Synthesis of Carbon–Phosphorus Bonds
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Robert Engel
JaimeLee Iolani Cohen
Preface to the Second Edition

It has been nearly 17 years since Synthesis of Carbon–Phosphorus Bonds was written. In the interim, numerous significant advances have been made regarding approaches toward the syntheses of organophosphorus compounds. While these new approaches have not necessarily replaced the older, established methods, they provide a major supplement to them.

In spite of heavy activity in the study of organophosphorus chemistry, it remains relatively rare to find university courses taught on the topic of synthesis of organophosphorus compounds. This Second Edition retains a purpose embodied in the First Edition: to provide a working guide for the practicing chemist with a need to perform organophosphorus syntheses.

Several new sections have been added to this Second Edition, and the presentations of the established methods have been updated to emphasize the recent advances in their use. In addition to the survey of the approaches toward carbon–phosphorus bond formation, details of specific preparations are provided as guides for the performance of these reactions without detailed recourse to the original literature. In this way, this work is anticipated to be of particular value to the synthetic organic chemist who is skilled in the general art but not particularly experienced in organophosphorus chemistry.

In this edition, my former student and now colleague, JaimeLee Iolani Cohen, who continues her own interests in organophosphorus chemistry, joins me.

Robert Engel
JaimeLee Iolani Cohen
Preface to the First Edition

Interest in the synthesis of organophosphorus compounds was at one time relatively limited, being of concern chiefly to those involved in the preparation of materials of certain commercial interest (e.g., insecticides, flame retardants, and detergents). With this situation existing, it has been relatively rare to find university courses being taught on the topic of synthesis of these materials.

However, recent developments have made an understanding of organophosphorus compounds and their syntheses of significantly more general value. Not only have there been found applications for organophosphorus compounds in a wide range of commercial applications, but also these materials have become of great utility for the facilitation of other organic transformations. Yet, the university-trained organic chemist is provided with little guidance to the performance of organophosphorus chemical conversions or to the organophosphorus literature. It is in an attempt to provide direction to the organic chemist lacking specific training in organophosphorus chemistry that this book is presented.

A major portion of the effort of preparing this manuscript was performed while I was on sabbatical leave from Queens College at the Rohm and Haas Company in Spring House, Pennsylvania. I wish to thank Queens College for the time and Rohm and Haas Company for their hospitality, both of which were important for this work. In addition, I would dedicate this work to my children, Cheryl and Erik.

Robert Engel
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References
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Dr. Engel has worked in several areas of chemistry, including the investigation of reaction mechanisms and the study of paramagnetic effects in nuclear magnetic resonance (NMR) spectrometry, in addition to his studies of organophosphorus compounds, including their syntheses, reaction mechanisms, and use as metabolic regulators. Most recently, his efforts have been concentrated on studies of polyphosphonium and polyammonium salts and their application to the generation of antimicrobial surfaces.

Dr. Engel is a member of the American Chemical Society, the International Council on Main Group Chemistry (currently executive secretary), the New York Academy of Sciences, Sigma Xi, and the Royal Society of Chemistry. He has published over 120 articles and more than 60 meeting presentations.

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Dr. Cohen’s work has been concerned particularly with the syntheses and investigations of polycationic salts and their application
to biological systems. Dr. Cohen is a member of the American Chemical Society, Sigma Xi, and the International Council on Main Group Chemistry. She is the author of 13 publications and 21 meeting presentations. Her work continues to be directed toward new methods for the preparation of carbon–phosphorus bonds.
Abstract

The present effort is intended to provide an update of the earlier edition, bringing to the chemist in concise form advances in the approaches to C–P bond formation previously discussed, as well as several other aspects of C–P bond formation. These latter aspects include the generation of organophosphorus compounds from elemental phosphorus (of particular industrial interest for purposes of cost containment); advances in the preparation of phosphoranes, including the use of transient oxophosphoranes as intermediates in organophosphorus compound syntheses; and new approaches toward the preparation of compounds with aromatic and vinylic carbon–phosphorus bonds.

As with the prior edition, this work will be of use not only to the dedicated “phosphorus chemist” but also to the practicing chemist who only occasionally is involved with organophosphorus chemistry, using it as an aspect of other synthetic pursuits. To this end, it contains numerous experimental examples from the literature with added notes from the authors’ own experiences in utilizing these reactions. It is intended to be not only a source of critical and annotated references but also a working guide for the chemist in the laboratory.
chapter 1

Introduction

1.1 Recent advances in C–P bond formation

Interest in the preparation of organophosphorus compounds has continued to expand in recent years. This is a direct result of developing applications for phosphorus compounds in numerous synthetic procedures as well as an understanding of the role of the element in biological systems. The several “classical” efforts in regard to applications of organophosphorus compounds — the preparation of pesticides, agricultural chemicals, flame retardants, medicinal agents, and reagents for olefination reactions — continue to be highly active topics in organophosphorus chemistry.

However, other developments in applications and potential applications of carbon–phosphorus bonded materials have spurred an even wider interest in organophosphorus chemistry. Several of these areas of developmental activity are noted here.

Significant potential is promised for the performance of stereospecific syntheses through the use of chiral diphosphorus reagents associated with metals. Numerous reaction systems have been noted involving such species facilitating asymmetric induction. For example, BINAP systems (Figure 1.1) have been studied as catalysts for asymmetric carbon–carbon bond formation, and similarly, MiniPHOS (Figure 1.2) for asymmetric hydrogenation processes. Additional synthetic investigations should be conducted to press the advantages such species promise for facile production of chiral organic products, containing or not containing phosphorus themselves. Similarly, P-chiral monophosphorus species have demonstrated potential for stereospecific C–P bond formation in association with transition metal species.

In recent years, the potential for phosphorus-containing dendrimers and related materials to serve as templates for the
modification of surfaces has been explored and promises to provide access to designed nanostructures. An example of such species is the second-generation phosphorus dendrimer (Figure 1.3) with a C–P bond at the core.

Recent years have also seen the development of a variety of complexation reagents incorporating C–P bonds and their associated functionalities, such as phosphoryl linkages. For example, substituted calixarenes (Figure 1.4) have been developed for extraction of radio- nuclides, and phosphorus-derivatized cyclodextrins for stereospecific inclusion interactions.

With these developments of applications for organophosphorus compounds, more powerful synthetic approaches toward their syntheses have similarly been sought and found. In the following chapters, we revisit some of the older approaches toward C–P bond

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**Figure 1.1** BINAP complexed with Ru.

**Figure 1.2** MiniPHOS (R ≠ CH₃).

**Figure 1.3** Second-generation phosphorus dendrimer.
formation, noting recent advances and providing exemplary experimental procedures. In addition, we are expanding the range of reaction types considered for C–P bond generation. Some of these are new developments on old approaches that were not reviewed in the prior edition of this work. Others are fundamentally new approaches that allow facile preparation of organophosphorus compounds available previously only with significant difficulty.

Prior to considering synthetic approaches toward C–P bond formation, we review two areas related to the literature of organophosphorus chemistry that are of particular value to those chemists who do not focus primarily on phosphorus.

### 1.2 Nomenclature of C–P compounds

Quite often, we find nonsystematic nomenclature used in the literature dealing with organophosphorus compounds. This results in unnecessary confusion, as systematic nomenclature is easy to use and understand. Nomenclature based on the oxidation state of the phosphorus center eliminates the confusion and helps to promote understanding of the chemistry as well as to facilitate communication. Table 1.1 shows structures for tricoordinate and tetracoordinate phosphorus compounds related to oxyacids with their English general names. Also noted are the names for simple esters of the parent acids. They are organized based on oxidation state and the number of bonds of the carbon–phosphorus type.
At times, confusion arises in noting oxides of primary and secondary phosphines (Figure 1.5). These species participate in equilibria much as the phosphonous and phosphinous acids do and can be named as types of phosphonous and phosphinous acids.

The tetracoordinate phosphorus species related to the oxyacids may be considered to be pentavalent. (For nomenclature purposes we will consider the phosphoryl group, P=O, to be an ordinary double bond.) A variety of tetracoordinate phosphorus compounds that are also clearly tetravalent are common. With four carbon groups (alkyl, aryl, olefinic, or acetylenic) attached to phosphorus, the phosphorus bears a positive charge and these species are simple phosphonium salts (Figure 1.6A). When ligands are attached to phosphorus through atoms other than carbon, the term *quasiphosphonium ion* is generally applied (Figure 1.6B). These species exhibit certain chemical and physical characteristics quite similar to those of ordinary phosphonium cations but often also bear special reactivity. For example, the oxyphosphonium species involved as intermediates in the Michaelis–Arbuzov reaction are referred to as quasiphosphonium species.

Pentacoordinate phosphorus compounds are generally referred to as *phosphoranes* (Figure 1.7) or *oxyphosphoranes* depending on the

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**Table 1.1 Nomenclature of phosphorus compounds.**

<table>
<thead>
<tr>
<th>Coordination Number</th>
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<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>P=O</td>
<td>O=P(OH)</td>
<td>O=P(OH)R</td>
<td>O=PR'</td>
</tr>
<tr>
<td></td>
<td>dialkylphosphinous acid</td>
<td>alkylphosphorous acid</td>
<td>alkylphosphonic acid</td>
<td>tertiary phosphine</td>
</tr>
<tr>
<td></td>
<td>O=P(OR)</td>
<td>O=P(OR)</td>
<td>O=P(OR)</td>
<td>O=P(OR)</td>
</tr>
<tr>
<td></td>
<td>dialkylphosphinic acid</td>
<td>alkylphosphonous acid</td>
<td>alkylphosphonite</td>
<td>tertiary phosphine oxide</td>
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<tr>
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<td>dialkylphosphite</td>
<td>dialkylphosphine</td>
<td>dialkylphosphine</td>
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<td>dialkylphosphinate</td>
<td>dialkylphosphine</td>
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absence or presence of oxygen linking directly to the phosphorus. Wittig reagents, while generally involving coordination of phosphorus to only four ligands, are also often referred to as phosphorananes.

1.3 Information sources for C–P compounds

This section is organized as an annotated listing of compendia for data relating to techniques used in organophosphorus syntheses, characteristics of organophosphorus compounds, and mechanisms of reactions of organophosphorus compounds. While not exhaustive, these references provide working chemists with additional sources of data useful for the performance of their efforts with organophosphorus compounds. (We will be excused if we begin this list with our own review works in this area.)


Methoden der Organischen Chemie, Vol. 12 (Parts 1 and 2), Sasse, K., Ed., Georg Thieme Verlag, Stuttgart, Germany, 1963; continued in Methoden der Organischen Chemie — Supplement, Vols. E1 and E2, Regitz, M., Ed., Georg Thieme Verlag, Stuttgart, 1982 — This major work is particularly concerned with the methods of syntheses of organophosphorus compounds and derivatives of phosphorus oxyacids. The work is organized according to

![Figure 1.7 Pentaphenylphosphorane](image-url)
structural type and provides extensive detailed preparations for numerous representative compounds (in German).


chapter 2

Synthesis of organophosphorus compounds from elemental phosphorus

2.1 Introduction

Using elemental phosphorus to prepare compounds containing the carbon–phosphorus bond is an approach with both advantages and drawbacks. The advantages relate to availability of the elemental material; elemental phosphorus is readily available in a condition of high purity and at a relatively low cost. The disadvantages of using the most reactive form of elemental phosphorus, “white phosphorus,” relate first to its high reactivity toward oxygen; it ignites in ordinary air at temperatures above 34°C. Other forms of elemental phosphorus are less reactive toward oxygen but are correspondingly less reactive in desired processes as well. Further, when elemental phosphorus is used to prepare organophosphorus compounds, fundamental difficulties of several types arise.

In this chapter, we first review the nature of the several forms of elemental phosphorus and then proceed to consider their uses for specific types of syntheses of compounds containing the carbon–phosphorus bond. Prior reviews have also been concerned with these topics.\textsuperscript{1,2} Our purpose here is to update these presentations and provide fundamentals for the practicing chemist venturing into the use of elemental phosphorus. We limit this discussion to the more-or-less direct syntheses of organophosphorus compounds from elemental phosphorus. We will consider reactions that generate monophosphorus species without C–P bonds as critical intermediates, pro-
vided that these intermediates may be converted to organophosphorus compounds in a “one-pot” process. We will not review processes in which elemental phosphorus is initially converted to a species that must first be isolated and purified prior to use in C–P bond introduction.

2.2 Availability of elemental phosphorus

2.2.1 White phosphorus

Early investigations of this fundamental form of the element determined that (in the vapor phase) it is composed of tetraatomic units ($P_4$), with the phosphorus atoms held in a tetrahedral array containing six equivalent phosphorus–phosphorus bonds (Figure 2.1). Calculations indicating that the unshared electron pairs on each phosphorus atom are held in $3s$ orbitals led to an understanding that the bonding in this molecule is much akin to that of carbon atoms in cyclopropane rings. Bonds within the tetrahedron are relatively weak, owing to poor orbital interactions, and are cleaved with relative ease.

The term “white” is derived from its appearance, which is actually a very pale yellow. Generally stored under water, in which it has negligible solubility and with which it is inert, this form of elemental phosphorus possesses a waxy surface and has a relatively low melting point (44.1°C) with a specific gravity of 1.82. As noted, although it is inert toward water, this material is extremely reactive toward oxygen, igniting in ordinary air at 34°C. This characteristic commonly produces difficulties in handling the material in the open atmosphere. Transfer and weighing of the material often pose problems. (One approach to alleviating some of this difficulty — which is not necessarily recommended by the authors — involves storing the material under acetone, which will evaporate rapidly and cool the white phosphorus during transfer.) Toxicological characteristics and handling

![Figure 2.1 Structure of the tetraatomic phosphorus molecule.](image)
procedures have been summarized. Analysis for elemental phosphorus by chromatographic means has been described.

The existence of three equivalent bonds to each of the phosphorus atoms, which must be broken in the formation of mono-phosphorus organophosphorus compounds, might appear to be a problem at first; all must be broken as new bonds are being generated to phosphorus. However, the fundamental approaches toward the use of white phosphorus accomplish this necessary action with relatively few extraneous reaction processes.

2.2.2 Red phosphorus

Upon heating to 400˚C, white phosphorus is converted to red phosphorus, a material somewhat less reactive with oxygen and capable of being used with fewer difficulties. In this treatment, a portion of the P–P bonds within the tetrahedra are broken, and new P–P bonds linking (former) tetrahedral units are generated, yielding chains of phosphorus units (Figure 2.2). Although the reactivity of red phosphorus is decreased from that of white phosphorus, it remains useful in certain synthetic processes.

2.2.3 Black phosphorus

Black phosphorus may be either amorphous or crystalline. It exhibits quite low reactivity, both with oxygen and other reagents, compared to white or red phosphorus, and is stable in air. Because it has a puckered shape, the phosphorus remains tricoordinated in black phosphorus and crystallizes in sheets in a way similar to the behavior of graphite. Black phosphorus is generated from white phosphorus either by heating under pressure or in the presence of mercury. It is of relatively little value for the synthesis of organophosphorus compounds.

\[ \text{Figure 2.2 Linked structure found in red phosphorus.} \]
2.2.4 General reactivity

Although black phosphorus is generally inert, red phosphorus and particularly white phosphorus are capable of undergoing reactions to generate organophosphorus compounds. Several different sets of conditions may be used to form C–P bonds from elemental phosphorus. These will be discussed in the following sections.

2.3 Attack on elemental phosphorus by nucleophiles

Elemental phosphorus in white or red forms is subject to attack by a variety of nucleophilic reagents. Aqueous bases provide one of the most useful reagent systems for organophosphorus syntheses, although other nucleophiles can also be used for specific synthetic processes.

Both white phosphorus and red phosphorus are attacked by a hydroxide ion to cleave the P–P bonds of individual units. The exact nature of the products generated (and the mechanism by which they are formed) is dependent on the reaction conditions, particularly the relative amounts of base and water compared to the P\textsubscript{4} used.\textsuperscript{10–13} Under any conditions, as a disproportionation reaction is involved, some portion of the starting phosphorus component is converted to one or another of the conjugate bases of phosphorus oxyacids. Of particular interest for the generation of C–P bonds is the ultimate formation of phosphine (PH\textsubscript{3}) (Figure 2.3), along with salts of H\textsubscript{3}PO\textsubscript{2}, via a stepwise (idealized) mechanism. It is this fundamental phosphine molecule that, under basic conditions, provides entry to the preparation of the organophosphorus species.

In situ reaction of the resultant phosphine, converted to its conjugate base, with several types of electrophiles has been investigated for organophosphorus syntheses. While early reports of the use of white phosphorus in basic solution with haloalkanes did not in themselves provide procedures for the efficient preparation of organophosphorus compounds, they pointed the way for the development of more useful techniques.

For example, direct treatment of red phosphorus with potassium hydroxide in a mixture of dioxane and water with a phase-transfer catalyst (benzyltriethylammonium chloride) allows direct reaction with primary haloalkanes to form the trialkylphosphine oxide in moderate (60–65%) yield.\textsuperscript{14,15} Allylic and benzylic halides are similarly reported to generate the corresponding tertiary phosphine oxides. When the reaction is performed with α,ω-dihalides, cyclic products are generated only with four- and five-carbon chains; the third site
on the tertiary phosphine oxide is occupied by a carbon substituent with unsaturation (Figure 2.4) at the end of the chain. Apparently, initial substitution is followed by elimination at the remaining reactive halide site of the \( \alpha,\omega \)-dihalide. However, even in the best of instances, yields are low in these reactions (<25%).

A similar approach, using toluene instead of dioxane and molten white phosphorus rather than a suspension of red phosphorus, has been described in two patents for the preparation of alkylphosphonic

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**Figure 2.3** Generation of phosphine from white phosphorus with aqueous base.

**Figure 2.4** Direct formation of an organophosphorus compound from red phosphorus under basic conditions.
acids, particularly methylphosphonic acid (Figure 2.5). Similarly, low yields of cyclic compounds (phosphine oxides with one acyclic ligand on phosphorus bearing an unsaturated linkage at the end) can be obtained from α,ω-dihalides of five or six carbon atoms using dioxane and a phase transfer catalyst.

Modifying the reaction medium to involve liquid ammonia with metallic lithium, t-butyl alcohol, and white phosphorus, to which is added the haloalkane, is reported to provide the primary alkylphosphine derived from the haloalkane. Similar results are reported for the reaction of red phosphorus with sodium acetylides and by treatment of red phosphorus with sodium metal in an organic medium followed by the addition of two equivalents of t-butyl alcohol and the haloalkane. The latter approach is noteworthy in that moderate yields (45%) are obtained for primary phosphines derived from secondary haloalkanes (Figure 2.6). Mixtures of tertiary phosphines bearing one or two acetylenic linkages are produced in low yield (~15%) by the reaction of lithium acetylides with white phosphorus in liquid ammonia followed by addition of a haloalkane.

Red phosphorus in an aqueous basic medium has also been used in the preparation of α-hydroxyphosphonites (Figure 2.7). Aromatic and α,β-unsaturated aldehydes added to the reaction mixture undergo nucleophilic attack by the intermediate phosphine species in a manner reminiscent of the approach of Pudovik and Arbuzov using partially esterified phosphites and aldehydes. Reaction of the red phosphorus suspension is noted to be enhanced by the use of ultrasonication; an excess of elemental phosphorus is used, and excess unreacted red phosphorus must be removed by filtration in the product isolation process.

The same report describes the generation of C–P bonds using red phosphorus under acidic conditions. The intermediate reactive species under these conditions is hypophosphorous acid. Using aqueous HI (57%) with dioxane, a 25% (purified) yield of benzylphosphonic acid could be isolated from the reaction involving benzaldehyde (Figure 2.8). Under the conditions of reaction, aqueous HI with...
red phosphorus, the \(\alpha\)-hydroxyphosphonite initially formed undergoes a reduction/oxidation to provide the benzylphosphonic acid.

Reasonable yields (55–85%) of dialkylphosphinic acids have been reported from a complex reaction system beginning with red phosphorus, iodoalkane, and elemental iodine.\(^{26}\) Presumably, the phosphorus trihalide is generated as an intermediate. The reaction is worked up with a nitrous acid system from aqueous HCl/NaNO\(_2\).

A Michael-type addition reaction of phosphine generated from red phosphorus in concentrated aqueous KOH solution has been noted to provide moderate isolable yields of pure organophosphorus products.\(^{27}\) For example, tris-(2-cyanoethyl)phosphine is produced in 45% isolable yield from acrylonitrile, and tris-(2-\(\gamma\)-pyridyl)ethyl)phosphine oxide is isolated in 40% yield from 4-vinylpyridine under these conditions. Excellent yields of the tertiary phosphine oxide, tris-(2-cyanoethyl)phosphine oxide, have been reported using white phosphorus in absolute ethanol with KOH at ice/salt-bath temperatures.\(^{28}\) A variety of solvent systems were examined for this reaction involving a Michael-type addition to acrylonitrile. Similarly, tris-(z-styryl)phosphine is produced from phenylacetylene under these conditions in 55% isolated yield. It is noteworthy that this last cited reaction involves stereospecific syn- addition of the phosphine to the alkyne.

Lower yields (~20%) of bis-(2-arylethyl)phosphinous acids have been generated in a similar system using KOH in polar aprotic

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**Figure 2.6** Formation of phosphide from red phosphorus and its use in forming an alkylphosphine.

**Figure 2.7** Use of red phosphorus for direct formation of a 1-hydroxyphosphonous acid.
solvents with arylalkenes. Starting with red phosphorus with KOH in dimethyl sulfoxide (DMSO) medium, tris-(2-arylethyl)phosphine oxides are reported to be formed upon heating with arylalkenes in 40–60% yield. Steric factors appear to play an important part in the degree of substitution on phosphorus, as ortho-substitution on the aromatic ring provides poorer yield of the tertiary phosphine oxide product. The same research group has reported that bis-(2-arylethyl)phosphines are formed when a small amount of water is present in the same fundamental heated DMSO reaction system. Clearly, the degree of substitution and the oxidation state at phosphorus are quite sensitive to changes in temperature of reaction and solvent mixture.

Formation of the conjugate base of phosphine under the conditions of aqueous dioxane and KOH with red phosphorus allows also for the formation of C–P bonds by attack of oxiranes. Under these conditions, mixtures of phosphines and phosphine oxides are formed. Using red phosphorus in liquid ammonia with sodium metal and t-butyl alcohol, good yields of primary (2-hydroxyalkyl)phosphines are obtained.

Organometallics have also been investigated for their ability to generate C–P bond-containing species by direct interaction. The most positively productive of these investigations for synthetic applications involves the treatment of white phosphorus, initially melted (50°C) and cooled with stirring to provide a finely dispersed material, with aryl lithium reagent, followed by aqueous work-up. In this way, a 40% yield of phenylphosphine (C₆H₅PH₂) could be isolated.

Figure 2.8 Use of red phosphorus for the direct generation of an alkylphosphonic acid.
using phenyl lithium (Figure 2.9). Attempts to combine this approach with subsequent addition of haloalkanes or oxiranes to generate mixed tertiary phosphines led to product mixtures that were less than satisfactory. Similarly, the use of Grignard reagents for this purpose was less than satisfactory for synthetic purposes.

2.4 Radical attack on elemental phosphorus

A most significant report by Barton and Zhu\textsuperscript{37} was concerned with elemental white phosphorus serving as a trapping agent for organic radicals. While other reports have been made concerning radical reactions of elemental phosphorus, this approach is the only one noted to involve the generation of C–P bonds with an efficiency suitable for organophosphorus syntheses.

Fundamentally, O-esters of N-hydroxy-2-thiopyridone are photo-lyzed in the presence of an excess of white phosphorus in a methylene chloride/carbon disulfide medium. On solvent removal, hydrolysis, and oxidation with hydrogen peroxide, good yields of phosphonic acids (Figure 2.10) bearing the carbon functionality of the parent acid are isolated.

A reaction of red phosphorus with arylhalides (chlorobenzene) in phosphorus trichloride and in the presence of a variety of catalysts has been reported to provide moderate yields of the arylidichlorophosphine.\textsuperscript{38} No reaction occurs in the absence of the catalysts, and a free radical mechanism is presumed to be involved.

2.5 Direct addition to $\pi$-systems

Several reports have appeared concerning the addition of elemental phosphorus to $\pi$-systems, either involving addition–elimination or direct addition across a $\pi$-linkage. These proceed in reasonable yield for the preparation of pure organophosphorus materials.

Krespan and coworkers have reported\textsuperscript{39,40} the preparation of a bicyclic perfluorinated bis-phosphate (Figure 2.11) by the addition of
1,1,1,4,4,4-hexafluoro-2-butyne to red phosphorus at elevated temperature. The reaction is catalyzed by elemental iodine, providing the purified product in 45% yield.

Figure 2.10 Preparation of phosphonic acids from O-esters of N-hydroxy-z-thiopyridones.

1,1,1,4,4,4-hexafluoro-2-butyne to red phosphorus at elevated temperature. The reaction is catalyzed by elemental iodine, providing the purified product in 45% yield.

Figure 2.11 Formation of a bicyclic from red phosphorus.
Another related bicyclic species (Figure 2.12) has been produced in 20% yield by the reaction of red phosphorus with 1,2-dichlorobenzene on heating in the presence of a Lewis acid catalyst. This reaction presumably occurs by an addition–elimination route.

Finally, Cristau and coworkers have reported on a quite efficient preparation of triphenylphosphine oxide (Figure 2.13) by a similar addition–elimination reaction of red phosphorus with iodobenzene in the presence of a Lewis acid catalyst followed by oxidation of an intermediate tetraarylphosphonium salt. This approach holds the potential for the preparation of a variety of triarylphosphine oxides without proceeding through the normally used Grignard reagent. Of course, a variety of approaches is available for the efficient reduction of phosphine oxides and quaternary phosphonium salts to the parent phosphine, including the use of lithium aluminum hydride, methylpolysiloxane, trichlorosilane, and hexachlorodisilane.

2.6 Oxidative additions with olefins

Walling and coworkers (among others) have investigated the reaction of white phosphorus with alkenes in the presence of molecular oxygen. The reaction is noted to proceed “quantitatively” to a polymeric species, referred to as a “phosphorate,” in which the unit P₂O₄ has been added to the alkene (Figure 2.14). Some evidence is
presented that upon treatment with aqueous nitric acid this interme-
diate can be degraded to the alkenylphosphonic acid, although yields
are not good and identification has not been definitive. This approach
to α, β-unsaturated alkenylphosphonic acids has promise but requires
some efforts yet to define the particular conditions for final conversion
of the “phosphorate” species.

2.7 Experimental procedures

2.7.1 Preparation of tris(2-carbamoylethyl)phosphine oxide
— Preparation of a tertiary phosphine oxide from white phosphorus under aqueous basic conditions

A solution of 10 ml of 10 N aqueous KOH diluted to 25 ml with
absolute ethanol was added dropwise over a period of 30 min to a
well-stirred mixture of 0.4 g-atom (12.4 g) of finely divided white phosphorus, 1.2 mol (85.2 g) of acrylamide, and 200 ml of absolute ethanol under a nitrogen atmosphere. The temperature was main-
tained at –5 to 0°C by a cooling bath. After stirring for an additional
45 min, the white solid generated was recovered by filtration. This
solid was dissolved in 125 ml of hot glacial acetic acid, and the
solution was cooled to room temperature. (Any unreacted white phosphorus could be removed at this point by decantation under a nitrogen atmosphere.) The solution was filtered through diatoma-
ceous earth, diluted with 600 ml of absolute ethanol, and cooled at
5°C for 30 min. The resultant white solid was collected by filtration,
washed with absolute ethanol, and dried to produce the pure tris(2-
carbamoylethyl)phosphine oxide in 74% yield.
2.7.2 Preparation of phenylphosphine — Preparation of a primary phosphine from white phosphorus with an organometallic

White phosphorus (15.5 g, 0.5 g-atom) was cut into approximately 0.1-g pieces under water, washed with acetone followed by ether, and then added in one portion to the reaction mixture. The reaction mixture consisted of 1.0 mol of phenyl lithium in 750 ml of diethyl ether. The exothermic reaction was continued by heating at reflux for 3 h. Water was then added to hydrolyze the remaining organometallic; this resulted in the precipitation of a yellow solid. The solid was removed by filtration, and the two phases of the remaining liquid portion were separated. The aqueous portion was extracted with three 50-ml portions of diethyl ether, which were combined with the organic layer, dried over anhydrous sodium sulfate, and evaporated to give the product phenylphosphine in 40% yield.

2.7.3 Preparation of α-hydroxy-p-methylbenzylphosphonous acid — Preparation of a phosphonous acid from red phosphorus in aqueous medium

To a solution of red phosphorus (3.1 g, 0.1 mol) in DMSO (6 ml) the following was added successively: potassium hydroxide (0.95 g, 17 mmol) in water (50 mmol) and aldehyde, 4-methylbenzaldehyde (0.90 g, 7.5 mmol). The reaction mixture was sonicated for 10 min, after which it was filtered to remove excess phosphorus. The filtrate was then acidified to pH = 2–3 with 37% aqueous HCl and extracted with chloroform. The aqueous portion was concentrated to dryness, and the residue dissolved in a minimum of acetic acid. The supernatant layer was separated from the solid and concentrated to dryness to give the product α-hydroxy-p-methylbenzylphosphonous acid in 30% yield.

2.7.4 Preparation of benzylphosphonic acid — Preparation of a phosphonic acid from red phosphorus in aqueous acid

Red phosphorus (0.31 g, 0.01 mol) was added to a solution of benzaldehyde (1.06 g, 0.01 mol) in 57% aqueous HI (3 ml). The mixture was heated under reflux for 6 h. After cooling, the excess of red phosphorus was removed by filtration and the filtrate concentrated
to dryness under vacuum. The residue was dissolved in water that was then extracted with diethyl ether. The aqueous layer was concentrated to dryness, and the residue was recrystallized from 2-propanol/acetone to give the product benzylphosphonic acid in 25% yield.

2.8 Summary
We have not been concerned with an attempt to be encyclopedic here. Rather, we are looking to provide:

1. Reference to processes that are known to provide organophosphorus species in reasonable yield from elemental phosphorus
2. Reference to processes of potential value for the preparation of organophosphorus species from elemental phosphorus

In the first instance, we must note the processes generating phosphine (PH₃) from the elemental substance in aqueous basic medium to be a useful approach with particular types of substrates with which PH₃ (or the derived PH₂⁻ anion) can act as a nucleophile. Production of a particularly desired type of organophosphorus compound is clearly dependent on both the substrate and the nature of the solvent.

In the second instance, two approaches seem to be worthy of special note. The synthetic utility of elemental phosphorus based on it acting as a radical trap appears to be quite valuable, but additional effort is required to determine the variability of the source of the organic free radicals. (Is there some other, more efficacious, source of organic free radicals that works better with this system than acylated N-hydroxy-2-pyridones?) The other approach that appears ripe for development is the hydrolysis/elimination with “phosphorates” derived from the oxidative addition of white phosphorus to alkenes. We look forward to the continued development of such facile approaches toward the preparation of fundamental phosphonic acids.

References


chapter 3

C–P bond formation using nucleophilic trivalent phosphorus reagents

3.1 Introduction

The use of an electron-rich trivalent phosphorus center for addition to or substitution at an electrophilic site is a long-established approach to the formation of carbon–phosphorus bonds. The classical studies of the Michaelis–Arbuzov, Michaelis–Becker, Abramov, Pudovik, and related reactions and their mechanisms and synthetic utilities have been thoroughly reviewed. In this chapter, we present only a brief introduction to these reactions and provide several examples of their more facile uses from the older literature. More attention is given to relatively recent developments regarding such reactions that are seen as improvements in their general utility.

Of particular note is the application of such reactions for the preparation of organophosphorus compounds bearing heteroatom substitution at the \( \alpha \)-carbon site (carbon of the C–P bond). Herein we review the approaches to this intriguing category of compounds, with some discussion of their applicability to probing and modifying metabolic processes. This topic has also received recent review, and we survey the available review literature along with the original reports.

3.2 Substitution reactions using neutral trivalent phosphorus reagents

3.2.1 General

The well-known Michaelis–Arbuzov reaction is historically the fundamental approach to generating C–P bonds using a neutral trivalent
phosphorus reagent substituting for some leaving group on carbon. As reviews of the mechanistic aspects, as well as early established synthetic utility, of this reaction are available,\textsuperscript{1-5} we will not go into great detail concerning early work. Instead, we will briefly summarize the pertinent aspects of the reaction and refer the reader to the earlier reviews.

In most instances, a haloorganic subject to either $S_N$2 displacement reaction or $S_N$1 substitution is heated at reflux with the trivalent phosphorus ester with the concomitant formation of the valence-expanded organophosphorus compound and haloorganic by-product, as illustrated with an example in Equation 3.1.

\begin{equation}
(\text{CH}_3\text{O})_3\text{P} + \text{ClCH}_2\text{OCH}_3 \xrightarrow{\text{reflux 20 h}} \text{CH}_3\text{O}P\text{OCH}_3\text{OCH}_3 + \text{CH}_3\text{Cl}
\end{equation}

\text{(3.1)}

It is generally understood that the reaction proceeds in two stages, the first one generating an intermediate quasiphosphonium ion followed by attack of the associated counteranion on an ester linkage at the atom attached to phosphorus through oxygen (Equation 3.2).

\begin{equation}
\text{Step 1}
\end{equation}

\begin{equation}
\text{Step 2}
\end{equation}

\text{(Note: In Equation 3.2, the product dialkyl alkylphosphonate is shown with the phosphoryl group represented by P=O. It should be noted}
that this bond is highly polar and is often represented in other ways (Figure 3.1). For simplicity, we will herein use the P=O designation only, recognizing the polar nature of the linkage.)

3.2.2 Mechanism

A variety of mechanistic investigations have established:

- Step 1 is fundamentally an $S_N2$ reaction (kinetics related to structural variations of the reactants\(^{1,6-8}\), retention of stereochemistry at phosphorus\(^{9-12}\)), except in those instances wherein a particularly stable carbocation is produced from the haloalkane component.\(^{13}\) A critical experiment concerned with verification of the $S_N2$ character of Step 1 by inversion of configuration at the carbon from which the leaving group is displaced was inconclusive because elimination rather than substitution occurred with the chiral secondary haloalkane used.\(^{14}\) An alternative experiment suggested by us in our prior review using a chiral primary substrate apparently has not yet been performed.\(^2\)

- Step 2 generally is understood to involve an $S_N2$ displacement at carbon, as determined by a classical stereochemical investigation (Figure 3.2).\(^{15}\) However, the facile occurrence of reaction in those instances for which an inversion upon displacement is not possible (Figure 3.3)\(^{16}\) indicates that other modes for completion of the reaction can occur.

![Figure 3.1](image1) Representations of the phosphoryl linkage.

![Figure 3.2](image2) Stereochemistry in the Michaelis–Arbuzov reaction.
• Under commonly used reaction conditions, the intermediate species is indicated to be a quasiphosphonium ion. Isolation of the intermediates from reactions in which the initial substrate is sufficiently reactive not to require heating, thereby precluding the second step from occurring rapidly, has provided evidence (nuclear magnetic resonance [NMR] and x-ray) of a quasiphosphonium ion species rather than a phosphorane species.17–26

• A stereoelectronic effect is operating in the accomplishment of the first step of the reaction.27 Acyclic fully esterified phosphites undergo the Michaelis–Arbuzov reaction quite readily in spite of the attached electronegative oxygens withdrawing electron density from the nucleophilic phosphorus site. However, with the bicyclic phosphite ester bearing the phosphorus at a bridgehead site, reaction of the phosphorus as a nucleophile in the initial step of the reaction does not occur. In acyclic systems, an n/n filled/filled interaction is present involving the unshared electron pairs of attached oxygen atoms in an anti-periplanar array with that on phosphorus, facilitating the action of the phosphorus as a nucleophile. In the bicyclic system, the unshared electron pairs on oxygen are held in a gauche array relative to the phosphorus unshared electron pair, and support of the nucleophilic action is not provided.

3.2.3 Reagents

A wide variety of reagents have been found to undergo the Michaelis–Arbuzov reaction in a facile manner. Established approaches toward the generation of new C–P bonds using this variety of reagents are briefly summarized in the following:

3.2.3.1 Trialkyl phosphites, dialkyl alkylphosphonites, and alkyl dialkylphosphinites

All of these undergo reaction readily with primary aliphatic halides; the conversion is generally accomplished by simple heating of the
reagent pair in the absence of a solvent.\textsuperscript{28} At times the halide component is heated initially and the phosphorus reagent added slowly to the hot reaction medium.\textsuperscript{29} Difficulties can arise as a result of the normal generation of a haloalkane species by-product during the second step of the reaction; the thus-generated haloalkane may itself be able to undergo reaction with the trivalent phosphorus reagent giving undesired side products. These side products can occur particularly when the ester linkage of the trivalent phosphorus reagent is related to a methyl or other primary haloalkane or the halide reagent is a secondary aliphatic halide. One approach to avoiding this difficulty involves strongly heating the halide reagent using a minimally cooled condenser and slowly adding the phosphorus reagent. This allows the more volatile haloalkane to escape the reaction system as it is generated.\textsuperscript{30}

All of these reagents also undergo reaction spontaneously with acyl halides to generate the corresponding acyl-phosphoryl products (Figure 3.4). Reaction is easily accomplished by the slow addition of the acyl halide to the stirred phosphorus reagent, upon which an exothermic reaction ensues. This approach has been extensively exploited for the preparation of a wide range of $\alpha$-ketophosphonates.\textsuperscript{31–52}

Simple reaction occurs with aryl halides only when the ring is sufficiently substituted with electron-withdrawing functions to allow attack by the nucleophilic phosphorus.\textsuperscript{53–56} Generally, reaction with aryl halides requires the presence of a Lewis acid catalyst or some other means of reaction initiation. These reactions will be considered in detail in Chapter 6 of this work. Interestingly, while reactions involving vinylic halides seem to correlate with those of aromatic halides (see Chapter 6), acetylenic halides undergo facile reaction with these phosphorus reagents.\textsuperscript{57,58}

A variety of leaving groups (other than simple halide) may be associated with the electrophilic component of the reaction with these phosphorus components. These include haloepoxides (leading to $\beta$-ketophosphoryl compounds),\textsuperscript{59} quaternary ammonium salts,\textsuperscript{60–64}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{acetyl_chloride_reaction.png}
\caption{Reaction of an acyl chloride in the Michaelis–Arbuzov reaction.}
\end{figure}
acetate esters,\textsuperscript{65–67} \(N\)-acylaziridines (leading to \(N\)-acyl-\(N\)-ethyl-\(\beta\)-aminophosphoryl compounds),\textsuperscript{68,69} and acetals of aromatic aldehydes (in the presence of boron trifluoride etherate — presumably proceeding through an intermediate carbocation) to give \(\alpha\)-alkoxyphosphoryl compounds.\textsuperscript{70}

Reaction of these phosphorus reagents with halo-carbonyl reagents usually leads to “abnormal” products. The fundamental reaction of \(\alpha\)-halocarbonyl compounds with standard Arbuzov reagents results in the formation of enol phosphate esters, a reaction generally referred to as the Perkow reaction.\textsuperscript{71–81} The mechanism (Figure 3.5) of the Perkow reaction has been established as involving initial attack of phosphorus at the carbonyl carbon, followed by rearrangement through a phosphorane to an enol phosphonium ion and subsequent dealkylation.\textsuperscript{79,81–89} In only certain instances could the reagent system be induced to provide “normal” Michaelis–Arbuzov-type products.\textsuperscript{90–92} Generally, to avoid the formation of Perkow-type product, masking of the carbonyl group as a ketal or acetal is required.\textsuperscript{93–97} Even electrophilic components of the reaction wherein the halogen and carbonyl group are more distant (Figure 3.6) yield “abnormal” products, with such reactions involving both carbonyl and halide sites.\textsuperscript{98,99} The breadth and limitations of the Perkow reaction have been thoroughly reviewed.\textsuperscript{100}

\[
\begin{align*}
\text{Figure 3.5} \quad \text{Mechanism of the Perkow reaction.}
\end{align*}
\]
3.2.3.2 Triaryl phosphites, diaryl alkylphosphonites, and aryl dialkylphosphinites

These phosphorus reagents generally undergo (albeit more slowly than their alkyl ester counterparts) alkylation of phosphorus under typical Michaelis–Arbuzov conditions to generate quasiphosphonium species,\textsuperscript{101,102} although the following ester-displacement does not occur without special intervention. This is not unusual, as the second step of the normal Michaelis–Arbuzov reaction is fundamentally an S\textsubscript{N}2 reaction that does not readily occur at sp\textsuperscript{2} hybridized carbon. Some success at bringing these reagents to completion in a Michaelis–Arbuzov manner has been obtained through the use of various Lewis acids.\textsuperscript{103–113}

3.2.3.3 Silyl esters of phosphorous, phosphonous, and phosphinous acids

In the instances of phosphorous and phosphonous acid systems, the generation of a new C–P bond via the classical Michaelis–Arbuzov reactions as noted above leads to products that are esters themselves. Isolation of the free acid product requires cleavage of the ester linkage in a separate reaction step, generally after isolation and purification of the initial product. The advent of silyl phosphorus reagents for the Michaelis–Arbuzov reaction allowed free acid products to be isolated simply by water workup of the reaction system. Further, since the by-product was a silyl-halide, the general concern that the by-product halide would participate in an extraneous Michaelis–Arbuzov reaction was obviated.

Several methods for the preparation of the parent compound in this system, tris(trimethylsilyl)phosphite, have been reported.\textsuperscript{114–118} The application of this and related reagents in reaction with alkyl halides has been reported and used for the preparation of a variety of phosphonic acid analogues of phospholipids.\textsuperscript{114,119–124} Interestingly, alkyl chlorides appear to be more reactive with the silyl reagents than do alkyl iodides, a reversal of the normally observed trend with alkyl esters of the phosphorus acids. (The particular use of silyl phosphorus reagents for the synthesis of biologically significant compounds has
been reviewed.\textsuperscript{125} Reaction with acyl halides permits preparation of the free $\alpha$-ketophosphonic acids under mild conditions, for which the danger of cleavage of the newly formed C–P bond is minimized.\textsuperscript{118,125–129} Finally, silyl esters of phosphonous\textsuperscript{130–132} and phosphinous\textsuperscript{133,134} acids have also been prepared and used in these types of reactions.

3.2.4 \textit{Recent advances}

A significant experimental advance concerned with the method of performing the Michaelis–Arbuzov reaction involves the use of microwave heating\textsuperscript{135} instead of the usual heating at 150°C or above for several hours. High yields have been reported with heating in a commercial microwave oven for 1 to 1.5 min on “High” intensity in a pressure tube. At times, repeated heating for additional 1- to 1.5-min intervals is required. (\textit{Experimental note: Do not} use longer heating times. If the reaction requires more time than 1.5 min, allow it to cool and then re-treat in the microwave for an additional session of no more than 1.5 min. Longer heating times can result in damage to the standard O-ring seals and possibly fire in the oven.) Similarly, microwave irradiation has been used for the facilitation of the formation of phosphonium salts.\textsuperscript{136}

In the general area of C–P compounds being used as metabolic regulators and probes in biological systems, phosphonylphosphinyl analogues of isoprenoid diphosphates have been prepared using the Michaelis–Arbuzov reaction on a phosphonylphosphinite prepared in a series of reactions involving 1,1-bisdichlorophosphinomethane in a selective oxidation with dimethyl sulfoxide (DMSO).\textsuperscript{137} The overall reaction scheme, suitable for application to other geminal phosphonylphosphinyl species, is shown in Equation 3.3.
Additional advances have been made in the use of leaving groups other than halide for the nonphosphorus component of the Michaelis–Arbuzov reaction. The sensitive species 3,5-di-t-butyl-4-hydroxybenzyl acetate has been noted to undergo efficient reaction (75–85% isolated yields) with a series of trialkyl phosphites upon heating at relatively low temperature (95°C) without the use of excess phosphite or additional catalyst. Chromatographic analysis of the reaction mixture indicates virtually quantitative conversion in the process.

A useful approach for the preparation of chiral β-aminophosphonic acids from the naturally occurring α-amino acids has been reported. The overall scheme (Equation 3.4) involves formation of the phthalimide–acid halide from the starting α-amino acid followed by a Michaelis–Arbuzov reaction with triethyl phosphite to give the acylphosphonate. Complete reduction of the carbonyl group in three steps followed by hydrolysis of the ester and amide linkages provides the target material in very high yield without racemization (>99% ee).

\[ \text{Equation 3.4} \]

\[
\begin{align*}
\text{N} & \text{O} \\
\text{R} & \text{C(O)Cl} \\
\text{N} & \text{O} \\
\text{R} & \text{C} \\
\text{P(O)(OEt)}_2 \\
\text{OH} \\
\text{1. NaBH}_3 & \text{CN} \\
\text{2. thiocarbonyldiimidazole} \\
\text{3. } & \text{Bu}_3 \text{SnH} \\
\text{1. } & \text{H}_2 \text{NNH}_2 \\
\text{2. } & \text{H}_3 \text{O}^+ \\
\text{3. thiocarbonyldiimidazole} \\
\text{1. } & \text{NaBH}_3 \text{CN} \\
\text{2. thiocarbonyldiimidazole} \\
\text{3. } & \text{Bu}_3 \text{SnH} \\
\end{align*}
\]

An intriguing reaction has been reported that does not exactly fit into the category of Michaelis–Arbuzov reaction but does involve nucleophilic attack of a neutral trivalent phosphorus for generation of a new C–P bond. Phenyl- and methyldichlorophosphine have been reported to attack the strained cyclopropane ring system of 1,3-dehydrod adamantane, overall adding P–Cl across the most strained bond of the ring system (Equation 3.5).

\[ \text{Equation 3.5} \]

\[
\begin{align*}
\text{RPCl}_2 & \text{Cl} \\
\text{CH}_2 \text{Cl}_2, 20–30^\circ \text{C} & \text{R} \text{PCl} \\
\end{align*}
\]
The full range of strained ring systems capable of undergoing such a reaction has yet to be determined. A similar reaction has been reported with the 1,3-dehydroadamantane and R₂PCl (relatively poor yields) as well as trialkyl phosphites (relatively high yields of adducts) (Equation 3.6).\(^{141}\)

\[\begin{array}{c}
\text{Cl} \\
\text{P} \quad \text{OR} \\
\text{OR} \\
\text{OR} \\
\end{array}
\begin{array}{c}
\text{Cl} \\
\text{P} \quad \text{OR} \\
\text{OR} \\
\text{OR} \\
\end{array}
\begin{array}{c}
\text{Cl} \\
\text{P} \quad \text{OR} \\
\text{OR} \\
\text{OR} \\
\end{array}
\begin{array}{c}
\text{Cl} \\
\text{P} \quad \text{OR} \\
\text{OR} \\
\text{OR} \\
\end{array}
\begin{array}{c}
\text{Cl} \\
\text{P} \quad \text{OR} \\
\text{OR} \\
\text{OR} \\
\end{array}
\begin{array}{c}
\text{Cl} \\
\text{P} \quad \text{OR} \\
\text{OR} \\
\text{OR} \\
\end{array}
\]

(3.6)

3.3 Substitution reactions using anionic trivalent phosphorus reagents

3.3.1 General

Virtually simultaneously with the development of the Michaelis–Arbuzov reaction, another closely related approach toward C–P bond formation was introduced. This involved the reaction of the salts of trivalent phosphorus-centered oxyacids with the same haloalkanes as used in the Michaelis–Arbuzov reaction. First reported by Michaelis and Becker,\(^{142}\) this approach is commonly known as the “Becker reaction” or the “Michaelis–Becker reaction.” Fundamental aspects of this reaction system have been reviewed previously.\(^{1,2,143}\)

3.3.2 Mechanism

The mechanism of the reaction is understood to involve direct attack of the phosphorus nucleophile on the electrophilic substrate generating the new C–P bond, as shown in Equation 3.7.\(^{144,145}\)

\[\begin{array}{c}
\text{(RO)}_2\text{P} = \text{O} \\
\text{R'} - \text{X} \\
\text{(RO)}_2\text{P} = \text{O} \\
\text{R'} \\
\end{array}\]

(3.7)
The reaction proceeds with retention of configuration at phosphorus, as has been demonstrated in several elegant experiments using chiral phosphorus precursors.\textsuperscript{144,146–152}

### 3.3.3 Reagents

While classically the reaction uses the sodium salt of the parent phosphorus(III) oxyacid, this at times presents difficulties. Often, this salt is relatively insoluble in the reaction medium, including use of the oxyacid as solvent, leading to problems of rate of reaction in the heterogeneous system. With dibutyl phosphite, however, the sodium salt is soluble in the parent reagent and the reaction proceeds smoothly. An alternative approach has been to use a tertiary amine as activating agent, particularly in instances where the substrate is highly reactive. Several instances of facile use of triethylamine as the activating agent have been noted with imidoyl chlorides,\textsuperscript{145} simple carboxylic acid chlorides,\textsuperscript{153} and chloroformates.\textsuperscript{154,155} Several of these instances have used silyl esters of the phosphorous acids.\textsuperscript{154,155} In some instances, cyclic tritertiary amines are able to serve both as base for the reaction and as a masked substrate. This approach has been used successfully for the preparation of 1-aminoalkylphosphonates, analogues of the naturally occurring amino acids (Equation 3.8).\textsuperscript{156,157} Another alternative that has proved successful is the use of phase transfer agents\textsuperscript{158–160} or crown ether adjuncts.\textsuperscript{161}

![Equation 3.8](image)

A variety of substrates have been noted to serve in the reaction with anionic forms of the parent oxyacid. These include the following in particular:

- Haloalkanes are the most common substrates for the Michaelis–Becker reaction.\textsuperscript{162–170} Of course, primary and benzylic halides provide more favorable reactions than secondary halides.
do, and tertiary halides present serious problems for isolation of substitution products. Worthy of note is that the antibiotic phosphonic acids synthesized by this approach have recently been found to inhibit a nonmevalonate pathway for isoprenoid biosynthesis and are of use in malaria treatment. This presents an interesting and useful area for continuing organophosphorus synthesis exploration.

- While a "Perkow-route" for product formation generally ensues when α-halocarbonyl substrates are challenged with Michaelis–Becker reagents, ethyl 4-bromoacetylacetone provides a simple substitution product. Simple substitution occurs also with α-haloesters and α-halophosphonates.

- Tertiary amines serve the dual role of base, to generate the Michaelis–Becker reagent from the parent dialkyl phosphorous or thiophosphorous acid, and subsequently (in the protonated state) as the leaving group for displacement by the anion.

The closely related Todd reaction, useful for the preparation of dialkyl phosphorochloridates and phosphoramidates, also involves the use of amines with dialkyl phosphites. Although the reaction proceeds using preformed salts of the dialkyl phosphites, the use of tertiary amines facilitates the reaction by allowing all reagent materials to be in solution. Biphasic reaction systems utilizing phase-transfer catalysts and crown ethers have also been successful for this reaction.

### 3.3.4 Recent advances

A Michaelis–Becker approach using the sodium salt of dialkyl phosphites has been successful for the formation of C–P bonds to aromatic rings. Reaction of the dialkyl phosphite in DMF with the appropriate diaryliodonium halide provides the corresponding dialkyl arylphosphonate in good yield (81 to 93%). This approach to the arylphosphonate esters proceeds in superior yield under relatively mild conditions and therefore is one to be accorded serious consideration for the preparation of such materials.

An intriguing reaction of salts of dialkyl phosphites with the methylenetriphenylphosphoranylideneamino derivative of benzo-
triazole provides entry to several useful categories of materials.\textsuperscript{185} The intermediate generated in the initial reaction, dialkyl [(triphenylphosphoranylidene)aminomethyl]phosphonate, can readily be converted to amino acid analogues or to vinyl imines in good yield (Equation 3.9).

\begin{equation}
\text{(3.9)}
\end{equation}

Advances in the use of anionic stereogenic phosphorus have been interesting. Acylation of lithium \(\sigma\)-anisylphenylphosphide with chloroformates bearing chiral alkyl groups provided a diastereomeric mixture that could be induced to undergo an inversion at phosphorus (at relatively low temperature) to form the more favorable diastereoisomer in a crystalline lattice.\textsuperscript{186} Subsequent conversion to the quaternary phosphonium species was followed by removal of the acyl group and isolation of the chiral tertiary phosphine as the borane derivative (Equation 3.10).
In an earlier investigation using borane-stabilized chiral methyl phenyl(hydrogen)phosphonites, arylation with complete retention of configuration at phosphorus could be attained (depending on the solvent used), using \( o \)-iodoanisole mediated with tetrakis(triphenylphosphino)palladium in catalytic amount (Equation 3.11).

This approach provides a convenient entry to chiral phosphonites.

\[
\begin{align*}
\text{(equal mixture as formed)} \\
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{C}_6\text{H}_5
\end{array}
\end{array}
\end{align*}
\]

A significant recent report of epoxides in reaction with anionic trivalent phosphorus is of general use for synthetic purposes. Dialkyl phosphite anions react with the less substituted oxirane carbon of arylsulfonyl epoxides to generate in good yield the corresponding \( \beta \)-ketophosphonates (Equation 3.12).

\[
\begin{align*}
\text{(3.11)}
\end{align*}
\]
3.4 Preparations of $\alpha$-substituted phosphoryl compounds

3.4.1 General

In recent years, the use of $\alpha$-substituted phosphoryl compounds has mushroomed as they have become recognized as useful analogues of $\alpha$-substituted carboxyl compounds (including the $\alpha$-amino acids), as well as materials with their own applications. We will begin here by reviewing the well-established approaches toward such materials, specifically the Abramov and Pudovik reactions, including the associated conjugate addition reactions, and then consider the newer approaches toward such compounds.

3.4.2 Neutral trivalent phosphorus addition to unsaturated carbon

The original effort of Abramov for the addition of neutral trivalent phosphorus to carbonyl carbon required extremely stringent conditions (high temperature, pressure reactor) for the isolation of the simple $\alpha$-alkoxyphosphoryl product.\(^{189}\) These stringent conditions were necessary to allow the intermolecular transfer of an alkyl group between a pair of intermediate species (Equation 3.13).

\[
\begin{align*}
\text{(RO)}_3P + R'CHO & \rightarrow \text{RO}_2P(O)O\text{H} \\
\text{RO}_2P(O)O\text{H} + \text{RO}_2P(O)O\text{H} & \rightarrow \text{RO}_2P(O)O\text{H} + \text{RO}_2P(O)O\text{H}
\end{align*}
\]

Intramolecular alkyl transfer is a fundamental problem with this reaction; this problem can be addressed with modification in structure of the reagents. Neutral trivalent phosphorus reagents do react with carbonyl compounds at much lower temperatures, but lead to several types of pentacoordinated phosphorus products.\(^{190-198}\) More will be noted about the use of such pentacoordinated phosphorus species for carbon–phosphorus bond formation in Chapter 5.
Trivalent phosphorus–halogen reagents have been noted to be of use in obtaining simple Abramov-type products with chloral\(^{199,200}\) and with aldimines.\(^{201}\) Similarly, phosphorus–carboxylate anhydrides have been useful in overcoming the stereochemical difficulties associated with alkyl transfer for obtaining Abramov-type products in a direct manner.\(^{202-205}\)

Several approaches have been used to overcome the stereochemical difficulties for intramolecular “alkyl transfer.” One of these is to use a “trapping agent” in the reaction mixture with which the oxyanion site of the intermediate can react. A silyl halide works nicely for this purpose; the halide anion facilitates the required dealkylation.\(^{206-210}\)

The other major approach toward overcoming the “alkyl transfer” difficulty of the Abramov reaction involves the use of silyl esters of the trivalent phosphorus acids. Unlike carbon, silicon does not have the stereochemical restraints associated with ordinary alkyl groups for intramolecular transfer.\(^{211}\) The preparation of mixed alkyl–silyl esters of trivalent phosphorus acids paved the way for the Abramov reaction to be of general utility.\(^{204,208,212}\) An example is shown in Equation 3.14.

\[
(CH_3)_2POSi(CH_3)_3 + C_6H_5CHO \longrightarrow C_6H_5CH(OSi(CH_3)_3)P(O)(OCH_3)_2
\]

Of course, the use of tris(trimethylsilyl) phosphite\(^ {213,214}\) provides facile access to the free \(\alpha\)-hydroxyphosphonic acids. These silyl reagents have been used for the preparation of a wide range of \(\alpha\)-substituted phosphonates and phosphonic acids, starting with ketene,\(^ {215}\) \(\alpha\)-ketophosphonates,\(^ {216}\) ketoesters,\(^ {217,218}\) and \(\alpha,\beta\)-unsaturated carbonyl compounds,\(^ {207,219-221}\) as well as simple aldehydes and ketones.\(^ {205-210,215-221}\) Their use for the preparation of compounds of significant biological interest has been reviewed.\(^ {125}\)

The preparation of optically active analogues of the natural amino acids has proven reasonable using the reaction of tris(trimethylsilyl) phosphite with chiral aldimines prepared from optically active amines.\(^ {225}\) The asymmetric induction has been observed to be as high as 80%, a significant competitive process compared to the multistep approaches available.\(^ {226,227}\) An alternative one-step approach involving asymmetric induction upon addition to an aldime derived from a chiral \(N\)-substituted urea provided a product with less desirable optical purity.\(^ {228}\)
In contrast to the Michaelis–Arbuzov reaction, triaryl phosphites prove to be quite useful for addition to \( \alpha,\beta \)-unsaturated carbonyl compounds in this type of reaction. A wide variety of unsaturated compounds have been utilized successfully as substrates for such additions, including condensation products of the simple carbonyl compounds with urea, thiourea, \( N \)-substituted thioureas, ethyl carbamate, 2-imidazolidinone, 2-imidazolidinethione, and benzyl carbamate.

Phosphorous acid has also been of use for additions to imines. Originally investigated by Moedritzer and Irani, who developed a Mannich-type procedure for the preparation of phosphorus-centered species, the approach was found later to be useful for both primary and secondary amines in reaction with formaldehyde and phosphorous acid. The approach was later used for the preparation of a cationic exchange resin using a polymer substrate.

Although the \( \alpha \)-substituted-\( \alpha \)-aminoalkylphosphonic acids can be generated using phosphorous acid, initial separate preparation of the imine is necessary. The reaction of the imine with phosphorous acid is complete in a few minutes at 110°C, and yields are good to excellent. However, using imines derived from aldehydes using amides rather than amines, a "one-pot" approach is viable. The resultant material is immediately hydrolyzed to the target \( \alpha \)-amino acids. Several other related reactions have also been reported, including a direct addition of phosphorous acid to aldehydes to provide \( \alpha \)-hydroxyalkylphosphonic acids in excellent yield.

An intriguing application of the phosphorous acid addition process has been devised with nitriles. This allows direct formation in high yield of the useful 1-aminoalkyl-1,1-diphosphonic acids (Equation 3.15).

\[
\text{H}_3\text{PO}_4 + \text{CH}_3\text{CN} \rightarrow \text{H}_2\text{C}–\text{C}((\text{PO}_3\text{H}_2)_2)\text{NH}_3 + \text{NH}_3 \\
85\% \text{ yield}
\]

(3.15)

Similar addition reactions have been conducted using thio carbonyl compounds, starting with the geminal dithiols and trialkyl phosphites. On heating, hydrogen sulfide is released. While the process of dealkylation varies with the reagents, often resulting in product mixtures, using silyl reagents guarantees that only the silyl group will be transferred (Equation 3.16).
A reaction of dimethyl(bistrimethylsilylamino)phosphine with aldehydes and ketones occurs readily to generate the corresponding N-trimethylsilylphosphinamines in very good yield. 256

3.4.3 Anionic trivalent phosphorus addition to unsaturated carbon

The use of an anionic reagent for addition at carbonyl carbon rather than a fully esterified form of a trivalent phosphorus acid obviates a troublesome aspect of the Abramov reaction. Specifically, no dealkylation step is required. Mechanistic investigations257,258 indicate that the reaction proceeds much as a simple “aldol”-type reaction in which the anionic phosphorus site adds directly to the carbonyl center. While the initial efforts concerned with the “Pudovik reaction”259 were directed toward the use of sodium salts of the simple dialkyl phosphites, as shown in Equation 3.17,260–266 with \( \alpha,\beta \)-unsaturated carbonyl systems (vide infra) competition between sites for addition can occur. Addition at the carbonyl carbon site is the kinetically favored route.267–270

While sodium salts have been used most prominently for these types of reactions, other forms of the phosphorus anion have also been used significantly. Excellent yields have been observed using Grignards for the generation of the anionic phosphorus reagent.271,272 Tertiary amines have been used for generation of the anionic reagent, often in catalytic amount, both with added solvent and with excess of the phosphorus reagent as the solvent.273–278 Excellent yield of the carbonyl addition product is observed under these conditions even with \( \alpha \)-halocarbonyl compounds, for which a Perkow-type product is commonly observed.279 Numerous types of carbonyl and imine
substrates have been used in the Pudovik reaction to good effect using tertiary and other amines as base. These include selective attack of ketones in preference to imines and are of use with paraformaldehyde, fluorenone, chloral, \( \alpha \)-ketosulfonates, glyoxal, glyoxalate esters, and hexafluoroacetone. Chiral amines have been of use in providing asymmetric induction in the Pudovik reaction.

Other reagents have been used as adjuncts for the Pudovik addition as well. Particularly to be noted are the uses of basic alumina and potassium fluoride. The latter has provided an excellent route for the preparation of a phosphonate directly related to an aldonic acid (Equation 3.18).

\[
\text{(3.18)}
\]

Pudovik-type addition to imines, preformed or generated \textit{in situ}, has been used to great advantage for the preparation of a variety of \( \alpha \)-aminophosphonates and phosphonic acids. These have been used for a variety of purposes, including serving as analogues of naturally occurring amino acids, herbicidal agents, antibacterials, synthetic reagents, and a range of further substituted phosphonates. Oximes constitute a particularly interesting type of imine for these reactions as they generally do not require the addition of a basic reagent.

Symmetrical triazines, although not formally unsaturated, in the presence of the dialkyl phosphites undergo ring opening and self-catalysis for Pudovik-type addition. An example is shown in Equation 3.19.

\[
\text{(3.19)}
\]
A variety of reaction conditions have been employed for Pudovik-type additions to imines, including the use of additional tertiary amines,323,324 sodium hydride,325 and sodium ethoxide,326,327 as well as monobasic trivalent phosphorus-containing acids.319,328–340

Finally, two reports have been made in which chiral adjuncts, a chiral amine341 or a chiral dialkyl phosphite,342 have been used in the preparation of optically active Pudovik-type adducts.

3.4.4 Recent advances

A series of 1-aminoalkanediphosphonic acids has been reported by the treatment of the \(N\)-phenylthiourea derivatives of \(\omega\)-diethoxyphosphinoylaldehydes with triphenyl phosphite.343 This constitutes an approach toward the analogues of aspartic and glutamic acid in which both carboxylate sites have been replaced by phosphonic acid functions. A similar approach has also been reported to be of use for the preparation of (diphenyl ester) phosphonate analogues of ornithine, lysine, and homolysine.344,345

Addition of triethyl phosphite to \(\alpha\)-halosubstituted ketones has been reported to provide the \(\alpha,\beta\)-epoxyphosphonate (as the diester) in reasonable yield (51%).346 Similar results were obtained using diethyl phosphite under basic conditions.346,347

Addition of trimethyl phosphite to substituted 2,5-bis(methoxy-carbonyl)cyclones provides products with addition both at the carbonyl carbon (phosphates) and at the \(\alpha\)-carbon (phosphonates).348

Symmetrical cyclic triazines (masked imines) have been used in reaction with diethyl trimethylsilyl phosphite to provide phosphonates bearing silyl-substituted \(\alpha\)-aminophosphonates.349

Another approach toward the preparation of analogues of natural amino acids has been reported using the salt of a phosphonous acid with an aldehyde and a substituted urea in acetyl chloride as a solvent/facilitator.350 This approach provides analogues that bear a single acidic hydrogen at the "acid site," although the attached alkyl group at phosphorus renders the species sterically less like the natural compounds.

Anionic phosphorus has been used as well in a number of recent reports of additions to carbonyl compounds. Addition of dialkyl phosphite to aromatic aldehydes in the presence of catalytic amounts of La-BINOL and dilithium (\(R\))-binaphthoxide occurs enantiosele-
tively to provide the α-hydroxyphosphonates in good yield. The enantioselectivity, which ranged from 17 to 82%, was found to be dependent on the electronic nature of substituents on the aromatic aldehyde.\textsuperscript{351}

α-Amino-substituted phosphonates have been prepared from aromatic imines bearing tetrazoles substituted on the imine nitrogen.\textsuperscript{352} These materials, produced in good to excellent yield, exhibit antibacterial activity.

A most intriguing cycloaddition reaction of phosphoryl isocyanates with poly-α-haloaldehydes provides a heterocyclic phosphonate monoester/monoamide as an isolable but reactive species (Equation 3.20).\textsuperscript{353}

\begin{equation}
(\text{CH}_3\text{O})_2\text{P} = \text{N} = \text{C}=\text{O} + \text{Br}_3\text{C}^{\text{CH}}\text{H} \rightarrow \text{H}_2\text{CO} + \text{OCH}_3
\end{equation}

The heterocycle decomposes readily, and the intermediate zwitterion alternatively rearranges to a vinylic ester that retains the phosphoryl isocyanate linkage.

An unusual approach toward the preparation of α-bisphosphonates began by treatment of an oxime with a phosphorus nucleophile (trialkyl or dialkyl phosphite) and phosphorus oxychloride (as promoter).\textsuperscript{354} The oxime undergoes a Beckman rearrangement; the phosphorus nucleophile attacks the intermediate cation leading to an imine, which is then further attacked by the phosphorus nucleophile to give the α-bisphosphonate (Equation 3.21).
Two reports have been made of the preparation of \( P \)-chiral phosphine oxides through reaction of chiral \( t \)-butylphenylphosphine oxide treated with LDA and electrophiles. The electrophiles included aldehydes, ketones, and benzylic-type halides. Optically active \( \alpha \)-hydroxyphosphonate products have also been generated from aldehydes and dialkyl phosphites using an asymmetric induction approach with LiAl-BINOL.

Finally, in the presence of triethylamine as the base, phthaloyl chloride has been used with a primary phosphine (1-adamantylphosphine) for the preparation of a diacylpshophine that is an analogue of an \( N \)-substituted phthalimide.

3.5 Conjugate addition reactions

3.5.1 General

A logical extension of the Abramov- and Pudovik-type reactions at carbonyl carbon is the conjugate addition of the phosphorus reagents at distant sites of conjugated carbonyl and related systems. A wide range of such Michael addition reactions, many of significant practical
utility, has been observed with phosphorus reagents. In this section, we will survey these reactions based on the type of phosphorus reagent used.

3.5.2 Neutral phosphorus reagents in conjugate additions

Trialkyl phosphites readily undergo conjugate addition with α,β-unsaturated carbonyl compounds in the presence of a proton source, such as a protic solvent.\(^{359}\) The use of a protic solvent, such as an alcohol, obviates the difficulties found in the performance of the simple Abramov-type reaction with α,β-unsaturated carbonyl compounds.\(^{189–198}\) In alcohol medium, an ether is generated as a by-product in the dealkylation process (Equation 3.22).

\[
\text{R'OH} + \text{R'O} - + \text{R'O} \rightarrow \text{R'O} + \text{R'O} + \text{R'O} + \text{R'O}
\]

Difficulties that arise using simple primary alcohols (ketal and enol-ether formation) may be avoided by using phenol or t-butyl alcohol.\(^{360}\)

A variety of substrates has been used in this type of conjugate addition reaction with trialkyl phosphites, with assorted proton sources.\(^{361–384}\) Other types of trivalent phosphorus reagents without acidic (or conjugate base of acidic) sites have also been used successfully for this conjugate addition process, including triaryl phosphites (without dealkylation),\(^{369}\) phosphoramidites,\(^{385–389}\) phosphonites,\(^{363,380,390}\) and phosphinites.\(^{360,380}\)

Two unusual reactions should be noted here. Although quinones generally react with trialkyl phosphites to generate phosphate esters,
when an acyl group is on the quinone ring, conjugate addition to form a new C–P bond occurs (Equation 3.23).

\[
\begin{align*}
\text{arylquinone} + (\text{CH}_3\text{O})_3\text{P} & \quad \text{(18 h, r.t.)} \\
& \quad \rightarrow \begin{array}{c}
\text{arylquinone} \quad \text{PH} \quad \text{C}_6\text{H}_5 \\
& \quad \text{OH} \\
\end{array} + \begin{array}{c}
\text{arylquinone} \quad \text{PH} \quad \text{C}_6\text{H}_5 \\
& \quad \text{OH} \\
\end{array} \\
\end{align*}
\]

(3.23)

Finally, β-bromoacrylate esters react with trialkyl phosphites to provide the unsaturated phosphonates (Equation 3.24), presumably through an addition–elimination route.

\[
\begin{align*}
\text{Br-acylate ester} + [(\text{CH}_3)_2\text{CHO}]_3\text{P} & \quad \rightarrow \begin{array}{c}
\text{br-acylate ester} \quad \text{PH} \quad \text{OCH}_3 \\
& \quad \text{BrCH(CH}_3)_2 \\
\end{array} + \begin{array}{c}
\text{br-acylate ester} \quad \text{PH} \quad \text{OCH}_3 \\
& \quad \text{OH} \\
\end{array} \\
\end{align*}
\]

(3.24)

As with other reactions, silyl esters of phosphorus acids constitute an important and useful category of reagents for conjugate addition reactions. With aldehydes, ketones, and esters, the silyl ester linkage is transferred to the carbonyl oxygen, facilitating the completion of the reaction, generating the free carbonyl or ester upon workup with a protic solvent (Equation 3.25).

\[
\begin{align*}
\text{silyl ester} + \text{aldehyde} & \quad \rightarrow \begin{array}{c}
\text{silyl ester} \quad \text{PH} \quad \text{OCH}_3 \\
& \quad \text{OSi(CH}_3)_3 \\
\end{array} \\
& \quad \text{OH} \\
\end{align*}
\]

(3.25)
Silyl esters of trivalent phosphorus acids have been used successfully in conjugate addition reactions using acrylates,393–395 nitriles,394 amides,396,397 ketones and aldehydes,398–404 and nitro compounds.387

3.5.3 Anionic phosphorus reagents in conjugate additions

Monobasic forms of trivalent phosphorus acids also undergo conjugate addition reactions. In fact, since dealkylation is not required with such reagents, reaction often proceeds with greater facility. A range of \( \alpha,\beta \)-unsaturated aldehydes and ketones have been observed to undergo this conjugate addition reaction under mild conditions with the dialkyl phosphites in the presence of the corresponding alkoxide anion.407–411 With methyl styryl ketone, the site of addition (conjugate vs. carbonyl) is dependent on the reaction temperature used.412,413 A reaction corresponding to that previously noted as an addition–elimination reaction392 occurs with enol ethers and the conjugate base of dialkyl phosphites (Equation 3.26).414

\[
\begin{align*}
\text{RC(O)CHO} + (\text{C}_2\text{H}_5\text{O})_2\text{POH} & \rightarrow \text{RC(O)P(O)(OC}_2\text{H}_5\text{)}_2 \\
\text{RC(O)CHO} + \text{C}_2\text{H}_5\text{ONa} & \rightarrow \text{RC(O)P(O)(OC}_2\text{H}_5\text{)}_2
\end{align*}
\]

(3.26)

A wide range of substrates have been reported to proceed successfully to conjugate addition products with the monobasic forms of phosphorous acids, including esters,371,415,416 amides,417–419 nitriles,415,420 acid chlorides,421 enamides,375 and nitro compounds.422–424 Similarly, monobasic forms of other trivalent phosphorus species have been used successfully in such conjugate addition processes, including monoesters of phosphonous acids375,425,426 and secondary phosphine oxides.427–429 The notable exception to the last of these species is the addition of the anion from diphenyl phosphine oxide to unsaturated aldehydes, which appears always to proceed by addition to the carbonyl carbon.427

Dibasic forms of phosphorus (III) species also have been reported to undergo Michael-type additions to unsaturated substrates. Hypophosphorous acid adds to acrylamides to generate free phosphonous acids in good yield,430 as well as to vinyl acetate.431 Further, methyl hypophosphite adds to a variety of unsaturated substrates,432 as does the ammonium salt of mono(2-ethylhexyl) phosphite (Equation 3.27).433
A special category of substrate for conjugate addition studies is the substituted cyclopentadieneone series. Numerous reaction conditions have been investigated, leading to a variety of products with new C–P bond formation. The nature of product formation appears to be very dependent on details of the reaction conditions, and systematic evaluation is required before the reaction can be used for synthetic purposes.

3.5.4 Recent advances in addition to conjugated and unconjugated olefinic sites

Several reports have been made of the addition of dialkyl phosphites and related monobasic trivalent phosphorus species to alkenes in the presence of an organic peroxide and acetic acid (Equation 3.28).

\[
(\text{RO})_2 \text{P(O)H} + (\text{CH}_3)_2 \text{COOH} \rightarrow (\text{RO})_2 \text{P} + \text{CH}_3 \text{CO}_2 \text{H}
\] (3.28)

With cyclic alkenes, the reaction proceeds with variable regioselectivity and stereoselectivity depending on the substituents, although the overall reaction proceeds in moderate to good yield. The approach is of particular value for those systems where regiochemistry and stereochemistry are not variable.

A very nice ring closure system has been reported involving the Michael addition of a fully esterified β-bromovinyl phosphonite to maleic ester. After initial Michael addition of the phosphorus to the olefinic linkage, the intermediate zwitterion undergoes a ring-closing addition–elimination reaction with the β-site bearing the halogen with subsequent dealkylation (Equation 3.29). The reaction also occurs with fumaric ester, but with poorer yield.
The utilization of phosphine–boranes as stable forms of the phosphine has been exploited for addition reactions with alkenes. With several types of \(\alpha,\beta\)-unsaturated compounds, Michael addition of primary phosphine–boranes has been accomplished in excellent yield for the preparation of secondary phosphine–boranes (Equation 3.30).

\[
\text{H}_2\text{C}_6\text{Br} + (\text{C}_2\text{H}_5\text{O})_2\text{P} \rightarrow \text{H}_2\text{C}_6\text{PO}_{\text{CO}_2\text{CH}_3}\text{CO}_2\text{CH}_3
\]

(3.29)

Michael addition in the absence of any catalytic agent has been reported for dialkyl and diaryl phosphites and thiophosphites with \(\alpha\)-cyanoacrylate esters and \(\alpha\)-cyanoacrylic acid. Yields of the conjugate addition products were moderate to good. The regiochemistry of this process is the opposite of that previously reported for similar additions to ketene acetics, the latter presumably proceeding by initial protonation of the distal olefinic carbon site.

The preparation in good yield of \(\beta\)-mercaptoethylphosphines has been accomplished by the free radical-induced addition of primary and secondary phosphines across the olefinic linkage of 2-(vinylthio)tetrahydropyran. The target materials were isolated by hydrolysis of the intermediate substituted thiotetrahydropyran.

Free radical-initiated chlorophosphonation has been reported for alkenes bearing electron-donating substituents. Oxygen-induced addition of phosphorus trichloride across olefinic linkages leads to formation of the corresponding \(\alpha\)-chlorophosphonyl dichlorides. Again, regioselectivity is not good, so the reaction appears to be of greatest value with symmetrical olefins. With conjugated dienes, a photochemically induced reaction of phosphorus trichloride provided conjugate addition products, which could be converted to a derived conjugated diene in moderate yield by treatment with a
tertiary amine. This reaction, performed in the absence of oxygen, provides the free dichlorophosphine.

The generation of aromatic C–P linkages can be accomplished by the reaction of dialkyl phosphites with quinones in the presence of catalytic amounts of acetic acid. Excellent yield of the mono-phosphorus product is reported using benzene as the solvent.

Anionic trivalent phosphorus reagents have also been found to be of use in the preparation of some intriguing species. For example, an approach to L-phosphinothricin and related materials has been accomplished by addition of the conjugate base of alkyl methylphosphonites to protected L-vinylglycine species (Equation 3.31). The starting protected L-vinylglycine species are readily available from L-methionine and L-glutamic acid.

\[
\text{H}_2\text{C}=\text{CH}\left(\text{CH}_2\text{O}_2\text{C}\right)\text{H}_4\text{C}_6\text{CH}_2\text{O}_2\text{C} + \text{H}_3\text{CPH(O)(OR)} \xrightarrow{1. \text{base}} \text{H}_3\text{CP(O)(OH)}\text{CH}_2\text{CH}_2\text{NH}_2 \xrightarrow{2. \text{hydrolysis}} \text{H}_3\text{CP(O)(OR)}\text{CH}_2\text{CH}_2\text{NH}_2
\]

(Equation 3.31)

The addition of anionic forms of trivalent phosphorus reagents (diethyl phosphite or diphenylphosphinite) to quinonemethides bearing two phosphoryl linkages on the exocyclic double bond provides \(\alpha,\alpha,\alpha\)-triphosphoryl species (Equation 3.32).

\[
\text{P(O)(OC}_2\text{H}_5)_2 - \text{P(O)(OC}_2\text{H}_5)_2 \xrightarrow{\text{base}} \text{P(O)(OC}_2\text{H}_5)_2 - \text{P(O)(OC}_2\text{H}_5)_2
\]

(Equation 3.32)

Starting with unlike phosphoryl groups in the quinomethide, a product that had phosphorus addition to the ring could be isolated.

Reaction of the conjugate base of diethyl phosphite with 3-carboxyethyl-substituted 2,5-halomethylfurans provided interesting products as alternatives to the normally anticipated Michaelis–Becker substitution-type products. Rather than simple substitution, overall reduction of the halomethyl linkage(s) to methyl(s) were observed with a Michael-type addition of phosphorus to the 4-position of the ring.

Finally, preparation of a structurally unusual phosphonocylobutenedione (Figure 3.7) has been accomplished by a conjugate
addition of the lithium salt of dibenzyl phosphite to diethyl squarate. With the influenza ribonucleic acid (RNA) polymerase test, the new compound exhibited activity nearly as great as that of phosphonoformic acid.

A most significant area of advance in recent years for the formation of new carbon–phosphorus bonds by addition across a variety of olefinic linkages is that involving transition metal complexes of appropriate phosphorus reagents. This general topic has been reviewed recently. Among the catalytic metal species involved have been nickel, cobalt, titanium, zinc, lithium/aluminum complexes, platinum, palladium, and lanthanides. In addition to the transition metal-associated systems, uncatalyzed processes are described for the overall “insertion” of the olefinic portion of \( \alpha,\beta \)-unsaturated systems into P–H linkages (Equation 3.33). This type of reaction system holds potential for a wide range of applications.

\[
\begin{align*}
\text{P-H} & + \text{H}_2\text{C}=\text{CHCN} & \text{base} & \rightarrow \\
\text{P-CH}_2\text{CH}_2\text{CN} & & & \\
\end{align*}
\]

(3.33)

3.6 Experimental procedures

3.6.1 Preparation of trisodium phosphonoformate — Reaction of a chloroformate with a trialkyl phosphite and cleavage of the ester linkages

Triethyl phosphonoformate was prepared by the dropwise addition of ethyl chloroformate (10.85 g, 0.1 mol) to triethyl phosphite (16.6 g, 0.1 mol) with vigorous stirring at ambient temperature. After the
exotherm had subsided, the volatile materials were removed under reduced pressure and the residue vacuum distilled to give pure triethyl phosphonoformate (17.2 g, 82%) of boiling point (bp) 86 to 88°C/0.25 torr, which exhibited NMR, infrared (IR), and mass spectra in accord with the proposed structure.

To the resultant triethyl phosphonoformate (105 g, 0.5 mol) was added sodium hydroxide solution (250 ml, 1 M) over a period of 15 min at ambient temperature. The solution became hot, and ethanol by-product boiled off from the reaction mixture. Upon cooling, a precipitate formed, which was recrystallized from water to give colorless crystals of the pure trisodium phosphonoformate hexahydrate (27.5 g, 19%), which exhibited IR and NMR spectra and x-ray crystal analysis in accord with the proposed structure.

3.6.2 Preparation of tris(trimethylsilyl) phosphite — Preparation of a silyl ester of a trivalent phosphorus acid for Michaelis–Arbuzov reaction

An aqueous solution (100 ml) of trisodium phosphonoformate (2.83 g, 9.43 mmol) was eluted through a column (3 × 20 cm) of Diaxon SK 1B in the pyridinium form using a pyridine:water mixture (1:4, 500 ml). The eluents were evaporated under reduced pressure, coevaporated with dry pyridine several times, and dissolved in dry THF (30 ml). Triethyl amine (3.2 g, 31.1 mmol) and chlorotrimethylsilane (3.4 g, 31.1 mmol) were added, and the mixture was stirred vigorously at room temperature. After 2 h, dry ether (15 ml) was added, and the resulting precipitate was removed by filtration and washed with dry ether (10 ml). The filtrate and washings were combined and evaporated under reduced pressure, and the residue was vacuum distilled (76 to 77°C/10 torr) to give pure tris(trimethylsilyl) phosphite (2.27 g, 81%).

3.6.3 Preparation of 2,3-dioleloyloxypropylphosphonic acid — Reaction of an alkyl halide with a silyl phosphate ester

To 2,3-dioleoyloxy-1-iodopropane (3.65 g, 5 mmol) was added tris(trimethylsilyl) phosphate (15.05 g, 50 mmol), along with a trace of butyl hydrogen phthalate. The reaction mixture was stirred under a static nitrogen atmosphere with heating at 125°C for 16 h. After this time, excess tris(trimethylsilyl) phosphate and iodo(trimethylsilyl) were removed by high vacuum distillation (bath 100°C) to leave a colorless oil. The residue was dissolved in THF:water (9:1, 50 ml) and allowed to stand in the dark at room temperature for 12 h. The solvent was
removed under reduced pressure and the residue dried by repeated azotropic distillation with 2-propanol at reduced pressure. The residual oil was dissolved in chloroform and chromatographed on a column of silicic acid, eluted first with chloroform (500 ml) and then chloroform:methanol (9:1, 500 ml). The eluents were evaporated under reduced pressure, and the viscous residue was dissolved in a minimum of chloroform and passed through a Gelman Metricel® (0.45 μm) filter to remove suspended silicic acid. Removal of the solvent under reduced pressure gave the pure 2,3-dioleoyloxypropyl-phosphonic acid (2.8 g, 81%) as a viscous oil.

3.6.4 Preparation of dimethyl (4-methoxybenzyl)phosphonate
— Reaction of a benzyl halide with a trialkyl phosphite

Trimethyl phosphite (12.4 g, 0.1 mol) and p-methoxybenzyl chloride (15.6 g, 0.1 mol) were heated at reflux under a nitrogen atmosphere for 20 h. The residue was vacuum distilled (141°C/0.45 torr) to give the pure dimethyl (4-methoxybenzyl)phosphonate (12.6 g, 59%) as an oil, which exhibited spectra in accord with the proposed structure.

3.6.5 Preparation of 5-(3-benzoylpropionyl)-3-deoxy-3-diisopropoxyphosphinylmethyl-1,2-di-O-acetyl-β-ribofuranose
— Reaction of an alkyl bromide in a carbohydrate series with triisopropyl phosphate

A solution of 5-O-(3-benzoylpropionyl)-3-deoxy-3-bromomethyl-1,2-di-O-acetyl-β-ribofuranose (2.35 g, 4.89 mmol) in triisopropyl phosphate (17 g, 81 mmol) was heated at 160 to 180°C with exclusion of moisture for 72 h. Volatile materials were removed under reduced pressure, and the residue was purified by chromatography on a silica gel column (48 × 2.7 cm) eluting with chloroform:ethyl acetate (1:1). From the 150 to 500 ml eluent, there was isolated the pure 5-(3-benzoylpropionyl)-3-deoxy-3-diisopropoxyphosphinylmethyl-1,2-di-O-acetyl-β-ribofuranose (1.73 g, 68%) as an oil that exhibited IR and NMR spectra and analyses in accord with the proposed structure.

3.6.6 Preparation of triethyl 2-phosphonobutanoate
— Reaction of a trialkyl phosphite with a 2-halocarboxylate ester

A reaction flask was equipped with stirrer, thermometer, dropping funnel, and a steam-jacketed condenser that would allow ethyl
bromide to pass through while condensing higher boiling materials. To the flask was added ethyl 2-bromobutanoate (195 g, 1 mol), and it was heated to 160°C. The triethyl phosphite (199 g, 1.2 mol) was added dropwise over a period of 2 h. After completion of the addition, the temperature was increased to 190°C and maintained there until the evolution of ethyl bromide ceased. The mixture was distilled rapidly below 3 torr and then redistilled using a 24-in. spinning band column. In this manner was isolated the pure triethyl 2-phosphonobutanoate (219 g, 87%) of bp 118°C/0.6 torr.

3.6.7 **Preparation of 1-isopropoxy-2-methylpropylphosphonate** — Reaction of a trialkyl phosphite with a 1-chloroether

Trimethyl phosphite (24.8 g, 0.2 mol) was added dropwise at room temperature to 1-isopropoxy-1-chloro-2-methylpropane (30.1 g, 0.2 mol). As heating was begun, methyl chloride began to be evolved. After heating at 100°C for 2 h, the reaction mixture was vacuum distilled. There was thus isolated pure dimethyl 1-isopropoxy-2-methylpropylphosphonate (27.8 g, 62%) of bp 94 to 95°C/0.8 torr.

3.6.8 **Preparation of diphenyl benzyloxycarbonylaminomethanephosphonate** — Reaction of a triaryl phosphite with an N-acetoxyethylcarbamate generated in situ

A mixture of benzylcarbamate (30.6 g, 0.2 mol), paraformaldehyde (6 g, 0.2 mol), acetic anhydride (25.5 g, 0.25 mol), and acetic acid (20 ml) was stirred for 3 h at 60 to 70°C. Triphenyl phosphite (62.1 g, 0.2 mol) was then added, and the mixture was stirred for 2 h at 110 to 120°C. After evaporation of acetic acid and the remaining acetic anhydride under reduced pressure, the residue was dissolved in methanol (150 ml). The mixture was allowed to stand at −10°C for 4 h, after which the precipitate was isolated by suction filtration, washed with methanol, and air-dried. The precipitate was recrystallized from chloroform:methanol to give pure diphenyl benzyloxycarbonylamino-methanephosphonate (38 g, 48%) of mp 114 to 116°C, which exhibited IR and NMR spectra and analyses in accord with the proposed structure.
3.6.9 **Preparation of diethyl isobutyrylphosphonate** —
*Reaction of a trialkyl phosphite with a carboxylic acid chloride*

Isobutyryl chloride (25.9 g, 0.24 mol) was added dropwise to triethyl phosphite (43.9 g, 0.26 mol) with stirring under a nitrogen atmosphere, and the temperature was maintained at 30 to 40˚C. After the addition was complete, the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was vacuum distilled to give the pure diethyl isobutyrylphosphonate (43.9 g, 88%) of bp 75 to 83˚C/3–4 torr, which exhibited IR spectral characteristics in accord with the assigned structure.

3.6.10 **Preparation of (diethyl phosphonomethyl) acetyl sulfide** —
*Reaction of a trialkyl phosphite with a 1-halosulfide*

Bromomethyl acetyl sulfide (26.8 g, 0.16 mol) and triethyl phosphite (28.4 g, 0.17 mol) were combined in a flask fitted with a Dean–Stark trap. The mixture was stirred at 130˚C for 2.5 h, during which time ethyl bromide collected in the Dean–Stark trap. The reaction mixture was vacuum distilled to give the pure (diethyl phosphonomethyl) acetyl sulfide (23.5 g, 65%) as a clear oil of bp 105 to 106˚C/0.03 torr, which exhibited NMR spectra in accord with the proposed structure.

3.6.11 **Preparation of diethyl 1-oxo-2-(3-indolyl)ethanephosphonate** —
*Reaction of a trialkyl phosphite with a carboxylic acid chloride in solution*

Triethyl phosphite (16.6 g, 0.1 mol) was added dropwise to a solution of 3-indolylacetyl chloride (19.35 g, 0.1 mol) in dry ether (200 ml) at 0 to 5˚C. The reaction was stirred for 1 h at this temperature and a further 4 h at room temperature. The resulting precipitate was filtered, washed with dry ether, and vacuum dried to give pure diethyl 1-oxo-2-(3-indolyl)ethanephosphonate (18.9 g, 64%) of mp 107 to 110˚C.

3.6.12 **Preparation of 1-ethoxybenzylphosphonate** —
*Reaction of a trialkyl phosphite with an acetal in the presence of boron trifluoride*

Benzaldehyde diethyl acetal (5.94 g, 32.9 mmol) and triethyl phosphite (5.45 g, 32.9 mmol) were dissolved in dichloromethane (60 ml) under an inert atmosphere and cooled to ~20˚C. Boron trifluoride etherate (3.57 g, 35.2 mmol) was then added dropwise. The resulting mixture was allowed to return to ambient temperature over an 18-h
period. The reaction was quenched by the addition of water (10 ml) with stirring for 5 min. The organic layer was separated and dried over magnesium sulfate, and the volatile materials were evaporated under reduced pressure. The residue was dissolved in a small amount of chloroform and applied to a silica gel column in chloroform. After unreacted starting material was removed by chloroform elution, the column was eluted with 20% ethyl acetate in chloroform. In this manner was isolated pure diethyl 1-ethoxybenzylphosphonate (6.52 g, 73%) of bp 108 to 110˚C/0.2 torr, which exhibited NMR and mass spectra in accord with the proposed structure.

3.6.13 Preparation of 1,10-diphenyl-1,10-diphosphyclooctadecane 1,10-dioxide — Reaction of an alkyl halide with a phosphinite ester generated in situ by reduction of a phosphinate

A solution of sodium bis(2-methoxyethoxy)aluminum hydride (2.82 g, 14 mmol) in benzene (50 ml) was added dropwise to a well-stirred solution of diisopropyl octamethylenebis(phenyl-phosphinate) (2.48 g, 5 mmol) in benzene (60 ml) in a 2-l, round-bottomed flask at 25°C. Vigorous evolution of hydrogen took place throughout the addition. When all the material had been added, the reaction mixture was stirred for 5 min until the evolution of hydrogen ceased. The reaction mixture was then diluted with benzene to a total volume of 1 l, and then there was added 1,8-dibromoóctane (1.36 g, 5 mmol). Precautions were taken to prevent oxygen entry to the reaction system during dilution and addition. The reaction mixture was heated at 80˚C for 12 h. After cooling and concentrating the reaction mixture to 500 ml, water (3 ml) was added at 25˚C, and the mixture was filtered. The precipitate was washed with benzene (100 ml), and the combined filtrate and washings were evaporated under reduced pressure. The residue was subjected to thin-layer chromatography from which was isolated the two isomeric forms of 1,10-diphenyl-1,10-diphosphyclooctadecane 1,10-dioxide (combined 310 mg, 12.8%).

3.6.14 Preparation of diethyl 3,5-di-t-butyl-4-hydroxybenzylphosphonate — Reaction of a benzylic acetate with a trialkyl phosphite

Triethyl phosphite (16.6 g, 0.1 mol) and 3,5-di-t-butyl-4-hydroxybenzyl acetate (27.8 g, 0.1 mol) were heated with stirring for 4 h at 90 to
95°C in a stream of inert gas. On cooling, white crystals precipitated from the mixture. The precipitate was recovered by filtration and washed with hexane (10 ml) to yield pure 3,5-di-t-butyl-4-hydroxybenzylphosphonate (28.4 g, 80%) of mp 122°C, which exhibited NMR and analyses in accord with the proposed structure.

3.6.15 Preparation of diethyl 3,3-diethoxypropynyl-1-phosphonate — Reaction of a sodium salt of a dialkyl phosphite with an acetylenic halide

A solution of sodium diethyl phosphite was prepared by the addition of sodium hydride (3.72 g, 0.155 mol) to diethyl phosphite (20.7 g, 0.15 mol) in tetrahydrofuran (200 ml). The resultant solution was cooled to –70°C and stirred rapidly while 3,3-diethoxypropynyl-1-bromide (30.05 g, 0.15 mol) in tetrahydrofuran (20 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature. The reaction mixture was centrifuged and the solution decanted from the precipitated sodium bromide. The solid material was dissolved in water (40 ml) and extracted with diethyl ether (2 × 20 ml). The organic phases were combined, dried over magnesium sulfate, filtered, and evaporated under reduced pressure to give an oil. This oil was vacuum distilled (192 to 130°C/0.13 torr) to give the diethyl 3,3-diethoxypropynyl-1-phosphonate (17 g, 64%). Trace amounts of an impurity could be detected in this material. This could be removed by preparative scale thin-layer chromatography using silica PF-254 eluting with hexane–acetone (9:1).

3.6.16 Preparation of bis-(2,2-dimethyltrimethylene)yl [(2,5-dimethyl-1,4-phenylene)dimethylene] diphosphonate — Reaction of the sodium salt of a cyclic phosphite diester with a bis-phenylic halide

A solution of the sodium salt of the cyclic 2,2-dimethyltrimethylene phosphite was prepared by the addition of a 57% mineral oil dispersion of sodium hydride (8.42 g, 0.2 mol) to a solution of the cyclic 2,2-dimethyltrimethylene phosphite (30 g, 0.2 mol) in dry dimethylformamide (150 ml) while the temperature was maintained below 30°C. To the resultant solution was added a solution of 1,4-bis(chloromethyl)-2,5-dimethylbenzene (20.3 g, 0.1 mol) in dry dimethylformamide (150 ml). After the addition was complete and the exotherm subsided, the reaction mixture was heated at 60 to 65°C for 15 h. After the reaction mixture was cooled to room temperature, the solid that formed was
filtered. The solid was washed with dimethylformamide and dried in a vacuum oven. The dried solid was washed with warm water, filtered, rinsed with water again, and dried in a vacuum oven to give the pure bis(2,2-dimethyltrimethylene)yl [(2,5-dimethyl-1,4-phenylene)dime-thylene]diphosphonate (32 g, 74.4%) of mp 231 to 233°C.

3.6.17 Preparation of di-n-butyl N,N-diethylcarbamoylmethylphosphonate — Phase transfer-catalyzed reaction of a dialkyl phosphate with an alkyl chloride

Into a 500-ml, three-necked, round-bottomed flask equipped with a thermowell, a 125-ml pressure-equalizing addition funnel, a mechanical stirrer, inert gas fittings, and a septum was placed a solution of N,N-diethylchloroacetamide (14.95 g, 0.1 mol) and methyltricaprylammonium chloride (0.5 g) in methylene chloride (75 ml), along with 50% sodium hydroxide (100 ml). The solution was stirred at 200 r/min under a gentle purge of nitrogen and maintained at 5 to 10°C while a solution of di-n-butyl phosphite (21.34 g, 0.11 mol) and methyltricaprylammonium chloride (0.5 g) in methylene chloride (75 ml) was added dropwise. The addition was complete in 1 h. After 2 h additional, di-n-butyl phosphite (1.94 g, 0.01 mol) was added, the stirring was continued for 2 h, and then the phases were separated. The aqueous layer was extracted with pentane (50 ml), and the combined organic solutions were washed with 50% aqueous methanol (3 x 50 ml) and saturated sodium chloride solution (50 ml). After the mixture was dried over anhydrous potassium carbonate and filtered, the filtrate was evaporated under reduced pressure to give the pure di-n-butyl N,N-diethylcarbamoylphosphonate (27.9 g, 91%).

3.6.18 Preparation of [1-(diethoxyphosphinyl)ethoxy]dimethylsilane — Reaction of an aldehyde with a trialkyl phosphate in the presence of a silyl halide

To a mixture of dimethyldichlorosilane (64.5 g, 0.5 mol) and triethyl phosphate (166 g, 1.0 mol) in a 500-ml flask was added freshly distilled acetaldehyde (47 g, 1.07 mol) over a period of 18 min while the temperature was maintained at 15 to 22°C. The
mixture was then warmed to 100°C and vacuum distilled (148 to 154°C/0.2 to 0.4 torr) to give the desired [1-(diethoxyphosphinyl)ethoxy]dimethylsilane (165 g, 79%) as a colorless liquid, which exhibited analytical data in accord with the proposed formulation.

3.6.19 Preparation of O,O-diphenyl 2-methylthio-1-(N-phenylthiourea)ethylphosphonate — Reaction of triphenyl phosphite with an imide generated in situ in the presence of acetic acid

To a solution of triphenyl phosphite (6.2 g, 0.02 mol) and thiomethoxyacetaldehyde (2.25 g, 0.025 mol) in glacial acetic acid (18 ml), powdered N-phenylthiourea was added in a single portion. The reaction mixture was stirred at room temperature for 30 min and then for 30 min at 80°C. After the mixture was cooled to room temperature, water (5 ml) was added and the solution was maintained at room temperature for 10 h. The precipitate was removed by suction filtration, washed with 1:1 acetic acid:water (2 × 10 ml), dried over potassium hydroxide in an evacuated dessicator, and recrystallized from chloroform/methanol. In this manner there was isolated pure O,O-diphenyl 2-methylthio-1-(N-phenylthiourea)ethylphosphonate (8.61 g, 94%) of mp 136 to 138°C, which exhibited spectra and analytical data in accord with the proposed structure.

3.6.20 Preparation of 1-aminoethane-1,1-diphosphonic acid — Reaction of phosphorous acid with a nitrile

Phosphorus acid (260 mg, 3.17 mol) was placed into a 250-ml, three-necked, round-bottomed flask suspended in an oil bath. The flask was equipped with a three-way adapter, carrying a pressure-equalizing addition funnel, a reflux condenser with a drying tube, a mechanical stirrer, and a thermometer. Acetonitrile (33 g, 0.80 mol) was introduced to the reaction flask dropwise over a 2-h period while the phosphorous acid was agitated and maintained at a temperature of 138 to 142°C. After completion of the addition, the reaction mixture was maintained at that temperature for an additional 12 h. Methanol was then added to precipitate the pure 1-aminoethane-1,1-diphosphonic acid (13.9 g, 85%), which exhibited spectral and analytical data in accord with the proposed structure.
3.6.21 Preparation of N-benzyl α-aminobenzylphosphonic acid — Reaction of phosphorous acid with an imine

The imine from benzaldehyde and benzyl amine (65 g, 0.33 mol) was added to phosphorous acid (27.3 g, 0.33 mol), and the mixture was stirred with heating. As the temperature reached 95 to 100˚C, the entire mixture became a homogeneous liquid, which reacted vigorously as the temperature reached 115 to 120˚C. After the reaction mixture became very viscous, it was allowed to cool, whereupon it condensed to a glass. The material was dissolved in aqueous sodium carbonate, which upon acidification precipitated pure N-benzyl α-aminobenzylphosphonic acid (90 g, 98%) of mp 233 to 234˚C. The material exhibited analyses in accord with the proposed structure.

3.6.22 Preparation of benzyliminodimethylenediphosphonic acid — Reaction of phosphorous acid with a formaldimine generated in situ

Benzylamine (53.5 g, 0.5 mol) and crystalline phosphorous acid (82 g, 1.0 mol) were dissolved in water (100 ml), concentrated hydrochloric acid (100 ml) was added, and the mixture was heated to reflux. Over the course of 1 h, 37% aqueous formaldehyde (160 ml, 2.0 mol) was added dropwise, and the reaction mixture was maintained at reflux for another hour. After cooling, the solvent was evaporated, and the residual syrup was dissolved in hot ethanol. Upon cooling, the crude benzyliminodimethylenediphosphonic acid precipitated and was recrystallized from hot dilute hydrochloric acid to give the pure material (127 g, 85.7%) of mp 248˚C, which exhibited analytical data in accord with the proposed structure.

3.6.23 Preparation of diethyl 1-(trimethylsiloxy)octylphosphonate — Reaction of a mixed silyl–alkyl phosphite with an aldehyde

Octanal (9.7 g, 75.4 mmol) at room temperature was added dropwise to a solution of diethyl trimethylsilyl phosphate (18.3 g, 87.1 mmol) in dry benzene (10 ml). After stirring for 3 h the solvent was removed, and distillation of the residual oil (104 to 105˚C/0.04 torr) gave pure diethyl 1-(trimethylsiloxy)octylphosphonate (23.1 g, 91%), which exhibited spectra and analytical data in accord with the proposed structure.
3.6.24 **Preparation of (S)-t-butyl(phenyl)(α-hydroxybenzyl)phosphine oxide — Reaction of a chiral secondary phosphine with an aldehyde under basic conditions**

LDA (0.118 g, 1.1 mmol) was added to (S)-t-butyl(phenyl)phosphine oxide (0.182 g, 1 mmol) in tetrahydrofuran (5 ml) under an atmosphere of nitrogen at –78˚C. After 15 min, the solution was treated with a solution of benzaldehyde (0.117 g, 1.1 mol) in tetrahydrofuran (2 ml), and the resultant mixture was stirred at –78˚C for 3 h. Evaporation of the solvent and flash chromatography of the residue provided the (S)-t-butyl(phenyl)(α-hydroxybenzyl)phosphine oxide (0.22 g, 77%) with a diastereoisomeric ratio of 98:2, which exhibited spectral data in accord with the proposed structure.

3.6.25 **Preparation of diethyl (S)-α-hydroxybenzylphosphonate — Reaction of an aldehyde with a dialkyl phosphite facilitated by a chiral BINOL complex**

(R)-aluminum-lithium-BINOL complex (0.024 g, 0.04 mmol) was dissolved in toluene (0.4 ml), and to this solution was added dimethyl phosphite (0.044 g, 0.4 mmol) at room temperature; the mixture was stirred for 30 min. Benzaldehyde (0.042 g, 0.4 mmol) was then added at –40˚C. After having been stirred for 51 h at –40˚C, the reaction mixture was treated with 1 N hydrochloric acid (1.0 ml) and extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 20% acetone/hexane) to give the diethyl (S)-α-hydroxybenzylphosphonate (78 mg, 90%) with 85% enantiomeric excess as a colorless solid of mp 86 to 87˚C.

3.6.26 **Preparation of 1-aminobutyl-1,4-diphosphonic acid — Reaction of an aldehyde with a triaryl phosphite in the presence of a thiourea**

Triphenyl phosphite (4.65 g, 0.015 mol) was added in one portion to a solution of 4-(diethoxyphosphinoyl)butanal (2.08 g, 0.01 mol) and N-phenylthiourea (2.26 g, 0.015 mol) in glacial acetic acid (20 ml). The mixture was stirred at 60˚C for 1 h and then left to stand
at room temperature overnight. It was then diluted with water (2 ml). After 6 h, the resultant precipitate was filtered off and washed with acetic acid/water (1:1) to give the intermediate thioureido phosphonate. This material was dissolved in glacial acetic acid (50 ml) and hydrochloric acid (100 ml, 1:1), and the solution was heated to reflux for 12 h. The mixture was then cooled to room temperature, diluted with water (100 ml), and extracted with toluene (2 × 50 ml). The aqueous layer was evaporated to dryness under reduced pressure, and the solid residue was dissolved in water (10 ml). The solution was passed through a DOWEX® 50W ×8 column, and fractions testing positive with the ninhydrin test were collected. The combined fractions testing positive were concentrated under reduced pressure to 5 ml and were precipitated by the addition of ethanol (25 ml). The residue was dried in a desiccator over phosphorus pentoxide to give the pure 1-aminobutyl-1,4-diphosphonic acid (1.63 g, 70%), which exhibited spectral and analytical data in accord with the proposed structure.

3.6.27 Preparation of diphenyl 1-(benzylcarbamoyl)-4-(phthalimido)-1-phosphonate — Reaction of a phthalimido-protected aminoaldehyde with a triaryl phosphite

4-phthalimidobutanal (21.7 g, 0.1 mol) was mixed with benzyl carbamate (15.1 g, 0.1 mol) and triphenyl phosphite (31 g, 0.1 mol) in glacial acetic acid (500 ml) and heated at 80 to 85°C for 1 h. The reaction mixture was concentrated under reduced pressure to give a dark oil, which was dissolved in methanol and was left at –20°C for 3 h. The white solid that then precipitated was recrystallized from methanol to give the pure diphenyl 1-(benzylcarbamoyl)-4-(phthalimido)-1-phosphonate (32.1 g, 55%), which exhibited spectra and analyses in accord with the proposed structure.

3.6.28 Preparation of ethyl methyl(2-carbomethoxy-3-phenylpropyl)phosphinate — Addition of a monobasic phosphinous ester to an unsaturated ester in the presence of a silylating agent

To a solution of ethyl methylphosphonite (0.66 g, 0.006 mol) in methylene chloride (7.5 ml) was added methyl 2-benzylacrylate (0.9 g,
0.0047 mol) and bis(trimethylsilyl)acetamide (1.03 g, 0.00474 mol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was then washed with water followed by extraction with ether, and the volatile materials were removed under reduced pressure. The residue was subjected to chromatographic purification using neutral alumina (activity 3) from which was isolated the pure ethyl methyl(2-carbomethoxy-3-phenylpropyl)phosphinate (1.14 g, 80.7%), which exhibited spectral and analytical data in accord with the proposed structure.

3.6.29 Preparation of 2-dimethoxyphosphinyl-2-methoxy-2-phenylacetaldehyde oxime — Reaction of an unsaturated nitro compound with a trialkyl phosphite in the presence of an alcohol

A solution of β-nitrostyrene (30 g, 0.2 mol) in t-butyl alcohol (300 ml) was placed in a three-neck flask equipped with a condenser, a pressure-equalizing dropping funnel, and a thermometer. Trimethyl phosphite (62 g, 0.5 mol) was then added. An initial cooling of about 4°C was observed, followed by an increase in temperature to a maximum of 65 to 75°C within 20 min. After 3 h, the solvent was removed under reduced pressure, and the residue was cooled. The red oil was induced to crystallize by the addition of a seed crystal and the scratching of the vessel walls. After standing overnight, the crystals were filtered, washed with toluene (2 × 20 ml), and recrystallized from ethylene glycol dimethyl ether to give, in two crops, the pure 2-dimethoxyphosphinyl-2-methoxy-2-phenylacetaldehyde oxime (11.85 g, 34%), which exhibited spectral and analytical data in accord with the proposed structure.

3.6.30 Preparation of 3-diethoxyphosphinyl-2-methylpropionamide — Addition of a monobasic trivalent phosphorus acid to an unsaturated amide in the presence of an alkoxide base

A mixture of diethyl phosphite (15.18 g, 0.11 mol) and 2-methylacrylamide (8.5 g, 0.1 mol) was heated at 60 to 70°C, and an exothermic reaction was initiated by the further dropwise addition of a 3 M ethanolic sodium ethoxide solution (5 ml). After the completion of the exotherm, the reaction was further heated for 1 h at 110°C. The
The reaction mixture was then cooled, diluted with ethanol, and neutralized with concentrated hydrochloric acid. The solution was then filtered and the solvent evaporated under reduced pressure. The residue solidified upon standing and was then recrystallized from benzene to yield the pure 3-diethoxyphosphinyl-2-methylpropionamide (17.84 g, 80%) of mp 75 to 77˚C, which exhibited spectra and analytical data in accord with the proposed structure.

3.6.31 Preparation of di-n-butyl di-n-butoxyphosphinylsuccinate — Addition of a monobasic trivalent phosphorus reagent to an unsaturated ester in the presence of base

To an agitated mixture of di-n-butyl phosphite (194 g, 1.0 mol) and sodamide (5 g, 0.13 mol) in a flask provided with a reflux condenser, di-n-butyl maleate (228 g, 1.0 mol) was added dropwise over a period of 30 min while the reaction temperature was maintained at 50˚C by cooling with a water bath. Further stirring for 1.25 h without cooling was performed to allow the reaction to proceed to completion. The reaction mixture was then neutralized with glacial acetic acid and filtered. The neutralized mixture was fractionally distilled under vacuum using a Claisen-type still to give the pure di-n-butyl di-n-butoxyphosphinylsuccinate (358.7 g, 85%) as an oily liquid of bp 190˚C/1.2 torr.

3.6.32 Preparation of phenyl(mesitylyl)(β-cyanoethyl)phosphine — Addition of a secondary phosphine to an unsaturated nitrile under aqueous basic conditions

An aqueous 50% KOH solution (0.5 ml) was added to a solution of phenyl(mesitylyl)phosphine (1.0 g, 4.4 mmol) and acrylonitrile (400 mg, 7.5 mmol) in acetonitrile (10 ml). The flask was heated at 50˚C for 2 h, producing a yellow solution. Extraction with ether caused separation of a yellow insoluble material and gave a clear solution that, upon cooling to –25˚C, gave white crystals of the product, which were washed with a small amount of petroleum ether. An additional crop was obtained from the mother liquor to provide pure phenyl(mesitylyl)(β-cyanoethyl)phosphine (857 mg, 70%), which exhibited spectra and analytical data in accord with the proposed structure.
3.6.33 Preparation of 1-ethoxy-2-phenyl-4,5-dimethoxycarbonyl-\(\Delta^2\)-5-phospholene 1-oxide —
Reaction of a vinylicphosphonite diester with an unsaturated carboxylate ester\(^{442}\)

A mixture of diethyl 2-bromo-1-phenylethenylphosphonite (30.3 g, 0.1 mol) and dimethyl maleate (14.4 g, 0.1 mol) was stirred for 4 h at room temperature under an argon atmosphere. At this time, hexane was added to the reaction mixture sufficient for complete precipitation, and the resultant crystals (unreacted dimethyl maleate) were removed by filtration. The oily residue was treated on a silica gel column (40/100 \(\mu\)m) using a pentane/acetic (8:2) mixture, allowing the elution and isolation after evaporation of pure 1-ethoxy-2-phenyl-4,5-dimethoxycarbonyl-\(\Delta^2\)-5-phospholene 1-oxide (8.9 g, 27%), which exhibited spectra and analytical data in accord with the proposed structure.

3.6.34 Preparation of phenyl(\(\beta\)-carbomethoxyethyl)phosphine–borane —
Reaction of a primary phosphine–borane with an unsaturated ester\(^{443}\)

To a solution of phenylphosphine–borane complex (0.87 g, 7 mmol) in benzene (6 ml), methyl acrylate (0.68 g, 8 mmol) was added slowly under nitrogen. The reaction mixture was stirred at room temperature, monitoring the progress of the reaction using \(^{31}\)P NMR. When the signal for the starting phosphorus reagent had disappeared, indicating it had been consumed (7 days), the solvent was removed under reduced pressure, and the residue was treated by chromatography on silica gel to provide the pure phenyl(\(\beta\)-carbomethoxyethyl)phosphine–borane (0.81 g, 55%), which exhibited spectra and analyses in accord with the proposed structure.

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chapter 4

C–P bond formation via displacement, addition, or rearrangement

4.1 Introduction

The use of organometallic species, either as primary reagents or as catalytic adjuncts, for the generation of carbon–phosphorus bonds by displacement reaction is historically significant. Of increasing importance today is the use of transition metal complexes for displacements and additions. This latter aspect has already been discussed briefly in Chapter 3, but is noted again here. We also review other approaches toward C–P bond formation, including additions to unsaturated linkages and rearrangements of P–O–C linkages to P–C linkages.

As in prior chapters, we review historically significant approaches toward C–P bond formation, noting the advantages and disadvantages of classical approaches, contemplate the more recent advances, and consider the opportunities associated with each. Detailed experimental procedures for examples of each of the types of reactions are provided.

We begin, however, with a brief consideration of a group of phosphorus compounds of significance for their utility in the formation of carbon–phosphorus bonds via reaction with organometallic reagents in displacement reactions.

4.2 Phosphorus–halogen compounds

4.2.1 General

Compounds containing a phosphorus–halogen linkage historically have been useful in preparing organophosphorus species. Two modes
of reactivity that facilitate the generation of the carbon–phosphorus linkage are generally available with such reagents. First, as such species are really acid halides, the phosphorus–halogen linkage is one of high reactivity, susceptible to facile displacement by nucleophilic reagents including, of particular note for the present, carbanionic nucleophilic reagents. Further, for P(III) halogen compounds, the available valence-level unshared electron pair at phosphorus allows the species to serve as a nucleophilic reagent itself. By whatever means the species is intended to serve in reaction, the high reactivity of the phosphorus–halogen linkage can present difficulties for the successful completion of a desired synthetic process. Fundamentally, the phosphorus–polyhalogen species are capable of undergoing multiple reactions with nucleophilic reagents and of providing reactions with a wide range of functional groups in a challenging reagent system. Nonetheless, the construction of a proper phosphorus–halogen species for ultimate incorporation of a phosphorus–carbon bond needs to be considered.

4.2.2 Generation of the phosphorus–halogen linkage

Common “parent” phosphorus–halogen species include particularly the P(III) system PCl$_3$ and the P(V) species P(O)Cl$_3$. Of course, the pentacoordinated species PCl$_5$ must also be considered for its availability as reagent precursor. These are species that often serve not only in a direct manner in carbon–phosphorus bond formation but also in the construction of partially or fully esterified species prior to carbon–phosphorus bond incorporation.

For example, introduction of a single alkyl ester linkage into a P(V) system can be accomplished by controlled reaction of POCl$_3$ with an alcohol in an inert solvent, as illustrated in Equation 4.1.\(^{12}\)

$$\text{OP(O)Cl}_2 + \text{HCl} \rightarrow \text{PO(O)Cl}_3$$

Base is to be avoided in this reaction as it facilitates breakdown of the intermediate to form the chloroalkane rather than having it remain as the ester. Alternatively, the solid phosphorus reagent PCl$_5$ may be used, but two equivalents of alcohol are required; the first is converted to chloroalkane with concomitant formation of P(O)Cl$_3$, with which the second equivalent of alcohol can react to generate the desired product, the alkyl phosphorodichloridite.\(^{3}\)
For the preparation of aryl esters from phosphorus oxychloride, a Lewis acid is generally added as a catalyst. Commonly, aluminum chloride with an excess of phosphorus oxychloride added to the phenol provides excellent yields (Equation 4.2).

\[
\text{PhOH} + \text{POCl}_3 + \text{AlCl}_3 \rightarrow \text{PhOP(O)Cl}_2
\]

Equation 4.2

In a corresponding manner, the mono-esters of P(III) systems can be produced by controlled reaction of the P(III) halides with the appropriate hydroxyl compound. Significantly better yields are obtained for the aryl esters (from phenols — Equation 4.3) than for alkyl esters (from alcohol), and primary alcohols provide better yields than do secondary alcohols.

\[
\text{PhOH} + \text{PCl}_3 \rightarrow \text{PhOPCl}_2
\]

Equation 4.3

The use of a tertiary amine as an adjunct is not advised as it leads to increased formation of haloalkane; the hydrogen halide generated is simply vented from the reaction system. Caution needs to be applied in handling the product alkyl (or aryl) phosphorodichloridites. They are extremely susceptible to moisture, and many are flammable upon contact with air.

The difficulties attendant with the direct preparation from alcohol and phosphorus halide of partial ester/partial halide systems may be overcome through the use of a variety of alternative approaches. We will briefly consider a few of these here.

Trialkyl phosphites undergo reaction with molecular halogen via a mechanism reminiscent of the Michaelis–Arbuzov reaction to form the dialkyl phosphorochloridate in good yield (Equation 4.4). With cyclic esters, the halogen performing the displacement reaction at carbon remains attached within the molecule.
An approach involving mild conditions and beginning with the phosphite diesters is that commonly known as the Todd reaction. An excess of carbon tetrachloride is used as the solvent as well as the chlorine source, and to it the phosphite diester along with a catalytic amount of a tertiary amine is added. Reaction begins exothermically upon addition of the amine catalyst. The reaction is understood to involve the anion of the phosphite diester with the carbon tetrachloride, proceeding through a pentacoordinated phosphorus intermediate, and yielding ultimately the target phosphorochloridate and chloroform (Equation 4.5).

\[
\text{CCl}_4 + (\text{C}_2\text{H}_5\text{O})_2\text{POH} \xrightarrow{(\text{CH}_3\text{CH}_2)_3\text{N}} (\text{C}_2\text{H}_5\text{O})_2\text{POCl} + \text{CHCl}_3
\]

\[78\% \text{ yield}\] (4.5)

Small amounts of amine salt are also generated as a side product.\(^8\)–\(^{10}\) Other oxidative chlorinating approaches have been used with dialkyl phosphites as well, including methods using copper(II) chloride,\(^{11}\) sulfonyl chloride,\(^{12}\) and elemental chlorine.\(^{13}\) All of these provide the target dialkyl phosphorochloridate in high yield.

For the generation of P–Cl linkages as intermediates in species already bearing a carbon–phosphorus bond, selective conversion of an ester linkage to a P–Cl linkage is desired. This selective conversion can be accomplished using several reagents, among them phosgene (preferred to thionyl chloride) (Equation 4.6),\(^{14}\) phosphorus pentachloride (Equation 4.7),\(^{15}\) and related pentacoordinate phosphorus reagents (Equation 4.8).\(^{16,17}\)

\[
\text{H}_3\text{C}\left\langle \begin{array}{c} \text{O} \\ \text{OCH(CH}_3)_2 \end{array} \right\rangle \xrightarrow{\text{COCl}_2} \text{H}_3\text{C}\left\langle \begin{array}{c} \text{O} \\ \text{OCH(CH}_3)_2 \end{array} \right\rangle \xrightarrow{\text{CO}_2} \text{H}_3\text{C}\left\langle \begin{array}{c} \text{O} \\ \text{OCH(CH}_3)_2 \end{array} \right\rangle + \text{CO}_2 + (\text{CH}_3)_2\text{CHCl}
\]

\[95\% \text{ yield}\] (4.6)
The last of these systems has been adapted to a solid-phase reagent system (Equation 4.9) that obviates the problems associated with by-product removal, and the by-product may be recycled (treatment with phosgene) to regenerate the active insoluble reagent.\textsuperscript{18,19}

\[
\begin{align*}
\text{H}_2\text{C}=\text{CH}\begin{array}{c}O \text{OCH}_2\text{CH}_2\text{Cl} \\ \text{Cl} \end{array} \text{PCL}_3 & \rightarrow \text{H}_2\text{C}=\text{CH}\begin{array}{c}O \text{OCH}_2\text{CH}_2\text{Cl} \\ \text{Cl} \end{array} + \text{CH}_3\text{CH}_2\text{Cl} + \text{POCl}_3 \\
& \text{62\% yield}
\end{align*}
\]

(4.7)

\[
\begin{align*}
\text{H}_2\text{C}=\text{CH}\begin{array}{c}O \text{OCH}_2\text{CH}_2\text{Cl} \\ \text{Cl} \end{array} \rightarrow \text{H}_2\text{C}=\text{CH}\begin{array}{c}O \text{OCH}_2\text{CH}_2\text{Cl} \\ \text{Cl} \end{array} + (\text{C}_4\text{H}_9)_2\text{P(O)} + \text{CH}_3\text{Cl} \\
& \text{99\% yield}
\end{align*}
\]

(4.8)

The last of these systems has been adapted to a solid-phase reagent system (Equation 4.9) that obviates the problems associated with by-product removal, and the by-product may be recycled (treatment with phosgene) to regenerate the active insoluble reagent.\textsuperscript{18,19}

\[
\text{POLYMER} - \text{P(C}_4\text{H}_9)_2\text{Cl}_2 + \text{H}_3\text{CP(O)(OCH}_2\text{CH}_3)_2 \rightarrow \text{CP(O)(OCH}_2\text{CH}_3(\text{Cl}) + \text{POLYMER} - \text{P(C}_4\text{H}_9)_2(\text{O})
\]

(4.9)

When thionophosphonic esters are used for conversion to the phosphonothiochloridates, observation of the stereospecificities of the reactions is possible. Alternative results may be attained through judicious choice of the reagent system. For example, the optically active \(O\)-isopropyl methylphosphonothioate, as shown in Equation 4.10, reacts with phosgene at sulfur only to form the \(O\)-isopropyl methylphosphonochloridate with inversion of configuration at phosphorus.\textsuperscript{20}

\[
\begin{align*}
\text{Na}^+ \\
\text{H}_3\text{C}...\text{S} \begin{array}{c}O \text{(CH}_3)_2\text{CHO} \\ \text{P} \end{array} \text{COCl}_2 & \rightarrow \text{H}_3\text{C}...\text{O} \begin{array}{c}O \text{(CH}_3)_2\text{CHO} \\ \text{P} \end{array} + \text{O}=\text{C=S}
\end{align*}
\]

(4.10)
(The fully esterified species, the $O,S$-dialkyl alkylphosphonothioates, do not react with phosgene; the free thiophosphoryl group appears to be required for reaction to occur.\textsuperscript{20} In contrast to phosgene, phosphorus pentachloride reacts with the same $O$-alkyl alkylphosphonothioate only at oxygen to remove the oxygen from the molecule (as phosphorus oxychloride) and produce the alkylphosphonothiochloridate with inversion of configuration at phosphorus (Equation 4.11).\textsuperscript{21}

\[
\text{CH}_3\text{CH}_2\text{O}\begin{array}{c}S\
\text{CH}_3\text{CH}_2\text{OH}
\end{array}\xrightarrow{\text{PCl}_3} \text{CH}_3\text{CH}_2\text{O}\begin{array}{c}P^{\text{Cl}}\
\text{S}
\end{array} + \text{POCl}_3
\]

(4.11)

Different options are available depending on the particular result desired. Other approaches toward conversion of phosphorus esters to the corresponding acid chlorides have been reviewed.\textsuperscript{22}

4.3 \textit{Substitution reactions on phosphorus–halogen compounds using organometallics and related reagents}

4.3.1 \textit{General}

The displacement of halogen from phosphorus by an anionic carbon reagent for the generation of a carbon–phosphorus bond is not new. In this section, we will review some of the historically useful approaches for the generation of carbon–phosphorus bonds using a variety of organometallics, including Grignards, mercury, tin, aluminum, cadmium, and lead compounds, as well as organolithium salts. We will further update the range of such reactions investigated in which displacement of halogen from phosphorus is involved.

Halogen on both trivalent and pentavalent phosphorus is susceptible to such displacement. Control of the reaction to provide synthetic utility will be noted. Both isolable organometallics and transient species generated and used \textit{in situ} will be surveyed.

4.3.2 \textit{Types of organometallic reagents}

4.3.2.1 \textit{Organomercury reagents}

Some of the earlier efforts utilizing organometallics for displacement of halogen from phosphorus for $C$–$P$ bond generation involved organomercury reagents. Of course, such reagents pose a serious toxico-
logical hazard, and it is recommended that their use be avoided except under the most stringent conditions of safety and when other methods fail.

Simple dialkylmercury reagents react with phosphorus trichloride replacing a single halogen and leading to the alkyldichlorophosphine in reasonable yield (Equation 4.12).\(^{23}\)

\[
\text{(C}_4\text{H}_8)_2\text{Hg} + \text{PCl}_3 \rightarrow \text{(C}_4\text{H}_8)\text{PCl}_2 \\
61\% \text{ yield}
\] (4.12)

The organomercury reagents have been found to be most convenient for the introduction of olefinic linkages directly on phosphorus.\(^{24}\) Of particular note is the preparation of vinyldifluorophosphine by reaction of divinylmercury with bromodifluorophosphine\(^{25}\) to provide vinyldifluorophosphine. Selective displacement of only the bromide from phosphorus was observed. The overall usage of organomercurials for carbon–phosphorus bond generation has been reviewed.\(^{26}\)

A further safety note should be made here. Some of the simple alkyldichlorophosphines are extremely corrosive and flammable in air. Extreme caution should be exercised in their handling.

4.3.2.2 Organolead compounds

An early alternative to the organomercury compounds was the organolead compounds, which have their own toxicological disadvantages. For example, tetraethyllead can be used in the displacement of a single chloride from phosphorus trichloride to generate ethyldichlorophosphine in good yield (Equation 4.13).\(^{27}\)

\[
\text{(CH}_3\text{CH}_2)_4\text{Pb} + \text{PCl}_3 \rightarrow \text{(CH}_3\text{CH}_2)\text{PCl}_2 \\
89\% \text{ yield}
\] (4.13)

Both of these types of organometallics have the disadvantages of difficulties in preparation and extreme toxicity. Their major advantage is that they provide a controlled reaction, allowing a single halogen of the phosphorus halide to be displaced, leaving the others untouched.

4.3.2.3 Grignard reagents

It was recognized very early that Grignard reagents could be used for displacement of halogen on phosphorus with the attendant formation of carbon–phosphorus bonds. The formation of tertiary
phosphines from phosphorus trichloride and excess Grignard reagent is a standard synthetic approach.\textsuperscript{28-33} However, limiting the reaction to monosubstitution, as is found commonly with the previously discussed reagent systems, is difficult or impossible.\textsuperscript{34}

A significant problem that can arise in the use of Grignard reagents results from the fact that such reagents can react with ester linkages on phosphorus,\textsuperscript{35,36} although selectivity for the more reactive halide site does exist in mixed halide/ester systems when a limited amount of the Grignard reagent is used. An example of this selectivity can be seen in the reaction of aromatic Grignard reagents (Equation 4.14) with diethyl phosphorochloridate.\textsuperscript{37}

\begin{align*}
\text{CF}_3 \text{P(O)(OCH}_2 \text{CH}_3)_2 & \xrightarrow{\text{1. Mg, ether}} \text{Ph} \text{P(O)(OCH}_2 \text{CH}_3)_2 \\
\text{Br} & \xrightarrow{\text{2. (CH}_3 \text{CH}_2 \text{O})_2 \text{P(O)Cl}} \text{93\% yield} \\
(4.14)
\end{align*}

This selectivity for preferred reaction displacing the halide is found with both P(III) and P(V) mixed halide/ester systems (Equation 4.15)\textsuperscript{38} and has been noted in several patents to be of value for phosphonite synthesis (Equation 4.16).\textsuperscript{39,40}

\begin{align*}
\text{HC}≡\text{CMgCl} + \text{CH}_3 \text{P(O)(OCH}_3)\text{Cl} & \xrightarrow{\text{THF, -20} \text{°C}} \text{HC}≡\text{CP(O)(OCH}_3)\text{CH}_3 \\
& \text{50\% yield} \\
(4.15)
\end{align*}

\begin{align*}
\text{(CH}_3 \text{CH}_2 \text{O})_2 \text{PCl} + \text{CH}_3 \text{MgBr} & \xrightarrow{\text{THF, 0} \text{°C}} \text{(CH}_3 \text{CH}_2 \text{O})_2 \text{PCH}_3 \\
& \text{(4.16)}
\end{align*}

A further selectivity is found with the preferential displacement of aromatic ester linkages compared to alkyl ester linkages using Grignard reagents.\textsuperscript{41} In the reaction of the chiral mixed-ester phosphonite shown in Equation 4.17, preferential displacement of the aromatic ester compared to the alkyl ester occurs with inversion of configuration at phosphorus.\textsuperscript{42}
Of course, the high reactivity of the Grignard reagents can be used to good advantage for exhaustive alkylation or arylation in the preparation of a wide range of phosphorus halides and esters.  

4.3.2.4 Aluminum-based systems
As an alternative to the Grignard reagent system noted previously, aluminum acetylides react selectively with mixed halide/ester species to replace only the halide (Equation 4.18).

\[
\begin{align*}
\text{Ar'MgX} & + (\text{RC}\equiv\text{C})\text{AlLi} \quad \text{ether} \quad \text{RC}\equiv\text{CP(O)(OR')_2} \\
\end{align*}
\]

(4.18)

In a rather different vein, aluminum halide-mediated systems have been used for introduction of both alkyl and aryl groups in place of halogen on phosphorus. For example, alkyldichlorophosphines, including haloalkylidihalophosphines, reagents of significant utility for the further syntheses of a wide range of organophosphorus compounds, are prepared conveniently and in high yield by the reaction of the chloroalkane with phosphorus trichloride in the presence of aluminum chloride (Equation 4.19).

\[
\begin{align*}
\text{CH}_3\text{I} + \text{PCl}_3 + \text{AlCl}_3 \quad \rightarrow \quad [\text{CH}_3\text{PCl}_3]^+ [\text{AlCl}_3\text{I}]^- \\
\text{Fe} \quad \text{KCl} \quad \text{CH}_3\text{PCl}_2 \quad 80\% \quad \text{yield}
\end{align*}
\]

(4.19)

(Safety precautions noted previously regarding the alkyldichlorophosphines remain for consideration by the experimentalist.)
Controlled alkylation of phosphorus oxychloride may also be accomplished using a modification of this approach. Reaction of alkyl-aluminum dichloride with phosphorus oxychloride generates the aluminum chloride complex of the alkylphosphonodichloridate, which may be isolated as the simple compound or directly used in reaction to generate other derivatives of the alkylphosphonic acid.

Facile preparations of aryldichlorophosphines and their derivatives have been accomplished with aluminum chloride in a Friedel–Crafts-type reaction system. While the reaction system has been used for more than a century, significant modifications have been made for improvement of yield. Conditions have been investigated that allow the destruction of the aluminum chloride complex to generate the product aryldichlorophosphine without the addition of water (Equation 4.20), or with water to isolate the free phosphonous acid.

$$\text{4.3.2.5 Organocadmium reagents}$$

These materials, generally prepared from the corresponding Grignard reagents by the addition of cadmium chloride, provide a milder reagent system than the Grignard that allows selectivity in reaction with phosphorus trichloride (Equation 4.21).

\[
\begin{align*}
\text{1 eqv. C}_4\text{H}_9\text{MgBr} & \xrightarrow{\text{CdCl}_2} (\text{C}_4\text{H}_9)_2\text{Cd} & \xrightarrow{\text{POCl}_3} \text{C}_4\text{H}_9\text{PCl}_2 \\
\text{10 eqv. POCl}_3 & \xrightarrow{\text{AlCl}_3 \ (0.5 \text{ eqv.})} \text{70% yield}
\end{align*}
\] (4.20)

This selectivity is attained by performing a reverse addition of the organometallic reagent to an excess of the phosphorus trichloride. (“Normal” addition produces a mixture of products.)
4.3.2.6 Organotin reagents
Organotin reagents have been used to generate carbon–phosphorus bonds where an unsaturated carbon is directly bound to phosphorus.\[^{64}\] While the reaction can be performed using either P(III) or P(V) reagents, with mixed organotin reagents the unsaturated functionality specifically is transferred to phosphorus, replacing a fluorine on phosphorus pentafluoride (Equation 4.22).

\[
\begin{align*}
(C_4H_9)_3Sn\text{C} & \equiv \text{CH} + \text{PF}_3 \\
& \quad \xrightarrow{71\% \text{ yield}} F_2\text{PC} \equiv \text{CH} \\
& \quad \xrightarrow{98\% \text{ yield}} \text{HC}_3\text{CP(O)}\text{F}_2
\end{align*}
\]

(4.22)

Isolation of the phosphonodifluoridate is accomplished by treatment of the phosphorane with a siloxane.

4.3.2.7 Lithium reagents
Both stabilized and unstabilized lithium reagents have been used as a source of anionic carbon for displacement of halogen from phosphorus in the generation of carbon–phosphorus bonds. Unstabilized organolithium reagents provide a very strong alkylating or arylating reagent system for the generation of carbon–phosphorus bonds. More reactive than the corresponding Grignard reagents, these organolithium reagents readily provide complete replacement of all available displaceable linkages at phosphorus.\[^{41,42}\]

Lithiated silanes have been used for displacement of halogen from dialkylhalophosphines as precursors to phosphonium salts bearing silicon functionalities (Equation 4.23).\[^{65}\]

\[
\begin{align*}
\text{LiCH}[\text{Si(CH}_3)_3]_2 & + \text{P} & \text{Cl} \\
& & \xrightarrow{\text{THF}} \text{P} & \text{CH}[\text{Si(CH}_3)_3]_2
\end{align*}
\]

(4.23)

Lithiated aromatics, generated by a transmetalation reaction, have been used for the generation of carbon–phosphorus bonds by displacement of chloride from phosphorus trichloride in the overall
synthesis of new types of crown ethers\textsuperscript{66} (Figure 4.1) and with diphenylchlorophosphine for the ultimate preparation of some intriguing triaryl phosphine oxides of interest for their optical properties.\textsuperscript{67}

Lithium salts of resonance-stabilized organic anions have also found a role in carbon–phosphorus bond formation by displacement at phosphorus. The generation of the lithium salt derived from acetonitrile (or other aliphatic nitriles by reaction with butyl lithium or lithium diisopropylamide) provides for carbon–phosphorus bond formation by displacement of halide from phosphorus (Equation 4.24).\textsuperscript{68}

\[
[(\text{CH}_3)_2\text{N}]_2\text{P}(\text{O})\text{Cl} + \text{LiCH}_2\text{CN} \rightarrow [(\text{CH}_3)_2\text{N}]_2\text{P}(\text{O})\text{CH}_2\text{CN} \\
95\% \text{ yield}
\]

(4.24)

Such materials provide entrance to a wide range of organophosphorus compounds with substitution at the \(\alpha\)-position relative to phosphorus.

The lithium salt of the stabilized anion derived from dithiane also provides displacement of halogen at phosphorus for the generation of species readily converted into additional functionalized organophosphorus compounds.\textsuperscript{69} The resultant materials are suitable for a wide range of applications, both as final products and as reagents for additional transformations.

The lithium salt of a substituted cyclopentadienyl anion has been used in reaction with phosphorus trichloride for carbon–phosphorus bond formation.\textsuperscript{70} The resultant simple displacement product ultimately undergoes dimerization and loss of four (from the dimer) equivalents of HCl (Equation 4.25).

\[\]

\[\]

\textbf{Figure 4.1} Phosphorus-centered crown esters.
The resultant material (isolated in low yield) is an intriguing tricyclic system that could be viewed as an overall antiaromatic system or as two aromatic rings with two phosphorus sites connecting them. In any event, this tricyclic product readily undergoes addition of water in even trace amounts to generate a bis-secondary phosphine oxide (Equation 4.26).

![Chemical structure diagram](image)

(4.25)

(4.26)
A resonance-stabilized lithium salt generated from a γ-substituted α,β-unsaturated carboxylate derivative has been found to undergo displacement of chloride from dialkyl chlorophosphites leading (on oxidation) to the formation of β-keto-δ-carboxyphosphonates (Equation 4.27).\(^71\)

![Diagram showing the reaction](image)

These compounds, rich in functionality, are valuable precursors for the preparation of a variety of interesting compounds, both containing and devoid of phosphorus.

### 4.3.2.8 Enamines

While technically not “organometallics,” enamines are reagents that can provide nucleophilic carbon for new bond formation. Two groups of researchers have reported on the use of such reagents for the formation of new carbon–phosphorus bonds through displacement of chloride from phosphorus.\(^72,73\) For example, displacement of bromide from phosphorus tribromide has been used for the introduction of a new thiophosphoryl functionality adjacent to an original carbonyl group (Equation 4.28).\(^72\) This approach provides a facile access to β-ketophosphonates.
4.4 Addition reactions of P–H compounds

In this section we will survey the use of transition metal-catalyzed additions, at times accompanied by rearrangement processes, that lead to the generation of new carbon–phosphorus bonds.

Several reports have been made of a successful catalyzed addition/substitution reaction resulting in direct attachment of phosphorus to aromatic rings. The preparation of mixed triarylphosphines has been accomplished by the reaction of tin- or silicon-substituted diphenylphosphines with aryl halides catalyzed by palladium reagents. A similar transformation has also been reported using nickel catalysis. The addition/substitution of diphenylphosphine to triflate functionalized phenolic linkages has been of use for the preparation of substances as analogues of tyrosine-related amino acid derivatives, accomplished with catalysis by palladium acetate (Equation 4.29).
The initial phosphine products were converted to the phosphine sulfides to protect them from oxidation and readily reconverted to the free phosphines by Raney nickel desulfurization.\textsuperscript{77}

Regioselective (Markovnikov) hydrophosphorylation of alkynes with dialkyl phosphites catalyzed by a series of Pd(0) complexes has been accomplished in excellent yield in THF solution.\textsuperscript{78} Although a variety of Pd(0) species served as catalysts, common Pd(II) species were ineffective. Several Pt(0) species were also able to catalyze the hydrophosphorylation process, but with lower efficiency.

While free radical addition reactions of phosphorus reagents across alkene linkages are well known,\textsuperscript{79–82} transition metal-catalyzed addition across alkene linkages is generally less efficient than the corresponding reactions involving alkynes.\textsuperscript{78,83–87} However, it has been noted that five-membered cyclic hydrogen phosphonates undergo the palladium(0)-catalyzed addition reaction with alkenes readily in high yield (Equation 4.30).\textsuperscript{88}

\begin{equation}
\text{CH}_3 \text{P(CH}_3\text{)}_2\text{CH}_3 + \text{H}_2\text{C}−\text{Pd−P(C}_6\text{H}_5\text{)}_2\text{CH}_3 \rightarrow \text{P}−\text{O}−\text{C}_6\text{H}_3 \rightarrow \text{C}_6\text{H}_3\text{P(O)H} \rightarrow 63\% \text{ yield}
\end{equation}

(4.30)

Although regioselective, the regioselectivity is variable depending on the substituents attached to the olefinic linkage. The reaction does not occur at all when acyclic or six-membered cyclic hydrogen phosphonates are used. The reaction is of general utility for phosphonate synthesis because the five-membered cyclic hydrogen phosphonates are readily prepared,\textsuperscript{89–94} and the ester linkages may readily be removed to generate the free phosphonic acid.

An addition–elimination reaction of substituted trimethylsilylphosphines with vinylic bromides catalyzed by Pd(II) complexes has been found to be of use for the preparation of vinylic phosphines (Equation 4.31).\textsuperscript{95}

\begin{equation}
\text{R}_2\text{PSi(CH}_3\text{)}_3 + \text{BrR'C=CHR''} \rightarrow \text{PdCl}_2(\text{P[C}_6\text{H}_5\text{]}_3)_2 \rightarrow \text{R}_2\text{PCR'=CHR''}
\end{equation}

(4.31)
The preparation of tertiary phosphines by this approach proceeds with fewer complications than does the preparation of secondary phosphines, although the reaction remains useful for secondary phosphines. Although transition metal-mediated $P\text{--}H$ addition across ordinary alkenes proceeds well only with five-membered cyclic hydrogen phosphonates, addition across the olefinic linkage of $\alpha,\beta$-unsaturated compounds occurs readily with a range of phosphorus species and catalytic agents. Of particular note are the reaction systems involving platinum,\textsuperscript{96–107} palladium,\textsuperscript{108–115} and the lanthanides.\textsuperscript{116–122}

### 4.5 Addition reactions of $P\text{--}Cl$ compounds

Phosphorus–halogen compounds undergo addition reactions at carbonyl and imine sites to form products reminiscent of those of the Abramov reaction (Chapter 3). In very early work, it was shown that phosphorus trichloride could add to aldehydes, and, upon addition of water, provide a facile approach for the preparation of $\alpha$-hydroxyalkylphosphonic acids.\textsuperscript{123–126} Although the products are reminiscent of those of the Abramov reaction, the mechanism would definitely appear to be different in nature. Evidence is available that the reaction proceeds through polymeric phosphorus–halogen species that react with \textit{in situ}-generated halo-organics leading to $\alpha$-halophosphorus dichlorides that provide the $\alpha$-hydroxyphosphonic acids on water workup.\textsuperscript{127,128}

Several reports have been made of the application of this procedure for the preparation of vinylphosphonates\textsuperscript{129–131} as well as tertiary vinylphosphine oxides\textsuperscript{132} in good yield. When formaldehyde is used, this approach provides a convenient method for the preparation of chloromethylphosphonic dichloride.\textsuperscript{133} Extreme caution needs to be exercised in the performance of this reaction because the extremely hazardous bis-chloromethyl ether is generated as an intermediate and may remain in the product or escape the reaction mixture during performance of the reaction.

In addition to carbonyl substrates, imines have been used extensively with phosphorus–halogen reagents for the preparation of a variety of phosphonates and phosphinates. Combined in a reaction medium, secondary amines react with formaldehyde and phosphorus trichloride\textsuperscript{134,135} or alkyldichlorophosphines\textsuperscript{136} to produce $N,N$-disubstituted aminomethylphosphonates or -phosphinates. These reactions occur under mild conditions with good yield. Similarly, aliphatic carboxylic amides react with aldehydes to generate imines, which can be used \textit{in situ} with diphenylchlorophosphine to produce
(N-acylated 1-aminoalkyl)diphenylphosphine oxides in good yield.\textsuperscript{137}

As an approach to phosphorus analogues of natural amino acids, a corresponding procedure may be used. Most conveniently, benzyl-carbamate serves as the amide component. A variety of phosphorus–halogen reagents have been used, including phosphorus trichloride as well as alkyl- and aryl dichlorophosphines, to generate analogues of alanine, phenylalanine, serine, proline, aspartic acid, and glutamic acid.\textsuperscript{138–142} This approach allows the preparation of monobasic analogues of the natural amino acids (Equation 4.32).

\begin{equation}
\text{CH}_3\text{CHO} + \text{CH}_3\text{PCl}_2 + \text{C}_6\text{H}_5\text{CH}_2\text{OCONH}_2 \xrightarrow{1. \text{CH}_3\text{COOH}} \text{CH}_3\text{CH(NH}_2\text{)P(CH}_3\text{)O}_2\text{H}} \xrightarrow{2. \text{H}_2\text{O, HCl}} \text{CH}_3\text{CH(NH}_2\text{)P(CH}_3\text{)O}_2\text{H}}
\end{equation}

(4.32)

Acetals have been used in the presence of Lewis acids, particularly zinc chloride and ferric chloride, for the addition of phosphorus–halogen species to prepare 1-alkoxyphosphonic dichlorides and dialkyl 1-alkoxyphosphonates (from phosphorus trichloride and dialkyl phosphinous chlorides, respectively).\textsuperscript{143–145} It should be noted that good yields of these types of products have also been reported in the absence of catalysts.\textsuperscript{146,147} Other types of substrates have also been used in these types of processes. These include acylals,\textsuperscript{148} amidals,\textsuperscript{149} orthoformates,\textsuperscript{150} and orthoacetates.\textsuperscript{151}

Phosphorus halides of use in this type of process have not been limited to P(III) species. Phosphorus pentachloride undergoes addition/elimination with olefinic linkages producing a new carbon–phosphorus bond.\textsuperscript{152} This reaction has been reported to proceed by initial formation of a vinylic trichlorophosphonium salt.\textsuperscript{153} Upon workup with an oxidizing agent, the phosphonic dichloride can be isolated. Numerous oxidizing agents have been utilized in this system, including sulfur dioxide (Equation 4.33),\textsuperscript{153} ethylene oxide,\textsuperscript{154} and ketones.\textsuperscript{155}

\begin{equation}
\text{OR} + 2 \text{PCl}_3 \rightarrow \text{Cl}_3\text{P} \rightarrow \text{SO}_2 \rightarrow \text{RO} \rightarrow \text{P(O)Cl}_2
\end{equation}

(4.33)
The formation of hydrogen chloride in the reaction medium can lead to products of its addition to the olefinic linkage.\textsuperscript{156} Yields of such adducts are increased by the use of solvents of low polarity that are weak electron acceptors, such as dichlorodimethylsilane (Equation 4.34).\textsuperscript{157}

\begin{equation}
\text{Cl}_2\text{H}_4 + \text{PCl}_5 \xrightarrow{1. (\text{CH}_3)_2\text{SiCl}_2, 20^\circ\text{C}} \rightarrow \text{Cl}\text{P(O)Cl}_2 \quad 88\% \text{ yield}
\end{equation}

(4.34)

Conjugated olefinic systems have also been used in reaction with phosphorus–halogen species. For example, methylphosphonic dichloride adds regioselectively to acrylic acid in the presence of phosphorus trichloride (used as solvent), to produce the acid chloride 3-phosphonopropionyl chloride (Equation 4.35).\textsuperscript{158}

\begin{equation}
\text{CH}_3\text{P(O)Cl}_2 + \text{H}_2\text{C}==\text{CHCO}_2\text{H} + \text{PCl}_3 \rightarrow \text{CH}_3\text{P(O)ClCH}_2\text{CH}_2\text{COCl} \quad 56\% \text{ yield}
\end{equation}

(4.35)

Zirconocene dichloride has been reported to serve as catalyst for the addition of dialkyl phosphorochloridates across the triple bond of terminal alkynes.\textsuperscript{159} DIBAL is used with the terminal alkyne system to generate the dialkyl 1-alkenylphosphonate products.

4.6 Rearrangements resulting in the formation of new P–C bonds

The reaction of propargyl alcohols with phosphorus trichloride, under appropriate conditions, has long been known as a standard procedure for the preparation of propargyl halides.\textsuperscript{160} However, performance of the reaction in the presence of amines as acid scavengers at times leads to the formation of allenicphosphonates via a rearrangement of the intermediate propargylphosphonous dichloride. A corresponding rearrangement of dialkyl esters of propargylphosphonites to allenicphosphonates has also been shown to occur thermally, even with long standing at room temperature.\textsuperscript{163,164}
intramolecular rearrangement (Equation 4.36) can be understood as being as an endo-5-dig process.\textsuperscript{165,166}

\[
\begin{array}{c}
\text{R} \quad \text{R'} \quad \text{R''} \\
\text{X}_2 \text{P} \quad \text{O} \\
\text{R} \quad \text{C} = \text{C} = \text{C} \\
\text{R'} \\
\text{X}_2 \text{P} \quad \text{O}
\end{array}
\] \quad \text{(4.36)}

Recently, reaction of a propargylic alcohol with diethyl chlorophosphite in the presence of a tertiary amine has been found to be a facile method for the direct preparation of allenic phosphonates (Equation 4.37).\textsuperscript{167}

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{N} \\
\text{Boc} \\
\text{C} = \text{C} \\
\text{H} \\
\text{H} \\
\text{P}(	ext{O})(\text{OC}_2 \text{H}_5)_2
\end{array} \quad \text{70\% yield}
\]

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{N} \\
\text{Boc} \\
\text{C} = \text{C} \\
\text{H} \\
\text{H} \\
\text{P}(	ext{O})(\text{OC}_2 \text{H}_5)_2
\end{array} \quad \text{70\% yield}
\]

\[
\begin{array}{c}
\text{OH} \\
\text{C}_2 \text{H}_5 \text{N} \\
\text{C}_2 \text{H}_5 \text{O}_2 \text{PCl/CH}_2 \text{Cl}_2 \\
\text{C}_2 \text{H}_5 \\
\text{C}_2 \text{H}_5
\end{array}
\] \quad \text{(4.37)}

The reaction is performed most simply by the addition of the propargylic alcohol to a solution of the phosphorus halide. Rearrangement of the phosphorus ester proceeds at ambient temperature or with mild heating. When phosphorus trihalides are used, the product can be isolated as the phosphonic dichloride.\textsuperscript{168,169} Aqueous workup provides the phosphonic acid.\textsuperscript{162} In most instances, however, a dialkyl phosphorochloridite with only a single halogen on phosphorus available for reaction with alcohol has been used.\textsuperscript{165,170–174}

An unusual variation on a P–O–C to P–C–O rearrangement involving an alkyne has been noted\textsuperscript{175} upon the reaction of a propargylic alcohol with diethyl phosphoro chloridate. Upon treatment with LDA at reduced temperature, the propargylic ester undergoes rearrangement to the α-hydroxy-α-acetylenicphosphonate (Equation 4.38).
The ester/alkyne rearrangement system can be extended by conjugation to involve a more distant site. The reaction of diethyl phosphorochloridate with 3-methylhex-4-yne-2-ene-1-ol leads to the vinylogous propargylic ester rearrangement as shown in Equation 4.39.  

\[
\text{R'}=\equiv\text{OH} \quad \text{(C}_2\text{H}_5\text{O})_2\text{P(O)Cl} \quad \text{base} \quad \text{R'}=\equiv\text{OP(O)(OC}_2\text{H}_5\text{)$_2$} \\
\text{LDA} \quad \text{toluene} \quad -5^\circ\text{C} \quad \text{R'}=\equiv\text{P(O)(OC}_2\text{H}_5\text{)$_2$} \quad \text{20–75\% yield}
\]

(4.38)

Variations of the rearrangement occurring in good yield are also noted with thioallylic\(^{177}\) and thiovinylic\(^{178}\) esters of phosphorous acid.

An allylic phosphorus ester rearrangement to form a new C–P bond has been reported under photochemical conditions.\(^{179}\) Under irradiation in the presence of 9,10-dicyanoanthracene, an allylic phosphite ester undergoes rearrangement to form the corresponding allylicphosphonite ester (Equation 4.40). Benzophenone serves only poorly as a photosensitizer in this reaction.
Two other reactions will be noted here that are technically not rearrangements forming new C–P bonds but are closely related and are of interest for the generation of new compounds containing the C–P linkage. The first is the rearrangement of $\alpha$-allyloxymethylphosphonic ester amides to $\alpha$-hydroxy-$\alpha$-allylmethylphosphonic ester amides via a classical sigmatropic rearrangement. Facilitated by butyl lithium at $–70^\circ C$, the reaction proceeds with excellent diastereo- and enantioselectivity (Equation 4.41).

\[ \text{Reaction 4.41} \]

An interesting report has been made of methylene insertion into the P–C linkage of $\alpha$-(acyloxy)iminoalkylphosphonates derived from carbohydrates. This reaction system, using diazomethane, allows extension of the chain by a single carbon atom, with that atom (methylene group) attached directly to the phosphorus.

### 4.7 Experimental procedures

#### 4.7.1 Preparation of diallyl phosphorochloridate — Preparation of a dialkyl phosphorochloridate from a dialkyl phosphate by the Todā reaction

To a stirred mixture of diallyl phosphite (32.4 g, 0.20 mol) and carbon tetrachloride (35 ml, 0.40 mol), cooled to 0°C, triethylamine (3.2 ml, 0.023 mol) was slowly added. The temperature was maintained at 0°C for 1 h, during which time a vigorous reaction ensued. After this time, the reaction was allowed to come to room temperature and was...
stirred overnight. The precipitate that had formed was removed by filtration, hydroquinone (0.5 g) was added, and the solvent was evaporated under reduced pressure at room temperature. The residue was vacuum distilled (65°C/4 torr) to give pure diallyl phosphorochloridate (8.5 g, 22%).

4.7.2 *Preparation of 2-chloromethyl-2-ethyl-1,3-propanediol phosphorochloridate* — *Preparation of a dialkyl phosphorochloridate by reaction of a trialkyl phosphite with chlorine*[^7]

1-Ethyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane (32.4 g, 0.20 mol) was dissolved in anhydrous diethyl ether (50 ml). The solution was cooled to –20°C, and chlorine gas was bubbled into the solution, giving rise to a voluminous precipitate. The gas was added until the solution took on the characteristic green color of chlorine gas. The solution was then allowed to come to room temperature. When the solution reached 0°C, an exothermic reaction ensued, which was controlled by means of an ice bath. The solution became completely clear and homogeneous upon completion of the reaction. The ether was evaporated from the solution under reduced pressure, and the residue was vacuum distilled (135°C/0.3 torr) to give the pure 2-chloromethyl-2-ethyl-1,3-propanediol phosphorochloridate (40.5 g, 87%).

4.7.3 *Preparation of isopropyl methylphosphonochloridate* — *Preparation of a phosphonochloridate by reaction of a phosphonate diester with phosgene*[^14]

A stream of phosgene was passed into diisopropyl methylphosphonate (270 g, 1.50 mol) for 10 h with stirring at 20 to 30°C. After completion of the addition, the mixture was allowed to stand overnight, and then the excess phosgene and isopropyl chloride were evaporated under reduced pressure. The residue was vacuum distilled (38°C/2 torr) to give isopropyl methylphosphonochloridate (222 g, 94%).

4.7.4 *Preparation of diethyl 3-trifluoromethylphenylphosphonate* — *Reaction of a Grignard reagent with a dialkyl phosphorochloridate*[^37]

The Grignard reagent of 3-trifluoromethylphenyl bromide was prepared by the addition of the 3-trifluoromethylphenyl bromide (112.5 g, 0.50 mol) to magnesium (12.5 g, 0.515 mol) in anhydrous diethyl ether. The Grignard reagent (122 g) was added with stirring at 20°C to diethyl phosphorochloridate (228 g, 0.90 mol), and the mixture was stirred overnight. The precipitate that had formed was removed by filtration, hydroquinone (0.5 g) was added, and the solvent was evaporated under reduced pressure at room temperature. The residue was vacuum distilled (65°C/4 torr) to give pure diethyl 3-trifluoromethylphenylphosphonate (105 g, 70%).
ether (280 ml). The dark-green Grignard solution was transferred to a 500-ml constant-addition funnel under a nitrogen atmosphere through septa using a double-pointed needle. The Grignard reagent was then added dropwise to a stirred solution of freshly distilled diethyl phosphorochloridate (172.55 g, 1.0 mol) in anhydrous diethyl ether (500 ml) at –76°C. After the addition, which was complete in 1.5 h, the mixture was poured into 5% hydrochloric acid (300 ml). The ether layer was washed with water (3 x 500 ml), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Fractional distillation of the residue (105°C/0.9 torr) gave pure diethyl 3-trifluoromethylphenylphosphonate (131.15 g, 93%).

4.7.5 Preparation of vinyl dichlorophosphine — Reaction of phosphorus trichloride with an organomercury compound

Freshly distilled phosphorus trichloride (420 g, 3.06 mol), together with dry degassed mineral oil (60 ml), was placed under a nitrogen atmosphere in a flat-bottomed flask equipped with magnetic stirrer, thermometer, dropping funnel, and reflux condenser. The flask was warmed to produce a gentle reflux of the phosphorus trichloride, and then divinylmercury (145 g, 0.57 mol) was added dropwise through a pressure-equalizing dropping funnel. The temperature of the reaction flask was maintained at 65–85°C during the addition and was continued at reflux for 1 h after completion of the addition. On cooling, a distillation head was substituted for the reflux condenser, and excess phosphorus trichloride (250 ml) was distilled at 200 torr. The remaining liquid was transferred under vacuum to a distillation flask cooled to –78°C, containing degassed mineral oil (25 ml). It was necessary to heat the flask to 100°C to complete the transfer. The liquid material was fractionated (63.4°C/200 torr) to yield the vinyl dichlorophosphine (36 g, 50%).

4.7.6 Preparation of n-butyl dichlorophosphine — Monoalkylation of phosphorus trichloride using an organocadmium reagent

Di-n-butylcadmium was prepared by the rapid addition of cadmium chloride (50.4 g, 0.275 mol) to a cooled solution of n-butylmagnesium bromide formed from magnesium (12.15 g, 0.50 mol) and n-butyl bromide (75.4 g, 0.55 mol) in anhydrous diethyl ether (550 ml). Following the addition, the reaction mixture was stirred at 0°C for 2 h. The di-n-butylcadmium reaction mixture, including the precipitate, was then added to a stirred solution of phosphorus trichloride (85.9 g,
0.625 mol) in anhydrous diethyl ether (100 ml) over a period of 25 min. The reaction mixture was maintained at –20°C. After the addition, anhydrous diethyl ether (100 ml) was flushed through the cadmium reagent vessel into the main reaction mixture. The reaction was allowed to come to room temperature and was then refluxed for 2.5 h. The reaction mixture was allowed to stand overnight, and the bulk of the ether solution was decanted. The residue was washed additionally with diethyl ether (100 ml) and the mixture filtered, and the solids further washed with diethyl ether (100 ml). (Care must be taken with the solution and the solids as both may catch fire upon hydrolysis of \( n \)-butyldichlorophosphine.) The combined ether washings and reaction mixture were evaporated under reduced pressure and the residue fractionated through a glass-helices packed column (56°C/22 torr) to give pure \( n \)-butyldichlorophosphine (37.4 g, 47%).

4.7.7 Preparation of diethyl 3-diphenylthiophosphoryl-2-morpholino-1-cyclohexenylphosphonous acid — Reaction of an enamine with a phosphorus halide and subsequent esterification

A mixture of diphenyl-3-(2-morpholino-1-cyclohexenyl)phosphine sulfide (3.25 g, 8.5 mmol) and triethylamine (0.91 g, 9 mmol) in benzene (20 ml) was added to a solution of phosphorus tribromide (2.30 g, 8.5 mmol) in benzene (20 ml). After 2 h, a mixture of methanol (0.55 g, 17 mmol) and triethylamine (1.82 g, 18 mmol) in benzene (20 ml) was added with stirring to the solidified mass. After 1 h, the mixture was filtered, the filtrate was evaporated, and the residue was ground with petroleum ether. There was thus isolated pure dimethyl 3-diphenylthiophosphoryl-2-morpholino-1-cyclohexenylphosphonous acid of melting point (mp) 193–196°C (3.14 g, 78%).

4.7.8 Preparation of bis(4-methoxyphenyl)phenylphosphine oxide — Reaction of a Grignard reagent with a phosphorus halide

Freshly distilled THF (200 ml) and magnesium turnings (25.2 g, 1.0 mol) were added to a flame-dried, 2-l flask equipped with a 500-ml dropping funnel. Then, \( p \)-bromoanisole (5.0 ml, 40 mmol) was added. After the Grignard reaction initiated, additional \( p \)-bromoanisole (96.0 ml, 0.77 mol) was added over 1 h. The flask contents were then stirred for 1 h at room temperature, and subsequently phenyldichlorophosphine (68.02 g, 0.38 mol) was slowly injected into the stirred mixture. The reaction mixture was stirred for 1 h and then poured into a
mixture of ice (100 g) and 10% hydrochloric acid (1 l). Extraction was performed with diethyl ether (3 × 1 l). The filtrate was dried, volatiles were evaporated under reduced pressure, and the residue was recrystallized from ethanol to give the pure bis(4-methoxyphenyl)phenylphosphine (92.98 g, 82%) as a colorless oil. Subsequent oxidation of the bis(4-methoxyphenyl)phenylphosphine (26.00 g, 0.078 mol) was accomplished using aqueous (800 ml water) KMnO₄ (13.00 g, 0.082 mol). Purification by recrystallization from hexane gave the pure bis(4-methoxyphenyl)phenylphosphine oxide as a crystalline solid of mp 94.5–95˚C (26.40 g, 97%).

4.7.9 Preparation of diethyl 1-hydroxy-2-butynephosphonate
— Reaction of a phosphorus halide with a 2-alkynol and subsequent rearrangement to generate a hydroxyphosphonate

2-Butyn-1-ol (2.24 g, 32 mmol) was added to a well-stirred mixture of diethyl phosphorochloridate (5.38 g, 38 mmol), NaOH (200 ml of a 50% aqueous solution), triethylbenzylammonium chloride (4.0 g, 17 mmol), and methylene chloride (100 ml). After being stirred for 1 h, the mixture was diluted with water (1 l), the aqueous layer was back-extracted with methylene chloride (1 l), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Kugelrohr distillation gave the intermediate ester as a colorless oil (5.54 g, 84%). To a stirred solution of this intermediate (combined preparations: 6.41 g, 31.1 mmol) in toluene (75 ml) at a temperature of −50˚C was added LDA (prepared in situ from N,N-diisopropylamine [6.9 ml] and butyl lithium [1.6 M, 29.2 ml]) in toluene (75 ml). The resulting mixture was stirred for 50 min, and the solution was quenched with acetic acid (1 M in diethyl ether, 100 ml). The gelatinous mixture was washed with water, the aqueous layer was back-extracted with methylene chloride (200 ml), and the combined organic layers were concentrated. Dry column chromatography (Florasil, ethyl acetate/hexane gradient) produced the pure diethyl 1-hydroxybutynephosphonate as an oil which solidified on standing (3.17 g, 49%).

4.7.10 Preparation of 2-[1,3]dithianyldiphenylphosphine oxide
— Reaction of a chlorophosphine with a stabilized carbanion reagent

Freshly sublimed 1,3-dithiane (1.0 g, 8.33 mmol) was placed in a flask equipped with a rubber septum. Tetrahydrofuran (20 ml) was added
to the flask via syringe through the septum. The flask was cooled to
–20˚C, and then a solution of n-butyl lithium in hexane (1.5 M, 6.67
ml, 10.0 mmol) was added, also via syringe through the septum while
maintaining a nitrogen atmosphere. The reaction mixture was stirred
at –20˚C for 1.5 h and was then treated with chlorodiphenylphosphine
(1.84 g, 8.33 mmol) in tetrahydrofuran (15 ml) with tetramethylethyl-
enediamine (1.0 g, 8.5 mmol). The reaction mixture was stirred at
–20˚C for 1.5 h and then at room temperature for an additional 3 h,
and then was quenched by the addition of saturated ammonium
chloride solution. The aqueous solution was extracted with chloro-
form, the solution dried, and solvent removed under reduced pres-
sure. The residual solid was recrystallized from benzene to give pure
2-[1,3]dithianyldiphenylphosphine oxide (1.07 g, 40%) as white crys-
tals of mp 242–243˚C.

4.7.11 Preparation of 2,5-dimethylbenzenephosphinic acid —
Aluminum chloride-mediated reaction of phosphorus
trichloride with an aromatic hydrocarbon57

To a flame-dried, three-neck, 1-l flask were added, in order, p-
xylene (107 g, 1.0 mol), phosphorus trichloride (412 g, 3.0 mol),
and anhydrous aluminum chloride (160 g, 1.2 mol). The reaction
mixture was slowly heated to reflux with stirring. After 2.5 h at
reflux, the reaction was allowed to cool to room temperature and
the volatile components distilled at reduced pressure. The residual
oil was slowly added to cold water (1 l) with stirring, and a white
solid formed. The solid was removed by filtration, washed with
water, and air dried. The solid was suspended in water (1 l) to
which was added 50% sodium hydroxide solution (90 ml) to cause
dissolution. The solution was saturated with carbon dioxide and
filtered through Celite®. The basic solution was washed with meth-
ylene chloride (200 ml) and acidified with concentrated hydrochlo-
ric acid (200 ml). The white solid that separated was isolated by
extraction with methylene chloride (3 × 250 ml). The extracts were
dried over magnesium sulfate, filtered, and evaporated under
reduced pressure to give the pure 2,5-dimethylbenzenephosphinic
acid (99 g, 60%) as an oil, which slowly crystallized to a solid of
mp 77–79˚C.
4.7.12 Preparation of (1-aminopropyl)phenylphosphinic acid — Reaction of a carbonyl compound with benzyl carbamate and a dichlorophosphine[139]

Freshly distilled propanal (4.4 g, 0.075 mol) was added at room temperature over a period of 20 min to a stirred mixture of benzyl carbamate (7.55 g, 0.05 mol), phenyldichlorophosphine (8.95 g, 0.05 mol), and glacial acetic acid (10 ml). The mixture was refluxed for 40 min, treated with 4 N hydrochloric acid (50 ml), and then refluxed again for 30 min. After cooling, the organic layer was removed, and the aqueous layer was boiled with charcoal (2 g) and evaporated to dryness in vacuum. The residue was dissolved in methanol (40 ml) and treated with propylene oxide until a pH of 6 to 7 was attained. The resultant precipitate was filtered, washed with acetone, and crystallized from methanol/water to give pure (1-aminopropyl)phenylphosphinic acid (4.08 g, 41%) of mp 256–258˚C.

4.7.13 Preparation of diethyl 5-methoxytetrahydrofuran-2-ylphosphonate — Reaction of an acetal with a phosphorochloridite[146]

Diethyl phosphorochloridite (0.714 ml, 5 mmol) was added dropwise to a stirred solution of 2,5-dimethoxytetrahydrofuran (0.65 ml, 5 mmol) in methylene chloride at 0˚C under an argon atmosphere. The solution was then stirred at room temperature for 12 h, after which the solution was concentrated under reduced pressure and the residue subjected to Kugelrohr distillation (120˚C/0.03 torr). There was in this manner isolated the pure diethyl 5-methoxytetrahydrofuran-2-ylphosphonate (0.475 g, 48%) as a colorless oil.

4.7.14 Preparation of propadienylphosphonic dichloride — Rearrangement of a propargylic trivalent phosphorus ester[168]

A 2-l Morton flask, provided with a motor stirrer, an immersion thermometer, and a condenser topped by a drying tube, was charged with phosphorus trichloride (824 g, 6.0 mol) and heated in an oil bath to 74˚C. With vigorous stirring, propargyl alcohol (11.2 g, 0.20 mol) was added subsurface through a thin delivery tube passing through the condenser. The addition was performed as quickly as possible (5 to 10 sec) under positive pressure. Gaseous hydrogen chloride was formed rapidly and passed out of the reaction system through the condenser. The solution was brought to reflux at 76˚C and maintained at that temperature for 3 h. Excess phosphorus trichloride was
removed under reduced pressure, and the residual oil was washed with toluene several times to remove the last traces of phosphorus trichloride. There was isolated by vacuum distillation (40°C/0.1 torr) pure propadienylphosphonic dichloride (25 g, 79%).

4.7.15 Preparation of 2-chlorohept-1-ylphosphonic dichloride — Reaction of an alkene with phosphorus pentachloride

While stirred, 1-heptene (9.8 g, 0.1 mol) was added at 20°C to a suspension of phosphorus pentachloride (41.7 g, 0.2 mol) in dimethyl-dichlorosilane (100 ml). The reaction mixture was stirred at 20°C for 3 h and cooled to −10°C. Sulfur dioxide dried over phosphorus pentoxide was bubbled into the reaction mixture until complete dissolution of the intermediate complex was observed. After evaporation of solvent, the residue was vacuum distilled to give pure 2-chlorohept-1-ylphosphonic dichloride (22.1 g, 88%).

4.7.16 Preparation of 6-amino-1-hydroxyhexyldenediphosphonic acid — Reaction of a carboxylic acid with phosphorous acid and phosphorus trichloride

A mixture of 6-aminocaproic acid (13 g, 0.1 mol) and phosphorous acid (12.7 g, 0.156 mol) in chlorobenzene (100 ml) was heated to 100°C with stirring. Phosphorus trichloride (22 g, 0.16 mol) was added dropwise to the mixture within a period of 30 min. The solution was then heated with stirring for 3 h. Insoluble material separated during this time. After cooling, the solvent was decanted, and the residue was boiled with water (60 ml) for 30 min and subjected to hot filtration with activated charcoal through a layer of Supercel. The solution was concentrated under reduced pressure and the crystals formed were collected by filtration. Methanol was added to the mother liquors to complete the precipitation. There was in this way isolated pure 6-amino-1-hydroxyhexyldenediphosphonic acid (15 g, 55%) of mp 245°C.

4.7.17 Preparation of diethyl 1-(4-pyridyl)-1,2-dihydropyridine-2-phosphonate — Reaction of phosphorus trichloride with a pyridylpyridinium chloride

Freshly powdered 1-(4-pyridyl)pyridinium chloride hydrochloride (11.45 g, 0.05 mol) and phosphorus trichloride (27.5 g, 0.2 mol) were placed in a flask protected from moisture. The mixture was heated at
reflux for 20 h. Excess phosphorus trichloride was evaporated under reduced pressure, and ethanol (20 ml) was added to the reaction mixture with cooling by an ice bath. After 2 h, the excess ethanol was evaporated, and a solution of potassium carbonate was added until the solution became basic. The oil that separated was extracted with diethyl ether (2 × 50 ml), the extracts were dried over magnesium sulfate, and the solvent evaporated under reduced pressure. The crude materials thus obtained were purified by column chromatography (silica gel; eluent: chloroform/ethanol, 8:1). There was thus isolated pure diethyl 1-(4-pyridyl)-1,2-dihydropyridine-2-phosphonate (8.1 g, 57%), which yielded a picrate salt of mp 163–164˚C.

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chapter 5

Pentacoordinate phosphorus

5.1 Introduction

In this chapter, we consider two aspects of carbon–phosphorus bond formation as they relate to pentacoordinated phosphorus species. The first aspect is the preparation of stable phosphorane species — compounds bearing five bonds to phosphorus with at least one of them being a C–P linkage. At present, this is an area of rather specialized interest, but one that has potential for broader applications.

The second aspect is concerned with using pentacoordinated phosphorus species as intermediates to prepare other compound classes bearing a C–P linkage, the syntheses of which by more “traditional” means is often complicated or obviated by numerous factors. Using phosphoranes as intermediates provides a facile approach to the general syntheses of C–P bond-containing substances. We anticipate the development and ultimate use of this approach to organophosphorus compound syntheses to expand greatly in the foreseeable future and to be worthy of special notation here.

5.2 General structure of pentacoordinate phosphorus

Two general structural types might be imagined for the array of five ligands about a central phosphorus atom. These are the square pyramidal configuration (sp) (Figure 5.1A) and the trigonal bipyramidal configuration (tbp) (Figure 5.1B). The latter of these is that generally found to exist in stable pentacoordinate phosphorus compounds.
5.3 Stable phosphoranes

5.3.1 General

It is generally known that phosphorus is capable not only of forming species with five formal bonds to the phosphorus atom, but also that such compounds can be stable under ordinary conditions. We are concerned here with those pentacoordinate phosphorus compounds that have at least one formal carbon–phosphorus bond. We will focus primarily on the processes that generate such a bond.

5.3.2 Stereochemistry

As noted previously, the trigonal bipyramidal configuration is the arrangement of ligands generally found about pentacoordinated phosphorus in phosphoranes or oxyphosphoranes.\(^1\) Such an arrangement of ligands provides phosphoranes and oxyphosphoranes with stereochemical characteristics significantly different from those associated with a tetrahedral array, as is commonly associated not only with saturated carbon but also tetracoordinated phosphorus in phosphonium salts, phosphoryl compounds, and even trigonal pyramidal tricoordinated phosphorus species.\(^2\)–\(^5\)

We may look at the general situation of such a pentacoordinated species by considering first the simplest system of this type, as may be seen with the (inorganic) species PF\(_5\). All ligands about the central phosphorus site are represented by the same species, but not all are in equivalent positions, and thereby not all are not chemically (or magnetically) equivalent. In the trigonal bipyramidal array, three fluorine atoms are located in so-called equatorial positions about the central phosphorus, in a planar–trigonal manner. These three atoms are chemically and magnetically equivalent to one another. The remaining fluorine atoms are arrayed directly above and below the central phosphorus (apical positions) and are chemically and magnetically equivalent to one another. Generally, bond distances from phosphorus to each of the two types of ligands are not identical, but even if they happen to correspond, the two positions are not equiv-

![Figure 5.1 A. sp configuration about P; B. tbp configuration about P.](image-url)
alent. (A fundamental concept from mathematics is that it is impossible to array five points on a sphere so that all are in equivalent relationships with one another.)

With the existence of two distinct types of ligand sites about the trigonal bipyramidal phosphorus, we might anticipate that we could observe chemical and physical differences between them even though they are nominally the same species (as in PF$_5$). However, an exchange of positions for such ligands is quite possible without breaking and reforming bonds and occurs through a process referred to as pseudo-rotation. The process of pseudorotation is graphically illustrated in Figure 5.2.

Overall, the process involved in an individual cycle of pseudorotation may be described as having one “static” equatorial ligand (ligand 1 of Figure 5.1), and four other ligands (two equatorial and two apical) that undergo an inversion. During this inversion, the two original equatorial ligands end up in apical positions and the two original apical ligands end up in equatorial positions. The “static” ligand remains in its starting position. Graphical methods (Figure 5.3) may be used to ascertain that for a species such as PF$_5$ undergoing successive cycles of pseudorotation all ligands will occupy each type of position for equivalent periods of time. Thus, rapid pseudorotation results in a single $^{19}$F NMR signal being observed for the fluorines of PF$_5$, rather than two signals, one for each of the types of positions occupied at any given instance by the five fluorine atoms.

With particular types of ligands (e.g., a variety of bidentate ligands), some modes of pseudorotation are prevented from occurring owing to steric restraints. This simplifies the overall situation for the interconversion of structural forms. For example, in the general situation with five nonidentical ligands about phosphorus (Pabxyz), exchange of the positions of the two apical ligands (a and b) results in the generation of the enantiomeric form of the original. Similarly,

![Figure 5.2 The pseudorotation process about a tbp phosphorus center.](image-url)
exchange of any two of the three equatorial ligands (x, y, and z) results in the generation of the enantiomeric form of the original. Further, exchange of any apical with any equatorial ligand results in the generation of a diastereoisomer of the original structure. Such racemization or formation of diastereoisomers can be obviated with cyclic bidentate ligands that preclude particular modes of pseudorotation from occurring, and enantiomeric forms can be isolated, whereas with monodentate ligands in Pabxyz, racemization and diastereoisomer formation occur readily.

A further point of phosphorane stereochemistry needs to be considered — the formation and dissociation of such pentacoordinated species, particularly as a variety of reactions involve tbp phosphorus species as intermediates. The formation of a tbp phosphorus array from a tetracoordinated tetrahedral species occurs by the addition of the incoming ligand to a tetrahedral face, generating a new apical site. That is, the incoming ligand occupies an apical position about the tbp phosphorus. Similarly, the loss of a ligand from a tbp phosphorus to generate a tetracoordinated tetrahedral phosphorus unit occurs from an apical position. With tbp phosphorus in general, the more electronegative ligands have a tendency to occupy apical positions. These several factors restrict the possibilities for pseudorotation in pentacoordinate phosphorus species and facilitate the isolation of particular stereoisomers.

\[ \text{Figure 5.3 Each juncture of lines represents a configuration for which the pair of numbers represents the ligands that are located in apical positions. The lines connecting the number pairs correspond to cycles of pseudorotation. The "static" position for a particular pseudorotation cycle is that ligand of the five not represented by a number at either end of the connecting line. Reversals of number pairs (such as "24" and "42") represent pairs of enantiomers for a system with five nonidentical ligands about the central phosphorus (Pabxyz).} \]
5.3.3 **Syntheses**

The preparation of stable phosphoranes in which all of the bonds to phosphorus are from carbon functionalities is based on the pioneering work of Wittig. During this preparation, a quaternary phosphonium salt is treated with an organolithium reagent, forming the neutral phosphorane and an inorganic salt (Figure 5.4). As long as no removable hydrogen is present on a carbon joined to phosphorus in the starting quaternary phosphonium species (which leads to an alkylidene phosphorane, or “Wittig reagent”), aryl lithium species can be used to add to phosphorus, providing a fifth ligand. This has been demonstrated with a trityl group attached to phosphorus in the phosphonium salt (Figure 5.5).

When an aminophosphonium species is used with an aryl lithium reagent, cleavage of the amino functionality from phosphorus is observed, producing the parent phosphine. This reaction has been used to prepare stable phosphoranes from aminophosphonium species using dilithium reagents (Figure 5.6). It should be noted that the

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\[ \text{Li}_3\text{P}^+ \text{Ph}_5^- + \text{LiI} \rightarrow \text{Li}_5\text{P} + \text{LiI} \]

*Figure 5.4* Formation of pentaphenylphosphorane.

\[ \text{Cl}^- [\text{Ph}_3\text{P}^+ - \text{C} - \text{Ph}_3\text{Li}] \rightarrow [\text{Ph}_3\text{P} - \text{C} - \text{Ph}_4]_3 \]

*Figure 5.5* Formation of a stable phosphorane from a quaternary phosphonium salt.

\[ \text{Br}^- \text{N(CH}_3\text{)}_2\text{P}^+ \rightarrow \text{Br}^- \text{N(CH}_3\text{)}_2\text{P} \]

*Figure 5.6* Formation of a phosphorane from an aminophosphonium salt.
product phosphorane in Figure 5.6 is one of those species with restricted pseudorotation; the phenyl ring will always be in an equatorial position, and for any pseudorotation it will serve as the “static” ligand.

A variety of stable phosphoranes have been prepared in this manner,\textsuperscript{11–14} including a pentaphosphonium phosphorane (Figure 5.7).\textsuperscript{15}

5.4 Carbon–phosphorus bond formation involving phosphorane intermediates

5.4.1 General

In recent years, a new and intriguing approach toward the generation of carbon–phosphorus bonds in phosphonates and related types of compounds has been developed. This approach depends on the initial formation of a phosphorane species in which only one of the five bonds to phosphorus is from a carbon functionality. The remaining bonds to phosphorus are from heteroatoms, generally oxygen. This approach is useful not only in the formation of phosphonates difficult to generate by other methods, but also for non-phosphorus-containing products proceeding through organophosphorus intermediates.

These developments are derived from the early work of Ramirez and coworkers\textsuperscript{16,17}, which was concerned with the formation of a type of cyclic oxyphosphorane that is formed by the addition of a trialkyl phosphite to either a diketone (Figure 5.8) or an \(\alpha,\beta\)-unsaturated carbonyl compound (Figure 5.9). Initially, developments from this effort

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{Figure57.png}
\caption{Zeroth generation dendrimer with a phosphorane core.}
\end{figure}
were concerned with stereochemical aspects of processes not involving the formation of carbon–phosphorus bonds and chemical conversions toward non-phosphorus-containing products. Our interest here is particularly with carbon–phosphorus bond forming processes, and development of this aspect has been relatively recent.

5.4.2 Carbon–phosphorus bond-forming reactions

The work of McClure et al. toward preparing a wide range of phosphonates of varied biological interest has provided the foundation for applying oxyphosphoranes toward new carbon–phosphorus bond formation procedures. Prepared by the addition of trialkyl phosphites to \(\alpha,\beta\)-unsaturated carbonyl compounds, the oxyphosphoranes bearing a single carbon–phosphorus bond are quite stable and may be stored for extended periods of time. Their reaction with electrophiles of varying types proceeds with relative ease, for example, with simple aldehydes to produce adducts that on hydrolysis have provided addition of the carbonyl carbon to the original \(\alpha\)-position of the \(\alpha,\beta\)-unsaturated carbonyl compound (Figure 5.10). For these syntheses, the process is regiospecific, but stereoselectivity may be only moderate.

A particular application of this type of synthesis involving aldehyde addition to the intermediate oxyphosphorane is in the preparation of

\[ O \quad P(\text{OR})_3 \quad + \quad \text{P(OR)}_3 \quad \rightarrow \quad \text{P(OR)}_3 \quad \text{OR} \quad \text{OR} \quad \text{OR} \]

**Figure 5.8** Reaction of a phosphite with a vicinal diketone.

**Figure 5.9** Formation of an oxyphosphorane by the addition of a phosphite to an \(\alpha,\beta\)-unsaturated carbonyl compound.
materials that can be used in subsequent Wadsworth–Horner–Emmons olefination reactions. For example, an application utilizing an intramolecular cyclic olefination process uses a silyl-protected α,β-unsaturated carbonyl compound (Figure 5.11) to prepare neocnidilides.

A variety of other electrophilic substrates have been used with the oxyphosphorane intermediate. This includes N-bromosuccinimide, to prepare β-phosphono-α,β-unsaturated carbonyl compounds (Figure 5.12); oxaziridines to prepare α-hydroxy-β-phosphonoketones after acid hydrolysis (Figure 5.13); and azodicarboxylates to prepare α-nitrogen-substituted-β-phosphonoketones (Figure 5.14). Reactions of the azodicarboxylates have been of particular significance for the generation of precursors in the preparation of phosphonic acid analogues of sphingolipids.

Similarly, the β-phosphono-α,β-unsaturated carbonyl compounds thus synthesized have been used as dienes in a Diels–Alder approach toward the preparation of analogues of myo-inositol 1,4,5-triphosphate, as well as other carbohydrate-related materials.

Reaction of the oxyphosphorane intermediate with arylisocyanates has also provided an approach to uracil phosphonate derivatives via a double addition of the arylisocyanate (Figure 5.15). Mono-addition products are also isolated in this system.

This approach to preparing phosphonates, be they ultimate targets for immediate use or intermediates in syntheses of other materials that do or do not bear phosphorus, is a powerful one. Each reaction proceeds through the same type of oxyphosphorane species produced (from a trivalent phosphorus reagent and an α,β-unsaturated carbonyl compound). The carbon–phosphorus bond-forming process is the initial conjugate addition of the nucleophilic phosphorus to the α,β-unsaturated carbonyl compound, and subsequent reactions of this species provide the variety of phosphonates that may be prepared. Through this approach, sensitive molecules otherwise not available, or prepared only with difficulty through numerous-step processes, are readily prepared.

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**Figure 5.10** Continuing reaction of an unsaturated oxyphosphorane with an aldehyde.
Figure 5.11 Approach to neocnidilides proceeding through an oxyphosphorane.

Figure 5.12 Preparation of β-phosphono-α,β-unsaturated carbonyl compounds from oxyphosphoranes.

Figure 5.13 Reaction of oxaziridines with oxphosphorane intermediates.
5.5 Experimental procedures

5.5.1 Preparation of tetra(p-methoxymethyl)phenylphosphonium bromide — Preparation of a tetraarylphosphonium salt precursor to a pentaarylphosphorane

A solution of tri(p-methoxymethyl)phenylphosphine (0.500 g, 1.26 mmol) in dry methanol (5 ml) was placed in a pressure tube with a Teflon® needle valve along with p-(methoxymethyl)bromobenzene (0.255 g, 1.26 mmol) and anhydrous nickel(II) bromide (0.007 g, 0.032 mmol). The tube was flushed with dry nitrogen and closed. The tube was maintained in an oil bath heated at 180°C for 48 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel (50 g) using 1:1 acetonitrile:ethanol as eluent. In this manner was isolated pure tetra(p-methoxymethyl)phenylphosphonium bromide (0.050 g, 7%), which exhibited spectra and analyses in accord with the proposed structure.
5.5.2 Preparation of pentaphenylphosphorane — Preparation of a phosphorane from a phosphonium salt and an organolithium reagent

A suspension of tetraphenylphosphonium iodide (2.0 g, 0.0043 mol) in anhydrous ether (5 ml) was combined with a 1 N solution of phenyl lithium (5 ml, 0.005 mol). The reaction mixture was allowed to stand for 8 days, after which the dark red supernatant solution was decanted. (In addition to the lithium salts, it still contained 10% phenyl lithium.) The residue was washed with anhydrous ether under nitrogen. Thereby was precipitated the pentaphenylphosphorane as crude crystals. The supernatant turbid suspension was discarded. This purification procedure was repeated until the supernatant ether remained clear. The thus isolated product was recrystallized from cyclohexane under nitrogen to yield the pure pentaphenylphosphorane (1.79 g, 60%) of melting point (mp) 124°C.

5.5.3 Preparation of 2,2,2-trimethoxy-3-phenyl-4-acetyl-5-methyl-Δ4-oxaphospholene — Preparation of an oxyphosphorane by reaction of a trialkyl phosphite with an α,β-unsaturated carbonyl compound

Trimethyl phosphite (11.3 g, 0.091 mol) was added to a solution of 3-benzylidene-2,4-pentanediene (16.35 g, 0.091 mol) in dry methylene chloride. The solution was maintained under nitrogen for 24 h at 20°C and for an additional 5 h at 40°C. After this time, the solvent was evaporated, and the residue was dissolved in hexane. These actions were performed in the absence of moisture. The clear hexane solution was seeded with a crystal of the pure crystalline product (obtained by crystallization from hexane by standing for 2 weeks at 0°C), and after 8 h at 0°C the crystals precipitated yielding pure 2,2,2-trimethoxy-3-phenyl-4-acetyl-5-methyl-Δ4-oxaphospholene (25.12 g, 88.4%) of mp 48–51°C.

5.5.4 Preparation of 2,2,2-triethoxy-2,2-dihydro-5-methyl-1,2Δ3-oxaphospholene — Preparation of an oxyphosphorane by reaction of a trialkyl phosphite with an α,β-unsaturated carbonyl compound

A neat mixture of distilled methyl vinyl ketone (2.0 g, 29 mmol) and triethyl phosphite (4.7 g, 29 mmol) was allowed to stir for 3 days at
room temperature. After this time, the unreacted triethyl phosphite was evaporated under vacuum at 55°C (12 torr). The residual liquid was distilled by bulb-to-bulb distillation (37°C, 0.32 torr) to give pure 2,2,2-triethoxy-2,2-dihydro-5-methyl-1,2\(\lambda^5\)-oxaphospholene (4.6 g, 69%) as a clear oil.

5.5.5 Preparation of diethyl [(2\(R^*\)*)-2-{1(\(S^*\)*)-hydroxyphenyl}-3-oxobutyl]phosphonate — Preparation of a functionalized phosphonate by reaction of an oxaphospholene with an aldehyde\(^5\)

Freshly distilled benzaldehyde (197 mg, 1.86 mmol) was added to 2,2,2-triethoxy-2,2-dihydro-5-methyl-1,2\(\lambda^5\)-oxaphospholene (440 mg, 1.86 mmol) in a flame-dried flask under argon. The reaction mixture was stirred at ambient temperature and monitored by \(^1\)H nuclear magnetic resonance (NMR) spectrometry. The reaction mixture was then heated at 40°C, and monitoring by \(^1\)H NMR was continued. After disappearance of the signals for the oxaphospholene, the reaction mixture was brought to ambient temperature, and water (10 ml) was added. The mixture was allowed to stir for 10 h, and the reaction products were extracted with methylene chloride. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated under vacuum. The crude product mixture was purified by column chromatography eluting with 2% methanol in methylene chloride to give an oil, which was a mixture of diastereoisomers (460 mg), which by \(^1\)H NMR was indicated to be 2:0.1:0 syn:anti. The oil solidified upon cooling and was recrystallized from hexane. The pure syn product, [(2\(R^*\)*)-2-{1(\(S^*\)*)-hydroxyphenyl}-3-oxobutyl]phosphonate, of mp 69–70°C, was collected by washing the recrystallized material with 50% ethyl acetate/hexane.

References


chapter 6

Aromatic and vinylic C–P bonds

6.1 Introduction

Earlier chapters in this work have been organized on the basis of particular types of reactions or reagent systems. In the present chapter, we change orientation and emphasize the particular type of C–P bond to be generated, regardless of the nature of the reaction or reagent system. We review the currently available methods for the preparation of C–P bonds wherein the bond involves a vinylic or aromatic carbon atom bound to a phosphorus atom in a variety of coordination and oxidation states.

A number of the reactions considered here have been reviewed already in earlier treatments within this volume with an emphasis on the reagent system and reaction type. Here, our emphasis is on the production of this particular type of linkage. We also review approaches not considered previously that are distinctly suited for generating vinylic and aromatic C–P bonds. As previously, classical approaches are reviewed, although greater emphasis is given to recent developments.

6.2 Aromatic carbon–phosphorus bond formation

6.2.1 Approaches reminiscent of reactions in aliphatic series

Classical Michaelis–Arbuzov or Michaelis–Becker approaches toward formation of C–P bonds involving aromatic carbon sites are (understandably) not generally feasible. Nucleophilic substitution reactions on aromatic carbon proceed only under particular circumstances relating to the nature of attendant additional substituents, and then often with mechanisms quite different from those observed in
aliphatic series. However, in some instances in which suitable substituents are present, introduction of phosphorus to the aromatic ring can be accomplished with ease.\textsuperscript{1-3}

For example, in the instance of 9-chloroacridine, the attachment of the halogen (leaving group) at a suitably electrophilic carbon site allows the occurrence of a replacement reaction, presumably occurring via an addition–elimination procedure for phosphorus attachment, followed by the common nucleophilic displacement (ester cleavage) of the Michaelis–Arbuzov process (Figure 6.1).\textsuperscript{4}

A somewhat more general approach for substitution on an aromatic ring involves the photoinitiated reaction of aryl iodides with trialkyl phosphites that produces products corresponding to those of a simple Michaelis–Arbuzov reaction. Aryl iodides are photolyzed in the presence of a trialkyl phosphite with subsequent reaction producing (possibly through an intermediate oxyphosphorane) the quasi-phosphonium salt, reminiscent of the Michaelis–Arbuzov process, which then undergoes the final nucleophilic displacement step generating the target arylphosphonate ester (Figure 6.2).\textsuperscript{5-8} Generally, low temperatures are used along with an excess of the trialkyl phosphite. The availability of the appropriate aryl iodide is the major difficulty in the general use of this approach.

\begin{figure}[h]
  \centering
  \includegraphics[width=0.5\textwidth]{reaction_9-chloroacridine}
  \caption{Reaction of 9-chloroacridine with triethyl phosphite.}
  \end{figure}

\begin{figure}[h]
  \centering
  \includegraphics[width=0.5\textwidth]{photoinduced_replacement}
  \caption{Photoinduced replacement of iodine by phosphorus on an aromatic ring.}
  \end{figure}
Less usable in general, although useful for specific applications, are:

- Electrochemical arylation of trialkyl phosphites by anodic oxidation in acetonitrile, a process that is troubled by low yield and formation of a variety of by-products.\(^9\)
- Nucleophilic attack by a trialkyl phosphite on a significantly electron-deficient aromatic ring involving addition–elimination of a nitro group (as nitrite anion), which completes the final step of the normal Michaelis–Arbuzov reaction (Figure 6.3), albeit in relatively low yield.\(^10\)
- Phosphorous acid attack on 1-(4-pyridyl)pyridinium salts, again proceeding with relatively low yield (<30%) (Figure 6.4).\(^11\) This approach is related to earlier reports by Redmore\(^12,13\) in which tritylpyridinium salts, pyridine-\(N\)-oxides, and pyridinium-\(O\)-methyl-\(N\)-oxides were caused to undergo substitution on the aromatic ring using Michaelis–Becker-type reagents (Figure 6.5). Recent developments in the preparation of nucleotide analogues have built on the use of both the tritylpyridinium salts and the pyridinium-\(O\)-methyl-\(N\)-oxide species (Figure 6.6).\(^14-18\) Similarly, other quaternized pyridinium species have been shown to undergo phosphorylation reaction with trialkyl phosphites leading directly to 4-phosphonopyridine species or 1,4-dihydropyridine derivatives.\(^19-21\) Correspondingly, an aromatic sulfonium species has been found to undergo phosphorylation (addition) under Michaelis–Becker conditions to give an uncharged adduct.\(^22\)
- Dialkyl phosphite addition to quinone monoimine species, followed by elimination and rearrangement (Figure 6.7).\(^23\)

Although these approaches to aromatic C–P bond formation resemble in some ways reactions useful for C–P bond formation in aliphatic systems, clearly there are structural/electronic restrictions and differences in mechanisms. Other approaches to aromatic C–P bond formation are of greater generality and usually more efficient.

![Figure 6.3](image)

*Figure 6.3* Replacement of a nitro group by phosphorus on an aromatic ring.
Figure 6.4 Reaction of a pyridyl (pyridinium) salt with phosphorus acid.

Figure 6.5 Substitution on the ring of an O-methyl-N-oxide of pyridine.

Figure 6.6 Formation of an aromatic C–P bond at phosphorus joining nucleoside units.

Figure 6.7 Quinone monoimine in reaction with a dialkyl phosphite.
6.2.2 Transition metal-assisted reactions

For quite some time, a variety of transition metal salts have been a useful reaction system in the facilitation of phosphorus addition to aromatic rings. In addition to the general approaches that have been so available, recent developments also exist. These latter reaction systems have to an extent been noted previously in this volume when considering particular “reaction types,” but will be noted again here in a discussion aimed toward a particular application.

Several reaction systems have been reported in which phosphorus was added to carbon of substrates in which the organic portion was $\pi$-complexed with a transition metal.\(^{24-27}\) Although interesting, these approaches have not proven to be of general utility for synthetic purposes.

The earliest developments in transition metal-assisted formation of aromatic C–P linkages were the result of the efforts of Tavs\(^{28}\) that were concerned with the use of Ni(II) halide salts for the reaction of aryl halides with trialkyl phosphites. These reactions involved conditions reminiscent of the Michaelis–Arbuzov reaction (heating at an elevated temperature) and produced arylphosphonate products in reasonable yield (Figure 6.8).

However, the mechanism of reaction is quite different. The role of the transition metal is catalytic, and initially it is reduced to Ni(0) by the phosphite, yielding tetrakis(trialkyl phosphite)Ni(0).\(^{29}\) As shown in Figure 6.9, this species then undergoes reaction with the aryl halide, ultimately completing the conversion with regeneration of the Ni(0) complex for continuing reaction. The intermediacy of free radical species and alkyl exchange processes has been ruled out by several experimental methods.\(^{28}\) The reaction system has also been used with other types of phosphorus reagents, including triaryl phosphites,\(^{30}\) phosphonite esters,\(^{31-33}\) and thiophosphinite esters.\(^{34}\) The validity of the tetrakis(trivalent phosphorus)Ni(0) reagent as a catalytic intermediate has been verified by other efforts wherein such species were generated independently and used to serve the same process.\(^{35,36}\)

$$\text{NiCl}_2 \xrightarrow{160^\circ C} \text{C}_6\text{H}_5\text{P(O)(OCH[CH}_3\text{]}_2)\text{Br}$$

Figure 6.8 Preparation of arylphosphonates.
Similarly, copper salts (cupric and cuprous) facilitate the reaction of aryl halides with trialkyl phosphites in the formation of dialkyl arylphosphonates under conditions like those found in nickel systems.\textsuperscript{37–39} Again, the copper salts appear to undergo an initial reaction with the phosphites to form a complex that subsequently undergoes reaction with the aryl halide. The requirement for copper is also similar to that for nickel salts: only a catalytic amount is needed. Further, a preference among halides on the aromatic ring is noted; iodide is replaced preferentially to other halides (Figure 6.10).\textsuperscript{40}

The use of palladium as a catalytic agent facilitating formation of carbon-to-phosphorus bonds on aromatic carbon has been prominent in recent years. With a Pd(0) catalyst, in the presence of a tertiary amine, a variety of P(O)H-type compounds undergo a substitution reaction on aromatic halides that is reminiscent of the Michaelis–Becker reaction.\textsuperscript{41–44} In fact, the reaction proceeds by a very different mechanism involving initial oxidative addition of the aryl halide to the Pd(0) system followed by phosphorus attack displacing the metal from the ring (Figure 6.11). The role of the tertiary amine, rather

![Figure 6.9 Mechanism of arylphosphonate formation.](image)

![Figure 6.10 Copper(I)-catalyzed formation of arylphosphonates.](image)

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than for phosphorus anion generation as with the Michaelis–Becker reaction, is to regenerate the catalytic Pd(0) species.

Mixed triarylphosphines have been generated by addition–elimination reactions mediated by both palladium and nickel catalysts.\(^{45-47}\)

6.2.3 Friedel–Crafts-type reactions

The classical Friedel–Crafts approach toward attaching a phosphorus site directly to an aromatic ring would seem a promising route. Phosphorus-centered acid halides would be anticipated to participate in electrophilic aromatic substitution much in the manner of ordinary acyl halides. Early efforts confirmed this concept\(^{48-52}\) However, difficulties have been encountered in the use of the classical conditions,\(^{53}\) and modifications to the approach have been necessary.

Although modifications of the classical aluminum chloride-mediated reaction have provided some improved results\(^{54-58}\) other Lewis acids such as stannic chloride have been reported to provide far superior yields with minimization of side reactions (Figure 6.12), including interactions with sensitive functional groups that may also be present.\(^{59}\) It is of particular note that the use of stannic chloride, soluble in organic media, limits electrophilic substitution reactions to occurring only once on the multiple-halogen–phosphorus center even with highly activated aromatic rings.

![Figure 6.11 Palladium(0)-catalyzed formation of arylphosphonates.](image1)

![Figure 6.12 Friedel–Crafts approach toward formation of an aryl C–P linkage.](image2)
The controlled occurrence of two electrophilic aromatic substitution reactions at a single phosphorus center using phosphorus trichloride has been accomplished using aluminum chloride as the catalyst, but with tris(2-chloroethyl) phosphite as the agent for the decomposition of the adduct–Lewis acid complex (Figure 6.13). 60

6.2.4 Use of organometallics

In Chapter 4, we noted the use of organometallics in the generation of aromatic C–P bonds. 61–68 Although the organometallics are generally of sufficiently high reactivity that multiple substitutions of halogen or ester linkages on phosphorus can occur, selectivity can be attained for controlled substitution reactions (Figure 6.14). 61

6.2.5 Other approaches

A variety of other approaches toward the introduction of C–P bonds directly on an aromatic nucleus have been explored. Intriguingly, an approach using aryl diazonium ions as reactants for phosphorus reagents has provided target products in only mediocre yield (Figure 6.15). 69 A significant problem in this work involves the formation of products with multiple substitutions at phosphorus. It would be of interest to see an application of this approach to phosphorus reagents that is incapable of such multiple reactions. It would also be useful to explore alternative conditions for treatment of the aryl diazonium salts, particularly those in which phosphorus reagents devoid of the extreme aqueous reactivity of phosphorus–halogen species could be used in the normal aqueous medium.

![Figure 6.13](image-url) Aluminum chloride-mediated C–P bond formation.

![Figure 6.14](image-url) Grignard-mediated C–P bond formation.

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A phosphate–phosphonate rearrangement process has also been explored in which a strong base is used to abstract a proton from the position adjacent to an aryl phosphate ester linkage. The product, an ortho-phosphonophenol, is generated in excellent yield (Figure 6.16). Further exploration of the variability of structure for this type of reaction seems desirable.

### 6.3 Vinylic carbon–phosphorus bond formation

#### 6.3.1 Transition metal-assisted reactions

The use of transition metals for the facilitation of substitution reactions on vinylic carbon has proven to be quite successful. For example, vinylic chlorides in the presence of nickel(II) chloride react with trialkyl phosphites to substitute phosphorus for the halide (Figure 6.17). While reminiscent of a direct Michaelis–Arbuzov reaction, including final dealkylation by a chloride ion, the reaction actually involves an addition–elimination process. It appears that chloride provides a more facile reaction than bromide, a characteristic noted in several reaction systems.

**Figure 6.15** Aryl diazonium salts in C–P bond formation.

**Figure 6.16** Oxygen-to-carbon migration of phosphorus in an aromatic system.

**Figure 6.17** Nickel(II)-mediated vinylic C–P bond formation.
Copper(I) halide salts have also been used to facilitate the replacement of halide on vinylic carbon by phosphorus (Figure 6.18). Preformation of the solid copper(I) complexes of trialkyl phosphites provides a convenient reagent for this reaction. While the overall reaction again resembles the Michaelis–Arbuzov reaction, the mechanism is quite different. It has been determined that the reaction involves generation of the quasiphosphonium ion intermediate, but by addition–elimination, and that halide exchange also occurs (chloride from the salt for bromide from the organic substrate) and is the only product-yielding process when complexes of triaryl phosphites are used.

Similar results for the replacement of halogen on an olefinic linkage by phosphorus have been accomplished using dialkyl phosphites with palladium(0) catalysts. Another reaction involving replacement of a vinylic halide by phosphorus utilizes palladium catalysis with a trimethylsilyl-substituted phosphine (Figure 6.19).

A palladium-assisted reaction has also been used in the preparation of vinylic carbon–phosphorus bonds by addition to terminal alkynes. This reaction (Figure 6.20) provides vinylic phosphonates in good yield with reasonable regioselectivity (9:1) favoring addition at the internal position of the terminal alkyne.

### 6.3.2 Uncatalyzed replacement of vinylic halogen

The addition of phosphorus reagents, either trialkyl phosphites or dialkyl phosphite anions, to the β-carbon atom of α,β-unsaturated carbonyl systems has been studied extensively. (This is the fundamental hydrophosphinylation reaction as considered in Chapter 3.) An interesting situation arises when the β-carbon site also bears a

**Figure 6.18** Copper(I)-mediated formation of vinylic C–P bonds.

**Figure 6.19** Palladium(II)-mediated formation of vinylic C–P bonds.
functionality that can serve as a leaving group. In such instances, the initial adduct is capable of undergoing loss of the leaving group, leading to the formation of the product and appearing as though a simple displacement had occurred. It has been demonstrated that this type of conversion is possible with either a halide or an alkoxy leaving group (Figure 6.21). The incoming phosphorus functionality may be either in the form of a trialkyl phosphite or a salt of a dialkyl phosphite, although most efforts have concentrated on the use of trialkyl phosphites with vinylic halides, and vinylogs of these systems are also known to proceed well in this type of reaction.

Another system involving conjugation of the vinylic linkage, but with an aromatic ring rather than a carbonyl group, has been noted through the use of β-bromostyrene with the lithium salt of diphenylphosphine. Presumably, the phenyl ring of the β-bromostyrene serves to stabilize the charge of the initial adduct; the halide is subsequently lost to generate the neutral product.

Corresponding replacement of halide from an unconjugated vinylic site has also been reported. The use of the sodium salts of dialkyl phosphites in tetrahydrofuran at low temperature has been found to provide the vinylic phosphonate in good yield, (Figure 6.22) and triisopropyl phosphite serves similarly to replace a fluoride of trifluoriodoethene (Figure 6.23). The reaction proceeds stereospecifically to replace the fluoride cis to the iodide, and in continuing reaction the iodide is replaced.

### 6.3.3 Miscellaneous reactions

A photoinitiated reaction has been reported of trialkyl phosphite with an electron-deficient vinylic halide for which an olefinic carbon is covalently bound to a metallic center (Figure 6.24). Unfortunately, only low yields of the target phosphonate are obtained. In another report involving a transition metal bound to carbon, an acetylenic carbon covalently bound to an iron center has been found to undergo
thermal reaction with triethyl phosphite to generate a species in which a carbon–phosphorus bond is present at a vinylic site.\(^93\) The initially formed zwitterionic quasiphosphonium species is internally stabilized by coordination of the anionic center to a second iron atom.

Two reports are available on the rearrangement of mixed vinyl phosphite esters to produce phosphonate diesters in moderate yield.\(^{94,95}\) In both instances, the vinyl phosphite esters were prepared by reaction of the dialkyl phosphorous chloride with highly enolized carbonyl compounds. The mixed ester products undergo thermal rearrangement to the phosphonate diesters (Figure 6.25).

A reaction involving phosphorus trichloride providing a free phosphonic acid apparently involves an enolized carbonyl compound as the species attacking the phosphorus.\(^96\) Methyl aromatic ketones thus provide access to the vinylic phosphonic acids (Figure 6.26).

We had earlier noted the utility of organomercurials for the preparation of alkyldichlorophosphines. The thermal reaction of divinylmercury with phosphorus trichloride results in the substitution of only one of the available chlorides to give vinyldichlorophosphine in moderate yield (Figure 6.27).\(^{97}\)
In a similar vein, the 1-alkenylmercury halides undergo photoini-
tiated free radical reaction with salts of dialkyl phosphites and alkyl
phosphonites. When irradiated in a Pyrex® vessel with dimethyl sul-
foxide as the solvent, the salts undergo addition of the vinylic function
to phosphorus in moderate to good yield, releasing the mercury and
maintaining the original stereochemistry about the olefinic link-
ge (Figure 6.28).

Figure 6.24 Replacement of chloride by phosphorus at vinylic carbon in an organo-manganese complex.

Figure 6.25 Oxygen-to-carbon rearrangement at vinylic carbon.

Figure 6.26 Phosphorus acid in formation of a vinylic C–P linkage.

Figure 6.27 Organomercury compounds in replacement of chloride at P(III) site.

In a similar vein, the 1-alkenylmercury halides undergo photoini-
tiated free radical reaction with salts of dialkyl phosphites and alkyl
phosphonites. When irradiated in a Pyrex® vessel with dimethyl sul-
foxide as the solvent, the salts undergo addition of the vinylic function
to phosphorus in moderate to good yield, releasing the mercury and
maintaining the original stereochemistry about the olefinic linkage
(Figure 6.28).
6.4 Experimental procedures

6.4.1 Preparation of diethyl phenylphosphonate — Reaction of an aryl halide with a dialkyl phosphite in the presence of a Pd(0) catalyst and a tertiary amine

Bromobenzene (0.63 g, 4.0 mmol) was added to a stirred mixture of diethyl phosphite (0.61 g, 4.4 mmol), triethylamine (0.44 g, 4.4 mmol), and tetrakis(triphenylphosphine)palladium (0.23 g, 0.2 mmol) under a nitrogen atmosphere. The mixture was stirred for 2.5 h at 90°C. At the end of this time, ether (50 ml) was added and the resultant precipitate of triethylamine hydrochloride was removed by filtration. After evaporation of the solvent, the residue was vacuum distilled (Kugelrohr) to give pure diethyl phenylphosphonate (0.79 g, 92%), which exhibited infrared (IR) and $^1$H nuclear magnetic resonance (NMR) spectra in accord with the assigned structure.

6.4.2 Preparation of dimethyl 2-methylphenylphosphonate — Photoinduced reaction of an aryl iodide with a trialkyl phosphite

A mixture of 2-iodotoluene (8.78 g, 0.04 mol) and trimethyl phosphite (24.8 g, 0.20 mol) was placed in a 45-ml, double-jacketed silica reaction vessel. The mixture was degassed by flushing with dry nitrogen for 5 min and irradiated with a 450-watt Hanovia (Model 679A-10) high-pressure quartz mercury vapor lamp fitted with an aluminum reflector head. The lamp was placed 5 cm from the inner portion of the reaction vessel. The reaction temperature was maintained at 0°C by the circulation of coolant from a thermostatically controlled refrigeration unit. Irradiation was continued at this temperature for 24 h. At the end of this time, the volatile materials were removed with a water aspirator, and the residue was vacuum distilled (96 to 97°C/0.25 torr) to give the dimethyl 2-methylphenylphosphonate (7.28 g, 91%).
6.4.3 Preparation of 4-methoxyphenylphosphonous dichloride
— Friedel–Crafts reaction of a substituted benzene with phosphorus trichloride

A solution of anisole (10.8 g, 0.1 mol), phosphorus trichloride (41 g, 0.30 mol), and anhydrous stannic chloride (2 ml) was refluxed under dry nitrogen for 76 h. An additional 2 ml of stannic chloride was added every 12 h. At the end of this time, the reaction mixture was concentrated under reduced pressure, and the residue was vacuum distilled (74 to 78°C/0.05 torr) through a 10-in. Vigreux column to give pure 4-methoxyphenylphosphonous dichloride (19.8 g, 91%).

6.4.4 Preparation of diethyl 4-acetylphenylphosphonate
— Reaction of an acyl halide with a trialkyl phosphite catalyzed by Ni(II)

Triethyl phosphite (50.0 g, 0.3 mol) was added dropwise over a period of 1 h to a suspension of nickel(II) chloride (2.6 g, 0.2 mol) in 4-bromoacetophenone (40.0 g, 0.2 mol) heated to a temperature of 160°C. Over a further period of heating for 1 h, ethyl bromide was distilled. The residue was vacuum distilled (155–158°C/0.06 torr) to give pure diethyl 4-acetylphenylphosphonate (39.5 g, 78%).

6.4.5 Preparation of dimethyl pyridin-4-ylphosphonate
— Reaction of an N-pyridonepyridinium salt with a trialkyl phosphite

To a stirred suspension of N-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium tetrafluoroborate (0.58 g, 2 mmol) in dry acetonitrile (20 ml) under nitrogen was added trimethyl phosphite (0.25 g, 2 mmol), followed by finely divided sodium iodide (0.30 g, 2 mmol). After 1 h at 25°C, the solvent was removed under reduced pressure, and water (20 ml) was added. The mixture was extracted with methylene chloride (3 × 15 ml), and the extracts were dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (40 ml), heated at reflux for 4 h, evaporated under reduced pressure, and eluted on an alumina column (grade 1, neutral) with chloroform to yield pure dimethyl pyridin-4-ylphosphonate (0.36 g, 96%) of melting point (mp) 139 to 140°C.
6.4.6 **Preparation of diethyl pyridine-2-phosphonate** —
Reaction of an N-methoxy pyridinium salt with a dialkyl phosphite salt

Butyllithium (23% in hexane) (63 ml, 0.15 mol) was added dropwise to diethyl phosphite (25 g, 0.18 mol) at −20 to −30°C over a period of 2 h. To the resulting mixture was added N-methoxypyridinium methosulfate in dimethyl phosphite (40 ml) over a period of 1 h at −15°C. The reaction mixture was stirred at room temperature overnight, and water (100 ml) was then added. The mixture was extracted with chloroform (3 × 75 ml), and the combined organic extracts were separated into neutral and basic fractions by extraction (4 N HCl), basification, and reextraction with chloroform. The basic portion was distilled yielding diethyl pyridine-2-phosphonate (22.9 g, 67%) of boiling point (bp) 105–112°C/0.08 torr.

6.4.7 **Preparation of diethyl (Z)-1-propenylphosphonate** —
Reaction of a vinylic bromide with a dialkyl phosphite catalyzed by Pd(0)

(Z)-1-bromo-1-propene (0.58 g, 4.8 mmol) was mixed with diethyl phosphite (0.55 g, 4.0 mmol), triethylamine (0.41 g, 4.0 mmol), and tetrakis(triphenylphosphine)palladium (0.23 g, 0.2 mmol) in toluene (1 ml). The mixture was heated at 90°C for 1.5 h. At the end of this time, ether (50 ml) was added, and the solution was filtered. The filtrate was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column to give pure diethyl (Z)-1-propenylphosphonate (0.70 g, 98%).

6.4.8 **Preparation of diisopropyl 2,2-diphenylvinylphosphonate** — Reaction of a vinyl bromide with a Cu(I) complex of a trialkyl phosphite

A mixture of (triisopropyl phosphito)copper(I) bromide (17.6 g, 0.05 mol) and 1-bromo-2,2-diphenylethylene (9.1 g, 0.035 mol) was heated at 200°C for 1 h under a nitrogen atmosphere in a flask equipped with a Vigreux column topped by a Dean–Stark trap. The alkyl halide produced in the reaction was collected in the trap. After cooling, the reaction mixture was poured into toluene (60 ml), and ethylenediamine was added (5 ml). After filtering and washing the precipitate with toluene, the combined toluene solutions were washed with 10% hydrochloric acid (10 ml) and water (10 ml), dried over magnesium
sulfate, and evaporated under reduced pressure. The residue was chromatographed on silica gel to give the pure diisopropyl 2,2-diphenylvinylphosphonate (12.1 g, 96%).

6.4.9 **Preparation of diisopropyl (E)-2-benzoylvinylphosphonate — Reaction of a trialkyl phosphite with a β-halovinylketone**

(E)-2-Chlorovinyl phenyl ketone (1.83 g, 11 mmol) and triisopropyl phosphite (2.08 g, 10 mmol) were heated under an argon atmosphere for 1 h at 120 to 130°C. When all of the isopropyl chloride formed had distilled, the residue was chromatographed on a column of silica gel (18 g) being eluted with a 1:1 mixture of methylene chloride–ethyl acetate. The eluent was evaporated of solvent and the residue vacuum distilled to give pure diisopropyl (E)-2-benzoylvinylphosphonate (1.33 g, 45%).

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