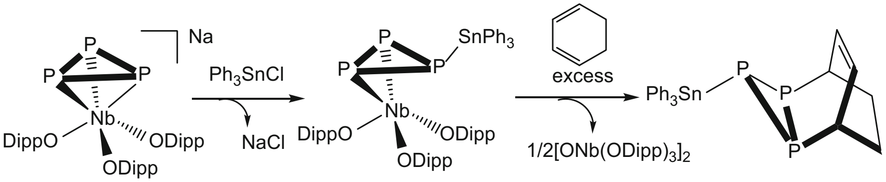
Scheme 3.4 Catalytic synthesis of triphenyl phosphate from white phosphorus

conversion of the desired triphenyl phosphate [7] producing only water as by-product. Mechanistic studies were carried out to understand the reaction pathway and in particular the rate-limiting steps in order to optimize the process. Iodine, also used in catalytic amount, served to oxidize P_4 to phosphorus(III) by forming instantaneously PI_3. Additionally, it was observed that the reaction did not proceed under anaerobic conditions, being oxygen indispensable first to oxidize P(III) to P (V) in the catalytic step where PI_3 reacted with phenol. Secondly, O_2 was responsible for the reoxidation of the by-product HI back to iodine as shown in Scheme 3.4. The reaction, carried out at 80 °C and with 25 mol% Fe(acac)$_3$ loading, was applied successfully also to functionalized phenols giving high conversion and very good selectivity.

Another advantage of this process is that iron is a desirable metal for the catalysis of industrial processes due to its low toxicity, low cost and ready availability.

However, phosphites cannot be synthesized through this route since the iron/ iodine catalyst system does oxidize phosphites to phosphates.

Unlike main-group and late-transition metal mediated activation of P_4, the applications of early transition metals in this field are far less common. Aiming to circumvent the use of PCl_3 as an intermediate in the synthesis of organophosphorus compounds and in the search for a catalytic process producing organophosphanes directly from white phosphorus, Cummins [8] has put a lot of efforts to study the activation of white phosphorus mediated by early transition metals. Indeed, niobium and molybdenum complexes have been shown by Cummins et al. to carry out



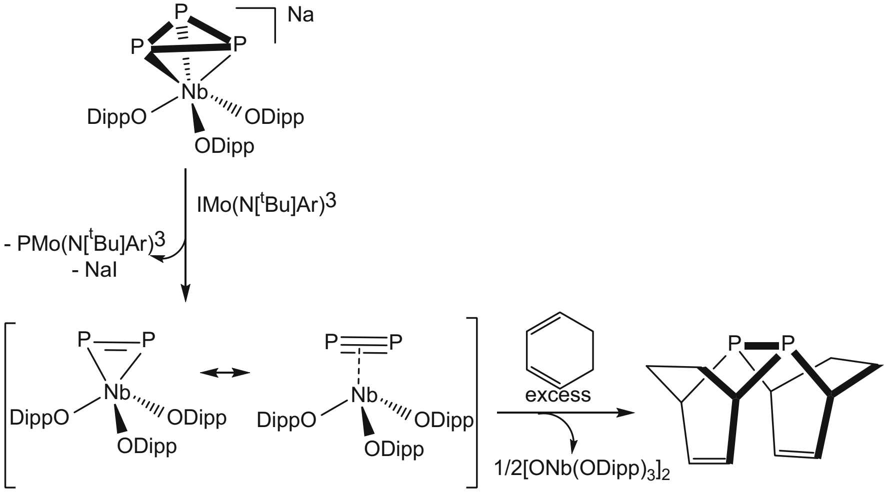
Scheme 3.5 Release of the P_3^- fragment from the niobium complex and subsequent cycloaddition reaction

in an efficient way the activation of molecular dinitrogen and to promote N-transfer reactions, thus synthesizing, for instance, organo-nitriles. This study was extended to other early transition metals and, intriguingly, it was observed that a niobium complex could firstly coordinate P_4 and, then, the phosphorus moiety could be transferred to an organic substrate. A beautiful example of this chemistry is shown in Scheme 3.5, where complex $[Na(thf)_3][(\eta^3\text{-}P_3)Nb(ODipp)_3]$ (Dipp = 2,6-$i\text{Pr}_2C_6H_3$), easily prepared by reduction of $[Cl_2Nb(ODipp)_3]$ in the presence of P_4, has an anionic nature which imparts to the P_3 ring a strong nucleophilic character which makes possible the straightforward reaction with a range of mild electrophiles [9]. For instance, the reaction with Ph_3SnCl, proceeds quickly at room temperature forming $[(\eta^3\text{-}Ph_3SnP_3)Nb(ODipp)_3]$ while sodium chloride is eliminated. To free from the metal center the triphosphirene moiety, Ph_3SnP_3, a stoichiometric amount of pyridine-*N*-oxide together with an excess of 1,3-cyclohexadiene were used. The latter serves as a trapping agent of the phosphirane, yielding the desired Diels-Alder adduct $Ph_3SnP_3(C_6H_8)$ as shown in Scheme 3.5.

The stable $Ph_3SnP_3(C_6H_8)$ can be regarded as a P_3^- synthon, since the reactive P-Sn bond can be cleaved with elimination of Ph_3SnCl and the cyclic olefin, formed by trapping the P=P unit with 1,3-cyclohexadiene, can be readily lost as it has been shown that retrocycloaddition reactions are accessible for such protected diphosphanes [10]. Significantly, the Ph_3Sn^+ moiety can be replaced by other electrophiles as Ph_3C^+, Ph_3Si^+ and Me_3Si^+ by the salt elimination procedure. This modularity may allow the assembly of a library of P_3^- transfer reagents opening the way to the synthesis of a wide range of organophosphorus compounds. Formal abstraction of P^- from $Na[(\eta^3\text{-}P_3)Nb(ODipp)_3]$ was mediated by the molybdenum complex $IMo(N[^tBu]Ar)_3$ and resulted in the formation a labile niobium complex [11] bearing a P_2 side-on coordinated ligand as shown in Scheme 3.6.

In the presence of a 20-fold excess 1,3-cyclohexadiene, the P_2 unit is released from the metal center and a formal [4 + 2] Diels-Alder cycloaddition takes place affording the diphosphane (Scheme 3.6).

Replacing the ancillary ligands ODipp at niobium center with the more hindered $(OC[^2Ad]Mes)_3$ where ^2Ad = 2-adamantylidene, Mes = 2,4,6-trimethylphenyl, Cummins discovered [12] that by reacting four equivalents of $[NbI\{(OC[^2Ad]Mes\}_3(thf)]$ with two equivalents of P_4, a new niobium complex was formed, $[(P_8)\{Nb(OC[^2Ad]Mes)_3\}_2]$, which is a unique dinuclear species having a P_7

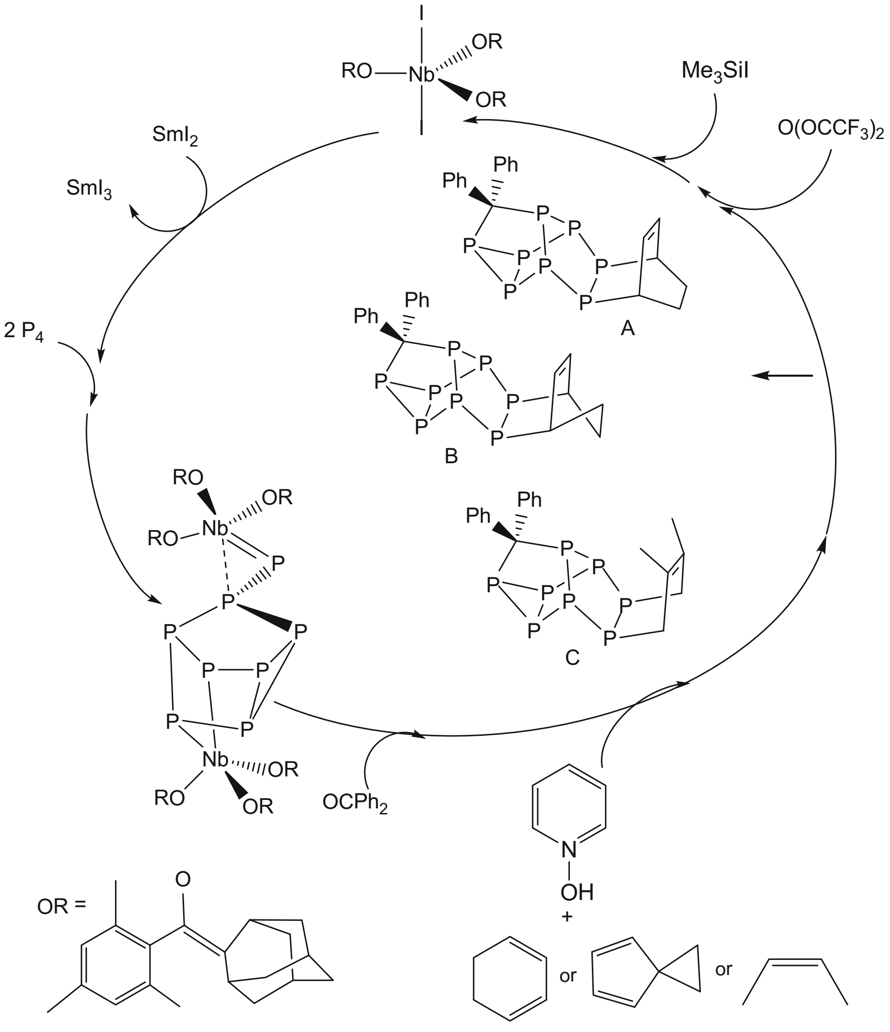


Scheme 3.6 Abstraction of P^- and trapping of the P_2 fragment by cycloaddition reaction

nortricyclic core with a phosphino-phosphinidene moiety connected to one of the two niobium center, as shown in Scheme 3.7. The phosphino-phosphinidene moiety is endowed with a special reactivity and easily reacts with a suitable organic substrate as benzophenone detaching the coordinated niobium fragment as oxide. Since the remaining niobium-phosphorus interaction in the complex can be regarded as a side-on coordination of a diphosphene unit (RP=PR) to a strongly π-donating d^2 niobium center, a 20-fold excess of 1,3-cyclohexadiene together with pyridine-*N*-oxide were added. The corresponding Diels-Alder cyclo-adduct A was obtained in good yield, eliminating a second niobium-oxo fragment as above. Herein, the synthetic cycle could be completed by addition of triflic anhydride (2 equiv) followed by Me_3SiI (4 equiv) to recycle the two niobium-oxo complexes to the catalytic precursor, $[I_2Nb\{(OC[^2Ad]Mes\}_3]$ as shown in Scheme 3.7. The latter in the presence of samarium (II) iodide, undergoes the displacement of one iodide, generating a coordinatively unsaturated species $[INb(thf)\{(OC[^2Ad]Mes\}_3]$, prone to react with P_4 [13].

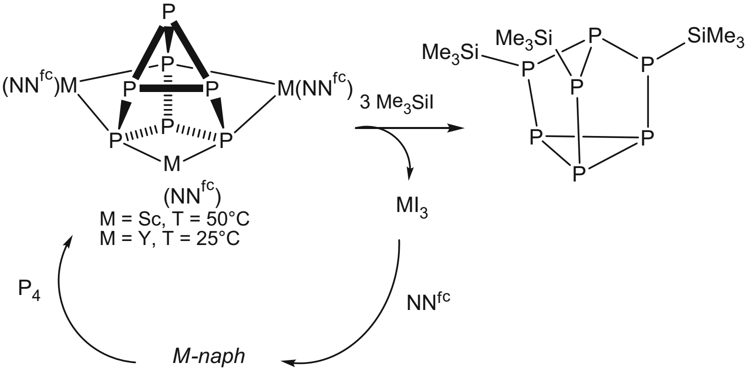
Noticeably, instead of 1,3-cyclohexadiene, spiro[2.4]hepta-1,6-diene and 2,3-dimethylbutadiene were also tested in the catalytic cycle. They resulted to be very reactive Diels-Alder diene, in particular the first one, and trapped efficiently the carbophosphorus cluster contained in the key intermediate complex $[Ph_2CP_8Nb(OC[^2Ad]Mes)_3]$ giving respectively the organophosphanes B and C (Scheme 3.7), in good yield.

Despite their potentially strong reducing nature, group 3 and 4f-block metals have been sparely considered for the activation of white phosphorus, presumably because of the hard-soft mismatch between the electropositive metal and soft phosphorus. The direct activation of P_4 using group 3 metal was only recently achieved in mild conditions by Diaconescu et al. [14]. Unexpectedly, the reaction



Scheme 3.7 Niobium-mediated cycle for the direct transformation of white phosphorus into organophosphanes A, B or C

between the scandium naphthalene complex, $[\{(NN^{fc})Sc\}_2(\mu\text{-}C_{10}H_8)]$ (*Sc-naph*: $NN^{fc} = 1,1'\text{-fc}(NSi^tBuMe_2)_2$, fc = ferrocenylene) and white phosphorus afforded two different metal complexes, containing respectively $[P_8]^{4-}$ and $[P_7]^{3-}$ unit, that could be separated thanks to their different solubilities. The bonding motif of $[P_8]^{4-}$ in the cluster Sc_4P_8 recalls a realgar-type structure with four $(NN^{fc})Sc$ fragments standing at the corners, each of them bonding to two phosphorus atoms, while the cluster Sc_3P_7 contains the $[P_7]^{3-}$ unit having a heptaphosphanortricyclane structure and represents the first example of the Zintl anion $[P_7]^{3-}$ obtained directly from P_4



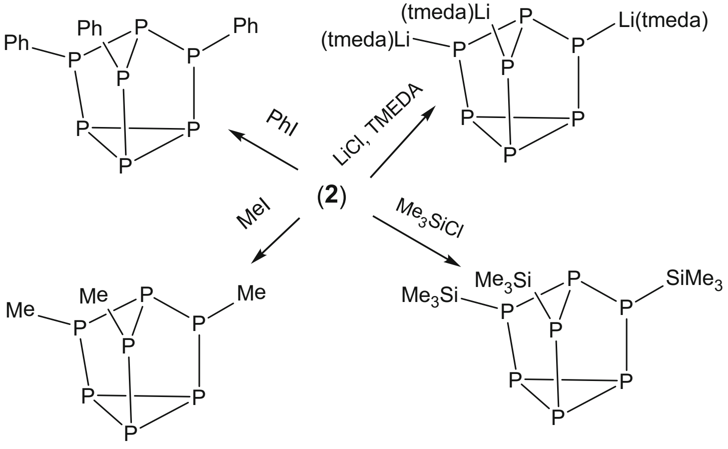
Scheme 3.8 Transferring a polyphosphide unit $[P_7]^{3-}$ from a metal center to an organic species

without using an alkali metal or its equivalent as a reducing agent. Interestingly, the reaction of white phosphorus with the yttrium analogue, $[\{(NN^{fc})Y(THF)\}_2(\text{-}\mu\text{-}C_{10}H_8)\}$ went to completion at room temperature in a much shorter time and afforded uniquely the product Y_3P_7.

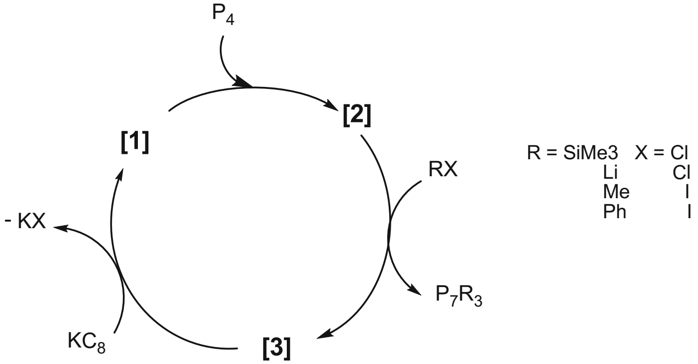
Aiming to activate the polyphosphide from the clusters Sc_3P_7 and Y_3P_7, these were allowed to react with three equivalents of Me_3SiI as shown in Scheme 3.8. These reactions led to $(Me_3Si)_3P_7$ and gave as by-product the scandium/yttrium iodide, which in turn can be recycled to synthesize the starting metal arene complex. This constitutes the first example of transferring the Zintl anion $[P_7]^{3-}$ to an organic species and establishes a synthetic cycle for the direct transformation of P_4 to organophosphorus compounds.

Studies on P_4 activation and functionalization mediated by 5f metals are exceptionally rare, there is one report concerning thorium [15] and a few about uranium [16, 17]. In the first publications concerning uranium [16], it was shown this metal can favor the cleavage of a P-P bond forming a $[P_4]^{2-}$ ring, but no fragmentation or catenation of P_4 was observed [16]. Recently, Liddle and co-workers [17] showed that a diuranium(V)-arene-tetraanion complex (**1**) reductively cleaves P_4 to form a triuranium cluster tris(triamidouranium)μ^3-η^2:η^2:η^2-heptaphosphanortricyclane (**2**) containing a heptaphosphanortricyclane cage connecting the three uranium centers. This represents not only the first example of fragmentation and catenation of P_4 to a higher oligomer promoted by uranium but also the first example of a molecular actinide $[P_7]$ Zintl complex. As shown in Scheme 3.9, by reaction of **2** with three equivalents of Me_3SiCl, the derivative $P_7(SiMe_3)_3$ was quantitatively afforded together with $[(Ts^{TOL})U(Cl)(\mu\text{-}Cl)U(THF)_2(Ts^{TOL})]$ (**3**) as a by-product where $Ts^{TOL} = HC(SiMe_2NAr)_3$, Ar = 4-$MeC_6H_4$. Other electrophiles have been tested, like LiCl, MeI and PhI, and in all cases the corresponding organophosphorus derivative was obtained in good yield while complex **3** was released.

This new pathway is of great relevance, since it makes feasible and straightforward the preparation of alkali-metal or organic derivatives of $[P_7]^{3-}$ that is



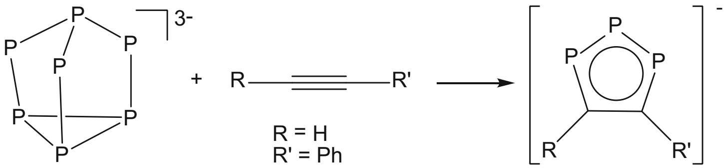
Scheme 3.9 Reaction of a tris(triamidouranium)μ^3-η^2:η^2:η^2-heptaphosphanortricyclane (**2**) towards diverse electrophiles



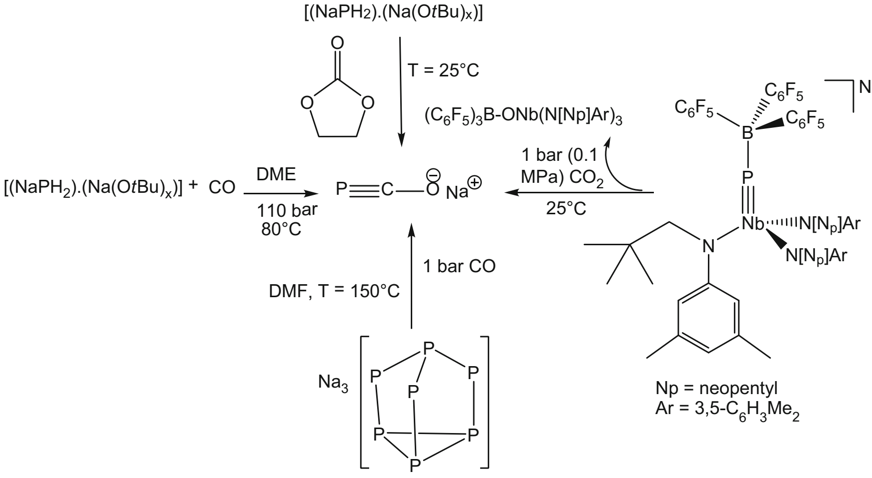
Scheme 3.10 Synthetic cycle for the direct transformation of P_4 into organophosphorus derivatives P_7R_3 mediated by an uranium complex

otherwise challenging. Moreover, the reduction of **3** with potassium graphite can restore complex **1** and in this way two turnovers can be achieved, demonstrating the ability of uranium complexes to activate and liberate P-functionalized organic molecules, working effectively as in a catalytic cycle (Scheme 3.10).

While in the past $[P_7]^{3-}$ and its derivatives were considered as a dead end in synthetic phosphorus chemistry, recent works involving the demolition of P_7 cage into P_5 and P_2 fragments indicate that P_7 compounds can be seen as useful platforms in the field of phospha-organic chemistry [18]. Recently, Goicoechea's group has shown that $[P_7]^{3-}$ clusters are reactive towards unsaturated organic substrates [19], in particular they react with alkynes with transfer of a $[P_3]^-$ unit to form an unusual class of cyclopentadienide analogue, the 1,2,3-tripnictolides (Scheme 3.11).



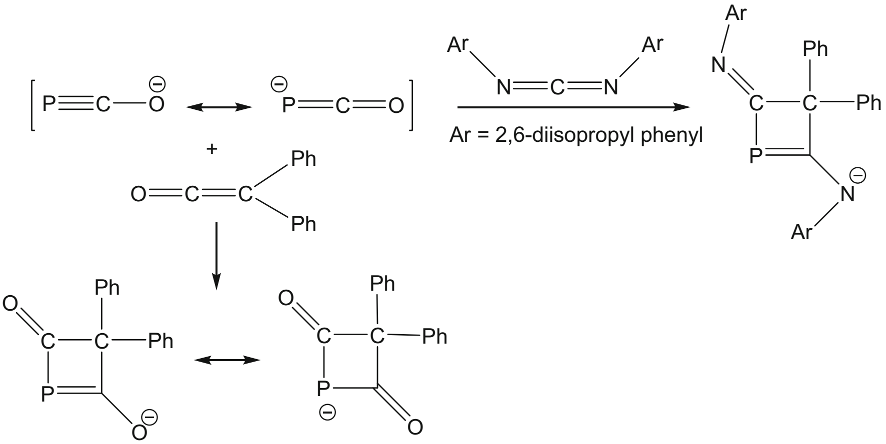
Scheme 3.11 Synthesis of 1,2,3-$[P_3C_2RR']$-anions



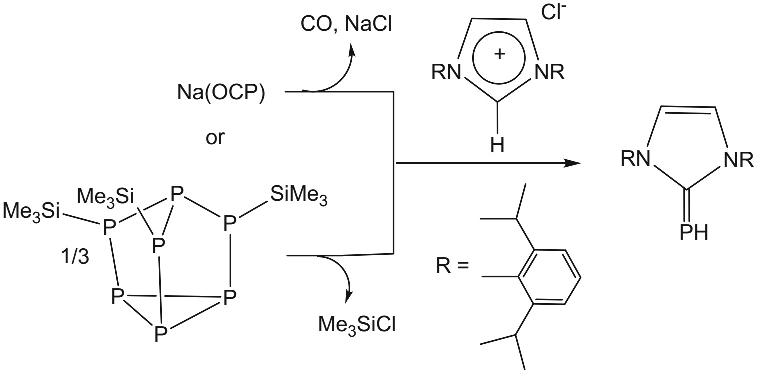
Scheme 3.12 Different ways to access Na(OCP)

The reaction mechanism that leads to the products is still unraveled, presumably the driving force for the formation of the 1,2,3-tripnictolide anions is their aromaticity. Routes to access this class of compounds are still scarce and underdeveloped, with only a few examples existing in literature [20]. Intriguingly, $[P_7]^{3-}$ is endowed with a special reactivity towards carbon monoxide, in refluxing dimethylformamide good yield of the phosphaethynolate anion, $[PCO]^-$ as $[K(18\text{-crown-}6)]^+$ salt, can be formed [21], see Scheme 3.12. This anion is known since decades [22], but no chemistry has been performed upon it, only recently it has been a renaissance and several studies have flourished. Among them, Grützmacher's group [23] has refined the synthesis obtaining Na(O-C≡P) through a large-scale procedure (hundreds of grams) based on the phosphination of carbon monoxide using $NaPH_2$ us "P" source or from the reaction of $NaPH_2$ with diethyl carbonate as source of CO (Scheme 3.12).

Cummins demonstrated that Na(OCP) can be synthesized also through a completely different way [24], using a niobium phosphide complex as source of "P" and carbon dioxide as source of CO, see Scheme 3.12. The salt Na(OCP) is remarkably stable and can be seen as a valuable building block for the synthesis of organophosphorus compounds. For instance, Goicoechea found out



Scheme 3.13 [2 + 2] cycloaddition of $[PCO]^-$ to diphenylketene and bis(2,6-diisopropylphenyl) carbodiimide



Scheme 3.14 [Na(OCP)] and $[P_7]^{3-}$ as valuable "P" synthon

that the reaction of [K(18-crown-6)][PCO] with diphenylketene or bis (2,6-diisopropylphenyl)carbodiimide, see Scheme 3.13, gives in both cases an anionic four-membered ring [21] resulting from a [2 + 2] cycloaddition product of P≡C triple bond across the C=C or C=N double bond.

This constitutes the first example of an isolated monoanionic four-membered phosphorus-containing heterocycle.

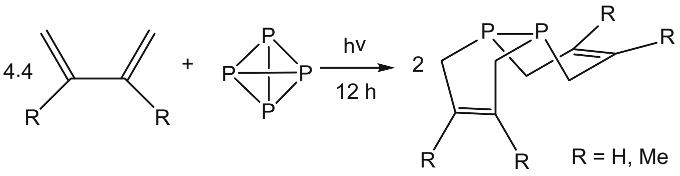
The $[OCP]^-$ anion can be regarded as an adduct of carbon monoxide and P^-, so it can work as a "P" transfer reagent, the by-product being simply gaseous CO, which facilitates the reaction work-up. On the other hand, $P_7(SiMe_3)_3$ (or similar derivatives) can also be regarded as a phosphorus donor, thus becoming highly promising building blocks to access organophosphorus derivatives in a sustainable way, avoiding the use of chlorine. An outstanding example of the synthetic relevance of the above-mentioned synthons is offered in Scheme 3.14, where starting from either Na(OCP) or $P_7(TMS)_3$, the N-heterocyclic carbene adduct was synthesized in high yield on the gram scale [25].

3.2 P-C Bond Formation by Photochemical Irradiation

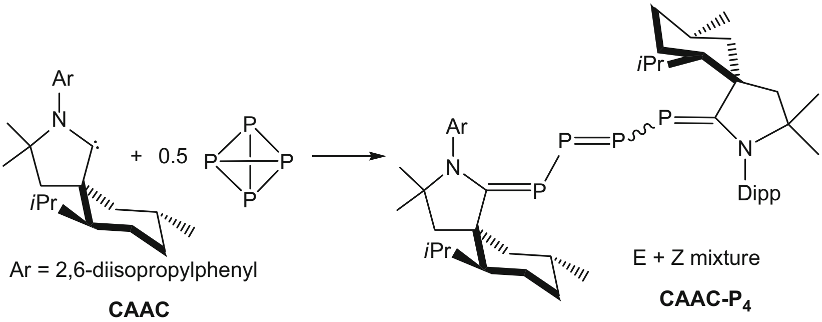
As underlined in the beginning of the chapter, a well-recognized imperative for the industrial synthesis of organophosphorus compounds is to avoid PCl_3 as an intermediate and to develop instead methods for the direct incorporation of phosphorus atoms into organic molecules using as building block elemental phosphorus, white or red. An old paper by von Rathenau [26] reported that photolysis of P_4 at room temperature using a mercury lamp induced polymerization of white phosphorus which is transformed into the less reactive red allotrope. Most importantly, he stated that the possible intermediate in this reaction is the transient species P_2, higher congener of N_2, generated by UV irradiation. A recent work by Cummins et al. has been inspired by this result and has shown that photolysis of white phosphorus under UV light generates a diphosphorus unit P_2 which may be immediately trapped by a diene molecule. The final product is consistent with a double Diels-Alder addition, affording the diphosphane derivative shown in Scheme 3.15. The process converts, in a straightforward way, P_4 into a phosphane; however the yield of the cycloadduct is moderate [27].

3.3 Carbene-Mediated Functionalization of P_4 as a Route to Organophosphorus Compounds

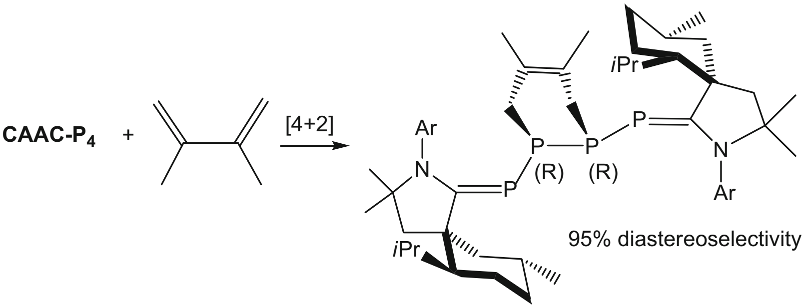
It is well known that transition metals can activate small molecules as white phosphorus and can stabilize highly reactive species. The group of Bertrand verified whether singlet carbenes may behave in a way similar to transition metals in the presence of P_4. It was shown that a bulky and rigid cyclic alkyl amino carbene, CAAC, see Scheme 3.16, is able to open P_4 and at the same time can stabilize the resulting highly reactive species, without inducing fragmentation or aggregation of



Scheme 3.15 One-pot synthesis of diphosphanes from white phosphorus by photochemical irradiation



Scheme 3.16 Reactivity of half equivalent of P_4 with CAAC

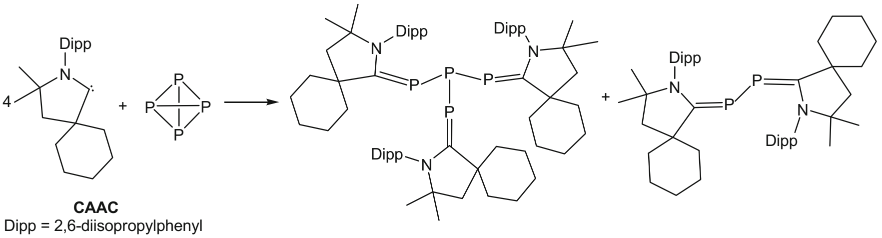


Scheme 3.17 Diastereoselective [4 + 2] cycloaddition of CAAC-P_4 adduct and 2,3-dimethylbutadiene

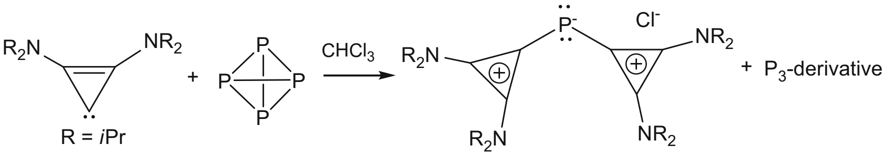
P_4. In this way, 2,3,4,5-tetraphosphatrienes constituted by an open chain of four P atoms bridging the two carbene units were isolated in good yields [28].

Moreover, it was studied the reactivity of the *(E)*-diphosphene with 2,3-dimethylbutadiene and surprisingly the reaction proceeded cleanly giving quantitatively the Diels-Alder product coming from a [4 + 2] cycloaddition of the diene with the phosphalkene, see Scheme 3.17. In this way, two phosphorus-carbon bonds were constructed and the isolated product shows very good diastereoselectivity.

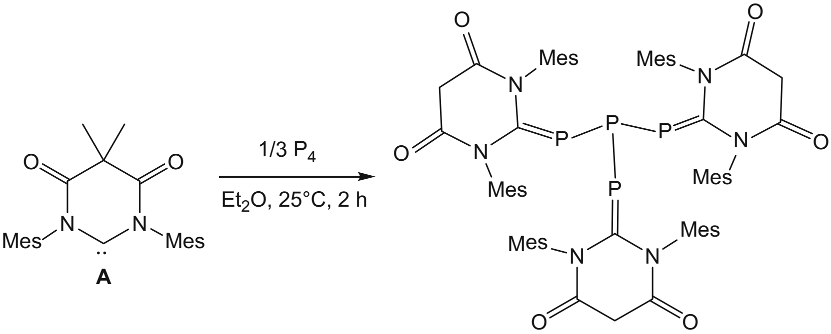
Since the chemical behavior of cyclic alkyl amino carbenes, CAACs, is usually different than that of N-heterocyclic carbenes, NHCs, these results pushed to investigate the reactivity of NHCs towards P_4. Bertrand and co-workers showed [29] that NHC not only reacts easily with P_4 but also induces an aggregation of three P_4 units and a P_{12} cluster is formed in high yield and stabilized by two NHC units. The architecture of P_{12} core is unprecedented and differs from that found in transition metal complexes having as ligand P_{12} derived from metal-mediated activation of white phosphorus [30]. Though it is not the largest cluster obtained from P_4: recently, a contribution by Scheer et al. was published [31] and demonstrated that via cobalt-mediated activation of P_4, a huge cluster of 24 phosphorus



Scheme 3.18 Reaction of P_4 with the non-hindered CAAC



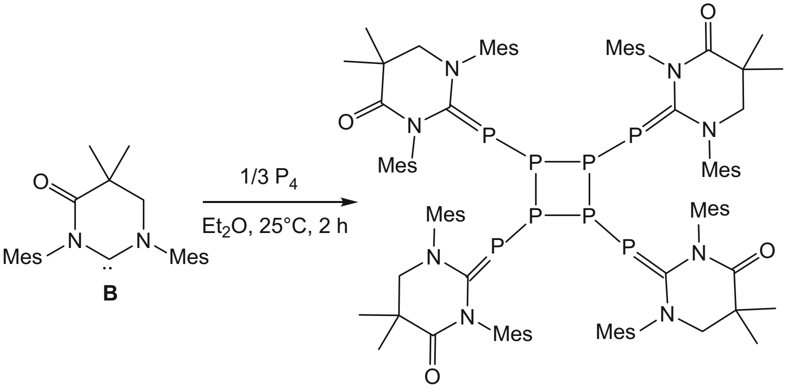
Scheme 3.19 Reaction of P_4 with cyclopropenylidene



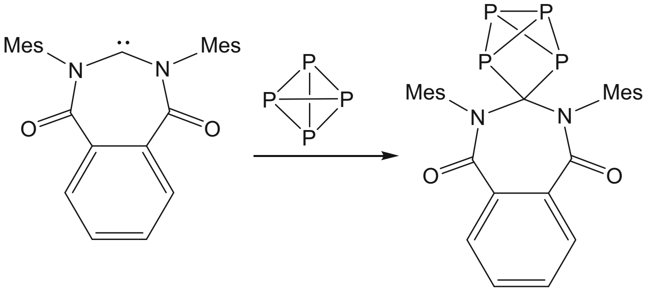
Scheme 3.20 Reactivity of white phosphorus towards carbonyl-functionalized carbene

atoms can be prepared. These results prove that singlet carbenes are excellent organic building blocks for the formation of organophosphorus compounds directly from white phosphorus without any need of a metal. Since the most synthetically useful organophosphorus compounds contain only one or two P atoms, it was mandatory to study the possible fragmentation, if any, of white phosphorus in the presence of a suitable carbene. Depending on the nature of the latter, carbene-stabilized P_3, P_2 and P_1 species have been isolated by Bertrand and co-workers [32] as shown in Schemes 3.18 and 3.19.

Carbonyl-decorated carbenes have been shown [33] to exhibit a rich and versatile reactivity, this motivated Hudnall and co-workers to investigate their reactivity towards white phosphorus. Gratifyingly, treatment of the latter with three equivalents of the highly electrophilic carbene **A** shown in Scheme 3.20 resulted in a rapid



Scheme 3.21 Reactivity of white phosphorus towards carbonyl-functionalized carbene



Scheme 3.22 Activation of P_4 mediated by a highly electrophilic carbene

activation at room temperature and formation of a triscarbene-P_4 cluster [34], analogue to the one prepared by Bertrand shown in Scheme 3.18.

Interestingly, the reaction of the less electrophilic carbene **B**, see Scheme 3.21, with white phosphorus in identical reaction conditions, provided a drastically different product, a neutral tetrakiscarbene-P_8 cluster. The X-ray analysis revealed a central P_4 butterfly structure that is capped at each P atom with a phosphalkene moiety. Taking into account that a tetraanionic P_8 cluster was previously prepared by Wiberg et al. [35] via a [2 + 2] cycloaddition dimerization of a linear P_4-diphosphene, Hudnall repeated the reaction of P_4 with carbene **B** by adding 2,3-dimethyl-1,3-butadiene and the corresponding Diels-Alder cycloaddition product was isolated, confirming the hypothesized reaction pathway. Therefore, it is evident the dramatic influence of the electrophilicity of the chosen carbene on the identity of the final product.

In the same time, Bertrand's group was working on this matter, and shortly after Hudnall, published that the tetrakis carbene P_8 cluster can be obtained from P_4 and the cyclic six-membered diamido carbene (as shown by Hudnall) and also by using a less electrophilic carbene as cyclic(alkyl)(amino)carbene [36]. Moreover, he demonstrated that a carbene can insert into a single P-P bond of P_4, resulting in the formation of a carbene-P_4 adduct (Scheme 3.22). Thus the extremely electrophilic seven-membered cyclic benzamido carbene can behave as a transition metal towards P_4 showing a η^2-coordination.

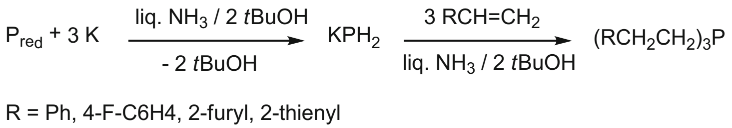
Future efforts will be necessary to investigate these compounds coming from the carbene-mediated activation of P_4, as potential phosphorus transfer reagents for the preparation of useful organophosphorus compounds.

3.4 Synthesis of Organophosphorus Compounds by Nucleophilic Addition

In this section, we review two main different approaches: (a) phosphorus-centered anion, usually directly derived from elemental phosphorus, which does a nucleophilic attack (addition) on organic substrates; (b) carbon-centered anion, which does a nucleophilic attack (addition) on P_4; in both cases a new P-C bond is formed.

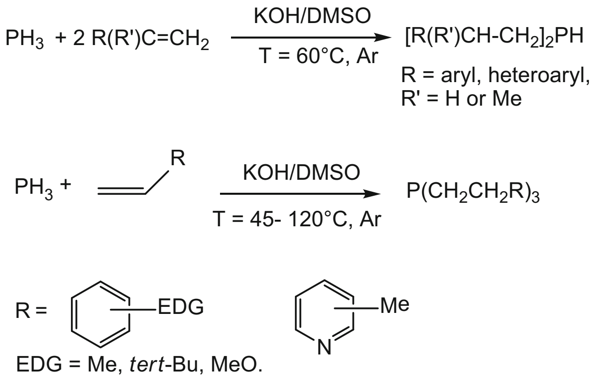
Concerning the chemistry of phosphorus-centered anion, it is worth mentioning the work developed by Trofimov and Gusarova. They choose red phosphorus as "P"-source to accomplish the phosphorylation of unsaturated organic compounds, as alkenes and alkynes. Since red phosphorus has a polymeric chain-like structure which reduces strain and reactivity in comparison to the white allotrope giving greater stability, harsher treatments are required for the activation of the red allotrope. Strongly basic conditions, as aqueous potassium hydroxide in dimethylsulfoxide under heating or microwave irradiation were used, and the final reaction mixtures gave primary, secondary and tertiary phosphanes and phosphane oxides. A similar procedure was applied by the same authors to carry out the direct phosphorylation of alkenes and alkynes with P_4, but using milder conditions, as shorter reaction time and heating at lower temperature [37]. From the mechanistic point of view, it is believed that in such heterogeneous and strongly basic media, highly active *P*-centered nucleophiles (as polyphosphides and polyphosphinites) are formed and prone to interact with the suitable electrophile (styrenes, vinylpyridines, acetylenes and similar). This methodology avoids the use of chlorine but has the disadvantage to produce mainly oxidized products, i.e. phosphane oxides.

In the late 1990s, Brandsma and Trofimov [38] refined this methodology and triggered a way to avoid the formation of the oxide selectively achieving the desired phosphane. They reacted the elements, red phosphorus and potassium in liquid ammonia and using *tert*-butanol as mild source of protons, potassium phosphide, KPH_2, was formed quantitatively (Scheme 3.23). Subsequent addition of an alkene brought the formation of tertiary phosphane and the reaction is supposed to proceed through a series of nucleophilic addition of the phosphides, formed *in situ*, to the double bond of the alkene. Importantly, the reaction generated selectively and exclusively tertiary phosphanes. Electrophilic alkenes are preferred being able to



Scheme 3.23 Synthesis of tertiary phosphanes from red phosphorus

Scheme 3.24 Selective synthesis of secondary and tertiary phosphanes from PH_3



react with the phosphorus-centered anion $[PH_2]^-$, while less electrophilic alkenes were left un-reacted.

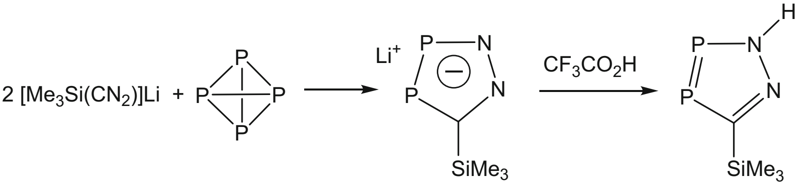
A similar method was followed for the preparation of primary alkylphosphanes [39].

Since the pioneer work of Rauhut et al. [40] and later by King et al. [41] described the nucleophilic addition of phosphane, PH_3 and R_2PH, respectively, to the C-C double bond of acrylonitrile and $[Ph_mP(CH{=}CH_2)_n](m{=}1,2;\ n{=}2,1)$ respectively, in the presence of bases, further contribution to this field came from Trofimov and co-workers [37] who foresee in the use of PH_3 as P-source replacing elemental phosphorus, a great advantage from the atom economy point of view, which is fully respected in the presence of phosphane.

Using as phosphorylating agent PH_3 produced *in situ* from the basic hydrolysis of red phosphorus, the hydrophosphination of weakly electrophilic double bonds of aryl- and heteroarylethenes was performed affording selectively secondary phosphanes previously unknown or difficult to prepare phosphane (Scheme 3.24).

As in the phosphorylation carried out with elemental phosphorus, strong basic conditions are required in this process as well, which is believed to proceed via a nucleophilic addition to the olefinic bond of the phosphorus-centered anion, PH_2^-, which can be generated only by action of a strong base on PH_3.

Complete and selective formation of tertiary aryl(heteroaryl) phosphanes was accomplished at atmospheric pressure of PH_3 in KOH/DMSO heating in the range 45–120 °C and with additional introduction of the alkene (styrenes or vinylpyridines) in the reaction mixture at the end of the process, see Scheme 3.23. Notwithstanding the reaction goes to completion in a selective way, working at



Scheme 3.25 Synthesis of 1,2,3,4-diazadiphosphole ring from P_4

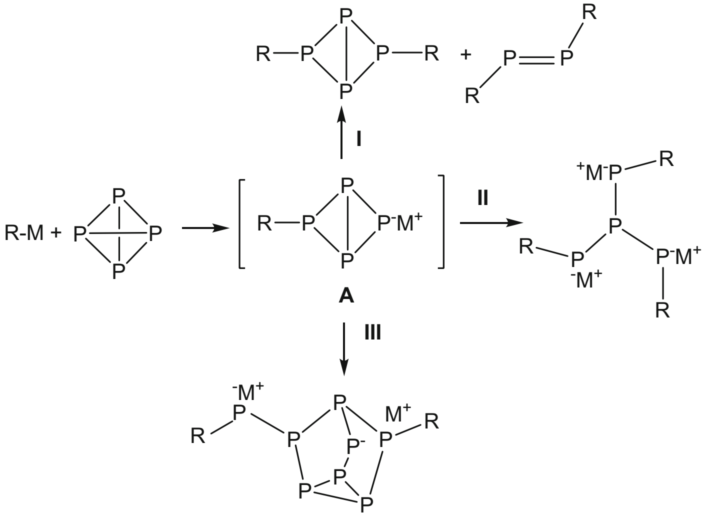
atmospheric pressure of PH_3 constitutes a great advantage, considering the flammability and toxicity of this gas. Previously, PH_3 was added to styrene in the presence of a radical initiator under elevated phosphane pressure [42] but a mixture of primary, secondary or tertiary phosphanes difficult to separate was obtained.

The first example of a suitable anionic carbon centered-nucleophile used to activate directly P_4 was published by Rauhut et al. in 1963. He reacted organo-alkali reagents with white phosphorus obtaining a complex mixture of polyphosphides and upon hydrolysis primary and secondary phosphanes were isolated in moderate yield [43]. Afterwards, the nucleophilic functionalization of P_4 has been widely explored using milder conditions and softer reagents with the aim to direct it selectively to one main product.

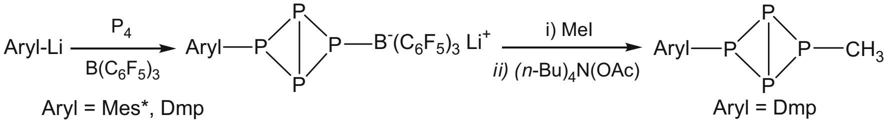
Mathey and co-workers studied the reaction of lithium(trimethylsilyl) diazomethanide with white phosphorus, considering that the first reagent can be seen as the synthetic equivalent of a $[RC]^-$ fragment and in principle could provide a direct way to get $[RCP_4]^-$ thanks to the driving force of the reaction due to the aromatic stabilization of the final five-membered ring. The reaction proceeded cleanly as a formal [3 + 2] cycloaddition between a P_2 unit, [P≡P], extruded from P_4, and the diazomethyl anion, giving as a sole product the previously unknown aromatic 1,2,3,4-diazadiphospholide anion, shown in Scheme 3.25. The protonation of the latter by trifluoroacetic acid at low temperature afforded the stable 2*H*-1,2,3,4-di-azadiphosphole. This work [44] showed for the first time that white phosphorus can be a useful starting material for the direct synthesis of new aromatic polyphosphorus compounds.

In the last decades, several efforts have been carried out to accomplish the direct synthesis of organophosphorus compounds by nucleophilic addition of an organic reagent to P_4 bypassing the use of a metal and are summarized in Scheme 3.26. The common intermediate in all these reactions is believed to be the highly reactive bicyclo[1.1.0]tetraphosphabutane anion **A** formed upon a P-P bond cleavage of the P_4 tetrahedron, which is susceptible of degradation and re-aggregation forming a complex mixture of products.

Fluck et al. found out that P_4 in the presence of Mes*Li (Mes* = 2,4,6-$C_6H_2{}^t$ Bu_3) is opened to give a di-substituted butterfly compound in low yield (Scheme 3.26, route I) and a diphosphene [45]. Lerner et al. [46] by using a threefold excess of the less bulky MesLi (Mes = 2,4,6-$C_6H_2Me_3$) obtained a complete degradation of the P_4 tetrahedron and isolated a trianionic tetraphosphide (Scheme 3.26, route II). Direct reaction of P_4 with hypersilyl complex $[(Me_3Si)_3Si]$



Scheme 3.26 Nucleophilic addition of carbon-centered anion to P_4



Scheme 3.27 Arylation and subsequent alkylation of white phosphorus

(K(18-crown-6)] gave a Zintl-type P_7-cage compound [47], probably arising from dimerization of anion **A** (Scheme 3.26, route III). A few years ago, Tamm and co-workers studied the behavior of P_4 in the presence of a frustrated carbene-borane Lewis pair. In this condition, the selective heterolytic cleavage of one of the six P-P bonds of the P_4 tetrahedron took place, and the resulting highly reactive P_4 butterfly was stabilized by formation of a P-C and P-B bond respectively at the two opposite site of the butterfly cage [48]. Recently, Lammertsma and his group [49] accomplished the activation and functionalization of P_4 with a bulky nucleophile as ArylLi [Aryl = Dmp (2,6-dimesitylphenyl), Mes*] in the presence of a Lewis acid as $B(C_6F_5)_3$, mimicking a frustrated Lewis pairs approach, similar to Tamm's group. Methylation of the P_4 butterfly derivative as shown in Scheme 3.27 favored the elimination of Lewis acid $B(C_6F_5)_3$ and the formation of a new P-C bond in quantitative yield.

This represents a new method enabling the formation of organophosphorus compounds starting directly from white phosphorus, forming two P-C bonds in a controlled stepwise fashion and avoiding chlorinated reagents.

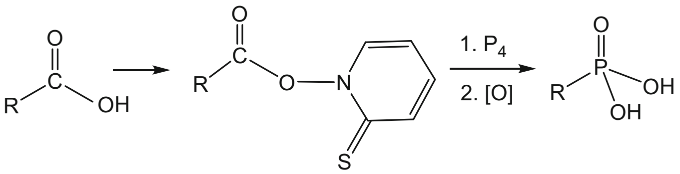
3.5 P-C Bond Formation Mediated by Radicals

White phosphorus can be an efficient radical trap and can react with carbon-centered radicals in solution under mild conditions. The work developed by Barton et al. [50] shows the great ability of P_4 to react in a long radical chain reaction with carbon radicals generated from carboxylic acids via photolysis of the corresponding Barton PTOC ester. Subsequent oxidation with aqueous hydrogen peroxide affords the phosphonic acid derivatives in good yields. In this way, a wide range of carboxylic acids, including those derived from natural products, as oleic and linoleic acid, can be converted into the corresponding phosphonic acids, see Scheme 3.28. Moreover, a clear mechanistic picture for the addition of carbon radicals to P_4 has been presented, where the chain reaction is initiated by the reaction of dioxygen with P_4.

Subsequent to the work of Barton, it has been shown by Sato et al. that P-P bonds other than those in P_4 may serve as a trap for organic radicals; for instance Ar · radical, coming from ArX, can react with the diphosphane $Ph_2P\text{-}PPh_2$ accomplishing in this way a radical phosphination of organic halides [51].

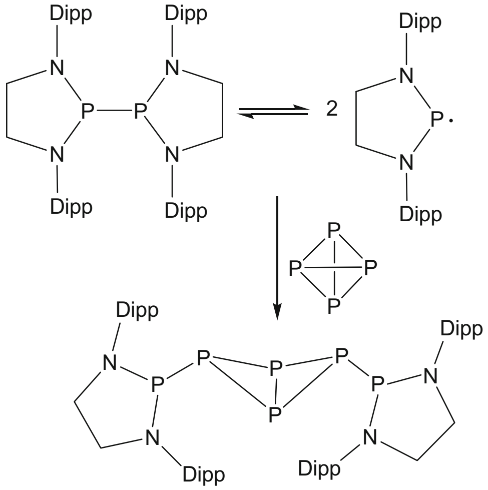
Lappert prepared the diphosphane $[P\{N\text{-}(Me_3Si)_2\}(NPr^i{}_2)]_2$ which reversibly dissociates in solution to phosphinyl radical and when refluxed for short time in toluene in the presence of white phosphorus, generated as main product a tetraphosphabicyclobutane derivative, present in solution as a 1:1 mixture of *meso*- and *rac*-diastereoisomers [52]. Similarly, the diphosphane $[(\{Me_3Si\}_2CH)_2P]_2$ is known in the literature as a molecular “jack in the box” radical [53] since it is endowed with potential energy stored in the central P-P bond, due to the strained rotation of the bulky peripheral trimethylsilyl ligands. As a result, the P-P bond in the diphosphane can easily undergo homolysis forming two equivalents of the phosphinyl radical. The latter can react at room temperature with half equivalent of P_4, causing the cleavage of one P-P bond of the tetrahedron, and the resulting tetraphosphabicyclobutane is stabilized by the highly hindered substituents on the heterocycle. The structure, shown in Scheme 3.29, was confirmed by X-ray crystallography [54] with the molecule assuming a *trans,trans* configuration to minimize steric interactions.

The contribution to this chemistry from Cummins and co-workers is based on the discovery that the three-coordinate titanium(III) complex $Ti(N[^tBu]Ar)_3$ ($Ar = 3,5\text{-}C_6H_3Me_2$) is a powerful abstractor of halogen-atoms, as chloride, bromide, iodide, from various donor molecules at room temperature in aprotic organic media

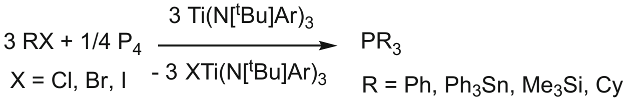


Scheme 3.28 Radical synthesis of phosphonic acids from P_4

Scheme 3.29 Reactivity of P_4 with a phosphinyl radical



Dipp = 2,6-diisopropylphenyl



$$3\ RX + 1/4\ P_4 \xrightarrow[-\ 3\ XTi(N[^tBu]Ar)_3]{3\ Ti(N[^tBu]Ar)_3} PR_3$$

X = Cl, Br, I R = Ph, Ph_3Sn, Me_3Si, Cy

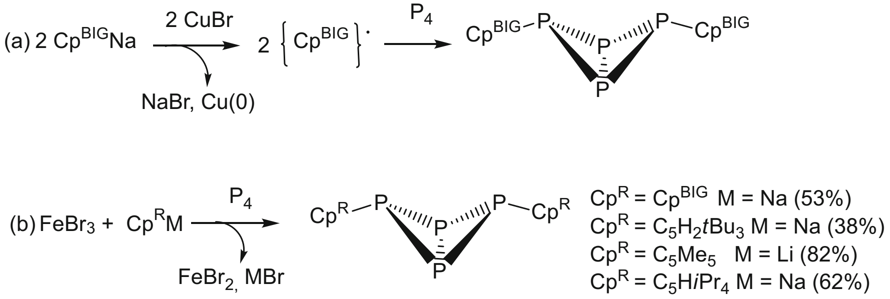
Scheme 3.30 Radical synthesis of tertiary phosphanes from P_4 catalysed by Ti(III) complex

[55]. On these basis, Cummins developed a high yield synthesis of phosphanes, PR_3, starting from P_4 and an alkyl or aryl halide in the presence of $Ti(N[^tBu]Ar)_3$ as promoter [56], according to the equation shown in Scheme 3.30. In terms of recycling, the titanium by-product $XTi(N[^tBu]Ar)_3$ (X = Cl, Br, I) can be reduced by Na/Hg amalgam back to the active species $Ti(N[^tBu]Ar)_3$.

This represents a powerful and clean method to prepare a wide array of phosphane directly from P_4; based on the ability of P-P bonds to work as efficient radical traps, the next step will be trying to make this process catalytic.

A recent paper by Scheer et al. [57] shows a new methodology involving the intermediary formation of Cp^R radicals that selectively open one P-P bond of the P_4 tetrahedron. The process is mediated by a transition metal which is in the end eliminated as a salt by-product, and the main product is a carbon-substituted bicyclic P_4 butterfly compound as shown in Scheme 3.31. Two different methods have been used: the first one (a) is based on the addition of a stoichiometric amount of Cu(I) salt, which readily reduces to Cu metal allowing the oxidation of $(Cp^{BIG})^-$ to Cp^{BIG} radical [$Cp^{BIG} = C_5(4\text{-}^nBuC_6H_4)_5$], and the second (b) can activate P_4 yielding a modest amount of $(Cp^{BIG})_2P_4$.

Any attempt to extend the reaction to smaller Cp^R radicals failed, probably the latter being less hindered and more reactive than Cp^{BIG}, which made a radical

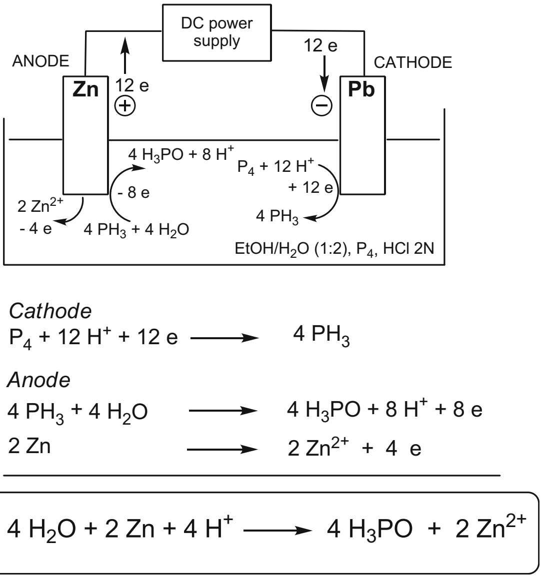


Scheme 3.31 Functionalization of P_4 mediated by a metal radical

decomposition faster than the reaction with P_4 so that the formation of the desired P_4 butterfly does not proceed. It is known [58] that $[\{Cp'''Fe(\mu\text{-}Br)\}_2]$ [Cp''' = 1,3,5-CpH^tBu_3) reacts with one equivalent of P_4 leading to the formation of $[\{Cp'''Fe\}_2(\mu,\eta^{4:4}\text{–}P_4)]$ as well as to the carbon-substituted butterfly compound $(Cp''')_2P_4$ together with a small amount of $FeBr_2$, meaning in the process an oxo-reduction takes place bringing initial Fe(III) to Fe(II) and $[Cp^R]^-$ to $[Cp^R]^{\cdot}$ radical. On this basis, Scheer et al. carried out the straightforward reaction of $FeBr_3$ and Cp^RM (M = Na or Li) in the presence of white phosphorus. The desired, symmetrically substituted, P_4-butterfly shown in Scheme 3.31, was isolated with good yield. Interestingly, while the "copper" route is feasible only in the presence of Cp^{BIG}, the "iron" route has a wider applicability.

3.6 Electrochemical Activation of P_4: An Alternative Way to Access Organophosphorus Compounds

Electrochemistry can be considered as a "green" technique since it uses electrons as reagents and generally the electrochemical processes proceed under mild conditions where the rate and selectivity of the process can be easily adjusted by tuning both the working electrode potential and electric current. Therefore, a chemical process can be directed in a very clean way, obtaining high purity products and avoiding the formation of waste. For all these reasons, electrochemical methods become attractive for synthesizing pharmaceuticals and fine chemicals. An outstanding contribution to the development of electrochemical synthesis of inorganic and organic phosphorus compounds starting directly from white phosphorus comes from the Arbuzov Institute of the Russian Academy of Sciences in Kazan [59]. It was shown that depending on the experimental conditions, as solvent (water or alcohol), electrode material (graphite, platinum, mercury) temperature and pH, the electrochemical process may be modulated to give predominantly the desired phosphorus derivatives. It is believed [60] that the first step is the reduction of P_4 at the cathode electrode with formation of a highly reactive phosphido radical anion



$$P_4 + 12\,H^+ + 12\,e \longrightarrow 4\,PH_3$$

$$4\,PH_3 + 4\,H_2O \longrightarrow 4\,H_3PO + 8\,H^+ + 8\,e$$

$$2\,Zn \longrightarrow 2\,Zn^{2+} + 4\,e$$

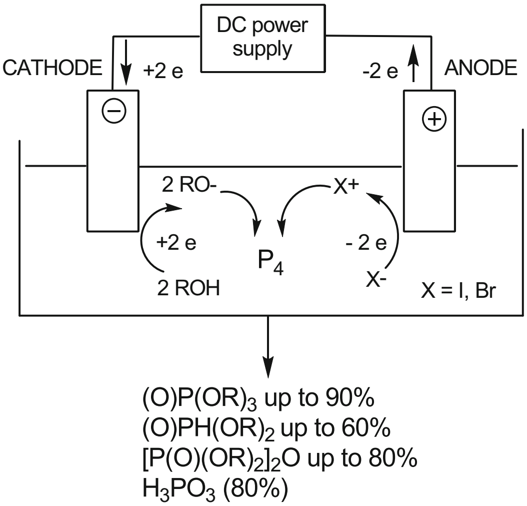
$$\boxed{P_4 + 4\,H_2O + 2\,Zn + 4\,H^+ \longrightarrow 4\,H_3PO + 2\,Zn^{2+}}$$

Schema 3.32 Electrochemical generation of H_3PO in acidic ethanol/water solution from white phosphorus

$[P_4]^-$. Soon after, a fast protonation of this species takes place being the process carried out in protic media, resulting in cleavage of P-P bonds and formation of P-H bonds. Several studies have been carried out on the electrochemical hydrogenation of white phosphorus, which can be considered as the suitable method for *in situ* generation of highly pure PH_3 directly from P_4. Gaseous PH_3, meanwhile is generated, can be collected in another reaction vessel in presence of the appropriate organic reagent to synthesize the desired organo-phosphorus derivative [60]. The yields of PH_3 vary in the range 60–83 % at the lead cathode in an aqueous solution of NaOH in a range of temperature from 70 to 100 °C. In a classical chemical process, operating without electrochemistry, boiling a basic emulsion of P_4 ends up with a mixture of products: hypophosphite (50 %), phosphite (25 %) and PH_3 (25 %) together with hydrogen evolution. Noteworthy, the electrochemical process transforming selectively P_4 into hypophosphorus acid has been studied [61] analyzing carefully the reaction mixture at equal interval of time by ^{31}P NMR spectroscopy. This allowed to intercept for the first time, a key intermediate, H_3PO, which is formed at the zinc anode as an oxidation product of PH_3 released at the lead cathode, as shown in Scheme 3.32.

The generation in solution of H_3PO was completely unexpected, being known as highly labile species that previously was generated only under extreme conditions and characterized in argon matrices [61]. A detailed study evidenced that the formation of this species is related to electrode-surface processes and it is observed only in the presence of a zinc electrode as anode and operating in acidic ethanol/water mixture.

Scheme 3.33 Electrochemical process for the transformation of P_4 into phosphates and phosphorous oxyacids



$$P_4 + 12\ ROH + 4\ H_2O \xrightarrow{\pm 20\ e-} 4\ (RO)_3PO + 10\ H_2$$

Scheme 3.34 Electrochemical synthesis of organophosphates

$$P_4 + 12\ R_2NH + 4\ ROH \xrightarrow{\pm 20\ e-} 4\ (NR_2)_3PO + 10\ H_2$$

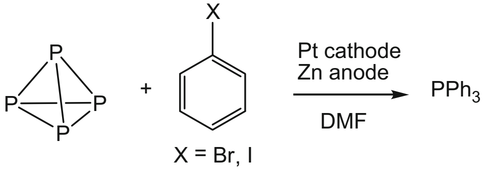
Scheme 3.35 Electrochemical synthesis of triamidophosphates

When the electrochemical reduction of white phosphorus is performed in the presence of alcohols and ammonium salts used as supporting electrolyte, in principle a mixture of esters of different phosphorus oxyacids may be produced. The accepted mechanism is based on the reduction of the alcohol at the cathode with formation of the alkoxide anion, RO^-, which does a nucleophilic attack on P_4; meanwhile at the anode, the oxidation of the halide coming from the supporting electrolyte takes place, generating an electrophilic reagent. The joint action of the alkoxy anion and the electrophile on P_4 results in various derivatives as shown in Scheme 3.33, depending on the nature of the alcohol, on the ratio water/P_4 and on the temperature used to carry out the process,

Under specific conditions, trialkyl phosphates were prepared in a quantitative yield; Scheme 3.34 shows the equation for the overall process which looks like highly clean, only gaseous hydrogen is formed as by-product [59].

Electrolysis of an emulsion of white phosphorus in the presence of an alcohol and an amine generates the corresponding triamidophosphates, as shown in Scheme 3.35 [60].

Interestingly, the electrolysis of an emulsion of P_4 and an aromatic halide in dimethyl formamide leads to triphenylphosphane without using any metal catalyst



Scheme 3.36 Electrochemical synthesis of triphenylphosphane directly from white phosphorus

as shown in Scheme 3.36. The process patented by Budnikova et al. works under mild conditions [62] and results in the selective formation of triphenylphosphane with up to 82 % yield relative to P_4.

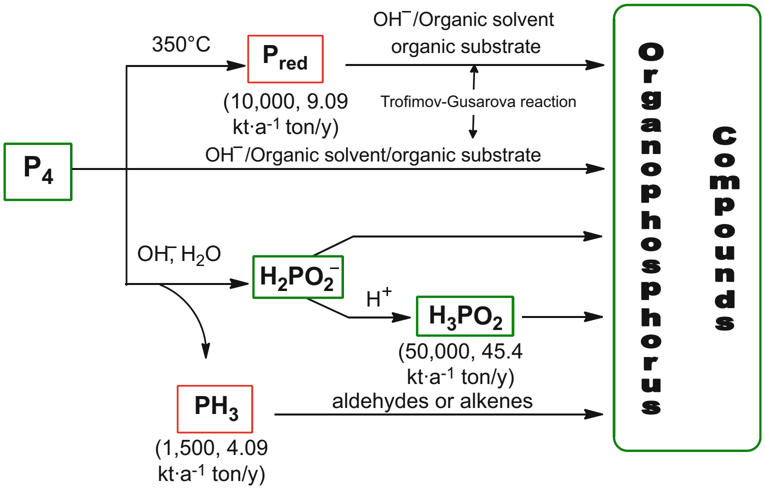
To shed light on the reaction mechanism, it was investigated the reactivity of organozinc species, as diphenylzinc, in the presence of white phosphorus outside the electrochemical cell. In the final reaction mixture, only phenylphosphane and diphenyl phosphane were identified, demonstrating that via the transition-metal mediated synthesis the process is not selective and stops at the product with maximum two phosphorus-carbon bonds [63]. On the other hand, under electrochemical conditions using zinc as sacrificial anode, the interactions of electrogenerated organozinc reagents with P_4 causes the opening of all P-P bonds of the tetrahedron, resulting in the selective formation of organophosphorus compounds with three phosphorus-carbon bonds.

In conclusion, the interest in the electrosynthesis of organophosphorus compounds from P_4 arises from a series of advantages compared to common chemical methods: (a) mild conditions required by the process (ambient pressure and temperature); (b) atom economy (the supporting electrolyte can be recycled at the end of the process); (c) high environmentally safety, avoiding the use of chlorinated reagents; (d) the electrosynthesis can be highly selective, affording high purity products.

3.7 Hypophosphorous Pathway: From H_3PO_2 and Its Alkali Salts to Organophosphorus Compounds

In the way to avoid PCl_3 as P-source for the preparation of organophosphorus compounds, many efforts have been devoted either to functionalize directly elemental phosphorus, both allotropes, white and red, or to transform elemental phosphorus into a variety of different inorganic phosphorus compounds as phosphane (PH_3) [64], hypophosphorous acid (H_3PO_2) and its alkali salts [65] as shown in Scheme 3.37.

However, white and red phosphorus usually uses hard conditions such as the superbasic system: aqueous solution KOH (86 %)/DMSO or HMPA/organic substrate (Trofimov-Gusarova reaction), and PH_3 is a highly toxic and pyrophoric gas. Nevertheless, as stated in the beginning of this chapter, all of them, together with the highly reactive and hazardous PCl_3, are currently the basis of organophosphorus manufacturing [66].

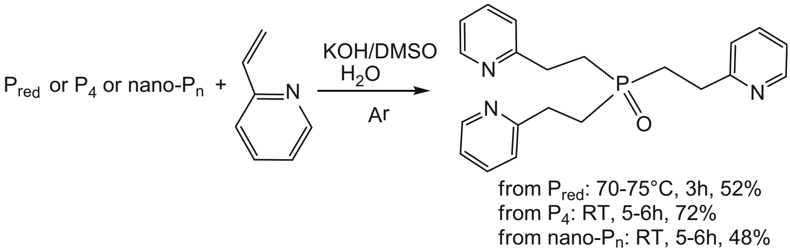


Scheme 3.37 Access to organophosphorus compounds avoiding the use of chlorine

The use of hypophosphorus acid and its derivatives in the synthesis of organophosphorus compounds is nowadays becoming a widespread methodology, due to its low toxicity and low environmental impact in comparison with PCl_3.

3.7.1 Phosphorylation with Elemental Phosphorus

While white phosphorus is formed by single tetrahedral molecules endowed with a certain tension due to ring strain, which makes it highly unstable and reactive, red phosphorus has a polymeric structure, where one of the P-P bond of the P_4 tetrahedron is broken and one additional bond is formed with a neighboring tetrahedron to form a chain-like structure. This polymeric network of P-atoms reduces strain and reactivity in comparison to the white allotrope and gives greater stability. The activation of red phosphorus requires therefore harsher treatments. According to the procedure developed by Trofimov and Gusarova in the late 1980s, using "superbasic" conditions, as aqueous KOH/DMSO under heating or microwave irradiation, directly convert a mixture of red phosphorus and unsaturated organic compounds, as alkenes and alkynes, into primary, secondary and tertiary phosphanes and phosphane oxides. A similar procedure was applied by the same authors to carry out the direct phosphorylation of alkenes and alkynes with P_4, but using milder conditions, *i.e.* shorter reaction time and heating at lower temperature. From the mechanistic viewpoint, it is believed that in such heterogeneous highly basic media, KOH/DMSO (or HMPA), KOH/organic solvent/phase-transfer catalyst as shown in Scheme 3.38, highly active *P*-centered nucleophiles



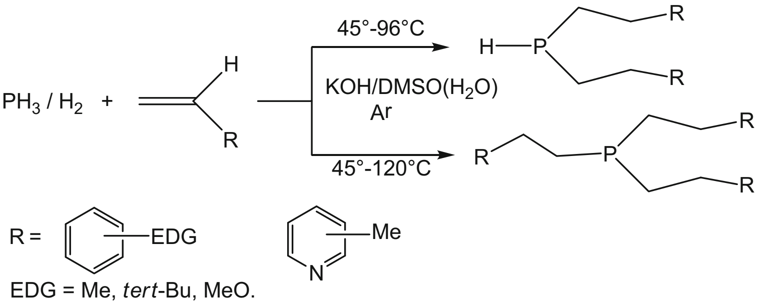
Scheme 3.38 Phosphorylation of elemental phosphorus using "superbasics" conditions (Trofimov-Gurasova reaction)

(as polyphosphides and polyphosphinites) are formed and prone to interact with the suitable electrophile (styrenes, vinylpyridines, acetylenes and similar) [67].

A further development has been lately introduced by Trofimov et al. which consists in the preparation of nanocomposites of red phosphorus, nano-P$_n$, with carbon, graphite or organophosphorus inclusions, obtained by radiation-induced polymerization (^{60}Co γ-radiation) of P_4 at room temperature [68]. Nano-P$_n$ contain mainly phosphorus (80 %), the rest is carbon, oxygen and hydrogen and consist of nanoparticles having diameter in the range of 30–50 nm. Interestingly, nano-P$_n$ have shown higher reactivity in the phosphorylation of styrene and its derivatives compared to common red phosphorus, see Scheme 3.38.

3.7.2 Phosphorylation with PH_3

The approach based on elemental phosphorus, white or red, does not solve the problem of phosphorus atom economy, since not all P-atoms of the reagent are found in the final product, but some are lost in the process usually as unidentified by-products. In this respect, PH_3 and MH_2PO_2 (M = H, metal, alkyl) have the potential to incorporate all the phosphorus content into an organic product. Alkali hypophosphites (and consequently hypophosphorus acid) and PH_3 come from the alkaline hydrolysis of white phosphorus, which is still nowadays a process not fully understood and its improvement would be desirable. PH_3 is a highly toxic and pyrophoric gas requiring very careful handling, its use is therefore strongly limited to small amounts in the electronic industry and as a starting material for the synthesis of trialkylphosphanes, R_3P, and related compounds. Since the pioneer work of Rauhut et al. [40] and later by King et al. [41] who described the nucleophilic addition of PH_3 to the C-C double bond of alkenes bearing strong electron-withdrawing substituents, in the presence of bases, further developments have been studied by Trofimov and co-workers [37]. Using as phosphorylating agent the mixture PH_3/H_2 coming from the basic hydrolysis of red phosphorus, they performed the hydrophosphination of weakly electrophilic double bonds of aryl- and heteroarylethene affording previously unknown or difficult to prepare secondary or tertiary phosphanes as shown in Scheme 3.39.



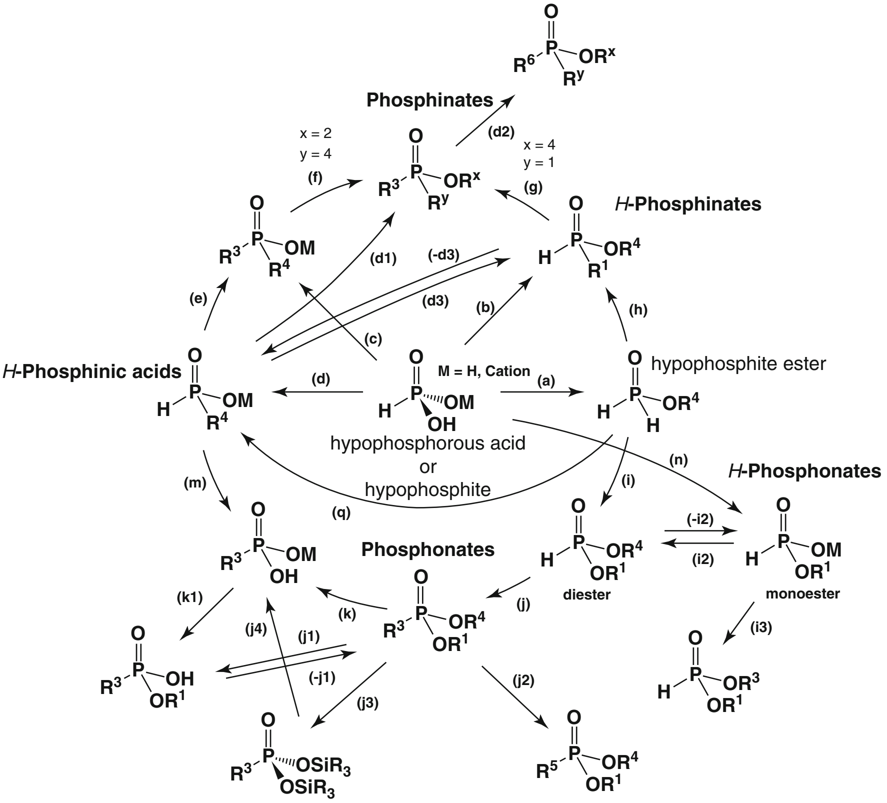
Scheme 3.39 Phosphorilation of PH_3 using alkenes under harsh conditions

As in the phosphorylation with elemental phosphorus, strong basic conditions have been used, notwithstanding the reaction goes to completion in a selective way, working at atmospheric pressure of PH_3, which constitutes a great advantage. Previously, PH_3 was added to styrene in the presence of a radical initiator under elevated phosphane pressure [42] to give a mixture of primary, secondary or tertiary phosphanes. In the process discovered by Trofimov, the pathway is not radical but entails a nucleophilic addition of PH_2^-, generated from PH_3 under strong basic conditions, to the olefinic bond in the presence of water.

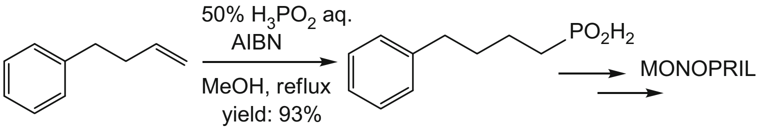
3.7.3 Organophosphorus Compounds from H_3PO_2 or Its Salts

Owing to the problem of toxicity and handling related to PH_3, only MH_2PO_2 and/or their derivatives represent a real alternative to PCl_3. The higher homologue, H_3PO_3, currently produced from the hydrolysis/alcoholysis of PCl_3, is much less reactive than H_3PO_2, so it is not a valuable option. Hypophosphorous acid, which can be prepared by boiling white phosphorus with an inorganic base and subsequent acidification, represents a much more environmentally benign phosphorous source than PCl_3, coming from the high temperature reaction of white phosphorus and chlorine. Hypophosphorous acid and its salts, being more easily handled and less toxic than other P-sources (P_4, red P, PCl_3, PH_3), constitute an industrial commodity, inexpensive and highly versatile. The key challenge is to find out the shortest pathway leading to the desired organophosphorus compound from the hypophosphorous acid or its derivatives, in particular *H*-phosphinate, *H*-phosphinic acid, *H*-phosphonate diester, *H*-phosphonate monoester, phosphonate, phosphinate and hypophosphite esters have the great advantage to offer access to various functional groups, see Scheme 3.40.

Unexpectedly, hypophosphites have not received a great attention yet from the industry, one of the best examples is the production of the heart drug Monopril, in



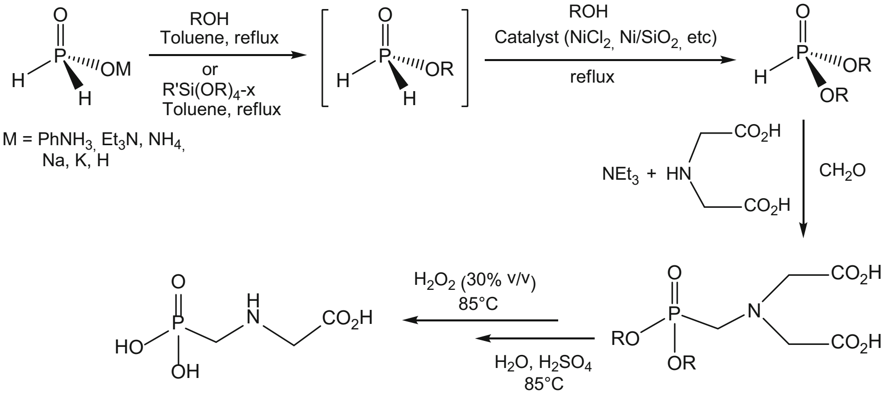
Scheme 3.40 Synthetic versatility of hypophosphorous acid its salts and their derivatives. (*a*) (*b*) [70, 83, 158], (*c*) [131–134], (*d*) (*e*) [69, 83, 131, 132, 135, 136, 144, 145, 147], (*e*) (*m*) [139, 147], (*f*) [69, 136], (*g*) [75–87], (*h*) (*i*) [65, 70, 83, 149], (*j*) [70, 88–112], (*k*) [70, 83, 109], (*m*) [83, 144, 145], (*d1*) (*d2*) [83, 146], (*d3*) [87, 147, 148, 158], (*−d3*) [149], (*n*) [83], (*q*) [158], (*i2*) [103], (*−i2*) (*i3*) [150], (*j1*) [83, 151], (*−j1*) [152–155], (*j2*) [113–137], (*j3*) [157], (*j4*) [155, 157], (*k1*) [155, 156]



Scheme 3.41 Radical addition of H_3PO_2 to a terminal double bond in the synthetic pathway to the drug Monopril

which the radical addition of H_3PO_2 to olefins, initiated by AIBN, is employed (Scheme 3.41) [69].

The other industrial process patented [70] and developed by Montchamp et al. is the synthesis of the herbicide Glyphosate, in which H_3PO_2 or its salts are converted



Scheme 3.42 Conversion of phosphinate to *H*-phosphonate and glyphosate

first to an alkyl phosphinate and then to an *H*-phosphonate diester, thus avoiding the use of PCl_3 as shown in Scheme 3.42.

The addition of H_3PO_2 to olefins under radical conditions was discovered by Williams and Hamilton [71] in 1955. Since then, improvements to the reaction were carried out by Nifant'ev, though the low solubility of H_3PO_2 and of its sodium salt in organic solvents, the need of high initiation temperature and large amounts of initiator, usually AIBN, make this reaction quite unfeasible.

In 2001, Montchamp [72] published that the radical addition of hypophosphorous derivatives to unsaturated hydrocarbons is feasible in mild conditions at room temperature by using a trialkylborane and air as the initiator. Another advantage of this methodology is its wide applicability with respect to the kind of alkene and phosphinate reagent. Another important discovery by the same group was the hydrophosphinylation of alkenes catalysed by palladium or nickel [73]. It was shown that in the presence of a suitable phosphane ligand, *i.e.* Xantphos, a low loading of palladium was enough to reach a complete conversion. An heterogenous catalyst, stable in aqueous environment, was prepared by supporting palladium on polystyrene and this allowed to carry out the reaction in water, which was advantageous since in this medium hypo acid and hypophosphite are perfectly soluble. On the other hand, the nickel-catalyzed hydrophosphinylation was less effective, since it gave only up to 70 % of conversion.

In the case of alkynes, the hydrophosphinylation in the presence of Et_3B worked well only for terminal ones, a nickel-catalysed reaction was developed to add alkyl phosphinates to internal alkynes [74]. Pd_2dba_3 together with a suitable phosphane ligand was used as a catalyst to accomplish a regioselective hydrophosphinylation of terminal alkynes to either (*E*)- or (*Z*)- alkenes. Both palladium- and nickel-catalyzed hydrophosphinylation proceed under microwave heating to deliver a high yield of the desired product in a few minutes.

In the last years, the most used precursors in the synthesis of organophosphorus compounds have been *H*-phosphinates [75–87], *H*-phosphonates [88–112], phosphonates [113–137] and *H*-phosphinic acids [138–149]. Although most of the precursors are still synthesized from chlorinated derivatives, some research groups, as Montchamp's [65, 83], are exploring new synthetic pathways based on hypophosphites and *H*-phosphinates. These synthetic procedures are working well at laboratory scale, therefore the challenge in the coming years will be to transfer the new synthetic routes based on hypophosphite to an industry level.

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