Organophosphorus Reagents

A Practical Approach in Chemistry

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OXFORD
UNIVERSITY PRESS

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Organophosphorus chemistry

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1. Introduction

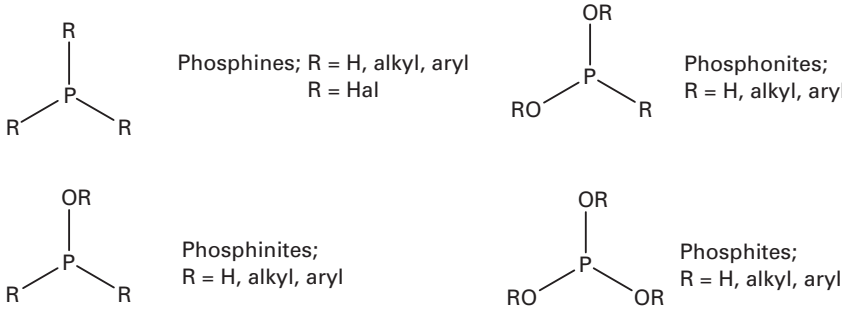
The impact of organophosphorus chemistry on modern synthetic chemistry is difficult to quantify, but one can safely assume that the study of this element has influenced all areas of chemical endeavour.[1] Organophosphorus chemistry, as a discrete area of study, is the study of compounds containing a C—P bond and this book is largely focused on this topic. However, other areas of interest including azaphosphorus, oxyphosphorus and metallophosphorus chemistry are discussed either explicitly as topics or in an implicit manner within the chemistry detailed in each chapter. The purpose of this introductory chapter is to cover many of the general aspects of organophosphorus chemistry and the chemical techniques required for their preparation, including practical methods commonly encountered and some aspects of spectroscopy.

Many texts on organophosphorus chemistry have been published ranging from in-depth studies of the subject as a whole[1,2] to more general texts,[3] which would serve as a general introduction to the field. Of the more comprehensive texts, the four-volume[2a–d] series entitled *The Chemistry of Organophosphorus Compounds* edited by Hartley provides core material published before 1990 and represents an excellent starting point for those new to the field. A considerable amount of organophosphorus chemistry is published in the core literature, which can be difficult to access, however, the periodical *Organophosphorus Chemistry*[4] published annually by the Royal Society of Chemistry offers a yearly review of the highlights and key developments in the field.[4] Several other periodicals, which are no longer published are worthy of note[5] and the two journals *Phosphorus, Sulfur and Silicon, and the Related Elements* and *Heteroatom Chemistry* provide a considerable quantity of useful information for the serious researcher.[6]

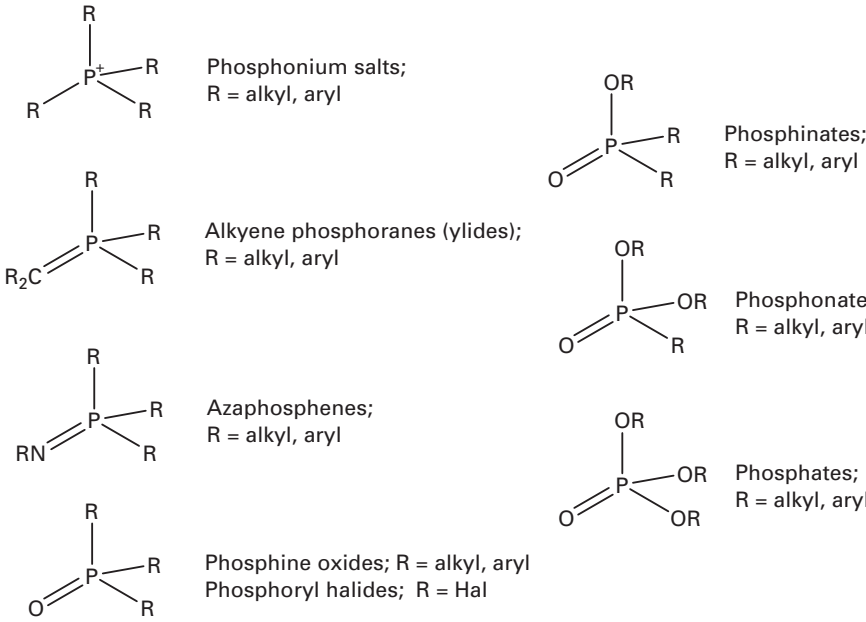
2. Nomenclature

The nomenclature of phosphorus-containing compounds is complicated to some extent by the overlap of inorganic and organic nomenclature, particularly with respect to compounds containing the P—O—H functionality. From the point of view of this volume, the basic nomenclature used for trisubstituted phosphorus

compounds is given in Scheme 1, and that for tetrasubstituted compounds is shown in Scheme 2.[1]



Scheme 1 Nomenclature for trisubstituted phosphorus compounds.



Scheme 2 Nomenclature for tetrasubstituted phosphorus compounds.

3. Practical methods

The reader is referred to more general texts for further information on general experimental techniques.[7] However, it is hoped that for those not experienced

with organic chemistry, enough information has been provided here to perform the experiments. This chapter is intended to familiarize the reader with the equipment and techniques, which are used in the protocols throughout the book.

3.1 Solvents

As with most synthetic organic chemistry, the availability of pure, and in many cases, dry and oxygen-free solvents is essential for both effecting synthetic transformations and for purification purposes. A wide range of organic solvents are employed in organophosphorus chemistry, and many are available from suppliers in an anhydrous form, packaged under nitrogen in SureSeal™ bottles, which are usually suitable for use in the reactions we will cover. However, an alternative method is to purchase technical-grade solvents, which are then treated with chemical drying agents to remove the moisture present and then distilled, either directly before use or onto a drying agent for storage, such as molecular sieves. A range of methods are available for drying solvents[8–10] and the typical solvents employed in organophosphorus chemistry and their method of distillation are detailed below.

3.1.1 Diethyl ether and tetrahydrofuran (THF)

These solvents can be dried efficiently by first drying over sodium wire and then distilling directly before use, from sodium metal under an inert atmosphere in the presence of a small amount of benzophenone. This combination produces a deep-blue/purple solution of sodium benzophenone ketyl if the solvent is dry, and the ketyl colour acts as an indicator, which, when it fades, indicates that additional sodium is needed. This is also an advantageous method as the ketyl is an extremely efficient oxygen scavenger.[8] It is important that peroxide-free diethyl ether and tetrahydrofuran (THF) are employed in the still, and it is also important to ensure that peroxides do not accumulate in stored samples of these solvents. A simple test for this is to mix a sample of the solvent (approximately 1 mL) with glacial acetic acid (1 mL) containing KI crystals (100 mg). A yellow colouration indicates the presence of a small quantity of peroxides, whilst a deep brown colouration indicates a higher concentration. Peroxides can be removed in a number of ways,[8,9] the most convenient being to wash repeatedly with an acidified $FeSO_4$ solution ($FeSO_4$ (60 g), concentrated H_2SO_4 (6 mL), and water (110 mL)), until a negative peroxide test is obtained. The solvent should then be washed with $KMnO_4$ solution (0.5%), NaOH solution (5%), water, and then dried over $CaCl_2$ for 24 h.

3.1.2 Benzene and toluene

These solvents are most conveniently dried by treatment with calcium hydride followed by distillation onto 4 Å molecular sieves.

3.1.3 Petroleum ether (petrol)

Petroleum ether can be dried by distillation onto activated 4 Å molecular sieves.

3.1.4 Dichloromethane

Dichloromethane can be dried by treatment with calcium hydride in a continuous still or can be stored by distillation onto 4 Å molecular sieves. **Caution!** Never treat chlorinated solvents with sodium or strong bases—an explosion may occur.

3.1.5 Dimethylformamide (DMF)

Stir over calcium hydride or phosphorus pentoxide for 24 h, filter under an inert atmosphere and distil (56°C at 20 mmHg) onto 3 Å molecular sieves. An alternative method is to dry over three batches of 3 Å molecular sieves (5% w/v, 3×12 h).

3.1.6 Molecular sieves

The immediate use of dried, deoxygenated solvents is recommended, although non-ethereal solvents can be stored over activated molecular sieves in thoroughly dried containers under N_2/Ar. It is recommended that new molecular sieves be dried before use by heating them in a well-ventilated oven at 320°C for 3 h followed by cooling them in an evacuated desiccator, which is filled with dry N_2/Ar. Sieves may be reused if they are free from residual solvents.

3.1.7 Distillation set-up

If regular amounts of solvent are required, it is convenient to set up a solvent distillation apparatus, commonly referred to as a solvent still. A solvent still enables a continuous supply of dry solvent to be available, which can be conveniently collected under an inert atmosphere. Common stills are those for drying diethyl ether, THF, and dichloromethane. The still shown in Figure 1.1 has an adaptation for removing solvents from the still-head collection reservoir through a septum cap by syringe or, if larger quantities are required, a flask can be connected to the Quickfit adapter on the still-head. These two methods minimize the exposure of the solvent to the atmosphere. When using a solvent still, the following precautions should be observed:

1. The still should be situated in an efficient fume hood, and all tubing for inert gas and water supplies should be securely attached using copper wire or plastic cable ties.
2. The heating mantle should be of such a design that there is no risk of sparks igniting the solvent. This also applies to all electric cables and plugs. The mantle should also incorporate an electricity cut-out device to operate if the water supply to the condenser fails.
3. It is imperative that the bottom flask containing the drying agent should not be allowed to boil dry. This risk can be minimized if the flask is of greater capacity than the collection reservoir and is regularly topped up with solvent.
4. During cooling, an adequate flow of inert gas should be maintained.

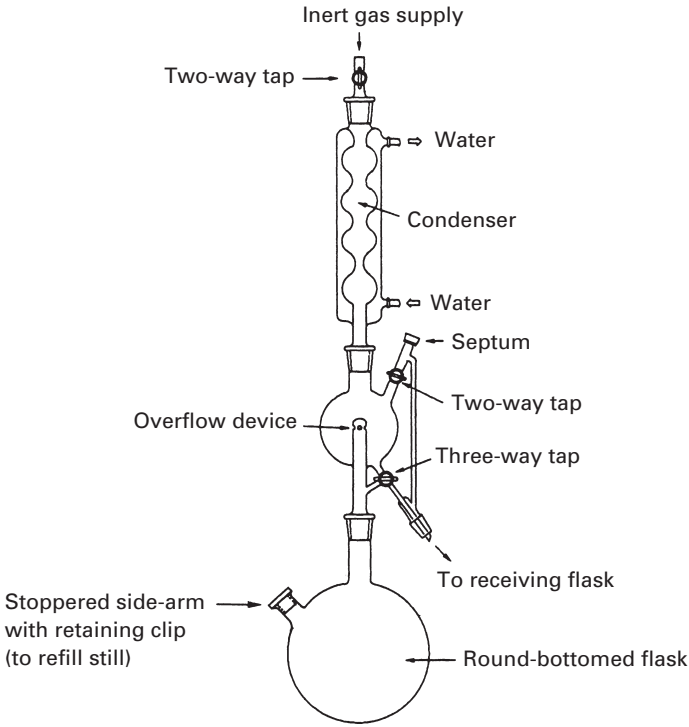


Fig. 1.1 General set-up for a solvent still (reproduced with permission from Ref. 13).

5. **Caution!** The use of a semi-permanent still for ethereal solvents can lead to a build-up of peroxides. The solvent should be checked for peroxides at frequent intervals, and if these are detected, the still should be dismantled and the drying agent and peroxides carefully destroyed. Also, when renewing the still, fresh batches of the solvent and drying agent should be used.

3.2 Working under an inert atmosphere

Many preparations require the use of an inert atmosphere and are thus carried out under an atmosphere of anhydrous nitrogen or argon. Argon has the advantage of being heavier than air and, therefore, provides a more effective barrier against the outside atmosphere, but nitrogen is more commonly used owing to its lower cost. The best method for ensuring that reactions are purged free of oxygen is to employ a purpose-built double manifold of the type shown in Figure 1.2. This apparatus provides the inert gas and a vacuum source *via* two-way stopcocks and allows several inert atmosphere experiments to be run simultaneously. It can also be fitted with a Quickfit adapter fitted with a septum, which can be used for

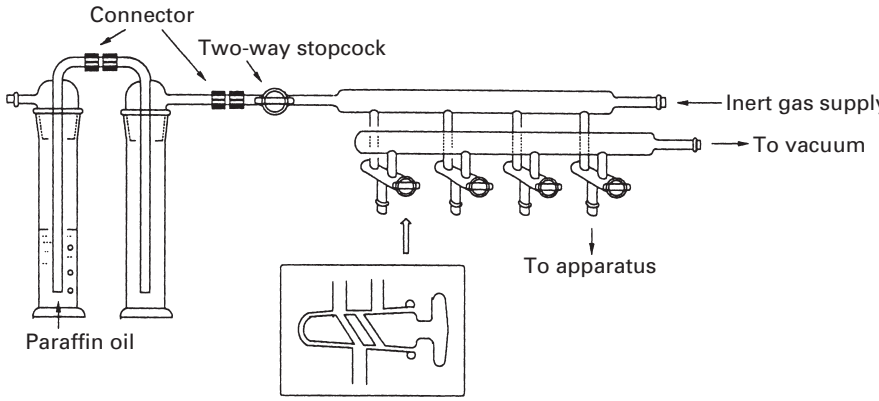


Fig. 1.2 Double manifold apparatus (reproduced with permission from Ref. 13).

purging syringes with inert gas. The supply of inert gas to the manifold should be controlled in two stages using a cylinder regulator and then a needle valve, and the apparatus should also be equipped with a bubbler to control the release of gas.

Further examples of apparatus designed for specific applications appear in the recommended experimental texts for organic synthesis.[7]

3.3 Reaction apparatus

A variety of experimental set-ups will be employed throughout this book. In cases where cooling of a process is required, an arrangement of glassware similar to that shown in Figure 1.3 will be suitable. This consists of a three-necked flask equipped with a magnetic stirring bar, a septum, a low temperature thermometer, and an inlet for inert gas and vacuum. Liquid reagents and solvents can be added via syringe through the septum and, provided that an adequate flow of inert gas is maintained, the septum can be removed to allow the addition of solids.

If heating of the reaction is required, the flask should be equipped with a reflux condenser and an efficient heating apparatus. Two options are generally available for heating a reaction, first, an isomantle which offers direct heating to the flask and can be equipped with a stirring mechanism. Alternatively, an oil-bath is more frequently used as illustrated (Figure 1.4) as this option offers more controlled heating. It is recommended that only fresh paraffin or silicone oil is used in the bath and that a temperature regulating device is fitted to the bath in conjunction with a water cut-out mechanism.

3.4 Standardization of organolithium reagents

In many of the preparations detailed in this book, the use of *n*-BuLi is required. It is recommended that for any purchased solution, this reagent is standardized before use as there is generally a considerable difference between the expected

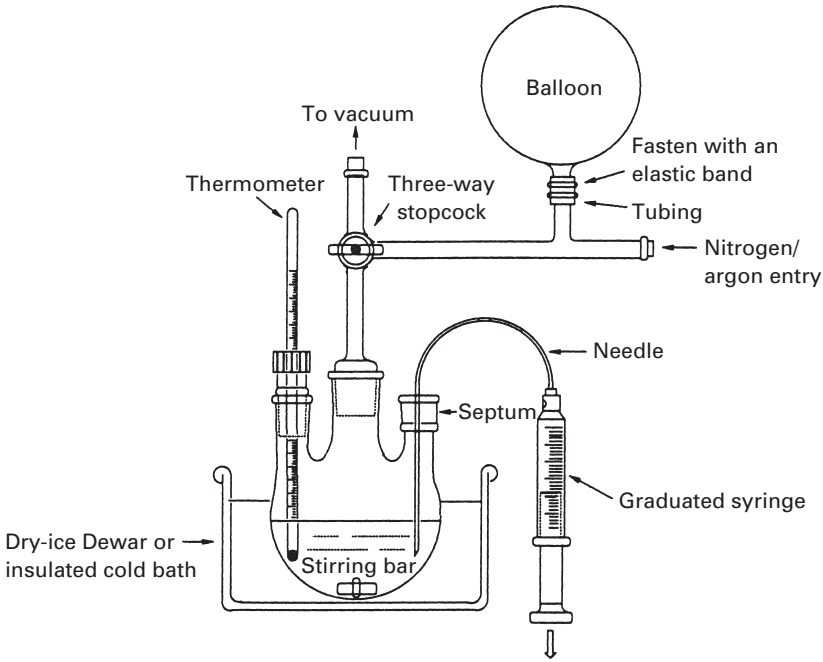


Fig. 1.3 Apparatus for performing a reaction at low temperature (reproduced with permission from Ref. 13).

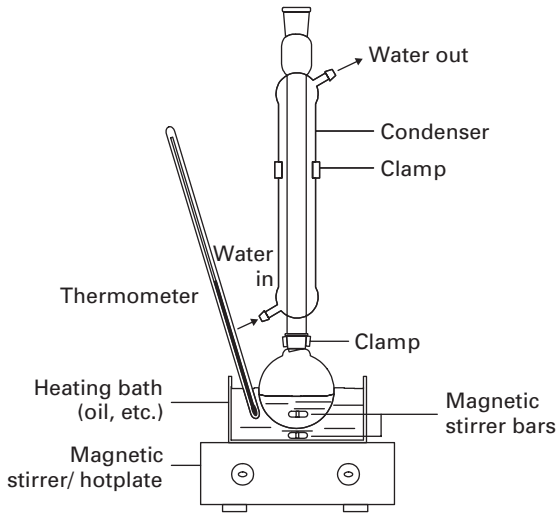


Fig. 1.4 Apparatus for performing a reaction under reflux.

concentration and the actual one, as the reagent may have deteriorated over time. Many methods are available for the standardization, but the most convenient are those which rely on the formation of coloured dianions.[11–13] A procedure (**Protocol 1**) using 1-pyreneacetic acid is one of the most convenient in view of the distinctive red end-point obtained and the fact that the reagent can be recovered easily from titration mixtures and then reused.[12,13] The procedure described can be used for the standardization of butyl-lithium and allows an estimation of the reagent concentration within approximately 0.1 M; it is recommended that the protocol be performed in duplicate.

Protocol 1.
Titration of *n*-butyl-lithium using 1-pyreneacetic acid[12,13]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment (see Figure 1.5)

- A pre-dried, two-necked, round-bottomed flask (50 mL) incorporating side-arm tap adapter (for inert gas inlet), with magnetic stirring bar, septum and gas outlet
- Dry, gas-tight syringes [1 mL, with 0.01 mL graduations (preferably fitted with a screwdriver plunger), and 10 mL]
- Inert gas supply

Materials

- Butyllithium solution to be standardized **pyrophoric**
- 1-Pyreneacetic acid (FW 260.3), pre-dried to constant weight *in vacuo*, (100–200 mg)
- Anhydrous THF 10 mL **flammable, irritant**

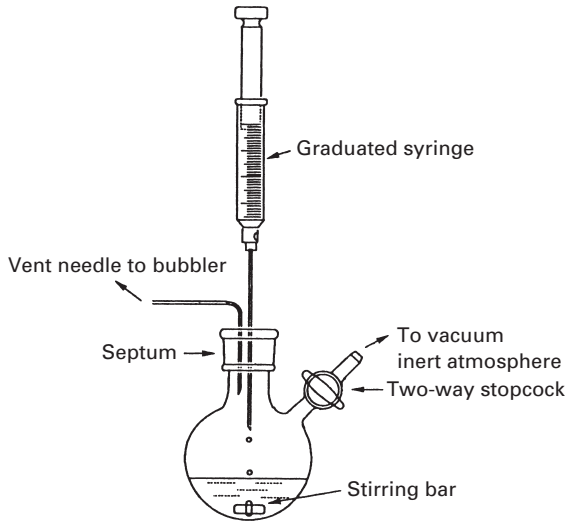


Fig. 1.5 Apparatus for standardization of *n*-BuLi (reproduced with permission from Ref. 13).

Method

1. Flush the round-bottomed flask and accessories with dry, oxygen-free N_2/Ar. Flame dry the flask and allow it to cool in a stream of inert gas. Maintain an inert atmosphere during the remaining steps.
2. Weigh out the 1-pyreneacetic acid accurately, using an analytical balance, and transfer to the round-bottomed flask. Add the THF and stir the mixture until a homogeneous solution is obtained.
3. Charge the 1 mL syringe with the organolithium reagent, and then insert the needle through the septum. Add the organometallic reagent slowly and dropwise (over a period of 3–4 min; slow addition is essential to minimize reaction between THF and BuLi). The end-point is when the red colour of the dianion just persists.
4. The molarity of the butyl-lithium can now be calculated from a consideration of the number of moles of 1-pyreneacetic acid utilized and the volume of BuLi required to obtain a permanent end-point (molarity (M) = mols/vol).

3.5 Cooling baths

Many reactions are carried out in the temperature range 0 to −100°C and a range of cooling systems are available for achieving these temperatures. Table 1.1 is a list of common slush bath compositions, however, many others are available.[9, 14, 15]

The temperature of the reaction mixture should be monitored by means of an internal thermometer (or a temperature probe), as shown in Figure 1.3, since the internal temperature may differ significantly from that of the cooling bath

Table 1.1 Common slush bath compositions

Solvent/additive	**Temperature** (°C)
Ice	0
Ice/salt (3 : 1)	−8
Carbon tetrachloride/CO_2	−23
Ice/$CaCl_2 \cdot 6H_2O$ (4 : 5)	−40
Acetonitrile/CO_2	−42
Chloroform/CO_2	−61
Ethanol/CO_2	−72
Acetone/CO_2	−78
Hexane/liquid N_2	−94
Ethanol/liquid N_2	−116
Liquid N_2	−196

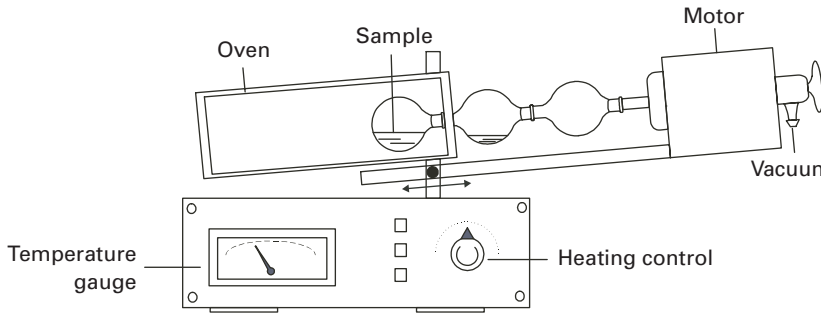


Fig. 1.6 A Kugelrohr bulb-to-bulb distillation apparatus.

medium, particularly during the addition of reagents which produce an exothermic reaction.

3.6 Vacuum distillation

Starting materials, reaction products and solvents often need to be distilled in order to enhance purity. For small-scale distillations, a Kugelrohr bulb-to-bulb distillation apparatus is convenient (Figure 1.6). The sample is placed in the end bulb, the system placed under vacuum if required and the oven temperature is raised. The sample distils into the next bulb (which is outside of the heating compartment) and collected. The distillate can then be redistilled into the next bulb, if required. If the sample has a relatively low boiling point under the pressure employed, it is common practice to cool the receptor bulb with ice, dry ice, or even liquid nitrogen (absorbed onto cotton wool).

A short-path distillation procedure may be used in situations where a simple distillation is required, as purification from non-volatile components/fractional distillation with a Kugelrohr apparatus is difficult. A water-jacketed, semi-micro distillation apparatus is illustrated in Figure 1.7. Heating can either be achieved with the aid of an oil-bath, an isomantle, or a flame (**Caution!** ensure that there are no flammable solvents nearby). For larger scale distillations, a round-bottomed flask should be attached to a distillation column, a still-head, and condenser. The column used in the distillation is variable, and may be either a Vigreux column or a column packed with glass helices.

3.7 Spectroscopic techniques

A variety of spectroscopic techniques are available to the practising organic chemist, and many sources of information are available with excellent coverage of the essential methods and analysis of spectroscopic data.[16] It is widely accepted that nuclear magnetic resonance (NMR) spectroscopy has become the most essential tool for the organic chemist and the reader is assumed to have

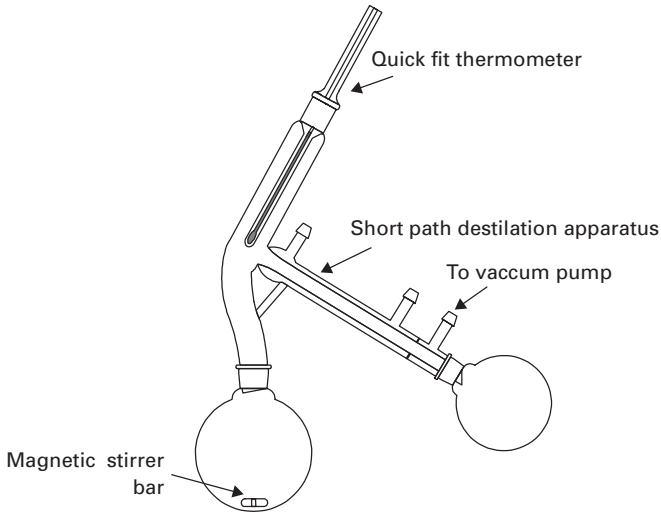


Fig. 1.7 A semi-micro distillation apparatus.

a basic understanding of the principals of the technique and the analysis of the spectra obtained from them.

The stable isotope of phosphorus ^{31}P has a spin of $I = 1/2$ and is, thus, NMR active. A considerable amount has been written[17] on ^{31}P NMR and the reader is referred to these texts for more specialized information. In the specific examples presented in this volume, ^{31}P chemical shifts will be referred to as and when they are required. In general, the magnitudes of the chemical shifts observed are dependent on both the electronegativity of the substituients directly attached to the phosphorus and the amount of back donation of electrons by π-bonding. Thus, increasing the electronegativity of the substituient groups decreases the electron density at the phosphorus atom and leads to a shift to higher frequency (deshielding). Phosphorus compounds resonate over a very wide range (circa +600 to −450 ppm relative to an 85% orthophosphoric acid standard), however, direct correlation between chemical shift and structure are not as predictable as those in ^{1}H and ^{13}C NMR spectroscopy. A small selection of chemical shifts for organophosphorus compounds is given in Table 1.2 for comparison and reference purposes.

Infrared spectroscopy can also be of diagnostic use for the identification of organophosphorus compounds and comprehensive data is available from several sources.[18] Diagnostic absorptions include the P—H stretch, which typically occurs in the region 2460–2450 cm^{-1}, the P═O stretch at 1320–1200 cm^{-1} and the P═N at 1440–1120 cm^{-1}. Other useful absorptions include the P—O—(C) stretch at 870–730 cm^{-1} and the P—O—P stretch at 800–650 cm^{-1} found in phosphate esters.

Table 1.2 Chemical shifts for some organophosphorus compounds

Structure	Chemical shift
PMe_3	−62
PPh_3	−6
PCl_3	+219
PCl_5	−80
PBr_3	+227
$MePCl_2$	+191
$PhPCl_2$	+162
Ph_2PCl	+81
Ph_2PH	−41
$P(OEt)_3$	+137
$P(OPh)_3$	+127
$(EtO)_2PCl$	+165
Et_3PO	+48
Ph_3PO	+29
$(MeO)_3PO$	+2
$(Me_2N)_3PO$	+24
$(MeO)_2POCl$	+8
$(MeO)_2POH$	+10
$Ph_3P{=}CH_2$	+20
$Ph_3PCH_3^+\ Br^-$	+23
H_3PO_4	0
H_3PO_2	+13
Me_2PO_2H	+49

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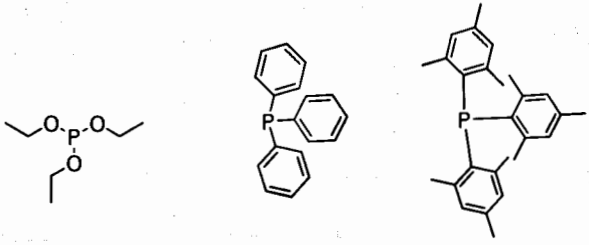
2

The synthesis and applications of phosphines

MATTHEW L. CLARKE and JONATHAN M. J. WILLIAMS

1. Introduction

Phosphines are the most widely used ligands for transition metals because they are extremely versatile: It is possible to vary the size and the donating properties of the phosphine and to introduce either chiral or heteroatom groups. The steric bulk of a phosphine ligand is most often defined by its cone angle.[1] This is a measure of how much volume the organic groups at phosphorus occupy. It is possible to vary widely the size of this angle by choice of organic groups (Scheme 1), and altering steric effects in this way can radically alter both how the phosphine binds to the metal and the reactivity of the metal itself.



1 Cone angle: 107°

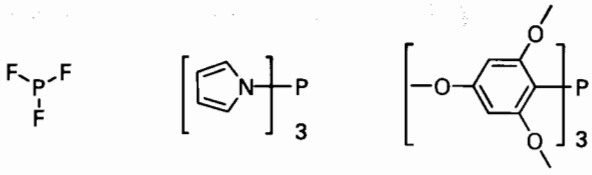
2 Cone angle: 145°

3 Cone angle: 212°

Scheme 1

In addition to having access to a variety of phosphine sizes, it is straightforward to synthesize phosphines of varying electron donor properties. The ability of a ligand to donate or receive electrons from a metal is a crucial factor in determining the relative stabilities of metal oxidation states and also the strength of other bonds within the complex. These two factors are of fundamental importance in the reactivity of homogeneous catalysts.

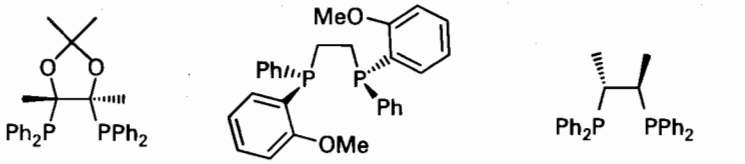
Various attempts have been made at quantifying the overall σ-donor and π-acceptor effects of the many different types of phosphine.[1,2] Chemists have access to π-acceptors such as tris-*N*-pyrrolyl phosphine, perfluoroalkyl phosphines and phosphites, right through to the potent σ-donor, tris(2,4, 6-trimethoxyphenyl)phosphine, **6** (Scheme 2). It is important to note that the donor/acceptor properties of a ligand are dependent on the metal, its oxidation state, and the ancillary ligands on the metal.



4 **5** **6**

Scheme 2

Another important feature of phosphines is their use as chiral ligands. It is possible to make phosphines that are chiral at phosphorus, and phosphines that have achiral phosphorus atoms with chiral groups attached to them (Scheme 3).



'(–)-DIOP®' '(*R*, *R*)-DIPAMP®' '(*R*, *R*)-CHIRAPHOS®'

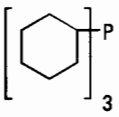
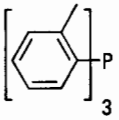
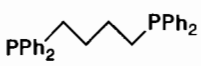
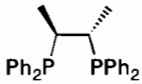
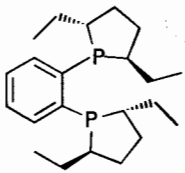
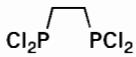
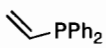
7 **8** **9**

Scheme 3

1.1 Commercially available phosphines

There are many phosphines which are commercially available. It is possible to buy triaryl phosphines with many different aromatic substituents, and phosphines containing a variety of alkyl chains are also easily available. There are about 20 different chiral phosphines commercially available. In addition, there are commercially available phosphines that are useful as synthons. A few examples are given in Table 2.1.

Table 2.1 Some commercially available phosphines

Phosphine	Name	Supplier[a]
	Tricyclohexylphosphine	Avocado
	Tri-*o*-tolylphosphine	Strem
	1,4-Bis(diphenylphosphino) butane	Avocado
	'Chiraphos®'	Fluka
	'Duphos®'	Strem
	1,2-Bis(dichlorophosphino) ethane	Avocado
	Diphenylvinylphosphine	Organo
$KPPh_2$	Potassium diphenylphosphide	Aldrich
Ph_2ClP	Chlorodiphenylphosphine	Avocado
$(Et_2N)PCl_2$	Diethylphosphoramidous dichloride	Aldrich

[a] Many of these phosphines are available from several suppliers.

1.2 Synthesis of phosphines

There are three general methods for the synthesis of phosphines.

1. Reaction of an organometallic reagent with a phosphorus halide (or any phosphine with a good leaving group) (see Protocol 1).
2. Reaction of a metal phosphide with an organic electrophile (Protocol 2).
3. Reduction of a phosphorus halide or oxide.

Some particularly useful specific methods will also be outlined. For further information on phosphine synthesis, the reader is directed to other books and reviews.[3–8]

2. Preparation of tertiary phosphines

2.1 Synthesis from organometallics and electrophilic phosphorus compounds

The classical way of preparing tertiary phosphines is the addition of an organometallic reagent to an electrophilic phosphorus reagent. Typically, Grignard reagents and organolithiums are reacted with phosphorus halides, although many other organometallics have been used, as have other phosphorus electrophiles. A recent example is the reaction of zinc organometallics with chlorodiorganophosphines.[2] It was found that the zinc reagents gave higher yields and allowed greater functionalization in the target phosphine when compared to the organolithium route. Changing the leaving group on phosphorus can give better yields, and alkoxide or amino groups have been used most often to replace chloride.[9,10] A typical synthesis of a tertiary phosphine containing three identical substituents is shown in Protocol 1. Some tertiary phosphine syntheses either require low reaction temperatures (to prevent side reactions) or higher temperatures for prolonged periods of time to obtain good yields of product. It should also be noted that most trialkyl phosphines require isolation and purification under an inert atmosphere. The synthesis of phosphines which have two different substituents, R_2R^1P, using a phosphorus electrophile, requires, as the most

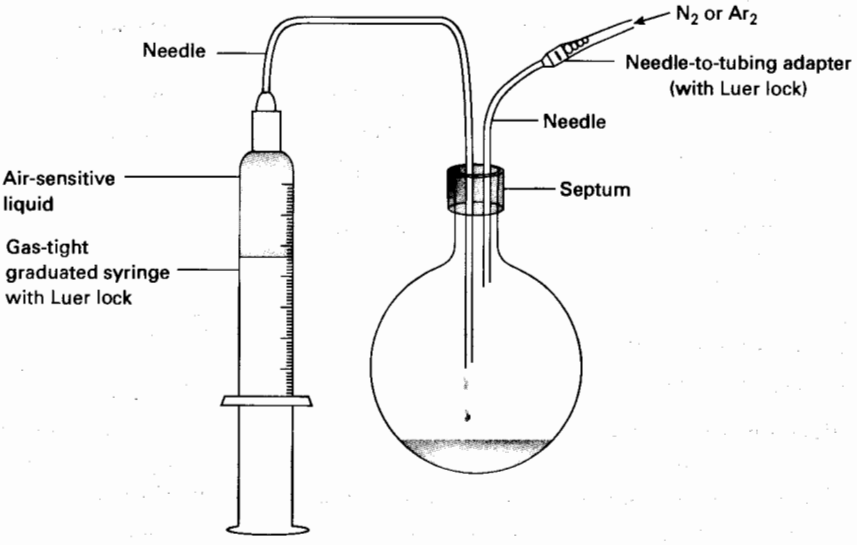


Fig. 2.1 Syringe addition of an air-sensitive liquid.

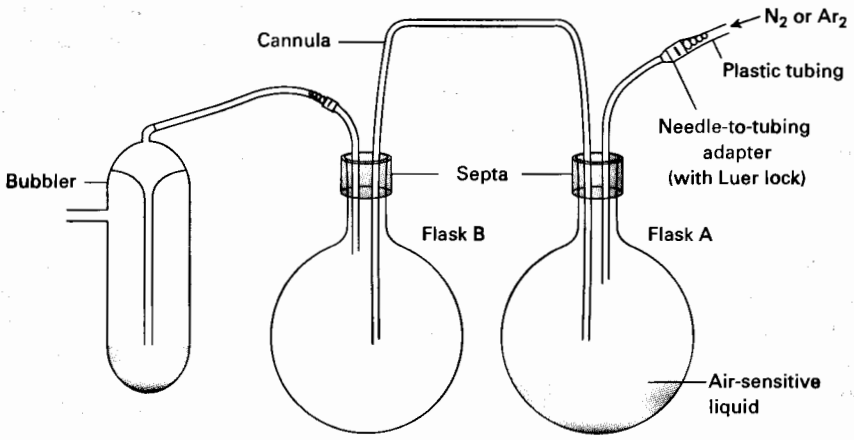


Fig. 2.2 Cannula transfer of an air-sensitive liquid.

demanding step, the synthesis of an intermediate phosphorus halide (Section 3.1). A phosphorus halide is then reacted with the appropriate Grignard reagent or organolithium to generate the tertiary phosphine.

Many of the experiments described in the following pages require the transfer of air-sensitive reagents by syringe or cannula. This can be done using the standard procedures shown in Figures 2.1 and 2.2.

Protocol 1.
Preparation of tris(3-aminophenyl)phosphine, 13 (Scheme 4)

Caution! All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety goggles should be worn.

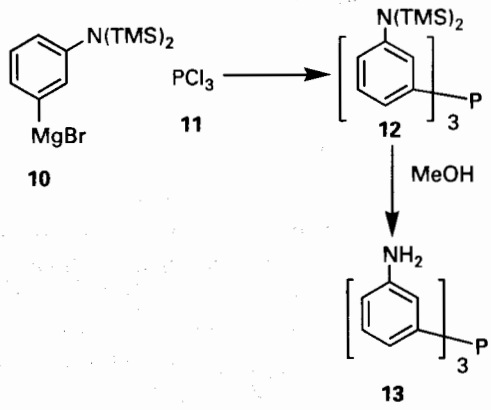
Equipment

- Three-necked, round bottom flask (250 mL)
- One-necked, round bottom flask (100 mL)
- Magnetic stirrer
- Two magnetic stirring bars
- Pressure-equalizing dropping funnel (100 mL)
- Septum (×2)
- Glass stopper
- Water-jacketed reflux condenser
- Ice bath
- Syringe and dry needle (1 × 2.5 mL, 4 × 20 mL)
- Source of dry nitrogen

Materials

- 3-(Bis[trimethylsilyl]amino)phenyl magnesium chloride **10** (FW 296.25), 1 M in THF, 50 mL, 50 mmol.[a] **harmful, highly flammable, causes burns**
- Phosphorus trichloride **11** (FW 137.33, d. 1.574) 1.32 mL, 15.13 mmol **causes burns, irritant**
- Dry THF, 60 mL **highly flammable, irritant**
- Dry methanol, 15 mL **flammable, toxic**
- Petroleum ether **flammable, irritant**

Protocol 1. *Continued*



Scheme 4

Method

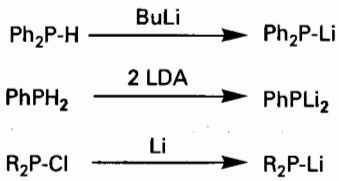
1. Ensure that all glassware is thoroughly clean and has been dried for at least 4 h in a 120°C oven before use. Assemble glassware while still hot.
2. Equip the three-necked flask with a magnetic stirring bar, a glass stopper, a septum and a pressure-equalizing addition funnel. Equip the funnel with the other septum.
3. Flush the system with nitrogen before placing at a static pressure.
4. Add PCl_3 (1.32 mL, 15.15 mmol) and dry THF (50 mL) to the flask via a syringe.
5. Close the tap to the addition funnel, and add the solution of 3-(bis[trimethylsilyl]amino)phenyl magnesium chloride (50 mL, 1 M in pentane) (**Caution!**).
6. Place the three-necked flask in an ice bath, and add the Grignard reagent dropwise over a period of 15 min. Remove the flask from the ice bath, and stir at room temperature for 2 h.
7. Remove the solvent from the reaction mixture using a rotary evaporator.
8. To the remaining residue, add petroleum ether (40/60) (50 mL) and transfer to a separating funnel. Add water (25 mL), extract the organic layer, dry ($MgSO_4$), and remove solvent to give tris-[bis(trimethylsilyl)amino]phenyl phosphine, **12**.
9. To this flask, add MeOH (15 mL) and THF (10 mL). Equip the flask with a reflux condenser, flush with nitrogen, and heat at reflux for 14 h.
10. Cool and remove volatiles under reduced pressure.

11. Triturate with petroleum ether (40/60) before filtering off the pure white solid, tris(3-aminophenyl)phosphine, **13** (2.74 g, 8.93 mmol, 59%).

[a]3-(Bis[trimethylsilyl]amino)phenyl magnesium chloride can be obtained from Aldrich Chemical Company.

2.2 From metal phosphides and an electrophile

There are several different preparations of metal phosphides. Secondary phosphines can be metallated by strong bases such as butyl-lithium or alkali metals (Scheme 5). Primary phosphines can be doubly lithiated using LDA or BuLi.[11] Both the anion and dianion metal phosphides can be generated *in situ* before adding the electrophile into the same pot.[12,13] Phosphorus halides can be metallated using lithium metal.



Scheme 5

These nucleophilic reagents react with most common electrophiles such as organohalides, tosylates, aldehydes, ketones, epoxides, and activated alkenes. It should be noted that many workers have found much higher yields if the phosphides are protected as phosphine oxide or borane anions (see Section 3). Phosphide reagents also react with activated arenes to give mixed aryl phosphines (Protocol 2). Metal phosphides therefore provide an alternative, complementary tertiary phosphine synthesis to the electrophilic routes outlined in Section 2.1.

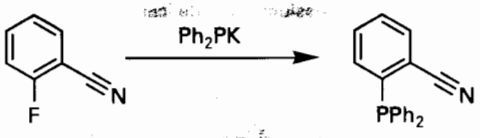
Protocol 2.
Preparation of *o*-(diphenylphosphino)benzonitrile, 15 (Scheme 6)

Caution! All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety goggles should be worn.

Equipment

- One-necked flask (25 mL)
- Two-necked flask (100 mL)
- Magnetic stirrer
- Magnetic stirring bar
- Septum (×2)
- Syringes with dry needles (2 × 20 mL, 1 × 1 mL)
- Reflux condenser
- Separating funnel
- Source of dry nitrogen combined with vacuum line

Protocol 2. *Continued*



14 **15**

Scheme 6

Materials

- Potassium diphenylphosphide (FW 224.29) 10 mL, 5 mmol, 0.5 M in THF [a] — **harmful, highly flammable, causes burns**
- *o*-Fluorobenzonitrile, **14** (FW 121.12, d. 1.116) 0.54 mL, 605 mg, 5 mmol — **harmful, irritant**
- Dry THF, 10 mL — **highly flammable, irritant**
- Dichloromethane (DCM) for extraction (2 × 50 mL) — **toxic**

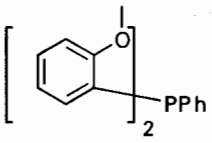
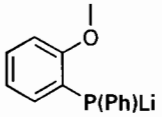
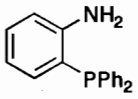
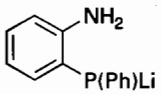
Method

1. Clean all the glassware, and dry in a 120°C oven for at least 4 h before use. Assemble glassware while still hot.
2. Equip the two-necked flask with magnetic stirring bar, septum, and reflux condenser. Flush with nitrogen.
3. Add the potassium diphenylphosphide solution (0.5 M in THF, 10 mL) via a syringe (**Caution!**). Heat the red solution to reflux.
4. To an evacuated one-necked flask equipped with a rubber septum, add *o*- fluorobenzonitrile **14** (0.54 mL, 605 mg, 5 mmol) and dry THF (10 mL) via a syringe. Flush with nitrogen.
5. Carefully syringe the *o*-fluorobenzonitrile solution into the refluxing diphenylphosphide solution. Continue refluxing for 30 min. (There should be a colour change from red to yellow.)
6. After cooling to room temperature, add water (50 mL), and extract the product using DCM (2 × 50 mL)
7. Dry the organic phase ($MgSO_4$), filter, and remove solvent under reduced pressure to yield *o*-(diphenylphosphino)benzonitrile, **15**, as a colourless crystalline solid. (1.26 g, 4.45 mmol, 89%).[b]

[a] Potassium diphenylphosphide can be obtained from Aldrich Chemical Company.
[b] We found the crude material to be essentially pure. However, analytically pure material can be obtained by a single recrystallization from methanol.

A less general route to metal phosphides, but one that is desirable due to the increased availability of tertiary phosphines is a reductive P—C bond cleavage

Table 2.2 Some metal phosphides that can be prepared from tertiary phosphines

Tertiary phosphine	Conditions	Ref.	Proposed phosphide
$Ph_2P(CH_2)_nPPh_2$ $n = 2$–6	(1) Li, 0°C, ultrasound (2) ^{t}BuCl (2 eq.)	14	$Ph(Li)P(CH_2)_nP(Li)Ph$ $n = 2$–6
	Na/K, 0°C, dioxane	15	
Ph_2Me	(1) Li, 0°C, ultrasound (2) ^{t}BuCl (2 eq.)	16	PhP(Me)Li
Ph_3P	Na/K alloy, 25°C, dioxane	17	Ph_2PK
	Li foil, 20°C, THF	18	

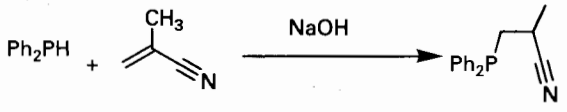
of a tertiary phosphine by an alkali metal. Various alkali metals and reaction conditions have been used, of which the simplest appears to be using lithium metal under ultrasonic radiation. The by-product aryl lithium can be quenched using butyl chloride, while leaving the metal phosphide untouched. It has been observed that trialkylphosphines do not cleave in this manner, whereas in the case of alkyl diarylphosphines, it is always the P—aryl bond that is broken. A few examples of tertiary phosphines that can be metallated in this fashion are given in Table 2.2.

2.3 From primary and secondary phosphines and an electrophile

It is not always necessary to prepare a stoichiometric amount of a metal phosphide in order to couple a phosphine fragment to an electrophile. Primary and secondary phosphines undergo a number of reactions with electrophiles that can be catalysed by acid, base, and radical initiators. A few examples are vinyl ethers adding to secondary phosphines under acid catalysis,[19] secondary phosphine boranes (Section 3) reacting with alkyl bromides, activated alkenes, aldehydes, and ketones to give the corresponding tertiary phosphine boranes,[20] and the base-catalysed reaction of diphenylphosphine, Ph_2PH, **16**, with methacrylonitrile, **17**, to give 3-(diphenylphosphino)2-methylpropionitrile, **18**.[21]

Protocol 3.
Synthesis of 3-(diphenylphosphino)2-methylpropionitrile, 18 (Scheme 7)

Caution! All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety goggles should be worn.



16 **17** **18**

Scheme 7

Equipment

- Three-necked round bottom flask (250 mL)
- Magnetic stirrer
- Magnetic stirring bar
- Septum (×2)
- Reflux condensor
- Tubing adapter
- Pressure-equalizing dropping funnel (50 mL)
- Dry syringes with steel needle (3 × 20 mL, 1 × 1 mL)
- Separating funnel
- Source of dry nitrogen combined with vacuum line

Materials

- Diphenylphosphine, **16** (FW 186.20, d. 1.070), 20.1 mL, 21.5 g, 0.115 mol — **spontaneously flammable in air, causes burns**
- Methacrylonitrile, **17** (FW 67.09, d. 0.80), 20 mL, 16.0 g, 0.238 mol — **highly flammable, toxic, sensitizer**
- 50% aqueous NaOH, 0.5 mL — **causes burns**
- Acetonitrile (50 mL) — **flammable, lachrymator**
- DCM (3 × 25 mL) — **flammable, toxic**
- Absolute ethanol — **flammable, toxic**

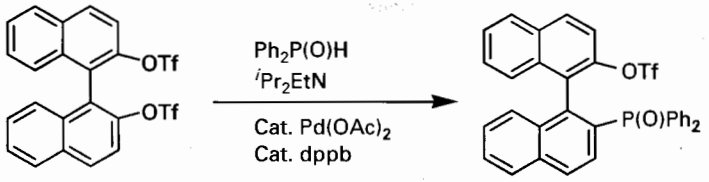
Method

1. Ensure that all glassware is thoroughly clean and has been dried for at least 4 h in a 120°C oven before use. Assemble glassware while still hot.
2. Equip a three-necked round bottom flask with a reflux condenser, pressure-equalizing dropping funnel, a stirring bar, and a septum. Equip the reflux condenser with a tubing adapter connected to the nitrogen/vacuum line, and the dropping funnel with a septum.
3. Add acetonitrile (50 mL) to the flask. Evacuate the vessel and then flush with nitrogen.
4. Using a syringe, add the diphenylphosphine, **16** (20.1 mL, 0.115 mol) (**Caution!**) to the flask.

5. Add 50% aqueous sodium hydroxide (0.5 mL) to the flask, and evacuate/flush with nitrogen. Heat the reaction vessel to 50°C.
6. Using a syringe, add freshly distilled methacrylonitrile, **17** (20.0 mL, 0.238 mol) to the dropping funnel. Add to the mixture dropwise over a period of 1 h.
7. After addition is complete, continue stirring at 50°C for a further 30 min before cooling to room temperature.
8. Add water (25 mL) and DCM (25 mL) to the vessel. Decant the mixture into a separating funnel, extract the DCM layer and perform two more extractions on the aqueous washings with DCM (2 × 25 mL).
9. Combine the organic extracts, dry ($MgSO_4$), and remove solvent under reduced pressure. Leave the resulting oil to solidify overnight (under an atmosphere of nitrogen).
10. Recrystallize the white solid from absolute ethanol to give the pure product, **18** (25.3 g, 0.1 mol, 87%).

2.4 Synthesis using transition metal catalysts

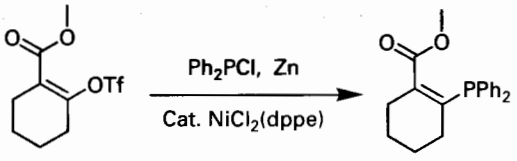
Another important method of synthesizing tertiary phosphines makes use of transition metal catalysts. A transition metal catalysed approach often enables the incorporation of sensitive functional groups into the target phosphine. A useful synthesis of the chiral ligand BINAP (Protocol 5) uses nickel catalysis to couple together secondary phosphines and an aryl ditriflate. Palladium catalysts, which are ineffective at coupling secondary phosphines, will catalyse the reaction between secondary phosphine oxides (and boranes) with aryl triflates and iodides (Scheme 8). These are readily converted to phosphine ligands. It should be noted that in the case of the ditriflate of 1,1′-binaphthol, **19**, only one triflate can be displaced.[22,23] The reagent Ph_2PSiMe_3 also undergoes palladium-catalysed coupling with aryl iodides and bromides.[24]



19 **20**

Scheme 8

A recently reported procedure which appears to be extremely useful is a nickel-catalysed cross-coupling between aryl and vinyl bromides or triflates with chlorodiphenylphosphine (Scheme 9). Zinc metal is used as an additive to reduce the nickel and to form Ph_2PZnCl.[25]



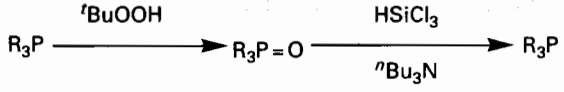
21 22

Scheme 9

3. Preparation and reactivity of primary and secondary phosphines

Primary and secondary phosphines, RPH_2 and R_2PH, are generally air and water sensitive, vile smelling, toxic compounds that are often technically demanding to synthesize and purify. As a result of this, much of the chemistry of these compounds has been conducted on their protected forms: phosphine oxide, $R_nH_{3-n}PO$, phosphine sulfide, $R_nH_{3-n}PS$, or phosphine borane, $R_nH_{3-n}PBH_3$. Protection in this way gives more stable compounds that are easier to purify, more configurationally stable, and that also show interesting reactivity all of their own.

In general, if a phosphine is to be protected as a phosphine oxide, the corresponding phosphorus oxide starting materials are employed. However, it is possible to oxidize a phosphine to a phosphine oxide with *tert*-butylhydroperoxide.[26] Several reagents are suitable for reducing phosphine oxides back to phosphines. A mixture of trichlorosilane and an amine is most often used to this end, as the conditions are quite mild and only a small degree of racemization occurs if chiral phosphine oxides are used (Scheme 10).[27]

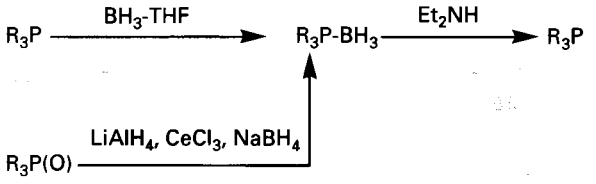


Scheme 10

Other successful reducing agents include diphenylsilane (Ph_2SiH_2), aluminium hydride (AlH_3) and $LiAlH_4$.[28,29] Phosphine sulfides are more rarely used, but can be made by reaction of the phosphine with elemental sulfur and are generally reduced by the same methods used to reduce phosphine oxides.

If phosphine oxide starting materials are not readily available, it seems that borane is the most useful protecting reagent, as shown by Imamoto and co-workers.[20] Phosphine boranes can be conveniently prepared in a number of ways (Scheme 11).

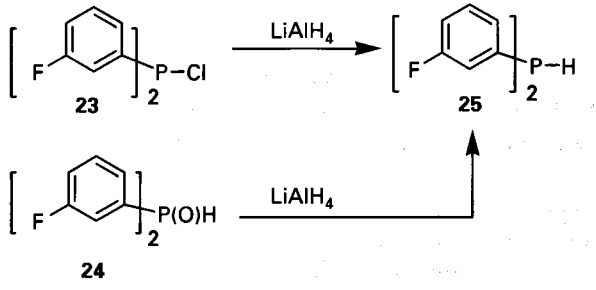
The phosphine boranes undergo a wide range of reactions, some of which are not possible for the corresponding phosphine. Removal of the borane is easily accomplished by treatment with a large excess of amine.



Scheme 11

Secondary phosphines can be prepared by three main routes. The first method, reduction of a phosphinous halide, R_2PCl with $LiAlH_4$ (Scheme 12) requires an efficient synthesis of the starting phosphorus halide, as both the starting material and the product may be difficult to purify.

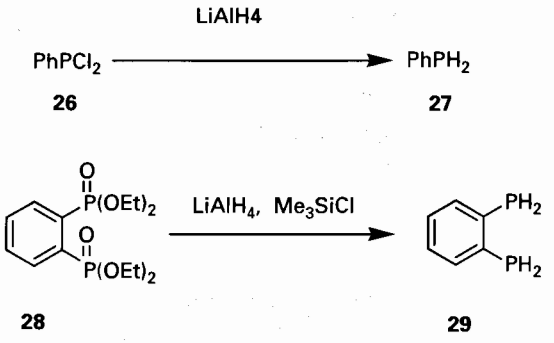
The second route is reduction of the corresponding secondary phosphine oxide. This is useful as secondary phosphines can be prepared from very inexpensive starting materials such as diethyl phosphite, and are often air-stable, easily purified compounds.[30]



Scheme 12

Third, a metal phosphide can be quenched with methanol. This method may be useful if the metal phosphide can be prepared from reductive P—C cleavage of a tertiary phosphine.

Primary phosphines are unpleasant and toxic reagents. They can be prepared from phosphonous halides, $RPCl_2$, using $LiAlH_4$. As is the case for secondary phosphines, easy access to pure phosphonous halides are required to make this route efficient. It has been found that compound **28** can be reduced to primary phosphine **29** using a mixture of $LiAlH_4$ and Me_3SiCl (Scheme 13).[31] This procedure appears useful, as phosphinates of type $RP(O)(OEt)_2$ are often robust compounds that can be prepared in a number of ways. (e.g. Michaelis–Arbusov reaction, palladium-catalysed coupling of diethyl phosphite with aryl bromides, etc.)



Scheme 13

3.1 Preparation of phosphorus halides

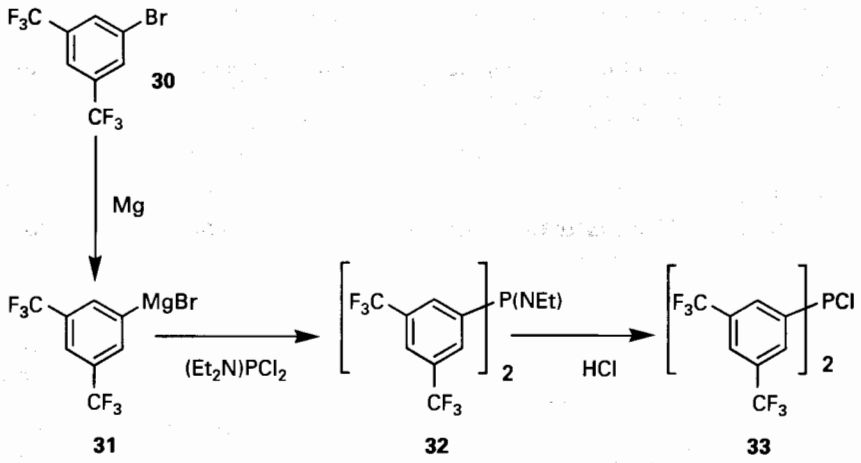
Many of the preparations of primary, secondary, and tertiary phosphines described in the preceding sections require a phosphorus halide compound at some stage in the synthesis. They are therefore very important intermediates in the synthesis of phosphine ligands. The original method of preparation of both phosphinous and phosphonous chlorides, R_2PCl and $RPCl_2$, was the controlled reaction of a less than stoichiometric amount of organometallic reagents with phosphorus trichloride. This procedure often gives side products that are difficult to separate, allthough there are examples of this reaction working effectively in the synthesis of sterically hindered phosphorus halide compounds.[32]

Phosphinous halides can be prepared from secondary phosphine oxides and phosphorus trichloride. The starting secondary phosphine oxides are easy to handle and can be prepared by treating readily available diethyl or dibutylphosphite with an organometallic reagent.[33]

Another efficient synthesis of these important synthons makes use of commercially available diethylaminodichlorophosphine (diethylphosporamidous dichloride).[33]

Protocol 4.
Synthesis of bis[3,5-bis(trifluoromethyl)phenyl]chlorophosphine, 33 (Scheme 14)

Caution! All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety goggles should be worn.



Scheme 14

Protocol 4A.
Preparation of [3,5-bis(trifluoromethyl)phenyl]magnesium bromide, 31

Equipment

- Three-necked round bottom flask (100 mL)
- Reflux condenser
- Pressure-equalizing addition funnel
- Magnetic stirrer
- Magnetic stirring bar
- Septum
- Dry syringe with steel needle (1×20 mL, 1×5 mL)
- Tubing adapter
- Hot air gun
- Source of dry nitrogen combined with vacuum

Materials

- Magnesium (FW 24.31) 0.636 g, 26.2 mmol — **flammable, water sensitive**
- 3,5-bis-(trifluoromethyl)bromobenzene, **30**, (FW 293.01) 4.10 mL, 6.97 g, 23.8 mmol — **irritant**
- Dry THF (25 mL) — **highly flammable, irritant**

Method

1. Clean all the glassware and other apparatus, and dry in an 120°C oven for at least 4 h before use. Assemble glassware while still hot.
2. Equip the three-necked flask with the septum, pressure-equalizing dropping funnel, reflux condenser and magnetic stirring bar. Add magnesium turnings to the flask.
3. Evacuate the vessel and heat with a hot air gun . Flush with nitrogen. Stir the magnesium turnings under an atmosphere of nitrogen overnight.
4. Using a syringe, add THF (10 mL) to the magnesium.
5. Using a syringe, add a solution of 3,5-bis-(trifluoromethyl)bromobenzene, **31** (6.97 g, 23.8 mmol) in dry THF (15 mL) to the addition funnel.

Protocol 4A. *Continued*

6. Add the above solution dropwise to the stirring magnesium. After addition is complete, stir for a further hour.

Protocol 4B.
Synthesis of bis[3,5-bis(trifluoromethyl)phenyl]chlorophosphine, 33

Equipment

- Two three-necked round bottom flasks (100 mL)
- Pressure-equalizing dropping funnel (100 mL)
- Dry syringe with steel needle (1 × 20 mL, 1 × 1 mL)
- Tubing adapter (×2)
- Magnetic stirrer
- Magnetic stirring bar (×2)
- Septum (×2)
- Steel cannula (2 mm × 40 cm) (×2)
- Schlenk tube (100 mL)
- Columns equipped with glass frit, septum, (at top) and adapter to fit neck of round bottom flasks (2 × 100 mL)
- Source of dry nitrogen combined with vacuum line
- Celite® filter aid

Materials

- Diethyl phosphoramidous dichloride (FW 174.01, d. 1.196) 1.7 mL, 2.0 g, 11.5 mmol.[a] **causes burns, explosive when hot, water sensitive**
- All of Grignard reagent **31** from Protocol 4A **assume toxic, water sensitive**
- Dry THF (12 mL) **highly flammable, irritant**
- Dry cyclohexane (40 mL) **highly flammable**
- Canister of anhydrous HCl **irritant, causes severe burns**

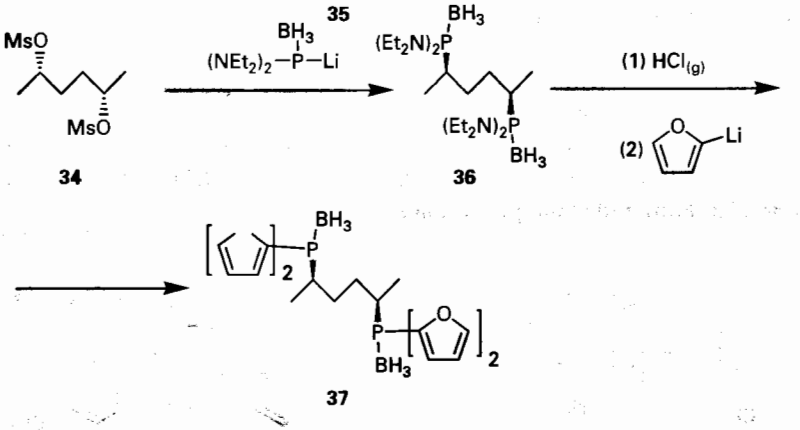
Method

1. Clean all the glassware and other apparatus, and dry in an oven for at least 4 h before use. Assemble glassware while still hot.
2. Equip the three-necked flask with pressure-equalizing dropping funnel, stirring bar, septum and tubing adapter. Evacuate, then flush with nitrogen.
3. Using a syringe, add diethyl phosphoramidous dichloride (1.7 mL, 11.5 mmol) and THF (12 mL) to the flask. Cool to 0°C.
4. Transfer the Grignard reagent **31** to the dropping funnel. Add to the reaction dropwise (**Caution!**).
5. After stirring for 2 h, remove the solvent using the vacuum line. Flush with nitrogen.
6. Syringe cyclohexane (40 mL) into the flask and swirl gently to form a solution.
7. Equip another three-necked flask with a septum, magnetic stirring bar, tubing adapter attached to the nitrogen/vacuum line, and a glass column equipped with a glass fit. Put a 2 cm high layer of Celite® on top of the frit and seal the top of the column with a rubber septum.
8. Using a steel cannula, blow or suck over the cyclohexane solution, through the celite and into the flask below. Flush with nitrogen.
9. Attach a short needle connected to a bubbler into the flask via the septum.

10. Using a long steel needle connected to a supply of HCl, gently bubble the gas directly into the cyclohexane solution for 60 min, stirring continuously.
11. Evacuate the reaction flask and flush with nitrogen.
12. Equip the Schlenk tube with a column containing Celite® as before, and seal with a rubber septum. Evacuate the flask.
13. Using a steel cannula, suck or blow the cyclohexane solution, through the Celite® and into the Schlenk tube.
14. Removal of solvent under high vacuum gives bis[3,5-bis(trifluoromethyl) phenyl]chlorophosphine, **33** (4.83 g, 9.8 mmol, 85% yield).

[a]Diethyl phosphoramidous dichloride can be purchased from Aldrich Chemical Company, or readily synthesized from PCl_3.[34]

A complementary approach to the above method has recently been reported.[35] Bis(diethylamino)chlorophosphine can be protected with borane, and then treated with lithium naphthalenide to generate **35**, which reacts with organic electrophiles. These can be treated with HCl to yield the phosphonous halide borane compounds, $RPCl_2{:}BH_3$ (Scheme 15). These need not be isolated and can be treated directly with an organolithium and deprotected to yield a tertiary phosphine, $R^1R^2{}_2P$.

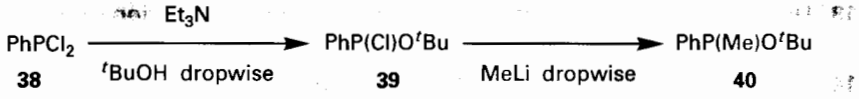


Scheme 15

3.2 Preparation of phosphites and related compounds

Phosphites can be very easily prepared by the reaction of a phosphorus halide with alcohol and an organic base, typically triethylamine or pyridine.[36] It is generally necessary to use low temperatures and to keep the reaction free from moisture and air. If diols are used, reaction conditions can be adjusted so that oxygen either

bridges or chelates phosphorus atoms.[37] It is possible to stop the reaction before full chloride substitution has occurred to give products of type $RP(Cl)OR^1$. These compounds react with organolithiums to give the phosphites of type $R^2RP(OR^1)$ (Scheme 16).[38]



Scheme 16

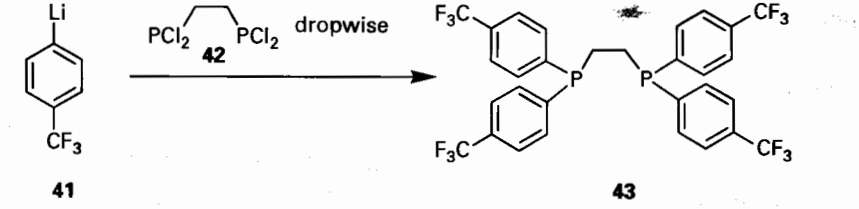
Phosphites are generally less robust than tertiary phosphines, and they should be stored in an inert atmosphere. Apart from receiving attention as ligands in their own right, (Section 7) the alkoxy group can act as an alternative leaving group in reaction with organometallic reagents.[28] A phosphorus–oxygen bond can also be cleaved using hydride reagents.

4. Polydentate phosphines and macrocycles

Phosphines that contain another one or more phosphorus atoms are particularly useful as ligands for transition metals. This stems from the fact that they can form a stronger bond to the metal with both phosphorus atoms donating and hence placing substituents in a well-defined position. (This has been exploited very successfully in the case of chiral bidentate phosphines.)

Similar procedures as described in the previous sections are still valid for the preparation of these compounds, but there are some specific synthetic methods which warrant attention.

The commercially available compounds 1,2-bis(dichlorophosphino)ethane, **42**, and 1,2-bis(dichlorophosphino)benzene will react with organolithiums to give the corresponding bidentate phosphines (Scheme 17).[35]

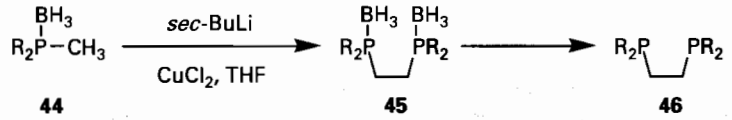


Scheme 17

Similarly, metal phosphides react with dibromo alkanes or other alkanes with two leaving groups to also give bidentate phosphines. If the leaving group is at a secondary carbon centre, the reaction is much slower and gives lower yields. These problems can sometimes be overcome by use of better leaving groups and

the potassium phosphide. An example of this is in the improved synthesis of Chiraphos®.[39]

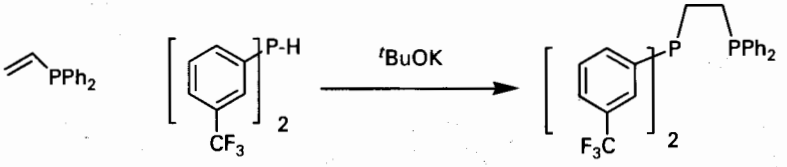
A common method used for the preparation of bisphosphinoethanes is the reductive coupling of a methyl phosphine oxide or phosphine borane (Scheme 18) using a strong base and copper salts.[27] This process occurs with no racemization of the adjacent phosphorus atom.



44 **45** **46**

Scheme 18

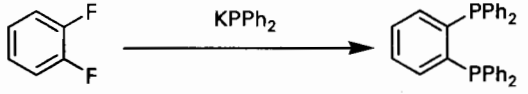
Another equally successful method for the preparation of bisphosphinoethanes is the base-catalysed addition of a secondary phosphine to a vinylphosphine.[40] The reaction (Scheme 19) itself seems very straightforward providing the starting materials are not too difficult to make.



47 **48** **49**

Scheme 19

In order to couple two phosphines *ortho* to each other on an aromatic framework, the metal phosphide must be prepared and reacted with dichloro- or difluorobenzene (Scheme 20).[41]

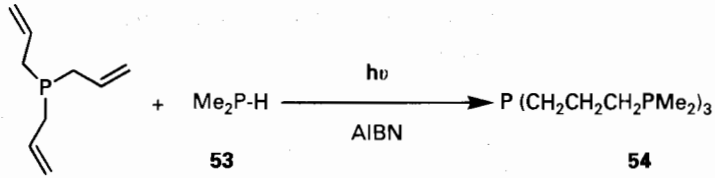


50 **51**

Scheme 20

In the related case of synthesizing phosphines joined by a propyl chain, allyl phosphines and secondary phosphines react together in a radical initiated reaction.[42] This has been used in the synthesis of ter- and tetradentate phosphines such as compound **54** (Scheme 21).

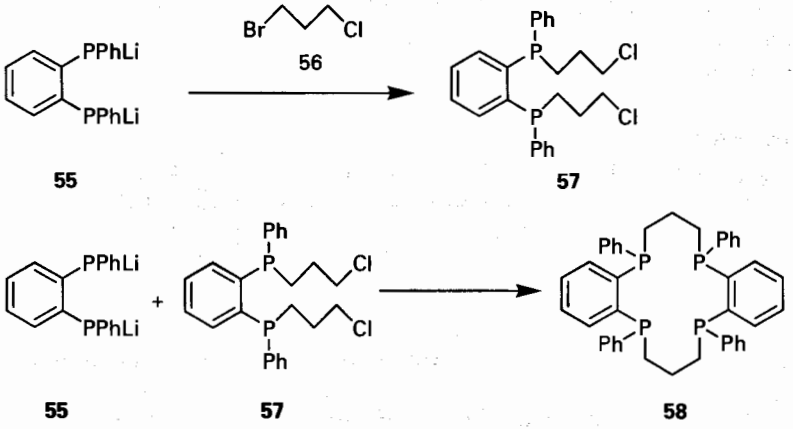
The synthesis of polyphosphine macrocycles requires the joining of a bidentate phosphine with other donor ligands via an alkyl or aryl chain. The synthesis of



52 53 54

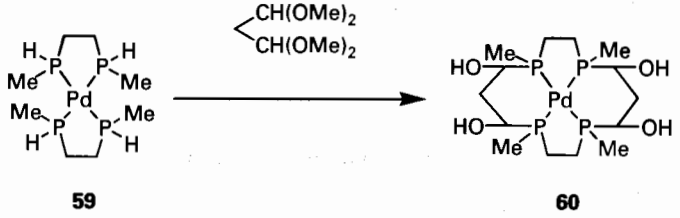
Scheme 21

tertiary phosphines that contain electrophilic sites in their alkyl chain facilitates this. 1,3-Bromochloropropane, **56**, will react with the dilithiophosphine, **55**, to form intermediate **57**, which contains two electrophilic sites. This can be reacted with the nucleophile, **55**, to produce the tetradentate phosphine **58** (Scheme 22).[43]



Scheme 22

An alternative strategy to a phosphine macrocycle involves template-assisted reaction of two coordinated bidentate secondary phosphines with two equivalents of a dielectrophile, to form tetradentate phosphine transition metal complexes, **60** (Scheme 23).[44]



59 60

Scheme 23

Coordinated secondary phosphines will also add vinyldiphenylphosphine to form terdentate ligands.

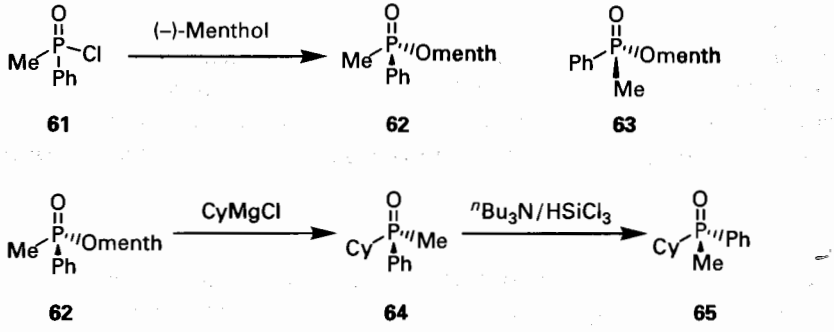
5. Chiral phosphines

Chiral phosphines can be divided into two main classes: those which are chiral at phosphorus and those which have chiral substituents or planar/axial chirality. In addition, mono-, bi-, and tridentate phosphines have been prepared and used successfully.

5.1 Phosphines that are chiral at phosphorus

Chemists who wish to prepare enantiomerically pure phosphines should consult the excellent review by Pietrusiewics and Zablocka,[45] which gives examples of most of the P-chiral phosphines that have been made efficiently. In the last 10 years, a number of effective asymmetric syntheses of P-chiral phosphines have been developed. Prior to this, many of the chiral phosphines prepared were synthesized in racemic form and then resolved using stoichiometric amounts of a chiral organic compound or chiral palladium, platinum, or iron complexes. Although some interesting phosphines have been prepared by this method, they are not mentioned here as the experimental procedures are not in widespread use.

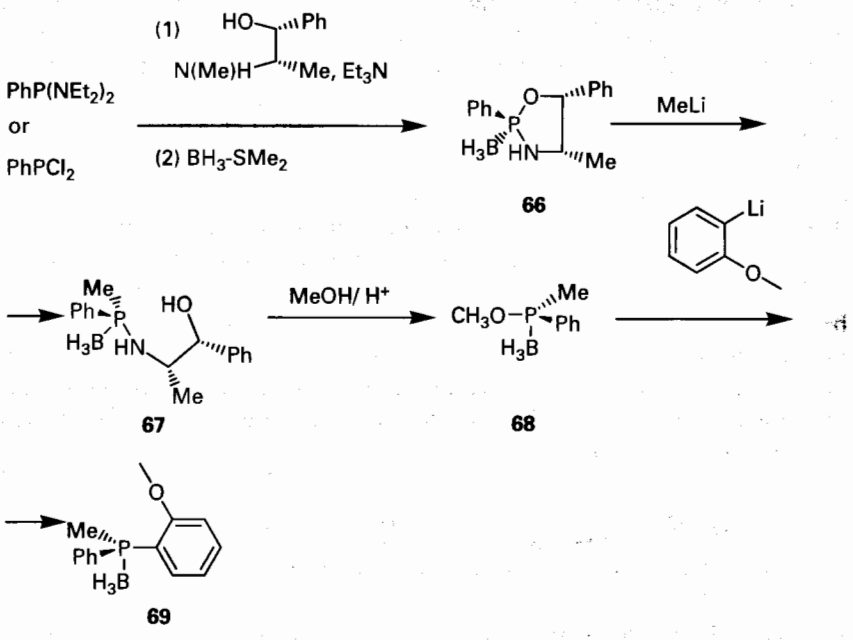
However, menthyl phosphinates, **62** and **63**, are useful intermediates which can be resolved by crystallization and then treated with a Grignard reagent to give the P-chiral phosphine oxides.[10] These can be reduced with predominant inversion of configuration using the combination $HSiCl_3/^nBu_3N$ to give phosphines of high enantiomeric excess (e.e.) (Scheme 24). Many menthyl phosphinates have been resolved by this method.



Scheme 24

From the point of view of generality, it is desirable if a phosphine intermediate with more than one easily interchanged group could be synthesized asymmetrically. This has been realized to some extent with the discovery that $PhPCl_2$ or $PhP(NEt_2)_2$ reacts with cheap and readily available ephedrine to form a

heterocycle **66** which is diastereomerically pure. This can be protected as the borane or oxide and then reacted with a Grignard or organolithium reagent to regioselectively cleave the P—O bond with retention of configuration (Scheme 25). The remaining P—N bond is broken by acidic methanolysis with inversion of configuration to yield phosphinites of high optical purity, which can then be reacted with a further organometallic (inversion) and then deprotected to form chiral phosphines with e.e. of 85–100%. [46–48] Chiral phosphine boranes can be deprotected with complete retention of stereochemistry. Although potentially a general method for any P-chiral phosphine, it has been found that not all Grignard and organolithium reagents give satisfactory products.

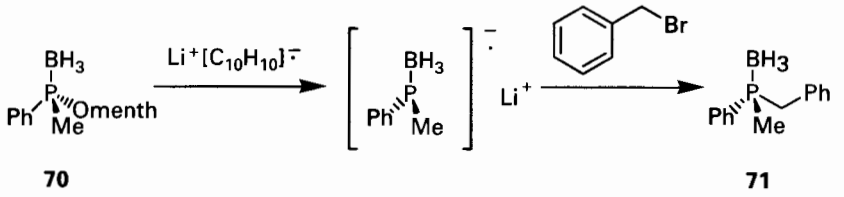


Scheme 25

So far we have discussed the synthesis of useful P-chiral phosphorus intermediates that can be converted into a variety of phosphines by reaction with a nucleophile (and deprotection). However, Imamoto and co-workers found that one-electron reducing agents react with resolved menthyl phosphine oxides and boranes to give metal phosphides that retain their configuration at phosphorus (Scheme 26).[49]

5.2 Phosphines with carbon centred chirality

The second main type of chiral phosphines are those which have carbon centred chirality on the substituents on phosphorus. These types of ligand can again



70 **71**

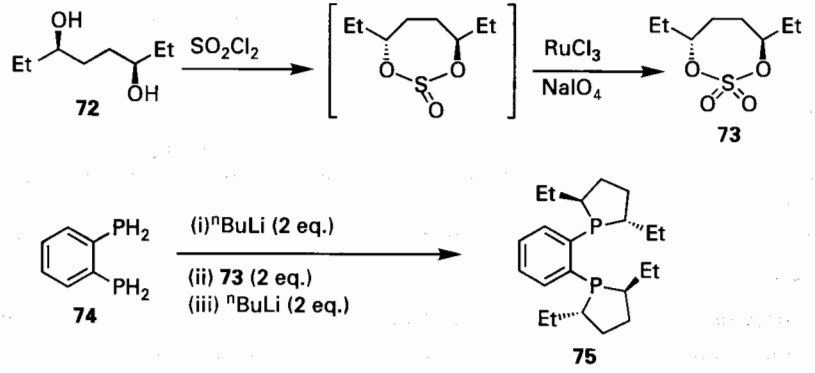
Scheme 26

be subdivided into symmetric diphosphines and monophosphines. The most common examples of diphosphine utilize a rigid chiral backbone connecting two diphenyl phosphino groups together. For the ligands to work effectively, it is necessary for the substituents at chiral positions in the backbone to be conformationally restricted and hence adopt only one position (equatorial) when forming a five-, six-, or seven-membered chelate with a metal atom. This forces a phenyl group on each phosphorus atom to be 'edge on' and push into other parts of the coordination sphere of the metal complex and the other phenyl group to be 'face on'. In this way chiral information is transmitted to organic substrates during catalytic reactions. Notable examples of this type are the ligands Chiraphos® and DIOP®.[50,51]

Other ligands have been synthesized more recently utilizing the same synthetic and theoretical philosophy.[52,53] A chiral ditosylate or dimesylate is generally reacted with a metal phosphide to produce the diphosphine ligand. There have been problems with these displacement reactions with secondary ditosylates as has been discussed earlier. More recent procedures report success with phosphine oxide or borane anions.

A very successful type of ligand, developed by Burk and co-workers employs a conceptually different approach.[54] The 1,4 chiral diols are converted into their cyclic sulfates, **73**, by reaction with thionyl chloride, followed by direct oxidation of the intermediate sulfites (not isolated). Dilithiation of a di-primary phosphine, and addition of sulfate, **73**, induces the first nucleophilic attack. Cyclisation commences on addition of a further two equivalents of ^{n}BuLi to deprotonate the remaining P-H bonds. A range of di-phosphines can be prepared using this methodology (Scheme 27). These ligands differ in design from those reported previously, as they are electron rich, and do not rely on face-on/edge-on aryl groups to impart the chiral information.

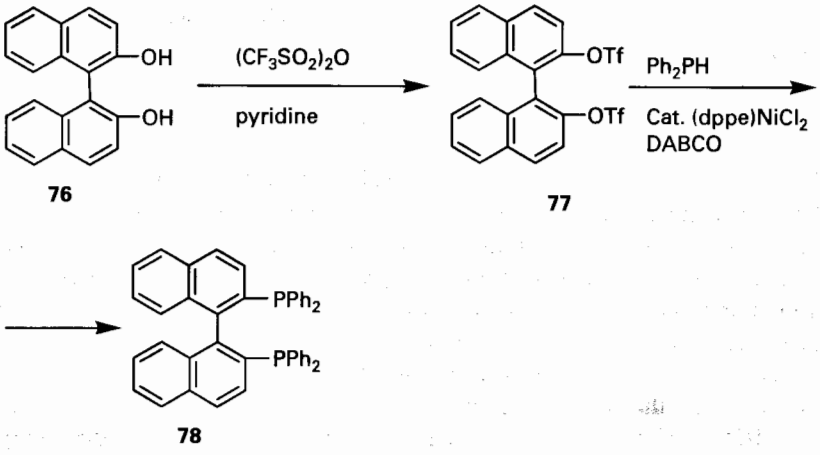
The 'BINAP®' ligand, **78**, which is often used in asymmetric catalysis, possesses axial chirality in the binapthyl ring system as opposed to an asymmetrically substituted carbon atoms. They are made from chiral precursors using a nickel-catalysed coupling as the key step.[23]



Scheme 27

Protocol 5.
Synthesis of (*R*)-2,2′-bis (diphenylphosphino)-1,1′-binaphthyl, 78 (Scheme 28)

Caution! All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety goggles should be worn.



Scheme 28

Protocol 5A.
Synthesis of (*R*)-2,2′-bis((trifluormethanesulfonyl)oxy)-1, 1′-binaphthyl, 77

Equipment

- Magnetic stirrer
- Magnetic stirring bar
- One-necked flask (2 × 100 mL)
- Ice bath
- Septum
- Dry syringe with steel needle (1 × 20 mL, 2 × 2.5 mL)
- Separating funnel (500 mL)
- Column for chromatography
- Source of dry nitrogen combined with vacuum line

Materials

- (*R*)-1,1′binaphthol, **76**, (FW 286.33), 1.8 g, 6.26 mmol — **irritant**
- Pyridine, (FW 79.10, d. 0.978), 1.5 mL, 1.47 g, 18.53 mmol — **highly flammable, harmful**
- Trifluoromethanesulfonic anhydride (FW 282.13, d. 1.677), 2.5 mL, 4.20 g, 14.90 mmol — **causes burns, water sensitive**
- Dry DCM, 25 mL — **toxic**
- Ethyl acetate, 25 mL — **highly flammable**
- 5% HCl, 25 mL — **causes burns**
- Sat. $NaHCO_3$, 25 mL
- Brine, 25 mL

Method

1. Ensure that all glassware is thoroughly clean and has been dried for at least 4 h in a 120°C oven before use. Assemble glassware while still hot.
2. Charge the one-necked flask with (*R*)-1,1′-binaphthol, **76** (1.8 g, 6.26 mmol) and stirring bead.
3. Equip the flask with a septum and evacuate by means of a needle connected to the nitrogen/vacuum line. Add the DCM via the syringe and place the flask under constant atmosphere of nitrogen.
4. Add the pyridine (1.5 mL, 18.53 mmol) and cool the flask to 0°C.
5. Using a syringe, add the trifluoromethanesulfonic anhydride (2.5 mL, 14.90 mmol) to the reaction vessel
6. Allow the mixture to warm to room temperature over a period of 6 h.
7. Remove solvent under reduced pressure. Add ethyl acetate (25 mL), and wash with 5% HCl, sat. $NaHCO_3$, and brine. Dry the organic extracts (Na_2SO_4) and remove solvent.
8. Purify the compound using chromatography on silica gel using DCM as eluent. This gives (*R*)-2,2′-bis[(trifluormethanesulfonyl)oxy]-1,1′-binaphyl, **77**, 3.1 g, 5.3 mmol, 90%.

Protocol 5B.
Synthesis of (*R*)-2,2′-bis (diphenylphosphino)-1,1′-binaphthyl, 78, via nickel-catalysed coupling

Equipment

- Three-necked round bottom flask (100 mL)
- Reflux condenser
- Magnetic stirrer
- Magnetic stirring bar
- Glass stopper
- Septum (×2)
- Tubing adapter
- Dry syringe with steel needle (2×20 mL, 1×1 mL)
- One-necked round bottom flask (50 mL)

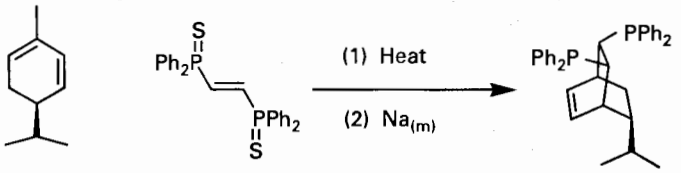
Materials

- (*R*)-2,2′-Bis[(trifluormethanesulfonyl)oxy]-1,1′-binaphthyl, **77** (FW 550.46), 3.0 g, 5.45 mmol **causes burns**
- [Bis(diphenylphosphino)ethane]nickel dichloride (FW 528.05), 0.288 g, 0.545 mmol **may cause cancer, harmful, irritant**
- Diphenylphosphine (FW 186.20, d. 1.070), 4 × 0.55 mL, 4 × 3.13 mmol) **spontaneously flammable in air**
- DABCO (FW 112.18), 2.45 g, 21.8 mmol **harmful, causes burns**
- Dry DMF, 25 mL **irritant**
- Dry methanol, 10 mL **flammable, toxic**

Method

1. Ensure that all glassware is thoroughly clean and has been dried for at least 4 h in a 120°C oven before use. Assemble glassware while still hot.
2. Equip the three-necked flask with a reflux condenser, magnetic stirring bar, glass stopper, and septum. Equip the reflux condenser with a tubing adapter connected to a combined nitrogen and vacuum line.
3. Add the nickel catalyst to the flask, close the stopper and evacuate. Add dry DMF (10 mL) and flush with nitrogen.
4. Using a syringe, add the diphenyl phosphine (0.55 mL, 3.13 mmol) to the flask. Evacuate and then flush with nitrogen. Heat this solution to 100°C, and maintain this temperature for 30 min.
5. Charge the one-necked flask with DABCO (2.45 g, 21.8 mmol) and (*R*)-2,2′-bis[(trifluoromethanesulfonyl)oxy]-1,1′-binaphthyl, **77** (3.0 g, 5.45 mmol). Fit the flask with a septum and evacuate. Add dry DMF (15 mL) and flush with nitrogen. Syringe this solution into the reaction vessel, keeping the temperature at 100°C.
6. Syringe three further amounts (3 × 0.55 mL, 3 × 3.13 mmol) of diphenylphosphine into the reaction vessel, 1, 3, and 7 h later.
7. Leave the reaction at 100°C for 60 h.
8. Cool the reaction to 0°C, filter off the white product, wash with methanol (2 × 5 mL) and dry under high vacuum to give (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, **78** (2.4 g, 3.82 mmol, 70%)

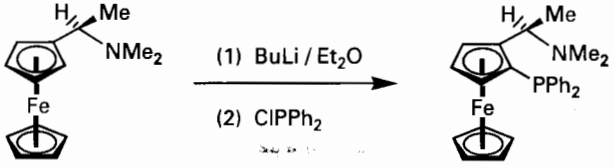
An alternative route to chiral diphosphines comes from the Diels–Alder cycloaddition of *trans*-diphosphinoethylene derivatives with a diene (Scheme 29).



79 **80** **81**

Scheme 29

There are fewer examples of unidentate chiral ligands that have been used effectively in asymmetric catalysis.[55,56] However, Hayashi and co-workers synthesized a series of monodentate ligands consisting of a diphenylphosphino group connected to a binapthyl moiety.[22] These showed excellent asymmetric induction in hydrosilation experiments. Some chiral ligands that have been synthesized contain an additional functional group that is capable of interacting with the substrate during catalysis. Much of the pioneering work in this field uses ferrocenyl phosphines.[57] These ligands are prepared by a stereospecific lithiation of ferrocene derivatives, followed by trapping by an electrophilic phosphine derivative (Scheme 30). They possess two elements of chirality; the chiral carbon centre and the planar chirality due to the specificity of the substitution in the ferrocene ring.

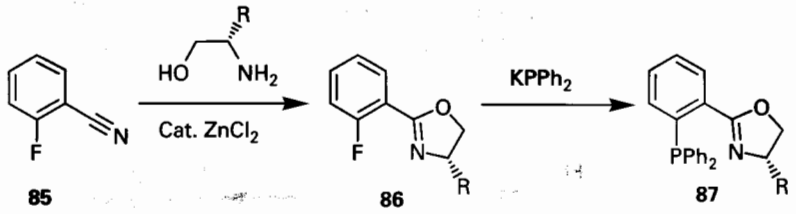


83 **84**

Scheme 30

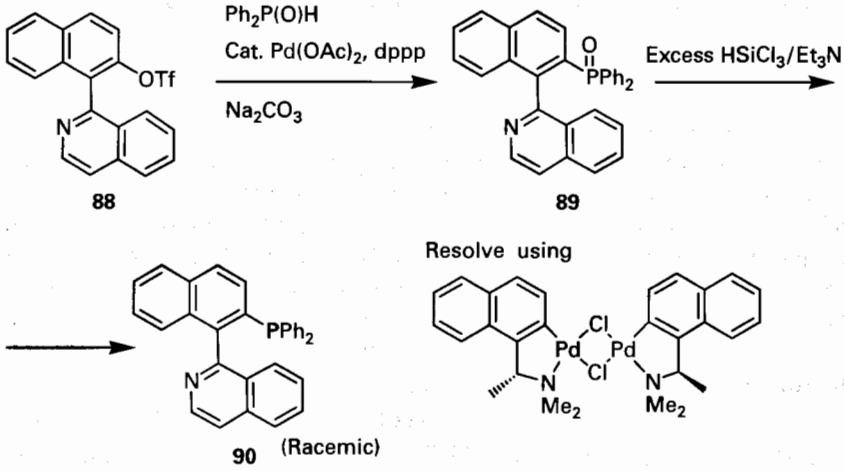
The amino position can be readily converted into a range of different functionalities. Catalysts made from these ligands showed unprecedented enantioselectivity in a number of reactions.

Chiral chelating ligands that contain only one phosphine and another donor atom have been successful in recent years. A readily synthesized example is the phosphino-oxazoline ligand **87** shown in Scheme 31. These types of ligand can be prepared in two steps from an amino alcohol, a substituted benzonitrile and either a electrophillic or nucleophilic phosphorus reagent. They have been used in a number of asymmetric reactions.



Scheme 31

Another heterobidentate chiral ligand that has been used with success in catalysis is the phosphine 'QUINAP®', **90**. It is prepared using a palladium-catalysed coupling procedure, followed by a resolution of the racemic product using a chiral palladium salt (Scheme 32).[58]



Scheme 32

6. Synthesis and applications of phosphines in environmentally benign catalysis

One area of phosphine chemistry that has attracted increasing attention over recent years is the synthesis of phosphines that have special solubility properties. Most common are ligands that contain polar hydrophilic groups which impart water solubility to metal complexes of these ligands. This has an important application to industrial scale organic synthesis: catalytic reactions can be carried out in which the organic products can be simply separated from the catalysts, which can be re-used. This is normally achieved by either conducting the reactions in a biphasic system, by doing a two phase extraction at the end of a conventional reaction, or by isolating the catalysts on hydrophilic beads. Other related methods involve

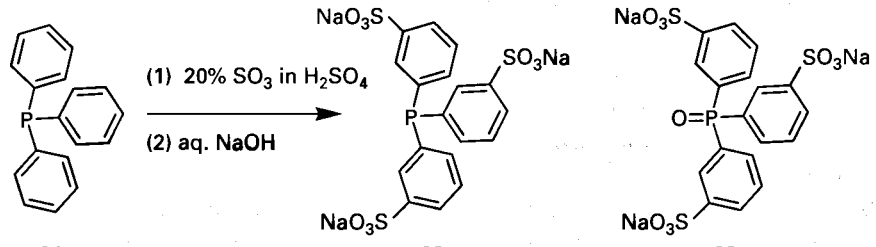
use of polymer-bound phosphines, and fluorinated phosphine catalysts that can be separated into a fluorinated solvent and re-used.

The first class of water soluble ligands to be prepared were sulfonated triphenylphosphine derivatives.[59] These have been studied in great detail, and even used industrially.

These ligands are made by the addition of oleum to the appropriate aryl phosphine (Protocol 6). The reaction is difficult to control as a number of substitution products are possible, and the phosphines are susceptible to oxidation under the reaction conditions. It should be noted that impure, uncharacterized ligands of this type are often used successfully in catalysis.

Protocol 6.
Synthesis of trisulfonated triphenylphosphine, 92 (Scheme 33)

Caution! All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety goggles should be worn.



91 **92** **93**

Scheme 33

Equipment

- Three-necked, round-bottom flask (1 × 500 mL, 1 × 1000 mL)
- One-necked, round-bottom flask (1 × 1000 mL)
- Septum (×8)
- Dry syringes with steel needles
- Ice bath
- Glass stoppers
- Magnetic stirrer
- Magnetic stirring beads (large)
- Tubing adapter
- Source of dry nitrogen combined with vacuum line
- Reflux condenser
- Steel cannula (2 mm × 500 mm)
- Glass column containing glass frit (250 mL)

Materials

- Triphenylphosphine, **91** (FW 262.29), 5 g, 19.0 mmol — **harmful**
- 20% fuming sulfuric acid (oleum), 50 mL — **causes severe burns, irritant, reacts violently with water**
- 20% aqueous sodium hydroxide, 1 L — **harmful, causes burns**
- Methanol, 1.5 L — **highly flammable, toxic**
- Acetone, 1 L — **highly flammable**

Protocol 6. *Continued*

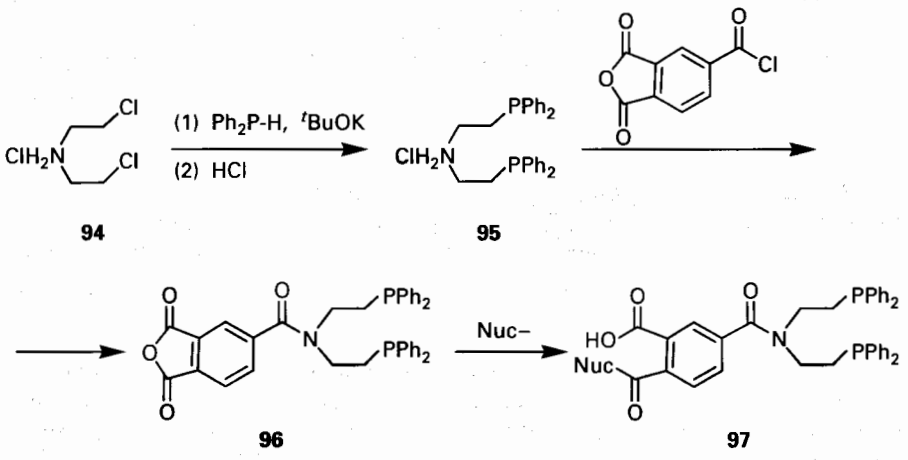
Method

1. Ensure that all glassware is thoroughly clean and has been dried for at least 4 h in a 120°C oven before use. Assemble glassware while still hot.
2. Equip the 500 mL three-necked round bottom flask with stirring bead, tubing adapter, septum, and glass stopper. Connect the flask to a bubbler via an outlet needle.
3. Charge the flask with oleum (**Caution!**) (20%, 50 mL), and blow a constant stream of nitrogen through the flask. Cool the oleum to 0°C.
4. Remove the glass stopper and carefully add a 0.5 g portion of triphenylphosphine to the flask. Close the stopper and allow the system to purge with nitrogen. Stir the reaction continuously.
5. Continue to add the triphenylphosphine in about 10 portions (5 g in total) to the cooled reaction flask.
6. Stir the reaction at room temperature for 6 days.[a]
7. Cool the reaction to 0°C, and slowly add cold 20% aqueous sodium hydroxide until the reaction reaches neutral pH.
8. Reduce the volume to about 100 mL by warming the solution under vacuum.
9. Equip a three-necked flask (1000 mL) with a reflux condenser, stirring bead, rubber septum, and glass stopper. Pour the reaction mixture into this flask, add methanol (500 mL), close the stopper and flush with nitrogen.
10. Heat to reflux. Using a steel cannula, transfer the hot solution through a column containing a glass frit into a one-necked round bottom flask (1000 mL). Take care to leave the residual solid in the original flask.
11. Add methanol (250 mL) to the residual solid in the three-necked flask, and again heat to reflux. Filter the hot solution into the one-necked flask.
12. Reduce the volume of solvent to about 100 mL on a rotary evaporator.
13. Slowly add acetone (400 mL) to this flask to precipitate crude product. Filter off the precipitate. This contains a significant amount (15–25%) of phosphine oxide by-product.
14. Recrystallize the product by adding acetone/methanol/water (10:5:1), (150 mL), heating to reflux and filtering hot to obtain a solution.
15. Reduce the volume of solvent by half by means of a rotary evaporator, cool, and add acetone to precipitate the product.

16. Collect this precipitate, and test for purity by NMR. If the product is not sufficiently pure, repeat steps 14 and 15. The yield is usually between 40% and 60%.

[a]The reaction can be monitored by doing a mini work-up and analysing by ^{31}P NMR: $\delta = -5.14(D_2O)$. As the purification is quite demanding, it is recommended that Ref. 59 is consulted.

The type of procedure described in the protocol has been used to synthesize sulfonated versions of 'BINAP®', 'DPPE®', and 'Chiraphos®' ligands. An easily prepared class of water-soluble phosphines can all be made from the same precursor, **95** (Scheme 34).



Scheme 34

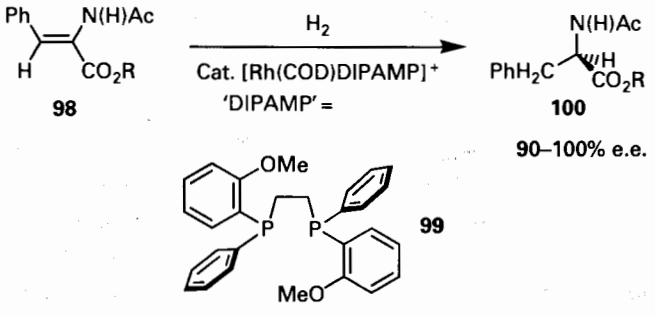
Phosphine ligands containing quaternized amines are useful water-soluble phosphines, and a number of them have been prepared. Other important types of water-soluble ligands are carboxylated phosphines, hydroxy phosphines and other quaternized derivatives. Phosphines that have long perfluorinated 'tails' form transition metal complexes that are preferentially soluble in fluorinated solvents such as $CF_3C_6F_{11}$. These solvents are often not miscible with standard organic solvents. Hence, the catalysts can be easily separated from the products after the reaction. A phosphine that has been used successfully in this type of catalysis is $P[CH_2CH_2(CF_2)_5CF_3]_3$.[60]

7. Applications of phosphines in catalysis

Phosphines have a found a huge variety of applications as ligands in catalytic reactions. The few examples outlined here are those in which particular structural features on the phosphine are crucial to successful catalysis.

7.1 Hydrogenation

Phosphines are the best ligands for metal-catalysed hydrogenations. It has been found that ligands that form seven-membered chelates with the metal catalyst make more active catalysts than their five- and six-membered ring counterparts. However, in the asymmetric reaction, five- and six-membered chelates give greater conformational rigidity, and hence higher enantioselectivities. The first asymmetric hydrogenation to give almost complete enantioselectivity was reported in 1975.[27] The P-chiral ligand, 'DIPAMP®' gives very impressive results in the rhodium-catalysed hydrogenation of α-acylaminoacrylic acids (Scheme 35).

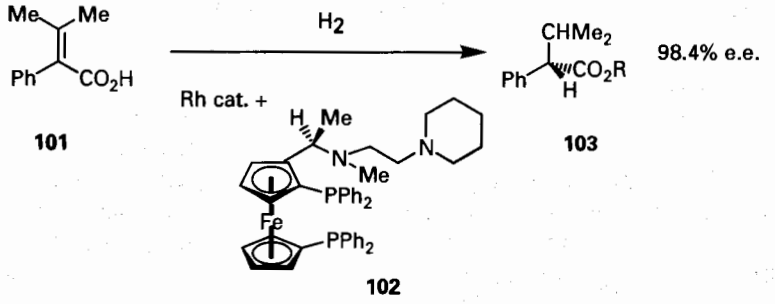


Scheme 35

Since that time, many chiral bidentate phosphines have been prepared that give excellent results in the hydrogenation of α-acylaminoacrylic acid substrates (Scheme 36). A feature of some of the better recent ligands is their easier preparation. It has recently been found that electronic tuning of the phosphine ligands can have such a pronounced effect on enantioselectivity that less selective seven-membered chelates can give very high e.e. for many of the substrates studied. The readily synthesized phosphinite ligands, **105**, give high enantiocontrol if 'R' is an electron-releasing group.[61] Hayashi and co-workers devised an elegant solution to the problem of obtaining high enantioselectivities in the hydrogenation of trisubstituted acrylic acids. The unsaturated carboxylic acid forms an ammomium carboxylate with the amino group on the chiral ligand, hence making a strong and well-defined interaction between the catalyst and the substrate.[62] This is crucial for high selectivities.

7.2 Hydroformylation

Phosphine-derived ligands are again the ligands of choice for this reaction. Asymmetric hydroformylation is a reaction in which structural and electronic changes on the ligands can have a large effect on both regio- and stereoselectivity. Phosphites are thought to give better regioselectivity and activity than the corresponding phosphine ligands, whereas the latter often give greater enantiocontrol.

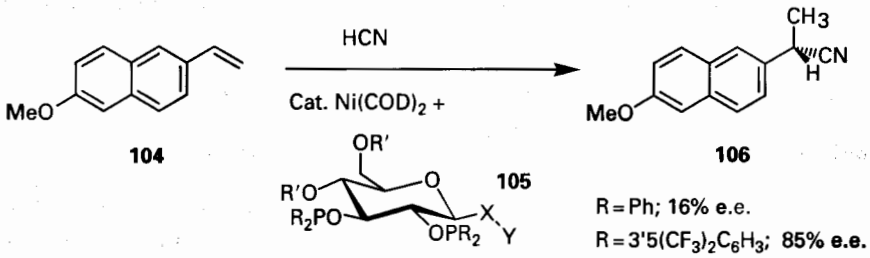


Scheme 36

In recent years, phosphite ligands have been synthesized that can combine the dual goals of high regio- and enantioselectivity. Good results have been achieved with phosphites derived from 1,3 diols and non-symmetrical phosphine/phosphite ligands with large bite angles.

7.3 Asymmetric hydrocyanation

Using nickel catalysts of electronically tuneable phosphinite ligands, **105**, an equally dramatic electronic effect on enantioselectivity has been observed (Scheme 37). An e.e. of 16% using an electron-rich ligand can be improved to 85–91% e.e. using an otherwise similar electron-poor ligand. This is the best e.e. observed for this reaction.



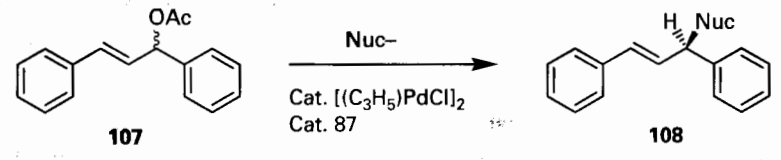
Scheme 37

7.4 Palladium- and nickel-catalysed coupling reactions

The choice of phosphine ligand for these reactions is often crucial if high yields are to be obtained. The choice of ligand is often specific for each type of reaction, although it is often the case that bidentate phosphines give higher yields. For example, in the palladium-catalysed arylation of amines, bis(diphenylphosphino)ferrocene or BINAP® appear to be the ligands of choice. In the Heck reaction, it is often necessary to use tri-*o*-tolylphosphine in order to get high yields.

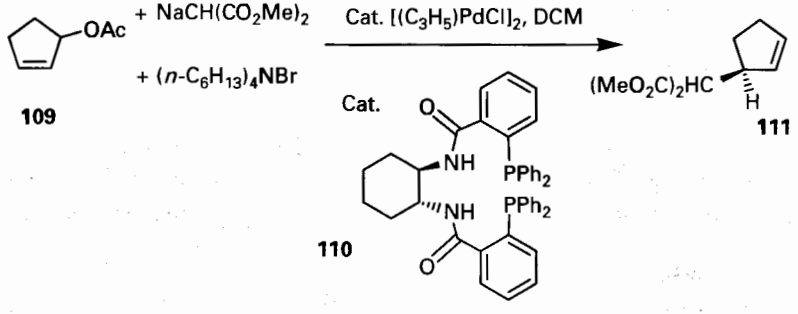
7.5 Allylic substitution

In general, phosphine ligands make for more reactive catalysts than those derived from nitrogen ligands. This reaction also proceed faster when catalysts are derived from bidentate phosphines. This can be ascribed to their bidentate coordination forcing the dissociation of the leaving group, and the formation of the reactive, cationic allyl complex. In the asymmetric variant of this reaction, heterobidentate ligands such as **87** can give very high selectivity for some substrates (Scheme 38).



Scheme 38

The ligand, **110**, prepared by Trost and co-workers, also gives excellent asymmetric induction, particularly for cyclic substrates (Scheme 39).[63]



Scheme 39

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3

Applications of phosphorus (III) and (V) compounds as reagents in synthesis

R. ALAN AITKEN and NAZIRA KARODIA

1. Introduction

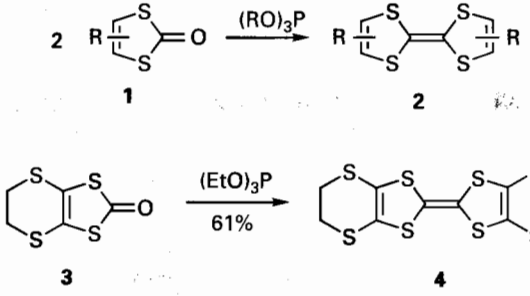
Phosphorus compounds play a key role in organic synthesis and in many cases they provide the reagent of choice to bring about a particular transformation. Central to this is the great affinity of phosphorus for oxygen and sulfur. The main reaction types which may be identified are: (i) deoxygenation and desulfurization, (ii) halogenation, (iii) dehydrative coupling and cyclization, (iv) sulfurization, and (v) miscellaneous processes. In this chapter these areas are considered in turn and examples of typical reaction protocols are given for each. In doing this we have included not only organophosphorus reagents but also some important inorganic phosphorus compounds, which are among the most valuable and powerful reagents available to the synthetic chemist. A detailed treatment of the use of organophosphorus reagents in many of the reaction types considered here is available in the relevant chapters of a 1979 monograph.[1]

2. Deoxygenation and desulfurization reactions

Tervalent phosphorus has a high affinity for oxygen and the P=O bond once formed is very strong. This fact, which also provides the driving force for the Wittig and related reactions, has led to the widespread use of P(III) compounds for direct deoxygenation of epoxides, ozonides, carbonyl compounds, and both *N*- and *S*-oxides.[2]

The deoxygenation of epoxides is not of great preparative value since it involves some loss of stereochemical integrity and the alkenes produced are more readily approached in other ways. Reductive cleavage of ozonides, for example, using triphenylphosphine, commonly forms part of the ozonolysis procedure for conversion of alkenes into carbonyl compounds. If a carbonyl compound is treated with an appropriate P(III) reagent then the reverse process may occur—reductive coupling to form a new C=C double bond. This has found a particularly important

application in the synthesis of tetrathiafulvalene analogues **2**, where treatment of the corresponding 1,3-dithiol-2-one **1** with a trialkyl phosphite has been used in literally hundreds of cases to obtain new examples of interest as components of organic conducting and superconducting materials.[3] It should be noted that the reaction is non-stereoselective and where **1** is unsymmetrically substituted, mixtures of (*E*)- and (*Z*)-isomers of **2** are produced. A typical procedure, illustrated by Protocol 1, is the synthesis of bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF) **4** (Scheme 1) by deoxygenative dimerization of **3** using triethyl phosphite.



Scheme 1

Protocol 1.
Synthesis of bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF)[4]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times.

Equipment

- Single-necked, round-bottomed flask (50 mL)
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Oil bath
- Reflux condenser
- Source of dry nitrogen
- Sintered glass funnel
- Plastic bucket (10 L)

Materials

- 2,5,7,9-Tetrathiabicyclo[4.3.0]non-1(6)-en-8-one **3**,[a] 0.50 g, 2.4 mmol
- Dry triethyl phosphite,[b] 20 mL (Aldrich T6,120–4, Lancaster 0339, Acros 42172, Fluka 90540) **toxic, stench**
- Diethyl ether, 10 mL **highly flammable**
- Sodium hypochlorite solution, 500 mL **corrosive**
- Liquid soap, 10 mL

Method

1. To a plastic bucket (10 L), add sodium hypochlorite solution (500 mL) and liquid soap (10 mL) and make up to two-thirds full with hot water. This solution will be used at the end of the procedure to dispose of the waste and decontaminate used equipment.

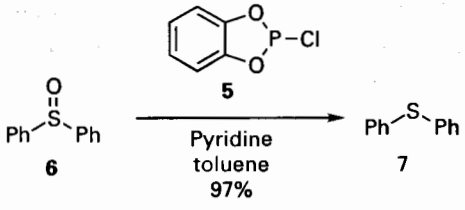
2. Place 2,5,7,9-tetrathiabicyclo[4.3.0]non-1(6)-en-8-one **3** (0.50 g, 2.4 mmol), dry triethyl phosphite (20 mL) and a magnetic stirrer bar in a single-necked, round-bottomed flask (50 mL). Equip the flask with a reflux condenser and nitrogen inlet. Flush out the system thoroughly with dry nitrogen.
3. Stir the solution and heat it slowly to 100–110°C. Maintain the mixture at this temperature for 35–40 min and then allow it to cool.
4. Cool the mixture in an ice bath for 10 min. Filter off the precipitate which forms and wash it with diethyl ether (10 mL) to give the product, m.p. 246–248°C, 0.28 g (61%). Proton NMR spectrum ($CDCl_3$): δ_H 3.29 (8H, s).
5. Carefully pour the filtrate containing triethyl phosphate and unreacted triethyl phosphite into the hypochlorite bucket. Decontaminate all equipment used in this protocol including gloves by placing in the hypochlorite bucket for at least 4 h or until no smell remains. After removing the equipment, dispose of the used hypochlorite solution by washing it down a sink in a well-ventilated hood with a large volume of water.

[a]This is obtained by oxidation of the corresponding thione using mercuric acetate in acetic acid/chloroform.[4]
[b]Triethyl phosphite may be dried by distilling from sodium wire under nitrogen (b.p. 156°C).

A further important application of P(III) reagents is deoxygenation of *S*-oxides. Sulfoxides can be deoxygenated to the corresponding sulfides using triphenylphosphine in the presence of a Lewis acid catalyst or, more readily, by using a trialkylphosphine or trialkyl phosphite. One of the most effective reagents, however, is the *P*-chloro benzodioxaphosphole **5**, whose use is illustrated in Protocol 2.

Protocol 2.
Synthesis of diphenyl sulfide[5]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 2).



Scheme 2

Protocol 2. *Continued*

Equipment

- Single-necked, round-bottomed flask (25 mL)
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Separating funnel (50 mL)
- Erlenmeyer flask (50 mL)

Materials

- Diphenyl sulfoxide **6**, 2.02 g, 10 mmol
- 2-Chloro-1,3,2-benzodioxaphosphole **5**, 1.74 g, 10 mmol (Lancaster 0197, Fluka 78405) **toxic, irritant**
- Pyridine, 0.79 g, 10 mmol **toxic, harmful**
- Toluene, 10 mL **flammable, harmful**
- Aqueous sodium hydroxide solution, 2 M, 30 mL **corrosive**
- Anhydrous magnesium sulfate, 5 g

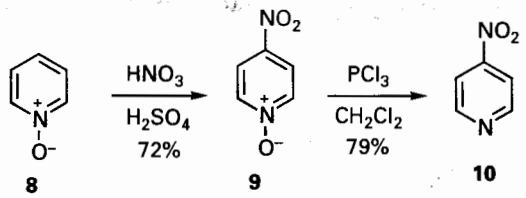
Method

1. To a single-necked, round-bottomed flask (25 mL), add diphenyl sulfoxide (2.02 g, 10 mmol), toluene (10 mL), pyridine (0.79 g, 10 mmol) and a magnetic stirrer bar.
2. Stir the mixture at room temperature and add slowly 2-chloro-1,3,2-benzodioxaphosphole **5** (1.74 g, 10 mmol). Continue stirring for 1 h.
3. Add aqueous sodium hydroxide solution (2 M, 10 mL) to the mixture and transfer it to a separating funnel (50 mL). Separate the organic layer and wash it with aqueous sodium hydroxide solution (2 M, 2 × 10 mL) and then water (10 mL). Dry the toluene solution using anhydrous magnesium sulfate (5 g, 1 h).
4. Filter off the drying agent and evaporate the solution using a rotary evaporator. The product is normally pure enough for use without further treatment but may be distilled if desired, b.p. 296°C, 1.80 g (97%).

Deoxygenation of heterocyclic *N*-oxides by phosphites and phosphines has been reported, but perhaps the most effective general reagent for this transformation is phosphorus trichloride. It is well known that the π-deficient heterocyclic compounds such as pyridine undergo electrophilic substitution with extreme reluctance but this obstacle may be overcome by *N*-oxidation to give the much more reactive *N*-oxides, substitution and finally deoxygenation. The example given in Protocol 3 shows that the final step may be efficiently achieved by treatment with PCl_3 to afford the most convenient synthesis of 4-nitropyridine **10**.

Protocol 3.
Synthesis of 4-nitropyridine[6]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 3).



Scheme 3

Equipment

- Single-necked, round-bottomed flasks (100 and 250 mL)
- Reflux condenser
- Magnetic stirrer bar
- Oil bath
- Thermostatted hot plate stirrer
- Beaker (250 mL)
- Sintered glass funnel
- Separating funnels (250 mL and 1 L)

Materials

- Pyridine *N*-oxide **8**,[a] 10 g, 105 mmol (Avocado 10419, Lancaster 8144, Acros 15769, Aldrich 13,165-2, Fluka 82811) **irritant**
- Concentrated sulfuric acid, 30 mL **corrosive**
- Fuming nitric acid, d 1.48, 12 g **corrosive, oxidizing**
- Sodium carbonate decahydrate, 100 g **irritant**
- Acetone, 100 mL **flammable**
- Dichloromethane, 350 mL **harmful**
- Phosphorus trichloride, 19 mL, 29.9 g, 217 mmol (Aldrich 15,799-1, Fluka 79670, Acros 16948) **irritant, corrosive**
- Sodium hydroxide solution, 2 M, 350 mL **corrosive**
- Anhydrous magnesium sulfate, 15 g
- Petroleum, b.p. 60–80°C, 100 mL **flammable**

Method

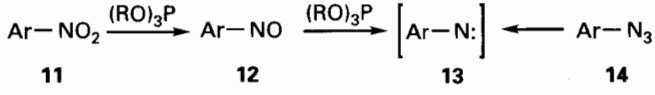
1. To a single-necked, round-bottomed flask (100 mL), add concentrated sulfuric acid (30 mL), fuming nitric acid (12 g), pyridine *N*-oxide (10 g, 105 mmol) and a magnetic stirrer bar. Fit a reflux condenser and heat the mixture with stirring at 128–130°C for 3.5 h. During this time toxic nitrogen oxide fumes are evolved which may be absorbed in water.
2. Pour the mixture slowly onto crushed ice (50 g) in a beaker (250 mL) and stir the mixture while adding solid sodium carbonate decahydrate (100 g). Filter off the precipitated product using a sintered glass funnel and wash it with ice-cold water (5 mL).

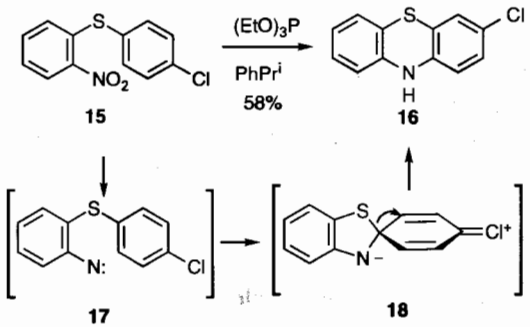
Protocol 3. *Continued*

3. Transfer the filtrate to a separating funnel (250 mL) and extract it with dichloromethane (2 × 50 mL). Dry the extracts using anhydrous magnesium sulfate (5 g, 1 h), filter off the drying agent and evaporate the solution using a rotary evaporator.
4. Recrystallize the combined solids obtained from steps 2 and 3 using acetone (100 mL) to give 4-nitropyridine *N*-oxide **9** as yellow crystals, m.p. 159°C, 10.6 g (72%).
5. To a single-necked, round-bottomed flask (250 mL), add 4-nitropyridine *N*-oxide **9** (10 g, 71 mmol), dichloromethane (150 mL) and a magnetic stirrer bar. Stir the suspension in an ice bath and slowly add phosphorus trichloride (19 mL, 29.9 g, 217 mmol).
6. Fit a reflux condenser to the flask and heat the mixture under reflux for 1 h. Allow the mixture to cool to room temperature and add it to a separating funnel (1 L) containing water (100 mL). Add 2 M sodium hydroxide solution (350 mL) to neutralize the acid present.
7. Separate the dichloromethane layer and extract the aqueous layer using dichloromethane (2 × 50 mL). Dry the combined extracts using anhydrous magnesium sulfate (10 g, 1 h), filter off the drying agent and evaporate the solution using a rotary evaporator. Recrystallize the resulting solid using petroleum (b.p. 60–80°C, 100 mL) to give the product, m.p. 50°C, 7.0 g (79%).

[a] This is commercially available or may be prepared from pyridine by treatment with hydrogen peroxide in acetic acid.[6]

The reaction of aromatic nitro compounds **11** with trialkyl phosphites results in stepwise deoxygenation, first to the nitroso compounds **12** and then to the arylnitrenes **13**. These reactive intermediates, which may also be generated by thermolysis of aryl azides **14**, undergo insertion and addition reactions with a variety of nearby functional groups leading to valuable synthetic methods for a wide range of heterocyclic nitrogen compounds.[7] This is illustrated by the reaction of 4-chlorophenyl 2-nitrophenyl sulfide **15** with triethyl phosphite (Protocol 4) to give 3-chlorophenothiazine **16**. The reaction (Scheme 4) involves an unexpected rearrangement of the initially formed nitrene **17** via the spiro intermediate **18** to give the 3-chloro product rather than its 2-chloro isomer. A minor by-product is the *N*-ethyl derivative of **16** (14%) formed by reaction of **16** with triethyl phosphate under the reaction conditions.





Scheme 4

Protocol 4.
Synthesis of 3-chlorophenothiazine[8]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times.

Equipment

- Single-necked, round-bottomed flask (100 mL)
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Oil bath
- Reflux condenser
- Source of dry nitrogen
- Chromatography column
- Plastic bucket (10 L)

Materials

- 4-Chlorophenyl 2-nitrophenyl sulfide **15**,[8] 2.0 g, 7.5 mmol
- Dry triethyl phosphite,[a] 5.0 g, 30 mmol (Aldrich T6,120-4, Lancaster 0339, Acros 42172, Fluka 90540) **toxic, stench**
- Freshly distilled cumene (isopropylbenzene), 75 mL **irritant**
- Alumina for chromatography, 200 g
- Toluene, 2 L **flammable, harmful**
- Sodium hypochlorite solution, 500 mL **corrosive**
- Liquid soap, 10 mL

Method

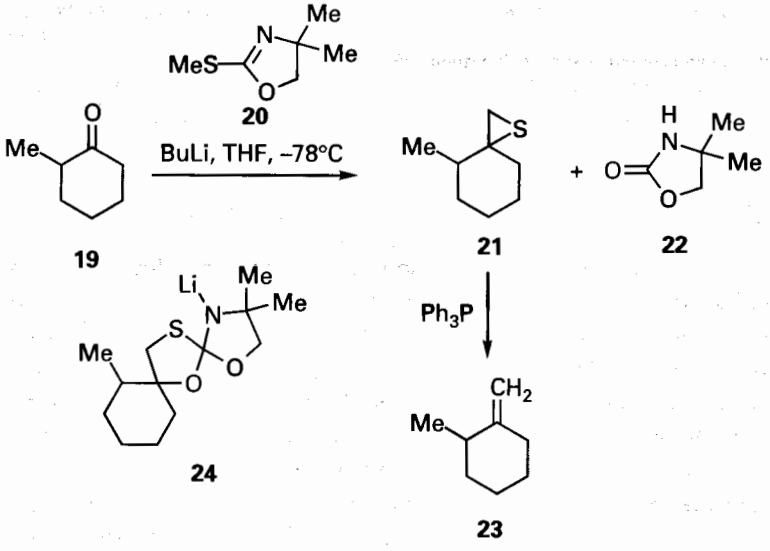
1. To a plastic bucket (10 L), add sodium hypochlorite solution (500 mL) and liquid soap (10 mL) and make up to two-thirds full with hot water. This solution will be used at the end of the procedure to dispose of the waste and decontaminate used equipment.
2. To a single-necked, round-bottomed flask (100 mL), add 4-chlorophenyl 2-nitrophenyl sulfide **15** (2.0 g, 7.5 mmol), freshly distilled cumene (75 mL), dry triethyl phosphite (5.0 g, 30 mmol) and a magnetic stirrer bar.
3. Fit a reflux condenser and nitrogen inlet and flush the system out thoroughly with dry nitrogen. Heat the mixture under reflux under nitrogen with stirring for 10 h.

Protocol 4. *Continued*

4. Evaporate the mixture using a rotary evaporator and put the solvent collected in the evaporator into the hypochlorite bath. Dissolve the residue in toluene (5 mL) and apply it to a chromatography column prepared using alumina (200 g) and toluene. Run the column using toluene as the eluant and combine the fractions shown by TLC to contain a single component. The products obtained are, in order, 2,3-dimethyl-2,3-diphenylbutane, 0.13 g (from dimerization of the solvent cumene), *N*-ethyl-3-chlorophenothiazine, m.p. 115–117°C, 0.33 g (14%) and 3-chlorophenothiazine **16**, m.p. 195–196°C, 1.06 g (58%).
5. Decontaminate all equipment used in this protocol including gloves by placing in the hypochlorite bucket for at least 4 h or until no smell remains. After removing the equipment, dispose of the used hypochlorite solution by washing it down a sink in a well-ventilated hood with a large volume of water.

[a]Triethyl phosphite may be dried by distilling from sodium wire under nitrogen (b.p. 156°C).

The P(III) reagents have an even greater affinity for sulfur than they do for oxygen and there are a number of useful synthetic procedures based on desulfurization.[9] In contrast to the deoxygenation of epoxides, the desulfurization of thiiranes is stereospecific and represents a potentially useful synthetic route to alkenes. Unfortunately, however, thiiranes were not easily obtained until the



Scheme 5

advent of the oxazoline-based method of Meyers in which a carbonyl compound is reacted with the anion of a 2-alkylthiooxazoline.[10] This is illustrated in Protocol 5 by the conversion of 2-methylcyclohexanone **19** into the thiirane **21** by reaction with the anion of oxazoline **20** and its desulfurization with triphenylphosphine to give the alkene **23** (Scheme 5). The overall transformation provides a useful alternative to the Wittig reaction with methylenetriphenylphosphorane (see Chapter 4). The thiirane is formed together with the oxazolidinone **22** by a mechanism involving the spiro intermediate **24**. By using chiral oxazolines the method can be used to generate chiral thiiranes but the ee values achieved are only in the 20–30% range.

Protocol 5.
Synthesis of 2-methylmethylenecyclohexane[10]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times.

Equipment

- Three-necked, round-bottomed flask (100 mL)
- Single-necked, round-bottomed flask (10 mL)
- Teflon-coated magnetic stirrer bar
- Source of dry nitrogen
- Rubber septum
- Glass syringe with metal Luer lock (5 mL)
- Needle with Luer hub, 30 cm, 18 gauge
- Thermostatted hot-plate stirrer
- Oil bath
- Separating funnel (250 mL)
- Chromatography column
- Kugelrohr distillation apparatus

Materials

- 2-(Methylthio)-4,4-dimethyl-4,5-dihydrooxazole,[a] 1.45 g, 10 mmol
- Dry THF, 50 mL — **flammable, irritant**
- Butyllithium solution in hexanes, 2.5 **M**, 4.0 mL, 10 mmol (Acros 21335, Lancaster 14775, Aldrich 23,070-7) — **flammable, corrosive**
- 2-Methylcyclohexanone, 1.12 g, 10 mmol (Avocado 14741, Lancaster 4077, Aldrich M3,840-0, Acros 12661, Fluka 66380) — **harmful**
- Diethyl ether, 105 mL — **highly flammable**
- Anhydrous magnesium sulfate, 10 g
- Silica for chromatography, 100 g
- Petroleum, b.p. 40–60°C, 500 mL — **flammable**
- Triphenylphosphine, 1.80 g, 6.9 mmol (Avocado 14089, Lancaster 2502, Fluka 93092, Aldrich T8,440-9, Acros 14042)

Method

1. To a three-necked, round-bottomed flask (100 mL), add 2-(methylthio)-4,4-dimethyl-4,5-dihydrooxazole (1.45 g, 10 mmol), dry THF (50 mL) and a magnetic stirrer bar. Equip the flask with a nitrogen inlet and rubber septum and connect to a source of nitrogen, flushing out the flask well.
2. Stir the solution while cooling to −78°C (dry ice/isopropanol[b] slush bath) under nitrogen. Add by syringe through the septum butyllithium solution in hexanes (2.5 M, 4.0 mL, 10 mmol) and stir at −78°C for 2 h.

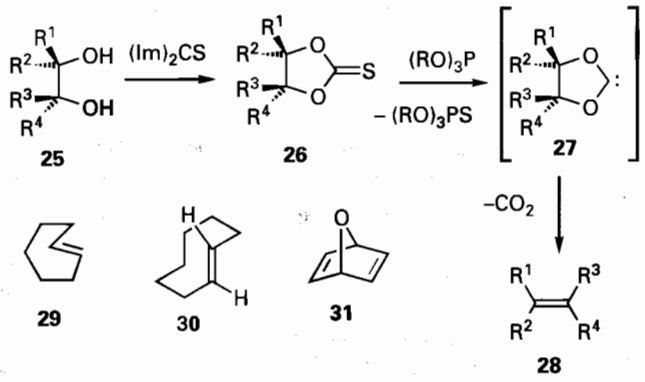
Protocol 5. *Continued*

3. Add by syringe through the septum 2-methylcyclohexanone (1.12 g, 10 mmol) and stir the mixture for 30 min at −78°C before allowing to warm up to room temperature (1–2 h).
4. Add the solution to water (100 mL) in a separating funnel (250 mL) and extract the mixture with diethyl ether (2 × 50 mL). Dry the combined extracts over anhydrous magnesium sulfate (10 g, 1 h), filter off the drying agent and evaporate the solution using a rotary evaporator.
5. Prepare a chromatography column using silica (100 g) and petroleum (b.p. 40–60°C). Dissolve the residue from evaporation in diethyl ether (5 mL) and apply to the column. Run the column using petroleum and collect the fractions containing the fastest moving component (TLC). Evaporate the combined product fractions using a rotary evaporator to give the thiirane **21**, 0.87 g (61%).
6. To a single-necked, round-bottomed flask (10 mL), add the thiirane (0.87 g, 6 mmol) and triphenylphosphine (1.80 g, 6.9 mmol) and heat the mixture at 90°C for 2 h.
7. Connect the flask to a Kugelrohr distillation apparatus and distil the mixture to give the product as a colourless liquid, b.p. 145°C, 0.37 g (56%). Proton NMR spectrum ($CDCl_3$): δ_H 4.60 (2H, br s) and 2.6–0.8 (12H, m).

[a]This is prepared from the commercially available 2-amino-2-methylpropan-1-ol (Avocado 17814, Lancaster 7093, Acros 10406, Aldrich A6,518-2, Fluka 08580) by reaction with carbon disulfide[11] followed by sodium hydride and iodomethane.[10]

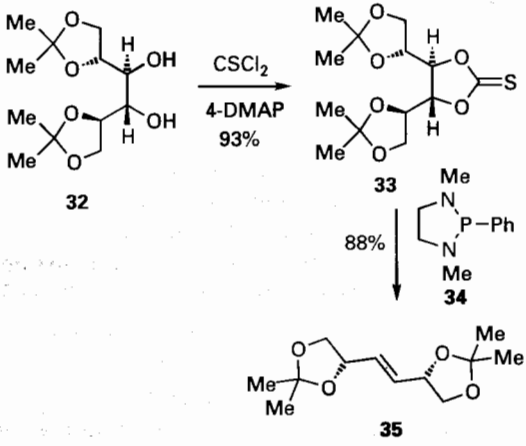
[b]This is preferable to the more commonly used combination of dry ice/acetone since the cold solvent is viscous and shows less tendency to foam up.

A useful method for the conversion of 1,2-diols to the corresponding alkenes is the so-called Corey Winter method which involves conversion of the diol **25** into the cyclic thiocarbonate (1,3-dioxolane-2-thione) **26**, most conveniently by treatment with thiocarbonyldiimidazole, and then desulfurization by treatment with a trialkyl phosphite. The resulting carbene intermediate **27** spontaneously loses CO_2 to give the alkene **28**.[12] As shown, the reaction is stereospecific and this has allowed it to be applied to the synthesis of some unusual alkenes such as (*E*)-cycloheptene **29**,[13] the (−)-enantiomer of the planar chiral (*E*)-cyclooctene,[14] and 7-oxabicyclo[2.2.1]hepta-2,5-diene.[15] The example given in Protocol 6 illustrates the use of a newer desulfurizing agent, the diazaphospholidine **34**, and also an alternative method of forming the thiocarbonate using thiophosgene in the presence of 4-dimethylaminopyridine. The diacetonide of D-mannitol **32** is thus converted into the synthetically useful alkene **35** in 82% overall yield.



Protocol 6.
Synthesis of (*Z*)-3,4-didehydro-3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-D-*threo*-hexitol[16]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 6).



Scheme 6

Equipment

- Double-necked, round-bottomed flask (10 mL)
- Single-necked, round-bottomed flask (2 mL)
- Reflux condenser
- Teflon-coated magnetic stirrer bar
- Source of dry nitrogen
- Thermostatted hot-plate stirrer
- Oil bath
- Glass syringe (100 μL)
- Rubber septum
- Chromatography column

Protocol 6. *Continued*

Materials

- 1,2:5,6-Di-*O*-isopropylidene-D-mannitol, 262 mg, 1.0 mmol (Lancaster 12127, Fluka 38410, Aldrich 29,640-6)
- 4-Dimethylaminopyridine, 293 mg, 2.4 mmol (Avocado 13016, Lancaster 1259, Aldrich 10,770-0, Acros 14827, Fluka 39405) **harmful**
- Dry dichloromethane, 4 mL **harmful**
- Thiophosgene, 92 μL, 138 mg, 1.2 mmol (Avocado 19154, Acros 15164, Aldrich 11,515-0, Fluka 89030) **toxic, corrosive**
- Silica for chromatography, 28 g
- Hexanes, 200 mL **flammable, harmful**
- Ethyl acetate, 200 mL **flammable**
- 1,3-Dimethyl-2-phenyl-1,3,2-diazaphospholidine **34**,[a] 0.29 mL, 310 mg, 1.6 mmol
- Diethyl ether, 25 mL **highly flammable**
- Dichloromethane, 475 mL **harmful**

Method

1. To a double-necked, round-bottomed flask (10 mL), add 1,2:5,6-di-*O*-isopropylidene-D-mannitol (262 mg, 1.0 mmol), 4-dimethylaminopyridine (293 mg, 2.4 mmol), dry dichloromethane (4 mL) and a magnetic stirrer bar. Fit a rubber septum and nitrogen inlet and flush the system thoroughly with dry nitrogen.
2. Stir the flask in an ice bath under nitrogen and then add thiophosgene (92 μL, 138 mg, 1.2 mmol) slowly through the septum using a glass syringe (100 μL). Wash the syringe out with dichloromethane immediately after use to avoid corrosion.
3. Stir the mixture at 0°C for 1 h and then add silica (2 g) and allow it to warm to room temperature. Evaporate the mixture using a rotary evaporator.
4. Prepare a chromatography column of silica (6 g) using hexanes/ethyl acetate (1:1) and apply the residue from evaporation directly onto the column. Run the column using hexanes/ethyl acetate (400 mL) and evaporate the combined product fractions using a rotary evaporator to obtain the thiocarbonate **33**, as a colourless solid, m.p. 152–156°C, 284 mg (93%).
5. Equip a single-necked, round-bottomed flask (2 mL) with a reflux condenser and nitrogen inlet. To the flask, add the above thiocarbonate **33** (164 mg, 0.54 mmol), the diazaphospholidine **34** (0.29 mL, 310 mg, 1.6 mmol) and a magnetic stirrer bar and flush out the system thoroughly with dry nitrogen.
6. Heat the mixture with stirring under nitrogen for 20 h. Cool the mixture to room temperature and prepare a chromatography column of silica (20 g) using dichloromethane/diethyl ether (19:1). Apply the reaction mixture directly to the column and run it using dichloromethane/diethyl ether (19:1, 500 mL). Evaporate the combined product fractions using a rotary evaporator to give the product **35** as a colourless solid, m.p. 80–81°C, 108 mg (88%). Proton NMR spectrum ($CDCl_3$): δ_H 5.77 (2H, m), 4.45 (2H, m), 4.05 (2H, dd,

J = 8, 6 Hz), 3.55 (2H, t, J = 8 Hz), 1.39 (6H, s) and 1.35 (6H, s). Specific rotation: $[\alpha]_D^{20}$ + 56.7 (*c*, 3.2 in $CHCl_3$).

[a]This is commercially available (Fluka 41411, Aldrich 37,367-2) or may be readily prepared from *N*, *N'*-dimethylethylenediamine and dichlorophenylphosphine (70%)[17] and should be stored under nitrogen at −20°C.

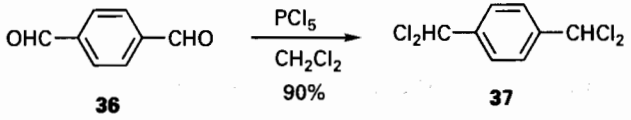
3. Halogenation reactions

Phosphorus reagents, both organic and inorganic, are among the most powerful and widely used halogenating agents. Conversion of alcohols into the corresponding halides is possible using PCl_3, PCl_5, PBr_3, PBr_5, or PI_3. In addition PCl_5 is widely used for conversion of carboxylic acids into the acid chlorides, although the $POCl_3$ produced as a by-product is not so easily removed as the gaseous by-products from thionyl chloride or oxalyl chloride. In all these processes, the affinity of phosphorus for oxygen provides the driving force for reaction.

Another reaction which can be brought about by PCl_5 is the conversion of aldehydes and ketones into the corresponding geminal dichlorides and this is illustrated in Protocol 7 by the conversion of terephthalaldehyde **36** into the tetrachloride **37**. Unusually for a reaction using PCl_5, no HCl is evolved here and the product is sufficiently unreactive to be isolated using an aqueous work-up. It should be noted that chlorination of aromatic aldehydes in this way is the method of choice for synthesis of benzylidene chlorides since the products obtained from the alternative chlorination of toluenes are always contaminated by the benzyl chlorides and benzotrichlorides.

Protocol 7.
Synthesis of α, α, α′, α′-tetrachloro-*p*-xylene [1,4-bis(dichloromethyl) benzene] (R. A. Aitken and A. O. Oyewale, unpublished data)

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 7).



36 **37**

Scheme 7

Equipment

- Single-necked, round-bottomed flask (250 mL)
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Powder funnel
- Separating funnel (250 mL)

Protocol 7. *Continued*

Materials

- Terephthalaldehyde (benzene-1,4-dialdehyde) **36**, 5.0 g, 37 mmol (Avocado 14930, Acros 13789, Fluka 86410, Aldrich T220-7, Lancaster 13270)
- Phosphorus pentachloride,[a] 16.0 g, 77 mmol (Fluka 79590, Aldrich 15,777-5, Lancaster 11627, Acros 16946) **corrosive, irritant**
- Dichloromethane, 100 mL **harmful**
- Petroleum, b.p. 60–80°C, 100 mL **flammable**
- Anhydrous magnesium sulfate, 10 g

Method

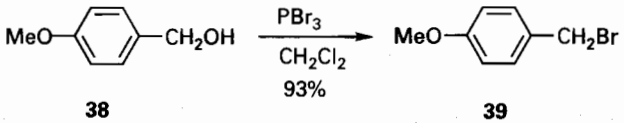
1. To a single-necked, round-bottomed flask (250 mL) add terephthalaldehyde **36** (5.0 g, 37 mmol), dichloromethane (100 mL) and a magnetic stirrer bar. Stir until a clear solution is obtained.
2. Using a powder funnel, cautiously add phosphorus pentachloride (16.0 g, 77 mmol) in portions, over a period of 10 min. Do not use a metal spatula for this since it will be corroded—if necessary use a glass rod.
3. Place a stopper on the flask and stir at room temperature for 2 h.
4. Cautiously add water (20 mL) dropwise to destroy the unreacted phosphorus pentachloride and transfer the mixture to a separating funnel (250 mL). Separate the organic layer and dry it using anhydrous magnesium sulfate (10 g, 1 h).
5. Filter off the drying agent and evaporate the solution using a rotary evaporator. Recrystallize the solid residue from petroleum (b.p. 60–80°C, 100 mL) to give the product as colourless crystals, m.p. 93–95°C, 8.1 g (90%). Proton NMR spectrum ($CDCl_3$): δ_H 6.70 (2H, s) and 7.60 (4H, s).

[a]Phosphorus pentachloride is an extremely aggressive and corrosive reagent and it commonly attacks the material of the top of the bottles in which it is supplied. To avoid this, it should be transferred upon receipt to a bottle with a ground glass stopper in which it can be stored indefinitely.

For conversion of alcohols into the corresponding bromides, PBr_3 is often the reagent of choice and is much more convenient than the alternative of gaseous HBr. The reactions proceed readily at or below room temperature and it should be noted that all three bromines are available for reaction. Typical conditions are illustrated in Protocol 8 for the synthesis of 4-methoxybenzyl bromide **39**.

Protocol 8.
Synthesis of 4-methoxybenzyl bromide (R. A. Aitken and B. M. Ryan, unpublished data)

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 8).



38 **39**

Scheme 8

Equipment

- Double-necked, round-bottomed flask (500 mL)
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Addition funnel (100 mL)
- Separating funnel (500 mL)

Materials

- 4-Methoxybenzyl alcohol **38**, 50 g, 362 mmol (Avocado 15559, Acros 15973, Lancaster 2566, Aldrich 13,690-5, Fluka 64840)
- Phosphorus tribromide, 32.7 g, 121 mmol (Lancaster 13638, Aldrich 15,778-3, Acros 16947, Fluka 79660) **corrosive, irritant**
- Dichloromethane, 150 mL **harmful**
- Diethyl ether, 300 mL **highly flammable**
- Anhydrous magnesium sulfate, 30 g

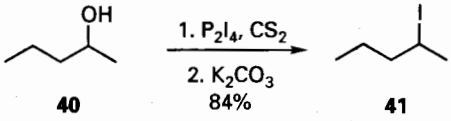
Method

1. To a double-necked, round-bottomed flask (500 mL), add 4-methoxybenzyl alcohol **38** (50 g, 362 mmol), dichloromethane (100 mL) and a magnetic stirrer bar. Stir this solution in an ice bath.
2. Using an addition funnel (100 mL), add dropwise a solution of phosphorus tribromide (32.7 g, 121 mmol) in dichloromethane (50 mL). After the addition, stir the solution at room temperature for 90 min.
3. Add the solution to water (100 mL) in a separating funnel (500 mL) and extract the mixture with diethyl ether (2 × 150 mL). Dry the combined extracts using anhydrous magnesium sulfate (30 g, 1 h).
4. Filter off the drying agent and evaporate the solution using a rotary evaporator to give the product as a colourless severely irritant liquid, 68 g (93%). This is sufficiently pure for most applications and it may decompose upon attempted distillation. Proton NMR spectrum ($CDCl_3$): δ_H 3.70 (3H, s), 4.50 (2H, s) and 6.80 and 7.20 (4H, AA′BB′ pattern, $J = 8$ Hz).

The less well-known diphosphorus tetraiodide, P_2I_4, is a powerful deoxygenating agent and it also allows efficient conversion of alcohols into the corresponding iodides as illustrated in Protocol 9 by the conversion of pentan-2-ol **40** into 2-iodopentane **41**. As for all the halogenating agents described in this section, reaction proceeds with inversion of configuration for chiral alcohols. The reagent is commercially available and has the advantage of being an easily handled crystalline solid.

Protocol 9.
Synthesis of 2-iodopentane[18]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 9).



40 **41**

Scheme 9

Equipment

- Single-necked, round-bottomed flask (250 mL)
- Pressure equalizing addition funnel (5 mL)
- Source of dry nitrogen
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Separating funnel (250 mL)
- Kugelrohr distillation apparatus

Materials

- Diphosphorus tetraiodide,[a] 1.48 g, 2.6 mmol (Acros 20393, Fluka 43430, Aldrich 21,865-0) **corrosive, irritant**
- Carbon disulfide,[b] 50 mL **highly flammable, toxic, irritant**
- Pentan-2-ol **40**, 0.88 g, 10 mmol (Avocado 21217, Aldrich P801-7, Acros 12998, Lancaster 4405, Fluka 76942) **harmful**
- Anhydrous potassium carbonate, 5 g **irritant**
- Saturated aqueous potassium carbonate solution, 25 mL
- Diethyl ether, 200 mL **highly flammable**
- Anhydrous magnesium sulfate, 10 g

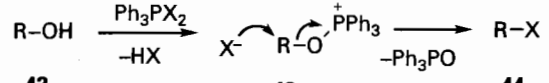
Method

1. To a single-necked, round-bottomed flask (250 mL), add diphosphorus tetraiodide (1.48 g, 2.6 mmol), carbon disulfide (50 mL) and a magnetic stirrer bar. Equip the flask with a pressure-equalizing addition funnel (5 mL) containing pentan-2-ol **40** (0.88 g, 10 mmol) and a nitrogen inlet. Connect a source of dry nitrogen and flush out the system thoroughly.

2. Stir the mixture at 0°C under nitrogen and add the pentan-2-ol dropwise over a period of 10 min. Continue stirring at 0°C for 2 h and then at room temperature for 20 h. During the reaction the initially orange solution turns brown and an orange precipitate forms.
3. Remove the addition funnel and carefully add anhydrous potassium carbonate (5 g) followed by saturated aqueous potassium carbonate solution (25 mL). Transfer the mixture to a separating funnel (250 mL) and extract it with diethyl ether (4 × 50 mL). Dry the combined extracts over anhydrous magnesium sulfate (10 g, 1 h).
4. Filter off the drying agent and evaporate the solution using a rotary evaporator. Distil the residual liquid using a Kugelrohr distillation apparatus to give the product as a colourless liquid, b.p. 143°C, 1.66 g (84%). Iodoalkanes are readily recognized by the dramatic shielding effect of iodine on the ^{13}C NMR signal for the carbon to which it is attached. Iodomethane gives a signal at δ_C – 23.2 and in this case the 2-carbon of **41** gives a signal at δ_C 31.2 as compared to 67.8 for **40**.

[a]This reagent should be stored under dry nitrogen but may be quickly weighed out in a normal laboratory atmosphere.
[b]Particular care must be taken in handling this material owing to its extremely unpleasant smell, high toxicity, high volatilty, low flash point (–33°C) and low autoignition temperature (102°C).

Triphenylphosphine forms crystalline addition compounds with elemental halogens, which allow convenient and efficient halogenation under milder conditions than using the halogen itself.[19] The conversion of alcohols and phenols **42** into the corresponding halides **44** using both Ph_3PCl_2 and Ph_3PBr_2 was reported some time ago,[20] and because the reactions proceed *via* the intermediate **43**, clean inversion of stereochemistry is observed for chiral alcohols. The combination of triphenylphosphine and iodine provides an effective reagent for the direct conversion of sulfonic and sulfinic acids, thiols and disulfides into the corresponding alkyl iodides.[21] The readily formed crystalline adduct of Ph_3P with HBr provides a convenient small scale laboratory source of this gas, which is liberated by boiling in xylene.[22]



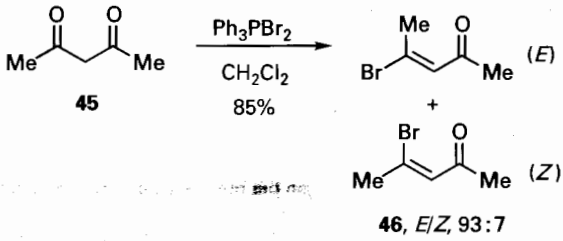
42 **43** **44**

The use of Ph_3PBr_2 is illustrated in Protocol 10 where pentane-2,4-dione (acetylacetone) **45** is converted into a mixture of (*E*)- and (*Z*)-bromoenones **46**, which upon treatment with triethylamine generate the interesting synthetic building block acetylallene.[23] The overall transformation may be regarded as

replacement of the OH in the enol form of **45** by Br. The proton NMR spectrum of the product showed it to consist almost entirely of the (*E*)-isomer.

Protocol 10.
Synthesis of (*E*/*Z*)-4-bromopent-3-en-2-one[23]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 10).



Scheme 10

Equipment

- Three-necked, round-bottomed flask (500 mL)
- Reflux condenser
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Oil bath
- Pressure equalizing addition funnel (50 mL)
- Source of dry nitrogen
- Thermometer
- Sintered glass filter funnel
- Kugelrohr distillation apparatus

Materials

- Triphenylphosphine, 52.4 g, 0.2 mol (Avocado 14089, Lancaster 2502, Fluka 93092, Aldrich T8,440-9, Acros 14042)
- Bromine, 32 g, 10.4 mL, 0.2 mol **corrosive, highly toxic**
- Pentane-2,4-dione (acetylacetone) **45**, 20 g, 0.2 mol (Avocado 14117, Lancaster 4363, Acros 12996, Aldrich P775-4, Fluka 00909) **harmful**
- Dichloromethane, 250 mL **harmful**
- Diethyl ether, 80 mL **highly flammable**
- Anhydrous magnesium sulfate, 10 g

Method

1. To a three-necked, round-bottomed flask (500 mL) add triphenylphosphine (52.4 g, 0.2 mol), dichloromethane (150 mL) and a magnetic stirrer bar. Stir at room temperature until a clear solution is obtained.
2. Equip the flask with a thermometer (side-neck), pressure equalizing addition funnel (50 mL, side-neck) and reflux condenser with nitrogen inlet (centre-neck) and cool it in an ice bath.

3. Place a solution of bromine (32 g, 10.4 mL, 0.2 mol) in dichloromethane (50 mL) in the addition funnel. Slowly add this solution to the stirred reaction mixture at such a rate that the temperature never exceeds 10°C.
4. Add a solution of pentane-2,4-dione (20 g, 0.2 mol) in dichloromethane (50 mL) through the addition funnel over a period of 10 min and then heat the mixture under reflux for 4–5 h. During this period HBr gas is evolved, which may be absorbed in sodium hydroxide solution.
5. After cooling, reduce the solution in volume to 150 mL using a rotary evaporator and add diethyl ether (40 mL). Filter off the resulting precipitate of Ph_3PO using a sintered glass funnel. Reduce the filtrate in volume to 150 mL using a rotary evaporator and again add diethyl ether (40 mL). Filter off the resulting precipitate of Ph_3PO using a sintered glass funnel. Dry the filtrate using anhydrous magnesium sulfate (10 g, 1 h), filter off the drying agent and evaporate the solution using a rotary evaporator.
6. Purify the residual liquid by short-path (Kugelrohr) distillation to give the product as a pale yellow severely irritant oil, b.p. 47 – 48°C at 8 mmHg, 27.7 g, 85%. Analysis by proton NMR shows this to consist of *E* and *Z* isomers in a ratio of 93:7: δ_H (*E*) 2.13 (3H, s), 2.70 (3H, d, $J = 3$ Hz) and 6.68 (1H, q, $J = 3$ Hz); δ_H (*Z*) 2.00 (3H, s), 2.43 (3H, d, $J = 1$ Hz) and 6.48 (1H, q, $J = 1$ Hz).

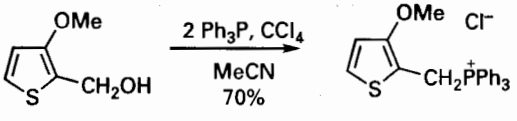
Halogenation of alcohols may also be effectively carried out by the combination of triphenylphosphine and a tetrahalomethane, CX_4, and the reagent system Ph_3P/CCl_4 in particular is widely used.[24] The reaction results in the formation of Ph_3PO and CHX_3, although the mechanism is not straightforward and proceeds much more rapidly in polar solvents such as acetonitrile than when an excess of CCl_4 is used as the solvent. Halogenation of 1,3-diketones in a similar way to Protocol 10 may also be carried out using Ph_3P and CCl_4 or CBr_4.[25] Treatment of an aldehyde RCHO with Ph_3P and CBr_4 results in formation of the 1,1-dibromoalkene, $RCH{=}CBr_2$ and subsequent reaction of this with butyllithium provides a high yielding synthesis of terminal alkynes, $RC{\equiv}CH$, in the so-called Corey–Fuchs procedure.[26] The corresponding reaction of aldehydes with Ph_3P and CI_4 gives the 1,1-diiodialkenes, $RCH{=}CI_2$.[27] Those attempting to analyse products from reactions involving carbon tetraiodide by ^{13}C NMR should be aware of the extreme chemical shift values of compounds of this type: δ_C (CI_4) −292.5; δ_C (CHI_3) −139.9, and the resulting danger of confusion from 'folded back' peaks if the observation frequency window is not set sufficiently wide.

Protocol 11 shows an example of the use of Ph_3P and CCl_4 to convert an alcohol into the corresponding chloride. The starting alcohol **47** is highly unstable towards acid and the corresponding chloride is expected to be even more so, hence a mild method such as this is ideal. The chloride was required for conversion into the corresponding quaternary phosphonium salt **48** for use in a Wittig reaction

(see Chapter 4) and so the steps could be combined by treating **47** directly with 2.5 equivalents of Ph_3P and one equivalent of CCl_4 in acetonitrile to give **48** in 70% yield. A similar method using Ph_3P·HBr to convert benzylic alcohols into the corresponding phosphonium salts has recently been reported.[28]

Protocol 11.
Synthesis of 3-methoxy-2-thienylmethyl(triphenyl)phosphonium chloride (R. A. Aitken and A. N. Garnett, unpublished data)

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 11).



47 **48**

Scheme 11

Equipment

- Double-necked, round-bottomed flask (250 mL)
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Syringe (10 mL) and needle
- Rubber septum
- Reflux condenser
- Sintered glass funnel
- Source of dry nitrogen

Materials

- 3-Methoxy-2-thiophenemethanol,[a] 13.45 g, 93 mmol
- Triphenylphosphine, 60.0 g, 229 mmol (Avocado 14089, Lancaster 2502, Fluka 93092, Aldrich T8,440-9, Acros 14042)
- Acetonitrile, 220 mL — **flammable, toxic**
- Carbon tetrachloride,[b] 9.0 mL, 14.35 g, 93 mmol — **toxic, cancer-suspect agent**

Method

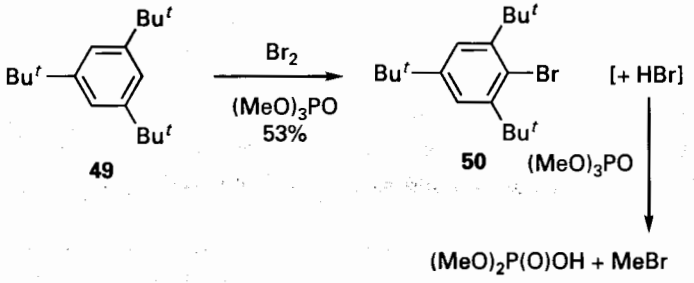
1. To a double-necked, round-bottomed flask (250 mL), add 3-methoxy-2-thiophenemethanol (13.45 g, 93 mmol), acetonitrile (100 mL), triphenylphosphine (60.0 g, 229 mmol) and a magnetic stirrer bar and stir at room temperature until a clear solution is obtained.
2. Equip the flask with a rubber septum and a reflux condenser connected to a source of dry nitrogen and flush out the flask with nitrogen. Heat the solution to 70°C.
3. Add carbon tetrachloride (9.0 mL, 14.35 g, 93 mmol) dropwise through the septum using a syringe (10 mL). This gives a vigorous exothermic reaction. After the addition, heat the mixture under reflux for 1.5 h.

4. Filter off the heavy white precipitate using a sintered glass funnel and wash it with cold acetonitrile (20 mL). Recrystallize the solid using acetonitrile (100 mL) to give the product, m.p. 233–235°C, 27.6 g (70%).

[a]This is prepared by $LiAlH_4$ reduction of methyl 3-methoxythiophene-2-carboxylate, followed by work-up under neutral conditions (R. A. Aitken and A. N. Garnett, unpublished data). All contact with acids must be avoided.

[b]The future availability of this is questionable since it is suspected of damaging the ozone layer and its production is prohibited under the terms of the Montreal Protocol.

An interesting example of a halogenation reaction where an organophosphorus compound plays a key role, although not as the reagent but as the solvent, is shown in Protocol 12. Attempts to ring-brominate 1,3,5-tri-*t*-butylbenzene **49** using bromine in CCl_4 result in loss of one *t*-butyl group to give 3,5-di-*t*-butylbromobenzene while in acetic acid no reaction occurs. Loss of the *t*-butyl group is caused by the HBr formed in the reaction and in order to avoid this the reaction is carried out in dry trimethyl phosphate. As shown in Scheme 12 this absorbs the HBr efficiently with formation of MeBr and the desired product **50** is formed in over 50% yield. Trimethyl phosphate may also be used as the solvent for chlorination, iodination and nitration of acid-sensitive substrates. The product **50** is important since it is the starting point for the synthesis of many sterically protected low-valent phosphorus compounds (see Chapter 8).



Scheme 12

Protocol 12.
Synthesis of 2,4,6-tri-*t*-butylbromobenzene[29]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times.

Equipment

- Single-necked, round-bottomed flask (500 mL)
- Reflux condenser
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Oil bath
- Separating funnel (1 L)
- Erlenmeyer flask (500 mL)

Materials

- 1,3,5-tri-*t*-butylbenzene, 19.0 g, 77 mmol (Aldrich 22,377-8, Fluka 90793, Acros 20797)
- Bromine, 14.0 g, 4.5 mL, 87.5 mmol **corrosive, highly toxic**
- Dry trimethyl phosphate,[a] 200 mL (Avocado 10595, Lancaster 3040, Aldrich 13,219-5, Acros 15797, Fluka 92720) **harmful**
- Hexanes, 350 mL **flammable, harmful**
- Anhydrous magnesium sulfate, 10 g
- Ethanol, 150 mL **flammable**

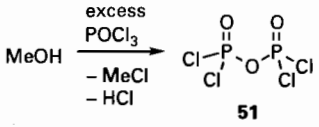
Method

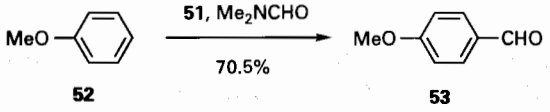
1. To a single-necked, round-bottomed flask (500 mL), add 1,3,5-tri-*t*-butylbenzene (19.0 g, 77 mmol), dry trimethyl phosphate (200 mL) and a magnetic stirrer bar. Heat the flask with stirring at 80°C until all the solid dissolves.
2. Reduce the temperature of the solution to 70°C and add bromine (14.0 g, 4.5 mL, 87.5 mmol) rapidly. Fit a reflux condenser and stir the solution at 70°C for 24 h. During this time some solid may sublime up into the reflux condenser but this does not affect the success of the reaction.
3. Allow the pale yellow solution, which contains some solid to cool and then add it to water (200 mL) in a separating funnel (1 L). Extract the mixture with hexanes (350 mL) and dry the extract with anhydrous magnesium sulfate (10 g, 1 h).
4. Filter off the drying agent and evaporate the solution using a rotary evaporator. Recrystallize the resulting solid from ethanol (150 mL) to give the product as colourless flakes, m.p. 171.5–173.5°C, 13.3 g (53%). Proton NMR spectrum ($CDCl_3$): δ_H 1.34 (18H, s), 1.60 (9H, s) and 7.42 (2H, s).

[a]Trimethyl phosphate is hygroscopic and readily absorbs water upon storage. Use of the newly purchased or freshly distilled material is essential for this protocol.

The standard Vilsmeier–Haack reaction involves combination of $POCl_3$ with DMF or *N*-methylformanilide to form a chloromethyleneiminium salt which efficiently formylates a variety of electron-rich aromatic and heteroaromatic

compounds.[30] Finally, in this section, we consider a newer variant of this reaction in which pyrophosphoryl chloride **51** is used in place of $POCl_3$ to give improved yields and different regioselectivity.[31] As shown in Scheme 13, the reagent is readily prepared by prolonged reaction of methanol with an excess of $POCl_3$. In the example of Protocol 13, formylation of anisole **52** using **51** and DMF gives 4-methoxybenzaldehyde **53** in 70.5% yield together with 4.5% of the 2-methoxy isomer. For comparison, the standard method using $POCl_3$ and DMF gives **53** (34%) and 2-methoxybenzaldehyde (4%).





Scheme 13

Protocol 13.
Synthesis of 4-methoxybenzaldehyde[31]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times.

Equipment

- Single-necked, round-bottomed flasks (100 and 10 mL)
- Reflux condenser
- Separating funnel (50 mL)
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Oil bath
- Kugelrohr distillation apparatus

Materials

- Phosphoryl chloride, 46 g, 300 mmol (Aldrich 20,117-0, Fluka 79580, Acros 19129) **corrosive, irritant**
- Methanol, 2.0 g, 60 mmol **flammable, toxic**
- Anisole **52**, 1.08 g, 10 mmol (Avocado 12997, Acros 15392, Aldrich 12,322-6, Lancaster 3948, Fluka 10520)
- DMF, 1.10 g, 15 mmol **harmful, irritant**
- Sodium hydroxide solution, 2 M, 10 mL **corrosive**
- Dichloromethane, 60 mL **harmful**
- Anhydrous magnesium sulfate, 5 g

Method

1. To a single-necked, round-bottomed flask (100 mL), add phosphoryl chloride (46 g, 300 mmol) and a magnetic stirrer bar. Stir the mixture in an ice bath

Protocol 13. *Continued*

and add dropwise methanol (2.0 g, 60 mmol). Fit a reflux condenser and heat the mixture under reflux for 21 days.

2. Evaporate the excess of phosphoryl chloride, which may be recovered for reuse in the same reaction, using a rotary evaporator. Kugelrohr distil the residual liquid to give pyrophosphoryl chloride **51** as a colourless liquid, b.p. 60–65°C at 0.1 mmHg, 7.36 g (49%).
3. To a single-necked, round-bottomed flask (10 mL), add anisole **52** (1.08 g, 10 mmol), DMF (1.10 g, 15 mmol) and a magnetic stirrer bar. Stir the mixture in an ice bath and add dropwise pyrophosphoryl chloride **51** (3.28 g, 13 mmol).
4. Fit a reflux condenser and heat the mixture at 100°C for 75 h. After cooling, add the resulting syrup to sodium hydroxide solution (2 M, 10 mL) in a separating funnel (50 mL). Extract the mixture with dichloromethane (3 × 20 mL) and dry the combined extracts using anhydrous magnesium sulfate (5 g, 1 h).
5. Filter off the drying agent and evaporate the solution using a rotary evaporator. Purify the residue by Kugelrohr distillation to remove the unreacted anisole (b.p. 154°C) and DMF (b.p. 153°C) and then raise the temperature to obtain the product **53** as a colourless liquid, b.p. 248°C, 1.04 g (75%). Analysis by proton NMR shows this to contain **53** and the 2-isomer in a ratio of 74.5 : 4.5. The 2-isomer (m.p. 37–39°C) may be separated from the main product (m.p. −1°C) by freezing the mixture in an ice–salt bath and allowing to partially thaw before pouring off the pure liquid **53** from the solid containing the 2-isomer.

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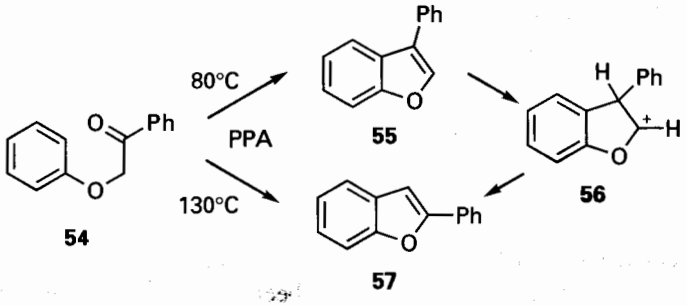
4. Dehydrative coupling and cyclization reactions

Condensation reactions, those in which two fragments are coupled with elimination of water, are among the most thoroughly studied in organic chemistry, not least because peptide coupling falls into this category. Phosphorus reagents have a key role to play in this area and they provide some of the most effective and widely used methods. The intramolecular variant of these reactions leads to cyclization and has been applied to all ring sizes from small rings to macrocycles.

The ring synthesis of many heteroaromatic compounds frequently involves cyclization of a suitable precursor with loss of either water or a simple alcohol such as methanol or ethanol. This may be brought about by treatment with polyphosphoric acid (PPA), which is prepared by dissolving phosphorus pentoxide in concentrated phosphoric acid. In the example of Protocol 14 this approach is used to prepare 3-phenylbenzofuran **55** from phenoxymethyl phenyl ketone **54**. The temperature must be carefully controlled, however, since as shown in Scheme 14, an acid-catalysed rearrangment by way of **56** gives the isomeric 2-phenylbenzofuran **57** at higher temperature. This useful feature allows the convenient preparation of either **55** or **57** uncontaminated by the other isomer.



Scheme 14

Protocol 14.
Synthesis of 3- and 2-phenylbenzofuran[32]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times.

Equipment

- Single-necked, round-bottomed flask (250 mL)
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Oil bath
- Thermometer
- Separating funnel (3 L)

Materials

- Phenoxymethyl phenyl ketone **54**,[a] 12.0 g, 56.6 mmol
- PPA,[b] 120 g (Lancaster 14856, Fluka 81340, Acros 19695, Aldrich 20,821-3) **corrosive**
- Diethyl ether, 300 mL **highly flammable**
- Anhydrous magnesium sulfate, 15 g
- Ethanol, 50 mL **flammable**

Method

1. Place PPA (120 g) and a magnetic stirrer bar in a single-necked, round-bottomed flask (250 mL) and heat to a steady temperature of either 80°C or 130°C according to which isomer is desired.
2. Add all at once phenoxymethyl phenyl ketone **54** (12.0 g, 56.6 mmol) and stir the mixture at the specified temperature for 2 h.
3. Pour the contents of the flask into a separating funnel (3 L) containing water (2 L) and extract the mixture with diethyl ether (3 × 100 mL). Dry the combined extracts using anhydrous magnesium sulfate (15 g, 1 h).
4. Filter off the drying agent and evaporate the solution using a rotary evaporator. Recrystallize the residual solid from ethanol (50 mL) to give the product [from reaction at 80°C] 3-phenylbenzofuran **55**, m.p. 42–43°C, 9.0 g (82%) or [from reaction at 130°C] 2-phenylbenzofuran **57**, m.p. 120–121°C, 7.8 g (71%).

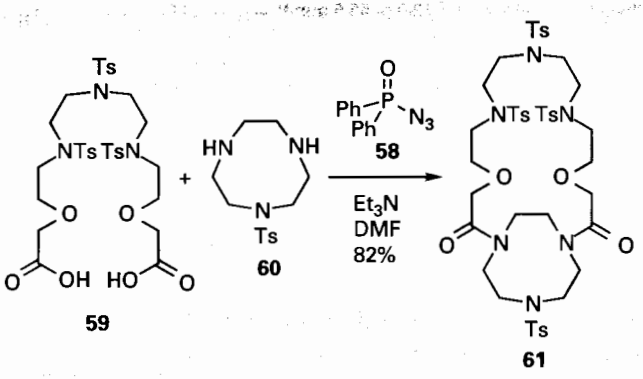
Protocol 14. *Continued*

[a]This may be prepared by reaction of ω-bromoacetophenone with phenol and potassium carbonate in acetone (71%).[32]
[b]Commercially available or may be prepared by dissolving phosphorus pentoxide with stirring in concentrated phosphoric acid.[32]

Diphenylphosphoryl azide (DPPA) **58** was first introduced as a reagent for peptide synthesis by Yamada in 1972[33] and has been widely used since it gives good yields and very little racemization. It may also be used to bring about a modified Curtius reaction in which a carboxylic acid, R^1CO_2H and an alcohol, R^2OH, react in the presence of triethylamine to afford the carbamate $R^1NHCO_2R^2$.[33] In Protocol 15, the use of DPPA to form a macrocyclic lactam **61** is illustrated. The 82% yield of the product using this method should be compared with the value of 24% for reaction of the bis(acid chloride) of **59** with the diamine **60**.

Protocol 15.
Synthesis of a macrocyclic lactam[34]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 15).



Scheme 15

Equipment

- Single-necked, round-bottomed flask (250 mL)
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Separating funnel (100 mL)
- Chromatography column

Materials

- 6,9,12-Tri(tolyl-4-sulfonyl)-3,15-dioxa-6,9,12-triazaheptadecanedioic acid **59**,[34] 0.769 g, 1.0 mmol
- 1-(Tolyl-4-sulfonyl)-1,4,7-triazacyclononane **60**,[34] 0.283 g, 1.0 mmol
- Dry DMF,[a] 100 mL — **harmful, irritant**
- Triethylamine, 0.505 g, 5.0 mmol — **flammable, irritant**
- Diphenylphosphoryl azide **58**, 1.215 g, 5.0 mmol (Avocado 12124, Lancaster 0396, Aldrich 17,875-6, Acros 40904, Fluka 79627) — **toxic, irritant**
- Dichloromethane, 1025 mL — **harmful**
- Methanol, 200 mL — **flammable, toxic**
- Aqueous sodium hydroxide solution, 2 M, 25 mL — **corrosive**
- Hydrochloric acid, 2 M, 25 mL — **corrosive**
- Anhydrous magnesium sulfate, 10 g
- Silica for chromatography, 100 g

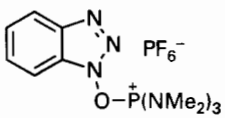
Method

1. To a single-necked, round-bottomed flask (250 mL), add 6,9,12-tri(tolyl-4-sulfonyl)-3,15-dioxa-6,9,12-triazaheptadecanedioic acid **59** (0.769 g, 1.0 mmol), 1-(tolyl-4-sulfonyl)-1,4,7-triazacyclononane **60** (0.283 g, 1.0 mmol), dry DMF (100 mL), triethylamine (0.505 g, 5.0 mmol) and a magnetic stirrer bar. Stir the solution at room temperature for 10 min.
2. Add diphenylphosphoryl azide **58** (1.215 g, 5.0 mmol) dropwise. Stir the resulting solution at room temperature for 16 h.
3. Evaporate the solution using a rotary evaporator with a hot water bath. Difficulty may be experienced in removing the DMF due to its high boiling point (b.p. 153°C) and connecting the evaporator to a vacuum pump rather than the usual water aspirator may prove advantageous.
4. Dissolve the residue in dichloromethane (25 mL) and add the solution to a separating funnel (100 mL). Wash the solution with sodium hydroxide solution (2 M, 25 mL), hydrochloric acid (2 M, 25 mL) and finally with water (25 mL) and dry the solution using anhydrous magnesium sulfate (5 g, 1 h).
5. Filter off the drying agent and evaporate the solution using a rotary evaporator. Prepare a chromatography column of silica (100 g) using dichloromethane/methanol (5:1). Dissolve the residue from evaporation in this solvent mixture (2 mL) and apply it to the column. Run the column using dichloromethane/methanol (5:1).
6. Evaporate the combined product fractions using a rotary evaporator to give the product **61**, 0.83 g (82%).

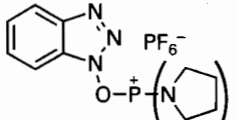
[a]The DMF for this procedure should be dried by distillation under vacuum from freshly activated 4 Å molecular sieves and stored over molecular sieves.

Few reactions in organic chemistry have been the subject of so much detailed study as the coupling of two suitably protected amino acid fragments to form a peptide. In addition to the usual goal of high yields, the minimization of racemization is critical. Among the most effective reagents is

benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) **62** first introduced by Castro and co-workers in 1975.[35] An improved preparation of the reagent was later introduced,[36] and it has also been used to convert protected amino acids to their phenyl esters.[37] The only drawback with BOP is that its reactions produce hexamethylphosphoramide, $(Me_2N)_3PO$, as a by-product, which has been shown to be highly carcinogenic, causing the development of tumours in experimental animals at levels as low as 0.4 ppm. To avoid this the tris(pyrrolidinyl) analogue PyBOP **63** may be used.[38]



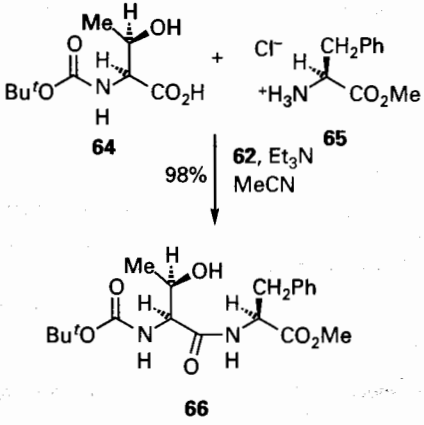
62



63

Protocol 16.
Synthesis of *N*-*t*-butoxycarbonyl-(*S*, *S*)-threonyl-(*S*)-phenylalanine methyl ester[36]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 16).



Scheme 16

Equipment

- Single-necked, round-bottomed flask (50 mL)
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Separating funnel (250 mL)

Materials

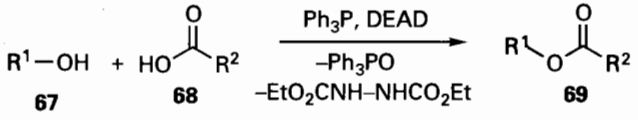
- *N*-*t*-butoxycarbonyl-(2*S*,3*R*)-threonine **64**, 438 mg, 2.0 mmol (Acros 27568, Lancaster 9111, Aldrich 35,971-8, Fluka 15505)
- (*S*)-phenylalanine methyl ester hydrochloride **65**, 431 mg, 2.0 mmol (Avocado 11455, Lancaster 4138, Fluka 78090, Acros 13032, Aldrich P1,720-2)
- Triethylamine, 404 mg, 4.0 mmol **flammable, irritant**
- Acetonitrile, 30 mL **flammable, toxic**
- BOP **62**, 884 mg, 2.0 mmol (Acros 20980, Avocado 16140, Lancaster 11542, Fluka 12802, Aldrich 22,608-4) **irritant**
- Ethyl acetate, 150 mL **flammable**
- Saturated aqueous sodium chloride solution, 100 mL
- Aqueous sodium hydrogen carbonate solution, 5% w/v, 50 mL
- Hydrochloric acid, 2 M, 50 mL **corrosive**
- Anhydrous magnesium sulfate, 10 g

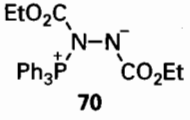
Method

1. To a single-necked, round-bottomed flask (50 mL), add *N*-*t*-butoxycarbonyl-(2*S*,3*R*)-threonine **64** (438 mg, 2.0 mmol), (*S*)-phenylalanine methyl ester hydrochloride **65** (431 mg, 2.0 mmol), BOP **62** (884 mg, 2.0 mmol), acetonitrile (30 mL) and a magnetic stirrer bar. Stir the solution at room temperature and add triethylamine (404 mg, 4.0 mmol) dropwise.
2. After the addition, stir the mixture at room temperature for 1.5 h. Add the mixture to saturated aqueous sodium chloride solution (100 mL) in a separating funnel (250 mL). Extract the mixture with ethyl acetate (3 × 50 mL). **Caution!** at this stage be aware that the mixture contains the *dangerous carcinogen* hexamethylphosphoramide (HMPA). Although the quantity involved is relatively small (326 mg) and it is involatile (b.p. 235°C), the separation must be carried out in a well-ventilated hood and wearing thick rubber gloves. Although the HMPA will mostly remain in the aqueous layer, some may be carried through to the next stage in the ethyl acetate solution but should be removed by the washes there. The presence of HMPA in reaction products is readily recognized from its distinctive proton NMR signal: δ_H 2.65 (18H, d, $^3J_{P-H} = 12$ Hz).
3. Wash the combined extracts in turn with hydrochloric acid (2 M, 50 mL), water (50 mL), sodium hydrogen carbonate solution (5% w/v, 50 mL) and water (50 mL). Dry the solution using anhydrous magnesium sulfate (10 g, 1 h).
4. Filter off the drying agent and evaporate the solution using a rotary evaporator to give the product **66** as a colourless solid, m.p. 94–96°C, 748 mg (98%). Specific rotation: $[\alpha]_D^{22} + 14$ (*c* 1.0, ethyl acetate); $[\alpha]_D^{22} - 3.1$ (*c* 1.0, $CHCl_3$).

One of the most widely used procedures for dehydrative coupling and cyclization reactions is the Mitsunobu reaction in which the components are treated with triphenylphosphine and diethyl azodicarboxylate (DEAD, $EtO_2C{-}N{=}N{-}CO_2Et$). The overall equation for reaction of an alcohol **67** with an acid **68** to form the ester **69** is as shown and the active species is the zwitterionic

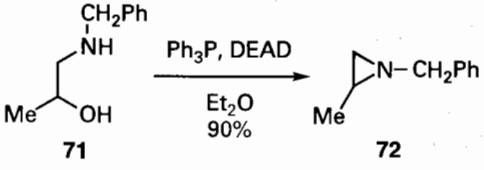
adduct **70**. The reaction takes place with inversion of configuration at the alcohol and formation of esters in this way, particularly the benzoates, followed by hydrolysis, is commonly used as a means of inverting the configuration of a chiral alcohol. The procedure has found widespread application in total synthesis, particularly of large-ring compounds,[39] but as shown in the example of Protocol 17, it may also be used to prepare small-ring compounds. The formation of the aziridine **72** from the amino alcohol **71** is conveniently achieved in high yield. It should be noted that aziridines are reactive alkylating agents and *should be regarded as being highly toxic and potentially carcinogenic.*





Protocol 17.
Synthesis of 1-benzyl-2-methylaziridine[40]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 17).



Scheme 17

Equipment

- Double-necked, round-bottomed flask (250 mL)
- Source of dry nitrogen
- Rubber septum
- Glass syringe with metal Luer lock (10 mL)
- Needle with Luer hub, 15 cm, 18 gauge
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Sintered glass funnel
- Kugelrohr distillation apparatus

Materials

- 1-Benzylaminopropan-2-ol **71**,[a] 4.95 g, 30 mmol
- Triphenylphosphine, 11.8 g, 45 mmol (Avocado 14089, Lancaster 2502, Fluka 93092, Aldrich T8,440-9, Acros 14042)
- DEAD, 95%, 7.5 mL, 8.3 g, 45 mmol (Avocado 18988, Fluka 11624, Aldrich D9,000-8)
- Dry diethyl ether, 150 mL — **highly flammable**
- Hexanes, 50 mL — **flammable, harmful**

Method

1. To a double-necked, round-bottomed flask (250 mL), add 1-benzylaminopropan-2-ol **71** (4.95 g, 30 mmol), triphenylphosphine (11.8 g, 45 mmol), dry diethyl ether (100 mL) and a magnetic stirrer bar. Equip the flask with a rubber septum and nitrogen inlet and flush out the system thoroughly with dry nitrogen.
2. Cool the flask in an ice bath and stir it under nitrogen while adding dropwise through the septum by means of a syringe (10 mL) DEAD (95% , 7.5 mL, 8.3 g, 45 mmol).
3. After the addition remove the ice bath and stir the mixture at room temperature under nitrogen for 2 h.
4. Filter the mixture using a sintered glass funnel and wash the solid collected on the funnel using a mixture of diethyl ether (50 mL) and hexanes (50 mL). Evaporate the combined filtrate and washings using a rotary evaporator. Purify the residual liquid by Kugelrohr distillation to give the product **72** as a colourless liquid, b.p. 58–60°C at 2 mmHg, 3.97 g (90%).

[a]This may be prepared by reaction of benzylamine with propylene oxide in a sealed tube (62%).[41]

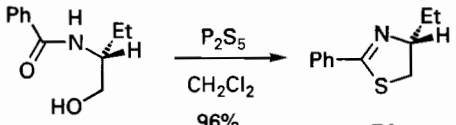
5. Sulfurization reactions

The direct replacement of an oxygen, particularly in a carbonyl group, by sulfur is readily achieved by treatment with phosphorus pentasulfide. This is a rather unpleasant reagent, however, since it is readily flammable and upon storage, particularly in a damp atmosphere, it slowly releases the highly poisonous and malodorous hydrogen sulfide. In Protocol 18 typical conditions for its use are illustrated in the synthesis of the chiral thiazoline **74** from the benzoylamino alcohol **73**.

Protocol 18.
Synthesis of (4*R*)-4-ethyl-2-phenyl-4,5-dihydro-1,3-thiazole[42]

Caution! The products from this protocol have an extremely unpleasant smell and all stages including disposal must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 18).

Protocol 18. *Continued*



73 **74**

Scheme 18

Equipment

- Single-necked, round-bottomed flask (500 mL)
- Reflux condenser
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Oil bath
- Powder funnel
- Plastic bucket (10 L)
- Sintered glass filter funnel
- Separating funnel (500 mL)
- Kugelrohr distillation apparatus

Materials

- (2*R*)-2-Benzoylaminobutan-1-ol **73**,[a] 9.25 g, 48 mmol
- Phosphorus pentasulfide, 17.8 g, 80 mmol (Avocado 17419, Fluka 79600, Acros 19672, Aldrich 23, 210-6) **flammable, harmful**
- Dichloromethane, 300 mL **harmful**
- Aqueous sodium hydroxide solution, 2 M, 300 mL **corrosive**
- Anhydrous magnesium sulfate, 10 g
- Sodium hypochlorite solution, 500 mL **corrosive**
- Liquid soap, 10 mL

Method

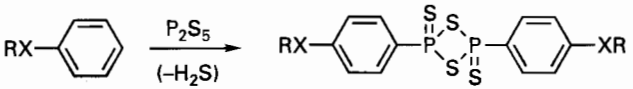
1. To a plastic bucket (10 L), add sodium hypochlorite solution (500 mL) and liquid soap (10 mL) and make up to two-thirds full with hot water. This solution will be used throughout the procedure to decontaminate used equipment and neutralize wash solutions.
2. To a single-necked, round-bottomed flask (500 mL), add (2*R*)-2-benzoylaminobutan-1-ol **73** (9.25 g, 48 mmol) and dichloromethane (250 mL) and a magnetic stirrer bar.
3. While stirring the solution vigorously, slowly add phosphorus pentasulfide (17.8 g, 80 mmol) through a powder funnel. Place the used funnel in the hypochlorite bucket and if any phosphorus pentasulfide sticks to the inside of the ground-glass neck, remove it using a paper towel, which is then put in the hypochlorite bucket.
4. Equip the flask with a reflux condenser and heat under reflux with stirring for 40 h. During this time the solid in the flask may become sticky and stop the stirrer bar from operating but this will not affect the outcome of the reaction.
5. After allowing the mixture to cool, decant off the solution and filter it through a sintered glass funnel. Add dichloromethane (50 mL) to the flask, swirl it

around and filter the solution. Place the reaction flask, which will contain some solid, and the sintered glass funnel in the hypochlorite bucket.

6. Put the combined dichloromethane solution in a separating funnel (500 mL) and wash successively with 2 M sodium hydroxide solution (3 × 100 mL) and then water (2 × 100 mL). The sodium hydroxide washes must be put in the hypochlorite bucket.
7. Dry the dichloromethane solution using anhydrous magnesium sulfate (10 g, 1 h), filter off the drying agent and evaporate the solution using a rotary evaporator. Distil the residual oil using a Kugelrohr distillation apparatus to give the product **74**, b.p. (oven temperature) 92–93°C at 0.4 mmHg, 8.9 g (96%), specific rotation $[\alpha]_D^{25} + 55.9$ (*c* 0.8 in $CHCl_3$).
8. Decontaminate all equipment used in this protocol including gloves by placing in the hypochlorite bucket for at least 48 h or until no smell remains. After removing the equipment, dispose of the used hypochlorite solution by washing it down a sink in a well-ventilated hood with a large volume of water.

[a]This compound (m.p. 93–94°C) can be prepared by reaction of commercially available (2*R*)-2-aminobutan-1-ol (Fluka 07180, Acros 24403) with benzoyl chloride and triethylamine in dichloromethane.[42]

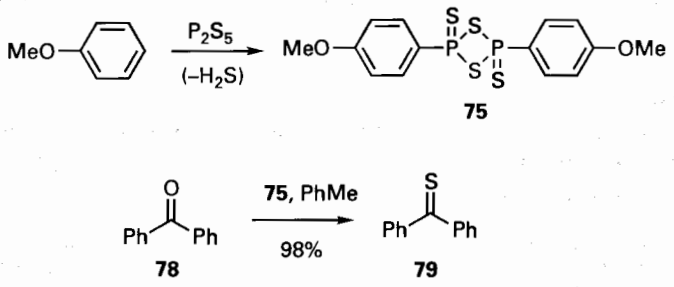
Phosphorus pentasulfide is only slightly soluble in most organic solvents and the heterogeneous nature of the reactions means that a large excess may have to be used to achieve complete conversion. It should be noted, however, that P_2S_5 is fully soluble in hot chloroform to give a very powerful sulfurization medium. To address this problem, a number of more soluble derivatives have been introduced and the best known of these, the so-called Lawesson reagent **75**, is readily prepared by heating P_2S_5 with anisole.[43] This reagent has been used to convert a variety of ketones into the corresponding thiones by reaction in boiling toluene and is also effective in converting amides to the corresponding thioamides and even as a peptide coupling agent.[44] The closely related reagents **76** and **77** are similarly prepared from diphenyl ether and diphenyl sulfide, respectively, and are more soluble in common solvents such as THF.[45,46] It should be noted that, while the structures **75–77** shown adequately explain the reactivity of these compounds, various species are present in solution and the ^{31}P NMR spectrum of **75** in THF shows at least nine lines.[47] The preparation of **75** and its use to convert benzophenone **78** into thiobenzophenone **79** are illustrated in Protocol 19.



75 X = O, R = Me
76 X = O, R = Ph
77 X = S, R = Ph

Protocol 19.
Synthesis of thiobenzophenone[43]

Caution! The products from this protocol have an extremely unpleasant smell and all stages including disposal must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 19).



Scheme 19

Equipment

- 2 Single-necked, round-bottomed flasks (250 mL)
- Reflux condenser
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Oil bath
- Sintered glass filter funnel
- Plastic bucket (10 L)
- Powder funnel
- Chromatography column

Materials

- Anisole, 54 g, 0.5 mol (Avocado 12997, Acros 15392, Aldrich 12,322-6, Lancaster 3948, Fluka 10520)
- Phosphorus pentasulfide, 22.2 g, 0.1 mol (Avocado 17419, Fluka 79600, Acros 19672, Aldrich 23,210-6) **flammable, harmful**
- Dry toluene, 200 mL **flammable, harmful**
- Dichloromethane, 30 mL **harmful**
- Diethyl ether, 2020 mL **highly flammable**
- Benzophenone **78**, 18.2 g, 100 mmol (Avocado 10739, Lancaster 2489, Aldrich B930-0, Acros 10556, Fluka 12750)
- Silica for chromatography, 500 g
- Sodium hypochlorite solution, 500 mL **corrosive**
- Liquid soap, 10 mL

Method

1. To a plastic bucket (10 L), add sodium hypochlorite solution (500 mL) and liquid soap (10 mL) and make up to two-thirds full with hot water. This solution will be used throughout the procedure to decontaminate used equipment.
2. To a single-necked, round-bottomed flask (250 mL), add anisole (54 g, 0.5 mol), a magnetic stirrer bar, and phosphorus pentasulfide (22.2 g, 0.1 mol)

through a powder funnel. Place the used funnel in the hypochlorite bucket and if any phosphorus pentasulfide sticks to the inside of the ground-glass neck, remove it using a paper towel, which is then put in the hypochlorite bucket. Fit a reflux condenser and heat the mixture with stirring at 150°C for 6 h. During this time hydrogen sulfide (8.5 g, circa 5.6 L) is evolved and may be absorbed in a solution of sodium hydroxide.

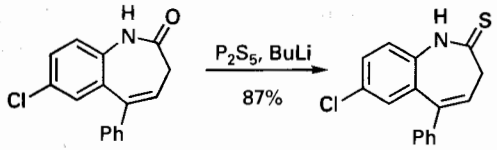
3. Add toluene (100 mL) slowly through the condenser to the hot solution and allow it to cool to room temperature. Filter off the resulting precipitate using a sintered glass funnel and wash the product with dichloromethane (20 mL) and diethyl ether (20 mL) to give the reagent **75**,[a] m.p. 228–230°C, 28.8 g (71%). The product is moisture-sensitive and should be stored in a closed bottle in a desiccator. Place all equipment from the preparation of **75** in the hypochlorite bucket.
4. To a single-necked, round-bottomed flask (250 mL), add benzophenone (18.2 g, 0.1 mol), toluene (100 mL), the reagent **75** (24.2 g, 0.06 mol) and a magnetic stirrer bar. Heat the mixture under reflux with stirring for 12 h. During this time the intense blue colour of the product appears.
5. Allow the mixture to cool and then evaporate off the toluene using a rotary evaporator. Dissolve the residue in the minimum volume of dichloromethane (circa 10 mL). Do not attempt to dissolve any yellow-coloured residue on the side of the flask.
6. Prepare a chromatography column using silica gel (circa 500 g) and diethyl ether. Apply the product solution and run the column using diethyl ether as the eluant. Collect all blue-coloured fractions, combine and evaporate them using a rotary evaporator to give the product **79** as dark blue crystals, m.p. 53°C, 19.4 g (98%). The ^{13}C NMR spectrum shows a remarkable shift to higher frequency in going from C=O to C=S: δ_C ($CDCl_3$) 238.5 (C=S), 147.2 (4ry), 131.9 (2 CH), 129.6 (4 CH) and 127.9 (4 CH). The blue colour is associated with an absorption in the visible spectrum due to C=S (λ_{max} circa 570 nm).
7. Decontaminate all equipment used in this protocol including gloves by placing in the hypochlorite bucket for at least 48 h or until no smell remains. After removing the equipment, dispose of the used hypochlorite solution by washing it down a sink in a well-ventilated hood with a large volume of water.

[a]The reagent **75** is commercially available (Avocado 14530, Lancaster 0975, Acros 21089, Aldrich 22,743-9, Fluka 61750) but is rather expensive and also deteriorates upon storage. It is preferable to prepare it freshly using the simple method given here. Those using the reagent that has been bought should omit steps 2 and 3 of the protocol.

Phosphorus pentasulfide may also be converted into a powerful soluble sulfurization agent by reaction with butyllithium in THF, and the use of this reagent to convert the lactam function of a benzodiazepine drug **80** to the corresponding thiolactam **81** is illustrated in Protocol 20.

Protocol 20.
Conversion of the diazepine 80 into the corresponding thiolactam 81[47]

Caution! The products from this protocol have an extremely unpleasant smell and all stages including disposal must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 20).



80 **81**

Scheme 20

Equipment

- Three-necked, round-bottomed flask (500 mL)
- Reflux condenser
- Teflon-coated magnetic stirrer bar
- Source of dry nitrogen
- Rubber septum
- Glass syringe with metal Luer lock (50 mL)
- Needle with Luer hub, 30 cm, 18 gauge
- Separating funnel (1 L)
- Thermometer
- Addition funnel (100 mL)
- Thermostatted hot-plate stirrer
- Oil bath
- Sintered glass filter funnel
- Plastic bucket (10 L)

Materials

- Diazepine **80**,[48] 21.65 g, 80 mmol
- Phosphorus pentasulfide, 9.3 g, 21 mmol (Avocado 17419, Fluka 79600, Acros 19672, Aldrich 23,210-6) **flammable, harmful**
- Dry THF, 200 mL **flammable, irritant**
- Butyllithium solution in hexanes, 2.5 M, 33.6 mL, 84 mmol (Acros 21335, Lancaster 14775, Aldrich 23,070-7) **flammable, corrosive**
- Dichloromethane, 300 mL **harmful**
- Anhydrous magnesium sulfate, 20 g
- Sodium hypochlorite solution, 500 mL **corrosive**
- Liquid soap, 10 mL

Method

1. To a plastic bucket (10 L), add sodium hypochlorite solution (500 mL) and liquid soap (10 mL) and make up to two-thirds full with hot water. This solution will be used throughout the procedure to decontaminate used equipment.
2. To a three-necked, round-bottomed flask (500 mL), add phosphorus pentasulfide (9.3 g, 21 mmol), dry THF (170 mL) and a magnetic stirrer bar. Fit the flask with a reflux condenser and nitrogen inlet, thermometer and a rubber septum. Connect it to a source of dry nitrogen and flush out the system thoroughly.

3. Cool the suspension with stirring under nitrogen to 5°C in an ice bath. Slowly add a solution of butyllithium in hexanes (2.5 M, 33.6 mL, 84 mmol) by means of a syringe (50 mL) through the septum ensuring that the temperature does not exceed 10°C. After the addition allow the mixture to warm to room temperature and stir it for 1 h.
4. Remove the thermometer and replace it with an addition funnel (100 mL) containing a solution of the diazepine **80** (21.65 g, 80 mmol) in dry THF (30 mL). Stir the mixture and add the diazepine solution over a period of 5 min. After the addition heat the mixture under reflux for 16 h.
5. Allow the mixture to cool and then carefully add water (50 mL) through the addition funnel. Pour the mixture into water (200 mL) in a separating funnel (1 L). Extract the mixture using dichloromethane (3 × 100 mL), wash the combined extracts with water (100 mL) and dry the solution using anhydrous magnesium sulfate (20 g, 1 h). Place the aqueous solutions from this stage in the hypochlorite bucket.
6. Filter off the drying agent and evaporate the solution using a rotary evaporator to give the product **81** as an off-white solid, m.p. 233–234°C, 19.95 g (87%).
7. Decontaminate all equipment used in this protocol including gloves by placing in the hypochlorite bucket for at least 48 h or until no smell remains. After removing the equipment, dispose of the used hypochlorite solution by washing it down a sink in a well-ventilated hood with a large volume of water.

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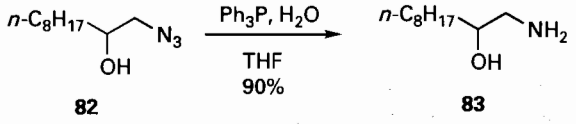
6. Miscellaneous reactions

Azides, RN_3, react readily with triphenylphosphine in the so-called Staudinger reaction, with loss of nitrogen, to afford the phosphinimines, $RN{=}PPh_3$. Since these are easily hydrolysed to RNH_2 and Ph_3PO, simply carrying out the reaction in the presence of water allows direct conversion of the azide function to a primary amine. This constitutes a valuable synthetic procedure due to the ease of introduction of the azide group by nucleophilic substitution. Azido alcohols are also readily obtained by reaction of epoxides with sodium azide and, in the example of Protocol 21, 1-azidodecan-2-ol **82** obtained in this way from 1,2-epoxydecane is reduced to the corresponding amino alcohol **83**.

Protocol 21.
Synthesis of 1-aminodecan-2-ol[49]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 21).

Protocol 21. *Continued*



82 **83**

Scheme 21

Equipment

- Single-necked, round-bottomed flask (250 mL)
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Sintered glass funnel
- Kugelrohr distillation apparatus

Materials

- 1-Azidodecan-2-ol **82**,[a] 5.0 g, 25 mmol
- Triphenylphosphine, 6.60 g, 25 mmol (Avocado 14089, Lancaster 2502, Fluka 93092, Aldrich T8,440-9, Acros 14042)
- THF, 100 mL — **flammable, irritant**
- Diethyl ether, 100 mL — **highly flammable**
- Petroleum, b.p. 40–60°C, 100 mL — **flammable**

Method

1. To a single-necked, round-bottomed flask (250 mL), add 1-azidodecan-2-ol (5.0 g, 25 mmol), THF (100 mL), triphenylphosphine (6.60 g, 25 mmol), water (0.7 mL, 39 mmol) and a magnetic stirrer bar.
2. Stir the solution at room temperature for 12 h and then evaporate it using a rotary evaporator.
3. To the residue add diethyl ether (50 mL) and petroleum (b.p. 40–60°C, 50 mL) and filter off the resulting precipitate of triphenylphosphine oxide using a sintered glass funnel. Evaporate the filtrate using a rotary evaporator.
4. Repeat step 3 to give the product **83** as a colourless liquid, which can be purified by Kugelrohr distillation, b.p. (oven temperature) 100–110°C at 0.5 mmHg, 3.91 g (90%). Proton NMR spectrum ($CDCl_3$): δ_H 0.91 (3H, t, J = 7 Hz), 1.13–1.75 (14H, m), 2.39 (2H, br s, NH_2), 2.53–2.98 (2H, m) and 3.2–3.9 (2H, m, CH and OH).

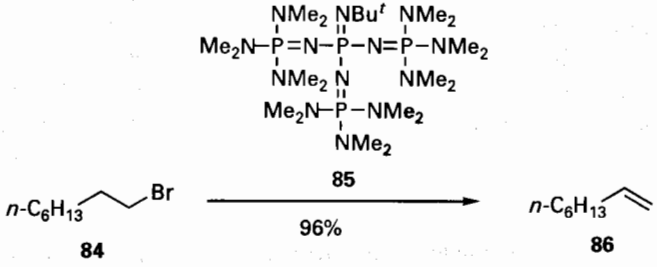
[a]This can be prepared in 90% yield by reaction of 1,2-epoxydecane with sodium azide in boiling ethanol–water (4 : 1).[49]

The highly hindered phosphazene base **85**, termed P_4-*t*-Bu, is one of a family of similar compounds introduced by Schwesinger, which are completely non-nucleophilic and are useful in performing alkylation and elimination reactions.[50–52] Its use in the latter application is illustrated in Protocol 22 by the

formation of oct-1-ene in 96% yield from 1-bromooctane. For comparison, the same transformation using LDA gives a mixture of oct-1-ene and oct-2-ene in 43% yield. The bases of this type are extremely hygroscopic and must be stored under dry conditions.

Protocol 22.
Synthesis of oct-1-ene using a phosphazene base[52]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 22).



Scheme 22

Equipment

- Single-necked, round-bottomed flask (2 mL)
- Source of dry nitrogen
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Separating funnel (25 mL)

Materials

- 1-Bromooctane **84**, 193 mg, 1.0 mmol (Avocado 14722, Lancaster 2863, Aldrich 15,295-1, Fluka 17810, Acros 16681) **harmful**
- Phosphazene base **85**,[a] 700 mg, 1.1 mmol (Fluka 79421)
- Dry THF, 1 mL **flammable, irritant**
- Pentane, 25 ml **highly flammable**
- Aqueous phosphate buffer, 0.5 M, 5 mL
- Anhydrous magnesium sulfate, 2 g

Method

1. To a single-necked, round-bottomed flask (2 mL), add 1-bromooctane (193 mg, 1.0 mmol), dry THF (1 mL), the phosphazene base **85** (700 mg, 1.1 mmol) and a magnetic stirrer bar. Attach a nitrogen inlet and flush out the system thoroughly with dry nitrogen.
2. Stir the solution at room temperature under nitrogen for 6 h. Add the mixture to a separating funnel (25 mL) containing aqueous phosphate buffer (0.5 M, 5 mL) and pentane (5 mL).

Protocol 22. *Continued*

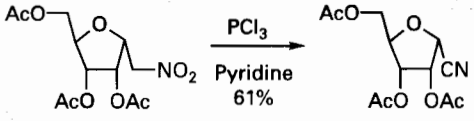
3. Separate the organic layer and extract the aqueous layer with pentane (2 × 10 mL). Dry the combined pentane solution using anhydrous magnesium sulfate (2 g, 1 h).
4. Filter off the drying agent and evaporate the solution using a rotary evaporator with a cold water bath to give the product **86** as a colourless liquid, b.p. 122–123°C, 104 mg (96%).

[a]The reagent is commercially available as a 1 M solution in hexane or may be prepared using the literature procedure.[52]

Treatment of an amide, $RCONH_2$, with phosphorus pentoxide is one of the most useful ways of preparing a nitrile, RC≡N, and the reaction is often performed simply by heating the components together in the absence of solvent and distilling off the more volatile nitrile. Access to the nitrile function may also be achieved in a less well-known way by combined dehydration and reduction of an aliphatic nitro compound, RCH_2NO_2. This is illustrated in Protocol 23 by reaction of the ribose-derived nitro compound **87** with PCl_3 to give **88**, in which the configuration at the anomeric centre has been preserved. The starting material is readily prepared by reaction of ribose with the anion of nitromethane followed by dehydration and acetylation.[53] The nitrile function in the product may be easily recognized both by its IR absorption at 2240–2260 cm^{-1} and the characteristic C≡N signal at δ_C 110–120 in the ^{13}C NMR spectrum.

Protocol 23.
Synthesis of 2,3,5-tri-*O*-acetyl-α-D-ribofuranosylcyanide[53]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 23).



87 **88**

Scheme 23

Equipment

- Single-necked, round-bottomed flasks (5 and 50 mL)
- Teflon-coated magnetic stirrer bar
- Magnetic stirrer
- Separating funnel (50 mL)

Materials

- 2,3,5-Tri-*O*-acetyl-α-D-ribofuranosylnitromethane **87**,[a] 0.22 g, 0.69 mmol
- Pyridine, 3 mL (Avocado 12005, Lancaster 2469, Fluka 82703, Aldrich P5,750-6, Acros 41854) **flammable, harmful**
- Phosphorus trichloride, 0.105 g, 0.76 mmol (Aldrich 15,799-1, Fluka 79670, Acros 16948) **corrosive, irritant**
- Hydrochloric acid, 1 M, 20 mL **corrosive**
- Dichloromethane, 30 mL **harmful**
- Anhydrous magnesium sulfate, 2 g

Method

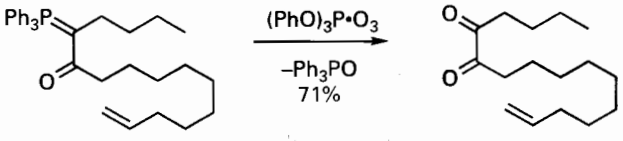
1. To a single-necked, round-bottomed flask (5 mL), add 2,3,5-tri-*O*-acetyl-α-D-ribofuranosylnitromethane **87** (0.22 g, 0.69 mmol), pyridine (3 mL) and a magnetic stirrer bar. Stir the mixture at 0°C.
2. Add phosphorus trichloride (0.105 g, 0.76 mmol). After the addition, allow the mixture to warm up to room temperature slowly and stir for 4 h.
3. Pour the mixture into a single-necked, round-bottomed flask (50 mL) containing hydrochloric acid (1 M, 20 mL), and stir the mixture for 30 min.
4. Transfer the mixture to a separating funnel (50 mL) and extract it with dichloromethane (3 × 10 mL). Dry the combined extracts using anhydrous magnesium sulfate (2 g, 1 h).
5. Filter off the drying agent and evaporate the solution using a rotary evaporator to give the product **88** as a syrup, 0.12 g (61%). Specific rotation: $[\alpha]_D^{20} + 115.7$ (*c*, 2.4 in $CHCl_3$). ^{13}C NMR spectrum ($CDCl_3$): δ_C 170.0, 169.5, 169.1, 114.8 (C≡N), 80.6, 70.4, 69.9, 67.7, 62.4, 20.1 and 19.9 (2 C).

[a]This may be prepared from D-ribose by treatment with the anion of nitromethane followed by dehydration and acetylation.[53]

The use of triphenylphosphine for the reductive cleavage of the ozonides derived from alkenes is well known, but a valuable oxidizing agent may be formed by the direct interaction of ozone with triphenyl phosphite at low temperature. It was initially thought that the active species was singlet oxygen formed by deoxygenation of the O_3 molecule by the phosphite but, at least in some reactions, this has been shown not to be the case and the phosphorus is involved in the actual reactive species. The reagent may be used for *S*-oxidation of sulfides and disulfides, for cycloaddition reactions of dienes to give endoperoxides, or as shown in the example of Protocol 24, for oxidative cleavage of the C=P bond of a stabilized phosphorus ylide. Since the ylide **89** is readily prepared in one step from pentyltriphenylphosphonium bromide, base and undec-10-enoyl chloride,[54] the method allows the rapid and convenient construction of the long chain 1,2-diketone **90**.

Protocol 24.
Synthesis of hexadec-15-en-5,6-dione[54]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 24).



89 **90**

Scheme 24

Equipment

- Double-necked, round-bottomed flasks (100 and 250 mL)
- Rubber septa (2)
- Gas inlet tube
- Teflon-coated magnetic stirrer bars (2)
- Magnetic stirrer
- Source of dry oxygen
- Gas inlet tube
- Cannula, 30 cm, 18 gauge
- Electrical ozone generator (the 500 series of generators made by Fischer, Germany, or similar models are suitable)
- Source of dry nitrogen
- Chromatography column
- Kugelrohr distillation apparatus

Materials

- 5-Triphenylphosphoranylidenehexadec-15-en-6-one **89**,[a] 4.98 g, 10 mmol
- Dry dichloromethane, 100 mL — **harmful**
- Triphenyl phosphite, 3.02 g, 10 mmol (Avocado 18662, Fluka 93120, Aldrich T8,465-4, Lancaster 13882, Acros 22008) — **toxic**
- Petroleum, b.p. 40–60°C, 100 mL — **flammable**
- Silica for chromatography, 250 g
- Toluene, 1 L — **flammable, harmful**

Method

1. To a double-necked, round-bottomed flask (100 mL), add triphenyl phosphite (3.02 g, 10 mmol), dry dichloromethane (50 mL) and a magnetic stirrer bar. Fit the flask with a gas inlet tube and cool the solution to –78°C (dry ice/isopropanol[b] slush bath). Connect the gas inlet tube to an electrical ozone generator, which is connected to a source of dry oxygen.
2. Start the flow of oxygen and switch on the ozone generator. Pass ozone through the stirred phosphite solution at –78°C until a blue colour persists. Ozone is highly toxic, and this must be carried out in an efficient hood. Change over the gas inlet tube to a source of dry nitrogen and pass nitrogen through the solution for 20 min during which time the blue colour will disappear.

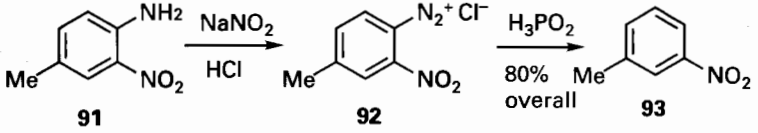
3. To a double-necked, round-bottomed flask (250 mL), add 5-triphenylphosphoranylidenehexadec-15-en-6-one **89** (4.98 g, 10 mmol), dry dichloromethane (50 mL) and a magnetic stirrer bar. Fit the flask with a rubber septum and nitrogen inlet and flush out the system thoroughly with dry nitrogen. Cool the solution with stirring under nitrogen to −78°C (dry ice/isopropanol slush bath).
4. Disconnect the gas inlet tube from the flask containing the phosphite–ozone adduct and replace it by a rubber septum. Connect the two flasks by a cannula and, while maintaining both at −78°C under nitrogen, add dropwise by means of applying a positive pressure of nitrogen, the phosphite–ozone solution through the cannula to the stirred solution of the ylide **89** over a period of 50 min. Maintain the mixture at −78°C for 1 h and then allow it to warm to room temperature.
5. Evaporate the solution using a rotary evaporator and extract the solid residue with petroleum (b.p. 40–60°C, 100 mL) until the solid is colourless and yellow-coloured product is entirely in solution. Evaporate the solution using a rotary evaporator.
6. Prepare a chromatography column of silica (250 g) using toluene. Apply the material to the column and run the column using toluene. Collect all yellow-coloured fractions and combine and evaporate them using a rotary evaporator. Kugerohr distillation of the residue under reduced pressure gives the product **90** as a yellow liquid, b.p. (oven temperature) 115–118°C at 0.2 mmHg, 1.79 g (71%).

[a]This prepared in 72% yield by acylation of pentylidenetriphenylphosphorane with 0.5 eq. undec-10-enoyl chloride.[54]
[b]This is preferable to the more commonly used combination of dry ice/acetone since the cold solvent is viscous and shows less tendency to foam up.

Hypophosphorous acid, H_3PO_2, is readily available as an aqueous solution and is the best reagent for conversion of aromatic diazonium salts into the corresponding arenes. Since diazonium salts are easily prepared by diazotization of anilines, this allows the overall conversion of $ArNH_2$ into ArH. This can be useful in obtaining compounds with substitution patterns not readily accessible by electrophilic substitution since the amino group can be used for its powerful activating and directing effect and then removed. This is illustrated in Protocol 25, where 4-amino-3-nitrotoluene **91**, readily prepared by nitration of *p*-toluidine, is diazotized and then treated with hypophosphorous acid to provide the best synthesis of 3-nitrotoluene **93**. Since diazonium salts are potentially explosive, no attempt should be made to isolate the intermediate **92** and the temperature of the reaction mixture must be carefully controlled. Specific deuterium labelling of aromatic rings at a particular position is also possible by using D_3PO_2 in D_2O.

Protocol 25.
Synthesis of 3-nitrotoluene[55]

Caution! This protocol must be undertaken in an efficient hood, and disposable vinyl gloves and chemical-resistant safety goggles must be worn at all times (Scheme 25).



Scheme 25

Equipment

- Double-necked, round-bottomed flask (1000 mL)
- Addition funnel (250 mL)
- Teflon-coated magnetic stirrer bar
- Thermostatted hot-plate stirrer
- Oil bath
- Thermometer
- Separating funnel (1 L)

Materials

- 4-Amino-3-nitrotoluene **91**,[a] 30.4 g, 200 mmol — **irritant**
- Concentrated hydrochloric acid, 95 mL — **corrosive**
- Sodium nitrite, 14.5 g, 204 mmol — **oxidising, toxic**
- Aqueous hypophosphorous acid, 50%, 104 mL, 1 mol (Acros 20100, Lancaster 14752, Aldrich 21,490-6) — **corrosive**
- Toluene, 250 mL — **flammable, harmful**
- Aqueous sodium hydroxide solution, 2 M, 250 mL — **corrosive**
- Anhydrous magnesium sulfate, 10 g

Method

1. To a double-necked, round-bottomed flask (1000 mL), add water (90 mL), concentrated hydrochloric acid (45 mL) and a magnetic stirrer bar. Heat the mixture to boiling and with vigorous stirring add 4-amino-3-nitrotoluene (30.4 g, 200 mmol). When this has completely dissolved, allow the mixture to cool and add concentrated hydrochloric acid (50 mL).
2. Cool the mixture in an ice–salt bath and by means of an addition funnel add a solution of sodium nitrite (14.5 g, 204 mmol) in water (35 mL) over a period of 1 h at such a rate that the temperature does not exceed 0°C.
3. To the resulting orange-yellow solution of the diazonium salt **92**, slowly add aqueous hypophosphorous acid (50%, 104 mL, 1 mol), which has previously been cooled to 0°C at such a rate that the temperature does not exceed 0°C. This should take approximately 30 min and care must be taken since the

nitrogen evolved will cause the mixture to froth up. After the addition stir the mixture for a further 1 h at 0°C and then place it in a refrigerator at 0°C for 24 h.

4. Add toluene (125 mL) to the mixture and transfer it to a separating funnel (1 L). Separate the organic layer and extract the aqueous layer with toluene (125 mL). Wash the combined organic solution with aqueous sodium hydroxide solution (2 M, 250 mL), water (250 mL) and dry it using anhydrous magnesium sulfate (10 g, 1 h).
5. Filter off the drying agent and evaporate the solution using a rotary evaporator. Distil the residue under reduced pressure to give the product **93** as a liquid, b.p. 100–102°C at 10 mmHg, 22.4 g (80%).

[a]This is readily prepared by nitration of *N*-acetyl-*p*-toluidine followed by alkaline hydrolysis to remove the acetyl group (90%).[56]

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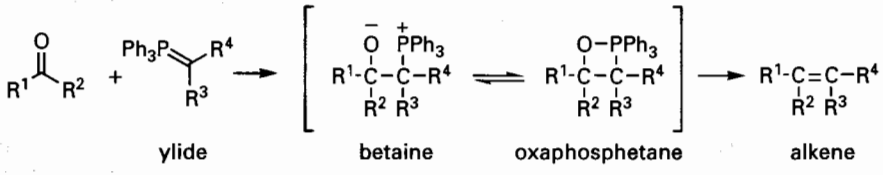
4

The Wittig and related reactions

ANDREW D. ABELL and MICHAEL K. EDMONDS

1. Introduction

The synthesis of alkenes, by replacement of the carbonyl oxygen of an aldehyde or a ketone with a =CRR′ group, was first developed by Georg Wittig in 1953.[1] Over the ensuing years, this reaction has been modified and refined to provide one of the most powerful carbon–carbon bond forming reactions in organic synthesis.[2,3] The classic Wittig reaction involves the nucleophilic attack on a carbonyl carbon by a phosphorane (phosphorus ylide) to give an oxaphosphetane, which then undergoes loss of triphenylphosphine oxide to give an alkene product (Scheme 1). It was long assumed that a diionic betaine intermediate was the initially formed species in this reaction but little or no evidence for its formation has come forth. On the other hand, much evidence for the intermediacy of an oxaphosphetane has been obtained, primarily from low temperature ^{31}P NMR studies.[4,5]



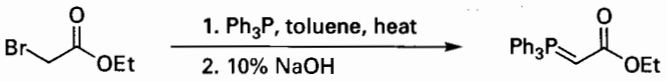
Scheme 1

The classic Wittig reaction is carried out under relatively mild conditions and is very general in that the starting carbonyl compound and phosphorane can contain a variety of substituents. The other real synthetic advantage of this reaction is that the position of the carbon–carbon double bond in the product is not in doubt.

Phosphoranes are conveniently classified as stabilized or non-stabilized depending on their substitution. Phosphoranes in which R^3 and R^4 (Scheme 1) are hydrogen or alkyl are classified as non-stabilized and these are more reactive than the so-called stabilized phosphoranes, which possess an electron-withdrawing substituent (e.g. COR, CN, CO_2R) at the α-carbon. Both classes

of phosphorane are conveniently prepared by the reaction of triphenylphosphine with the corresponding halide, in a reaction that follows normal S_N2 reactivity trends, followed by treatment with base (see Protocol 1).[6] Non-stabilized phosphoranes are very reactive and are unstable in the presence of water. As a consequence, these derivatives are generally prepared under scrupulously anhydrous conditions and the carbonyl compound is added without isolation of the phosphorane (see Protocol 5 for an example of this sequence). As might be expected, this method of preparing phosphoranes is not directly applicable to hindered bromides without resorting to high pressures. Stabilized phosphoranes can also be prepared by acylation of non-stabilized phosphoranes (see Section 4 for further discussion). In summary, Wittig reactions are easy to carry out, yield alkenes with well-defined geometry and use readily available starting materials.

Protocol 1.
Synthesis of (ethoxycarbonylmethylidene)triphenylphosphorane[7]



Caution! All procedures should be carried out in a well-ventilated fume-hood, and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Two-necked round-bottomed flask (100 mL)
- Glass syringe with needle-lock Luer (25 mL)
- Magnetic stirrer
- Separating funnel (100 mL)
- One medium gauge syringe needle
- Magnetic stirrer bar
- One-necked round-bottomed flask (250 mL)
- Rubber septum

Materials

• Triphenylphosphine,[a] 14.0 g, 53.4 mmol	**irritant**
• Toluene[b]	**flammable, irritant**
• Ethyl bromoacetate,[a] 9.5 g, 6.33 mL, 56.8 mmol	**corrosive, lachrymator**
• Pentane	**flammable, irritant**
• Phenolphthalein[a]	**flammable, toxic**
• 10% Sodium hydroxide solution	**corrosive, toxic**
• Sodium sulfate	**moisture sensitive**
• Petroleum ether	**flammable, irritant**

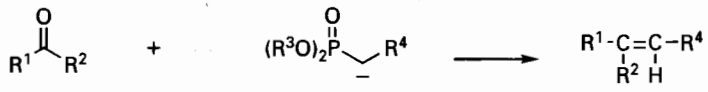
Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. In a two-necked round-bottomed flask (100 mL) equipped with a magnetic stirrer, rubber septum and under a nitrogen atmosphere, dissolve triphenylphosphine (14.0 g, 53.4 mmol) in toluene (25 mL).

3. Add a solution of ethyl bromoacetate (9.5 g, 6.33 mL, 56.8 mmol) in toluene (25 mL). Shake the solution vigorously and then let it stand overnight.
4. Filter off precipitate, washing with additional toluene (50 mL) followed by pentane (50 mL). Allow to dry.
5. Place the precipitate in a one-necked round-bottomed flask (250 mL) equipped with a magnetic stirrer and add water (100 mL), toluene (90 mL) and several drops of phenolphthalein indicator.
6. Add 10% sodium hydroxide solution until the solution turns pink (pH 8.0–10.0).
7. Separate off the toluene layer and dry over sodium sulfate. Filter the solution, then remove most of the solvent by rotary evaporation. Add petroleum ether to promote crystallization and filter off the crystals. Concentrate supernatant and add more petroleum ether and isolate a second crop of crystals.
8. Recrystallize the combined samples from toluene/petroleum ether and dry under high vacuum to give the desired product as a white crystalline solid, m.p. 128–130°C (16.8 g, 90%).

[a]Commercially available.
[b]Distil from sodium/benzophenone ketyl radical prior to use.

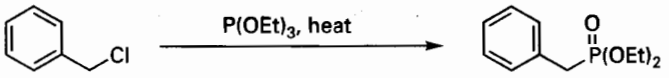
Alternatives to the standard Wittig reaction have been developed, including the Horner–Wadsworth–Emmons (HWE) reaction which involves the reaction of a phosphonate stabilized carbanion with a carbonyl compound (Scheme 2). These carbanions are generally more reactive than the traditional phosphoranes and they will often react with ketones that are unreactive to stabilized phosphoranes.[2,3,8]



Scheme 2

A practical advantage of the HWE reaction over the Wittig reaction is that the phosphorus by-product is water soluble and hence is easily removed from the desired product. The starting phosphonates are also cheap and readily prepared by the Arbuzov reaction[9] between trialkylphosphites and an organic halide (see Protocol 2).

Protocol 2.
Synthesis of diethyl benzylphosphonate[10]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- One-necked round-bottomed flask (100 mL)
- Drying tube
- Magnetic stirrer/hot-plate
- Vacuum adapter
- Reflux condenser
- Magnetic stirrer bar
- Distillation head

Materials

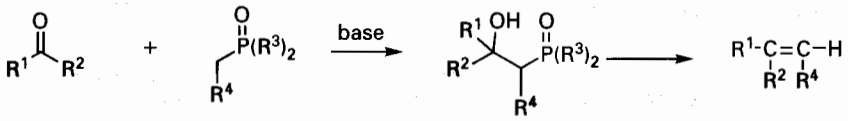
- Triethylphosphite,[a] **12.5 g, 13.3 mL, 75 mmol** — **flammable, lachrymator, irritant**
- Benzyl chloride,[a] 9.5 g, 8.6 mL, 75 mmol — **toxic, suspected carcinogen, irritant**

Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a one-necked round-bottomed flask (100 mL) equipped with a condenser, drying tube and a magnetic stirrer bar, add triethylphosphite (12.5 g, 13.3 mL, 75 mmol) and benzyl chloride (9.5 g, 8.6 mL, 75 mmol).
3. Heat the reaction mixture under reflux for 18 h.
4. Allow the reaction mixture to cool, set up the distillation unit and then distil under reduced pressure[b] to afford the desired diethyl benzylphosphonate (b.p. 106–109°C/1 mmHg) as a colourless liquid (quantitative).

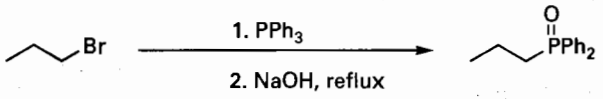
[a]Commercially available.
[b]Diethyl benzylphosphonate can be used without distillation. However, a lower yield in subsequent HWE reactions may result.

A second variant of the Wittig reaction involves the Horner–Wittig reaction of phosphine oxide anions.[11] The use of a potassium base to generate the anion, followed by reaction with a carbonyl compound, gives alkenes with moderate to high stereoselectivity (Scheme 3). Alternatively, the use of a lithium base in these reactions allows the isolation and purification of the intermediate β-hydroxyphosphine oxides which can then be transformed into the alkenes (see later for further discussion and Protocols 7 and 8 for an example). The synthesis of the phosphine oxide precursors is conveniently carried out by thermal decomposition of the corresponding alkyltriphenylphosphonium hydroxides (see Protocol 3).[12,13]



Scheme 3

Protocol 3.
Synthesis of diphenylpropylphosphine oxide[13]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Two one-necked round-bottomed flasks (250 mL)
- Magnetic stirrer
- Distillation head
- Separating funnel (250 mL)
- Magnetic stirrer bar
- Reflux condenser
- Receiver adapter

Materials

• Triphenylphosphine,[a] 14.0 g, 53.4 mmol	**irritant**
• 1-Bromopropane,[a] 98.4 g, 0.8 mol	**flammable liquid, irritant**
• Diethyl ether	**flammable, irritant**
• 30% Aqueous sodium hydroxide	**corrosive, toxic**
• Dichloromethane	**toxic, irritant**

Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. In a one-necked round-bottomed flask (250 mL) fitted with a condenser, heat triphenylphosphine (26.2 g, 0.1 mol) with 1-bromopropane (98.4 g, 0.8 mol) under reflux for 2 h.
3. Filter off the precipitated phosphonium salt, washing well with diethyl ether (30 mL).
4. In a one-necked round-bottomed flask (250 mL) fitted with a condenser, heat a mixture of the phosphonium salt and 30% aqueous sodium hydroxide (150 mL) with vigorous stirring. Cool the reaction mixture and set up for distillation. Distil off the resulting benzene then allow the reaction mixture to cool to room temperature.

Protocol 3. *Continued*

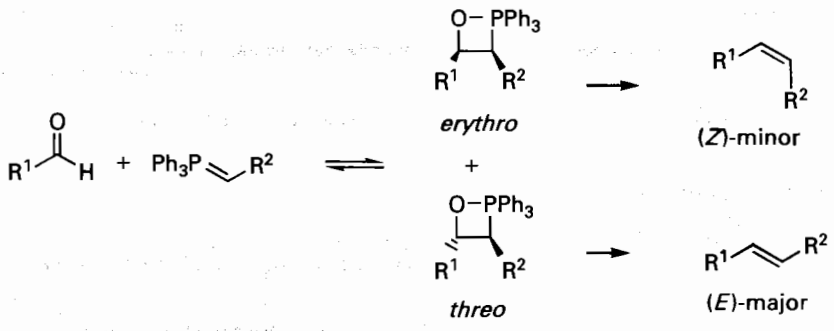
5. Extract the reaction mixture with dichloromethane (3×50 mL), dry the extracts over magnesium sulfate and remove solvent under reduced pressure to afford diphenylpropylphosphine oxide. Recrystallize from ethyl acetate to give needles, m.p. 99–100°C (21.7 g, 96%).

[a]Commercially available.

The remainder of this chapter will detail examples of the main types of Wittig reaction using examples to highlight: (i) those factors that influence the stereoselectivity of the above methods, (ii) modifications to the standard procedures, and (iii) uses of these reactions in organic synthesis.

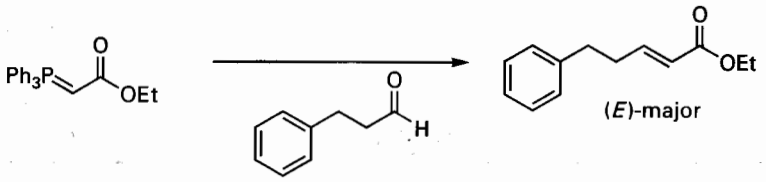
2. Standard reagents and procedures

The stereochemistry of the alkene product in Wittig reactions is thought to be influenced by the reversibility of formation of the isomeric *threo* and *erythro* oxaphosphetanes (or betaines) which undergo stereospecific loss of triphenylphosphine oxide to give the *trans* (*E*) and *cis* (*Z*) alkenes, respectively (Scheme 4). Factors that enhance the reversibility of this initial step favour the *threo* intermediate and hence the (*E*) alkene. Stabilized phosphoranes give a predominance of the (*E*) alkene while non-stabilized phosphoranes give the (*Z*) alkene. In general, stabilized phosphoranes react readily with aldehydes (see Protocol 4) while non-stabilized phosphoranes will react with aldehydes, hemiacetals (see Protocol 5) and ketones.[2,3]



Scheme 4

Protocol 4.
Synthesis of (*E*)-ethyl-5-phenyl-2-pentenoate[14]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Two-necked round-bottomed flask (50 mL)
- Magnetic stirrer bar
- Glass syringe with needle-lock Luer (1.0 mL)
- Magnetic stirrer
- One medium gauge syringe needle
- Rubber septum

Materials

- (Ethoxycarbonylmethylidene)triphenylphosphorane,[a] 2.62 g, 7.5 mmol — **irritant**
- 3-Phenylpropanal,[b] 0.49 mL, 3.7 mmol — **irritant**
- Dry dichloromethane[c] — **toxic, irritant**

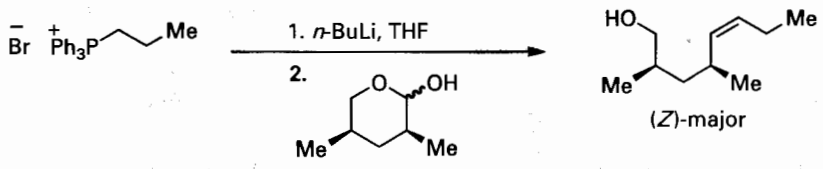
Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a two-necked round-bottomed flask (50 mL) equipped with a magnetic stirrer, rubber septum and under a nitrogen atmosphere, add (ethoxycarbonylmethylidene)triphenylphosphorane (2.62 g, 7.5 mmol) and dry dichloromethane (15 ml).
3. Add 3-phenylpropanal (0.49 mL, 3.7 mmol) from the syringe (1.0 mL) and stir at room temperature for 24 h.
4. Remove the solvent by rotary evaporation. Purify the residue by column chromatography on silica gel (9 : 1 petroleum ether : ethyl acetate v/v as eluant) to give the desired product as a colourless oil (quantitative yield, *E* : *Z* ratio **14** : 1).

The ^{1}H NMR spectrum is diagnostic: ^{1}H NMR (300 MHz, $CDCl_3$) (*E*) isomer δ 7.01 (m, 1H, $CH_2CH{=}C$), 5.85 (dt, J = 1.8, 15.6 Hz, $C{=}CHCO_2$).

[a] Prepared as per Protocol 1.
[b] Commercially available.
[c] Distil from CaH_2 or P_2O_5 prior to use.

Protocol 5.
Synthesis of (2*R*,4*S*)-2,4-dimethyl-5-octen-1-ol[15]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- One two-necked round-bottomed flask (25 mL)
- Gas-tight syringe with needle-lock Luer (5.0 mL)
- Magnetic stirrer
- Separating funnel (250 mL)
- One medium gauge syringe needle
- Magnetic stirrer bar
- One medium gauge cannula
- Rubber septum

Materials

• Propyltriphenylphosphonium bromide[a]	**irritant, harmful, moisture sensitive**
• (3*S*,5*R*)-3,5-dimethyltetrahydropyran-2-ol[b]	**irritant, harmful, moisture sensitive**
• Dry tetrahydrofuran[c]	**highly flammable, irritant**
• *n*-Butyllithium[a] (2.5 M in hexanes), 2.4 mL, 6.0 mmol	**highly flammable, hygroscopic**
• Diethyl ether	**flammable, irritant**
• Petroleum ether	**flammable, irritant**
• Saturated sodium chloride solution	
• Magnesium sulfate	**moisture sensitive**

Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a two-necked round bottomed flask (25 mL) equipped with a magnetic stirrer, rubber septum and under a nitrogen atmosphere add dry tetrahydrofuran (6 mL) and propyltriphenylphosphonium bromide (2.36 g, 6.13 mmol).
3. Cool the reaction mixture to 0°C and add a 2.5 M solution of *n*-butyllithium in hexanes (2.4 mL, 6.0 mmol) from a gas-tight syringe (5 mL) over a period of 10 min.
4. Add a solution of (3*S*,5*R*)-3,5-dimethyltetrahydropyran-2-ol (362 mg, 2.78 mmol) in dry tetrahydrofuran (6 mL) by cannula.
5. Heat the reaction mixture under reflux for 3 h. Allow to cool to room temperature and quench with ice-water (5 ml).
6. Add saturated sodium chloride solution (10 ml) and extract the mixture with a 1 : 1 mixture of diethyl ether and petroleum ether (3 × 100 mL). Combine the organic layers and dry over magnesium sulfate. Filter and remove the solvent under reduced pressure to afford an oily residue.

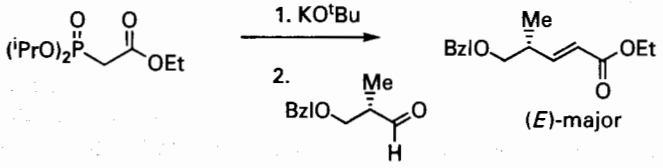
7. Purify the residue by column chromatography on silica gel (petroleum ether : ethyl acetate 9 : 1 v/v as eluant) to give the desired compound as a colourless oil (360 mg, 83%; *Z* : *E* ratio 8 : 1).

The ^{1}H NMR spectrum is diagnostic: ^{1}H ($CDCl_3$, 200 MHz) (*Z*) isomer δ 5.29 (dt, J = 11.2, 7.6 Hz, CHMeC*H*=), 5.01 (dd, J = 11.0, 9.8 Hz, =C*H*CH_2).

[a] Commercially available.
[b] Prepared as per Ref. 15.
[c] Distil from sodium/benzophenone ketyl radical prior to use.

In the case of HWE reactions of phosphonate esters containing a charge-stabilizing electron-withdrawing group, for example, as in trimethyl phosphonoacetate, the carbanion is often generated by reaction with potassium *tert*-butoxide, sodium hydride, *n*-butyllithium or similar base. Direct reaction with an aldehyde or ketone then gives the (*E*)-α,β-unsaturated ester as the major product (see Protocol 6). The nature of the phosphonate (see Section 3), and the substitution of the aldehyde or ketone, can influence the stereochemical outcome of these reactions as can, to a lesser extent, the reaction temperature and solvent.[16]

Protocol 6.
Synthesis of ethyl (*R*)-5-benzyloxy-4-methylpent-2-enoate[17]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Two-necked round-bottomed flask (50 mL)
- Glass syringe with needle-lock Luer (10 mL)
- Magnetic stirrer
- Rubber septum
- One medium gauge syringe needle
- Magnetic stirrer bar
- One-necked round-bottomed flask (250 mL)
- Separating funnel (100 mL)

Materials

- Diisopropyl ethoxycarbonylmethylphosphonate,[a] 2.45g, 8.99 mmol — **irritant**
- Dry tetrahydrofuran[b] — **flammable liquid, irritant**
- Potassium *tert*-butoxide,[a] 909 mg, 8.09 mmol — **flammable solid, corrosive**

Protocol 6. *Continued*

• 2-(*S*)-3-benzyloxy-2-methylpropanal,[c] 400 mg, 2.23 mmol	
• Saturated ammonium chloride solution	**irritant, harmful**
• Dichloromethane	**toxic, irritant**
• Saturated sodium chloride solution	**irritant**
• Magnesium sulfate	**moisture sensitive**

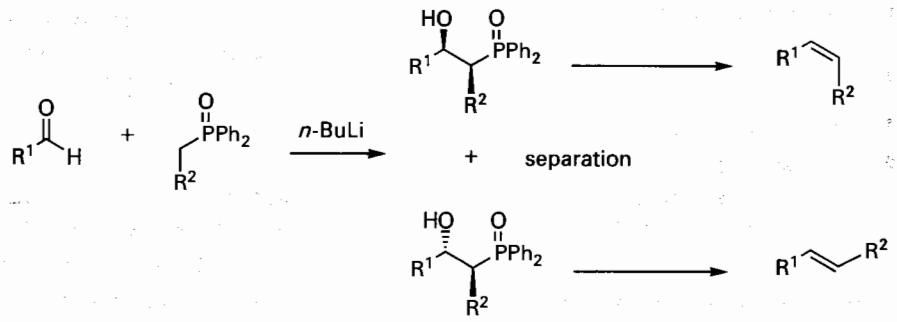
Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. In a two-necked round-bottomed flask (50 mL) equipped with a magnetic stirrer, rubber septum and under a nitrogen atmosphere, stir together diisopropyl ethoxycarbonylmethylphosphonate (2.45 g, 8.99 mmol) and dry tetrahydrofuran (20 mL).
3. Cool the reaction mixture in an ice bath and add potassium *tert*-butoxide (909 mg, 8.09 mmol).
4. Stir at 25°C for 1 h then cool to −78°C in a dry ice/acetone bath.
5. Add a solution of 2-(*S*)-2-methyl-3-benzyloxypropanal (400 mg, 2.25 mmol) in dry tetrahydrofuran (5 mL). Stir at −78°C for 20 min.
6. Pour the reaction mixture into a separating funnel containing diethyl ether (25 mL) and a saturated aqueous solution of ammonium chloride (20 mL).
7. Remove the ether layer and extract the aqueous layer with dichloromethane (3 × 20 mL). Combine the organic layers and wash with saturated sodium chloride solution (20 mL) then dry over magnesium sulfate.
8. Remove the solvent under reduced pressure. Purify the residue by column chromatography on silica gel (hexane : diethyl ether 2 : 1 v/v as eluant) to give as colourless oils the *E* isomer (480 mg, 81%) and *Z* isomer (10 mg, 2%).

The ^{1}H NMR spectrum is diagnostic: ^{1}H NMR ($CDCl_3$, 80 MHz) δ *E* isomer 5.33 (dd, J = 15.5, 1.9 Hz, COC*H*=C), 6.91 (dd, J = 15.5, 6.8 Hz, CHMeC*H*=C); *Z* isomer 5.76 (d, J = 11.5 Hz, COC*H*=C), 6.20 (dd, J = 11.5, 9.0 Hz, CHMeC*H*=C).

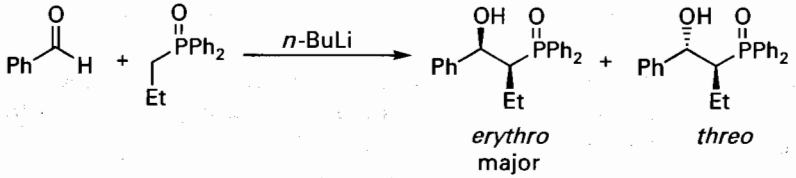
[a] Commercially available.
[b] Distil from sodium/benzophenone ketyl prior to use.
[c] Prepared as per Ref. 17 by Swern oxidation of the corresponding alcohol.

Unlike the carbanions derived from phosphonate esters, the carbanions of dimethyl methylphosphonate[18] and, in some instances phosphine oxides (Horner–Wittig reaction), do not react directly with aldehydes and ketones to give the corresponding alkene.[2,3] Rather, the reaction yields an intermediate β-hydroxy derivative that can be isolated and purified to high diastereoisomeric purity. Subsequent reaction then gives the desired alkene with control of stereochemistry (see Schemes 3, 5 and Protocols 7, 8).



Scheme 5

Protocol 7.
Synthesis of 2-diphenylphosphinoyl-1-phenylbutan-1-ol[13]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Two-necked round-bottomed flask (100 mL)
- Gas-tight syringe with needle-lock Luer (5 mL)
- Magnetic stirrer
- Separating funnel (100 mL)
- Two medium gauge syringe needles
- Glass syringe with needle-lock Luer (1.0 mL)
- Magnetic stirrer bar

Materials

• Diphenylpropylphosphine oxide,[a] 1.0 g, 4.1 mmol	
• *n*-Butyllithium[b] (1.5 M in hexanes), 2.7 ml, 4.1 mmol	**flammable liquid, moisture sensitive**
• Dry tetrahydrofuran[c]	**highly flammable, irritant**
• Benzaldehyde,[b] 435 mg, 4.1 mmol	**toxic, irritant**
• Dichloromethane	**toxic, irritant**
• Acetone	**toxic, irritant**
• Ethyl acetate	**flammable liquid, irritant**
• Saturated sodium chloride solution	**irritant**
• Magnesium sulfate	**moisture sensitive**

Protocol 7. *Continued*

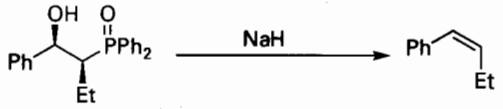
Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a two-necked round-bottomed flask (100 mL) equipped with a magnetic stirrer, rubber septum and under a nitrogen atmosphere, add diphenylpropylphosphine oxide (1.0 g, 4.1 mmol) and dry tetrahydrofuran (30 mL).
3. Cool the reaction mixture to 0°C and add dropwise a 1.5 M solution of *n*-butyllithium in hexanes (2.7 mL, 4.1 mmol) from a gas-tight syringe (5 mL). Stir at 0°C for 30 min. The reaction mixture should be dark red in colour.
4. Lower the temperature to −78°C and add benzaldehyde (435 mg, 4.1 mmol) slowly from a syringe (1.0 mL). The solution should turn pale yellow.
5. Allow the reaction mixture to warm to room temperature over a period of 2 h.
6. Add water (20 mL). Remove the tetrahydrofuran under reduced pressure and add saturated sodium chloride solution (15 mL). Extract the mixture with dichloromethane (3 × 30 mL). Combine the organic layers, dry over magnesium sulfate and remove solvent to afford an oil.
7. Separate the isomers by flash column chromatography on silica gel (ethyl acetate then acetone as eluant). The first diastereomer eluted from the column is the *erythro* adduct, with further elution affording the corresponding *threo* isomer. The diastereomers are recrystallized separately from ethyl acetate to afford the *erythro* diastereomer (1*RS*,2*SR*)-2-diphenylphosphinoyl-1-phenylbutan-1-ol (1.05 g, 73%) and the *threo* diastereomer (1*RS*,2*RS*)-2-diphenylphosphinoyl-1-phenylbutan-1-ol (180 mg, 13%) as needles.

The ^{1}H NMR spectra are diagnostic: ^{1}H NMR (360 MHz, $CDCl_3$) δ *erythro* diastereomer 0.4 (t, J = 8 Hz, CH_2*Me*), 2.45 (ddt, J = 1,5,7 Hz, CHP), 4.7 (s, OH), 5.3 (dd, J = 1, 9 Hz, C*H*OH). δ *threo* diastereomer 0.7 (t, J = 7 Hz, CH_2*Me*), 2.65 (ddt, J = 7, 7 Hz, CHP), 5.1 (dt, J = 7, 17 Hz, C*H*OH), 5.5 (s, OH).

[a] Prepared as per Protocol 3.
[b] Commercially available.
[c] Distil from sodium/benzophenone ketal prior to use.

Protocol 8.
Synthesis of (*Z*)-1-phenylbut-1-ene[13]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Two-necked round-bottomed flask (100 mL)
- Glass syringe with needle-lock Luer (25 mL)
- Magnetic stirrer
- Separating funnel (100 mL)
- Two medium gauge syringe needle
- Magnetic stirrer bar
- Rubber septum

Materials

- (1*RS*,2*SR*)-2-diphenylphosphinoyl-1-phenylbutan-1-ol,[a] 800 mg, 4.56 mmol
- Dry dimethylformamide[b] **irritant**
- Sodium hydride[c] (80% dispersion in oil), 136 mg, 4.56 mmol **flammable solid, moisture sensitive**
- Saturated sodium chloride solution **irritant**
- Diethyl ether **flammable liquid, irritant**
- Magnesium sulfate **moisture sensitive**

Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a two-necked round-bottomed flask (50 mL) equipped with a magnetic stirrer, rubber septum and under a nitrogen atmosphere, add the *erythro* compound (1*RS*,2*SR*)-2-diphenylphosphinoyl-1-phenylbutan-1-ol (800 mg, 2.28 mmol, see Protocol 7) and dimethylformamide (25 mL).
3. Add sodium hydride (80% dispersion in oil; 136 mg, 4.56 mmol) in one portion. Warm to 50°C for approximately 1 h. A white precipitate should form.
4. Cool the reaction mixture and add water (20 mL) to dissolve the precipitate. Add saturated sodium chloride solution (20 mL) and extract the resulting mixture with diethyl ether (3 × 30 mL).
5. Dry the combined organic layers over magnesium sulfate and remove the solvent under reduced pressure. Distil using a bulb-to-bulb (Kugelrohr) apparatus to afford the desired (*Z*) alkene as a colourless liquid (238 mg, 79%), b.p. 79–81°C/20 mmHg. The (*E*) isomer is not detectable by GLC.[d]

The ^{1}H NMR spectrum is diagnostic for the (*Z*) isomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ *Z* isomer 6.35 (dt, $J = 2$, 11 Hz, PhC*H*=C), 5.60 (dt, $J = 7$, 11 Hz, C=CH).

[a] Prepared as per Protocol 7.
[b] Distil under reduced pressure and store over 4 Å molecular sieves prior to use.
[c] Commercially available.
[d] Synthesis of the corresponding (*E*) alkene is possible in 89% yield by using the same method but starting with the *threo* isomer, (1*RS*,2*RS*)-2-diphenylphosphinoyl-1-phenylbutan-1-ol, also prepared in Protocol 7. ^{1}H NMR (360 MHz, $CDCl_3$) δ (*E*) isomer 6.35 (d, $J = 16$ Hz, PhC*H*=C), 6.15 (dt, $J = 6$, 16 Hz, C=CH).

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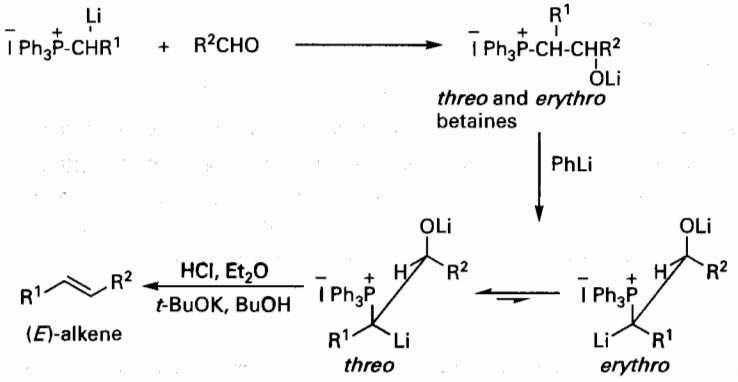
3. Modifications to the standard reagents and procedures

The nature of the phosphorane used in Wittig reactions with aldehydes and ketones can have an influence on both the ease of the reaction and also its stereochemical outcome. For example, $Bu_3P{=}CHCO_2Me$ is generally more reactive than $Ph_3P{=}CHCO_2Me$ and a greater (*E*) selectivity is often observed with stabilized phosphoranes in which the α-carbon is alkylated. The stereocontrol of these

reactions can also be influenced by the choice of solvent, reaction temperature and nature of the base.[2,3]

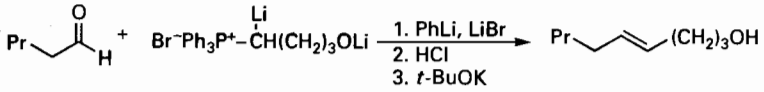
The normal preference for (*Z*) alkenes in reactions of non-stabilized phosphoranes can be reversed by employing the Schlosser modification of the Wittig reaction (Scheme 6).[19] Here, equilibration of the initially formed *erythro* and *threo* betaine intermediates is achieved by reaction with additional strong base, usually an alkyl lithium. The resulting betaine ylide then gives the (*E*) alkene on treatment with a proton source followed by potassium *tert*-butoxide.



Scheme 6

This reaction has been further modified by intercepting the betaine ylide with electrophiles other than a proton to give trisubstituted alkenes in which the electrophile is introduced at what was the phosphorane α-carbon. This reaction is referred to as the α-substitution plus carbonyl olefination via β-oxodphosphorus ylides (SCOOPY) reaction.[20]

Protocol 9.
Synthesis of (*E*)-4-decen-1-ol[19c]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Two-necked round-bottomed flask (250 mL)
- Magnetic stirrer bar
- Glass syringe with needle-lock Luer (5 mL)
- Magnetic stirrer
- One pressure-equalizing funnel (50 mL)

Materials

- Phenyllithium,[a] 20 mmol — **irritant**
- Dry tetrahydrofuran[b] — **flammable liquid, irritant**
- Dry diethyl ether[b] — **irritant**
- 4-Hydroxybutyltriphenylphosphonium bromide, 8.3 g, 20 mmol — **toxic, irritant**
- Hexanal, 2.0 g, 20 mmol — **flammable liquid, irritant**
- Hydrochloric acid (4.2 M solution in diethyl ether) — **irritant**
- Potassium *tert*-butoxide, 5.0 g, 45 mmol — **flammable solid, corrosive**
- Magnesium sulfate — **moisture sensitive**
- Pentane — **flammable, irritant**

Method

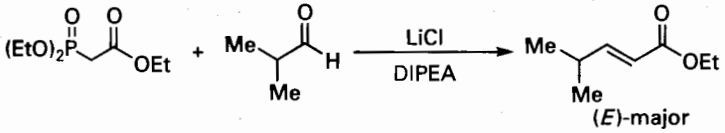
1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. In a two-necked round-bottomed flask (250 mL) equipped with a pressure-equalizing funnel, prepare a slurry of 4-hydroxybutyltriphenylphosphonium bromide (8.3 g, 20 mmol) in tetrahydrofuran (60 mL).
3. Add dropwise a solution of phenyllithium (40 mmol) in tetrahydrofuran (25 mL) and diethyl ether (15 mL) via the pressure-equalizing funnel. Stir for 20 min then cool the clear red solution to −75°C.
4. Add hexanal (2.0 g, 20 mmol). Stir for 20 min then, at −30°C, add a solution of phenyllithium (40 mmol) in tetrahydrofuran (25 mL) and diethyl ether (15 mL) to the cream coloured precipitate.
5. Stir the resulting dark red betaine-ylide solution for 30 min at 25°C then for 15 min at −75°C. Add a solution of hydrochloric acid in ether (10 mL, 4.2 M, 42 mmol).
6. Add potassium *tert*-butoxide (5.0 g, 45 mmol) to the decolourized reaction mixture and stir for 1 h at 25°C.
7. Pour the reaction mixture in water (25 mL). Extract the resulting mixture with diethyl ether (2 × 25 mL). Dry the combined organic layers over magnesium sulfate then remove the solvent under reduced pressure to afford a semi-solid residue.
8. The residue was extracted with pentane (50 mL). The solvent was removed under reduced pressure and the resulting oil was purified by distillation under reduced pressure to afford the desired 4-decen-1-ol as a colourless oil (2.45 g, 78%), b.p. 111-113°C/13 mm Hg.

The ^{1}H NMR spectrum is diagnostic for the (*E*) isomer:[c] ^{1}H NMR (360 MHz, $CDCl_3$) δ *E* isomer 5.47 (dt, J = 15.3, 5.9 Hz, C*H*=C), 5.40 (dt, J = 15.3, 5.9 Hz, C=C*H*).

[a] In order to obtain phenyl-lithium containing a greater than stoichiometric concentration of LiBr (crucial for achieving stereocontrol), phenyl-lithium was prepared as per Ref. 21.
[b] Distil from sodium/benzophenone ketyl radical prior to use.
[c] Compared with the corresponding (*Z*) isomer, synthesized via the instant-ylid method. ^{1}H NMR (360 MHz, $CDCl_3$) δ (*E*) isomer 5.42 (dt, J = 10.4, ~6 Hz, CH=C) , 5.36 (dt, J = 10.4, ~6 Hz, C=CH).

Milder reaction conditions have been developed for the HWE reaction of phosphonate-stabilized carbanions to increase yields, accommodate sensitive substrates and to minimize undesired side reactions such as double bond migrations, the Cannizzaro reaction, Knoevenagel condensation and Michael addition. For example, a number of different bases have been employed to generate the carbanion. These include sodium hydroxide under phase-transfer conditions, potassium carbonate, barium hydroxide, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (see Protocol 10).[22]

Protocol 10.
Synthesis of ethyl (*E*)-4-methylpent-2-enoate[23]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- One-necked round-bottomed flask (250 mL)
- Glass syringe with needle-lock Luer (2.0 mL)
- Magnetic stirrer
- One medium gauge syringe needle
- Magnetic stirrer bar
- Separating funnel (250 mL)

Materials

• Lithium chloride[a,b]	**irritant, hygroscopic**
• Acetonitrile[c]	**flammable liquid, lachrymator**
• Triethyl phosphonoacetate[b]	
• Diisopropylethylamine[b]	**flammable liquid, corrosive**
• Isobutyraldehyde	**flammable liquid, irritant**
• 10% Aqueous hydrochloric acid	**corrosive, toxic**
• Diethyl ether	**flammable, irritant**
• Magnesium sulfate	**moisture sensitive**

Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a one-necked round-bottomed flask (250 mL) equipped with a magnetic stirrer, rubber septum and under a nitrogen atmosphere, add lithium chloride (509 mg, 12 mmol) and dry acetonitrile (120 mL).
3. Add triethyl phosphonoacetate (2.69 g, 12 mmol), diisopropylethylamine (1.29 g, 1.74 mL, 10 mmol) followed by isobutyraldehyde (721 mg, 0.91 mL, 10 mmol).
4. Stir the reaction mixture for 7 h. Most of the salt should dissolve.

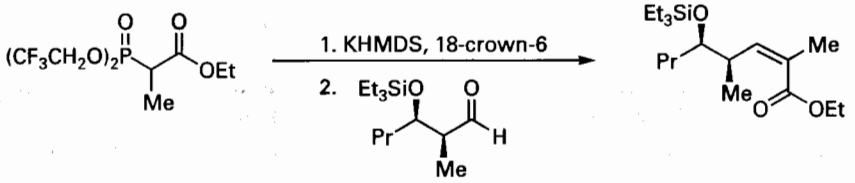
5. Quench the reaction with saturated ammonium chloride solution (50 mL) and extract with diethyl ether (3 × 50 mL).
6. Dry the combined organic layers over magnesium sulfate and remove the solvent under reduced pressure to afford the desired product (1.38 g, 97%). *E*/*Z* ratio >20:1.

The ^{1}H NMR spectrum is diagnostic: ^{1}H NMR ($CDCl_3$, 80 MHz) δ (*E*) isomer 5.76 (dd, J = 16, 1 Hz, COC*H*=C), 6.95 (dd, J = 16, 7 Hz, CHC*H*=C).

[a]Dry in a 120°C oven prior to use.
[b]Commercially available.
[c]Distil from CaH_2 and store over 4 Å molecular sieves prior to use.

The nature of the substituents on a stabilized phosphonate carbanion is known to influence the stereochemical outcome of their reactions with aldehydes. For example, a bis(2,2,2-trifluoroethyl) substituent reverses the normal preference for (*E*) alkenes in a sequence referred to as the Still modification of the HWE reaction (see Protocol 11).[24] This substituent is thought to favour formation of the (*Z*)-isomeric alkene by greatly enhancing the rate of the elimination of the phosphine oxide to give the alkene, which then suppresses equilibration to the thermodynamic product.

Protocol 11.
Synthesis of ethyl (*Z*,4*R*,5*R*)-5-[(triethylsilyl)oxy]-2,4-dimethyloct-2-enoate[25]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- One-necked round-bottomed flask (50 mL)
- Glass syringe with needle-lock Luer (1.0 mL)
- Magnetic stirrer
- One medium gauge syringe needle
- Magnetic stirrer bar
- Separating funnel (100 mL)

Materials

- Ethyl bis(2′,2′,2′-trifluoroethyl)-2-phosphonopropionate,[a] 385.4 mg, 1.113 mmol — **irritant**
- 18-Crown-6,[b] 1.43 g, 5.41 mmol — **irritant**
- Potassium hexamethyldisilazane,[b] 218.1 mg, 1.100 mmol — **corrosive, moisture sensitive**

Protocol 11. *Continued*

- Dry tetrahydrofuran[c] — **highly flammable, irritant**
- (2*S*,3*R*)-3-[(triethylsilyl)oxy]-2-methylhexanal,[d] 245.4 mg, 1.004 mmol
- Saturated ammonium chloride solution — **irritant**
- Pentane — **flammable, irritant**
- Diethyl ether — **flammable, irritant**
- Saturated sodium bicarbonate solution
- Saturated sodium chloride solution — **irritant**
- Magnesium sulfate — **moisture sensitive**

Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a two-necked round-bottomed flask (50 mL) equipped with a magnetic stirrer, rubber septum and under a nitrogen atmosphere, add ethyl bis(2′,2′,2′-trifluoroethyl)-2-phosphonopropionate (385.4 mg, 1.113 mmol) and 18-crown-6 (1.43 g, 5.41 mmol). Add dry tetrahydrofuran (22 mL).
3. Cool the reaction mixture to 0°C and add potassium hexamethyldisilazane (218.1 mg, 1.10 mmol). Stir at 0°C for 30 min.
4. Lower the temperature to −78°C and add (2*S*,3*R*)-3-[(triethylsilyl)oxy]-2-methylhexanal (245.4 mg, 1.00 mmol) dropwise from the syringe (1.0 mL) Rinse the syringe three times with tetrahydrofuran (0.25 mL).
5. Continue stirring the reaction at −78°C for 18 h.
6. Remove coolant bath and add saturated ammonium chloride solution (10 mL). Allow reaction mixure to warm to room temperature then pour into a separating funnel (100 mL) containing water (25 mL) and a 1:1 pentane/ether mixture (25 mL).
7. Separate the layers and extract the water layer with additional pentane/ether mix (3 × 10 mL). Wash the combined organic extracts with water (3 × 2 mL), 5% sodium bicarbonate solution (1 × 5 mL) and saturated sodium chloride solution (1 × 5 mL) then dry over magnesium sulfate. Filter then remove solvent by rotary evaporation to afford the desired (*Z*) product as a colourless oil (quantitative).

The ^{1}H NMR spectrum is diagnostic: ^{1}H ($CDCl_3$, 360 MHz) (*Z*) isomer δ 5.80 (d, J = 10.1 Hz, C*H*=C).

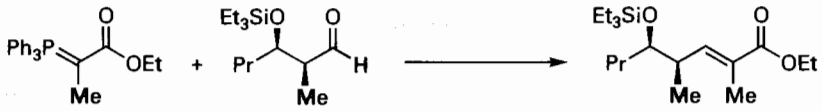
[a] Prepared as per Ref. 26.
[b] Commercially available.
[c] Distil from sodium/benzophenone ketyl radical.
[d] Prepared as per the method described in Ref. 25.

4. Role in synthesis

The versatility of the Wittig, and related reactions, has resulted in examples being used as key steps in many organic syntheses of complex natural products.[2,3]

Wittig-based reactions have been used in both the late stages of multi-step synthetic sequences and also to produce large quantities of key synthetic intermediates (see Ref. 2 for a discussion and some examples). A real advantage of this chemistry is that both the (*Z*) and (*E*) isomers of the alkene are generally available by careful choice of conditions (compare Protocols 11 and 12). The products of Protocols 11 and 12 have been conveniently converted into isomeric tetrahydrofurans which bear substituents at all four atoms of the ring. These ring systems form the basis of many complex natural products.[25]

Protocol 12.
Synthesis of ethyl (*E*,4*R*,5*R*)-5-[(triethylsilyl)oxy]-2,4-dimethyloct-2-enoate[25]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- One-necked round-bottomed flask (10 mL)
- Magnetic stirrer
- Sintered glass filter funnel
- Reflux condenser
- Magnetic stirrer bar

Materials

• (2*S*,3*R*)-3-[(triethylsilyl)oxy]-2-methylhexanal,[a] 168 mg, 0.678 mmol	**unknown**
• Dry dichloromethane[b]	**toxic, irritant**
• [1-(Ethoxycarbonyl)ethylidene]triphenylphosphorane[a] 299 mg, 0.743 mmol	**irritant**
• Silica gel	**irritant**

Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a one-necked round-bottomed flask (10 mL) equipped with a magnetic stirrer, water condenser and under a nitrogen atmosphere, add (2*S*,3*R*)-3-[(triethylsilyl)oxy]-2-methylhexanal (168 mg, 0.678 mmol), [1-(ethoxycarbonyl)ethylidene]-triphenylphosphorane (299 mg, 0.743 mmol) and dry dichloromethane (5 mL).
3. Heat the reaction under reflux for 5 days.
4. Allow the solution to cool then filter through a 2 inch plug of silica gel, washing with dichloromethane.
5. Remove solvent by rotary evaporation to afford the desired (*E*) alkene as a colourless oil (quantitative yield).

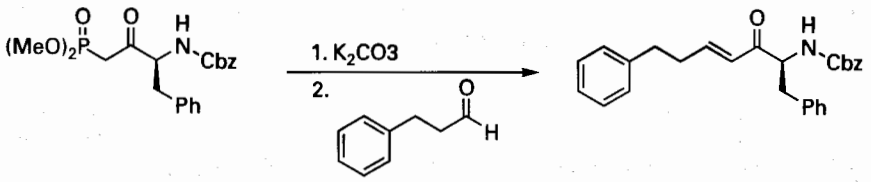
Protocol 12. *Continued*

The ^{1}H NMR spectrum is diagnostic: ^{1}H ($CDCl_3$, 360 MHz) (*E*) isomer δ 6.67 (d, J = 12.7 Hz, C*H*=C).

[a]Prepared as per the method described in Ref. 25.
[b]Distil over CaH_2 prior to use.

The Wittig, and related reactions, have also found application in the synthesis of peptidomimetics—mimics of natural peptides that possess modified biological properties such as increased bioavailability, biostability, bioselectivity, and bioefficiency relative to the parent peptide. As an example, the phenylalanine-based HWE reagent shown in Protocol 13 reacts with aldehydes to give a modified amino acid that can be used as a building block for the construction of extended peptidomimetics.

Protocol 13.
Synthesis of (6*S*)-6-[*N*-(benzyloxycarbonyl)amino]-1,7-diphenyl-3-hepten-5-one[27]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Two-necked round-bottomed flask (10 mL)
- Magnetic stirrer bar
- Glass syringe with needle-lock Luer (100 μL)
- Magnetic stirrer
- One medium gauge syringe needle
- Separating funnel (50 mL)

Materials

- Dimethyl[(3*S*)-4-phenyl-3-[(benzyloxycarbonyl)amino]-2-oxobutyl]phosphonate,[a] 50 mg, 130 μmol
- 3-Phenylpropanal,[b] 17.4 mg, 130 μmol — **irritant**
- Oven-dried potassium carbonate,[c] 18 mg, 130 μmol — **irritant, moisture sensitive**
- Dry ethanol,[d] 1.3 mL — **flammable, toxic**
- Glacial acetic acid — **corrosive, hygroscopic**
- Saturated sodium bicarbonate solution
- Ethyl acetate — **highly flammable**
- Magnesium sulfate — **irritant**

Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a round-bottomed flask (10 mL) equipped with a magnetic stirrer and under a nitrogen atmosphere, add dimethyl[(3*S*)-4-phenyl-3-[(benzyloxycarbonyl)amino]-2-oxobutyl]-phosphonate (50 mg, 130 μmol) and dissolve in ethanol (1.3 mL).
3. Add 3-phenylpropanal (17.4 mg, 130 μmol) via a syringe and oven-dried potassium carbonate (18 mg, 130 μmol) and stir for 4 h.
4. Filter the reaction mixture and neutralize the reaction with glacial acetic acid (one drop). Remove the solvent by rotary evaporation and partition the residue between ethyl acetate (20 mL) and saturated sodium bicarbonate solution (15 mL). Wash the aqueous layer with ethyl acetate (15 mL) and combine the organic layers. Dry over magnesium sulfate then remove the solvent by rotary evaporation.
5. Purify the residual oil by column chromatography on silica gel (4:1 petroleum ether:ethyl acetate v/v as eluant) to afford the desired compound as a colourless oil (27 mg, 50%), R_f = 0.54 (SiO_2, 4:1 petroleum ether:ethyl acetate v/v).

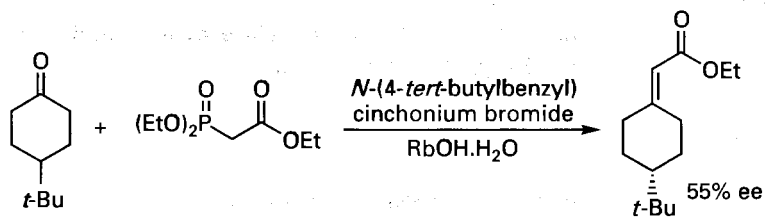
The ^{1}H NMR spectrum is diagnostic: ^{1}H ($CDCl_3$, 300 MHz) (*E*) isomer δ 7.0 (m, C=C*H*CH_2), 6.2 (d, J = 15.6 Hz, COC*H*=C)

[a]Prepared as per Ref. 28.
[b]Commercially available (hydrocinnamaldehyde).
[c]Dry in a 120°C oven overnight prior to use.
[d]Distil from magnesium ethoxide prior to use.

Polymer-supported Wittig reagents have recently been developed as an extension to the traditional reagents.[29] For example, polystyryldiphenylphosphine has been developed in an attempt to replace the use of triphenylphosphine in the preparation of phosphoranes (see Protocol 1). The hope is that these polymer-bound regents will overcome the practical problem of removing the triphenylphosphine oxide by-product formed in Wittig reactions. Polymer supported phosphonates and Wittig substrates have also been prepared for use in solid phase synthesis and combinatorial chemistry.[30]

Catalytic Wittig-like reactions[31] and more recently, asymmetric Wittig reactions[32] have been developed. Most of the asymmetric systems developed to date use internal chiral ligands (chiral phosphonates, phosphoranes and phosphine oxides) to effect asymmetric induction, however, some recent work has focused on the use of external ligands.[33] The first reported catalytic asymmetric Wittig reactions[34] made use of chiral phase-transfer catalysts to effect moderate enantiomeric excesses of one isomer (Protocol 14).

Protocol 14.
Catalytic asymmetric synthesis of ethyl (*R*)-4-*tert*- butylcyclohexylideneacetate[34]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- One-necked round-bottomed flask (10 mL)
- Glass syringe with needle-lock Luer (1.0 mL)
- Magnetic stirrer
- Fluted filter paper
- One medium gauge syringe needle
- Magnetic stirrer bar
- Filter funnel

Materials

- 4-*tert*-Butylcyclohexanone,[a] 100 mg, 0.65 mmol
- Dry benzene[b] — **flammable liquid, cancer suspect agent**
- Triethyl phosphonoacetate,[a] 0.26 mL, 1.30 mmol — **irritant**
- *N*-(4-*tert*-butylbenzyl)cinchonium bromide,[c] 68 mg, 0.13 mmol
- Rubidium hydroxide monohydrate,[a] 390.6 mg, 3.2 mmol — **corrosive**
- Concentrated hydrochloric acid — **corrosive, toxic**
- Ethanol — **flammable liquid, toxic**
- Hexane — **flammable liquid, irritant**
- Diethyl ether — **flammable liquid, irritant**

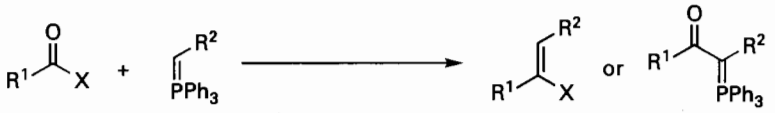
Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. To a one-necked round-bottomed flask (10 mL) equipped with a magnetic stirrer and under a nitrogen atmosphere, add 4-*tert*-butylcyclohexanone (100 mg, 0.65 mmol). Add benzene (3.2 mL).
3. To the resulting solution add triethyl phosphonoacetate (0.26 mL, 1.30 mmol) and *N*-(4-*tert*-butylbenzyl)cinchonium bromide (68 mg, 0.13 mmol) followed by rubidium hydroxide monohydrate (390.6 mg, 3.2 mmol). Stir at room temperature for 8 days.
4. Acidify the reaction mixture with concentrated hydrochloric acid until pH ~3, then add ethanol (10 mL). Stir the reaction mixture for a further 4 days.

5. Filter the reaction mixture and remove the solvent under reduced pressure.
6. Purify the residue by column chromatography on silica gel (2:1 hexane:diethyl ether v/v as eluant) to afford the desired product as a colourless oil (109.2 mg, 75%, 55% ee).

[a]Commercially available.
[b]Distil from sodium/benzophenone ketyl radical prior to use.
[c]Prepared from cinchonine and 4-*tert*-butylbenzyl halide heated under reflux in tetrahydrofuran.

Phosphoranes and phosphonate derived carbanions are also known to react with carbonyl compounds other than aldehydes and ketones, in reactions often referred to as 'non-classical' Wittig reactions.[35] Wittig olefination products can be obtained from the reaction of esters, anhydrides and some amides and imides with a range of stabilized and reactive phosphoranes. The reaction of stabilized and semi-stabilized phosphoranes with esters gives alkenes (Scheme 7). However, non-stabilized phosphoranes, such as methylenetriphenylphosphorane, tend to give β-keto phosphoranes on reaction with esters (Scheme 7)—the careful choice of the reaction conditions can also permit the preparation of the alkene in these reactions.

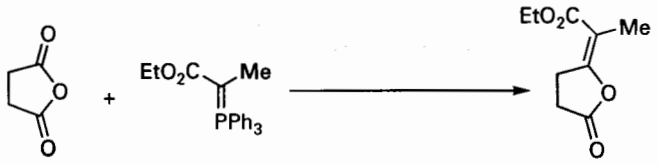


Scheme 7

These 'non-classical' Wittig reactions of esters have been used to prepare a number of oxygen-containing heterocycles.[35] Phosphonate stabilized carbanions, for example, those derived from dimethyl methylphophonate, also react with esters to give, in this case, a β-keto phophonate which can react further with aldehydes and ketones.

Thioesters are also known to undergo 'non-classical' Wittig reactions in a sequence pioneered by Woodward.[36] While amides and imides tend to react sluggishly with stabilized phosphoranes, cyclic anhydrides readily yield enol-lactones in these reactions (see Protocol 15). Five-membered, six-membered and phthalic-based anhydrides are known to undergo this reaction and the stereochemical outcome is very much dependant on the nature of the starting anhydride.[37] In many cases, a β-keto phosphorane intermediate can be isolated[38] (see Protocol 16) which simply gives rise to the hydrogen enol-lactone on heating (see Protocol 17) or the corresponding bromo enol-lactones on treatment with bromine[39] (see Protocol 18). Such a sequence has been used to prepare peptidomimetic mechanism-based inhibitors of serine proteases.[40]

Protocol 15.
Synthesis of ethyl (*E*)-2-(5-oxotetrahydrofuran-2-ylidene)propionate[41]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Round-bottomed flask (5 mL)
- Magnetic stirrer
- Magnetic stirrer bar

Materials

- Succinic anhydride,[a] 50 mg, 0.50 mmol — **moisture sensitive, irritant**
- (Ethoxycarbonylethylidene)triphenylphosphorane,[a] 182 mg, 0.50 mmol
- Dry dichloromethane,[b] 2 mL — **toxic, irritant**
- Petroleum ether — **flammable, irritant**

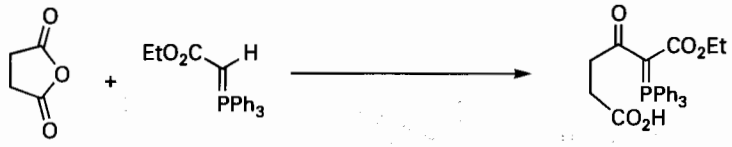
Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. In a round-bottomed flask (5 mL) equipped with a magnetic stirrer and under a nitrogen atmosphere, dissolve succinic anhydride (50 mg, 0.50 mmol) in dichloromethane (2 mL).
3. Add (ethoxycarbonylethylidene)triphenylphosphorane (182 mg, 0.50 mmol) and stir at room temperature overnight.
4. Evaporate to dryness under reduced pressure and purify the residue by chromatography on silica gel (ether as eluant) to give the desired product, which is recrystallized from petroleum ether as fine needles, m.p. 56–57°C (65 mg, 71%).

The ^{1}H NMR spectrum is diagnostic: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, $J = 7$ Hz, OCH_2CH_3), 1.91 (t, $J = 1.8$ Hz, CH_3), 2.73 (m, CH_2), 3.33 (m, CH_2), 4.21 (q, $J = 7$ Hz, OCH_2CH_3).

[a] Commercially available.
[b] Distil from CaH_2 prior to use.

Protocol 16.
Synthesis of 1-ethyl 3-oxo-2-(triphenylphosphonio)hexanedioate[38]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Round-bottomed flask (100 mL)
- Magnetic stirrer bar
- Magnetic stirrer

Materials

- Succinic anhydride,[a] 2.6 g, 26.0 mmol — **moisture sensitive**
- (Ethoxycarbonylmethylidene)triphenylphosphorane,[b] 9.1 g, 26.0 mmol
- Dry chloroform,[c] 30 mL — **highly toxic, cancer suspect agent**
- Petroleum ether — **flammable, irritant**
- Ethyl acetate — **flammable, irritant**

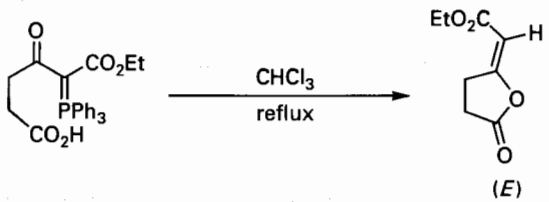
Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. In a round-bottomed flask (100 mL), dissolve succinic anhydride (2.6 g, 26.0 mmol) in chloroform (30 mL).
3. Add (ethoxycarbonylmethylidene)triphenylphosphorane (182 mg, 0.5 mmol) and stir at room temperature for 16 h.
4. Evaporate to half volume under reduced pressure and pour the residue onto petroleum ether to give a white solid.
5. Recrystallize the solid from ethyl acetate with minimal heating to give the desired compound as colourless crystals, m.p. 130–132°C (6.95 g, 60%).

The ^{1}H NMR spectrum is diagnostic: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.65 (t, $J = 7$ Hz, OCH_2CH_3), 2.50 (t, CH_2), 3.30 (t, CH_2), 3.75 (q, $J = 7$ Hz, OCH_2CH_3), 7.4–7.8 (Ar).

[a]Commercially available.
[b]Prepared as per Protocol 1.
[c]Distil from P_2O_5 prior to use.

Protocol 17.
Synthesis of ethyl (*E*)-5-oxotetrahydrofuran-2-ylideneacetate[38]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Round-bottomed flask (50 mL)

Materials

- 1-Ethyl 3-oxo-2-(triphenylphosphonio)hexanedioate,[a] 1.0 g, 2.2 mmol — **heat sensitive**
- Dry chloroform,[b] 20 mL — **highly toxic, cancer suspect agent**
- Petroleum ether — **flammable, irritant**
- Diethyl ether — **flammable, irritant**

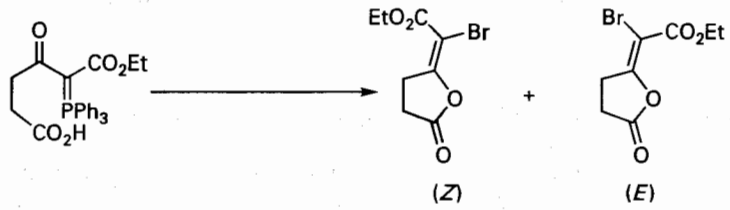
Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. In a round-bottomed flask (50 mL) dissolve 1-ethyl 3-oxo-2-(triphenylphosphonio)hexanedioate (1.0 g, 2.2 mmol) in chloroform (20 mL).
3. Reflux the solution for 4 h.
4. Evaporate under reduced pressure and purify the residue by chromatography on silica gel (2:1 ether:petroleum ether v/v as eluant) to give the desired product which is recrystallized from chloroform and petroleum ether as fine needles, m.p. 96–97°C (310 mg, 82%).

The ^{1}H NMR spectrum is diagnostic: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.25 (t, OCH_2CH_3), 2.55–2.85 (m, CH_2), 3.20–3.53 (m, CH_2), 4.14 (q, OCH_2CH_3), 5.65 (t, $J = 2$ Hz, $CH{=}CO_2Et$).

[a] Prepared as per Protocol 16.
[b] Distil from P_2O_5 prior to use.

Protocol 18.
Synthesis of ethyl (*E*) and ethyl (*Z*)-bromo-(5-oxotetrahydrofuran-2-ylidene)acetate[39]



Caution! All procedures should be carried out in a well-ventilated fume-hood and chemical resistant gloves and safety glasses should be worn at all times.

Equipment

- Round-bottomed flask (25 mL)
- Two glass syringes with needle-lock Luer (100 μL)
- Magnetic stirrer
- Two medium gauge syringe needles
- Magnetic stirrer bar

Materials

- 1-Ethyl 3-oxo-2-(triphenylphosphonio)hexanedioate,[a] 200 mg, 0.5 mmol — **heat sensitive**
- Bromine, 25 μL, 0.5 mmol — **highly toxic, oxidizer**
- Triethylamine, 68 μL, 0.5 mmol — **flammable liquid, corrosive**
- Dry dichloromethane[b], 10 mL — **toxic, irritant**

Method

1. Dry all glassware and stirrer bar in an electric oven (105°C) prior to use.
2. In a round-bottomed flask (25 mL) dissolve 1-ethyl 3-oxo-2-(triphenylphosphonio)hexanedioate (200 mg, 0.5 mmol) in dichloromethane (10 mL) and cool the solution in ice under nitrogen.
3. Triethylamine (68 μL, 0.5 mmol) and bromine (25 μL, 0.5 mmol) are added and the solution is stirred for 20 min at 0°C and then allowed to warm to room temperature (heat under reflux) for 4 h.
4. Evaporate under reduced pressure and purify the residue by chromatography on silica gel (dichloromethane as eluant) to give a 7 : 3 mixture of the desired (*E*) and (*Z*) isomers (86 mg, 77%).

The ^{1}H NMR spectrum is diagnostic: ^{1}H NMR ($CDCl_3$, 300 MHz) *E* isomer δ 1.36 (t, J = 7 Hz, OCH_2CH_3), 2.78 (m, CH_2), 3.10 (m, CH_2), 4.31 (q, J = 7 Hz, OCH_2CH_3). *Z* isomer δ 1.35 (t, J = 7 Hz, OCH_2CH_3), 2.85 (m, CH_2), 3.41 (m, CH_2), 4.31 (q, J = 7 Hz, OCH_2CH_3).

[a]Prepared as per Protocol 16.
[b]Distil from CaH_2 prior to use.

The Wittig reaction currently occupies a central position in the arsenal of the synthetic organic chemist due to its versatility and generality. Ongoing advances in understanding its reaction mechanism and the ensuing catalytic, asymmetric and solid phase applications will permit its continued application to new and exciting synthetic problems.

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5

Applications of the Wittig reaction in the synthesis of heterocyclic and carbocyclic compounds

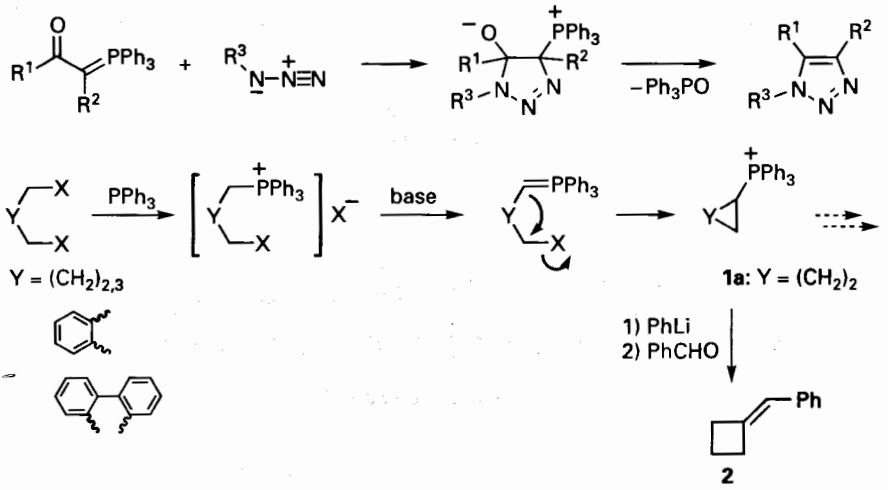
RAINER SCHOBERT

1. Introduction

Since its discovery,[1] the Wittig olefination reaction has been widely used in organic synthesis for the construction of olefinic double bonds from various types of carbonyl functionalities (aldehydes, ketones, esters, amides, etc.) and phosphorus ylides of different reactivity.[2–4] Although the mechanism of this important C=C bond forming process is still under debate,[5–8] insights into the principles governing its regio- and stereoselectivity are now sufficiently deep, to allow for it, to be harnessed reliably in retrosynthetic strategies. From the early days of 'Wittig chemistry', its possible application to the formation of cyclic target structures attracted considerable interest and consequently, access to a host of carbocyclic as well as of heterocyclic compounds has been opened by this reaction. In the following brief overview only such applications are to be mentioned where the Wittig reaction makes for the actual ring closure step in an *intramolecular* process, thus reactions which merely lead to precursors of the cyclization step proper are excluded. Likewise, non-Wittig-type cyclizations involving phosphorus ylides such as cycloadditions between acyl ylides and azides to give 1,2,3-triazoles[9] will not be considered here. S_N2-type ring-closure reactions of ω-halo-ylides[10] belong to the same category; nonetheless, one example of their use towards the synthesis of small ring systems with exocylic double bond is given in Section 2.1 (Scheme 1).

Performing Wittig olefination reactions in an *intramolecular* manner on difunctional starting compounds has several advantages over *intermolecular* variants:

1. Due to the chelate effect, functional groups normally less prone or inert to Wittig olefination, such as esters and amides, can react, even with stabilized ylides.[11]



Scheme 1 Types of cyclization reactions not to be considered in detail.

2. *In situ* generation of ylides that swiftly undergo Wittig olefination with their remote carbonyl groups is easily possible. This gives rise to low steady-state concentrations in normally sized solvent volumes thus avoiding polymerization and cumbersome dilution techniques in the case of macrocycle synthesis. For the synthesis of cyclic compounds with normal- and medium-sized rings there is absolutely no danger of polymerization as the intramolecular process clearly prevails over any intermolecular alternatives regardless of the overall reactivity of the respective ylide/carbonyl combination.
3. The Wittig olefination is normally a chemoselective ring-closure reaction with a preference for five- and six-membered ring formation. So even complex constellations of functional groups of similar carbonyl activity at different distances from the ylide function in the starting materials give rise to well-defined cyclic products. Such Wittig reactions can also be part of more extended cascade processes in combination with other reactions or can be performed repetitively.

In the following sections, typical applications of intramolecular Wittig olefinations leading to cyclic structures are given. These are mainly categorized by the method of generation of the reactive ω-carbonyl-ylide species and by the overall reactivity and ease of the ring-closure step. It goes without saying, that this selection is at best representative and far from being comprehensive. Figure 5.1 depicts the most common combinations of ylide types and carbonyl compounds together with their typical reactivity in intramolecular Wittig olefinations.

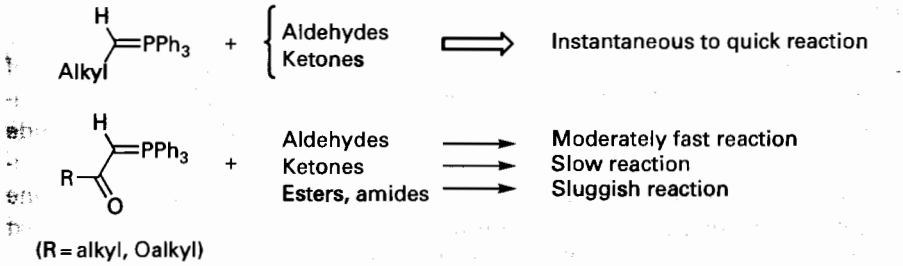


Fig. 5.1 Reactivities of typical ylide/carbonyl compound combinations in intramolecular Wittig olefinations.

2. Ring-closure variants utilizing highly reactive ω-carbonyl-ylides

2.1 Simple example of a ring-closure reaction of ω-halo-ylides and synthesis of small rings featuring exocyclic alkenes

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Protocol 1.
Cyclobutyltriphenylphosphonium bromide 1a[10d] and alkene 2[10a] (Scheme 1)

Equipment

- Hot-plate stirrer and Teflon-coated magnetic stirrer bar
- Oil bath
- Single-necked round-bottomed flask with a lateral stopcocked gas inlet (250 mL)
- Reflux condenser, water-cooled
- Gas-tight syringe (50 mL) and Lüer-lock needle
- Mercury float valve
- Chromatography column (50 cm × 1.5 cm)
- Büchner funnel
- Standard vacuum still

Materials

- Triphenylphosphane, 13 g, 50 mmol — **harmful, irritant**
- 1,4-Dibromobutane (ALDRICH 14,080–5), 12 g, 57 mmol — **lachrymator**
- Phenyl-lithium, 1 M solution in diethyl ether (Et_2O), 44 mmol — **corrosive, harmful**
- Et_2O, dry, 1000 mL — **extremely flammable**
- Toluene, 500 mL — **flammable**
- Tetrahydrofuran, dry, 100 mL — **flammable, irritant**
- Silica gel 60 (0.2–0.06 mm), 20 g — **harmful by inhalation**
- Hexane, 1000 mL — **irritant, flammable**

Method

Synthesis of (4-bromo-butyl)triphenylphosphonium bromide

1. Charge a single-necked round-bottomed flask (250 mL) with triphenylphosphane (13 g, 50 mmol), 1,4-dibrombutane (12 g, 57 mmol), toluene (50 mL), and a magnetic stirrer bar. Equip the flask with a condenser and put it in an oil bath mounted on a hot-plate stirrer.

Protocol 1. *Continued*

2. Heat and stir the mixture at 100°C for 14 h, whereupon a precipitate of the product phosphonium salt will form. Let the flask cool to ambient temperature, filter the suspension over a Büchner funnel, and wash the crude solid repeatedly with 100 ml portions of hot toluene to remove residual triphenylphosphane. Dry the product *in vacuo* at 100°C to obtain a crystalline colourless solid, m.p. 207°C, 23 g (97%). It is sufficiently pure for the next step, but may be recrystallized from chloroform/acetone.

Synthesis of cyclobutyltriphenylphosphonium bromide **1a**

3. Assemble a set-up consisting of a single-necked flask (250 mL) with a stop-cocked side-arm and charged with the above phosphonium salt (9.56 g, 20 mmol), and a water-cooled reflux condenser topped by a mercury float valve. Connect the set-up to a source of dry nitrogen and flush it thoroughly.
4. Remove the valve and against a continuous stream of inert gas fill into the flask first dry Et_2O (100 mL) and then an ethereal solution of phenyl-lithium (22 mmol), withdrawn from the bottle and transfered into the flask by means of a gas-tight syringe with needle. Replace the valve and allow the, by now deep red, mixture to stir for a further 24 h at room temperature.
5. For isolation of **1a**, filter the suspension, which should be once again almost colourless, on a Büchner funnel and wash the remaining solid with ether. Recrystallize it first from minimum amount of water, and then from chloroform/acetone mixtures to obtain pure **1a**, m.p. 271°C, 7.5 g (94%). For the preparation of **2**, the ethereal suspension resulting from step 4 can be used right away.

Synthesis of alkene **2**

6. To the colourless suspension of **1a** resulting from step 4 add another 22 mmol of phenyl-lithium by means of a syringe. Stir the mixture for a couple of minutes, then remove the condenser altogether and, under a strong stream of nitrogen, add benzaldehyde (2.2 g, 20 mmol) to the red solution.
7. Allow the mixture to stir for another 2 h, then add dry tetrahydrofuran (50 mL), filter the resulting brown solution, and evaporate the filtrate on a rotary evaporator. Purify the remaining crude product first by column chromatography on silica gel 60 (20 g) with Et_2O/hexane (1 : 3, v/v) to remove triphenylphosphane oxide and finally by vacuum distillation of the crude oily product to furnish pure **2** as a colourless oil, b.p. 62°C/0.6 mm Hg, 1.62 g (56%).

2.2 Cycloalkenes by partial oxidation of symmetric bisylides

Oxidation of symmetric bisylides with oxygen yields the corresponding symmetric cycloalkenes by intramolecular Wittig olefination of the initially formed ω-carbonyl-ylide.[3,12] This reaction only works well for unstabilized reactive

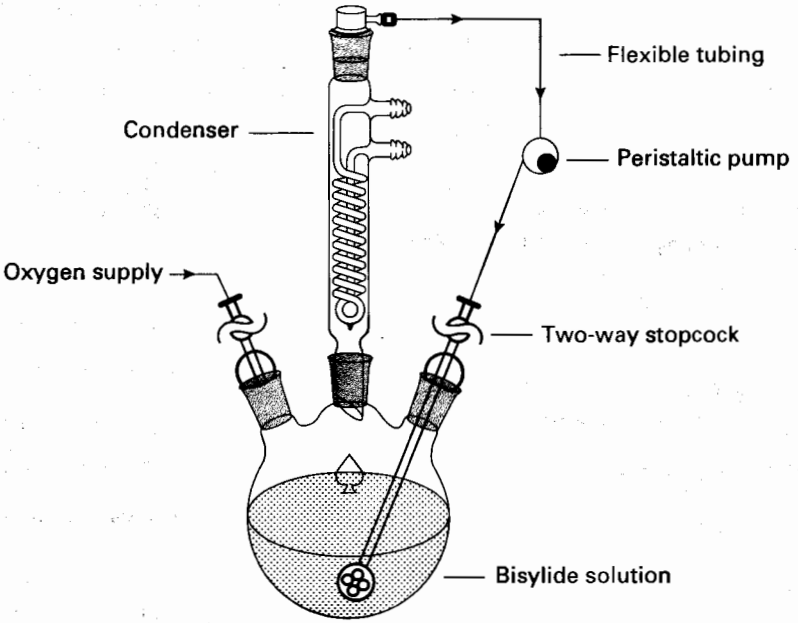
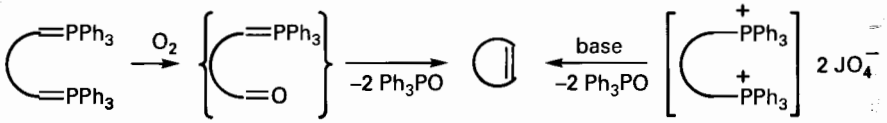


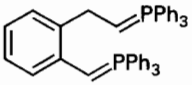
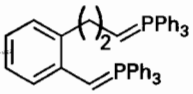
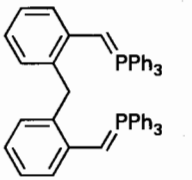
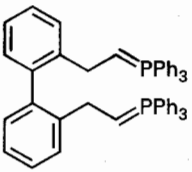
Fig. 5.2 Apparatus for the oxidation of bisylides to give cycloalkenes.

ylides, where the rate of the Wittig reaction is greater than the rate of the oxidation process itself. It can thus be carried out at normal concentrations in a closed apparatus (Figure 5.2), with the oxygen gas being circulated by means of a peristaltic pump until consumption is complete. The same set-up is equally suited for intermolecular variants, for instance the synthesis of β-carotene from two equivalents of axerophtylidene triphenylphosphorane.[13] In a very similar autoxidative way, bisphosphonium periodates give the corresponding cycloalkenes once treated with base to generate the bisylide intermediate (Scheme 2). Table 5.1 presents a collection of cycloalkenes prepared by oxidation of bisylides.



Scheme 2

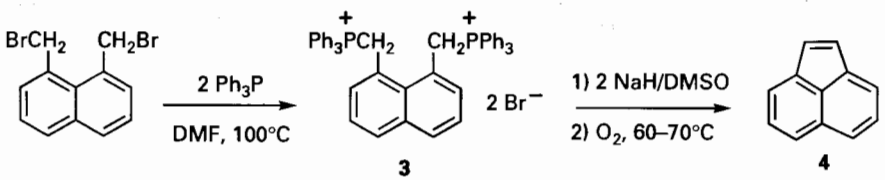
Table 5.1 Cycloalkenes by oxidation of bisylides[3]

Bisylide	Cycloalkene	Yield (%)	m.p. (°C)
$Ph_3P{=}CH-(CH_2)_3-CH{=}PPh_3$	Cyclopentene	68	–
$Ph_3P{=}CH-(CH_2)_4-CH{=}PPh_3$	Cyclohexene	60	–
$Ph_3P{=}CH-(CH_2)_5-CH{=}PPh_3$	Cycloheptene	61	–
$Ph_3P{=}CH-(CH_2)_6-CH{=}PPh_3$	Cyclooctene	52	–
	Indene	65	–[a]
	1,2-Dihydronaphthalene	46	–[b]
	5*H*-Dibenzo-[a,d]-cycloheptatriene	51	130
	5,8-Dihydrodibenzo-[a,c]-cyclooctatetraene	40	105

[a] b.p. 70°C/14.
[b] b.p. 85°C/12.

Protocol 2.
Acenaphthylene 4 (Scheme 3)

This is a simple example of the oxidation of unstabilized bisylides to give symmetric cycloalkenes.



Scheme 3

Equipment

- Oxidation apparatus (see Figure 5.2), consisting of a 500 mL three-necked round-bottomed flask, a water-cooled reflux condenser, a male stopcocked Schlenk-type adaptor, and a stopcocked long glass tube with a male ground-glass joint both serving as gas inlets, several bits of plastic hose, some flexible plastic tubing, and a simple peristaltic pump
- Hot-plate stirrer and Teflon-coated magnetic stirrer bar
- Oil bath
- Sources of dry nitrogen and oxygen
- Single-necked round-bottomed flask (250 mL)
- Büchner funnel
- Oil pump
- Mercury float valve
- Sublimation device

Materials

- Bis(bromomethyl)naphthalene, 8 g, 25 mmol — **corrosive**
- Triphenylphosphane, 13 g, 50 mmol — **harmful, irritant**
- Dry dimethylformamide (HPLC grade, ALDRICH), 50 mL — **harmful, irritant**
- Toluene, 500 mL — **flammable**
- Sodium hydride,[a] 0.75 g, 30 mmol — **contact with water liberates extremely flammable gases**
- Dimethylsulfoxide, dried over calcium hydride, 100 mL — **harmful, irritant**
- Petroleum ether, 200 mL — **highly flammable, irritant**
- Water, 50 mL
- Magnesium sulfate, 20 g

Method

Synthesis of 1,8-bis(methyltriphenylphosphonium)naphthalene dibromide **3**

1. Charge a single-necked round-bottomed flask (250 mL) with 1,8-bis(bromomethyl)naphthalene (80 g, 25 mmol), triphenylphosphane (13 g, 50 mmol), freshly distilled dimethylformamide (50 mL), and a magnetic stirrer bar. Equip the flask with a condenser and put it in an oil bath mounted on a hot-plate stirrer.
2. Heat and stir the mixture at 100°C for 2 h, whereupon increasing amounts of product phosphonium salt will precipitate. Allow the flask to cool to ambient temperature, filter the resultant suspension on a Büchner funnel, and wash the crude solid repeatedly with 100 mL portions of hot toluene to remove residual triphenylphosphane. Dry the phosphonium salt **3** *in vacuo* to obtain a crystalline colourless solid, m.p. 311–313°C (decomp.), 20.2 g (98%). It is sufficiently pure to be used immediately in the next step.

Synthesis of acenaphthylene **4**

3. Dry all glassware parts of the apparatus depicted in Figure 5.2 in an oven. Assemble a set-up consisting of the three-necked flask (500 mL), the water-cooled condenser topped by a mercury float valve on the middle neck, a gas inlet adapter connected to a nitrogen line on the second, and a glass stopper on the third neck for now. Flush the set-up with dry nitrogen and put it in an oil bath supported by a hot-plate stirrer.
4. Remove the glass stopper and against a continuous stream of nitrogen fill sodium hydride (0.75 g, 30 mmol) and dry dimethylsulfoxide (100 mL) into the flask. Replace the stopper and heat and stir the mixture slowly to 70–80°C.[b]

Protocol 2. *Continued*

Once the evolution of hydrogen gas has ceased (after approximately 1 h), add the freshly prepared phosphonium salt **3** (12.5 g, 15 mmol), still with strict exclusion of air and moisture.

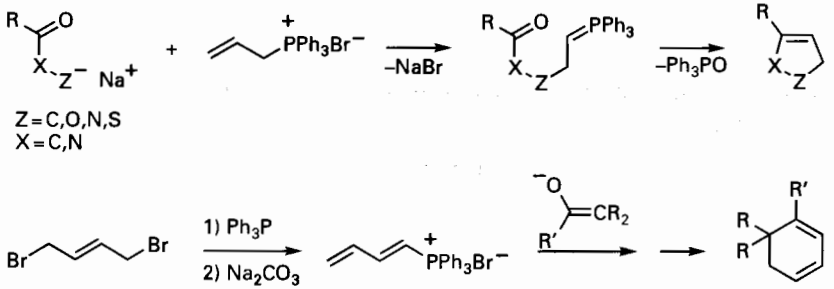
5. Under a stream of nitrogen, replace the stopper on the third neck by a stop-cocked long glass tube. Connect it with flexible plastic hoses to the outlet port of a peristaltic pump whose inlet port is directly fitted to the top of the condenser by means of adapters and/or a length of plastic hose. Your apparatus should by now resemble the one shown in Figure 5.2.
6. Connect the (left) gas inlet tube to an oxygen supply, maintain a temperature of about 60–70°C in the deep red solution, and flush the entire set-up thoroughly with dry oxygen. Close the left inlet tap and continuously pump the oxygen atmosphere through the reaction mixture by means of the peristaltic pump. Every now and then, a fresh load of oxygen may be flushed into the apparatus. After five hours the colour will have changed to brown and the oxidation should be complete.
7. Allow the flask to cool to ambient temperature and dismantle the set-up. Add an excess of water to the reaction mixture, collect the precipitate thus formed and repeatedly extract it with 50 mL portions of hot petroleum ether. Dry the combined organic extracts over magnesium sulfate, evaporate the solvent *in vacuo* and purify the crude product by sublimation at 70–80°C/0.1 mmHg to furnish colourless crystals of **4**, m.p. 89–90°C, 1.2 g (53%).

[a]Commercially available either neat or as 50% suspension in mineral oil, from which it can be obtained by washing it thoroughly with dry petroleum ether while on the glass sinter of a Schlenk-type filter funnel. CAS-# 7646-69-1.
[b]**Caution!** Do not overheat this mixture or heat it up to quickly. Vigorous decomposition may occur beyond 180°C, (CAS-# 67-68-5 and 7646-69-1).

2.3 Cycloalkenes by tandem addition–Wittig reactions of vinylphosphonium salts

By an unusual approach Schweizer *et al.*[14] prepared various types of unsaturated carbo- and heterocycles from different nucleophilic ω-carbonyl anions and vinyltriphenylphosphonium bromide. In the first step, the nucleophile adds to the terminal carbon atom of the vinyl residue to generate a reactive ω-carbonyl-ylide, which, in the second step, then undergoes a swift intramolecular Wittig olefination reaction. Suitable nucleophiles are species bearing anionic carbon, oxygen, nitrogen, or sulfur functionalities. This method is quite flexible in terms of ring size and heteroatom patterns, giving access, for example, to dihydrofurans, chromenes, pyridizines, and quinolines. It even works well for δ-carbonyl ylides of the amide type (X = NR) in which case pyrrole derivatives are formed upon prolonged heating in DMF.[15] Likewise, enolate systems can be used as

nucleophiles in similar reactions with butadienyltriphenylphosphonium bromide to yield 1,3-cyclohexadienes, as Fuchs has found (Scheme 4).[16]

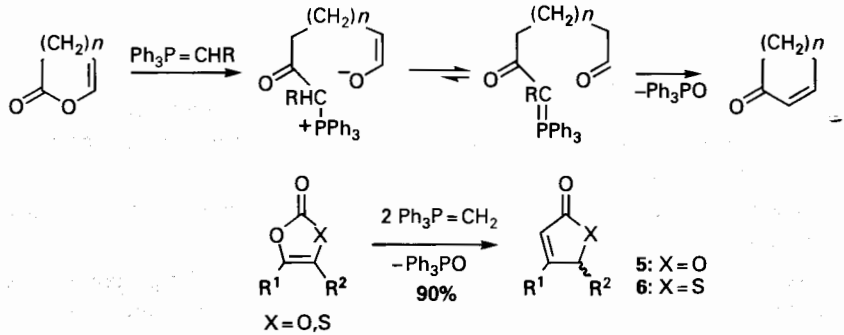


Scheme 4

3. Ring-closure variants employing less reactive ω-carbonyl ylides or 'non-classical' Wittig olefinations of esters and amides

3.1 Cycloalkenes from other heterocyclic precursors

Lactones of the enol ester type can be easily cleaved with reactive phosphoranes to give the corresponding ring-opened ω-carbonyl acyl ylides which normally undergo rapid Wittig recyclization (Scheme 5). This tandem approach has found use in steroid synthesis.[17] A similar sequence starting from cyclic vinylene carbonates or thiocarbonates and reactive ylides leads to the corresponding butenolides **5** or thiobutenolides **6**, respectively.[18] Interestingly, two equivalents of the ylide are required here as the enol–keto rearrangement is rather slow and transylidation of the initially formed phosphonio enolate with a second mole of starting ylide takes place instead. Formation of the keto tautomer has to be initiated by



Scheme 5

addition of a drop of water. It is also worth noting that it is always the oxygen and never the sulfur which is eliminated to form the heterocyclic product.

Protocol 3.
3,4-Diphenyl-γ-but-2-en-olide 5a (Scheme 5)

This is a simple example of a ring-opening/recyclization sequence to give γ-butenolides.

Equipment

- Single-necked round-bottomed flask with side-arm stopcock (250 mL)
- Stirrer and Teflon-coated magnetic stirrer bar
- Pressure-equalizing dropping funnel (50 mL)
- Source of dry nitrogen
- Oil pump
- Chromatography column (50 cm × g.5 cm)
- Erlenmeyer flask (100 mL)

Materials

- 4,5-Diphenyl-1,3-dioxolen-2-one,[a] 2.38 g, 10 mmol
- Methylenetriphenylphosphorane,[b] 5.5 g, 20 mmol — **harmful**
- Dry tetrahydrofuran,[c] 80 mL — **flammable, irritant**
- Et_2O, 500 mL — **extremely flammable, may form explosive peroxides**
- Hexane, 1000 mL — **irritant, flammable**
- Silica gel 60 (0.2–0.06 mm), 30 g — **harmful by inhalation**
- Water, 5 mL

Method

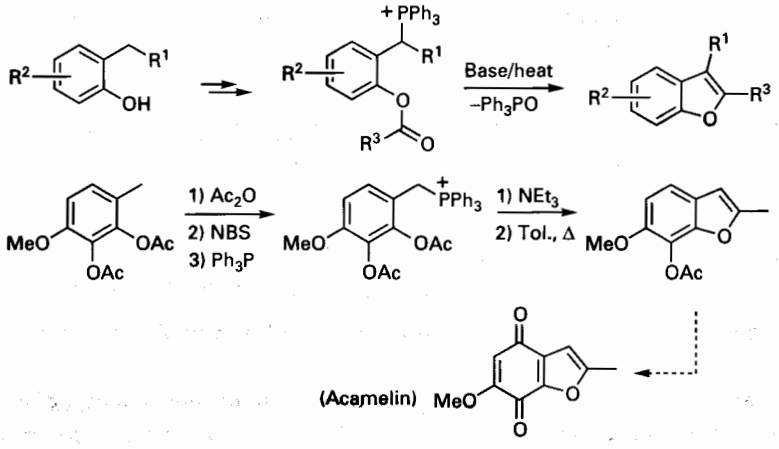
1. To an oven-dried single-necked round-bottomed flask (250 mL) equipped with a magnetic stirrer bar, add 4,5-diphenyl-1,3-dioxolen-2-one (2.38 g, 10 mmol). Connect it to a supply of dry nitrogen via its side arm, put a dropping funnel sealed with a mercury float valve on the neck of the flask. Flush the entire set-up thoroughly with inert gas for a couple of minutes.
2. Remove the valve and against a constant stream of nitrogen add first tetrahydrofuran (30 mL) to the flask, then close the tap of the funnel and charge it with a solution of methylenetriphenylphosphorane (5.5 g, 20 mmol)[b] in dry tetrahydrofuran (20 mL), and finally reseal the apparatus with the mercury valve.
3. Slowly (over a period of 30 min) add the phosphorane solution to the stirred solution of the dioxolenone, kept at ambient temperature. Once the addition is complete, continue stirring for a further 6 h at this temperature. Then add several drops of water to the clear solution until the initially formed yellow precipitate has entirely redissolved.
4. Allow the resulting bright red solution to stir for another 6 h, then remove all volatile components *in vacuo* (oil pump).
5. Prepare a silica gel 60 chromatography column (circa 30 g) using hexane, and then load the column by dissolving the residue in the minimum volume of tetrahydrofuran. Run the column with Et_2O/hexane (1:3, v/v) until no more organic material elutes. Evaporate the eluate *in vacuo* and purify the

remaining solid product by recrystallization from hot Et_2O to obtain colourless crystals of **5a**, m.p. 148°C, 2.12 g (90%).

[a]Commercially available from ALDRICH CHEMICAL COMPANY (24,583-6).
[b]Either neat, if in stock, or freshly prepared from 'instant ylide' (ALDRICH or MERCK) or by reaction of methyltriphenylphosphonium bromide (7.8 g, 22 mmol) and sodium bis(trimethylsilyl)amide (3.6 g, 20 mmol) in tetrahydrofuran (20 mL) at ambient temperature for 1 h.[19]
[c]Tetrahydrofuran is distilled from sodium benzophenone ketyl under nitrogen.

3.2 Oxacycles of the furan- and pyran-type from unstabilized ω-oxacarbonyl ylides

Intramolecular Wittig reactions of ester carbonyl groups are known with unstabilized, stabilized, and moderated phosphoranes.[11b] Hercouet and Le Corre[20] have developed several routes to benzofurans starting from *o*-alkylphenols which mainly differ in the order of events concerning esterification of the phenol group and the generation of the ylide function from the alkyl residue. Scheme 6 shows a typical application to the synthesis of acamelin, a natural component of the Australian blackwood, by McKittrick and Stevenson.[21] They first acylate the hydroxyl group and then brominate the methyl residue; subsequent conversion to the phosphonium salt, generation of the ylide by treatment with base, and finally Wittig-type cyclization gives rise to the corresponding benzofuran. It then takes two more steps to yield the desired natural product.



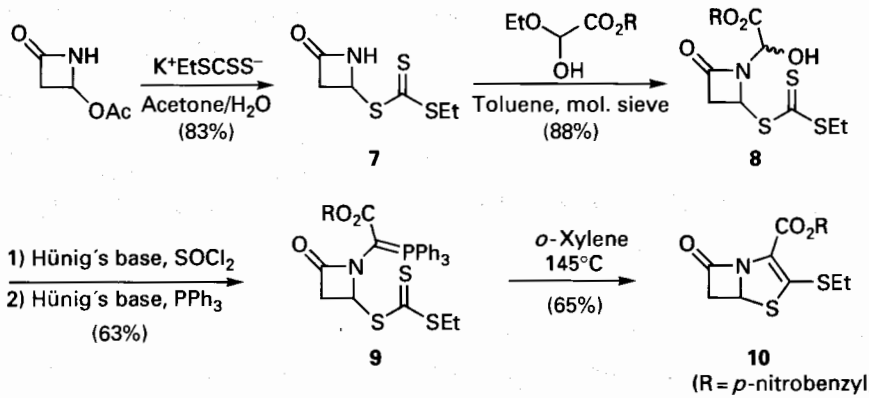
Scheme 6

3.3 Penem β-lactams from highly stabilized ω-thia- and ω-thiocarbonyl ylides

Intramolecular Wittig reactions are even possible between highly stabilized acyl ylides and thiolesters[22] or trithiocarbonate esters[23] of low 'carbonyl activity'.

This has been nicely demonstrated and exploited by Woodward's syntheses of bicyclic systems of the penem type. They are typically formed in moderate to good yields upon refluxing the requisite substituted starting β-lactams in toluene or xylene for extended periods. The key step is the introduction of the ylidic moiety into the 1-position of a 4-functionalized azetidin-2-one which itself can be obtained as a relay substance by degradation of natural penicillins or from easily available 4-acetoxyazetidin-2-one. The ester ylide function is built up by reaction first with alkyl hemiacetals of glyoxylates to give a hemiaminal and then successive replacement of the OH-group of the latter by Cl with thionyl chloride and finally of the chlorine atom by triphenylphosphane under basic conditions.

Protocol 4.
p-Nitrobenzyl 2-ethylthiopenem carboxylate 10 (Scheme 7)[23]



Scheme 7

This is an example of a penem synthesis by intramolecular reaction of an ylide with an ω-trithiocarbonate group

Equipment

- Single-necked round-bottomed flask with side-arm stopcock (100 mL)
- Hot-plate stirrer and Teflon-coated magnetic stirrer bar
- Pressure-equalizing dropping funnel (50 mL)
- Source of dry nitrogen
- Oil pump/water pump
- Mercury float valve or septa plus balloons
- Separating funnel (100 mL)
- Glass filter funnel and filter papers
- Reflux condenser
- Chromatography column
- Erlenmeyer flask (100 mL) with tapered ground-glass joint and suitable adapter

Materials

- 4-Acetoxyazetidin-2-one,[a] 1.32 g, 10.2 mmol — **corrosive**
- Potassium ethyl trithiocarbonate,[b] 2.25 g, 13 mmol — **harmful**
- *p*-Nitrobenzylglyoxylate ethylhemiacetal,[c] 1.7 g, 6.7 mmol — **harmful**
- Polymeric Hünig's base,[c] 9.1 g — **corrosive**
- Hydroquinone, 100 mg — **harmful**
- Thionyl chloride, 0.8 mL — **lachrymator**
- Triphenylphosphane, 1.42 g, 5.4 mmol — **harmful, irritant**
- Molecular sieves (3 or 4 Å)
- Silica gel 60 (0.2–0.06 mm), 50 g — **harmful by inhalation**
- Dry sodium sulfate, 5 g
- Acetone, 10 mL — **flammable**
- Brine, 50 mL
- Dichloromethane, 100 mL — **possible risks of irreversible effects**
- Et_2O, 100 mL — **extremely flammable, may form explosive peroxides**
- Dry dimethylformamide (HPLC grade), 20 mL — **harmful**
- Dry dioxane, 100 mL — **flammable, irritant**
- Ethyl acetate, 500 mL — **highly flammable**
- Toluene, 500 mL — **flammable**
- Water, 100 mL
- *o*-Xylene, 20 mL — **flammable, harmful**

Method

Synthesis of ethyl 2-oxo-azetidin-4-yl trithiocarbonate **7**

1. Transfer into a single-necked round-bottomed flask (100 mL), 4-acetoxy-2-azetidinone[a] (1.32 g, 10.2 mmol) and a magnetic stirrer bar. Pour acetone (1 mL) and water (3.5 mL) into the flask under a stream of nitrogen and equip the flask with a pressure-equalizing addition funnel (50 mL) containing a solution of potassium ethyl trithiocarbonate[b] (2.25 g, 1.28 mol-eq.) in water (12 mL).
2. Stir the mixture at room temperature and dropwise add the contents of the funnel, whereupon precipitation of a yellow solid will commence. Continue stirring for a further 30 min and then extract the mixture four times with dichloromethane (10 mL). Wash the combined organic extracts with brine and after drying (Na_2SO_4) evaporate the solvent *in vacuo* to obtain pure **7** as a yellow solid, m.p. 99.5–101.5°C, 1.76 g (83%).

Synthesis of ethyl [*N*-(p-nitrobenzyloxycarbonylmethyltriphenylphosphoranylidene)-2-oxo-azetidin-4-yl]trithiocarbonate **9**

3. Put **7** (621 mg, 3.00 mmol) and a magnetic stirrer bar in a single-necked round-bottomed flask and add dry toluene (35 mL) and dry dimethylformamide (9 mL). Under a stream of nitrogen add *p*-nitrobenzylglyoxylate ethylhemiacetal[c] (1.7 g, 6.7 mmol) and some freshly activated molecular sieves (3 or 4 Å). Stir the mixture under nitrogen at room temperature overnight and then for 2 h at 50°C. Remove the sieves by filtration and evaporate the solvents under reduced pressure to obtain crude aminal **8** as yellow oil, 1.1 g (88%).[d]

Protocol 4. *Continued*

4. Under a stream of nitrogen charge a single-necked round-bottomed flask (100 mL) with a magnetic stirrer bar, polymeric Hünig's base[c] (4.55 g), and dry dioxane (11 mL). Stir the mixture for 30 min, then add a solution of crude aminal **8** (1.1 g, 2.6 mmol) in dry dioxane (23 mL) followed by thionyl chloride (0.8 mL). Stir the mixture at room temperature under nitrogen for 3 h. Filter off the insoluable polymeric base and evaporate the filtrate *in vacuo* to obtain the crude halide.
5. Redissolve this material in dry dioxane (54 ml), transfer the solution to a single-necked round-bottomed flask (100 mL), flush it with nitrogen, and add polymeric Hünig's base (4.55 g) followed by triphenylphosphane (1.42 g, 5.4 mmol). Stir the resulting mixture at 50°C for 15 h under nitrogen. Filter the solution and evaporate the solvent under reduced pressure. Purify the residual crude product **9** by column chromatography on silica gel 60 (toluene/ethyl acetate, 2:3 v/v; $R_f = 0.4$). Yield 1.1 g (62%).

Synthesis of p-nitrobenzyl 2-ethylthiopenem carboxylate **10**

6. Charge a single-necked round-bottomed flask (100 mL) with phosphorane **9** (1.1 g, 1.65 mmol), a magnetic stirrer bar, *o*-xylene (20 mL), and a catalytic amount of hydroquinone. Furnish with a reflux condenser closed by a mercury valve or a septum/balloon combination and flush the entire set-up with nitrogen. Stir and heat the mixture to 145°C for 10 h.
7. Evaporate the solution *in vacuo* and purify the residue by column chromatography on silica gel. First elute triphenylphosphanesulfide (toluene/ethyl acetate 19:1, v/v), and then 0.40 g (65%) of pure penem **10** (toluene/ethyl acetate 9:1, v/v), m.p. 133–134°C (from dichloromethane/Et_2O).[e]

[a]Commercially available from ALDRICH CHEMICAL COMPANY or prepared acccording to a literature procedure.[24]
[b]Either purchased from ALDRICH CHEMICAL COMPANY or prepared according to the literature procedure.[25]
[c]Prepared according to the literature procedure.[22c]
[d]Can be used as such; purification is possible by column chromatography on 80 g of silica gel with toluene/ethyl acetate (9:1, v/v).
[e]The ^1H NMR spectrum is diagnostic ($CDCl_3$): 8.2 (m, 2H), 7.6 (m, 2H), 5.7 (d × d, 1H), 5.32 (m, 2H), 3.9–3.4 (m, 2H), 2.95 (m, 2H), 1.4 (t, 3H).

3.4 Tandem addition–Wittig olefination reactions of functionalized carbonyl compounds with cumulated phosphorus ylides

3.4.1 Five- to seven-membered O-, N-, and S-heterocycles

Acyl ylides with a tethered terminal ester function requisite for the construction of five- to seven-membered heterocycles are very conveniently accessible by reaction of the cumulated ylide ketenylidenetriphenylphosphorane **11** with various carboxylic esters bearing OH-, NHR-, and SH-groups in α-, β-, or γ-position.

Under the conditions necessary for the addition of the XH-acidic group onto the C=C bond of **11**, a rapid intramolecular Wittig olefination normally ensues, making for an expedient overall tandem reaction. Ylide **11** is readily prepared in molar quantities in three steps from methyl bromoacetate and triphenylphosphane.[26] It is fairly air-stable and can be stored at room temperature for months, and it is also commercially available from MERCK-SCHUCHARDT.

Protocol 5.
Ketenylidenetriphenylphosphorane 11[26]

Equipment

- Single-necked round-bottomed flask with stopcocked lateral gas inlet (×2, 2000 mL)
- Hot-plate stirrer and Teflon-coated magnetic stirrer bar (circa 5 cm)
- Source of dry nitrogen
- Reflux condenser
- Mercury float valve
- Oil bath
- Schlenk-type filter funnel (1000 mL)
- Oil pump

Materials

- Methoxycarbonylmethylenetriphenylphosphorane,[a] 167 g, 0.5 mol
- Sodium amide,[b] 19.5 g, 0.5 mol — **corrosive**
- Bis(trimethylsilyl)amine,[c] 1.6 g, 10 mmol — **harmful, corrosive**
- Toluene, 1000 mL — **flammable**
- Dry Et_2O, 200 mL — **extremely flammable**
- Celite,® 5 g

Method

1. Flush a single-necked round-bottomed flask with a stopcocked lateral gas inlet (2000 mL) thoroughly with nitrogen and then still against a stream of nitrogen charge it with methoxycarbonylmethylenetriphenylphosphorane[a] (167 g, 0.5 mol), toluene (1 L), sodium amide[b] (19.5 g, 0.5 mol) and a magnetic stirrer bar. Stir the entire mixture, equip with a reflux condenser topped by a mercury float valve, and place the flask into an oil bath mounted on a hot-plate stirrer.
2. Under a vigorous stream of nitrogen, remove the valve and add bis(trimethylsilyl)amine[c] (1.6 g, 10 mmol) through the condenser, whereupon effervesence and vigorous evolution of ammonia gas is likely to occur. Replace the valve, close the stopcock, and heat the entire mixture at 60–65°C for circa 24 h with stirring.
3. Equip a second stopcocked flask (2000 mL) with the Schlenk-type filter funnel. Stopper the upper joint of the funnel, connect its side-arm stopcock to a source of dry nitrogen, and the side-arm stopcock of the flask to a pump inlet.
4. Thoroughly flush this set-up by evacuating and flushing it with nitrogen in turn a couple of times. Close the stopcock at the flask, eventually, remove the stopper from the funnel under a constant stream of nitrogen, and then cover the sinter plate with a 2 cm layer of Celite®.

Protocol 5. *Continued*

5. Pour the hot reaction mixture from step 2, into the Schlenk filter funnel in two or three portions. To prevent contact with air or moisture during this operation either directly connect the reaction flask to the upper joint of the funnel and then turn the entire set-up slowly, or use suitable adapters, or an additional large funnel put onto the Schlenk funnel. While charging the funnel with the reaction mixture, apply a slight vacuum to the lower flask by opening its tap to the pump.
6. Once filtration is finished, flush the lower flask, which should now contain a clear red solution, with nitrogen, remove the filter funnel, and concentrate the solution by means of an oil pump to circa 500 mL. Add Et_2O (circa 200 mL), seal the flask with a stopper and put it in a freezer. After a couple of days most of the product will have precipitated in form of yellowish crystals.[d] It can be isolated by filtration using a set-up similar to the one described in step 3; m.p. 173°C, 97 g (0.31 mol; 66%).

[a] Available from ALDRICH CHEMICAL COMPANY or prepared according to a literature procedure. [26a]
[b] Purchased from FLUKA.
[c] Purchased from ALDRICH CHEMICAL COMPANY. The addition of this reagent is not necessary but is known to greatly expedite the reaction. A patent claim from H. J. Bestmann *et al.* is impending for this major improvement.
[d] The NMR spectra are diagnostic: ^{13}C NMR (100.5 MHz, C_6D_6): −10.36 [d, ^1J(α-C/P)=193.4 Hz, ylide C], 130.71 [d, ^1J(*ipso*-Ar/P)=98.8 Hz, *ipso*-ArC], 131.87, 132.38, 132.51 [ArCH], 146.95 [d, ^2J(β − C/P)= 43.0 Hz, carbonyl-C]; ^{31}P NMR (161.8 MHz; $CDCl_3$): 5.35.

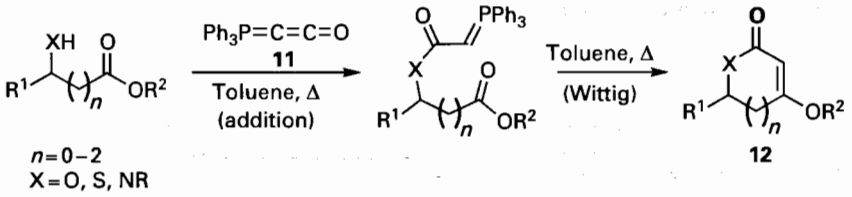
Table 5.2 Five-membered heterocycles **12** from α-functionalized esters and ylide **11**

12	X	R^1	R^2	Yield (%)	m.p. (°C)
a	O	Ph	Et	78	61
b	O	Me	Et	84	–[a]
c	O	Me	$CH(Me)_2$	90	–[b]
d	O	Me	CH_2Ph	92	–[c]
e	O	CH_2CO_2Me	Me	80	–[d]
f	O	(S)−$CH_2CH(OMe)_2$	Me	53	–[e]
g	NH	CH_2Ph	Me	60	157
h	NH	CH_2CH_2SMe	Me	76	90
i	S	Me	Et	50	–
j	S	H	Et	50	52

[a] b.p. 105°C/0.5.
[b] b.p. 83°C/0.02.
[c] b.p. 137°C/0.02.
[d] b.p. 104°C/0.4.
[e] b.p. 108°C/0.4.

By this approach, heterocycles with a wide range of ring sizes and heteroatom numbers and patterns have been prepared.[27] For instance, α-hydroxy esters give rise to tetronates, salicylates lead to 4-alkoxy coumarins,[28] and α-(hydroxylimino) esters give 1,2 oxazine-6-ones.[29] The reaction is fairly chemo- and regioselective and tolerates most of the common functional groups (aldehydes, ethers, acetals, and esters further than three bonds away from the XH-group). Table 5.2 shows some examples of five-membered monoheterocycles.

Protocol 6.
4-Ethoxy-5-phenyl-2,5-dihydrofuran-2-one 12a
(X = O, *n* = 0, R^1 = Ph, R^{Et}); Scheme 8[27]



Scheme 8

This is an example of a tetronate synthesis from an α-hydroxy ester and ylide **11**.

Equipment

- Single-necked round-bottomed flask with side-arm stopcock (100 mL)
- Hot-plate stirrer, Teflon-coated stirrer bar, and oil bath
- Reflux condenser
- Oil pump and/or rotary evaporator
- Mercury float valve (or rubber septa plus balloons) and source of dry nitrogen
- Chromatography column (circa 50 cm × 1.5 cm)
- Erlenmeyer flask (100 mL)

Materials

- (±)-Ethyl mandelate,[a] 0.94 g, 8 mmol
- Ketenylidenetriphenylphosphorane,[b] 3.0 g, 10 mmol
- Dry toluene, 75 mL — **flammable**
- Et_2O, 1000 mL — **highly flammable, may form explosive peroxides**
- Pentane, 1000 mL — **irritant, flammable**
- Dichloromethane, 10 mL — **possible risks of irreversible effects**
- Silica gel 60 (0.2–0.06 mm), 30 g — **harmful by inhalation**

Method

1. Charge an oven-dried single-necked round-bottomed flask possessing a side-arm stopcock (100 mL) with ketenylidenetriphenylphosphorane (3.0 g, 10 mmol), ethyl mandelate (0.94 g, 8 mmol), dry toluene (75 mL), and a magnetic stirrer bar. Equip the flask with a reflux condenser fitted with a mercury float valve (or a septum/balloon combination). Flush the entire

Protocol 6. *Continued*

set-up thoroughly with dry nitrogen and put it in an oil bath on a hot-plate stirrer.

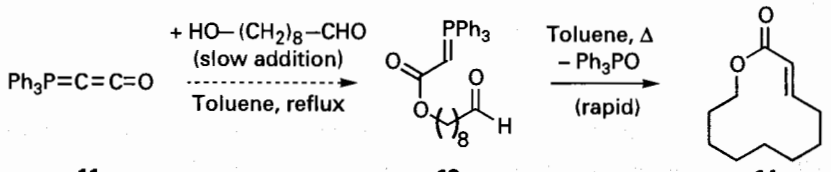
2. Heat and stir the mixture at gentle reflux for 12 h. Then allow it to cool to room temperature, dismantle the set-up and remove the solvent on a rotary evaporator. Re-dissolve the residue in the minimum amount of dichloromethane.
3. Prepare a silica gel 60 chromatography column (circa 20 g) using pentane/Et_2O (1:1, v/v), and then load the column with the solution of the crude product. Run the column with the same solvent mixture until no more tetronate **12a** comes off. Triphenylphosphaneoxide will stay at the top of the column under these conditions. Evaporate the eluate on an oil pump and purify the remaining solid by recrystallization from hot Et_2O to obtain yellowish needles of **12a**; m.p. 61°C, 1.27 g (78%).

[a]Commercially available from ALDRICH CHEMICAL COMPANY.
[b]Prepared by Protocol 5.

3.4.2 Macrolides

Alcohols react much faster with ketenylidenetriphenylphosphorane **11** than aldehydes, giving rise to the corresponding ester ylides, which in turn are of considerable 'Wittig reactivity' towards aldehydes. Thus, reacting long-chained ω-hydroxyaldehydes with **11** is an expedient way to access (*E*)-α,β-unsaturated macrocyclic lactones ('macrolides') avoiding the need to circumvent polymerization by high-dilution methods.[26a,30] The reaction is best performed by slowly adding solutions of the respective hydroxyaldehyde to a stirred and refluxing solution of **11** in toluene. High dilution is dispensable here as only ester ylides such as **13** undergo rapid Wittig olefination. If the rate of dropwise addition of the hydroxyaldehyde is sufficiently slow, such olefination is likely to occur exclusively intramolecularly. In summary, cumbersome high-dilution techniques were replaced by a slow addition procedure (normal addition funnels will do). Yields lie between 50 and 80% for ring sizes of 11–24. Again, important functional groups such as esters, ethers, olefins, and susceptible protective groups do not interfere with this mild and pH-neutral macrolactonization, which has been successfully applied to the synthesis of natural musk lactones as well as macrolide antibiotics.[31]

Protocol 7.
(2*E*)-11-Undecenolide 14 (Scheme 9)[26a]



11 **13** **14**

Scheme 9

This is a simple example for a macrolide synthesis from an ω-hydroxyaldehyde and ylide **11.**

Equipment

- Three-necked round-bottomed flask (500 mL)
- Hot-plate stirrer, Teflon-coated stirrer bar, and oil bath
- Reflux condenser
- Pressure-equalizing addition funnel (100 mL)
- Oil pump and rotary evaporator
- Mercury float valve, male stopcocked adaptor, and source of dry nitrogen
- Chromatography column
- Kugelrohr apparatus or other short-path distillation set-up

Materials

- 8-Hydroxynonanal,[a] 1.70 g, 10 mmol
- Ketenylidenetriphenylphosphorane,[b] 3.4 g, 11 mmol
- Dry toluene, 300 mL — **flammable**
- Et_2O, 500 mL — **extremely flammable, may form explosive peroxides**
- Pentane, 1000 mL — **irritant, flammable**
- Dichloromethane, 10 mL — **possible risks of irreversible effects**
- Silica gel 60 (0.2–0.06 mm), 20 g — **harmful by inhalation**

Method

1. Charge an oven-dried three-necked round-bottomed flask (500 mL) with ketenylidenetriphenylphosphorane (3.4 g, 11 mmol), dry toluene (200 mL), and a magnetic stirrer bar. Equip the flask with a reflux condenser surmounted by a mercury float valve on the first, a gas inlet adapter on the second, and a dropping funnel on the middle neck.
2. Flush the entire set-up thoroughly with dry nitrogen, put a circa 0.1 M solution of 8-hydroxynonanal (1.70 g, 10 mmol) in toluene (100 mL) into the addition funnel, close the funnel with a glass stopper, and place the flask into an oil bath on a hot-plate stirrer.
3. Heat and stir the mixture in the flask to gentle reflux and slowly add the hydroxyaldehyde solution over a period of 6–8 h. Once the addition is complete continue stirring for a further 2 h. Remove the toluene on a rotary

Protocol 7. *Continued*

evaporator under reduced pressure and re-dissolve the residue in the minimum amount of dichloromethane (3–5 mL).

4. Prepare a silica gel 60 chromatography column (circa 20 g) using pentane/Et_2O (3 : 1, v/v), and then load the column with the solution of the crude product. Elute the column until no more macrolide **14** comes off. Triphenylphosphaneoxide will remain at the top of the column under these conditions. Evaporate the eluate on an oil pump and purify the remaining residue by distillation in a Kugelrohr apparatus to obtain **14** as a colourless pleasant smelling oil, b.p. 58°C/0.01 mmHg, 1.18 g (65%).[c]

[a]Readily prepared by ozonolysis of oleyl alcohol (ALDRICH CHEMICAL COMPANY) or better, of oleyl acetate with subsequent saponification.
[b]Prepared by Protocol 5.
[c]The ^1H NMR spectrum is diagnostic ($CDCl_3$): 1.13–1.90 (m, 12H), 2.10–2.50 (m, 2H, $CH_2C{=}C$), 4.33 (t, J = 5 Hz, 2H, CO_2CH_2), 5.88 (dt, J = 16 Hz, J = 1 Hz, 1H, $C{=}CH{-}CO_2$), 7.04 (dt, J = 16 Hz, J = 1 Hz, 1H, $HC{=}CCO_2$).

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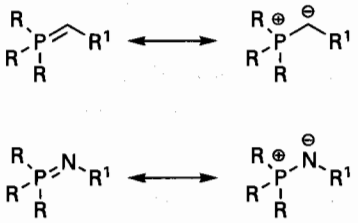
6

Preparation and reactions of iminophosphoranes and their synthetic applications in the aza-Wittig reaction

J. MIKE SOUTHERN and IAN A. O'NEIL

1. Introduction

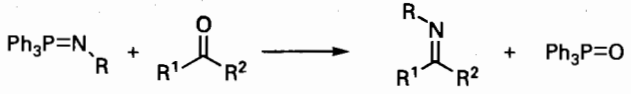
Iminophosphoranes (IMPs) were first reported by Staudinger and Meyer in 1919.[1] Initially, they were treated as little more than chemical curiosities, and it is only in the past three or four decades that their synthetic potential has been realized. IMPs consist of a phosphorus–nitrogen double bond and are isoelectronic with the phosphoranes employed in the Wittig reaction, although, in the case of IMPs, it is more accurate to depict the nitrogen–phosphorus bond as double rather than as an ylide (Scheme 1). This makes the IMPs more stable and less basic than the corresponding Wittig reagents, which exhibit more ylide-like character.



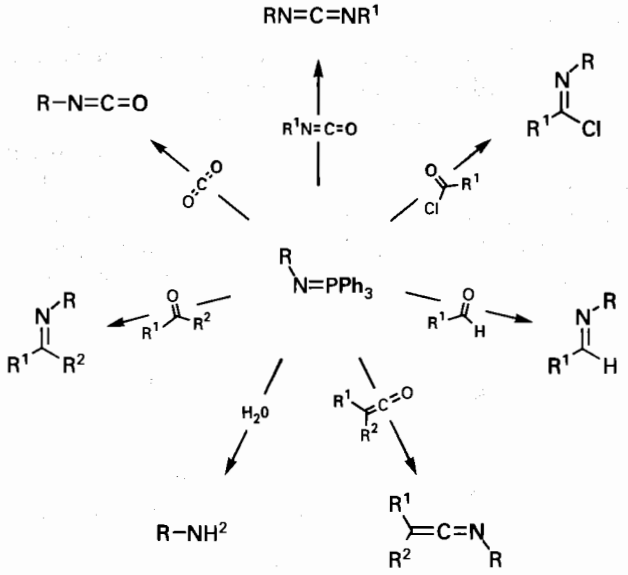
Scheme 1

The most widespread use of IMPs is in the aza-Wittig reaction. This is the reaction of an IMP with a carbonyl group to generate an imine, or derivative thereof, with concomitant formation of the corresponding phosphine oxide (Scheme 2). The reaction is successful with a wide range of carbonyl containing compounds such as aldehydes, ketones, acyl chlorides, amides, and in some cases esters.[2] Exposure to carbon dioxide, carbon disulfide, isocyanates, isothiocyanates, and

ketenes is an efficient method of generating heterocumulenes.[2] Scheme 3 shows some of the more common intermolecular reactions that have been documented. The aza-Wittig reaction has been employed in both inter- and intramolecular fashion, the latter being an extremely powerful method of generating heterocycles. Some electrophiles, for example, esters and amides will only react in an intramolecular fashion with IMPs, forming cyclic compounds directly. It should also be noted that in many cases, the products of intermolecular reactions of IMPs form products that either cyclize spontaneously or after further manipulation, greatly expanding the scope of the methodology.



Scheme 2

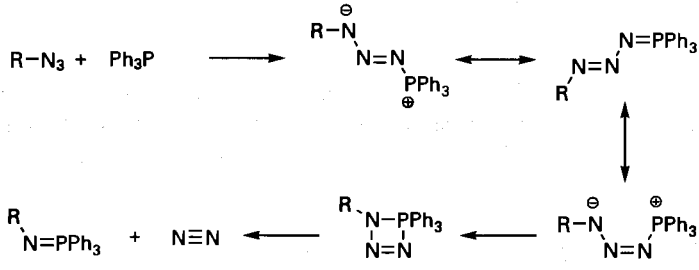


Scheme 3

2. Preparation of iminophosphoranes

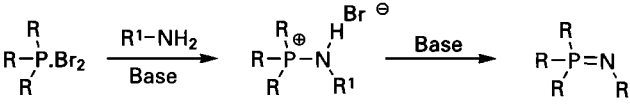
By far the most common method of formation of IMPs is the Staudinger reaction.[1] This is the reduction of an organic azide with triphenylphosphine (Scheme 4). It has been proven that attack of the phosphorus is at the terminal nitrogen of

the azide generating the zwitterionic phosphazide. Isomerization and cyclization give the intermediate, which then collapses, evolving nitrogen, to furnish the IMP. The rate-limiting step of the reaction is attack of the phosphine of the azide. As expected, electron withdrawing groups attached to the phosphorus retard the reaction, while the reaction is accelerated when these groups are associated with the azide. More recent reactivity studies have indicated that aliphatic phosphines react more efficiently than aromatic derivatives. However, if the IMP is to be isolated then triphenylphosphine is the phosphine of choice due to the stability of the resultant IMP. Further reduction to the amine is possible at this stage and can usually be accomplished by treatment of the IMP with water or in some cases either mild acid or alkali. The Staudinger reaction is extremely versatile, its apparent limitation being the availability of the required azides. Care should be taken with azides as they are heat and shock sensitive and prone to explosive decomposition!



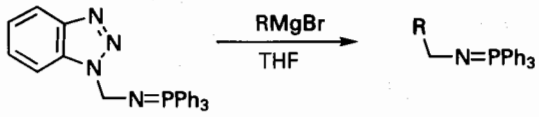
Scheme 4

A less commonly employed method of preparation is the Kirsanov reaction.[3] Strictly speaking, this is the reaction of phosphorus pentachloride with benzenesulfonamide, which can be reacted further to form benzenesulfonyliminophosphoranes. However, the name is now used generically to cover the reactions of triphenylphosphorus dihalides and amines in the presence of a base (Scheme 5). Attack of the amine on phosphorus gives the intermediate aminophosphonium salt and HBr, elimination of another equivalent of HBr generates the IMP. If the amine is aromatic, then 2 eq. of a mild base (e.g. triethylamine) are sufficient to perform the reaction in one pot.[4] However, in the case of alkylamines, it is generally necessary to isolate the phosphonium salt and treat it with sodamide to effect the deprotonation and generate the IMP.[5]



Scheme 5

Another approach worthy of note has been described by Katritzky,[6] who makes use of an IMP containing a benzotriazole moiety, which can serve as a common starting reagent for a wide range of IMPs. Treatment with a Grignard reagent results in an S_N2 displacement of the benzotriazole group to give the desired IMP (Scheme 6).



Scheme 6

3. Removal of triphenylphosphine oxide

A problem often associated with both the Wittig and aza-Wittig reaction is the removal of triphenylphosphine oxide from the desired products. The phosphine oxide has bizarre properties, in that attempts to remove it from the crude reaction mixture by column chromatography can be complicated by co-elution with the required products. Many experimental procedures precipitate the triphenylphosphine oxide with ether during the work-up and then titurate out the product with additional ether to leave the triphenylphosphine oxide as a crystalline solid. This protocol is facilitated using mixtures of ether with hexane, employing as much hexane as product solubility will allow. In other examples, the triphenylphosphine oxide is removed by precipitation from water (Protocol 2). It is also viable to use modified phosphines, which are either acid or base soluble and therefore, more easily extracted during work-up. The exploitation of the bis(phosphine) 1,2-bis(diphenylphosphino)ethane (DPPE or DIPHOS) has recently been reported (Protocol 3). In this case, the by-product of the Staudinger reaction is the bis phosphine oxide that is much easier to remove from the crude reaction mixture than triphenylphosphine oxide.

The first protocol describes the simple reduction of an organic azide employing triphenylphosphine and water in tetrahydrofuran

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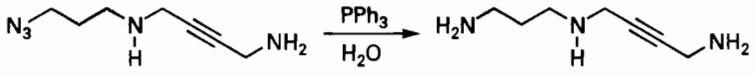
Protocol 1.
General procedure for the reduction of an azide[7]



Caution! All procedures should be performed in a well-ventilated hood. Wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Round bottom flask (25 mL)
- Syringe (50 μL) and needle
- Septum cap
- Magnetic stirrer plate
- Magnetic stirrer bar

Materials

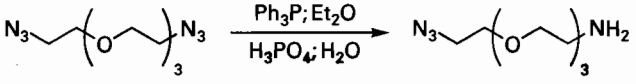
• Azide 340 mg, 2.04 mmol	**unknown, treat as toxic**
• Triphenylphosphine 558 mg, 2.24 mmol	**irritant, harmful**
• Tetrahydrofuran	**irritant, flammable**
• Dichloromethane	**irritant, harmful**
• Concentrated aqueous ammonia	**corrosive, lachrymator**
• Methanol	**flammable, toxic**
• **Distilled water**	

Method

1. Clean the apparatus and bake in an oven at a minimum of 120°C for 3–4 h. When required, allow the equipment to cool in a desiccator.
2. Set up the flask with a stirrer bar, septum cap and a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
3. Dissolve *N*-(3-azidopropyl)-1,4-diamino-2-butyne (340 mg, 2.04 mmol) in tetrahydrofuran (10 mL), then add triphenylphosphine (558 mg, 2.24 mmol) and water (40 μL).
4. Stir the resultant solution for 18 h at room temperature. Remove the volatiles at reduced pressure using a rotary evaporator.
5. Prepare a mixture of dichloromethane, methanol and concentrated aqueous ammonia in a ratio of 2 : 2 : 1. Take the bottom layer and use this as the eluent for purification by column chromatography on silica gel to give the amine (282 mg, 98%) as an oil.

With a clever modification of conditions it is possible to desymmetrize a diazide. This is achieved by selective reduction of one of the azide moieties. As soon as the reduction of the first azide has occurred, the resultant amine is protonated and carried into the phosphoric acid layer, preventing further interaction with triphenylphosphine.

Protocol 2.
Selective reduction of a diazide[8]



Caution! All procedures should be performed in a well-ventilated hood. Wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Protocol 2. *Continued*

Equipment

- Round bottom flask (1000 mL)
- Septum cap
- Magnetic stirrer plate
- Dropping funnel
- Magnetic stirrer bar
- Glass sinter funnel
- Buchner flask

Materials

• Diazide 42.7 g, 176 mmol	**unknown, treat as toxic**
• 0.65 M aqueous phosphoric acid 400 mL	**corrosive**
• Triphenylphosphine 39.9 g, 152 mmol	**irritant, harmful**
• Potassium hydroxide	**corrosive**
• Diethyl ether	**highly flammable**
• Dichloromethane	**irritant, harmful**
• Anhydrous sodium sulfate	**irritant, moisture sensitive**

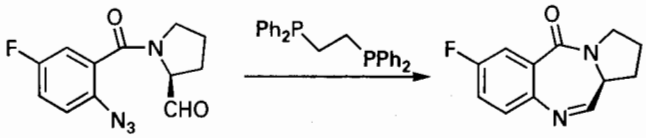
Method

1. Clean and dry the glassware required. Assemble a 1-L flask, equipped with a stirrer bar and a 500 mL dropping funnel.
2. In the flask, stir the diazide (42.7 g, 176 mmol) in 0.65 M aqueous phosphoric acid (400 mL).
3. Meanwhile, in the dropping funnel prepare a solution of triphenylphosphine (39.9 g, 152 mmol) in diethyl ether (300 mL). Add the solution dropwise, over a period of 45 min, to the phosphoric acid phase. Rinse the dropping funnel with a little more ether (35 mL).
4. Replace the dropping funnel with a septum cap and apply a positive pressure of nitrogen from either a balloon or line connected via a syringe needle. Stir the reaction mixture at room temperature for 24 h.
5. Separate and collect the aqueous layer and wash with ether (3 × 100 mL). Add solid potassium hydroxide (32.0 g) to the acidic aqueous layer and allow the traces of residual ether to evaporate.
6. Cool the solution to 4°C for 16 h and then filter out the precipitated triphenylphosphine oxide on a glass sinter funnel at the pump.
7. Add further solid potassium hydroxide (92 g) and extract with dichloromethane (16 × 75 mL).
8. Dry the combined organic phase with anhydrous sodium sulfate. Filter off the desiccant and remove the volatiles on a rotary evaporator to give the aminoazide (30.2 g, 82%) as an amber oil.

Protocol 3 is an example of an aza-Wittig reaction using 1,2-bis(diphenylphosphino)ethane (DPPE or DIPHOS). The IMP is generated by reduction of the azide by DPPE, intramolecular reaction with the aldehyde group then occurs. It is worth noting the replacement of triphenylphosphine with DPPE. In the reaction

only 0.55 equivalents of DPPE are employed. This means that the extremely polar bis(phosphine oxide) is generated, which greatly facilitates its removal from the crude reaction mixture.

Protocol 3.
A DPPE promoted intramolecular aza-Wittig reaction[9]



Caution! All procedures should be performed in a well-ventilated hood. Wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Round bottom flask (10 mL)
- Septum cap
- Magnetic stirrer plate
- Magnetic stirrer bar

Materials

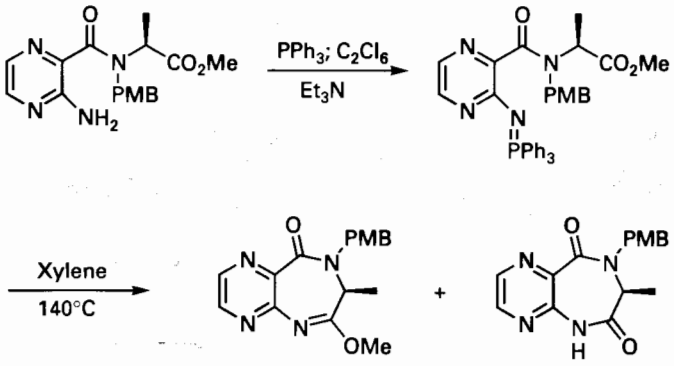
• Azidoaldehyde 82 mg, 0.31 mmol	**unknown, treat as toxic**
• Dry dichloromethane	**irritant, harmful**
• DPPE 68 mg, 0.17 mmol	**harmful**
• Ethyl acetate	**flammable**

Method

1. Clean the apparatus and bake in an oven at a minimum of 120°C for 3–4 h. When required, allow the equipment to cool in a desiccator.
2. Set up the flask with a septum cap, stirrer bar and a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
3. Introduce the azido aldehyde (82 mg, 0.31 mmol), dry dichloromethane (5 mL) and finally DPPE (68 mg, 0.17 mmol).
4. Stir at room temperature for 30 min then remove the solvent at reduced pressure on a rotary evaporator, to leave a yellow oil.
5. Purify the crude reaction mixture by column chromatography on silica gel, eluting with ethyl acetate. The pyrrolo-[1,4]-benzodiazepine was obtained as a pale yellow oil (53 mg, 77%).

Next, we see an alternative method of generating the IMP. In this method, the aza-Wittig reagent is generated from a primary amine, triphenylphosphine, triethylamine and hexachloroethane. In this case, the resultant IMP reacts with the carbonyl of an ester. Unfortunately, slight hydrolysis of the product is observed during this process.

Protocol 4.
Preparation of (3*S*-3,4-dihydro-2-methoxy-4-methoxyphenymethyl-3-methyl-pyrazino[2,3-*e*][1,4]diazepin-5-one[10]



Caution! All procedures should be performed in a well-ventilated hood. Wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Round bottom flask (25 mL)
- Septum cap
- Magnetic stirrer hot plate
- Magnetic stirrer bar
- Syringe (50 μL) and needle
- Water-jacketed reflux condenser
- Tubing
- Oil bath
- Sealed tube

Materials

• Aminoester 210 mg, 0.61 mmol	**unknown, treat as toxic**
• Triphenylphosphine 239 mg, 0.91 mmol	**irritant, harmful**
• Hexachloroethane 216 mg, 0.91 mmol	**harmful, cancer suspect agent**
• Triethylamine 0.25 mL, 1.79 mmol	**irritant, flammable**
• Dry benzene	**toxic, flammable, cancer suspect agent**
• Dry xylene	**irritant, flammable**
• Hexane	**irritant, flammable**
• Ethyl acetate	**flammable**

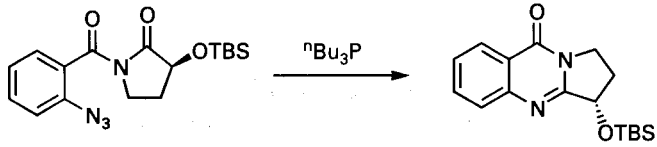
Method

1. Clean the apparatus and bake in an oven at a minimum of 120°C for 3–4 h. When required, allow the equipment to cool in a desiccator.
2. Set up the flask with a stirrer bar and a septum cap. Apply a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
3. Add sequentially aminoester (210 mg, 0.61 mmol), triphenylphosphine (239 mg, 0.91 mmol), hexachloroethane (216 mg, 0.91 mmol) and dry benzene (5.0 mL).

4. Add triethylamine (25 μL, 1.79 mmol) dropwise, via syringe, then replace the septum cap with a reflux condenser topped with a septum cap and apply a positive pressure of nitrogen, as before. Heat the reaction mixture at reflux for 2 h in an oil bath. Allow the reaction to cool to room temperature, then remove the precipitate by filtration.
5. Remove the solvent from the filtrate at reduced pressure using a rotary evaporator and dissolve the residue in dry xylene (9 mL). Heat the mixture for 24 h in a sealed glass tube (**Care!** see Protocol 10).
6. After cooling, remove the solvent at reduced pressure using a rotary evaporator or Kugelrohr. Purify the crude reaction mixture by column chromatography on silica gel. As the by-products are difficult to separate increasingly more polar eluents are used as the by-products are removed. Start with 50% hexane in ethyl acetate, then 33% hexane in ethyl acetate and finally ethyl acetate alone. This gives the title compound (170 mg, 85%) as a colourless oil, along with 11% of the corresponding hydrolysed product as a pale yellow oil.

The next example was used in the total synthesis of Vasicinone. In this case, tributylphosphine is employed to generate the IMP.

Protocol 5.
The preparation of (3*S*)-*O*-(*tert*-butyldimethylsilyl)vasicinone[11]



Caution! All procedures should be performed in a well-ventilated hood. Wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Round bottom flask (10 mL)
- Septum cap
- Magnetic stirrer bar
- Syringe (100 μL) and needle
- Magnetic stirrer hot plate
- Water jacketed condenser
- Tubing

Materials

- Azide 160 mg, 0.44 mmol — **unknown, treat as toxic**
- Tri-*n*-butylphosphine **98 mg, 0.48 mmol** — **irritant, flammable**
- Toluene — **irritant, flammable**
- Ethyl acetate — **flammable**
- Hexane — **irritant, flammable**

Protocol 5. *Continued*

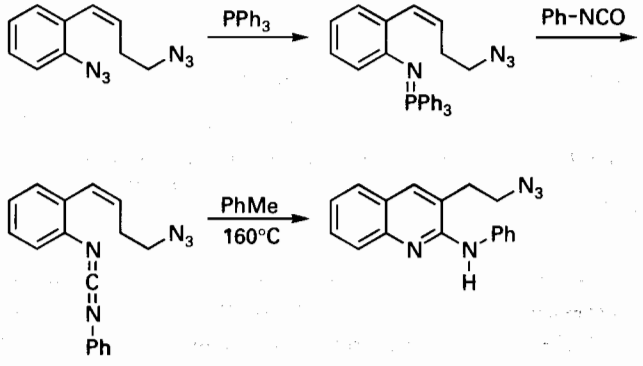
Method

1. Clean the apparatus and bake in an oven at a minimum of 120°C for 3–4 h. When required, allow the equipment to cool in a desiccator.
2. Set up the flask with a septum cap, stirrer bar and a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
3. Prepare a solution of the azide (160 mg, 0.44 mmol) in toluene (3.0 mL), then add tri-*n*-butylphosphine (98 mg, 0.48 mmol) dropwise via syringe.
4. Stir the reaction mixture at room temperature for 1 h, replace the septum cap with a reflux condenser topped with a septum cap and apply a positive pressure of nitrogen, as before. Heat at reflux for 2 h. Allow the reaction to cool to room temperature, then remove the volatiles at reduced pressure using a rotary evaporator.
5. Purify the residue by column chromatography on silica gel, eluting with 33% ethyl acetate in hexane to give the tricycle (106 mg, 76%) as a white solid.

In the remaining protocols, the IMPs are reacted with electrophiles in an intermolecular fashion. Further manipulation then brings about a cyclization.

Protocol 6 shows the chemoselective reduction of the more electrophilic aromatic azide. Reaction of the resultant IMP with phenyl isocyanate gives the carbodiimide, which upon heating in a sealed tube, undergoes cyclization.

Protocol 6.
Selective reduction of an aromatic azide[12]



Caution! All procedures should be performed in a well-ventilated hood. Wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Round bottom flasks (50, 25 and 10 mL)
- Septum cap ×3
- Stirrer bar ×3
- Ice bath
- Magnetic stirrer plate
- Syringe (10 and 5 mL) and needles
- Sealed tube

Materials

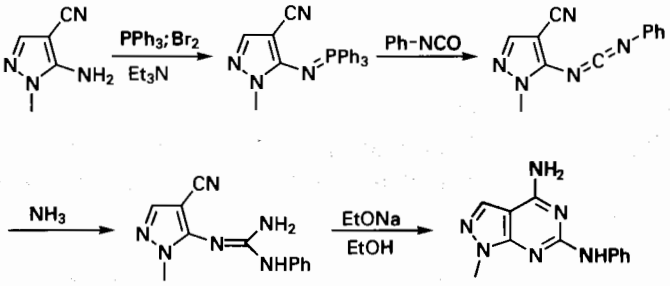
• Diazide 200 mg, 0.93 mmol	**unknown, treat as toxic**
• Triphenylphosphine 240 mg, 0.93 mmol	**irritant, harmful**
• Phenyl isocyanate 110 mg, 0.93 mmol	**highly toxic, moisture sensitive, lachrymator**
• Dry ether	**highly flammable**
• Dry toluene	**irritant, flammable**
• Ethyl acetate	**flammable**
• Hexane	**irritant, flammable**

Method

1. Clean the apparatus and bake in an oven at a minimum of 120°C for 3–4 h. When required, allow the equipment to cool in a desiccator.
2. Set up the 50 and 25 mL flasks, each with a septum cap, stirrer bar and a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
3. To the larger flask, introduce the diazide (200 mg, 0.93 mmol), dry ether (10 mL) and a stirrer bar, stir until homogeneous.
4. Meanwhile, in the 25 mL flask, prepare a solution of triphenylphosphine (240 mg, 0.93 mmol) in dry ether (10 mL) and add it via syringe to the azide solution. Stir at room temperature for 15 h.
5. Set up the 10 mL flask with a septum cap, stirrer bar and a positive pressure of nitrogen as before. Prepare a solution of phenyl isocyanate (110 mg, 0.93 mmol) in ether (5 mL).
6. Cool the reaction flask to 0°C, then add the solution of phenyl isocyanate via syringe. Allow the reaction mixture to warm to room temperature and stir for a further 2 h.
7. Remove the solvent at reduced pressure using a rotary evaporator. Redissolve the solid crude residue in dry toluene (30 mL) and heat in a sealed tube at 160°C for 8 h (**Care!** see Protocol 10).
8. After cooling, remove the solvent at reduced pressure with a rotary evaporator. Purify the crude reaction mixture by column chromatography, eluting with 20% ethyl acetate in hexane to give the quinoline (135 mg, 68%) as a brown oil.

Reaction of the carbodiimide derived from the aza-Wittig reaction with ammonia generates the gaunidine, which under basic conditions, attacks the nitrile moiety in a nucleophilic manner.

Protocol 7.
Preparation of 1-methyl-6-anilinopyrazolo-[3,4-*d*]-pyramid-4(3*H*)-one[13]



Caution! All procedures should be performed in a well-ventilated hood. Wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Round bottom flasks (250 and 2 × 10 mL)
- Septum cap ×4
- Stirrer bars
- Magnetic stirrer hot plate
- Ice bath
- Syringes (2 mL and 250 μL) and needles
- Water-jacketed condenser
- Tubing
- Oil bath

Materials

• Triphenylphosphine 7.37g, 28.11 mmol	**irritant, harmful**
• Bromine 1.45 mL, 28.11 mmol	**corrosive, lachrymator**
• Triethylamine 7.82 mL, 56.22 mmol	**irritant, flammable**
• Aminonitrile 3.43 g, 28.11 mmol	**unknown, treat as toxic**
• IMP 600 mg, 1.57 mmol	**unknown, treat as toxic**
• Phenyl isocyanate 0.17 mL, 1.57 mmol	**highly toxic, moisture sensitive, lachrymator**
• Carbodiimide 140 mg, 0.63 mmol	**unknown, treat as toxic**
• Ammonia (gas)	**harmful, lachrymator**
• Dry dichloromethane	**irritant, harmful**
• Diethyl ether	**highly flammable**
• Hexane	**irritant, flammable**
• Dry tetrahydrofuran	**irritant, flammable**
• Ethanol	**flammable, toxic**
• Sodium ethoxide	**corrosive, flammable, moisture sensitive**
• Anhydrous sodium sulfate	**irritant, moisture sensitive**
• Distilled water	

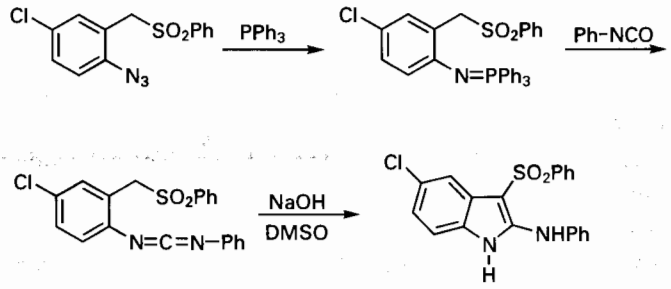
Method

1. Clean the apparatus and bake in an oven at a minimum of 120°C for 3–4 h. When required, allow the equipment to cool in a desiccator.
2. Set up the 250 mL flask with a septum cap, stirrer bar and a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
3. Prepare a solution of triphenylphosphine (7.37g, 28.11 mmol) in dry dichloromethane (120 mL).

4. Cool the reaction mixture to 0°C, carefully add the bromine (1.45 mL, 28.11 mmol) dropwise via syringe and continue stirring for a further 5 min.
5. While still at 0°C, add triethylamine (7.82 mL, 56.22 mmol), immediately followed by the aminonitrile (3.43 g, 28.11 mmol). Remove the cooling bath and stir for 20 h at room temperature.
6. Pour the reaction mixture into water (100 mL) and extract with dichloromethane (3 × 100 mL). Combine the washings and dry with anhydrous sodium sulfate, filter off the desiccant then remove the volatiles at reduced pressure using a rotary evaporator.
7. Purify the residue by column chromatography on silica gel, eluting with 50% diethyl ether in hexane to give the IMP (8.32g, 77%) as a pale yellow solid.
8. Set up a 10 mL flask with a septum cap, stirrer bar and a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
9. Prepare a solution of IMP (600 mg, 1.57 mmol) in dry tetrahydrofuran (5 mL). Add phenyl isocyanate (0.17 mL, 1.57 mmol) via syringe.
10. Stir the reaction mixture at room temperature for 1 h, then remove the solvent at reduced pressure using a rotary evaporator.
11. Purify the crude reaction mixture by column chromatography on silica gel, eluting with 50% diethyl ether in hexane to give the carbodiimide (223 mg, 64%) as a pale yellow solid.
12. Set up the 10 mL flask with a septum cap, stirrer bar and a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
13. Prepare a solution of carbodiimide (140 mg, 0.63 mmol) in dry tetrahydrofuran (2 mL). Gently bubble ammonia through the solution until it is saturated.
14. Stir the reaction mixture for 1 h and then remove the volatiles at reduced pressure using a rotary evaporator.
15. Add dry ethanol (2 mL) to the residue and equip the flask with a stirrer bar and a reflux condenser topped with a septum cap. Apply a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
16. Add sodium ethoxide in ethanol (360 μL of a 3.09 M solution, 1.1 mmol), then heat the reaction mixture at reflux for 18 h.
17. After cooling, remove the solvent at reduced pressure using a rotary evaporator. Purify the crude reaction mixture by column chromatography on silica gel, eluting with diethyl ether to give pyrimidine (117 mg, 77%) as a white solid.

In the next protocol, the carbodiimide derived from the aza-Wittig reaction reacts with the α-sulfonyl anion in an electrophilic manner to generate the indole shown.

Protocol 8.
Preparation of 2-anilino-3-phenylsulfonyl-5-chloroindole[14]



Caution! All procedures should be performed in a well-ventilated hood. Wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Round bottom flasks (500, 100, and 10 mL)
- Septum cap ×3
- Stirrer bars
- Pressure-equalizing dropping funnel
- Ice bath
- Syringe (1 mL) and needle
- Sinter funnel ×3
- Buchner flask ×3
- Water-jacketed condenser
- Tubing
- Oil bath

Materials

• Triphenylphosphine 7.86 g, 30 mmol	**irritant, harmful**
• Azide 9.23 g, 30 mmol	**unknown, treat as toxic**
• IMP 2.17 g, 4.0 mmol	**unknown, treat as toxic**
• Phenyl isocyanate 480 mg, 4.0 mmol	**highly toxic, moisture sensitive, lachrymator**
• Carbodiimide 383 mg, 1.0 mmol	**unknown, treat as toxic**
• Sodium hydroxide 200 mg, 5.0 mmol	**corrosive**
• 10% Aqueous ammonium chloride	**irritant**
• Anhydrous magnesium sulfate	**moisture sensitive**
• Dry dichloromethane	**irritant, harmful**
• Benzene	**toxic, flammable, cancer suspect agent**
• Chloroform	**harmful, cancer suspect agent**
• Hexane	**irritant, flammable**
• Methanol	**flammable, toxic**
• Anhydrous dimethyl sulfoxide	**irritant, hydroscopic, readily absorbed through skin**

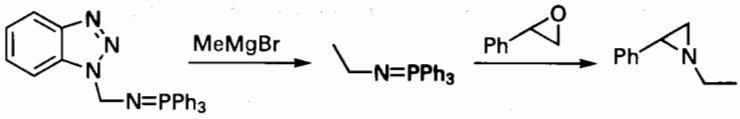
Method

1. Clean the apparatus and bake in an oven at a minimum of 120°C for 3–4 h. When required, allow the equipment to cool in a desiccator.
2. Set up the 500 mL flask with a pressure-equalized dropping funnel topped with a septum cap and a positive pressure of nitrogen from a balloon or line connected via a syringe needle.

3. Equip the 500 mL flask with a stirrer bar and make up a solution of triphenylphosphine (7.86 g, 30 mmol) in dry dichloromethane (150 mL). Cool to 0°C in an ice bath.
4. Meanwhile, in the dropping funnel, prepare a solution of the azide (9.23 g, 30 mmol) in dry dichloromethane (150 mL). Add the solution, in a dropwise manner to the cooled solution of triphenylphosphine. Stir at 0°C for 1 h, then allow the reaction mixture to warm slowly to room temperature.
5. Remove the solvent at reduced pressure using a rotary evaporator. Add benzene to the crude reaction mixture in order to facilitate precipitation of the product.
6. Collect the resultant solid by filtration on a glass sinter funnel at the pump. Recrystallize the solid from chloroform and hexane to give the IMP as a white solid (14.15 g, 87%).
7. Set up the 100 mL flask with a stirrer bar, septum cap and a positive pressure of nitrogen from a line or balloon connected via syringe needle.
8. Prepare a solution of IMP (2.17 g, 4.0 mmol) in dry dichloromethane (50 mL). Add phenyl isocyanate (480 mg, 4.0 mmol) via syringe.
9. Remove the septum and equip the flask with a reflux condenser topped with a septum cap and a positive pressure of nitrogen as before. Heat the reaction mixture at reflux in an oil bath for 12 h.
10. Allow the reaction mixture to cool to room temperature, then remove the solvent at reduced pressure using a rotary evaporator. Triturate the residue with hexane and recrystallize the resultant solid from dichloromethane and hexane to give carbodiimide (1.5 g, 98%) as white needles.
11. Set up the 10 mL flask with a septum cap, stirrer bar and a positive pressure of nitrogen, as above. Make up a solution of the carbodiimide (383 mg, 1.0 mmol) in anhydrous DMSO (3 mL). *Note*: it might be necessary to warm the DMSO gently in order to melt it. Add powdered sodium hydroxide (200 mg, 5.0 mmol) and stir at, or slightly above, room temperature for 30 min.
12. Neutralize the reaction mixture with 10% aqueous ammonium chloride solution, filter off the resultant precipitate on a glass sinter funnel at the pump.
13. Dissolve the precipitate in chloroform and dry the solution with anhydrous magnesium sulfate. Filter off the desiccant, then remove the solvent at reduced pressure using a rotary evaporator to give an oily residue.
14. Add a little methanol to precipitate the product, which is then removed by filtration at the pump. Recrystallize the crude reaction product from methanol to give the aminoindole (276 mg, 72%) as white needles.

The final example is slightly different from the previous protocols in two ways. First, the IMP is generated by S_N2 displacement of a benzotriazole moiety. The IMP then opens an epoxide, which generates a betaine with an extra carbon atom between phosphorus and the negatively charged oxygen. Collapse of this betaine results in the formation of an aziridine as opposed to a carbon–nitrogen double bond.

Protocol 9.
Reaction of an IMP with an epoxide to generate an aziridine[6]



Caution! All procedures should be performed in a well-ventilated hood. Wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Round bottom flasks (2 × 250 and 100 mL)
- Septum cap ×4
- Magnetic stirrer hot plate
- Magnetic stirrer bars
- Cannula
- Syringe (10 and 2 mL) and needles
- Sinter funnel ×2
- Buchner flask ×2
- Oil bath
- Water-jacketed condenser
- Tubing

Materials

- 1-Azidomethylbenzotriazole 11.8 g, 68 mmol — **unknown, treat as toxic**
- Triphenylphosphine 18.0 g, 68.6 mmol — **irritant, harmful**
- IMP 5.0 g, 12.2 mmol — **unknown, treat as toxic**
- Methylmagnesium bromide 13 mmol in tetrahydrofuran — **flammable, corrosive, reacts violently with water**
- Styrene oxide 1.47 g, 1.39 mL, 12.2 mmol — **toxic, carcinogen**
- Magnesium sulfate — **moisture sensitive**
- Dry diethyl ether — **highly flammable**
- Dry tetrahydrofuran — **irritant, flammable**

Method

1. Clean the apparatus and bake in an oven at a minimum of 120°C for 3–4 h. When required, allow the equipment to cool in a desiccator.
2. Set up the 250 and 100 mL flasks, each with a septum cap and a positive pressure of nitrogen from a balloon or line connected via a syringe needle.
3. Equip the 250 mL flask with a stirrer bar and prepare a solution of 1-azidomethylbenzotriazole (11.8 g, 68 mmol) in dry diethyl ether (100 mL).
4. In the 100 mL flask dissolve the triphenylphosphine (18.0 g, 68.6 mmol) in diethyl ether (50 mL). Add the resultant solution, via cannula, in a dropwise

manner, to the azide solution. Stir for 3 h at room temperature during which time a precipitate forms.

5. Collect the precipitate by filtration on a glass sintered funnel at the pump, wash with a little dry diethyl ether, then dry it under vacuum to give the IMP (26 g, 95%) as a white solid.
6. Set up the second 250 mL flask with a septum cap, stirrer bar and a positive pressure of nitrogen as above. Dissolve 1-(triphenylphosphorylideneaminomethyl) benzotriazole (5.0 g, 12.2 mmol) in anhydrous tetrahydrofuran (50 mL).
7. Add a commercial solution of methylmagnesium bromide (13 mmol) in tetrahydrofuran, dropwise, via syringe, over a period of 5 min. Stir at room temperature for 5 h during which time a white solid precipitates. Add styrene oxide (1.47 g, 1.39 mL, 12.2 mmol) via syringe.
8. Replace the septum cap with a reflux condenser topped with a septum cap and apply a positive pressure of nitrogen, as before. Heat the reaction mixture at reflux for 48 h in an oil bath.
9. Allow the reaction to cool, then dilute it with anhydrous diethyl ether (50 mL). Remove the precipitate by filtration on a glass sinter at the pump. Wash the solid with a little dry diethyl ether.
10. Dry the combined filtrate with anhydrous magnesium sulfate, filter off the desiccant and remove the volatiles at reduced pressure using a rotary evaporator.
11. Purify the crude reaction mixture by vacuum distillation to give the aziridine (988 mg, 55%) as a colourless oil, which distils between 55 and 57°C at a pressure of 0.6 Torr.

Protocol 10.
General procedure for a sealed tube experiment.

Firstly, it is important to note that specialist high pressure tubes are required for this technique. Under no circumstances should reaction mixtures be heated in a sealed system using normal laboratory glassware, as a serious explosion will ensue! It is necessary to use specifically designed, thick walled, high pressure tubes, which are available from most chemical glassware suppliers. A number of different designs are available but the least prone to explosion or cracking consist of a thick-walled main body topped with a Young's tap and a side-arm. Again, the method of heating can vary, with specialist ovens available, in which the glass tubes are contained within metal cases to prevent flying glass, should the tube explode. Clearly these ovens may not be available to everyone, so alternatively, a suitable heating bath (oil, sand, etc.) in a fume cupboard can be employed provided an extremely sturdy blast shield(s) is positioned to protect

Protocol 10. *Continued*

any passers by. Obviously, the experiment should be conducted in as remote a position as possible. As a result of these variations, anyone considering this technique should consult an experienced colleague and safety officer within their particular department. It cannot be stressed too much that in setting up a sealed tube experiment, one is potentially making a bomb!

Method

1. Select a tube of suitable size, such that the volume of the reaction mixture is no more than one-fifth of the volume of the tube. Check the tube for cracks and scratches, do not use tubes with such defects.
2. Wash and dry the tube in an oven at a minimum of 120°C for 3–4 h. When required, allow the tube to cool in a desiccator.
3. Prepare the reaction mixture and add it to the tube. If necessary, add a trace of a radical inhibitor, for example, hydroquinone, can be added. Close the tap and immerse the tube in a liquid nitrogen cooling bath.
4. While the solution is cooling, set up a high vacuum pump and connect it to the side-arm of the sealed tube.
5. When the solution is fully cooled (nearly all solvents are solid at this temperature) open the tap and evacuate the tube for about a minute. Close the tap and remove the tube from the cooling bath and allow it to warm to room temperature.
6. Repeat this freeze–evacuate–thaw procedure a further two times. The reaction mixture should now be completely degassed, removing any dissolved oxygen, which can cause problems at elevated temperatures.
7. With the tap closed, heat the sealed tube at the required temperature taking adequate safety precautions (see above). After the required time, allow the reaction mixture to cool to room temperature before opening the tap carefully.
8. Transfer the reaction mixture to a round bottom flask and remove the solvent at reduced pressure. Purify the crude reaction mixture in an appropriate manner.

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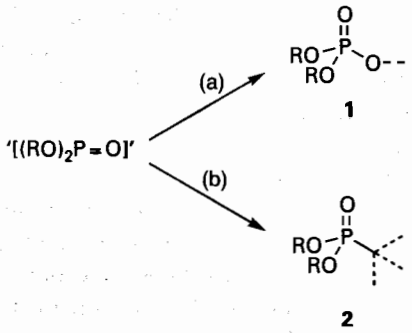
7

Phospho-transfer processes leading to [P—C] bond formation

MATTHEW D. FLETCHER

1. Introduction

A phospho-transfer process is the transfer of a phospho group, $[(RO)_2P{=}O]$ or derivative thereof, between chemical sites. When this process results in the formation of a new [P—O] bond it is called *phosphorylation*, a ubiquitous biological process, and the product is a phosphate ester, **1** (or derivative thereof) (Scheme 1). Phospho-transfer leading to [P—C] bond formation is termed *phosphonylation*, the product of which is a phosphonate, **2** (or derivative thereof) (Scheme 1).



Scheme 1 (a) Phosphorylation; (b) phosphonylation.

The patriarchs of phosphonylation are Michaelis and Arbuzov, whose work at the beginning of the 20th century culminated in the development of the Michaelis–Arbuzov reaction.[1,2] The Michaelis–Arbuzov reaction has been exploited extensively by organic chemists for the preparation of phosphonates for use in the Horner–Wadsworth–Emmons synthesis of alkenes.[3,4] Phosphonates are not only useful reagents for organic synthesis but synthetic targets in their own right, as many, especially α-amino and α-hydroxy phosphonates, are naturally occurring compounds (or mimics thereof) with interesting biological activity; they also find

industrial applications as, for example, heavy-metal extractants, flame retardants, surfactants, etc.

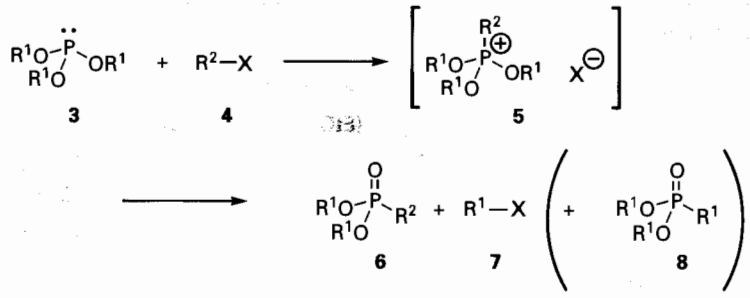
Phospho-transfer leading to [P—C] bond formation was reviewed in 1997 by Mitchell and Kee.[5] Engel surveyed methods of [P—C] bond formation in 1987, including the synthesis of phosphonates, phosphinates and phosphine oxides.[6] A review of the work of the Kazan' school of organophosphorus chemists (founded by Arbuzov) covering many of the topics discussed herein was published in 1967.[7] In 1951, Kosolapoff reviewed the synthesis of phosphonic and phosphinic acids, including phospho-transfer methods.[8] Marinetti, Savignac and co-workers reviewed synthetic routes to α-halogenated phosphonates in 1997.[9] Yudelevich *et al.* reviewed the chemistry of phosphinic acid (hypophosphorous acid, H_3PO_2) and its derivatives in 1980.[10] Extensive discussions of the chemistry of phosphonates, phosphinates and phosphine oxides may be found in the appropriate volumes of Patai's series *The Chemistry of Functional Groups*,[11,12] particularly the chapters by Edmundson.[13–15]

This chapter covers the main synthetically useful phosphonylation reactions, the corresponding processes of phosphinylation and tertiary phosphine oxide formation along with some related reactions. In all these reactions the phosphorus reactant (a phosphite, phosphonite, phosphinite, or derivative or tautomer thereof) is the nucleophilic component, herein these reactants are referred to collectively as phosphorus(III) reactants/acids, as appropriate; in general these reagents are best used freshly distilled. Syntheses of phosphonates, phosphinates and tertiary phosphine oxides by nucleophilic substitution at phosphorus is not covered (for reviews of this area see Refs 6 and 16).

2. The Michaelis–Arbuzov reaction

The Michaelis–Arbuzov reaction is also known as the Michaelis–Arbuzov–Kaehne reaction or the Michaelis–Arbuzov rearrangement and is sometimes named after Arbuzov only. For reviews of the reaction see Refs 6, 12, 17, and 18.

The Michaelis–Arbuzov reaction is the most used and well-known method for the synthesis of phosphonates and their derivatives and may also be used to synthesize phosphinates and tertiary phosphine oxides. The simplest form of the Michaelis–Arbuzov reaction is the reaction of a trialkyl phosphite, **3**, with an alkyl halide, **4**, to yield a dialkyl alkylphosphonate, **6**, and new alkyl halide, **7** (Scheme 2). During this transformation the phosphorus atom of a tervalent phosphorus(III) species (**3**) acts as a nucleophile resulting in the formation of an intermediate alkoxy phosphonium salt **5**, containing a new [P—C] bond. The precise structure of the intermediates **5** is a subject of debate—as reflected by common reference to them as 'pseudophosphonium salts'—with a pentacoordinate species (containing a [P—X] bond) being proposed and detected in some cases.[18] Decomposition (usually rapid under the reaction conditions) of the intermediate **5** by nucleophilic attack of X^- on one of the alkyl groups R^1, with concomitant formation of a [P═O] bond yields the product pentavalent phosphorus(V) compound (**6**) and the new alkyl halide, **7**.



Scheme 2 R^1 = alkyl, aryl, etc.; R^2 = alkyl, acyl, etc.; X = Cl, Br, I.

The scope of the Michaelis–Arbuzov reaction is wide, with a range of alkyl halides and trialkyl phosphites being compatible. Any alkyl halide susceptible to S_N2 attack is suitable (see Table 7.1), provided it contains no interfering functional groups [notably α-carbonyl groups (see Protocol 2 and Section 4) or nitro groups (which undergo reduction)]; thus primary alkyl halides react well, whereas secondary alkyl halides are much less reactive and usually fail, and tertiary alkyl halides are unreactive; secondary and tertiary alkyl halides frequently suffer elimination, which prevents the Michaelis–Arbuzov reaction of chiral secondary alkyl halides being useful in asymmetric synthesis. Alkyl iodides are more reactive than bromides, which are more reactive than chlorides, as one would expect. When the alkyl groups of the two reactants are identical ($R^1 = R^2$ in Scheme 2) then the Michaelis–Arbuzov reaction is an isomerization process. However, when the alkyl groups are different there is the possibility of a mixture of phosphonate products (**6** and **8**) due to reaction of the product alkyl halide **7** with unconsumed phosphite starting material **3**: Scheme 2. Formation of the undesired product **8** can be suppressed in a number of ways: by using a reactant alkyl halide **4** that is more reactive than the product alkyl halide **7** (see Protocol 1); by removing a volatile product alkyl halide **7** during the course of the reaction (see Protocols 2–4); and/or by using a large excess of the reactant alkyl halide **4**. These considerations are vital for the practical success of the Michaelis–Arbuzov reaction, so the most frequently used phosphites are trimethyl, triethyl, triisopropyl and tributyl phosphite, which yield relatively low boiling alkyl halides, trimethyl phosphite having the additional advantage that the methyl ester groups in the product may readily be converted to the free acids using chlorotrimethylsilane. Conversely, the highly reactive tribenzyl phosphite, for example, requires the use of high temperature (circa 140°C) and reduced pressure (4–20 mmHg) to remove the benzyl halide product, and a non-volatile alkyl halide reactant for successful reaction, otherwise rapid isomerization to dibenzyl benzylphosphonate dominates.[19] In addition to those mentioned above (and below), the other significant side reactions that may occur during the Michaelis–Arbuzov reaction are dehalogenation, dehydrohalogenation and the formation of cyclic phosphonates from dihaloalkanes.

Table 7.1 Representative Michaelis–Arbuzov phosphonate syntheses

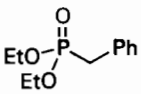
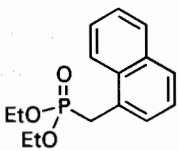
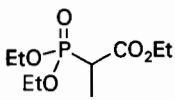
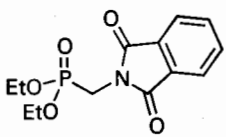
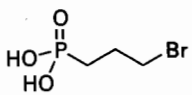
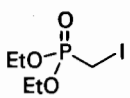
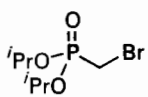
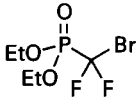
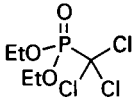
Entry	Phosphonate	Conditions	Reference
1	 Diethyl benzylphosphonate	$(EtO)_3P$, BnCl, reflux, 18 h	4
2	 Diethyl 1-naphthylmethylphosphonate	$(EtO)_3P$, 1-chloromethylnaphthalene, 150–160°C, 4 h, 90%	8
3	 Triethyl 2-phosphonopropionate	$(EtO)_3P$, ethyl 2-bromopropionate, reflux, 1 h, 59%	25, 30
4	 Diethyl phthalimidomethylphosphonate	$(EtO)_3P$, *N*-bromomethylphthalimide, 85–100°C, 4 h, 80–90%	31
5	 3-Bromopropylphosphonic acid	1) $(EtO)_3P$, 1,3-dibromopropane (5 equiv.), 150°C, 1.5 h; 2) HBr, H_2O, 80–90%	8
6	 Diethyl iodomethylphosphonate	$(EtO)_3P$, CH_2I_2, 185–220°C, 90%	9, 32, 33
7	 Diisopropyl bromomethylphosphonate	$(^iPrO)_3P$, CH_2Br_2, 145–150°C, 47 h, 48%	9, 34

Table 7.1 *Continued*

Entry	Phosphonate	Conditions	Reference
8	 Diethyl bromodifluoromethylphosphonate	$(EtO)_3P$, CF_2Br_2, 60°C, 1.5 h, 96%	9, 35
9	 Diethyl trichloromethylphosphonate	$(EtO)_3P$, CCl_4, reflux, overnight, 94%	9, 33, 36

The Michaelis–Arbuzov reaction is generally performed without solvent (as one or other, or both, of the reactants is usually a liquid), and the product phosphonate purified by distillation; if a solvent is required THF, acetonitrile, benzene or toluene are suitable. Lawrence has collected details of the syntheses and Horner–Wadsworth–Emmons reactions of some common Michaelis–Arbuzov products **6**;[4] many such phosphonates are commercially available.

Protocol 1.
Synthesis of diisopropyl methylphosphonate, 10 (Scheme 3)[20]

9 **10**

Scheme 3

This protocol is representative of the Michaelis–Arbuzov reaction in its simplest form, on a large scale. Protocol 1 may be used with minor modification to synthesize other simple dialkyl alkylphosphonates.[20] The combination of triisopropyl phosphite **9** and a primary alkyl halide (methyl iodide) means that the formation of the potential by-product diisopropyl isopropylphosphonate is negligible because the product alkyl halide (isopropyl iodide) is a secondary alkyl halide and thus reacts much more slowly with triisopropyl phosphite **9** than does the desired reactant methyl iodide.

Protocol 1. *Continued*

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Two-necked round-bottomed flask (2 L)
- Thermostat controlled hot-plate stirrer
- Oil bath
- Lab-jack
- Addition funnel (500 mL)
- Teflon-coated magnetic stirrer bar
- Water condenser
- Vigreux column (50–75 cm)
- Still head
- Thermometer
- Receiver
- One-necked round-bottomed flasks (500 mL)
- Pear-shaped flask (1 L)
- Fractional distillation receiver
- Water pump
- Vacuum pump
- Dry ice trap

Materials

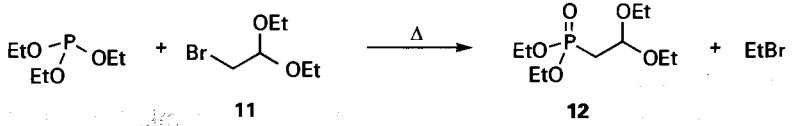
- Methyl iodide, 113 mL, 284 g, 2 mol — **harmful, toxic, irritant**
- Triisopropyl phosphite **9**, 453 mL, 416 g, 2 mol — **toxic, irritant**

Method

1. To a two-necked round-bottomed flask (2 L) equipped with a magnetic stirrer bar and fitted with an efficient water condenser and an addition funnel (500 mL), add methyl iodide (113 mL, 284 g, 2 mol).
2. Charge the addition funnel with triisopropyl phosphite **9** (453 mL, 416 g, 2 mol). Set the round-bottomed flask in the oil bath on the hot-plate stirrer, which is supported by the lab-jack.
3. Add approximately 50 mL of the triisopropyl phosphite **9** to the stirred methyl iodide and heat the mixture until an exothermic reaction begins. **Caution!** exothermic reaction!
4. Remove the heat source (best achieved by lowering the lab-jack), while continuing stirring. Add the remainder of the triisopropyl phosphite **9** at such a rate as to keep the reaction mixture boiling briskly. Towards the end of the addition it may be necessary to reapply heat (raise the lab-jack or use a heat gun).
5. After the addition is complete heat the reaction mixture under reflux for 1 h.
6. Cool the reaction mixture and replace the condenser with a Vigreux column (50–75 cm) and distillation set-up. Distil off the bulk of the isopropyl iodide (b.p. 85–95°C) at atmospheric pressure.
7. Transfer the residue to a pear-shaped flask (1 L), attach a Vigreux column (50–70 cm) and fractional distillation set up, with a dry ice trap between the receiver and the water pump. Distil off the remainder of the isopropyl iodide at water pump pressure. A total of 310 g (90%) of isopropyl iodide may be recovered.

8. Distil the residue at vacuum-pump pressure and, after a small fore-run, collect pure diisopropyl methylphosphonate, **10** (b.p. 51°C, 1.0 mmHg, 308–325 g, 85–90%), as a colourless liquid.

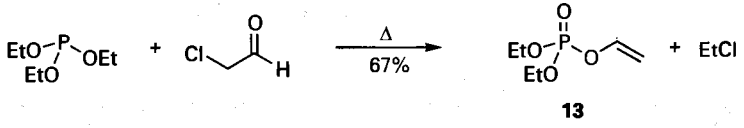
Protocol 2.
Synthesis of diethyl 2,2-diethoxyethylphosphonate, 12 (Scheme 4)[21,22]



11 **12**

Scheme 4

Protocol 2 produces the protected β-formylphosphonate **12**; β-ketophosphonates may also be synthesized by other methods,[23] however, they may not be prepared in unprotected form by the Michaelis–Arbuzov reaction because the Perkow reaction, in which an α-haloaldehyde or ketone and a trialkyl phosphite yield an enol phosphate (e.g. **13**, Scheme 5,[24] i.e. [P—O] bond formation), competes and frequently dominates (see Section 4). Conversely halocarboxylic acid derivatives (e.g. see Table 7.1, entry 3) and acyl halides (see Protocol 3) react well in the Michaelis–Arbuzov reaction to yield useful functionalized phosphonates. β-Ketophosphonates are useful reagents for the synthesis of α,β-unsaturated carbonyl compounds by the Horner–Wadsworth–Emmons reaction,[3,4,25] and have other applications.[23]



13

Scheme 5

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Three-necked round-bottomed flask (2 L)
- Teflon-coated magnetic stirrer bar
- Nitrogen inlet
- Addition funnel (500 mL)
- Still head
- Water condenser
- Receiver
- Ice bath
- Thermostat controlled hot-plate stirrer
- Oil bath
- Thermometer
- One-necked round-bottomed flasks (250 **and** 500 mL)
- Fractional distillation receiver
- Water pump
- Vacuum pump

Protocol 2. *Continued*

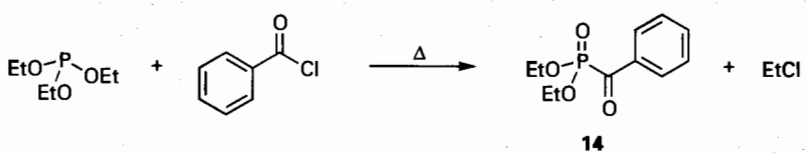
Materials

- Bromoacetaldehyde diethyl acetal **11**, 313 mL, 410 g, 2.08 mol — **flammable**
- Triethyl phosphite, 326 mL, 316 g, 1.90 mol — **flammable, harmful, irritant**

Method

1. Add bromoacetaldehyde diethyl acetal **11** (313 mL, **410 g, 2.08** mol) to a three-necked round-bottomed flask (2 L) equipped with a magnetic stirrer bar and fitted with a nitrogen inlet, an addition funnel (500 mL) and a still head, condenser and receiver (cooled in an ice bath). Maintain the flask under a gentle stream of nitrogen.
2. Charge the addition funnel with triethyl phosphite (326 mL, 316 g, 1.90 mol) and add it dropwise over 30 min to the stirred reaction mixture heated to 110–120°C.
3. After the addition is complete, heat the reaction mixture for a further 3 h at 160°C, during which time ethyl bromide (b.p. 37–40°C) is collected in the receiver. **Caution!** ethyl bromide is highly flammable, harmful and a suspected carcinogen.
4. Distil off the remaining low boiling material (<100°C) at water pump pressure.
5. Fractionally distil the residue at vacuum-pump pressure collecting pure diethyl 2,2-diethoxyethylphosphonate, **12** (b.p. 101–103°C, 0.8 mmHg, 338 g, 70%), as a colourless liquid.

Protocol 3.
Synthesis of diethyl benzoylphosphonate, 14 (Scheme 6)[8,26]

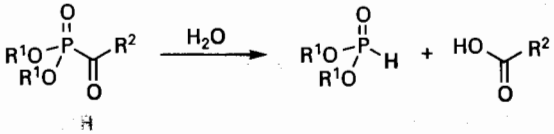


14

Scheme 6

α-Ketophosphonates (also known as acylphosphonates) have physical, chemical and biological properties unique among the phosphonates, due to the proximity of the two functional groups, and they are the subject of dedicated reviews.[23,27,28] Protocol 3 describes the Michaelis–Arbuzov synthesis of the α-ketophosphonate **14**. Acid anhydrides also undergo the reaction but other reactions interfere, preventing this from being a generally useful method for the synthesis of acylphosphonates. During the Michaelis–Arbuzov synthesis of

an α-ketophosphonate, the presence of traces of water in the reaction mixture reveals one of the unusual chemical properties of these phosphonates, that is, the propensity of the dialkylphosphonate group to act as a leaving group: hydrolysis is a common problem in the process (Scheme 7) and can lead to further reactions. Other complications can also arise during the Michaelis–Arbuzov synthesis of α-ketophosphonates, for example, additional reactions of the products.[27,28]



Scheme 7

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Two-necked round-bottomed flask (100 mL)
- Thermostat controlled hot-plate stirrer
- Oil bath
- Addition funnel (25 mL)
- Teflon-coated magnetic stirrer bar
- Water condenser
- Calcium chloride guard tube
- Still head
- Thermometer
- Receiver
- One-necked round-bottomed flasks (2 × 50 mL)
- Fractional distillation receiver
- Vacuum pump

Materials

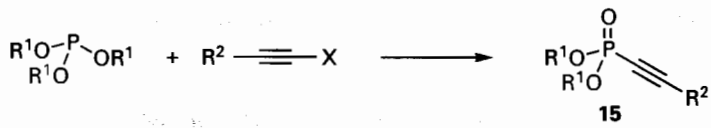
- Benzoyl chloride, 11.3 mL, 13.7 g, 97 mmol — **causes burns**
- Triethyl phosphite, 16.9 mL, 16.2 g, 97 mmol — **flammable, harmful, irritant**

Method

1. Add benzoyl chloride (11.3 mL, 13.7 g, 97 mmol) to a two-necked round-bottomed flask (100 mL) equipped with a magnetic stirrer bar, fitted with an efficient water condenser and an addition funnel (25 mL) and protected by a calcium chloride guard tube.
2. Charge the addition funnel with triethyl phosphite (16.9 mL, 16.2 g, 97 mmol) and add it over 30 min to the stirred benzoyl chloride at room temperature. During the addition the reaction mixture turns yellow-green in colour and evolves ethyl chloride. **Caution!** ethyl chloride (b.p. 12°C) is highly flammable and a suspected carcinogen.
3. Heat the reaction mixture to 100°C for 45 min.
4. Cool the reaction mixture and replace the condenser with a fractional distillation set up. Distil the product at vacuum-pump pressure, discarding any low boiling fore-run, and collect pure diethyl benzoylphosphonate, **14** (b.p. 141°C, 2.5 mmHg, 15.7 g, 67 %), as a yellowish liquid.

Many other organic halides undergo the Michaelis–Arbuzov reaction: Table 7.1 lists the Michaelis–Arbuzov syntheses of other phosphonates that are described in detail in the references given and for which the procedures differ little from Protocols 1–3.

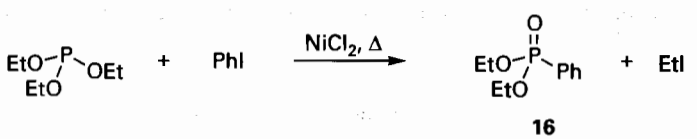
Allyl and propargyl halides participate in the Michaelis–Arbuzov reaction, though isomerization is sometimes observed. The Michaelis–Arbuzov reaction of alkynyl halides (**15**, Scheme 8) is synthetically useful when the alkyne is suitably substituted (e.g. Scheme 8, R^2 = aryl, substituted ethenyl, Me_3Si, Et_3Sn, Cl, X = Cl, Br) and the area has been reviewed.[37]



Scheme 8

Vinylphosphonates are useful reagents but simple vinyl halides do not undergo the Michaelis–Arbuzov reaction except in the presence of a transition metal catalyst [Ni(II) or Cu(I), cf. Protocol 4] so vinylphosphonates are usually synthesized from other functionalized phosphonates or by the palladium-catalysed Michaelis–Becker reaction (cf. Protocol 8).[38] Similarly, simple aryl halides undergo the Michaelis–Arbuzov reaction only under special conditions: palladium or nickel species (Protocol 4) are suitable catalysts. Indeed these and other catalysts have been applied to the Michaelis–Arbuzov reaction of various substrates, though they are generally essential only with vinyl and aryl halides, as described herein.[39]

Protocol 4.
Synthesis of diethyl phenylphosphonate, 16 (Scheme 9)



Scheme 9

This protocol is essentially Tavs' method[40] as reinvestigated by Balthazor and Grabiak.[41] Anhydrous nickel(II) chloride or bromide (5 mol%) may be used as the precatalyst and is reduced by triethyl phosphite to tetrakis(triethyl phosphite)nickel(0) (which may be prepared separately and used as the catalyst in the Michaelis–Arbuzov step).[41] The mechanism of the reaction has been

studied in detail and is summarized by Edmundson.[13,42] A slight excess of triethyl phosphite is used to compensate for diethyl ethylphosphonate formation. Phenyl bromides and chlorides and thienyl halides also undergo the reaction. This method accommodates a range of *meta* and *para* substituents on the phenyl ring but ortho substituents are more problematic and only give good yields when a directing process is possible (i.e. with *N*-secondary acylamido substituents).[40,43] Tavs and Weitkamp also developed a similar method for the synthesis of vinylphosphonates.[44]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Three-necked round-bottomed flask (50 mL)
- Thermostat controlled hot-plate stirrer
- Oil bath
- Teflon-coated magnetic stirrer bar
- Nitrogen inlet
- Addition funnel (25 mL)
- Still head
- Water condenser
- Receiver
- Ice bath
- Lab-jack
- One-necked round-bottomed flasks (3 × 25 mL)
- Fractional distillation receiver
- Thermometer
- Vacuum pump

Materials

- Iodobenzene, 5.5 mL, 10 g, 49 mmol, b.p.188°C — **harmful, irritant**
- Triethyl phosphite, 8.8 mL, 9.4 g, 57 mmol, b.p. 155°C — **flammable, harmful, irritant, penetrating odour**
- Anhydrous nickel(II) chloride, 318 mg, 2.5 mmol — **toxic, sensitizer, suspect carcinogen**

Method

1. Add iodobenzene (5.5 mL, 10 g, 49 mmol) and anhydrous nickel(II) chloride (318 mg, 2.5 mmol) to a three-necked round-bottomed flask (50 mL) equipped with a magnetic stirrer bar and fitted with a nitrogen inlet, an addition funnel (25 mL) and a still head, condenser and receiver (cooled in an ice bath). Maintain the flask under a gentle stream of nitrogen. Heat the mixture to 160°C using the oil bath on the hotplate stirrer supported by the lab-jack.
2. Charge the addition funnel with triethyl phosphite (8.8 mL, 9.4 g, 57 mmol) and add it in small portions to the stirred light yellow heterogeneous mixture of nickel(II) chloride and iodobenzene at 160°C. Upon the addition the mixture darkens in colour. After an induction period of about 1 min an exothermic reaction begins and ethyl iodide is evolved and collected in the receiver and the reaction mixture fades to light yellow. **Caution!** exothermic reaction! **Caution!** ethyl iodide (b.p. 72°C) is flammable, toxic, an irritant and a sensitizer.
3. Add the remaining triethyl phosphite gradually (over 10–30 min) to the reaction mixture at 160°C using the rate of addition to control the exotherm, lowering the oil bath on the lab-jack if necessary.

Protocol 4. *Continued*

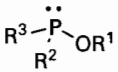
4. On completion of the triethyl phosphite addition and cessation of ethyl iodide evolution (less than 30 min after completion of the addition, up to 3.8 mL, 7.6 g, 99% is evolved, along with some triethyl phosphite) cool the reaction mixture and set up for fractional distillation. Distil the product at vacuum-pump pressure, discarding any low boiling fore-run, and collect pure diethyl phenylphosphonate, **16** (b.p. 94–101°C, 0.1 mmHg, 9.45 g, 90 %), as a liquid.

The Michaelis–Arbuzov reaction may be photoinitiated with appropriate substrates such as tetrahalomethanes and aryl iodides; suitable phosphites undergo photo-Arbuzov rearrangement (see below).

Substrates susceptible to S_N1 attack and those bearing leaving groups other than halides have also been employed in the Michaelis–Arbuzov reaction, for example, dialkyl sulfates, alkyl mesylates, alkyl tosylates, quaternary ammonium species, activated acetates; as have other electrophiles, for example, alkyl fluoroborates, lactones, lactams, aziridines, sulfones, iminium cations, and *ortho*-quinonoids.[6,13–15,18]

In all the examples of the Michaelis–Arbuzov reaction discussed thus far the phosphite reactant is a simple symmetrical trialkyl phosphite (**3**). Triaryl phosphites only undergo the reaction under special conditions (e.g. nickel catalysis) the problem being dealkylation. Other variations in the phosphorus(III) reactant are highly practicable: for the general phosphorus(III) reactant **17**, the minimum requirement for the Michaelis–Arbuzov reaction to proceed is that R^1 is aliphatic (or *O*-silyl, see Protocol 5) with reactivity decreasing from primary to secondary to tertiary alkyl. Phosphonates result when both R^2 and R^3 are alkoxy or aryloxy groups; when only one of R^2 and R^3 is an alkoxy or aryloxy group and the other an alkyl or aryl group (i.e. the reactant **17** is a phosphonite) the product is a phosphinate, and when R^2 and R^3 are both alkyl or aryl groups (i.e. the reactant **17** is a phosphinite), the product of the reaction is a tertiary phosphine oxide; these latter two scenarios are less frequently employed but nevertheless synthetically important and the procedures used are very similar to Protocols 1–5 but with milder conditions reflecting the increased reactivity of the phosphorus(III) reactants across the sequence phosphite < phosphonite < phosphinite. As discussed above the reaction requires nucleophilic attack by phosphorus so it is promoted by electron-donating groups R^2 and R^3, thus it proceeds more readily across the following sequence: R^2/R^3 = aryloxy < alkoxy < aryl < alkyl < dialkylamino. Many examples wherein R^1, R^2, and/or R^3 are part of a ring system are known. Strongly electron withdrawing groups, when present in R^1, R^2, and/or R^3, prevent the phosphorus(III) reactant from participating in the Michaelis–Arbuzov reaction. However, although weakly nucleophilic, dialkyl phosphorofluoridites, -chloridites and -cyanidites (**17**, R^1 = alkyl, R^2 = alkoxy, R^3 = F, Cl or CN), alkyl alkylphosphonofluoridites and -chloridites (**17**, R^1 = alkyl, R^2 = alkyl,

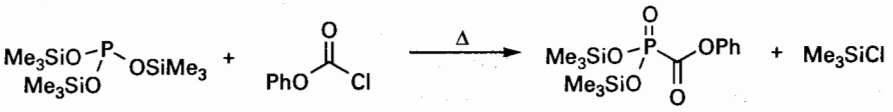
R^3 = F or Cl) and alkyl phosphorodifluoridites, -dichloridites and -dicyanidites (**17**, R^1 = alkyl, R^2 = R^3 = F, Cl or CN) will undergo the Michaelis–Arbuzov reaction; this area has been reviewed.[45]



17

When using mixed phosphites, some useful regioselectivity is possible in the dealkylation step, thus benzyl is lost in preference to alkyl groups, for example, from dibenzyl methyl phosphite,[19] and silyl in preference to alkyl groups (see below).

Protocol 5.
Synthesis of bis(trimethylsilyl) phenyloxycarbonylphosphonate, 19 (Scheme 10)[46]



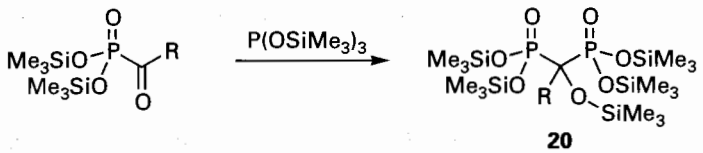
18 **19**

Scheme 10

Silyl phosphorus(III) esters[47] are more nucleophilic than simple phosphorus(III) esters and those used most commonly in the Michaelis–Arbuzov reaction are tris(trimethylsilyl) phosphite **18** to yield bis(trimethylsilyl) phosphonates (e.g. **19**), diethyl trimethylsilyl phosphite to yield diethyl phosphonates (i.e. desilylation always occurs rather than dealkylation) and bis(trimethylsilyl)phosphonite (**64**, cf. Protocol 17) to yield alkylphosphinic acids.[48] Silyl alkylphosphonites and silyl dialkylphosphinites are also useful,[47] particularly bis(trimethylsilyl) trimethylsiloxymethylphosphonite (**17**, R^1 = TMS, R^2 = OTMS, R^3 = CH_2OTMS) which yields synthetically useful α-functionalized phosphinates.[49] Chloride is the leaving group of choice when using such reagents in the Michaelis–Arbuzov reaction.

This protocol was used by Iyer and co-workers in their synthesis of potential antiviral prodrugs,[46] and is derived from the method of Sekine and Hata.[50] It is important not to use excess tris(trimethylsilyl) phosphite (**18**) in such reactions to avoid formation of carbonyl adducts (**20**: Scheme 11). Removal of the trimethylsilyl groups is facile (e.g. methanolysis yields the free phosphonic acids) and may be undertaken on the crude product.

Protocol 5. *Continued*



20

Scheme 11

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Two-necked round-bottomed flask (25 mL)
- Thermostat controlled hot-plate stirrer
- Ice bath
- Oil bath
- Teflon-coated magnetic stirrer bar
- Water condenser
- Argon inlet
- Still head
- Thermometer
- One-necked round-bottomed flasks (2 × 25 mL)
- Fractional distillation receiver
- Vacuum pump

Materials

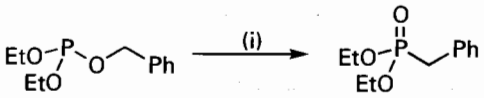
- Phenyl chloroformate, 1.48 mL, 1.84 g, 11.8 mmol — **toxic, causes burns**
- Tris(trimethylsilyl) phosphite **18**, 3.9 mL, 3.5 g, 11.7 mmol — **irritant**

Method

1. Add tris(trimethylsilyl) phosphite **18** (3.9 mL, 3.5 g, 11.7 mmol) to a two-necked round-bottomed flask (25 mL) equipped with a magnetic stirrer bar and fitted with an argon inlet, efficient water condenser and a septum under an argon atmosphere. Cool the flask in an ice bath.
2. Add phenyl chloroformate (1.48 mL, 1.84 g, **11**.8 mmol) over 15 min via a syringe to the cooled, stirred tris(trimethylsilyl) phosphite **18**. On completion of the addition, stir the reaction mixture at room temperature for 12 h and then at 60–80°C for 3 h.
3. Cool the reaction mixture and replace the condenser with a fractional distillation set up. Distil the product at vacuum-pump pressure, discarding any low boiling fore-run, and collect pure diethyl bis(trimethylsilyl) phenyloxycarbonylphosphonate, **19** (b.p. 145–155°C, 0.45 mmHg, 3.22 g, 78 %), as a colourless, viscous liquid.

The stereochemical outcome of the Michaelis–Arbuzov reaction of chiral phosphorus(III) reactants with a chiral phosphorus centre is retention, and such reactions have been employed in asymmetric synthesis.[51]

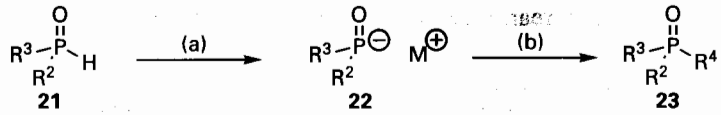
The photo-Arbuzov rearrangement of allylic[52] and benzylic[53] phosphites has been developed by Bentrude and co-workers, see, for example, Scheme 12. These reactions are completely regioselective for the benzyl and allyl groups and have been employed in synthesis (the requisite phosphites being obtained by standard methods).[54]



Scheme 12 (i) *hν*, benzene, 85–95%.

3. The Michaelis–Becker reaction

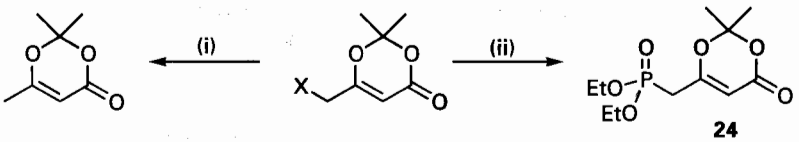
When $R^1 =$ H in the general phosphorus(III) reactant **17**, the tautomeric form **21** dominates. Nevertheless these reagents are usually referred to as dialkyl phosphites, or occasionally hydrogen phosphonates, ($R^2/R^3 =$ alkoxy or aryloxy) and alkyl monoalkylphosphinites, or occasionally hydrogen phosphinates, ($R^2 =$ alkyl or aryl and $R^3 =$ alkoxy or aryloxy). Such species react with alkyl halides to yield phosphonates and phosphinates respectively, or tertiary phosphine oxides ($R^2/R^3 =$ alkyl or aryl), **23**, after initial deprotonation; this reaction is called the Michaelis–Becker(–Nylen) reaction[55] [or occasionally, the Michaelis–Becker(–Nylen) modification of the Michaelis–Arbuzov reaction]: Scheme 13. The identification of optimum conditions for the reaction is troublesome. A suitable aprotic solvent is required, but the metal salts of the phosphorus(III) acids **22** suffer from low solubility therein. The sodium salts generally give the best results and may be formed using the classical deprotonation conditions using sodium metal, but anion formation is then generally slow, so sodium hydride (ethoxide or amide) in THF, dioxane or an aromatic solvent (e.g. toluene or xylene) is superior; alternatively the lithium salts may be formed with *n*-butyllithium. When the nature of the alkyl esters in the target is not a concern, then di-*n*-butyl phosphite may be used, as its sodium salt is more soluble than those of simpler dialkyl phosphites. Furthermore, it may be used as the solvent. The strong heating required for the Michaelis–Arbuzov reaction is not usually necessary for Michaelis–Becker reaction and so the associated side reactions are avoided; however other side reactions do arise due to the basicity of the salt and its ambident nucleophilicity (e.g. *O*-alkylation to yield the phosphite triester occasionally occurs). Disproportionation of dimethyl phosphite (**29**) to dimethyl methylphosphonate and monomethyl phosphonate anion occurs when it is treated with sodium hydride in THF or benzene at room temperature—conditions thus to be avoided—this reaction is less significant with diethyl phosphite (**25**) and negligible using **butyl**-lithium as base or with sodium hydride at −78°C.[56]



Scheme 13 (a) Base; (b) R^4X; see text.

The range of suitable participants in the Michaelis–Becker reaction is essentially the same as for the Michaelis–Arbuzov reaction. Halo-aldehyde and -ketone substrates suffer the competing reaction of direct attack at the carbonyl group leading to Perkow reaction products (with α-halocarbonyl compounds) or Pudovik reaction products, which often cyclize (cf. Sections 4 and 6).

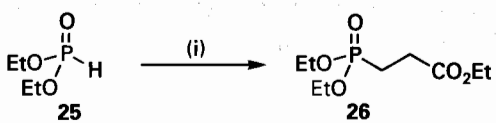
The Michaelis–Becker reaction is generally lower yielding than the corresponding Michaelis–Arbuzov reaction, however, it is frequently successful when the Michaelis–Arbuzov reaction fails, for example, the Michaelis–Becker synthesis of the useful reagent **24** is successful, whereas the Michaelis–Arbuzov approach resulted in dehalogenation (Scheme 14).[57,58]



Scheme 14 (i) X = Br, $(EtO)_3P$, Δ; (ii) X = Cl, $(EtO)_2(O)PH$, NaH, Et_2O, DMF, r.t., 88%; or $(EtO)_2(O)PH$, KO^tBu, DMF, THF, 50%.

For reviews of the Michaelis–Becker reaction, see Refs 6, 13, 14, and 59; the latter is one of a series of five reviews by Troev on the structure and reactions of dialkyl phosphites.[59–63]

Protocol 6.
Synthesis of triethyl 3-phosphonopropionate, 26 (Scheme 15)[8,64]



Scheme 15 (i) (a) NaOEt; (b) $Br(CH_2)_2CO_2Et$.

This protocol is representative of the Michaelis–Becker reaction in its simplest form, using sodium ethoxide as the base. It gives triethyl 3-phosphonopropionate **26** in better yield than the corresponding Michaelis–Arbuzov reaction (circa 60%), which suffers side reactions (substrates with β-electron withdrawing groups are susceptible to dehydrohalogenation during the Michaelis–Arbuzov reaction).[65]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Three-necked round-bottomed flask (2 L)
- Efficient magnetic stirrer
- Calcium chloride guard tube
- Addition funnel (250 mL)
- Teflon-coated magnetic stirrer bar
- Water condenser
- Ice–salt bath
- Steam bath
- One-necked round-bottomed flask (2 L)
- Filter funnel
- Vacuum pump
- Oil bath
- Still head
- Thermometer
- One-necked round-bottomed flasks (250 mL)
- Fractional distillation receiver

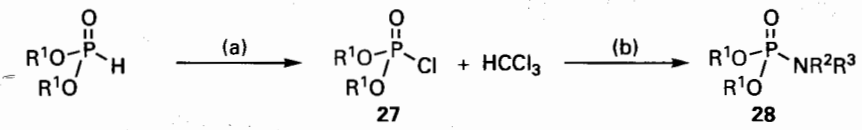
Materials

- Sodium ethoxide, 68 g, 1 mol — **highly flammable, causes burns**
- Anhydrous xylene, 500 mL — **flammable, harmful, irritant**
- Diethyl phosphite (diethyl phosphonate) **25**, 129 mL, 138 g, 1 mol — **irritant**
- Ethyl 3-bromopropionate, 128 mL, 181 g, 1 mol — **irritant**

Method

1. To a three-necked round-bottomed flask (2 L) equipped with a magnetic stirrer bar, fitted with an efficient water condenser and an addition funnel (250 mL) and protected by a calcium chloride guard tube, add sodium ethoxide (68 g, 1 mol) and anhydrous xylene (500 mL).
2. Slowly add diethyl phosphite **25** (129 mL, 1 mol) with stirring.
3. When the mixture has reacted completely, set the round-bottomed flask in the ice–salt bath. Charge the addition funnel with ethyl 3-bromopropionate (128 mL, 181 g, 1 mol) and add it dropwise to the reaction mixture with rapid stirring.
4. After the addition is complete, stir the reaction mixture overnight while allowing it to warm to room temperature.
5. Heat the reaction mixture on a steam bath for 2 h.
6. Cool and filter off the precipitate of sodium bromide.
7. Concentrate the filtrate by rotary evaporation, distil the residue at vacuum-pump pressure and, after xylene, collect pure triethyl 3-phosphonopropionate, **26** (b.p. 141–143°C, 9 mmHg, 193 g, 78%), as a colourless liquid.

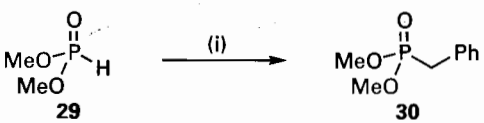
Tertiary amines may be used as the base in the Michaelis–Becker reaction with highly reactive substrates. This approach has the advantage of overcoming the common problem of the low solubility of the metal dialkylphosphonate salts **22**. However, amines are used as the base in the Atherton–Todd syntheses of phosphorochloridates **27** and phosphoramidates **28** (Scheme 16),[66] pathways which may thus compete with the Michaelis–Becker reaction of highly chlorinated substrates under such conditions; the precise mechanism of the Atherton–Todd reaction is a subject of debate.[61]



Scheme 16 (a) $NR^2R^3R^4$, CCl_4; (b) $R^4 = H$.

Biphasic conditions also circumvent the salt solubility problem but classic phase transfer conditions using aqueous sodium hydroxide suffer from competing hydrolysis of the phosphorus(III) esters. However, Kem and co-workers found that butyl esters (their substrate was dibutyl phosphonate) are sufficiently stable to provide Michaelis–Becker products in high yields; dialkylphosphine oxides were also suitable substrates.[67] Salvatore and co-workers have recently developed an efficient biphasic solid–liquid procedure utilising the cesium cation effect: Protocol 7.

Protocol 7.
Synthesis of dimethyl benzylphosphonate, 30 (Scheme 17)[68]



Scheme 17 (i) (a) Cs_2CO_3, Bu_4NI, DMF; (b) BnCl.

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Two-necked round-bottomed flask (100 mL)
- Efficient magnetic stirrer
- Nitrogen inlet
- Addition funnel (5 mL)
- Teflon-coated magnetic stirrer bar
- Conical flasks (2 × 250 mL)
- Filter funnel
- Vacuum pump
- One-necked round-bottomed flask (250 mL)
- Flash chromatography column and fractions

Materials

- Anhydrous dimethylformamide (DMF), 23 mL — **flammable, harmful, irritant**
- Dimethyl phosphite (dimethyl phosphonate) **29**, 0.42 mL, 0.50 g, 4.54 mmol — **irritant**
- Caesium carbonate, 4.44 g, 13.6 mmol
- Tetrabutylammonium iodide, 5.03 g, 13.6 mmol — **harmful, irritant**
- Benzyl chloride, 1.73 g, 1.6 mL, 13.6 mmol — **may cause cancer, harmful, toxic, irritant**

Method

1. To a solution of dimethyl phosphite **29** (0.42 mL, 0.50 g, 4.54 mmol) in anhydrous DMF (23 mL) in a two-necked round-bottomed flask (100 mL) equipped with a magnetic stirrer bar, fitted with an addition funnel (5 mL) and a nitrogen inlet, add cesium carbonate (4.44 g, 13.6 mmol) and tetrabutylammonium iodide (5.03 g, 13.6 mmol) while stirring vigorously at room temperature. Continue to stir the reaction mixture vigorously at room temperature for 1 h.
2. Charge the addition funnel with benzyl chloride (1.6 mL, 1.73 g, 13.6 mmol), add it to the reaction mixture and stir for an additional 24 h.
3. Pour the resultant milky white suspension into water (30 mL) and extract with ethyl acetate (3 × 30 mL). Wash the combined organic extracts with water (2 × 30 mL), then brine (30 mL), dry over anhydrous sodium sulfate, filter, and concentrate the filtrate *in vacuo*.
4. Purify the residue by flash chromatography on silica, eluting with hexanes : ethyl acetate (**9** : **1**) to yield dimethyl benzylphosphonate, **30** (0.88 g, 97%), as a clear yellow oil.

The palladium-catalysed cross-coupling of aryl halides or vinyl halides with dialkyl phosphonates (**31**) to yield dialkyl arylphosphonates and dialkyl vinylphosphonates, respectively, was first reported by Hirao and co-workers;[69] the halides used most frequently are bromides and the reaction is stereospecific with haloalkenes. Subsequently, analogous reactions of alkyl alkylphosphinates (**32**), alkyl arylphosphinates (**32**), alkyl phosphinates (**33**), and secondary phosphine oxides (**34**), replacing [P—H] bonds with [P—C] bonds to yield various phosphinates and tertiary phosphine oxides, have been developed (Figure 7.1). Alkyl phosphinates (**33**) may be mono- or diarylated as desired by the selection of appropriate conditions. Aryl and vinyl triflates have also found limited

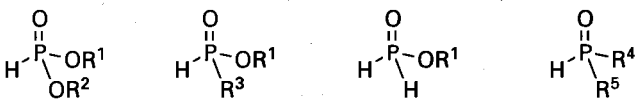
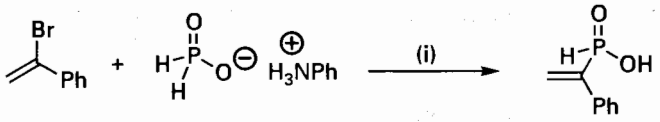


Fig. 7.1 Suitable phosphorus nucleophiles for palladium-catalysed phospho-transfer with [P—C] bond formation. R^1/R^2 = H, alkyl; R^3 = alkyl, aryl; R^4/R^5 = alkyl, aryl.

application in these reactions. Substrates with a chiral phosphorus centre retain their stereochemistry. Triethylamine is the usual base employed in these reactions but it has been replaced by *N*-methylmorpholine, propylene oxide or potassium carbonate. Given the rarity of the corresponding classical Michaelis–Arbuzov and Michaelis–Becker syntheses of such products (i.e. containing [P—C] bonds to aryl or vinyl groups) this constitutes a valuable approach and has been reviewed recently.[39,70]

Protocol 8.
Synthesis of (1-phenylvinyl)phosphinic acid, 36 (Scheme 18)[71]



35 36

Scheme 18 (i) NEt_3, $Pd(OAc)_2$, dppp, benzene, reflux.

Montchamp and co-workers have developed palladium-catalysed cross-coupling reactions of anilinium phosphinate (anilinium hypophosphite) **35** with aryl and benzyl halides and triflates[72] and vinyl haldes and triflates,[71] to yield monosubstituted phosphinic acids (e.g. **36**). They found that using the crystalline, non-hygroscopic anilinium salt **35** circumvents the problems associated with hazardous anhydrous phosphinic acid. The reaction is not especially air sensitive and though the use of anhydrous solvent is preferable it is not essential. The solvent of choice is acetonitrile or DMF for aryl substrates and benzene or tetrahydrofuran (THF) for vinyl substrates. The optimum catalyst is palladium(II) acetate/1,3-bis(diphenylphosphino)propane (dppp) [or 1,1′-bis(diphenylphosphino)ferrocene (dppf) for hindered *Z*-vinyl substrates]. Under these conditions, disubstitution is not significant and transfer hydrogenation (with the phosphinate acting as a reductant) is only competitive with easily reduced substrates. *ortho*-Substitution of aryl substrates impedes the reaction. 1,4-Addition to vinylphosphinate products (e.g. **36**) is suppressed by employing short reaction times and an excess of anilinium phosphinate **35**. This procedure provides (1-phenylvinyl)phosphinic acid, **36**, in 98% yield as determined by ^{31}P NMR spectroscopy of the crude reaction mixture and in 67% yield after aqueous work-up: isolation of these highly water soluble vinylphosphinic acids is unoptimized.

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Two-necked round-bottomed flask (25 mL)
- Hot-plate stirrer
- Nitrogen inlet
- Teflon-coated magnetic stirrer bar
- Condenser
- Conical flasks (3 × 100 mL)
- Separating funnel
- Filter funnel
- Vacuum pump
- One-necked round-bottomed flask (100 mL)

Materials

- α-Bromostyrene, 0.26 mL, 0.366 g, 2 mmol **irritant**
- Anilinium phosphinate **35**,[72] 0.382 g, 2.4 mmol
- Anhydrous triethylamine, 0.84 mL, 0.61 g, 6.0 mmol **highly flammable, harmful, causes burns**
- Palladium(II) acetate, 9.0 mg, 0.04 mmol
- 1,3-Bis(diphenylphosphino)propane (dppp), 19.8 mg, 0.048 mmol **irritant**
- Benzene, 10 mL **highly flammable, toxic, carcinogen**

Method

1. Charge a two-necked round-bottomed flask (25 mL) equipped with a magnetic stirrer bar and fitted with a condenser and nitrogen inlet, with α-bromostyrene (0.26 mL, 0.366 g, 2 mmol), anilinium phosphinate **35**[72] (0.382 g, 2.4 mmol), anhydrous triethylamine (0.84 mL, 0.61 g, 6.0 mmol), palladium(II) acetate (9.0 mg, 0.04 mmol), dppp (19.8 mg, 0.048 mmol), and benzene (10 mL).
2. Stir the reaction mixture and heat under reflux for 19 h.
3. Cool the reaction mixture and concentrate *in vacuo*.
4. Add water (20 mL) to the residue and wash with diethyl ether (20 mL). Acidify the aqueous layer with a 1 M aqueous potassium hydrogensulfate solution saturated with sodium chloride. Extract the resultant aqueous phase with ethyl acetate (3 × 20 mL).
5. Dry the combined organic extracts over anhydrous sodium sulfate, filter and concentrate the filtrate *in vacuo* to yield (1-phenylvinyl)phosphinic acid, **36** (0.225 g, 67%), as an oil.

Arylphosphonates may also be synthesized from sodium or potassium dialkyl phosphite salts and aryliodides by a $S_{RN}1$ reaction with photostimulation and such a procedure has been described in detail using liquid ammonia as solvent.[73]

Dialkyl phosphites (**31**, R^1/R^2 = alkyl) and alkyl monoalkylphosphinites (**32**, R^1/R^3 = alkyl) may be alkylated directly (i.e. without prior deprotonation) by carbenoid P—H insertion.[74,75]

4. The Perkow reaction

In the Perkow reaction, a trialkyl phosphite reacts with an α-halo-aldehyde or -ketone to yield an enol phosphate (i.e. [P—O] bond formation, e.g. Scheme 5).[76] α-Haloaldehydes react cleanly but with α-haloketones the Michaelis–Arbuzov reaction usually competes with the product distribution depending on the reaction

conditions and the nature and number of halogens. Mono α-haloesters and amides react according to the Michaelis–Arbuzov reaction with few exceptions, but many trichloroacetates undergo the Perkow reaction. α-Haloacyl halides undergo the Michaelis–Arbuzov reaction followed by the Perkow reaction with two equivalents of trialkyl phosphite. The scope of suitable phosphorus(III) reactants for the Perkow reaction is similar to that of the Michaelis–Arbuzov reaction. The Perkow reaction is generally performed by heating the reactants without solvent and the product purified by distillation, however cooling and/or solvent are sometimes necessary to moderate highly exothermic reactant combinations.

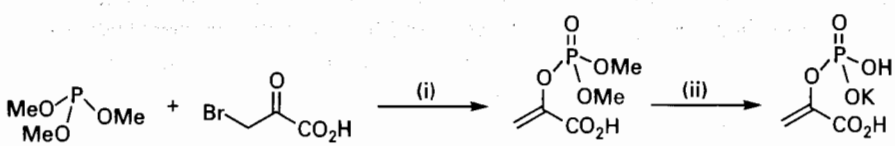
The mechanism of the Perkow reaction has been a subject of some debate but is now generally thought to proceed by initial attack of phosphorus at the carbonyl carbon atom, not by rearrangement of a Michaelis–Arbuzov intermediate **5**.[77,78]

Enol phosphates may be reduced to alkenes,[79] eliminated to alkynes,[80,81] employed as synthetic intermediates in organophosphorus chemistry and are useful in their own right, for example, as insecticides. For reviews covering enol phosphates and the Perkow reaction, see Refs 17, 82, and 83.

The reaction of a silyl phosphite with an α-haloaldehyde or ketone generally leads to a 1 : 1 adduct (i.e. addition at the carbonyl carbon atom to yield a silyloxyphosphonate by the Abramov reaction, cf. Section 5). However, both the Perkow and the Michaelis–Arbuzov pathways are significant and frequently dominate, the outcome depending on the nature of the reactants and the reaction conditions.[47]

Dialkyl phosphites and their metal salts seldom undergo the Perkow reaction with α-halo-aldehydes or -ketones but usually yield α-hydroxy- and/or epoxyphosphonate esters (i.e. Pudovik reaction products, cf. Section 6).[78]

Protocol 9.
Synthesis of phosphoenolpyruvate (Scheme 19)



37 **38** **39**

Scheme 19 (ii) $KOH_{(aq)}$.

This protocol is Whitesides and co-workers' modification of Clark and Kirby's procedure.[84,85] Dimethyl phosphoenolpyruvate **38** is synthesized on a large scale by the Perkow reaction and hydrolysed to potassium phosphoenolpyruvate **39**, which may be used as a phosphorylating agent for the

regeneration of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) in enzymatic synthesis.

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Three-necked round-bottomed flask (12 L)
- Stirrer
- Teflon-coated magnetic stirrer bar
- Nitrogen inlet
- Addition funnel (2 L)
- Water condenser
- One-necked round-bottomed flask (12 L)
- Ice bath
- Büchner flask (10 L)
- Büchner funnel
- Vacuum pump

Materials

- Trimethyl phosphite, 557 mL, 586 g, 4.72 mol, b.p. 112°C
  flammable, harmful, irritant, may cause heritable genetic damage, pungent odour
- Anhydrous diethyl ether, 5.1 L
  extremely flammable, harmful
- Bromopyruvic acid[84] 37, 730 g, 4.37 mol
  very toxic, may cause cancer, irritant, danger of very serious irreversible effects
- Distilled water, 1.67 L
- Potassium hydroxide (85% pure), 267 g, 4.0 mol
  corrosive, toxic, irritant
- Absolute ethanol, 3.5 L
  highly flammable, toxic, irritant

Method

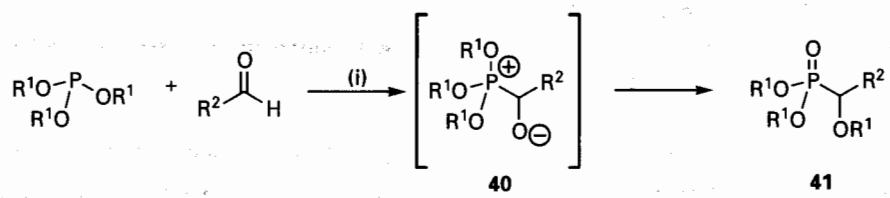
1. Charge a three-necked round-bottomed flask (12 L), equipped with a magnetic stirrer bar and fitted with a nitrogen inlet, an addition funnel (2 L) and condenser, with a solution of trimethyl phosphite (557 mL, 586 g, 4.72 mol) in anhydrous diethyl ether (3.85 L). Stir the solution.
2. Charge the addition funnel with a solution of bromopyruvic acid[84] **37** (730 g, 4.37 mol) in anhydrous diethyl ether (1.25 L) and add it dropwise at such a rate as to maintain the reaction mixture at reflux (i.e. over a period of circa 3.5 h). On completion of the addition, stir the reaction mixture for a further hour at room temperature. **Caution!** exothermic reaction! **Caution!** methyl bromide (b.p. 4°C) is evolved and is toxic, an irritant and may cause cancer.
3. Transfer the mixture to a one-necked round-bottomed flask (12 L) and remove the diethyl ether by rotary evaporation to yield crude dimethyl phosphoenolpyruvate **38** (1002 g) as a brown viscous oil.
4. Add water (1.67 L) to the crude dimethyl phosphoenolpyruvate **38** and stir the solution for 15 h at room temperature.
5. Cool the solution in an ice bath and add solid potassium hydroxide (267 g, 4.0 mol) to produce a solution of pH 2.8, then add ethanol (2.7 L).
6. Collect the resultant white precipitate by filtration, wash it with cold ethanol (800 mL) and dry under vacuum (0.1 mmHg) to yield potassium phosphoenolpyruvate **39** (531 g, 59%).

5. The Abramov reaction

The organophosphorus literature does not reach consensus on the attribution of the reactions discussed in Sections 5–7, but the demarcation followed here is that generally accepted. Collectively, by analogy with the corresponding organic reactions, these reactions are often referred to as phospho-aldol reactions and, in asymmetric variants, are an area of intense research because the product α-hydroxy- and α-aminophosphonates are vital components of a wide range of enzyme inhibitors, among other applications. Kee and co-workers have an active research programme in this area and they, and others, have produced reviews over recent years.[5,51,86–89] For more general reviews see Refs 6, 10, 90, and 91. There are, of course, other useful methods for the asymmetric synthesis of α-hydroxy- and α-aminophosphonates that fall outside the scope of this chapter.[51,87–89]

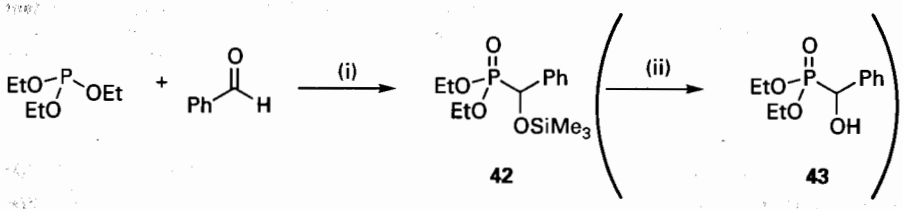
The Abramov reaction is the addition of a fully esterified phosphorus(III) acid to an aldehyde, ketone or imine, followed by alkyl group transfer (analogous to the second step of the Michaelis–Arbuzov reaction). The original Abramov reaction involved the heating of an aldehyde with a trialkyl phosphite to yield a dialkyl α-alkoxyphosphonate **41** (Scheme 20).[92] The first stage of the reaction, nucleophilic addition of the trialkyl phosphite to the aldehyde carbonyl group occurs readily under mild conditions with aliphatic aldehydes to form a tetrahedral adduct **40**. However, subsequent alkyl transfer does not occur under mild conditions and addition of a second molecule of aldehyde to the adduct **40** ultimately results in the formation of a cyclic product. This dealkylation difficulty (cf. Section 2) is acute (intramolecular transfer is a disfavoured 5-*endo-tet* process and when alkyl transfer does occur it is intermolecular) and the Abramov reaction is only synthetically useful when it is addressed: silyl groups offer the best solution to this problem, either as trapping reagents (Protocol 10) or as readily transferable esters (Protocol 11, cf. Protocol 5).[6,47] The Pudovik reaction (Section 6) is an alternative approach. Surprisingly triphenyl phosphite is a better Abramov reactant than trialkyl phosphites in the particular case of the acid-catalysed reaction with an aldehyde and urea (and similar reactants), cf. Section 2. This observation is attributed to a non-standard reaction mechanism and the lower basicity of triphenyl phosphite.[6,93]

With α-halo- and α,β-unsaturated carbonyl compounds the issue of chemo-/regioselectivity arises, these substrates are discussed in Sections 4 and 8, respectively.



Scheme 20 (i) Sealed tube 70–100°C.

Protocol 10.
Synthesis of diethyl 1-phenyl-1-(trimethylsiloxy)methanephosphonate, 42 (Scheme 21)[94]



Scheme 21 (i) TMSCl; (ii) TFA, MeOH.

Birum and Richardson used chloro- and bromo-alkylsilanes as convenient trapping reagents in the Abramov reaction.[95] Evans and co-workers demonstrated that the reaction proceeds by trapping of the tetrahedral adduct **40** rather than initial reaction of the trialkyl phosphite and halosilane to generate a silyl phosphite *in situ*.[96] Evans and co-workers and Hata and co-workers have undertaken extensive studies of the reactions of isolated silyl phosphorus(III) ester nucleophiles with various carbonyl compounds (see also Sections 4 and 8),[96] but this method of Birum and Richardson is generally operationally simpler as it does not require synthesis of a silyl phosphorus(III) ester; however, these reagents can be generated *in situ* (Protocol 11): the method of choice depends upon the desired product and the availability of the requisite starting materials. The product of this protocol (**42**), and other α-silyloxyalkylphosphonates have been studied as acyl anion equivalents.[96,97] Alternatively, if the α-hydroxy phosphonate (e.g. **43**) is the desired product the trimethylsilyl group may be removed readily (e.g. by methanolysis, steps 5 and 6).[98]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Two-necked round-bottomed flask (100 mL)
- Thermostat controlled hot-plate stirrer
- Teflon-coated magnetic stirrer bar
- Nitrogen inlet
- Addition funnel (25 mL)
- Ice bath
- Oil bath
- Water condenser
- Still head
- Thermometer
- Receiver
- One-necked round-bottomed flasks (50 mL)
- Fractional distillation receiver
- Vacuum pump
- One-necked round-bottomed flask (500 mL)
- Büchner flask (500 mL)
- Büchner funnel

Protocol 10. *Continued*

Materials

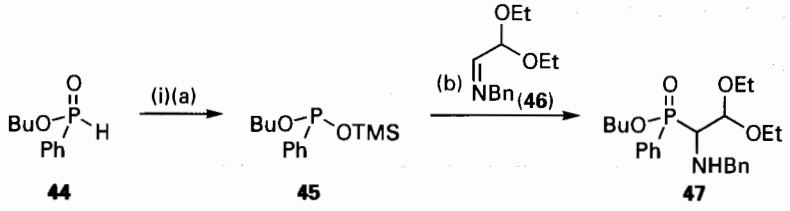
- Benzaldehyde 10 mL, 10.5 g, 99 mmol, b.p. 179°C **harmful**
- Triethyl phosphite 17 mL, 16.5 g, 99 mmol, b.p. 156°C **flammable, harmful, irritant**
- Chlorotrimethylsilane, 12.6 mL, 10.8 g, 99 mmol, b.p. 57°C **highly flammable, harmful, causes severe burns, irritant**
- Freshly prepared 1 mM solution of trifluoroacetic acid, 23 mL, 34 g, 0.3 mol, in methanol, 300 mL **highly flammable, toxic**

Method

1. Charge a two-necked round-bottomed flask (100 mL), equipped with a magnetic stirrer bar, addition funnel and fitted with a nitrogen inlet, with benzaldehyde (10 mL, 10.5 g, 99 mmol) and triethyl phosphite (17 mL, 16.5 g, 99 mmol). Stir the mixture at 0°C.
2. Charge the addition funnel with chlorotrimethylsilane (12.6 mL, 10.8 g, 99 mmol) and add it dropwise over 10 min to the reaction mixture stirred at 0°C.
3. Replace the ice bath with an oil bath and the addition funnel with a condenser and heat the stirred reaction mixture to 120°C for 6–8 h.
4. Cool the reaction mixture and replace the condenser with the distillation setup. Distil over the diethyl 1-phenyl-1-(trimethylsiloxy)methanephosphonate, **42** (b.p. 170°C, 10 mmHg, 28.8 g, 91 mmol, 92%), as a colourless liquid.
5. For desilylation: in a 500 mL round-bottomed flask stir a solution of diethyl 1-phenyl-1-(trimethylsiloxy)methanephosphonate **42** (28.8 g, 91 mmol) in 1 mM trifluoroacetic acid in methanol (300 mL) for 4–10 h at room temperature. The reaction may be monitored by gas chromatography (GC).
6. Remove the methanol by rotary evaporation and collect the diethyl 1-phenyl-1-hydroxymethanephosphonate, **43** (22.2 g, 91 mmol, quantitative), as a solid, by filtration.

Protocol 11.
Synthesis of butyl [1-(benzylamino)-2, 2-(diethoxyethane]phenylphosphinate, 47 (Scheme 22)[99]

Rees and co-workers have carried out an extensive study of the addition of trimethylsilyloxy phosphorus(III) derivatives (phosphites, phosphonites, and phosphinites, generated *in situ*) to aldimines to yield α-aminoalkyl-phosphonates, phosphinates and phosphine oxides (respectively, the transferred *N*-TMS group being lost during work-up). Competition experiments demonstrated that the addition to imines is faster than that to the parent aldehydes. They found that the presence of electron-withdrawing groups in the imine slows the reaction,



44 **45** **47**

Scheme 22 (i) (a) NEt_3, TMSCl, CH_2Cl_2.

suggesting that the rate determining step is nucleophilic attack of the imine nitrogen on a silylating species.[99]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Two-necked round-bottomed flask (100 mL)
- Stirrer
- Teflon-coated magnetic stirrer bar
- Argon inlet
- Ice bath
- Conical flasks (2 × 250 mL)
- Separating funnel
- Filter funnel
- Vacuum pump
- One-necked round-bottomed flask (250 mL)
- Flash chromatography column and fractions

Materials

- Butyl phenylphosphinate[100,101] **44**, 0.47 mL, 0.50 g, 2.53 mmol **treat as toxic**
- Anhydrous dichloromethane, 50 mL
- Anhydrous triethylamine, 0.39 mL, 0.28 g, 2.78 mmol **highly flammable, causes burns, harmful**
- Chlorotrimethylsilane, 0.35 mL, 0.30 g, 2.8 mmol, b.p. 57°C **highly flammable, harmful, causes severe burns, irritant**
- 2,2-Diethoxyethanal *N*-benzylimine[99] **46**, 0. 56 g, 2.53 mmol **irritant, harmful**

Method

1. Charge a two-necked round-bottomed flask (100 mL), equipped with a magnetic stirrer bar and fitted with an argon inlet, with a solution of butyl phenylphosphinate[100,101] **44** (0.47 mL, 0.50 g, 2.53 mmol) in anhydrous dichloromethane (50 mL). Stir the solution at 0°C.
2. Add anhydrous triethylamine (0.39 mL, 0.28 g, 2.78 mmol) followed by chlorotrimethylsilane (0.35 mL, 0.30 g, 2.8 mmol) to the solution and continue stirring at 0°C for 15 min. The formation of the butyl trimethylsilyl phenylphosphonite **45** may be monitored by ^{31}P NMR spectroscopy.
3. Add 2,2-diethoxyethanal *N*-benzylimine[99] **46** (0.56 g, 2.53 mmol) to the reaction mixture and stir the solution for 15 h at room temperature.
4. Pour the reaction mixture into water (50 mL) and extract with dichloromethane (2 × 75 mL). Dry the combined organic extracts over anhydrous sodium sulfate, filter and concentrate the filtrate *in vacuo*.

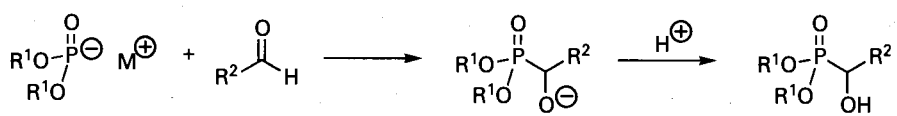
Protocol 11. *Continued*

5. Purify the residue by flash chromatography on silica, eluting with hexanes : ethyl acetate to yield butyl [1-(benzylamino)-2,2-(diethoxyethane] phenylphosphinate **47** (1.1 g, 81%), an oil.

The most successful asymmetric variants of the Abramov reaction employ chiral substrates, either chiral carbonyl compounds or aldimines, or chiral phosphorus(III) reagents.[5,51,86,88] However, the Pudovik reaction using chiral catalysts is a superior route for the asymmetric synthesis of α-hydroxy- and α-aminophosphonates (Section 6).

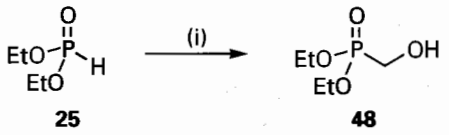
6. The Pudovik reaction

The Pudovik reaction is the addition of a monobasic phosphorus(III) acid to an aldehyde, ketone, or imine, usually under basic conditions (e.g. Scheme 23), and may be regarded as a Michaelis–Becker type variant of the Abramov reaction (cf. Sections 2 and 5, indeed it is occasionally called an Abramov reaction and its development was originally described in numerous papers from the Kazan' school[7]). Thus, the dealkylation difficulty encountered in the Abramov reaction is avoided. The usual mechanism of the Pudovik reaction is simple nucleophilic addition of the phosphorus centre of the ambident nucleophile to the substrate. Alkali metal (usually sodium) salts of dialkyl phosphites were used in early work (and are still used, Protocol 13) but it is now more common to use substoichiometric quantities of a strong base (e.g. an alkoxide, Protocol 14) or an amine (Protocol 12); sodium carbonate may be used as base in a phase transfer method. Alternatively, the reaction often occurs simply on heating the reactants together in the absence of base. The choice of solvent is determined by the choice of base and none may be necessary when using a liquid organophosphorus reactant. With α-halo-carbonyl compounds the Perkow reaction sometimes competes, with the product distribution depending upon the conditions, cf. Section 4. With α,β-unsaturated carbonyl compounds the course of reaction depends upon the reaction conditions, thermodynamic control favours 1,4-addition and kinetic control 1,2-addition, cf. Section 8. For reviews see Refs 63 and 102 (synthesis of α-amino phosphonates), and those cited in Section 5.



Scheme 23

Protocol 12.
Synthesis of diethyl hydroxymethylphosphonate, 48 (Scheme 24)[103,104]



25 **48**

Scheme 24 (i) $(CH_2O)_n$, NEt_3, Δ.

Tetrahydropyranyl (THP) protection of the hydroxy group of **48** yields a useful reagent for the Horner–Wadsworth–Emmons synthesis of enol ethers from carbonyl compounds.[103,104]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- One-necked round-bottomed flask (250 mL)
- Thermostat controlled hot-plate stirrer
- Teflon-coated magnetic stirrer bar
- Water condenser
- Oil bath
- Vacuum pump
- Kugelrohr distillation apparatus

Materials

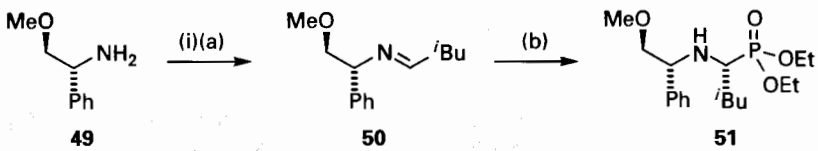
- Diethyl phosphite (diethyl phosphonite) **25**, 64.4 mL, 69 g, 0.50 mol — **irritant**
- Paraformaldehyde, 15 g, 0.50 mol — **causes burns, possible carcinogen, may cause sensitization by skin contact**
- Triethylamine, 7.0 mL, 5.1 g, 0.05 mol — **highly flammable, harmful, causes burns**

Method

1. Charge a one-necked round-bottomed flask (250 mL), equipped with a magnetic stirrer bar and fitted with a water condenser, with diethyl phosphite **25** (64.4 mL, 69 g, 0.50 mol), paraformaldehyde (15 g, 0.50 mol) and triethylamine (7.0 mL, 5.1 g, 0.05 mol).
2. Stir the reaction mixture at 120–130°C for 4 h.
3. Remove the triethylamine *in vacuo* (15 mmHg, rotary evaporator bath temperature circa 80°C).
4. Purify the product by Kugelrohr distillation at 125°C, 0.05 mmHg, to yield diethyl hydroxymethylphosphonate, **48** (41.4–54.9 g, 49–65%), as a liquid.

Chiral carbonyl and aldimine substrates can give good diastereoselectivity in the Pudovik reaction.[86,88,102] The Pudovik reaction of isolated imines generally proceeds in higher yield and de (where applicable) than if the imine is formed *in situ* (the Kabachnik–Fields reaction, Section 7).

Protocol 13.
Synthesis of diethyl (*R*)-{1-[(*N*-(*R*)-(1-phenyl-2-methoxyethyl)amino)-3-methylbutyl]}phosphonate, 51 (Scheme 25)[105,106]



49 **50** **51**

Scheme 25 (i) (a) $(Me)_2CHCH_2CHO$, Na_2SO_4, toluene, (b) $LiPO(OEt)_2$, THF.

In Smith and co-workers' procedure, the lithium salt of diethyl phosphite is added to a homochiral aldimine **50** with chelation control, the lithium cation being coordinated by the ether oxygen and imine nitrogen to give a rigid five-membered ring transition state with addition occurring anti to the phenyl ring. The corresponding sodium and potassium salts failed to react. The procedure gives high des with a range of aldimines. Hydrogenolysis of the Pudovik products (e.g. **51**) yields free α-amino phosphonates.[105,106]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Three-necked round-bottomed flask (1 L)
- Stirrer
- Teflon-coated magnetic stirrer bar
- Argon inlet
- Addition funnel (250 mL)
- Ice bath
- Filter funnel
- Vacuum pump
- One-necked round-bottomed flask (1 L)
- Conical flask (250 mL)
- Cannula (12-gauge)
- Conical flask (2 L)
- Separating funnel
- Filter funnel
- Flash chromatography column and fractions

Materials

- Isovaleraldehyde, 11.7 mL, 9.4 g, 109 mmol — **highly flammable, irritant**
- Anhydrous toluene, 440 mL — **highly flammable, harmful**
- (*R*)-1-Amino-1-phenyl-2-methoxyethane[105,106] **49**, 16.5 g, 109 mmol
- Anhydrous sodium sulfate, 125 g, 0.88 mol
- Diethyl phosphite (diethyl phosphonate) **25**, 27.3 mL, 29.3 g, 212 mmol — **irritant**
- Anhydrous THF, 110 mL — **highly flammable, irritant**
- *n*-Butyl-lithium 1.6 M in hexanes, 63 mL, 101 mmol — **highly flammable, causes burns,**

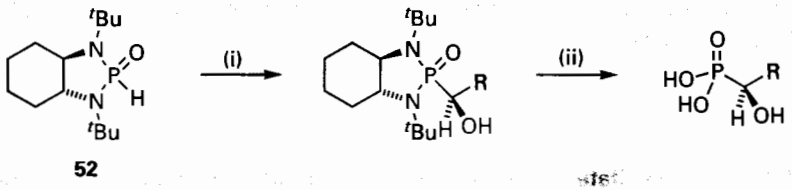
Method

1. Charge a three-necked round-bottomed flask (1 L), equipped with a magnetic stirrer bar and fitted with an addition funnel (250 mL) and argon inlet, with isovaleraldehyde (11.7 mL, 9.4 g, 109 mmol) and toluene (100 mL). Cool the solution to 0°C and stir.

2. Charge the addition funnel with a solution of (*R*)-1-amino-1-phenyl-2-methoxyethane[105,106] **49** (16.5 g, 109 mmol) in toluene (160 mL) and add it dropwise to the reaction mixture at 0°C over 45 min.
3. Remove the cooling bath and allow the reaction mixture to warm to room temperature.
4. Add sodium sulfate (125 g, 0.88 mol) to the turbid reaction mixture and stir for 1 h at room temperature.
5. Filter the reaction mixture and wash the precipitate with toluene (150 mL). Concentrate the filtrate (in a 1 L one-necked round-bottomed flask) *in vacuo* (rotary evaporator then on a vacuum line at <1 mmHg) to yield the imine **50** (23.3 g) as slightly yellow oil.
6. Add a magnetic stirrer bar and argon inlet to the flask containing the imine **50**, followed by toluene (180 mL). Stir the solution.
7. Charge a conical flask (250 mL) with diethyl phosphite **25** (27.3 mL, 29.3 g, 212 mmol) and THF (110 mL). Cool the solution to 0°C and stir.
8. Add a solution of butyl-lithium (1.6 M in hexanes, 63 mL, 101 mmol) dropwise over 20 min via a syringe to the diethyl phosphite solution stirred at 0°C. Stir at 0°C for a further 30 min, then remove the cooling bath and allow the mixture to warm to room temperature.
9. Add the lithium diethylphosphite solution to the imine **50** solution via a cannula and stir the resultant mixture at room temperature for 20 h.
10. Add water (200 mL). Concentrate the mixture *in vacuo* to remove THF.
11. Add sufficient sodium chloride to saturate the aqueous layer and then extract with ethyl acetate (3 × 300 mL). Dry the combined organic extracts over sodium sulfate, filter and evaporate the filtrate.
12. Purify the residue by flash chromatography on silica, eluting first with ethyl acetate : hexane (50 : 50, 1.2 L then 60 : 40, 6 L) to yield diethyl (*R*)-{1-[(*N*-(*R*)-(1-phenyl-2-methoxyethyl)amino)-3-methylbutyl]}phosphonate, **51** (30.5 g, 85%, >98% de), as a colourless oil.

Chiral phosphorus(III) reagents undergo the Pudovik reaction[51,88] with good diastereoselectivity being achieved by the reaction of Spilling and co-workers' diamide **52** with aldehydes (Scheme 26),[107] however, research on this chiral auxiliary approach to α-hydroxy phosphonates is now surpassed by chiral catalysis.

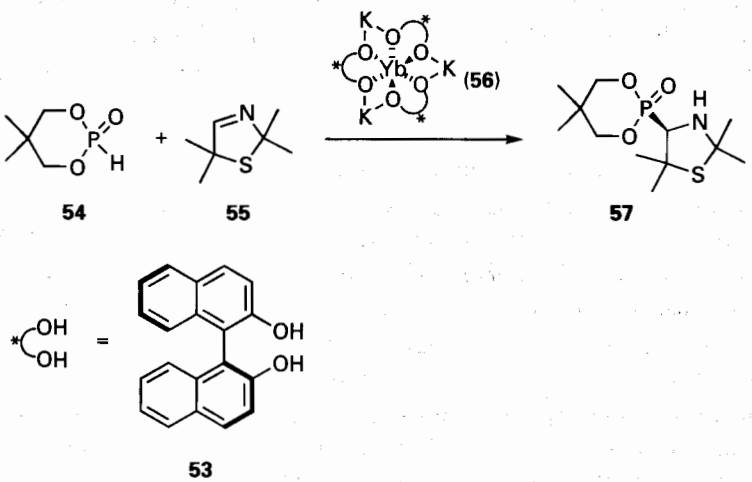
Asymmetric catalysis of the Pudovik reaction is an area of active study with numerous success stories, mostly featuring chiral Lewis acid catalysts, and further developments are anticipated.[39,86,87] Shibasaki and co-workers' heterobimetallic catalysts[108] are the best developed in this field, for both aldehyde and aldimine substrates.



52

Scheme 26 (i) LDA, THF, RCHO, d.e. 55–93% ; (ii) HCl, H_2O, dioxane.

Protocol 14.
Synthesis of (*R*)-4-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2,2,5,5-tetramethyl-3-thiazolidine, 57 (Scheme 27)[109,110]



54 **55** **57**

53

Scheme 27

Shibuya and co-workers[111] and Rath and Spilling[112] first reported the application of Shibasaki and co-workers' heterobimetallic catalysts to the enantioselective Pudovik synthesis of α-hydroxyphosphonates. Improvements were made by Shibasaki and co-workers, a vital factor being the method of preparation of the catalysts with the inclusion of water. Thus, their binaphthol-based heterobimetallic complexes, with the appropriate combination of metal cations, catalyse in good to excellent enantiomeric excess (e.e.), the enantioselective hydrophosphonylation of aldehydes {$Li_3[La(BINOL)_3]$[113] or $Li[Al(BINOL)_2]$ (higher e.e. with electron-deficient aromatic aldehydes)[114]} and the enantioselective hydrophosphinylation of aldehydes {$Li[Al(BINOL)_2]$[115]. The asymmetric Pudovik reaction of aldimines using heterobimetallic catalysis is more widely applied and gives even better e.e. in some cases. For the synthesis of α-aminophosphonates from

acyclic imines the best catalyst is $[K_3[La(BINOL)_3]$,[116] whereas with cyclic imines $[K_3[Yb(BINOL)_3]$ **56** is superior;[109,110] this process is used industrially.[117] The catalyst of choice for the asymmetric addition of diphenylphosphine oxide to cyclic imines is $[K_3[Pr(BINOL)_3]$.[118]

This procedure is a representative method for the enantioselective hydrophosphonylation of 3-thiazolines to yield pharmaceutically interesting thiazolidinylphosphonates (e.g. **57**) and is the best result achieved in an asymmetric Pudovik reaction (99% yield, 99% e.e., 2.5 mol% catalyst), it begins with the preparation of a stock solution of the catalyst (steps 1–3).[109,110] Lower catalyst loading decreases both yield and e.e.[110] This method is also successful with acyclic phosphites, but higher catalyst loadings are required (up to 20 mol%).[109,110] The work-up described here (direct column chromatography) minimizes losses of the product due to aqueous solubility, but an aqueous work-up is described for other substrates.[110] The details of the mechanism of this reaction have been investigated: essentially the lanthanide (Yb in this case) acts as a Lewis acid and activates the imine and the alkali metal alkoxide acts as a Brønsted base, deprotonating the phosphonate (the predominant tautomer of the phosphite reactant) resulting in a shift in the tautomeric equilibrium to the reactive phosphite anion.[86,110]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Three-necked round-bottomed flask (50 mL)
- Thermostat controlled hot-plate stirrer
- Teflon-coated magnetic stirrer bar
- Argon inlet
- Three-necked round-bottomed flask (25 mL)
- Water condenser
- Oil bath
- Conical flask (10 mL)
- One-necked round-bottomed flask (10 mL)
- Vacuum pump
- Flash chromatography column and fractions

Materials

- (*S*)-1,1′-Bi-2-naphthol **53**, 258 mg, 0.90 mmol — **toxic, irritant**
- Anhydrous THF, 9.9 mL — **highly flammable, irritant**
- 0.1 M Ytterbium(III) isopropoxide in THF, 3.0 mL, 0.30 mmol — **highly flammable, causes burns**
- 0.5 M Potassium bis(trimethylsilyl)amide (KHMDS) in toluene, 1.8 mL, 0.90 mmol — **highly flammable, toxic, causes burns**
- 1.0 M water in THF, 1.30 mL, 1.30 mmol
- Anhydrous toluene/THF 7 : 1, 14.1 mL — **highly flammable, harmful, irritant**
- 2,2,5,5-Tetramethyl-3-thiazoline[119] **55**, 43 mg, 0.30 mmol — **treat as toxic**
- 5,5-Dimethyl- 2-oxo-[1,3,2]dioxaphosphinane **54**, 225 mg, 1.5 mmol — **causes burns**

Method

1. Charge a three-necked round-bottomed flask (50 mL), equipped with a magnetic stirrer bar and fitted with an argon inlet, with (*S*)-1,1′-bi-2-naphthol **53** (258 mg, 0.90 mmol) and add THF (8.4 mL). Stir the solution at room temperature.

Protocol 14. *Continued*

2. Add 0.1 M $Yb(O^iPr)_3$ in THF (3.0 mL, 0.30 mmol), 0.5 M KHMDS in toluene (1.8 mL, 0.90 mmol) and 1.0 M water in THF (0.30 mL, 0.30 mmol), successively via syringes. Stir the mixture at room temperature for 1 h.
3. Remove the solvent *in vacuo* and add toluene/THF (7 : 1, 12 mL) to give a 0.025 M stock solution of $[K_3[Yb(BINOL)_3]$ **56**.
4. Charge a three-necked round-bottomed flask (25 mL), equipped with a magnetic stirrer bar and fitted with a condenser and an argon inlet, with 0.025 M $[K_3[Yb(BINOL)_3]$ **56** stock solution (0.30 mL, 7.5 μmol), dilute the solution with toluene/THF (7 : 1, 2.1 mL). Stir the solution.
5. Add a solution of 2,2,5,5-tetramethyl-3-thiazoline[119] **55** (43 mg, 0.30 mmol) in THF (0.5 mL) followed by a solution of 5,5-dimethyl-2-oxo-[1,3,2]dioxaphosphinane **54** (225 mg, 1.5 mmol) in THF (1.0 mL) to the reaction mixture and stir at 50°C for 48 h.
6. Cool the reaction mixture to room temperature, add 1.0 M water in THF (1 mL, 1 mmol) and stir overnight.
7. Decant the solution from the solids. Wash the solids with ethyl acetate (2 × 1 mL).
8. Combine the organic solvents and concentrate *in vacuo*.
9. Purify the residue by flash chromatography on silica, eluting first with diethyl ether [110 mL to separate (*S*)-binaphthol **53**] then diethyl ether : THF (1 : 1) to yield (*R*)-4-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2,2,5,5-tetramethyl-3-thiazolidine, **57** (87 mg, 99%, 99% e.e.), as a solid.

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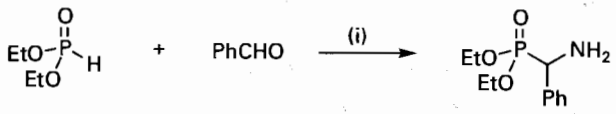
7. The Kabachnik–Fields reaction

The Kabachnik–Fields reaction is the three-component condensation of an aldehyde or ketone, an amine (secondary, primary, or ammonia) and a monobasic phosphorus(III) acid to yield an α-amino organophosphorus compound (a phosphonate, phosphinate, or tertiary phosphine oxide): Scheme 28. It was discovered independently in 1952 by Kabachnik and Medved'[120] and Fields,[121] and may be regarded as a variant of the Pudovik reaction (Section 6), which was discovered contemporarily. The yields of the reaction tend to be only moderate (cf. Section 6), and are generally unsatisfactory with phosphinate reactants, but it is wide in scope and simple to perform. For a recent review of the Kabachnik–Fields reaction, including discussion of the mechanism (which usually proceeds via the imine), see Ref. 102.

21

Scheme 28

Protocol 15.
Synthesis of diethyl 1-amino-1-benzylphosphonate, 58 (Scheme 29)[122]



25 **58**

Scheme 29 (i) NH_4OAc, 3 Å molecular sieves.

The original Kabachnik–Fields procedure employing ammonia as the amine component used ammonia in ethanol and the reactions were performed in sealed vessels at circa 100°C.[90,123] This method avoids such conditions by using ammonium acetate as the source of ammonia, and it is also thought to act as an acid catalyst for imine formation; other ammonium salts were unsatisfactory. Addition of water to produce a homogeneous reaction mixture resulted in diethyl 1-hydroxy-1-benzylphosphonate formation (i.e. from direct attack of diethyl phosphite **25** on benzaldehye, a common side reaction in the Kabachnik–Fields reaction). The yields of this reaction are serviceable, and better for aromatic than aliphatic aldehydes. The product **58** may be further purified by crystallization as the hydrochloride salt by treatment of **58** with hydrogen chloride in ethanol/diethyl ether.[122]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- One-necked round-bottomed flask (500 mL)
- Thermostat controlled hot-plate stirrer
- Teflon-coated magnetic stirrer bar
- Water condenser
- Oil bath
- Filter funnel
- Separating funnel
- Conical flasks (500 mL and 1 L)

Materials

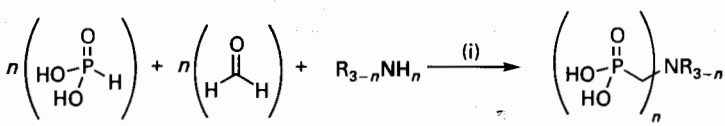
- Ammonium acetate, 7.70 g, 0.10 mol — **irritant**
- Ethanol, 200 mL — **highly flammable, toxic, irritant**
- 3 Å molecular sieves, 2.0 g — **irritant**
- Benzaldehyde, 10.2 mL, 10.6 g, 0.10 mol — **harmful**
- Diethyl phosphite (diethyl phosphonate) **25**, 12.9 mL, 13.81 g, 0.10 mol — **irritant**

Protocol 15. *Continued*

Method

1. Charge a one-necked round-bottomed flask (500 mL), equipped with a magnetic stirrer bar and fitted with a water condenser, with a solution of ammonium acetate (7.70 g, 0.10 mol) in ethanol (200 mL). Add 3 Å molecular sieves (2.0 g), benzaldehyde (10.61 g, 0.10 mol) and diethyl phosphite **25** (13.81 g, 0.10 mol) at room temperature.
2. Stir the reaction mixture and heat at 60°C for 44 h and then cool to room temperature.
3. Filter the reaction mixture and acidify the filtrate to pH 1 with 2 M hydrochloric acid.
4. Wash the solution with diethyl ether (2 × 200 mL).
5. Raise the pH of the aqueous solution to 11 with 2 M aqueous sodium hydroxide solution and extract with dichloromethane (3 × 200 mL).
6. Dry the combined organic extracts over anhydrous sodium sulfate, filter and concentrate the filtrate *in vacuo* to yield almost pure diethyl 1-amino-1-phenylmethanephosphonate, **58** (14.6 g, 59%), as a pale yellow oil.

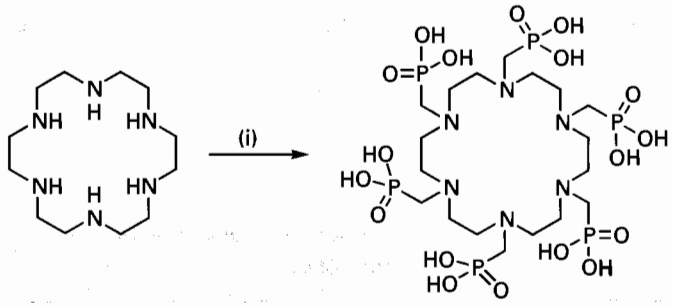
The particular case of the Kabachnik–Fields reaction with an amine (secondary, primary, or ammonia), formaldehyde and phosphorous acid (H_3PO_3), a Mannich type variant, is known as the Moedritzer–Irani reaction (Scheme 30). With ammonia the product of the reaction is the tris-adduct (**59**, $n = 3$), while primary amines and secondary amines yield the bis- and mono- adducts (**59**, $n = 2, 1$) respectively; the reaction yields are good, compromised only by the water solubility of the products.[124] As is generally true of the Kabachnik–Fields reaction, mono-adducts (**59**, $n = 1$) of primary amines are always contaminated by the bis-adducts when using 1 equiv. of formaldehyde and phosphorous acid but may be accessed using *N*-benzyl protection and subsequent hydrogenolysis. The Moedritzer–Irani reaction fails with other aldehydes and ketones,[125] except when the imines are preformed in a separate step[126] or in the case of Oleksyszyn and Gruszecka's modification, which employs phosphorous acid, aldehydes and primary amides (or carbamates) in the presence of acetic anhydride to yield, after *N*-deprotection, mono-adducts of ammonia.[127]



59

Scheme 30 (i) $HCl_{(c)}$, R = alkyl, functionalized alkyl, $n = 1$–3.

Protocol 16. Synthesis of 1,4,7,10,13,16-hexa-(*N*-phosphonomethyl)-azacyclooctadecane 61 (Scheme 31)[128]



60 **61**

Scheme 31 (i) H_3PO_3, CH_2O, $HCl_{(c)}$.

This procedure is Coveney, Whiting and co-workers' synthesis of the hexaphosphonic acid **61** by the Moedritzer–Irani reaction, the dodecasodium salt of which they investigated as a cement setting retarder. An attempt to synthesize the dodecaethyl ester of **61** using the Kabachnik–Fields reaction failed.[128]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Two-necked round-bottomed flask (100 mL)
- Hot-plate stirrer
- Teflon-coated magnetic stirrer bar
- Water condenser
- Addition funnel (10 mL)
- Oil bath
- One-necked round-bottomed flask (250 mL)
- Büchner flask (250 mL)
- Büchner funnel
- Vacuum pump

Materials

- 1,4,7,10,13,16-Hexaazacyclooctadecane (hexacyclen) **60** trisulfate, 4.58 g, 8.2 mmol **causes burns**
- Phosphorous acid, 2.5 mL, 4.13 g, 50 mmol **harmful, causes burns**
- Water, 18 mL
- Concentrated hydrochloric acid, 16 mL **irritant, causes burns**
- Formaldehyde (37% solution in water), 7.4 mL, 99 mmol **toxic, causes burns, possible carcinogen, may cause sensitisation by skin contact**
- Acetone, 100 mL **highly flammable, irritant**

Method

1. Charge a two-necked round-bottomed flask (100 mL), equipped with a magnetic stirrer bar and addition funnel (10 mL) and fitted with a water condenser,

Protocol 16. *Continued*

with 1,4,7,10,13,16-hexaazacyclooctadecane **60** trisulfate (4.58 g, 8.2 mmol), phosphorous acid (2.5 mL, 4.13 g, 50 mmol), water (18 mL) and concentrated hydrochloric acid (16 mL). Heat the mixture under reflux.

2. Charge the addition funnel with formaldehyde (37% solution in water, 7.4 mL, 99 mmol) and add it dropwise to the reaction mixture over 1 h.
3. Heat the reaction mixture under reflux for a further 4 h then cool to room temperature.
4. Concentrate the reaction mixture *in vacuo* and add acetone (100 mL) to the residue.
5. Cool the mixture to 0°C overnight.
6. Collect the off-white precipitate by filtration and dry it *in vacuo* for 8 h to yield 1,4,7,10,13,16-hexa-(*N*-phosphonomethyl)-azacyclooctadecane, **61** (6.73 g, 86%), as an extremely hygroscopic solid.

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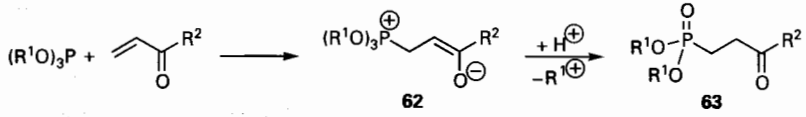
8. Conjugate additions of phosphorus(III) reagents

Nucleophilic phosphorus(III) reagents undergo 1,4-addition to α,β-unsaturated carbonyl compounds (and other substrates susceptible to conjugate addition) to yield the corresponding γ-functionalized organophosphorus compounds (e.g. **63**).[129] The precise course and outcome of the reaction depends upon the nature of the phosphorus nucleophile.

Trialkyl phosphites undergo conjugate addition to yield zwitterions **62**, subsequent dealkylation occurs in the presence of a proton source,[129] *tert*-butanol being a good choice to minimize side reactions (Scheme 32). Other nucleophilic phosphorus(III) reagents participate in these reactions: as for the Abramov reaction, the scope is much the same as for the Michaelis–Arbuzov reaction (cf. Sections 2 and 5), thus dialkyl alkylphosphonites and alkyl dialkylphosphinites are good reactants and silyl phosphorus(III) esters are excellent.[47] In the latter case, the product is the silyl enol ether (silyl transfer occurs exclusively from mixed esters such as diethyl trimethylsilyl phosphite), which is readily hydrolysed to the parent keto compound.[96,130] 1,2-Addition (Abramov reaction) often competes or dominates, especially with α,β-unsaturated aldehyde substrates and silyl phosphorus(III) ester nucleophiles. When the reaction of a trialkyl phosphite [or other fully esterified phosphorus(III) acid] and an α,β-unsaturated aldehyde, ketone, ester, nitrile, or carboxylic acid is performed in the presence of a silylating agent (such as trimethylsilyl chloride) the zwitterion **62** is trapped as the silyl enol ether and dealkylated by the liberated chloride; in such a procedure a silyl phosphorus(III) ester is not formed, that is, the trialkyl phosphite does not react with the silyl halide.[96,131]

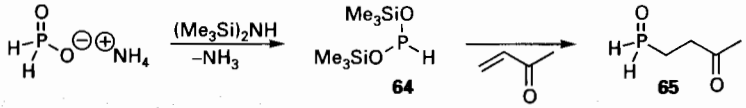
Dialkyl phosphites and other Michaelis–Becker type reagents undergo conjugate additions readily in the presence of (substoichiometric) base (usually



Scheme 32

alkoxide or sodium hydride); no dealkylation step is required in this process but competition from 1,2-addition (Pudovik reaction) is sometimes a problem especially with α,β-unsaturated aldehyde substrates; (note that the name Pudovik reaction is often used to refer to the addition of such organophosphorus reagents to *any* unsaturated system). This approach generally results in poorer yields than the corresponding synthesis using a fully esterified phosphorus(III) reagent. The 1,4-addition method of choice employs a silylated mono- (or di-)basic phosphorus(III) reagent, which may be generated readily *in situ* (e.g. using trimethylsilyl chloride and triethylamine or bis(trimethylsilyl) acetamide).[96,132] For reviews of this area, see Refs 6, 63, 90, and 91.

Protocol 17.
Synthesis of (3-oxo-butyl)-phosphinic acid, 65 (Scheme 33)[133]



Scheme 33

Regan and co-workers' protocol for the synthesis of γ-keto phosphinic acids by 1,4-addition of bis(trimethylsilyl)phosphonite (BTSP, **64**) to α,β-unsaturated ketones avoids the isolation of pyrophoric BTSP **64** by generating it *in situ*. This procedure may be modified to synthesize disubstituted phosphinic acids by addition of a second α,β-unsaturated ketone.[133] α,β-Unsaturated esters are also suitable reactants.[134] The products are isolated most conveniently as their adamantanammonium salts.[133]

Caution! Carry out all protocols in an efficient hood and wear disposable vinyl or latex gloves and chemical-resistant safety goggles at all times.

Equipment

- Three-necked round-bottomed flask (100 mL)
- Thermostat controlled hot-plate stirrer
- Teflon-coated magnetic stirrer bar
- Nitrogen inlet
- Water condenser
- Oil bath
- Ice bath
- Filter funnel
- Vacuum pump
- One-necked round-bottomed flask (100 mL)
- Büchner flask (250 mL)
- Büchner funnel
- Vacuum pump

Protocol 17. *Continued*

Materials

- Anhydrous ammonium phosphinate,[133] 2.5 g, 30.1 mmol
- Hexamethyldisilazane, 6.4 mL, 4.9 g, 30.1 mmol **highly flammable, causes burns, harmful**
- Anhydrous dichloromethane, 30 mL
- Methyl vinyl ketone, 2.6 mL, 2.2 g, 31.6 mmol **highly flammable, causes burns, very toxic, irritant**
- 1-Adamantanamine, 4.8 g, 31.7 mmol **harmful, irritant**
- THF **highly flammable, irritant**
- Methanol **highly flammable, toxic**

Method

1. Charge a three-necked round-bottomed flask (100 mL), equipped with a magnetic stirrer bar and fitted with a nitrogen inlet, septum and condenser, with ammonium phosphinate (2.5 g, 30.1 mmol) and hexamethyldisilazane (6.4 mL, 4.9 g, 30.1 mmol). Heat the stirred mixture at 100–110°C for 1–2 h, until evolution of ammonia has ceased. **Caution!** ammonia is flammable, toxic and causes burns.
2. Cool the reaction mixture to 0°C and add dichloromethane (30 mL) and methyl vinyl ketone (2.6 mL, 2.2 g, 31.6 mmol) in succession. Stir the reaction mixture overnight at room temperature.
3. Filter the reaction mixture and concentrate the filtrate by rotary evaporation.
4. Dissolve the residual oil in the minimum volume of THF and add a solution of adamantanamine (4.8 g, 31.7 mmol) in the minimum volume of methanol/THF (20 : 80) at 0°C. Stir the resultant mixture at room temperature overnight.
5. Collect the crystalline adamantammonium salt of (3-oxo-butyl)-phosphinic acid **65** (6.4 g, 74%) by filtration.

The hydrophosphonylation (addition of dialkyl phosphonates), hydrophosphinylation (addition of alkyl alkylphosphinates or alkyl phosphinates) and addition of secondary phosphine oxides to unfunctionalized alkenes and alkynes occur under free radical conditions or with transition metal catalysis.[10,39,63,90]

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8

Low-coordinated phosphorus compounds

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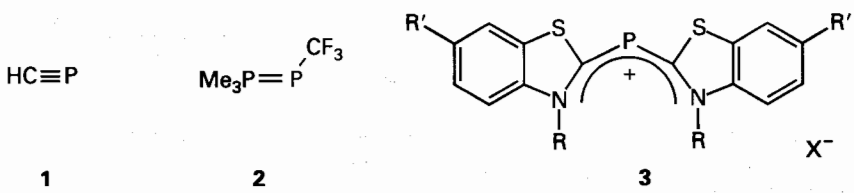
1. Introduction

'Phosphorus in Organic Chemistry—from Discovery to Repudiation of the Double Bond Rule' is the title of an article summarizing the history of this essential element.[1] Phosphorus was first mentioned by the German alchemist Hennig Brand in 1669 and recognized as an element by Lavoisier; since the beginning of the 20th century much effort has been devoted to the development of the chemistry of tri-, tetra-, and pentacoordinated compounds (σ^x) with tri-, tetra-, and pentavalent phosphorus (λ^x) centres. Milestones reached around the middle of the century were undoubtedly the olefination reactions of G. Wittig[2] and L. Horner[3] that have had such a decisive influence on strategies of organic synthesis.[1,4]

The double bond rule that limited (p,p)-π-bonds to elements of the first 8-atom period was violated for the first time in the 1960s. The generation of phosphaacetylenes **1**,[5] diphosphene **2**,[6] and phosphacyanine **3**[7] initiated dramatic developments, an end of which is not yet in sight (Figure 8.1).

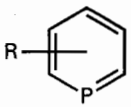
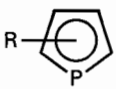
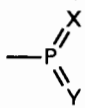
The major types of low-coordinated phosphorus compounds that have played decisive roles in the field are listed in Table 8.1 in order of increasing coordination number: phosphinidenes [and their $W(CO)_5$ complexes], phosphaalkynes,



1 **2** **3**

Fig. 8.1 First low-coordinated phosphorus compounds.

Table 8.1 Survey of most important low-coordinated phosphorous compounds

Coordination number 1	R—P: or R—P=W(CO)$_5$	Phosphinidenes or tungsten complexes	σ^1, λ^1–P
	R–C≡P	Alkylidynephosphines (λ^3-phosphaalkynes)	σ^1, λ^3–P
	P≡P	Diphosphorus units	σ^1, λ^3–P
Coordination number 2	$\overset{+}{P}$:	Phosphenium Cations	σ^2, λ^2–P
	C=P〰	Alkylidenephosphines (phosphaalkenes)	σ^2, λ^3–P
	X=P〰	Heteroatom-analogues X = B; Si; Sn; N; P; O; S; Se	σ^2, λ^3–P
		Phosphinines	σ^2, λ^3–P
		Phospholes	σ^2, λ^3–P
Coordination number 3		Phosphoranes X = Y = C or N ; X = C , Y = N , O, S, Se, ... X = N , Y = O, S, Se	σ^3, λ^5–P

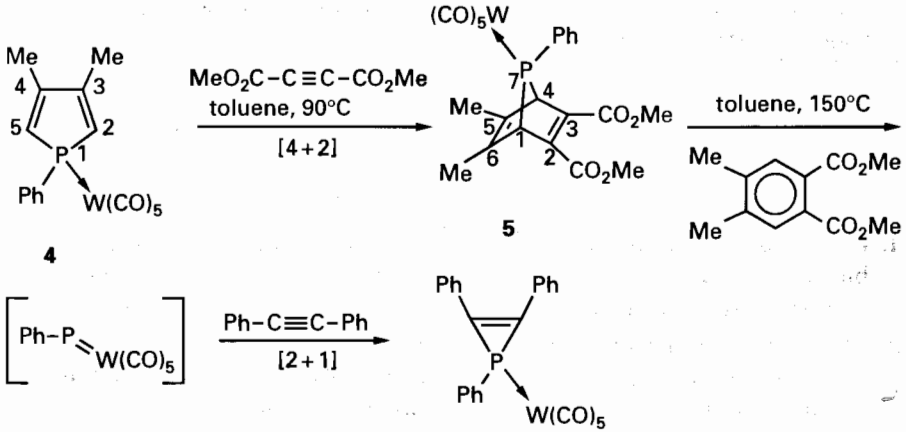
P_x increments (σ^1-P), phosphenium cations, phosphaalkenee and heteroatom analogues, λ^3-phosphinines, phospholes with further heteroatoms in the ring (σ^2-P) and, finally, the large field of phosphoranes with two, doubly bonded other elements as well as the λ^5-phosphaalkynes (σ^3-P).[8]

In this chapter we describe some typical experimental procedures for some short-lived and, especially, stable representatives of the above-mentioned classes of compounds.

2. Phosphorus compounds having coordination number 1

2.1 Phosphinidenes (IUPAC: phosphanylidenes) and terminal phosphinidene complexes[9,10]

Phosphinidenes (R-P), short-lived, reactive intermediates that are isoelectronic with nitrenes and carbenes, are accessible by fragmentation of phosphiranes, phosphol-3-enes, triazaphospholenes, and oxazaphospholenes and can be characterized by trapping reactions. The metal-complexed species [R-P-M, e.g., $M = W(CO)_5$] are more stable (but also not isolable) and react more selectively. As a model example we describe the transformation of (3,4-dimethyl-1-phenylphosphole)(pentacarbonyl)tungsten **4** with dimethyl acetylenedicarboxylate to the 7-phosphanorbornadiene derivative **5**.[11] The (phosphinidene)(pentacarbonyl)tungsten complex **6** is generated from the latter by a [4 + 1]-cycloreversion and trapped with diphenylacetylene via a [2 + 1]-cycloaddition to furnish the triphenyl-2-phosphirene complex **7** (Scheme 1).[12]



Scheme 1

Protocol 1.
Synthesis of [2,3-bis(methoxycarbonyl)-5,6-dimethyl-7-phenyl-7-phospha-norbornadiene](pentacarbonyl)tungsten (Structure 5 Scheme 1), the starting compound for the generation of (phenylphosphinidene)(pentacarbonyl)tungsten (Structure 6, Scheme 1) and its characterization by [2 + 1] cycloaddition to diphenylacetylene to form the triphenyl-2-phosphirene complex (Structure 7, Scheme 1)

Caution! This procedure must be performed in an efficient hood and gloves and goggles must be worn at all times. All operations must be carried out in the absence of oxygen and moisture. Prior to use, the reaction vessels must be heated with a heat-gun, evacuated twice to 10^{-3} mbar, and purged finally with argon (99.998%). All solvents must be carefully dried over alkali metals and distilled before use.

Equipment

- Dual-bank vacuum and argon gas manifold
- Source of dry argon
- Vacuum pump (10^{-3} mbar)
- Pressure-Schlenk tubes (100 mL)
- Heat-gun
- Thermostatted hot-plate stirrer
- Teflon-coated magnetic stirrer bars
- Chromatographic columns (60 cm long, Ø 4 cm) filled with silica gel (4% H_2O) (filled to a depth of 40 cm)

Materials

• (3,4-Dimethyl-1-phenylphosphole)(pentacarbonyl)tungsten,[a] 6.15 g, 12 mmol	**harmful**
• Dimethyl acetylenedicarboxylate, 5.12 g, 4.43 mL, 36 mmol	**corrosive**
• Toluene, 80 mL	**flammable, harmful**
• Toluene for chromatography	**flammable, harmful**
• *n*-Hexane for chromatography	**flammable, harmful**
• Diphenylacetylene, 2.02 g, 19 mmol	**flammable, harmful**

Method

1. Prepare a pressure-Schlenk tube (100 mL) equipped with a magnetic stirrer bar by heating the outer glass wall with the heat-gun, evacuate and purge with argon with the aid of the dual-bank vacuum and argon manifold.
2. To the pressure-Schlenk tube (100 mL) add toluene (40 mL), (3,4-dimethyl-1-phenylphosphole)(pentacarbonyl)tungsten (6.15 g, 12 mmol) and a threefold excess of dimethyl acetylenedicarboxylate (5.12 g, 4.43 mL, 36 mmol).
3. Heat the solution to 90°C for 24 h with stirring and determine the end of the reaction by ^{31}P NMR monitoring (**4**: $\delta = 7.5$; **5**: $\delta = 208$).
4. Evaporate the solvent in vacuum and purify the obtained product **5** by column chromatography on silica gel with toluene; m.p. 161°C, $\delta(^{31}P) = 208$, $^1J(^{183}W, P) = 237$ Hz, 4.08 g, 52%.

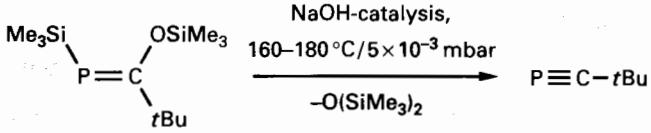
5. Prepare a pressure-Schlenk tube (100 mL) according to step **1**. Charge the tube with the phosphanorbornadiene complex **5** (4.80 g, 6.24 mmol), toluene (40 mL) and a threefold excess of diphenylacetylene (2.02 g, 19 mmol).
6. Heat the stirred solution to 150°C for 17 h and determine the end of the reaction by ^{31}P NMR monitoring (**5**: $\delta = 208$; **7**: $\delta = -169.5$). If necessary, add more diphenylacetylene.
7. Evaporate the solvent in vacuum and purify compound **7** by column chromatography on silica gel with hexane/toluene (90 : 10); m.p. 121°C, $\delta(^{31}P) = -169.5$, $^1J(^{183}W,P) = 259$ Hz, 2.28 g, 60%.

[a] (3,4-Dimethyl-1-phenylphosphole)(pentacarbonyl)tungsten **4** is prepared according to Ref. 13.

The decomplexation of compounds of the type **7** is achieved with iodine or perbromide, respectively, in the presence of methylimidazole or α,α-bipyridyl[14] and is a general reaction, hence phosphinidene complexes of this type can also be considered as synthetic equivalents of the free phosphinidenes.

2.2 Alkylidynephosphines (λ³-phosphaalkynes)[15–18]

Methylidynephosphine (HC≡P), the parent member of this class of compounds, is isoelectronic with acetylene. It stands at the very beginning of the history of phosphaalkyne chemistry;[5] two decades passed before the successful synthesis of the kinetically stabilized compound **9** (R = *t*-Bu, Scheme 2)[19,20] that is employed most frequently for studies on this class of compounds. Figure 8.2 shows a survey of the general reactions of this highly reactive triple bond system.



8 **9**

Scheme 2

Outstanding properties are the transformation to 1*H*- or 2*H*-phosphirenes after carbene addition (**9** → **10**),[12b,21,22] [3 + 2]-cycloadditions of 1,3-dipoles leading to a wide variety of heteroatom-substituted phospholes (**9** → **11**)[18] and Diels–Alder reactions (**9** → **12**) that make not only the phosphinines but also their valence isomers accessible.[23,24] In ene reactions phosphaalkynes

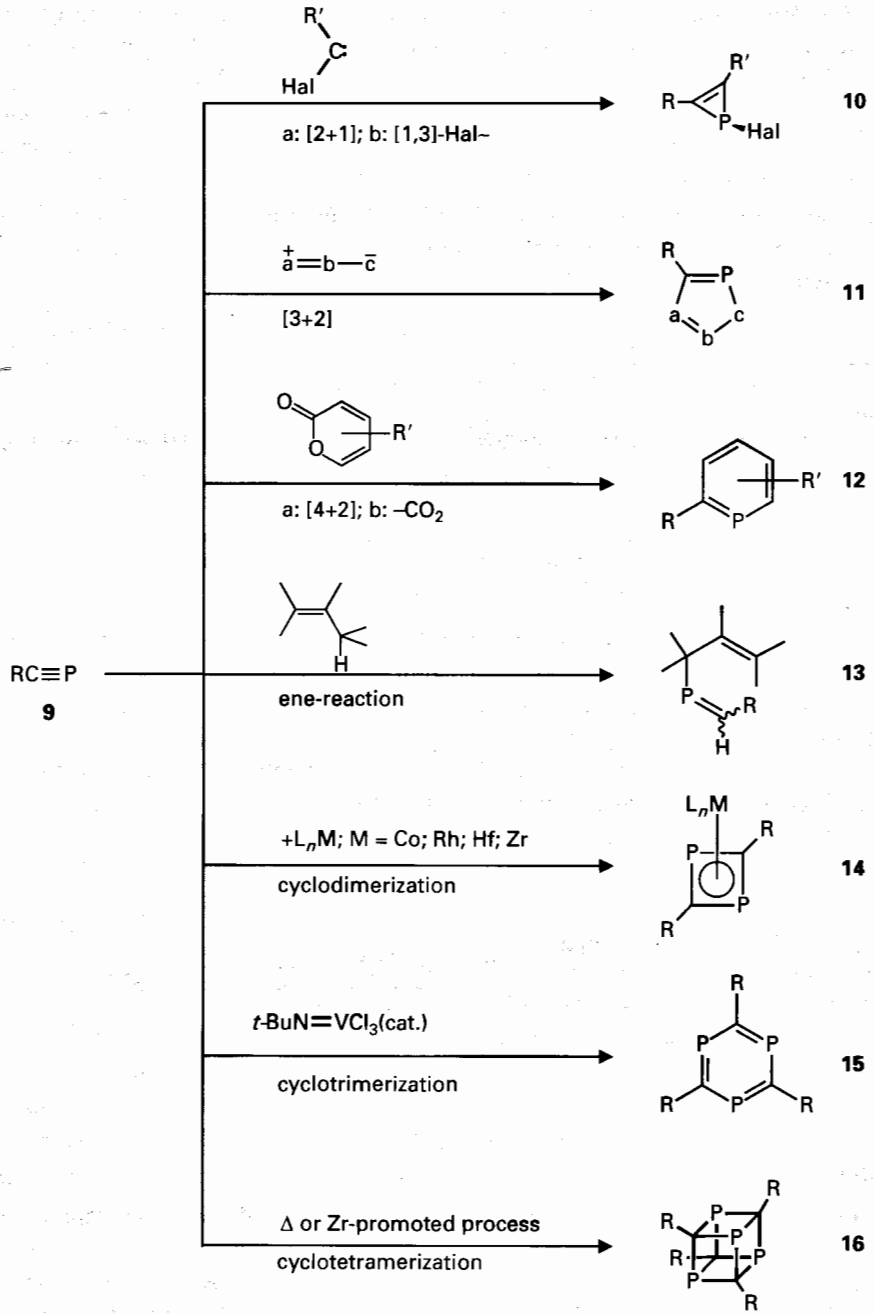


Fig. 8.2 General reactivity of λ^3-phosphaalkynes.

with the appropriate constitutions serve both as enophiles and as enes (**9** → **13**).[25] Cyclooligomerizations to 1,3-diphosphetes (**9** → **14**),[26] 1,3,5-triphosphabenzenes (**9** → **15**),[27,28] or tetraphosphacubanes (**9** → **16**)[29,30] complete the picture.

Phosphaalkynes **9** are obtained almost exclusively by β-elimination of hexamethyldisiloxane from appropriately substituted phosphaalkenes **8** (for their synthesis, see Protocol 3). The original elimination from **8** (R = *t*-Bu)[31] performed in solution at room temperature in the presence of sodium hydroxide was optimized (solid NaOH, temperatures between 160 and 180°C, vacuum distillation techniques) and also generalized. In particular cases, aluminium trichloride in dichloromethane has proved to be a useful reagent for the elimination.[32]

Protocol 2.
Synthesis of (2,2-dimethylpropylidyne)phosphine [*tert*-butylphosphaacetylene] (Structure 9, Scheme 2)

Caution! All operations must be carried out in the absence of oxygen and moisture. All reaction vessels must be heated with a heat-gun, evacuated repeatedly to 5×10^{-3} mbar, and purged with argon prior to use. For all manipulations of the air-sensitive materials, the Schlenk technique is employed.

Equipment

- Three-necked round-bottomed flask (100 mL, NS 14)
- Round-bottomed flask with side-arm stopcock (250 mL, NS 29)
- Round-bottomed flask with side-arm stopcock (25 mL, NS 14)
- Dimroth reflux condenser (NS 14, 25 cm length)
- Pressure-equalizing dropping funnel (250 mL, NS 14)
- Ground cone with stopcock, tubing adapter bent, 'argon inlet' (NS 14)
- Ground cone with stopcock, adapter bent, 'argon inlet' (NS 29)
- Cold trap (acetone/solid carbon dioxide) with ground cone (NS 29)
- Cold trap (liquid nitrogen) with ground cone (NS 14)
- Argon/vacuum line
- Source of dry argon
- Thermostatted hot-plate stirrer
- Silicone oil bath
- Thermometer (0–200°C)
- Dewar flask, dish-shaped for round-bottomed flask (250 mL)

Materials

- Ground sodium hydroxide 0.05 g — **corrosive**
- 2,2-Dimethyl-1-(trimethylsiloxy)propylidene(trimethylsilyl)phosphine, 8[a], 39.9 g, 150 mmol — **poisonous, flammable**
- Acetone for the cooling baths, 500 mL — **flammable**
- Liquid nitrogen for the cooling baths, 5000 mL

Method

1. Equip a dried three-necked, round-bottomed flask (100 mL) with a reflux condenser, a pressure-equalizing dropping funnel (250 mL), an argon inlet

Protocol 2. *Continued*

and an adapter with glass stopcock between the condenser and the cooling trap (see Figure 8.3).

2. Connect this part of the apparatus with the two cooling traps [trap A is equipped with a round-bottomed flask (250 mL) and trap B with a round-bottomed flask (25 mL)] and close trap B with an argon inlet with stopcock which is connected to a vacuum line.
3. Maintain the apparatus under vacuum (5×10^{-3} mbar) and purge with dry argon. Under a positive pressure of argon add ground sodium hydroxide (0.5 g) in the three-necked round-bottomed flask and transfer 2,2-dimethyl-1-(trimethylsiloxy)propylidene(trimethylsilyl)phosphine (39.9 g) in the dropping funnel.
4. Reduce the pressure in the apparatus to 5×10^{-2} mbar and heat the silicone oil bath to 160–180°C.
5. Fill the cold trap A with dry ice/acetone, cold trap B with liquid nitrogen and immerse the flask A in an liquid nitrogen bath (−196°C).
6. Then add the 2,2-dimethyl-1-(trimethylsiloxy)propylidene(trimethylsilyl) phosphine **8** (39.9 g) in small portions (2–3 mL) over a period of 90–120 min to the heated reaction flask with ground sodium hydroxide.
7. Over this time, the highly volatile (2,2-dimethylpropylidyne)phosphine **9** (R = *t*-Bu) and hexamethyldisiloxane are passed through the reflux condenser and condensed in trap A or in the flask A cooled to −196°C.
8. After the addition is complete, close the stopcock between the condenser and the cold trap A, remove the liquid nitrogen bath from flask A, and leave the reaction apparatus under vacuum (5×10^{-2} mbar) for a period of 3–4 h.
9. During this time (2,2-dimethylpropylidyne)phosphine **9** (R = *t*-Bu) distills from flask A to the cold trap B (−196°C) and hexamethyldisiloxane condensed on trap A (−78°C).
10. Then purge the apparatus with dry argon and remove immediately the liquid nitrogen in cold trap B by means of a stream of pressure air.
11. When the cold trap B reaches room temperature, the phosphaalkyne collects in the flask B as a colourless, mobile liquid, b.p. 61°C (normal conditions), 13.5–14.0 g, 93–96%. The ^{31}P NMR is diagnostic (C_6D_6): $\delta = -69.2$ (H_3PO_4 as external standard).

[a] 2,2-Dimethyl-1-(trimethylsiloxy)propylidene(trimethylsilyl)phosphine **8** is prepared by the reaction of pivaloyl chloride with tris(trimethylsilyl)phosphine (see Protocol 3).

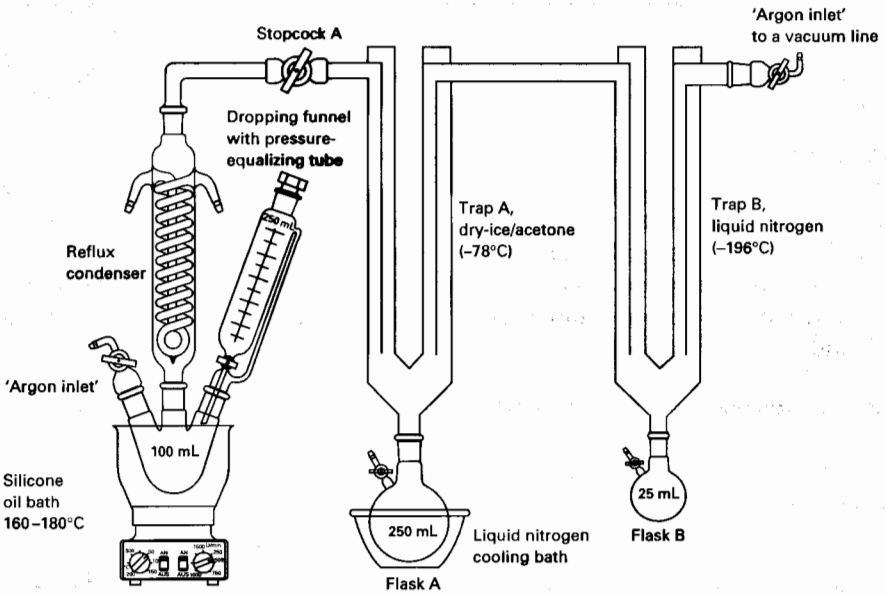


Fig. 8.3 Apparatus for the preparation of (2,2-dimethylpropylidyne)phosphine (*tert*-butylphosphaacetylene) **9** (R = *t*-Bu).

3. Phosphorus compounds having coordination number 2

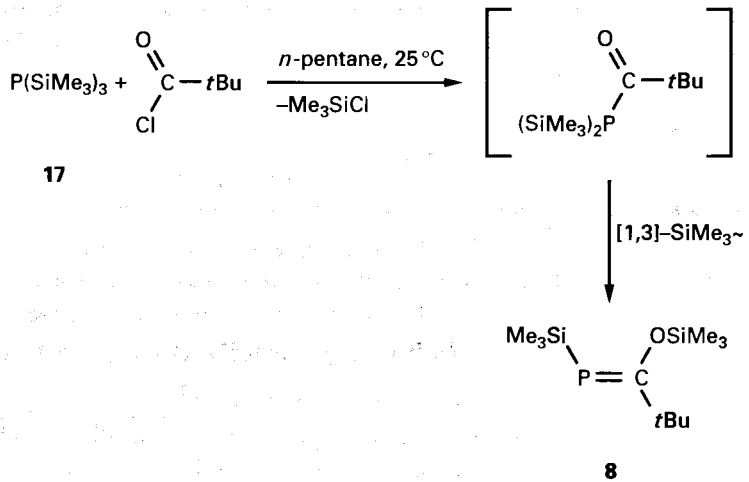
3.1 Alkylidenephosphines (λ^3-phosphaalkenes)[33–35]

In the case of the phosphaalkenes—in analogy to the phosphaalkynes—kinetic stabilization of the localized double bond by bulky substituents such as, *tert*-butyl-, trimethylsilyl-, adamantyl-, or 2,4,6-tri-*tert*-butylphenyl groups has again proved useful (Scheme 3). In addition, however, electronic effects also have a significant influence on the stability; thus, it has been shown that a sufficient overlap of the p orbitals in such double bond systems can be realized by reducing the polarity of the P—C bond—for example, by the presence of electron-withdrawing substituents at the phosphorus atom.

The class of phosphaalkenes with isolated P=C double bonds was first synthesized by Becker.[33] His synthetic strategy starting from trimethylsilylphosphines and acyl chlorides is still the most versatile (Protocol 3). The principle is based on the easily achievable, 1,3-silatropic migration of a silyl group bonded to phosphorus to a doubly bonded element such as nitrogen, oxygen, or sulfur. The process is favoured energetically by the construction of the P=C double bond with concomitant formation of a very stable silicon-element bond.

Protocol 3.
Synthesis of 4-*tert*-butyl-2,2,6,6-tetramethyl-3-oxa-5-phospha-2, 6-disilahept-4-ene (Structure 8, Scheme 3)

Caution! All operations must be carried out in the absence of oxygen and moisture. All reaction vessels must be heated with a heat-gun, evacuated repeatedly at 5×10^{-3} mbar, and purged with argon prior to use. For all manipulations of the air-sensitive materials, the Schlenk technique is employed. Pivaloyl chloride is harmful on inhalation. Tris(trimethylsilyl)phosphine **17** is toxic and extremely sensitive towards oxygen and water and highly inflammable upon contact with air and organic materials.



17 **8**

Scheme 3

Equipment

- Three-necked round-bottomed flask (500 mL, NS 14, NS 29, NS 14)
- Two round-bottomed flasks with side-arm stopcock (100 mL, NS 14)
- Two round-bottomed flasks with sidearm stopcock (25 mL, NS 14)
- Dimroth reflux condenser (NS 29, ca 20 cm)
- Pressure-equalizing dropping funnel (250 mL, NS 14)
- Ground cone with stopcock, tubing adapter bent, 'argon inlet' (NS 14)
- Claisen distilling links with standard ground joints, Liebig condenser with vertical delivery tube and vacuum adapter and pig receiver for three flasks
- Magnetic stirrer
- Magnetic stirrer bar

Materials

- Tris(trimethylsilyl)phosphine,[a] 50.0 g, 200 mmol — **poisonous, highly flammable, malodorous**
- Pivaloyl chloride,[b] 26.5 g, 200 mmol — **corrosive, harmful on inhalation**
- Dry *n*-pentane, 300 mL — **flammable**

Method

1. To a dried three-necked round-bottomed flask (500 mL) with magnetic stirrer bar, a reflux condenser (closed by blubber), a pressure-equalizing dropping funnel (250 mL) and an argon inlet, add dry *n*-pentane (200 mL) and tris(trimethylsilyl)phosphine (50 g).
2. To this solution add dropwise under magnetic stirring pivaloyl chloride (26.5 g) dissolved in *n*-pentane (100 mL).
3. When the addition is completed stir the solution at 25°C, maintaining the argon atmosphere for 4 days.
4. Remove all volatile materials by evaporation under reduced pressure (25°C, 10^{-2} mbar).
5. Transfer the residue to a dry round-bottomed flask (100 mL) and connect this flask with the distilling link.
6. Purification by distillation under reduced pressure to give a yellow oil, b.p. 45–48°C (10^{-3} mbar), 47.2 g, 90%. The ^{31}P NMR is diagnostic (C_6D_6): $\delta = 120.0$ (H_3PO_4 as external standard).

[a]Tris(trimethylsilyl)phosphine is prepared by the reaction of white phosphorus with sodium naphthalide and chlorotrimethylsilane according to literature.[36]
[b]Pivaloyl chloride is commercially available and is distilled and stored over calcium hydride prior to use.

The historical significance of bis(trimethylsilyl)chlorophosphaethene **18** lies in its conversion to the phosphaalkyne Tms—C≡P through thermal elimination of trimethylchlorosilane.[37] Furthermore, it has been used with success as an enophile in type II phospha-ene reactions.[25b]

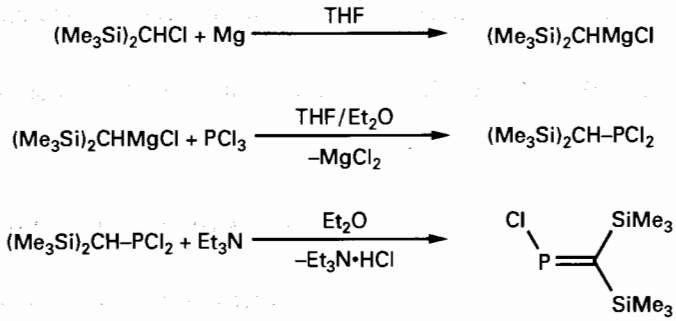
For the synthesis of **18** trichlorophosphine is alkylated to dichloro[bis(trimethylsilyl)methyl]phosphine by means of the appropriate Grignard reagent. The subsequent elimination of HCl can be achieved with, for example, diazabicyclooctane (DABCO), however, the use of triethylamine is advantageous for the work-up.[37,38]

Protocol 4.
Synthesis of bis(trimethylsilyl)methylenephosphinous chloride (Structure 18, Scheme 4)

Caution! All operations must be carried out in the absence of oxygen and moisture. All reaction vessels must be heated with a heat-gun, evacuated repeatedly at 5×10^{-3} mbar, and purged with argon prior to use. All reaction apparatus must be closed by a mercury blubber and connected to an argon and vacuum

Protocol 4. *Continued*

line. For all manipulations of the air-sensitive materials, the Schlenk technique is employed.



18

Scheme 4

Equipment

- Three-necked round-bottomed flask (250 mL, NS 14, NS 29, NS 14)
- Round-bottomed flasks with sidearm stopcock (500 mL, NS 29)
- Three round-bottomed flasks with sidearm stopcock (25 mL, NS 14)
- Dimroth reflux condenser (NS 29)
- Pressure-equalizing dropping funnel (100 mL, NS 14)
- Ground cone with stopcock, tubing adapter bent, argon inlet (NS 29)
- Claisen distilling links with standard ground joints, Liebig condenser with vertical delivery tube with vacuum adapter and pig receiver for three flasks
- Reversal sinter (G3)
- Magnetic stirrer

Materials

- [Chloro(trimethylsilyl)methyl](trimethyl)silane, 23.3 g, 119.6 mmol — **irritant**
- Magnesium turnings, 3.0 g, 120.4 mmol — **flammable**
- Dry tetrahydrofuran, 60 mL — **flammable, irritant**
- Dry diethyl ether, 200 mL — **highly flammable**
- Dry *n*-pentane, 400 mL — **flammable**
- Phosphorus(III) chloride, 17 g, 10.8 mL, 123 mmol — **corrosive**
- Triethylamine, 50 mL, 360 mmol — **flammable, corrosive**

Method

1. To a three-necked round-bottomed flask (250 mL) equipped with a magnetic stirrer bar and a reflux condenser with argon inlet (three-way stopcock connected to an argon/vacuum line and a blubber), magnesium turnings (3.0 g, 120.4 mmol) are added. For activation of the magnesium turnings, add 0.1 g iodine and heat the flask under vacuum.

2. Transfer tetrahydrofuran (40 mL) to the flask and bis(trimethylsilyl)chloromethane (23.3 g, 119.6 mmol) to the pressure-equalizing dropping funnel.
3. Open the three-way stopcock to the blubber and heat the tetrahydrofuran to reflux, then add 3–5 mL of bis(trimethylsilyl)chloromethane, stop heating and observe the reaction mixture. Beginning of the reaction is indicated by gas evolution and a light green colour.
4. Add dropwise the remaining bis(trimethylsilyl)chloromethane in the same way, so that a gentle reflux can be observed.
5. After addition is complete rinse the dropping funnel with 10 mL tetrahydrofuran and heat the solution under reflux for 1 h until the magnesium has disintegrated and the solution exhibits a deep olive green colour.
6. Now cool the solution to 0°C and transfer phosphorus(III) chloride (17 g, 10.8 mL, 123 mmol) and diethyl ether (50 mL) to the dropping funnel applying argon pressure.
7. Open the three-way stopcock to the blubber and add dropwise the phosphorus(III) trichloride solution to the Grignard reagent at 0°C.
8. The solution is stirred overnight and allowed to warm up to room temperature. Remove all volatile components by evaporation under reduced pressure on the vacuum line using an efficient cooling trap. It is necessary to remove all traces of phosphorus(III) chloride from the dichloro [bis(trimethylsilyl)methyl]phosphine before the next step.
9. Extract the residue with *n*-pentane (150 mL) and filter the suspension over a reversal glass sinter (G3) charged with celite. Then wash the filtercake with small portions of *n*-pentane until it is colourless and the *n*-pentane washings are no longer yellowish.
10. Evaporate the *n*-pentane under reduced pressure and use the residue without purification for the next step.
11. Add [bis(trimethylsilyl)methyl]dichlorophosphine (17 g, 65 mmol) and dry diethyl ether (100 mL) to a three-necked round-bottomed (500 mL) flask with argon inlet, reflux condenser with blubber, magnetic stirrer bar and pressure-equalizing dropping funnel.
12. Transfer a mixture of triethylamine (50 mL, 360 mmol) and dry diethyl ether (50 mL) to the dropping funnel and add it dropwise at 0°C to the [bis(trimethylsilyl)methyl]dichlorophosphine solution. Then warm up to room temperature and stir for 5 days.
13. Disappearance of the ^{31}P NMR signal at $\delta = 223.5$ for the [bis(trimethylsilyl) methyl]dichlorophosphine indicates completion of the reaction. Remove all volatile components under reduced pressure.
14. Extract the residue with *n*-pentane (100 mL) and transfer it to a reversal sinter (G3 with Celite), wash the filtercake with small portions of *n*-pentane, until it is colourless.

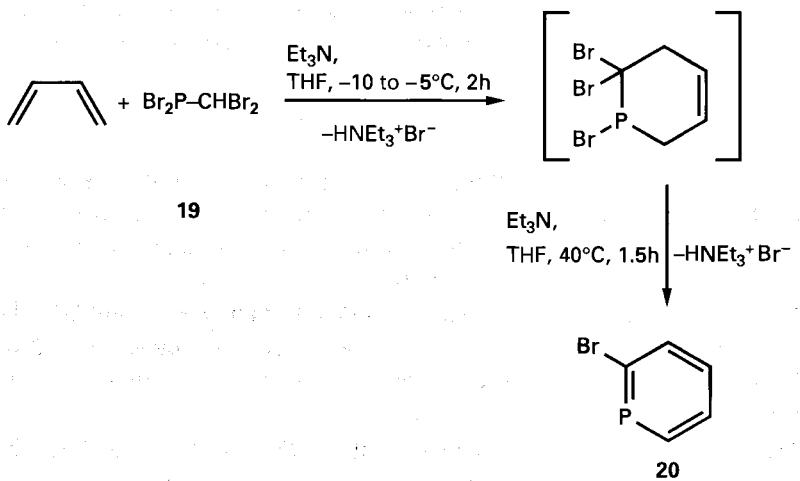
Protocol 4. *Continued*

15. Remove the *n*-pentane by distillation under reduced pressure and distill the product into a receiver flask, cooled with a dry-ice/acetone bath as a colourless liquid, b.p. 28–30°C (1.3×10^{-3} mbar), 10.2 g, 70%. The ^{31}P NMR is diagnostic, (C_6D_6): $\delta = 343.0$ (H_3PO_4 as external standard).

3.2 Phosphinines (phosphabenzenes)

λ^3-Phosphinines are Hückel aromatic systems even though their properties show pronounced differences to those of the homologous pyridines. Thus, for example, phosphininium salts are not stable (in contrast to pyridinium salts), whereas the formation of phosphininyl anions and radicals as reactive intermediates is known (neither species has been described in the case of pyridine).

One of the most elegant methods for the preparation of phosphinine proceeds through and intermediately formed trihalophosphacycloalkene (Scheme 5). When (dihalomethyl)dihalophosphines are heated with reactive dienes (e.g. alkyl-substituted buta-1,3-dienes) in the presence of excess triethylamine, the corresponding 2-halophosphinine is obtained in a simple, one-pot reaction.[39,40] 2-Bromophosphinine is of particular interest because it readily participates, for example, in palladium-catalysed coupling reactions.[41]



Scheme 5

Protocol 5.
Synthesis of 2-bromophosphinine (Structure 20, Scheme 5)

Caution! This procedure must be undertaken in an efficient hood and gloves and goggles must be worn at all times. All operations must be carried out in the absence of oxygen and moisture. All reaction vessels must be heated with a heat-gun, evacuated repeatedly to 5×10^{-3} mbar, and purged with argon prior to use. For all manipulations of the air-sensitive materials, the Schlenk technique is employed.

Equipment

- Three-necked round-bottomed flask (3000 mL, NS29, NS29, NS29)
- Dry ice condenser
- Pressure-equalizing dropping funnel (250 mL, NS29)
- Magnetic stirrer equipped with a Teflon-coated paddle
- Ice bath
- Argon/vacuum line
- Rotary evaporator
- Filter funnel
- Oil bath
- Column for flash chromatography (circa 20 cm × 2.5 cm)

Materials

• Dibromo(dibromomethyl)phosphine,[a] 120 g, 340 mmol	**corrosive, irritant**
• Butadiene, 1000 mL, ~12 mol	**highly flammable, poisonous**
• Tetrahydrofuran,[b] 175 mL	**highly flammable**
• Triethylamine,[c] 300 mL, 4.2 mol	**flammable, irritant**
• Hexane, 3.5 L	**flammable, irritant**
• Silica gel for flash chromatography (70–230 mesh)	**harmful on inhalation**
• Ice	
• Salt for ice–salt bath	
• Dry ice	**harmful on skin contact**

Method

1. Dry all glassware in an electric oven (circa 100°C) prior to use.
2. Flush a three-necked round-bottomed flask (3 L) with nitrogen and cool it to −15°C with the aid of an ice-salt bath.
3. Charge the flask with triethylamine (200 mL, 2.8 mol) and tetrahydrofuran (75 mL) and equip the flask with a dry ice condenser fitted with a gas inlet tube and a dropping funnel. Connect the head of the dropping funnel with the blubber.
4. Pass butadiene over the cold surface (−78°C) of the dry ice condenser and condense it into the mixture (circa 1 L, circa 12 mol).
5. Add dropwise dibromo(dibromomethyl)phosphine (120 g, 330 mmol) from the dropping funnel at a temperature between −10 and −5°C.
6. After addition, continue stirring for 1 h, remove the dry ice condenser and replace it by the blubber. Bring the mixture gently to room temperature in order to evaporate the excess of butadiene.

Protocol 5. *Continued*

7. Add triethylamine (100 mL, 1.4 mol) and tetrahydrofuran (100 mL) to the mixture, and heat it to 40°C for 1 h. Evaporate the solvents on a rotary evaporator, extract the residue twice with *n*-hexane (each 1 L), and filter the hexane solution.
8. Remove the hexane on a rotary evaporator to yield crude 2-bromophosphinine. Prepare a column for flash chromatography using silica gel and hexane as solvent, and chromatograph the residue rapidly under a slight nitrogen pressure.
9. Evaporate the hexane eluates on a rotary evaporator to yield the desired product as a colorless oil, 28 g, 48%.

[a]Dibromo(dibromomethyl)phosphine is prepared according to literature.[41]
[b]Tetrahydrofuran should be distilled over alkali metals or lithium aluminium hydride under nitrogen prior to use.
[c]Triethylamine is distilled over potassium hydroxide prior to use.

3.3 Phospholes

The phospholes are a well-studied class of compounds and have been described comprehensively in review articles[43,44] and books.[45,46] An outstanding property of the phospholes is their ability to undergo η^5-bonding with transition metals, in analogy to the isolobal cyclopentadienyl ligands. Recently, increasing interest has been directed to the synthesis and study of phospholes containing one or two further heteroatoms in addition to phosphorus in the ring.[18]

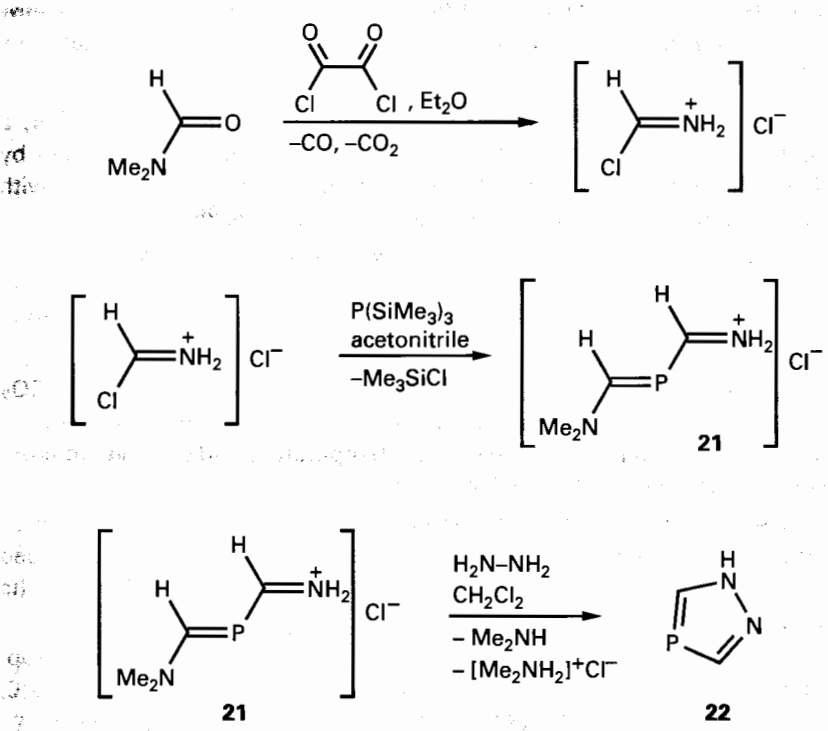
As an example we describe here the synthesis of the 1*H*-1,2,4-diazaphosphole **22** that, on account of its easy accessibility and as parent compound of the class, is of general interest. The synthesis proceeds through condensation of the cation **21**. The reaction of **21** with hydrazine involves cleavage of an ammonium salt to furnish the phosphole **23**.[46] The cation **21** is obtained via a methanaminium chloride—generated as an intermediate from *N*,*N*-dimethylformamide and oxalyl chloride—by condensation with tris(trimethylsilyl)phosphine.

This reaction sequence is representative for the synthesis of 1,2,4-diazaphospholes, which are the phosphorus analogues of the 1,2,4-triazoles. The reaction behaviour resembles that of pyrazoles with an additional reaction centre provided by the P=C double bond.

Protocol 6.
Synthesis of 1*H*-1,2,4-diazaphosphole (Structure 22, Scheme 6)

Caution! Oxalyl chloride is harmful on inhalation. Carbon monoxide evolved in the first step is toxic. Tris(trimethylsilyl)phosphine is toxic and extremely sensitive towards oxygen and water. It is spontaneously inflammable upon contact

with air and organic materials. Dimethylamine is corrosive and gives off an unpleasant smell. This procedure must be performed in an efficient hood and gloves and goggles must be worn at all times. All operations must be carried out in the absence of oxygen and moisture. Prior to use, the reaction vessels must be heated with an heat-gun, evacuated twice to 10^{-3} mbar, and purged finally with argon (99.998%). All solvents must be carefully dried over alkali metals and distilled before use.



Scheme 6

Equipment

- Dual-bank vacuum and argon gas manifold
- Source of dry argon
- Vacuum pump (10^{-3} mbar)
- Schlenk-type flasks (500 mL)
- Heat-gun
- Pressure-equalizing dropping funnel (10 mL)
- Blubber
- Magnetic stirrer
- Teflon-coated magnetic stirrer bar
- Fortuna pipette (2 mL)
- Ice bath
- Glass horn
- Schlenk-type glass sinter funnel
- Round-bottomed flasks with side-arm stopcock (100 mL, 250 mL)
- Sublimation apparatus
- Oil bath
- Dry ice
- Distillation apparatus

Protocol 6. *Continued*

Materials

• Dimethylformamide, 7.74 mL (7.31 g), 100 mmol	**poisonous, irritant**
• Diethyl ether, 200 mL	**highly flammable**
• Oxalyl chloride, 8.73 mL (12.70 g), 100 mmol	**poisonous, corrosive, irritant**
• Acetonitrile, 200 mL	**poisonous, flammable**
• Tris(trimethylsilyl)phosphine,[a] 8.90 g, 35.5 mmol	**poisonous, malodorous, highly flammable**
• Dichloromethane, 100 mL	**harmful on inhalation**
• Ethanol, 50 mL	**flammable**
• Hydrazine (98%)	**carcinogenic, poisonous, corrosive**

Method

1. Prepare a Schlenk tube (500 mL) equipped with a magnetic stirrer bar, a pressure-equalizing dropping funnel which is stoppered with a blubber by heating the outer glass wall with the heat-gun, evacuate and purge with argon with the aid of the dual-bank vacuum/argon line.
2. To this Schlenk tube (500 mL), add dimethylformamide (7.74 mL, 7.31 g, 100 mmol) and diethyl ether (150 mL) at room temperature, stirrer and cool the solution in an ice bath. Transfer oxalyl chloride (8.73 mL, 12.70 g, 100 mmol) in the pressure-equalizing funnel.
3. Slowly add oxalyl chloride within 15 min while a mixture of CO and CO_2 gases evolves and a white crystalline precipitate is formed. Raise the temperature of the reaction mixture to room temperature and stir until no more gases are evolved.
4. Remove the funnel and connect the tube with the horn. Transfer the reaction mixture under argon into the Schlenk glass sinter funnel which is equipped at the end with a round-bottomed flask with side-arm stopcock, wash the residue with diethyl ether (50 mL).
5. Transfer the residue into another round-bottomed flask with side-arm stopcock and dry it under high vacuum using the vacuum line, m.p. 140–145°C, 12.12 g, 95%.
6. Prepare a Schlenk tube (500 mL) as described in step 1. Charge the tube with *N*-(chloromethylene)-*N*-methylmethanaminium (9.10 g, 71.1 mmol) prepared in step 5 and dissolve it in acetonitrile (200 mL).
7. Place the tube in a water bath and add slowly from the pressure-equalizing dropping funnel tris(trimethylsilyl)phosphine (8.90 g, 35.5 mmol) at room temperature with stirring over 30 min. The colour of the mixture changes to orange and finally to brown.
8. Continue stirring for 10 h at room temperature and remove the solvent using the vacuum line. Take up the orange–yellow residue in diethyl ether (150 mL) and stir the suspension until a powder has formed.

9. Treat the residue according to steps 4 and 5, yield 6.15 g (96%). Recrystallize an analytical sample from ethanol to obtain pale yellow needles, m.p. 135–136°C.
10. Prepare an oven-dried (electric oven, 105°C, 1 h) round-bottomed flask with side-arm stopcock (250 mL) equipped with a magnetic stirrer bar, purge it with argon, place it in a water bath, and charge it with phosphaallylic chloride **22** (5.85 g, 32.4 mol) prepared in step 9. Add under argon at room temperature hydrazine (1.05 mL, 1.07 g, 32.8 mmol) from a Fortuna pipette (2 mL). The solution warms, evolves gas and darkens.
11. After 1 h, connect the tube with the distillation apparatus and remove the solvent by distillation.
12. Transfer the residue into the sublimation apparatus, crumble it, and sublime it slowly under reduced pressure (10^{-3} mbar) at 40–60°C for several days, m.p. 77–78°C, 1.52 g, 58% colourless crystals with a characteristic, unpleasant odour.[6]

[a]Tris(trimethylsilyl)phosphine is prepared by the reaction of white phosphorus with sodium naphthalide and chlorotrimethysilane according to literature.[36]
[6]1*H*-1,2,4-Diazaphosphole can be also prepared by 1,3-dipolar cycloaddition of diazomethane onto ethylidynephosphane (HC ≡ P).[48]

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9

Phosphorus methods in nucleotide chemistry

DAVID M. WILLIAMS and VICKI H. HARRIS

1. Introduction

There are currently many reagents available for the chemical synthesis of nucleotides via phosphorylation of nucleosides. Although much of the early chemistry in this area was based on the use of relatively unstable phosphorus(V) intermediates, there are now reliable methods in common usage, which employ both phosphorus(V) and the more reactive phosphorus(III) intermediates. The main impetus for the development of nucleotide chemistry in recent years has been the desire for the preparation of the 5′-triphosphates of nucleoside analogues containing both modified bases and modified sugars. It is not possible to cover all the practical aspects of nucleotide chemistry in a single chapter, so we have endeavoured to present general protocols describing the chemistry involved for the preparation of 2′-deoxyribonucleotides and have indicted the variations in these protocols for specific cases. Many of the protocols are also suitable for ribonucleotide synthesis, and readers are recommended to consult the referenced texts pertaining to these in this latter instance. We have also included the syntheses of several phosphate analogues of nucleosides, which have applications from increased chemical and/or enzymatic stability, to uses in studying stereochemical and other aspects of enzyme mechanisms. Practical methods for the synthesis of oligonucleotides comprising DNA, RNA or containing modified phosphate diester linkages have been adequately described previously in this series[1] and the current chapter is intended to complement this information by concentrating on methods for the synthesis of simple nucleotides.

2. Outline of chemistry

2.1 Nucleoside monophosphates

Although there are many methods available, there are two main routes for the synthesis of nucleoside monophosphates. These involve either the reaction of the nucleoside with 2-cyanoethylphosphate in the presence of a condensing agent such as dicyclohexyl carbodiimide (DCC)[2,3] or phosphorylation of the nucleoside

using a reactive phosphorus(V) reagent.[4] Both methods are selective for the more reactive primary hydroxyl group, but varying degrees of specificity are achieved. The latter procedure is probably the simplest and most convenient method of these two and involves the phosphorylation procedure developed by Yoshikawa.[4] This involves the regioselective phosphorylation of the nucleoside at the 5′-position using phosphoryl chloride ($POCl_3$) in trimethylphosphate at 0°C to give the highly reactive phosphorodichloridate intermediate as shown in Figure 9.1.

Hydrolysis of this intermediate with aqueous triethylammonium bicarbonate (TEAB) buffer gives the monophosphate. Some modifications of this protocol have been described, whereby a phosphorotetrazolide has also been used for phosphorylation of nucleoside analogues bearing acid labile functional groups.[5] In the Yoshikawa procedure, no protection of the base or sugar is required, although biproducts arising from phosphorylation of the secondary hydroxyl groups of the sugar vary depending on the nature of the nucleoside. The route is highly versatile, since the phosphorodichloridate intermediate can also be reacted *in situ* with pyrophosphate[6] as a route to nucleoside triphosphates (see Section 2.3), whilst replacement of phosphoryl chloride by thiophosphoryl chloride allows the preparation of nucleoside thiophosphate analogues.[7] (see Section 2.3).

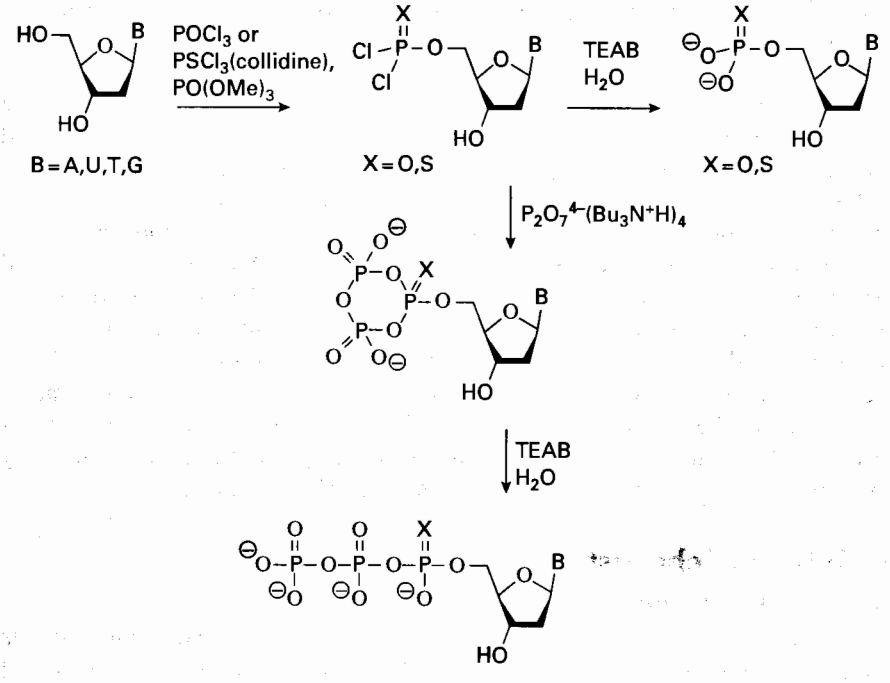


Fig. 9.1 Synthesis of nucleoside mono- and triphosphates and (1-thio)triphosphates using phosphorus(V) chemistry.

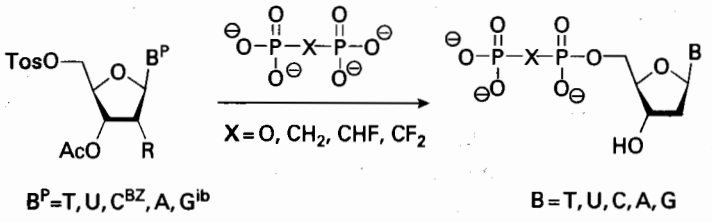


Fig. 9.2 Synthesis of nucleoside diphosphates.

In contrast, the synthesis of nucleoside 3′-phosphates is best achieved by DCC-mediated condensation of suitably protected nucleosides with 2-cyanoethylphosphate.[3]

2.2 Nucleoside diphosphates

Although the treatment of a phosphorodichloridate with the tri-*n*-butylammonium salt of phosphoric acid seems a plausible route to nucleoside diphosphates, this has recently been shown instead to be a means of preparing the triphosphate.[8] Probably the most reliable method for preparing diphosphates is that described by Poulter,[9] in which the tetra-*n*-butylammonium salt of a nucleophilic phosphorus component, for example, pyrophosphate is reacted with a nucleoside 5′-tosylate in acetonitrile (Figure 9.2).

The method has the added advantage in that it provides a route not only to nucleoside diphosphates (upon reaction with pyrophosphate) but also allows the preparation of phosphonate analogues by the use of methylene or difluoromethylene bisphosphonates.[10] The latter analogues are both stable to hydrolysis.

2.3 Nucleoside triphosphates

Earlier methods for the synthesis of nucleoside 5′-triphosphates generally involved the activation of a nucleoside 5′-phosphomonoester, followed by its reaction with pyrophosphate. The main methods involve either conversion of the monoester into a phosphoromorpholidate[11] or activation of the monoester with reagents such as carbonyl diimidazole followed by reaction with pyrophosphate.[12] Although both these methods, especially the latter, are still used, the convenience of a one-pot reaction for conversion of the free nucleoside to its triphosphate has led to two methods being most widely used. The most common method for the synthesis of nucleoside triphosphates is based on the Ludwig modification[6] to the Yoshikawa phosphorylation procedure, which involves reaction of the intermediate phosphorodichloridate *in situ* with pyrophosphate to produce a cyclic triphosphate by an intramolecular cyclization. Upon addition of aqueous buffer the cyclic triphosphate rapidly decomposes to the linear triphosphate (Figure 9.1).

For the initial phosphorylation step of this method, no protection of the base or sugar is required, although biproducts arising from phosphorylation

of the secondary hydroxyl groups of the sugar vary depending on the nature of the nucleoside. Nucleoside analogues bearing modified bases with reactive functionality require protection prior to phosphorylation. Consequently, many modifications to the Ludwig protocol have been described, which allow the use of nucleoside analogues containing modified bases, which might otherwise react during the phosphorylation procedure. These include the use of a proton-sponge® (1,8-bis(dimethylamino)naphthalene) for modified bases such as pyrimidines and purines bearing alkene and alkyne modifications, which might otherwise react with HCl liberated during the reaction[13] and the protection of reactive primary aminoalkyl functional groups with the base-labile, trifluoroacetyl group.[14,15] The addition of proton-sponge® also dramatically increases the rate of phosphorylation. Thus, even when its inclusion is not specifically necessary, for phosphorylations of several C5-modified pyrimidines which are very slow (more than 4 h) its inclusion can be beneficial.

With a small adjustment to this procedure, using thiophosphoryl chloride ($PSCl_3$) in place of phosphoryl chloride ($POCl_3$), the nucleoside 5′-(1-thio)triphosphates can be easily synthesized.[7] These compounds have been used extensively for applications *inter alia* for site-directed mutagenesis, sequencing of nucleic acids and investigation of enzyme mechanisms.[16] Phosphorylation with thiophosphoryl chloride is generally slower than with phosphoryl chloride but still occurs at a reasonable rate for purine nucleosides. However, for pyrimidine nucleosides, it is necessary to add 2,4,6-collidine as a catalyst, which forms a reactive intermediate with the thiophosphoryl chloride *in situ*.

There is also good methodology available for the one-pot synthesis of triphosphates using phosphorus(III) chemistry.[17] The phosphorylating agent used in this case is salicyl chlorophosphite, which produces a phosphite intermediate which is subsequently reacted with pyrophosphate again via an intramolecular cyclization to form a cyclic species with an α-phosphite moiety (Figure 9.3). Oxidation of this intermediate with iodine in aqueous pyridine produces the cyclic triphosphate species, which can be rapidly hydrolysed as described above to give the linear triphosphate. The advantages of this phosphorus(III) method are twofold. First, the cyclic phosphorus(III) species can alternatively be oxidized with sulfur to give, following hydrolysis, nucleoside 5′-(1-thio)triphosphates. Also, the method is much more rapid than the phosphorus(V) chemistry and has advantages for nucleosides, which are phosphorylated only slowly by phosphoryl chloride. However, the regioselectivity for 5′-phosphorylation is less, which necessitates protection of the 3′-hydroxyl groups of 2′-deoxynucleosides. The method has been widely used for nucleosides which lack 2′ or 3′-hydroxyl groups, such as 2′-deoxy-2′-azido[18] and others. The removal of the base-labile protecting groups with aqueous ammonia solution is completely compatible with the stability of the nucleoside triphosphates.

Enzymatic routes to analogues of nucleoside triphosphates have also been described but are not included here.[19]

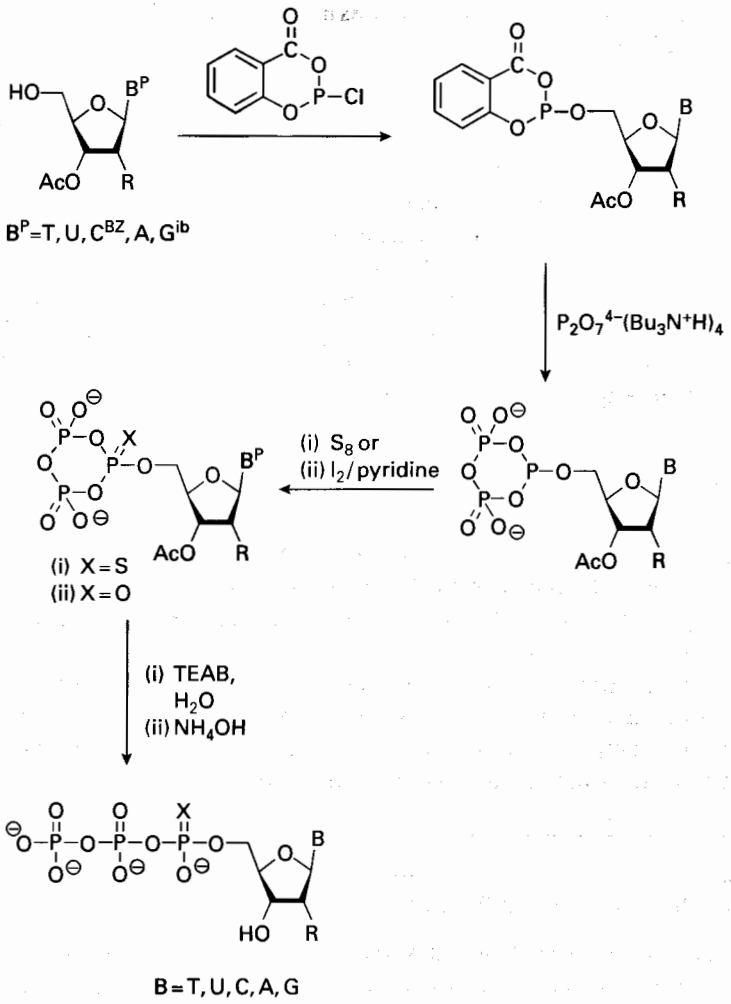


Fig. 9.3 Synthesis of nucleoside triphosphates and (1-thio)triphosphates using phosphorus(III) chemistry.

3. Synthesis

3.1 Materials and methods

The following list contains general equipment and reagents, which are used in the protocols.

Preparative reversed-phase HPLC column used was a Zorbax SB-C18 column 21 × 250 mm (Anachem, UK, Ref 880975-102).

Semi-preparative reversed-phase HPLC column was a Waters μbondapak C18 column 7.8 × 300 mm (Waters, UK, Ref. 84176).

Analytical reversed-phase column was a Zorbax SB-C18 column 4.6 × 250 mm (Anachem, UK, Ref 880975-902).

A variety of MPLC columns suitable for use with Sephadex® and Sepharose® resins are available from Amersham Phamacia Biotech.

3.1.1 Chemicals and reagents

AnalaR glacial acetic acid and tetra-sodium pyrophosphate decahydrate were from BDH. Chemicals/reagents from Aldrich: acetonitrile, anhydrous 1,4-dioxane (dioxan), barium 2-cyanoethylphosphate hydrate, 2,4,6-collidine (99%), anhydrous DMF, phosphoryl chloride (phosphorus oxychloride) (99 and 99.999%), thiophosphoryl chloride (98%), salicyl chlorophosphite (2-chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one), tri-*n*-butylamine (99+%), triethylamine (99%), tri-*n*-octylamine (99+%), trimethylphosphate (99+%), 3 Å molecular sieves.

The following resins were used; Dowex® 50W × 8 in the H^+ form (100–200 mesh), from BDH, Sephadex®—DEAE A-25, ion exchange resin (40–120 μm) from Aldrich.

Purification of chemicals: most of the chemicals can be used as bought but the chemicals listed below need further purification before use. Triethylamine and 2,4,6-trimethylpyridine (2,4,6-collidine) should be refluxed and distilled from potassium hydroxide pellets before use.

Drying of solvents: acetonitrile and pyridine should be refluxed and distilled from calcium hydride as required. Before use, store sufficient anhydrous acetonitrile, anhydrous DMF, trimethyl phosphate, anhydrous dioxan, tri-*n*-butylamine, tri-*n*-octylamine over activated 3 Å sieves.

Protocol 1.
Preparation of 2 M TEAB solution

The following protocol is suitable for preparing TEAB for use in the reactions described in subsequent protocols and for ion exchange chromatography. When TEAB is required for HPLC, the distilled water should be replaced by HPLC grade water.

Materials

- Triethylamine (distilled from KOH pellets)—568 mL — **extremely flammable, irritant**
- Distilled water—about 1.5 L
- CO_2 pellets — **causes burns**

Method

1. Add 560 mL of distilled triethylamine to 1 L of distilled water in a clean 2.5-L bottle cooled in an ice bath.
2. Bubble carbon dioxide gas though the solution (stir or swirl occasionally) until the pH is below 8. This takes a few hours. The CO_2 is easily produced by

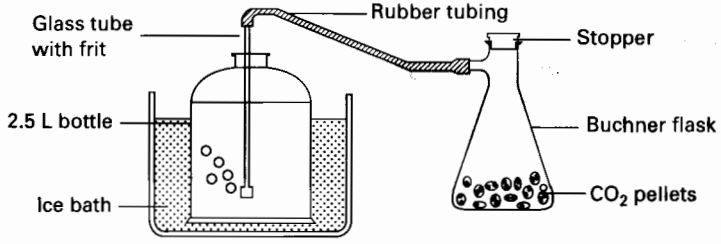


Fig. 9.4 Equipment for the preparation of triethylammonium bicarbonate (TEAB).

placing a few CO_2 pellets in a 2-L Buchner flask, which is connected from its side-arm with plastic tubing with a glass frit, the flask is then gently stoppered with a rubber stopper/bung as in Figure 9.4.

3. Once the required pH has been achieved, make the solution up to 2 L final volume with distilled water. It can then be stored in the fridge for several weeks (the pH does increase with time, but can be simply readjusted by bubbling more CO_2 through the solution).
4. To de-gas the solution just before use, reduce the pH of the solution to be de-gassed to about 7 (by bubbling CO_2 through the solution) and stir magnetically in a stoppered 5-L Buchner flask.
5. Connect the flask to a water vacuum pump. The de-gassing only takes about 2–3 min until the bubbles have cleared slightly but not totally. Another method of de-gassing is by filtering the solution through a membrane (particularly useful for de-gassing HPLC solutions).

Protocol 2.
Use of DEAE Sephadex® A-25 ion exchange resin

Method

1. Allow the Sephadex® resin (DEAE A-25, ion exchange resin, 40–120 μm, from Aldrich) to swell before use, by leaving it overnight in 50 mM TEAB in the fridge (it can also be stored in this way).
2. Following several purification procedures, to regenerate used 'stock' Sephadex® resin, place in a clean bottle at 40°C for 4 h in 2 M TEAB (**Caution!** Do not fill more than 2 L).
3. Filter the resin using a large glass sintered (small pore size) Buchner filter (this can take a fairly long time!).
4. Wash the resin with distilled water until the pH of the filtrate is about 7.
5. Transfer the resin to a screw-top flask and store in 50 mM TEAB in the fridge.

Protocol 3.
Use of Dowex® H^+ ion exchange resin

Materials

- Methanol — **highly flammable, toxic**
- Pyridine — **highly flammable, harmful, irritant**

Method

1. Place the desired amount of Dowex® 50W × 8 H^+ form (100–200 mesh from Aldrich) according to the relevant protocol and wash with two column volumes of HPLC grade methanol (toxic, flammable) followed by five column volumes of distilled water (the pH should be about 7).
2. To regenerate the Dowex® resin after use, place in a glass column, wash with 0.1 M hydrochloric acid (corrosive) until the pH of the effluent is acidic and then wash with distilled water until it is neutral.
3. To prepare Dowex® pyridinium form, Dowex® 50W × 8 H^+ form, wash the resin in a glass column, with 10% (v/v) pyridine in distilled water until the effluent is basic, then wash with distilled water until the effluent is neutral.

Protocol 4.
Distillation of phosphoryl and thiophosphoryl chloride

Although gold label phosphoryl chloride may be purchased (99.999%, Aldrich), we prefer to freshly distil standard grade phosphoryl chloride and thiophosphoryl chloride immediately prior to use.

Materials

- Phosphoryl chloride/thiophosphoryl chloride — **harmful, corrosive, irritant, causes burns, reacts violently with water**

Method

1. Set up the dry equipment according to Figure 9.5. For convenience, we have obtained a small single piece of equipment consisting of a 50 mL pear-shaped distillation flask with a B10 stopper, connected via a short (12 cm) Vigreux column to a condenser (12 cm) and receiver head.
2. Place about 15 mL of phosphoryl or thiophosphoryl chloride in the distillation flask together with a small dry magnetic stirrer bar, and stopper the flask.
3. Start heating the flask slowly, stirring the reagent vigorously.
4. Then turn the water vacuum pump on slowly, the $CaCl_2$ will protect the phosphoryl chloride or thiophosphoryl chloride from any water vapours.

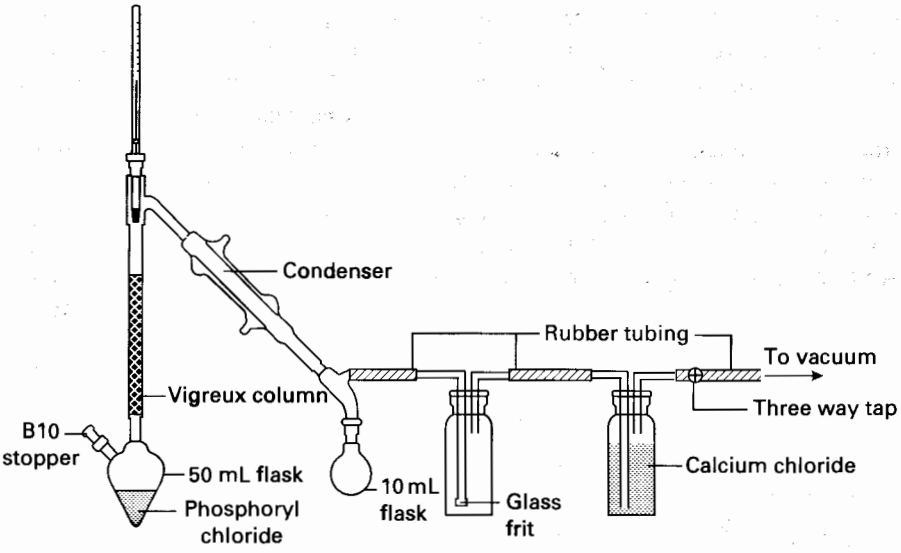


Fig. 9.5 Equipment for the distillation of phosphoryl and thiophosphoryl chloride.

5. Collect 5–10 mL of distillate (boiling point is around 50°C at reduced pressure).
6. Let argon into the equipment by connecting the three-way tap to a balloon filled with argon.
7. Stopper the flask with a septum.
8. Use the distilled reagent immediately.
9. Small quantities of undistilled reagent (<5 mL) can be destroyed by adding it dropwise and **extremely cautiously** to dry methanol cooled in an ice bath (wear gloves, safety glasses and perform in fume cupboard—note that the reaction of phosphorylchloride with water is delayed and extremely violent and should be avoided).

3.2 Phosphorylation of nucleosides using the Yoshikawa procedure—synthesis of nucleoside 5′-monophosphates

The phosphorylation of free nucleosides using phosphoryl chloride in trimethylphosphate to give a nucleoside phosphorodichloridate is known as the Yoshikawa procedure[4] (Protocol 5). Hydrolysis of this intermediate in aqueous TEAB provides a route to nucleoside 5′-monophosphates (Protocol 8) although it is mainly used to prepare nucleoside triphosphates, whereby pyrophosphate is reacted with the nucleoside intermediate (see Section 3.3 and Protocol 10). In practice, a compromise between formation of the 5′-phosphorodichloridate that is,

disappearance of starting material is balanced with phosphorylation at the 3′ position of 2′-deoxynucleosides to give the 3′,5′-bisphosphate. The formation of the monophosphorylated species can be monitored either by ion exchange HPLC or silica TLC and when this is judged optimal (minimal starting material and minimal bisphosphate), the butylammonium salt of pyrophosphate is then added. This forms the cyclic triphosphate species, which upon addition of aqueous triethylammonium bicarbonate buffer, undergoes hydrolysis to the linear triphosphate product. The method described here is suitable for most nucleosides and we have found it suitable for the preparation of nucleoside 5′-monophosphates and 5′-triphosphates on a scale between 100 μmol and 1 mmol (refer to Figure 9.1).

Protocol 5. Yoshikawa phosphorylation

Materials

- Nucleoside (0.2 mmol)
- Trimethyl phosphate, 99+%, 15 mL (0.5 mL for reaction) **harmful, possible mutagen**
- Anhydrous dimethyl formamide, 15 mL **harmful, irritant, flammable**
- Activated 3 Å molecular seives
- Phosphoryl chloride (phosphorus oxychloride) 23 μL (freshly distilled, Protocol 4 or 99.999%) **harmful, corrosive, irritant, causes burns, reacts violently with water**

Method

1. Three quarter fill two dry 10 mL round-bottomed flasks with anhydrous DMF and add some activated 3 Å molecular sieves (about 1 cm^3) and stopper with septums. Do the same with some trimethylphosphate, mark one of each as the 'wash' and the other as the 'reagent'. For convenience, these can all be clamped to the same retort stand making a 'phosphorylation tree'.
2. Weigh the nucleoside (0.2 mmol) to be phosphorylated into a dry 10 mL pear-shaped flask containing a small, dry magnetic stirrer bar and seal the stopper with a piece of filter paper and a rubber band.
3. Dry the sample overnight in the presence of phosphorus pentoxide in a vacuum oven set to 50°C.
4. Open the oven to a balloon filled with argon so that the flask is filled with argon and the atmosphere is kept dry.
5. Seal the flask with a septum and insert a dry needle through this into the flask.
6. Place the flask in the vacuum oven set to 50°C in the presence of phosphorus pentoxide (corrosive, reacts violently with water) for 10 min, then repeat step 4.

7. Remove the needle out of the septum which is sealing the flask.
8. Place a small balloon filled with argon through the septum, sealing the flask in order to maintain a positive pressure of argon in the flask.
9. Dry the gas-tight syringe first by drawing some of the DMF 'wash' from the phosphorylation tree into the syringe barrel and then ejecting it. This is then repeated with the trimethylphosphate 'wash'.
10. Add trimethylphosphate (0.5 mL) into the reaction flask using the dry, gas-tight syringe.
11. Make sure the nucleoside is fully dissolved—this may require a little heating.
12. Put the flask into an ice bath and stir for 10 min.
13. Add phosphoryl chloride (23 μL, 0.24 mmol) dropwise with a dry gas-tight syringe. The solution may go a little cloudy.
14. After 30 min, then each hour, remove a small sample of the reaction mixture for analysis by either by ion exchange HPLC (Protocol 6) or silica TLC (Protocol 7) until the reaction has gone to completion (85–90% phosphorylation). In practice, the phosphorylation is a compromise between consumption of starting material and minimal bisphosphate formation). It is normally complete within 2 h, although with some analogues, for example, C5-modified pyrimidine nucleosides, reactions may take 10 h.

Protocol 6.
Monitoring phosphorylation reactions by anion exchange HPLC

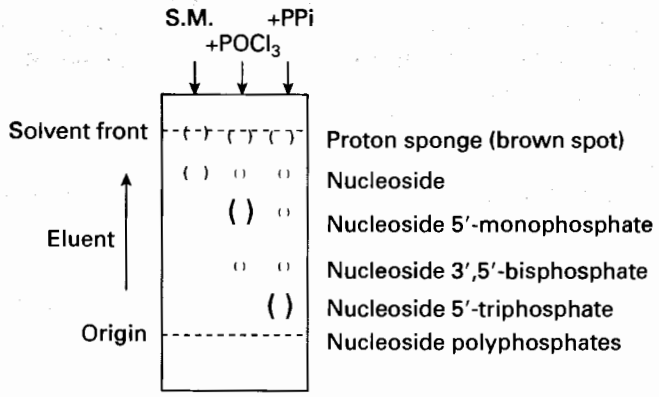
Method

1. Set up a SAX-10 HPLC column (4.6 × 30 cm) with a gradient of 10–500 mM aqueous potassium phosphate, pH 6.6 over a period of 20 min with flow rate of 1 mL/min.
2. Dry a 10 μL gas-tight syringe by drawing some of the DMF wash from the phosphorylation tree into the syringe barrel and then ejecting it and repeating with the trimethylphosphate wash.
3. Remove 2 μL of the reaction mixture and add to 400 μL of 0.1 M TEAB, pH 7.5.
4. Analyse the reaction mixture using conditions in step 1 (injection of 50 μL is generally sufficient).
5. Retention times vary for different nucleotides, but as a very rough guide, they are approximately; nucleoside 5 min, monophosphate 9 min, 3′,5′-bisphosphate 17 min and triphosphate 19 min.

Protocol 7.
Monitoring phosphorylation reactions by silica TLC

Method

1. Dry a 10 μL gas-tight syringe by drawing some of the DMF wash from the phosphorylation tree into the syringe barrel and then ejecting it and repeating with the trimethylphosphate wash.
2. Remove about 3 μL of the reaction mix using the syringe and add this to 50 μL of 0.1 M TEAB to quench the reaction.
3. Spot this onto a silica TLC plate and check that it is possible to visualize the compound under an UV lamp (**Caution!** UV lamps can cause sunburn).
4. Develop the plate using an eluent of concentrated aqueous ammonia solution (33%), isopropanol and water (11:7:2, v/v/v). Tip: The plates take much longer to run than silica TLC plates using organic eluents, but cutting slightly narrower plates than normal can help speed up the process.
5. Examples of typical TLC plates for the phosphorylation (Protocol 5) and triphosphate and (1-thio)triphosphate synthesis are shown in Figure 9.6. Typically the thiophosphates have slightly higher R_f values than the corresponding phosphates, but the overall order of components on the silica TLC remains the same. Proton-sponge® (brown spot) and collidine both run at the solvent front, whilst using the phosphorus(III) chemistry, a small number of fluorescent non-nucleoside spots are observed with higher R_f



Typical silica TLC for phosphorylation with P(V) chemistry with proton-sponge (if added)

Fig. 9.6 Typical silica TLC for analysis of nucleotides.

values than the free nucleoside (Tip: nucleosides can be visualized as purple/black spots after dipping the silica TLC plate in anisaldehyde solution (**Caution!** Corrosive—wear gloves) and heating: this contains anisaldehyde (9.2 mL), acetic acid (3.75 mL), conc. H_2SO_4 (1.25 mL) and 95% ethanol (388 mL)).

Protocol 8.
Preparation of nucleoside 5′-monophosphates

Materials

- 0.1 M TEAB (see Protocol 1) — **irritant**
- Diethyl ether, 30 mL — **highly flammable**

Method

1. Phosphorylate the nucleoside (0.2 mmol) as described in Protocol 5, steps 1–14. When the reaction has gone to about 85–90% completion, immediately transfer the contents of the flask into 20 mL of 0.1 M TEAB in a 100 mL round-bottomed flask.
2. Stir the contents of the flask in step 1 for 1 h at room temperature.
3. Transfer the contents of the flask in step 2 into a 100 mL separating funnel and extract with diethyl ether (2 × 15 mL) and retain the aqueous layer in a conical flask (100 mL).
4. Dilute the aqueous layer with one volume of distilled water and purify the crude product by MPLC anion exchange chomatography (see Protocol 19). Yields after MPLC are between circa 25 and 50%.

3.3 Synthesis of nucleoside 5′-triphosphates using phosphorus(V) chemistry

Following phosphorylation using the Yoshikawa procedure, the reaction of pyrophosphate with the intermediate phosphorodichloridate followed by aqueous work-up provides a convenient one-pot synthesis for triphosphates. With slight modification to this procedure, thiophosphoryl chloride can be used in place of phosphoryl chloride to give 5′-(1-thio)triphosphates as a mixture of two diastereoisomers (*S*p and *R*p). Both procedures require the prior preparation of the DMF-soluble, bis(tri-*n*-butylammonium) salt of pyrophosphate. This is prepared as a 0.5 M solution, can be stored in the fridge and is converted to its *tetrakis*(tri-*n*-butylammonium) salt immediately prior to reaction. Rates of nucleoside phosphorylation vary considerably and it is necessary to monitor the formation of the phosphorodichloridate during the Yoshikawa procedure in order

to judge when to add the pyrophosphate. The cyclic triphosphate is formed rapidly and in the absence of water is stable for several hours. However, a slow reaction with excess pyrophosphate in the solution is possible and generally hydrolysis of this intermediate with TEAB after 10 min is recommended.

The liberation of HCl during the Yoshikawa phosphorylation can lead to undesired side reactions of unsaturated side chains of modified pyrimidines. Protocol 11 describes a modified procedure for the phosphorylation step, whereby a strong, non nucleophilic base (proton-sponge®, 1,8-bis(dimethylamino)naphthalene) is added. We have found that addition of proton-sponge® also increases the rate of phosphorylation and in circumstances even when it is not specifically required, its addition can also be beneficial for particularly slow phosphorylation reactions.

In the synthesis of 5-aminopropenyl derivatives of dUTP[14] and other 5-amino-modified dUTPs,[15] the amino group has been protected with trifluoroacetyl group. This is a useful modification to the triphosphate synthesis where bases modified with alkylamino groups are involved. In this instance the trifluoroacetyl group is partially hydrolysed during ion exchange chomatography and its complete removal prior to this step is recommended according to step 5 of Protocol 11.

Protocol 9.
Preparation of bis(tri-*n*-butylammonium) pyrophosphate

Materials

- AnalaR tetrasodium pyrophosphate decahydrate, 2.23 g — **irritant**
- Anhydrous dimethyl formamide, 50 mL — **harmful, irritant, flammable**
- Dowex® 50W × 8 H^+ (100–200 mesh) (Protocol 3)
- Distilled water
- Tri-*n*-butylamine (Aldrich) 2.38 mL — **irritant, flammable**
- Absolute ethanol, 170 mL — **highly flammable**
- Universal indicator paper

Method

1. Weigh out 2.23 g (5 mmol) of tetrasodium pyrophosphate decahydrate and dissolve it in 50 mL of distilled water in a 100 mL conical flask (it may require a little heating to allow it to fully dissolve).
2. Fill a column (about 1.5 cm in diameter) with Dowex® 50W × 8 in the H^+ form, about 8 cm deep. Wash the resin with 100 mL of deionized water and check the pH with universal indicator paper to ensure that the water coming out from the bottom of the column is neutral.
3. Add the solution of pyrophosphate to the top of the column taking care not to disturb the packing. Allow the effluent from the column to drip into a stirred solution of 2.38 mL (10 mmol) of tri-*n*-butylamine in 20 mL of ethanol contained in a 250 mL round-bottomed flask cooled in an ice bath.

4. Add a further 10 mL of deionized water to the top of the column and continue adding the effluent to the solution of tri-*n*-butylamine.
5. Continue adding water to the top of the column as in step 4 until all of the pyrophosphoric acid solution has eluted. This may be checked by taking a small portion from a drip from the bottom of the column using a TLC spotter and checking the pH with universal indicator paper. If the effluent is still acidic the column should be washed further with deionized water until the pH of the effluent is neutral.
6. Remove the water on a rotary evaporator to give an oil, whilst maintaining the water bath temperature below 30°C. In practice this requires a good membrane pump or an oil pump designed for use with a rotary evaporator.
7. Add absolute ethanol (about 50 mL) to the residual oil and re-evaporate. Repeat three times. A very pale yellow gum is obtained.
8. Add approximately 30 mL of anhydrous DMF to the pale yellow gum and evaporate this using the rotary evaporator as in step 6.
9. Open the rotary evaporator to a balloon filled with argon, remove the flask and stopper with a septum.
10. Using a dry 10 mL syringe, add a further 5 mL of dry DMF through the septum to the gum in the flask.
11. Gently swirl the flask from step 10 to dissolve the gum, and transfer it via a dry 10-mL syringe into to a dry 25-mL pear-shaped flask sealed with a septum.
12. Repeat steps 10 and 11 in order to transfer all the pyrophosphate salt into the pear-shaped flask.
13. Evaporate the solution in the pear-shaped flask to a gum, and add a further 10 mL of dry DMF according to steps 9 and 10, evaporate again and repeat step 9.
14. Inject about 9 mL of dry DMF through the septum into the flask.
15. Ensure that the gum is fully dissolved and check the volume in the flask by taking it up into a dry 10 mL syringe then reinjecting it back into the flask.
16. Add additional dry DMF if necessary so that the total volume of the pyrophosphate solution in step 11 is 10 mL. This gives a 0.5 M solution of bis(tri-*n*-butylammonium) pyrophosphate.
17. Add about 1 cm^3 of activated 3 Å molecular sieves to the solution in the pear-shaped flask and store sealed with a septum in the fridge. It should generally be used within 2 weeks.

Protocol 10.
Synthesis of triphosphates using phosphorus(V) chemistry

Materials (see Protocols 5 and 8)

- 0.5 M solution of bis(tri-*n*-butylammonium) pyrophosphate in DMF (Protocol 9), 1.2 mL **harmful, irritant, flammable**
- Dry DMF, 1.2 mL **harmful, irritant, flammable**
- Dry tri-*n*-butylamine (see Section 3.1), 290 μL **irritant, flammable**

Method

1. Phosphorylate the nucleoside (0.2 mmol) as outlined in Protocol 5 until about 85–90% phosphorylation is observed by either HPLC or silica TLC.
2. Take a dry 10 mL pear-shaped flask filled with argon and stoppered with a septum. To this add 0.5 M solution of bis(tri-*n*-butylammonium pyrophosphate in DMF (1.2 mL, 0.6 mmol) prepared in Protocol 9, 2 mL of dry DMF and finally dry tri-*n*-butylamine (290 μL, 1.2 mmol). Vortex/mix this mixture for about 30 s and then add to the reaction immediately in one portion. Triphosphate formation may be monitored by ion exchange HPLC (Protocol 6) or silica TLC (Protocol 7) but should be complete within 10 min. A typical silica TLC plate is shown in Figure 9.6. (Note: In our experience, 3 eq. of the pyrophosphate/tributylamine is generally adequate in this step, although in some circumstances we have used 4 eq., notably for smaller-scale reactions. In this latter case, the triphosphate will probably require HPLC purification following MPLC in order to remove all the excess pyrophosphate—see Protocols 19 and 20).
3. After 10 min, add 20 mL of 0.1 M TEAB and leave it to stir for 1 h at room temperature.
4. Extract the sample with diethyl ether (2 × 15 mL), dilute the aqueous layer with one volume of distilled water and purify by MPLC anion exchange chromatography (see Protocol 19). Yields after MPLC are generally between 30 and 60%.
5. If required, analyse the crude sample by ^{31}P NMR (this is normally more informative after MPLC—see Protocol 19). ^{31}P NMR of triethylammonium salt in D_2O relative to 85% phosphoric acid should be approximately: −9.7 (d, γ-P), −10.5 (d, α-P), −22.5 (dd, β-P) (note that the γ-P can shift between −5 and −10 ppm dependent on pH).

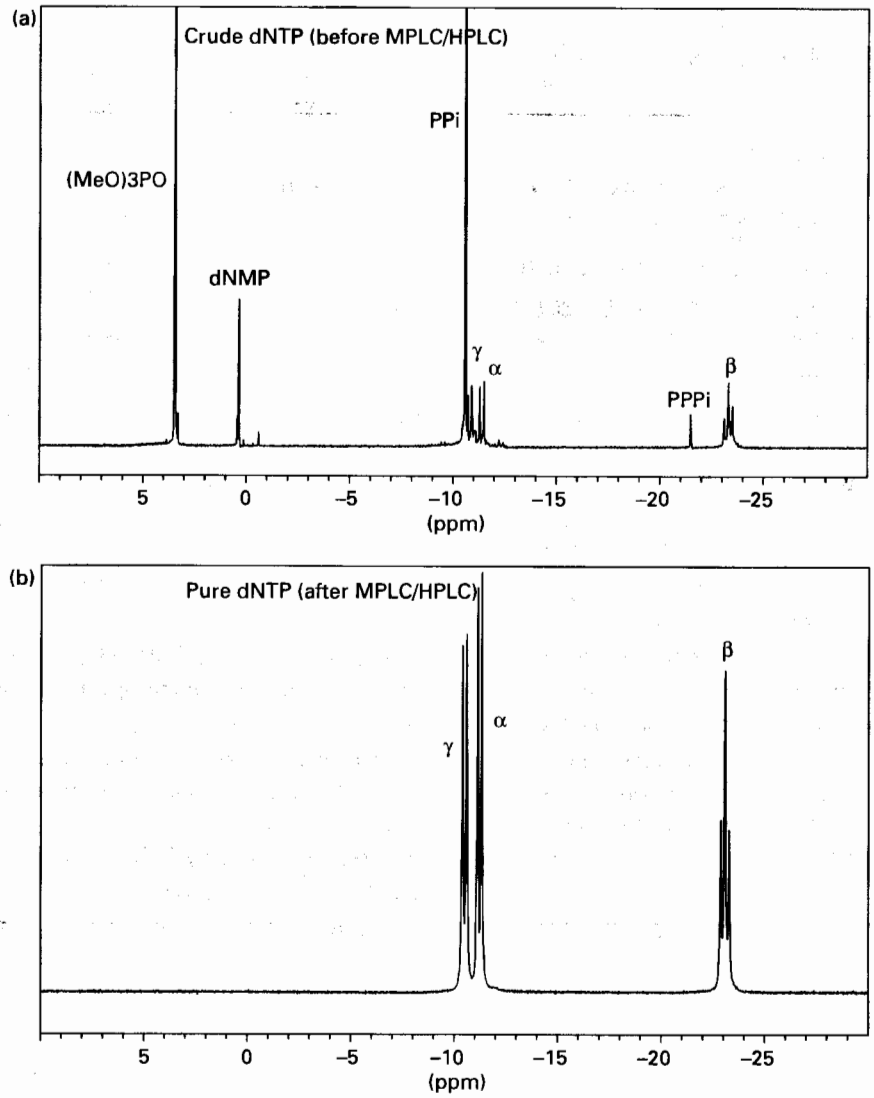


Fig. 9.7 ^{31}P NMR spectra obtained from a nucleoside triphosphate synthesis using phosphorus(V) chemistry. (a) Before MPLC/HPLC; (b) After MPLC/HPLC.

The ^{31}P NMR spectrum of a crude sample of nucleoside triphosphate prepared according to Protocol 10 is shown in Figure 9.7a (the sample shown is of TTP produced using a larger excess of phosphoryl chloride than normal to indicate likely minor impurities). After MPLC, the only usual contaminants are pyrophosphate

(singlet around −10 ppm). Figure 9.7b shows the ^{31}P NMR spectrum of a pure sample of triphosphate after MPLC and HPLC.

Protocol 11.
Modifications to Protocols 5 and 10 for use with modified nucleosides bearing alkene or alkyne groups

Materials (see Protocols 5 and 10)

- 1,8-bis(dimethylamino)naphthalene (proton-sponge®, Aldrich) 55 mg

Method

1. Follow steps 1–11 of Protocol 5 (0.2 mmol scale) and additionally, dry the proton-sponge® (55 mg, 0.26 mmol, 1.3 eq.) in a sample tube overnight in the vacuum oven as in step 3 of Protocol 5.
2. After step 10, quickly add the proton-sponge® in one portion and seal the flask with the septum.
3. Ensure the proton-sponge® is fully dissolved—gentle warming of the flask may be necessary.
4. Follow steps 12–14 of Protocol 5 (and steps 1–4 of Protocol 10, when phosphorylation is complete). Phosphorylation is more rapid in the presence of proton-sponge® and is generally complete in 30 min–2 h.
5. For modified nucleosides bearing trifluoroacetyl-protected amino groups, after step 3 of Protocol 10, add one volume of 33% aqueous ammonia solution to the reaction and stir at room temperature overnight. Then evaporate the solution to an oil, redissolve in 50 mM TEAB and purify by MPLC according to Protocol 19.

3.4 The synthesis of nucleoside (1-thio)triphosphates using phosphorus(V) chemistry

Simple modification of the Yoshikawa phosphorylation allows the synthesis of (1-thio) triphosphates (α-thiotriphosphates) (Protocol 12). The initial phosphorylation with thiophosphoryl chloride is slower than that using phosphoryl chloride and requires the addition of 2,4,6-collidine as a catalyst for the pyrimidine nucleosides.[7] Protocol 12 is intended for pyrimidine nucleosides on a 0.2 mmol scale and should be modified where indicated for purine nucleosides. The diastereoisomers of nucleoside (1-thio)triphosphates can be distinguished by both ^{31}P NMR (the signal for the α-phosphate of the *S*p diastereoisomer is downfield relative to that of the *R*p diastereoisomer) and reversed-phase HPLC (the *S*p diastereoisomer elutes first). Preparative separation can also be achieved using the latter method (see Protocols 21–23).[17]

Protocol 12.
The synthesis of (1-thio)triphosphates using phosphorus(V) chemistry

Materials

- Nucleoside (0.2 mmol)
- Trimethyl phosphate, 99+% 15 mL (0.3 mL for reaction) **harmful, possible mutagen**
- Anhydrous dimethyl formamide, 15 mL **harmful, irritant, flammable**
- Activated 3 Å molecular seives
- Thiophosphoryl chloride (freshly distilled, Protocol 4), 51 μL **harmful, corrosive, irritant, causes burns, reacts violently with water**
- Dry 2,4,6-trimethylpyridine (collidine); for pyrimidines, 53 μL **flammable, harmful, irritant**
- Dry tri-*n*-octylamine; for purines, 92 μL **flammable, harmful, irritant**
- 0.5 M solution of bis(tri-*n*-butylammonium) pyrophosphate in DMF (Protocol 9), 1.6 mL **harmful, irritant, flammable**
- Dry tri-*n*-butylamine (see Section 3.1), 385 μL **irritant, flammable**

Method

1. Follow steps 1–9 as in Protocol 5 (using a 5 mL pear-shaped flask).
2. Add trimethylphosphate (0.3 mL) into the reaction flask using the dry, gas-tight syringe.
3. Make sure the nucleoside is fully dissolved—this may require a little heating.
4. Put the flask into an ice bath and stir for 10 min.
5. Add thiophosphoryl chloride (51 μL, 0.5 mmol) dropwise to the stirred solution with a dry 100 μL gas-tight syringe.
6. For pyrimidine nucleosides only—add dry 2,4,6-timethylpyridine (collidine) (53 μL, 0.4 mmol) with a dry gas-tight syringe and continue stirring at 0°C. The solution should become cloudy. For purine nucleosides—in place of collidine, add dry tri-*n*-octylamine (92 μL, 0.21 mmol).
7. After 30 min, then each hour, remove, a small sample of the reaction for analysis silica TLC (see Protocol 7) until the reaction has gone to completion (85–90%) phosphorylation. In practice, the phosphorylation is a compromise between consumption of starting material and minimal bisphosphate formation and is normally complete within 2 h. A typical silica TLC is shown in Protocol 7.
8. Take a dry 10 mL pear-shaped flask filled with argon and stoppered with a septum. To this, add a 0.5 M solution of bis(tri-*n*-butylammonium) pyrophosphate in DMF (1.6 mL, 0.8 mmol) prepared in Protocol 9 and dry tri-*n*-butylamine (385 μL, 1.6 mmol), vortex/mix this mixture for about 30 s and then add to the reaction immediately in one portion. Thiotriphosphate formation can be monitored by silica TLC, but leave for 1 h.
9. Follow steps 3 and 4 of Protocol 10 and purify by MPLC anion exchange chomatography (Protocol 19). Yields after MPLC are generally between 30 and 60%.

Protocol 12. *Continued*

10. Typical ^{31}P NMR in D_2O relative to 85% phosphoric acid is +44.4 (d, *S*p-α-P), +43.8 (d, *R*p-α-P), −9.04 (d, *S*p and *R*p, γ-P), −23.1 (dd, *S*p-β-P), −23.2 (dd, Rp-β-P).

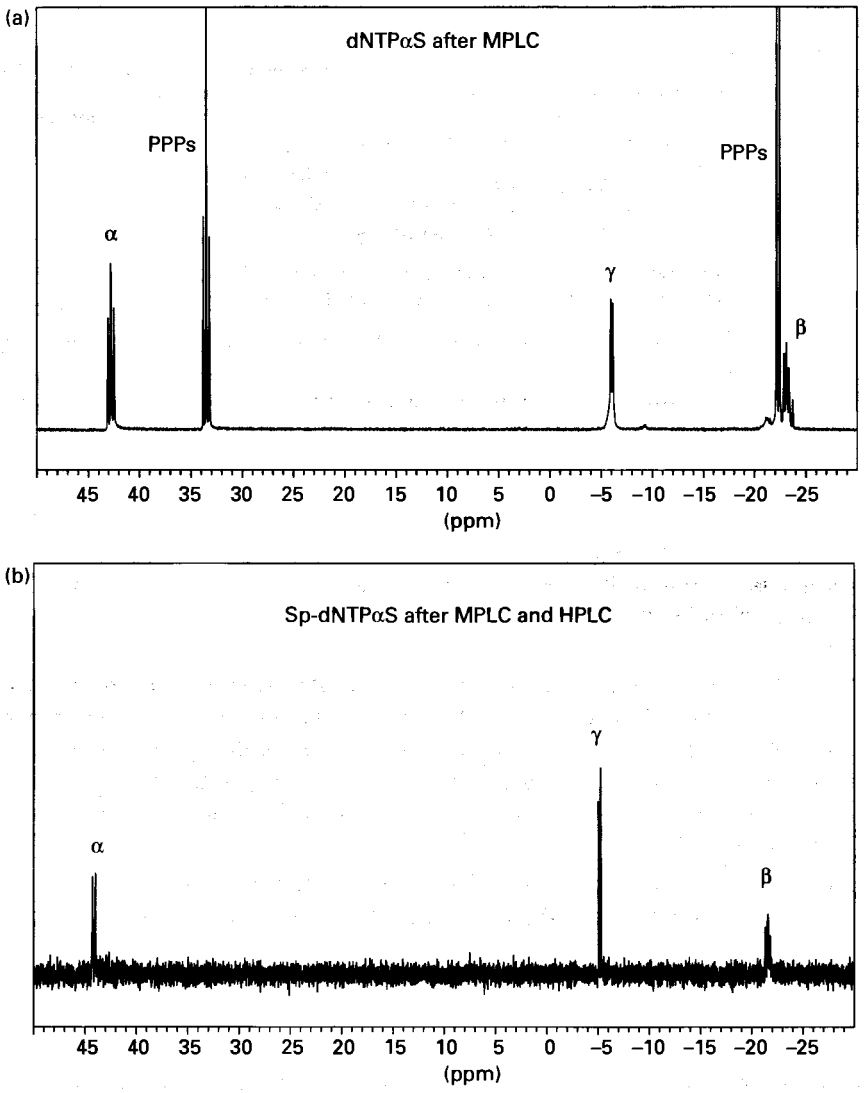


Fig. 9.8 ^{31}P NMR spectra obtained from a nucleoside (1-thio)triphosphate synthesis using phosphorus(V) chemistry. (a) After MPLC; (b) After MPLC/HPLC (pure *S*p isomer).

The ^{31}P NMR spectrum after MPLC of a sample of (1-thio)triphosphate prepared according to Protocol 12 is shown in Figure 9.8a. Figure 9.8b shows the ^{31}P NMR spectra of a pure sample of *S*p (1-thio)triphosphate after MPLC and HPLC.

3.5 Synthesis of nucleoside 5′-triphosphates and 5′-(1-thio) triphosphates using phosphorus(III) chemistry

The phosphorylation and thiophosphorylation of modified nucleosides, especially bearing bulky substituents on the heterocyclic base, are often rather slow and inefficient using phosphorus(V) chemistry. Salicyl chlorophosphite phosphorylates nucleosides rapidly at the 5′-hydroxyl group and the procedure of Ludwig and Eckstein[17] is well suited to relatively unreactive nucleosides, or ones lacking 2′ and 3′ hydroxyl groups. Following phosphorylation and reaction with pyrophosphate, a cyclic phosphite species is formed, which may be converted *in situ* to normal triphosphates and (1-thio)triphosphates dependent on the choice of oxidant—iodine or sulfur. However, the high reactivity of salicyl chlorophosphite requires the use of nucleosides protected with acyl groups on the 3′-OH (and 2′-OH of ribonucleosides). Although the method does not necessitate protection of the exocyclic amino groups of the normal heterocyclic bases, the synthesis of the precursors for the phosphorylation, that is, 3′-*O*-acylated 2′-deoxynucleosides generally involves base acylation anyway. Practical aspects and references related to the syntheses of protected nucleosides are contained in Ref. 17 and 20.

Protocol 13.
Synthesis of triphosphates using phosphorus(III) chemistry

Materials

- Nucleoside (0.2 mmol)
- Anhydrous dioxan, 15 mL (0.2 mL for reaction) **highly flammable, harmful**
- Anhydrous dimethyl formamide, 15 mL **harmful, irritant, flammable**
- Activated 3 Å molecular sieves
- Dry pyridine, 2.6 mL (0.6 mL for reaction) **highly flammable, harmful, irritant**
- Salicyl chlorophosphite, 100–200 mg (2-chloro-4 *H*-1,3,2-benzodioxaphosphorin-4-one) **toxic, lachrymator, irritant, causes burns, reacts violently with water**
- 0.5 M solution of bis(tri-*n*-butylammonium) pyrophosphate in DMF (Protocol 9), 1.6 mL **harmful, irritant, flammable**
- Dry tri-*n*-butylamine (see Section 3.1), 145 µL **irritant, flammable**
- 1% Iodine solution (w/v) in pyridine and water (1 : 1 v/v), 2 mL **iodine is harmful and causes burns**
- 5% (w/v) Aqueous sodium bisulfite solution, few drops **irritant**
- 33–35% Aqueous ammonia solution, 20 mL **irritant, causes burns**

Method

1. Follow steps 1–9 of Protocol 5 using 0.2 mmol of nucleoside and replacing trimethylphosphate with anhydrous dioxan.

Protocol 13. *Continued*

2. Dry the gas-tight syringe first by drawing some of the DMF wash from the phosphorylation tree into the syringe barrel and then ejecting it. This is then repeated with the dioxan wash.
3. Dissolve the nucleoside (0.2 mmol) (prepared as in Protocol 5) in dry pyridine (4 mL) and evaporate to a gum.
4. Open the evaporator to a balloon filled with argon and seal with a septum.
5. Place a small balloon filled with argon through the septum sealing the flask in order to maintain a positive pressure of argon in the flask.
6. Inject a mixture of dry dioxan/pyridine (1:3 v/v) (800 μL) into the flask in step 5.
7. Make sure the nucleoside is fully dissolved—this may require a little heating.
8. Quickly weigh out between 100–200 mg of salicyl chlorophosphite into a dry, 5 mL round-bottomed flask sealed with a septum (**Caution!** Salicyl chlorophosphite is corrosive and fumes in air—ideally weigh in glove box if available or quickly weigh in fume cupboard and wear gloves).
9. Add an appropriate amount of dry dioxan through the septum via a dry gas-tight syringe (see step 2) to give a final concentration of 1 M salicyl chlorophosphite. (230 mg/mL gives a 1 M solution).
10. Add the 1 M solution of salicyl chlorophosphite (220 μL) to the rapidly stirred solution of the nucleoside. The solution should go slightly cloudy.
11. After 30 min take a dry 10 mL pear-shaped flask filled with argon and stoppered with a septum. To this, add a 0.5 M solution of bis(tri-*n*-butylammonium) pyrophosphate in DMF (0.6 mL, 0.3 mmol) and dry tri-*n*-butylamine (145 μL, 0.6 mmol). Vortex/mix this mixture for about 30 s and then add to the reaction immediately in one portion.
12. Leave the reaction stirring for 10 min. The precipitate should dissolve.
13. Add 2 mL of a 1% iodine solution (w/v) in pyridine and water (1:1 v/v).
14. After stirring for a further 15 min, add three drops of a 5% $NaHSO_3$ solution and evaporate it to dryness using a rotary evaporator equipped with a good membrane or oil pump.
15. Add 10 mL of water to the residue and leave to stir for 30 min. Then add 20 mL of concentrated NH_4OH leaving it to stir for 2 h before evaporating it to dryness. This deprotects the 3′ (and 2′) hydroxyl groups (for deprotection of bases, the length of ammonia treatment depends on the nature of the protected base, e.g. benzoyl protected A and C and isobuteryl protected G, 5 h at 60°C should be used). It is then ready to purify by MPLC anion exchange chromatography (see Protocol 19). Yields after MPLC are generally between 30 and 70%.

Protocol 14.
Synthesis of (1-thio)triphosphates using phosphorus(III) chemistry

Method

1. Follow steps 1–12 of Protocol 13.
2. Add a suspension of sulfur (6.4 mg, 200 mmol) in dry DMF (200 μL) and leave to stir for 10 min. Add another 100 μL of dry DMF to the pot, which contained the sulfur and transfer this as well to ensure that all the sulfur is in the reaction.
3. Add 5 mL of water and stir for 30 min before evaporating to dryness.
4. Add 20 mL of concentrated NH_4OH leaving it to stir for 2 h before evaporating it to dryness. This deprotects the 3′ (and 2′) hydroxyl groups (for nucleosides with protecting groups on the bases, deprotection time should be increased accordingly—see Protocol 13).
5. Purify the crude product using MPLC anion exchange chromatography (Protocol 19). Yields after MPLC are generally between 30 and 60%.

3.6 Synthesis of nucleoside 5′-diphosphates

The synthesis of nucleoside diphosphates is best achieved using the Poulter reaction,[9] which involves reaction of the tris(tetra-*n*-butylammonium) salt of pyrophosphate with a nucleoside 5′-tosylate in acetonitrile. A general procedure for the synthesis of nucleoside tosylates of thymidine and 2′-deoxyadenosine is included (Protocol 15), whilst the syntheses of the other tosylates (including ribonucleosides) have been described using related procedures. Simple modification of the protocol, whereby the tetra-*n*-butylammonium salt of pyrophosphoric acid is replaced by methylene or difluomethylene bis phosphonate, allows the synthesis of hydrolytically stable dNTP analogues.[10]

Protocol 15.
Synthesis of 5′-tosylthymidine

Materials

- Dry pyridine, 50 mL — **highly flammable, harmful, irritant**
- Dry thymidine, 5 g — **assume toxic**
- Tosyl chloride (*p*-toluenesulfonyl chloride), 4.8 g — **irritant, harmful, causes burns**
- Ethyl acetate — **flammable, harmful**
- Ethanol — **flammable, harmful**

Method

1. Dissolve the thymidine (5.0 g, 20.66 mmol) in dry pyridine (50 mL) in a dry 250 mL round-bottomed flask and evaporate. Repeat.

Protocol 15. *Continued*

2. Redissolve the nucleoside in 25 mL of dry pyridine and add a dry magnetic stirrer bar.
3. Cool the flask in an ice bath and place a dry 100 mL pressure equalizing dropping funnel in the flask.
4. Dissolve tosyl chloride (*p*-toluene sulfonylchloride) (4.8 g, 25 mmol) in dry pyridine (25 mL), place in the dropping funnel and stopper the funnel.
5. Add the tosyl chloride solution dropwise to the stirred, cooled solution of thymidine, and when this is complete, stir at 0°C.
6. Monitor the reaction by silica TLC (R_f product 0.3 in 10% EtOH/$CHCl_3$, thymidine is 0.14).
7. When the reaction is complete (about 16 h at 0°C), add the solution to crushed ice/water (about 250 mL) and stir at room temperature for 10 min.
8. Extract the product from the solution in step 8 into ethyl acetate (2 × 300 mL) and wash the organic layer successively with saturated aqueous sodium bicarbonate solution (50 mL) and water (50 mL).
9. Dry the organic phase over magnesium sulfate, filter and evaporate.
10. Recrystallize the residue from absolute ethanol (about 150 mL).
11. Expect about 5 g of product (60%) as white crystals.
12. Analytical data for 5′-tosylthymidine; m.p. should be 167–169°C; ^{1}H NMR is described in Ref. 9.
13. The above protocol can also be used for preparing 5′-*O*-tosyl-2′-deoxyadenosine-Tosylation of 1.0 g of adenosine with 0.8 g of tosyl chloride in 10 mL pyridine at 0°C for 20 h. Following work-up (steps 8 and 9), the crude product should be purified by silica gel flash chomatography using a gradient of 8–20% ethanol in chloroform (R_f of product is 0.17 in 10% EtOH/$CHCl_3$, 2′-deoxyadenosine is 0.14); Expect about 0.8 g (50%) of product, m.p. should be 146–148°C, ^{1}H NMR is described in Ref. 9.

Protocol 16.
Preparation of tris(tetra-*n*-butylammonium) pyrophosphate

Materials (see also Protocol 9)

- AnalaR tetrasodium pyrophosphate decahydrate, 2.68 g — **irritant**
- Anhydrous dimethyl formamide, 30 mL — **harmful, irritant, flammable**
- Distilled water
- 10% Aqueous tetra-*n*-butylammonium hydroxide solution — **irritant**
- Dry acetonitrile, about 100 mL — **highly flammable, toxic**

Method

1. Weigh out 2.68 g (6 mmol) of tetrasodium pyrophosphate decahydrate, follow steps 1–3 of Protocol 9, but allow the effluent from the column to drop into an empty 250-mL conical flask cooled in an ice bath.
2. Stir the solution of pyrophosphoric acid (obtained in step 1) in an ice bath and add a 10% solution of tetra-*n*-butylammonium hydroxide dropwise until pH 7.3 is reached (note: use a pH meter). This will be around 50 mL (for methylenebisphosphonic acid and difluoromethylenebisphosphonic acid, the solutions should be titrated to pH 10 and 7.3, respectively).
3. Remove the water on a rotary evaporator to give an oil, whilst maintaining the water bath temperature below 30°C. In practice this requires a good membrane pump or an oil pump designed for use with a rotary evaporator.
4. Add dry DMF (30 mL) to the residual oil and re-evaporate.
5. Add dry acetonitrile (50 mL) to the gum and re-evaporate. Repeat two more times. A very pale yellow gum is obtained.
6. Add 10 mL of dry acetonitrile to the gum, transfer it via a dry syringe into to a dry 25 mL pear-shaped flask, rinse the inside of the flask with 5 mL of dry acetonitrile and transfer this as well.
7. Evaporate the solution to a gum, dissolve in a further 10 mL of dry acetonitrile, evaporate again and open the evaporator to a balloon filled with argon.
8. Seal the pear-shaped flask with a septum and inject about 3 mL of dry acetonitrile.
9. Ensure that the gum is fully dissolved and check the volume in the flask by taking it up into a dry 5 mL syringe, then reinjecting it back into the flask.
10. Add more dry acetonitrile if necessary so that the total volume of the pyrophosphate solution in step 9 is 4 mL. This gives a 1.5 M solution of tris(tetra-*n*-butylammonium) pyrophosphate.
11. The solution should generally be used immediately.

Protocol 17.
Preparation of nucleoside 5′-diphosphates

Materials

- 5′-Tosyl nucleoside, 0.5 mmol — **assume toxic**
- Dry acetonitrile, 15 mL — **highly flammable, toxic**
- 1.5 M tris(tetra-*n*-butylammonium) pyrophosphate, 0.5 mL (Protocol 16) — **harmful, irritant, flammables**

Protocol 17. *Continued*

Method

1. Fill two dry 10 mL round-bottomed flasks three-fourths with dry acetonitrile and add some activated 3 Å molecular sieves (about 1 cm^3) to both and stopper with septums. Mark one flask as the 'wash' and the other as the 'reagent'.
2. Weigh the 5′-tosyl nucleoside (0.5 mmol) into a dry 5 mL pear-shaped flask containing a small, dry magnetic stirrer bar, seal with a septum and insert a dry needle through this into the flask.
3. Dry the sample overnight in a vacuum desiccator connected to an oil pump in the presence of phosphorus pentoxide (corrosive, reacts violently with water).
4. Open the desiccator to a balloon filled with argon so that the flask is filled with argon and the atmosphere is kept dry.
5. Remove the needle out of the septum which is sealing the flask.
6. Dry the gas-tight syringe first by drawing some of the acetonitrile wash solution into the syringe barrel and then ejecting it.
7. Inject 0.5 mL of the 1.5 M tris(tetra-*n*-butylammonium) pyrophosphate solution in acetonitrile (0.5 mL) and stir at room temperature (this can be modified to use instead, the methylene or difluoromethylene phosphonates).
8. Monitor the reaction by silica TLC as described in Protocol 7, but wash the gas-tight syringe with dry acetonitrile rather than DMF. Reactions generally require between 1 and 4 days.
9. When complete, add the reaction mixture to 10 mL of 0.1 M TEAB and evaporate.
10. Add 25 mL of 0.5 M TEAB to the residue from step 9, filter any insoluble material and purify by anion exchange MPLC according to Protocol 19. Yields after MPLC are generally between 40 and 70% . ^{31}P NMR of triethylammonium salt in D_2O relative to 85% phosphoric acid should be approximately: −5.6 (d, β-P), −10.2 (d, α-P).

3.7 Synthesis of nucleoside 3′-monophosphate

The preparation of nucleoside 3′-monophosphates can be achieved most reliably by coupling 5′-O and N-protected nucleosides with cyanoethylphosphate in pyridine in the presence of DCC.[3] The syntheses of these nucleosides have been described adequately in the Practical Approach series.[1]

Protocol 18.
Preparation of nucleoside 3′-monophosphates

Materials

• Protected nucleoside, 0.5 mmol	**assume toxic**
• Barium 2-cyanoethylphosphate hydrate, 967 mg	**toxic**
• Dry pyridine, 50 mL	**highly flammable, harmful, irritant**
• Dowex® 50W × 8 pyridinium form (Protocol 3), 6 g	**irritant**
• *N*, *N*′-dicyclohexyl carbodiimide, 1.55 g	**severe irritant, harmful**
• 1.5 M tris(tetra-*n*-butylammonium) pyrophosphate, 0.5 mL	**harmful, irritant, flammable**
• Chloroform, 150 mL	**harmful**
• Diethyl ether, 50 mL	**flammable**
• AnalaR glacial acetic acid, 20 mL	**irritant, corrosive, causes burns**
• 33–35% Aqueous ammonia solution, 20 mL	**irritant, causes burns**

Method

1. Weigh barium cyanoethylphosphate (967 mg, 3 mmol) into a 100 mL round-bottomed flask. Add 40 mL of distilled water and gently stir for 30 min with 6 g Dowex® 50W × 8 pyridinium form (100–200 mesh from Aldrich). The salt is initially in suspension, but should give rise to a clear solution.
2. Remove the resin by Buchner filtration, wash it with distilled water (30 mL) and evaporate the combined filtrates to a gum.
3. Add dry pyridine (30 mL) and evaporate. Repeat.
4. Dissolve the gum in dry pyridine (10 mL) and transfer to a dry 25 mL pear-shaped flask. Evaporate to a gum once more and dissolve in dry pyridine (2 mL) and seal the flask with a septum.
5. Add a small, dry magnetic stirrer bar, followed by N,N′-dicyclohexyl carbodiimide (DCC, 1.55 g, 7.5 mmol) and the 5′-O and N-protected nucleoside (0.5 mmol). Reseal the flask (**Caution**! DCC is an extreme irritant—weigh in fume cupboard, wear gloves).
6. Stir the mixture at room temperature and monitor by silica TLC (solvent 20% methanol/chloroform—a slower-running spot will be observed, which will give a positive trityl test—orange spot upon dipping the TLC in dilute acid). The reaction will take up to 2 days).
7. Filter the precipitate, and wash it with a solution of pyridine/water (1 : 1, v/v, 50 mL) and evaporate to a gum.
8. Dissolve the gum in chloroform (150 mL) and wash with 0.5 M TEAB (30 mL).
9. Dry the organic layer over sodium sulfate, filter and evaporate to a solid.
10. Remove traces of pyridine by addition of distilled water (20 mL) and evaporation.
11. Add a solution of Analar glacial acetic acid/distilled water (4 : 1 v/v, 20 mL) and stir at room temperature for 1 h.
12. Add HPLC grade methanol (1 mL) to the solution in step 11, evaporate and remove traces of acetic acid as in step 10.

Protocol 18. *Continued*

13. Triturate the residue with diethyl ether (50 mL), then add concentrated (35%) aqueous ammonia solution (20 mL) and stir at room temperature overnight.
14. Evaporate the solution to dryness and purify by MPLC anion exchange chromatography (see Protocol 19). Yields are generally between 25 and 50%.
15. ^{31}P NMR in D_2O relative to 85% phosphoric acid should be a singlet between +2 and +3 ppm.

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4. Analysis and purification

The protocols for HPLC and silica TLC analysis are fairly informative in assessing the success of the reactions described, and although a crude ^{31}P NMR spectrum can be taken, it is often complicated by the presence of inorganic phosphorus species. There are generally two steps in the purification of nucleotides; the first uses DEAE Sephadex A25 for anion exchange chromatography with MPLC using a TEAB (triethylammonium bicarbonate) buffer gradient, whilst the second purification stage is often required using reversed-phase HPLC with a gradient of acetonitrile in aqueous TEAB. In both cases, the volatile buffer can be conveniently removed during rotary evaporation to produce the triethylammonium salt of the nucleotide. After MPLC, ^{31}P NMR spectroscopic analysis should be used as a check of product purity. MPLC generally achieves good separation of nucleotides and although samples are sometimes of a suitable purity at this stage, they are often contaminated with inorganic phosphate species, which possess a similar charge. This is particularly the case with nucleoside triphosphates and pyrophosphate. Nucleotide diphosphates and triphosphates are reasonably stable, providing the solution pH is slightly basic (pH 7.5–8.0). However, care should be taken during evaporation steps during purification such that buffer is removed either by freeze-drying the samples or by rotary evaporation below 30°C using an evaporator equipped with a dry ice cold finger and an oil pump. For nucleoside (1-thio)triphosphates there is also the possibility of having to separate the two diastereoisomers (*S*p and *R*p). Only the *S*p isomer is used as a substrate for DNA polymerase enzymes[16] but since the *R*p isomer is not an inhibitor, separation is not always necessary. The two diastereomers generally co-elute on DEAE sephadex, but separation may be achieved by using either an analytical or semi-preparative reversed-phase HPLC column and injecting small amounts. Although this can take some time, only small amounts of the *S*p isomer are required for most biological applications. The *S*p diastereoisomer always elutes first. The use of Tris/Mg buffer for HPLC rather than triethylammonium bicarbonate provides better resolution of the diastereoisomers, but requires subsequent desalting of the separated samples. The enhanced resolution is based on the differential complexation of Mg by the two diastereoisomers (see Ref. 16). Useful HPLC data and ^{31}P NMR data for (1-thio)triphosphates can be found in Ref. 17.

The basic pH of TEAB buffers used with reversed-phase HPLC columns often leads to degradation of column material. We have used Zorbax columns, which contain fully silylated packing material and have a much longer lifetime in TEAB. Although the resolution of these columns seems to be less, most separations are relatively easy and column lifetime is of more importance.

The triethylammonium salts of nucleotides are generally sticky and hygroscopic, and following purification, they are best stored as aqueous solutions (buffered with 10 mM Tris–HCl pH 7.5 if required) of known concentration (generally 10 or 100 mM) at −20°C. For longer term storage, nucleoside (1-thiotriphosphates) can be stabilized by the addition of DTT (up to 100 mM) and stored as described above. Alternatively they may be converted to the corresponding sodium salts according to protocol 24 and stored as solids in the freezer.

Analysis of the nucleotides may be done by electrospray negative ion mass spectrometry and ^{31}P NMR spectroscopy of the triethylammonium salts. On the scale of most reactions, generally 50 μmol of sample will give a good NMR spectrum on most spectrometers in less than quarter of an hour and will provide plenty of sample for biological assay (5 mL of a 10 mM solution). Line broadening of ^{31}P NMR peaks due to the presence of trace quantities of paramagnetic metal ions can be resolved by running samples in D_2O containing 10 mM EDTA, pH 8.0. Alternatively, passing the NMR sample in D_2O down a short column of chelex (EDTA) resin contained in a pasteur pipette avoids adding EDTA to the sample.

Protocol 19.
Purification by anion exchange chromatography (MPLC)

The following may be used for most triphosphate syntheses up to 0.5 mmol. For purification of other nucleotides, a useful guideline to buffers required is shown in Table 9.1.

Method

1. Make up two solutions of TEAB buffer from the 2 M stock (see Protocol 1) according to Table 9.1: 2 L of 50 mM TEAB (50 mL of the stock solution made up to 2 L) and 0.7 M TEAB (700 mL of the stock made up to 2 L).
2. Pour the pre-swelled Sephadex into an MPLC column (2.5 cm diameter and 40 cm long) and leave it to settle. About 5 cm of space should be left at the top of the column to allow 3–4 cm of buffer to sit on the top. Set the pump flow rate to about 4 mL/min.
3. Set the UV detector to 260 nm and equilibrate the column for about 15 min with 50 mM TEAB.
4. Set up simple buffer gradient system according to Figure 9.9.

Protocol 19. *Continued*

5. Fill the right hand bottle with 2 L of 50 mM TEAB and the other with 2 L of the higher concentration buffer (see Table 9.1)
6. Draw buffer from each bottle up the glass tubing past the two-way tap using a pipette bulb filler, then close the tap. Ensure that no air bubbles are present in the tubing.
7. Place a large magnetic stirrer bar in the 50 mM buffer and stir the solution.

Table 9.1 Suggested TEAB buffer gradients and retention times for purification of nucleotides by MPLC

Sample/ synthesis	MPLC buffer gradient (2 L of each)	Approximate TEAB concentration for elution	Other likely impurities (approx. [TEAB] for elution)
Monophosphate	0.05–0.40 M	0.20–0.3 M	Phosphate (>0.3 M) cyanoethylphosphate may co-elute—can remove by HPLC
diphosphate	0.05–0.55 M	0.35–0.5 M	Pyrophosphate may co-elute—can be removed by HPLC
triphosphate	0.05–0.7 M	0.45–0.6 M	Nucleoside (0.05–0.1 M) monophosphate (0.2–0.3 M) pyrophosphate may co-elute—can be removed by HPLC
1-thiotriphosphate	0.05–0.8 M	0.5–0.7 M	Pyrophosphate or 1-thiocyclo-triphosphate—can be removed by HPLC

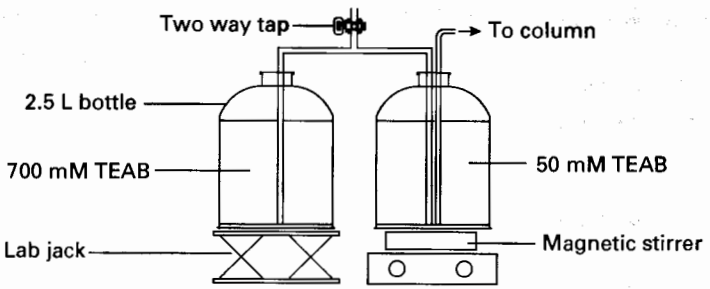

Fig. 9.9 Equipment for running buffer gradient for MPLC.

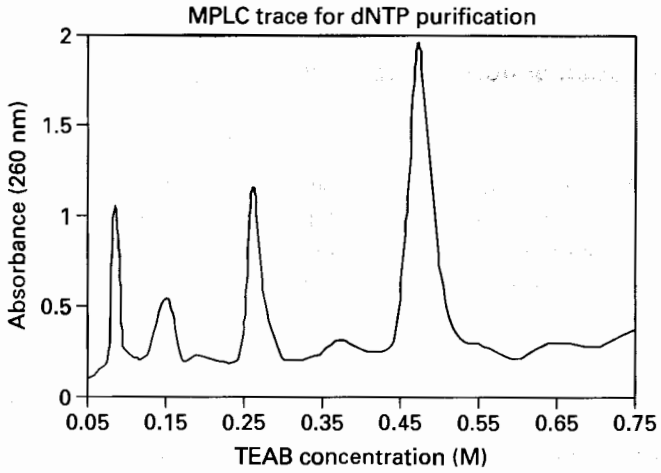

Fig. 9.10 Typical MPLC trace for a nucleoside triphosphate synthesis using phosphorus(V) chemistry (larger peaks from left to right are reaction solvent, nucleoside, monophosphate and triphosphate, respectively).

8. Add the reaction mixture to the top of the column (note it is important that the solution is not too concentrated (it should be <50 mM) otherwise the compounds will not bind efficiently to the column).
9. Once the sample is loaded onto the column, start the fraction collector and pump the buffer from the 50 mM buffer to the column at a rate of about 4 mL/min. As this buffer is used up, the higher concentration buffer will be drawn into the flask via the tubing to provide the buffer gradient.
10. Typical concentrations of TEAB required for elution are shown in Table 9.1. A typical MPLC UV trace for a triphosphate sample is shown in Figure 9.10 (note that for nucleotide analogues which possess a modification which bears a partial positive charge under the MPLC conditions e.g. aminoalkyl-modified bases, then these will elute under slightly lower TEAB concentrations than expected).
11. Combine the tubes that contain the triphosphate and remove the buffer using rotary evaporator (the temperature of the sample should not be raised above 30°C).
12. Determine yields of the reaction by UV determination (or after further purification by HPLC—Protocol 20).

Protocol 20.
HPLC purification of nucleotides

Method

1. Make up two solutions from the stock solution of 2 M TEAB (Protocol 1). Solution A is 0.1 M TEAB (100 mL of stock made up to 2 L with HPLC grade water) and solution B is 0.1 M TEAB with 30% acetonitrile (100 mL of stock plus 600 mL of acetonitrile made up to 2 L with HPLC grade water). These need to be de-gassed or filtered though a millipore 5 μM filter before they can be used for HPLC.
2. For the Zorbax reversed-phase column (21 × 250 mm), set the flow rate to 7.5 mL/min.
3. Set the UV monitor to 260 nm (or 280 nm to inject larger amounts of sample).
4. Set up a gradient of 0–30% of solution B over a period of 30 min, and then back down to 0% in 10 min can be used to achieve separation. The retention times of triphsophates are between 20 and 30 min but these can vary according to the nucleoside with mono- and diphosphates eluting earlier (note the order of elution on reversed-phase HPLC using the conditions above is mono-, di- and then triphosphate last).
5. If necessary, alter the gradient following a trial run to achieve the best separation.
6. Collect the fractions in a round-bottomed flask. The buffers can then be removed using a freeze dryer or rotary evaporator.

Protocol 21.
HPLC separation of nucleoside (1-thio)triphosphate diastereoisomers using TEAB buffer

Method

1. Follow step 1 of protocol 20.
2. For the Waters μbondapak reversed-phase column (7.8 × 300 mm), set the flow rate to 3 mL/min, or the Zorbax SB column (4.6 × 250) to 1 mL/min.
3. Set the UV monitor to 260 nm (or 280 nm to inject larger amounts of sample).
4. Set up an isocratic gradient of 15% solution B (Protocol 20). Retention times of (1-thio)triphosphates are normally between 10 and 20 min but can vary according to the nucleoside (Note the *S*p diastereoisomer always elutes first). A typical HPLC trace is shown in Figure 9.11.
5. Using a trial run check the separation of the two isomers.

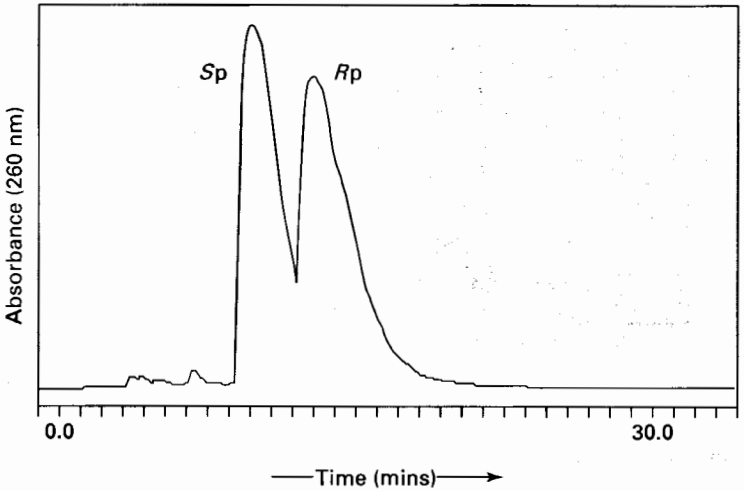

Fig. 9.11 Typical HPLC trace for *S*p and *R*p diastereoisomers of a nucleoside (1-thio)triphosphate using TEAB buffer (see Protocol 21).

6. Collect the fractions in a round-bottomed flask, remove the buffer using a freeze dryer or rotary evaporator, and check the purity by ^{31}P NMR spectroscopy (see Protocol 12).

Protocol 22.
HPLC separation of nucleoside (1-thio)triphosphate diastereoisomers using Tris–HCl buffer

Method

1. Make up a 120 mM Tris–HCl containing 20 mM $MgCl_2$ solution at pH 7.65 ± 0.05 using HPLC grade water. This is used for both solutions A and B since the HPLC gradient used is isocratic. The solution needs to be de-gassed or filtered through a millipore 5 μM filter before it can be used for HPLC.
2. For the Zorbax preparative reversed-phase column (21 × 250 mm), set the flow rate to 7.5 mL/min.
3. Set the UV monitor to 260 nm (or 280 nm to inject larger amounts of sample).
4. Set up an isocratic gradient of 50% solution A and B (i.e. the same solution is used for both pumps A and B). Retention times of (1-thio)triphosphates are normally between about 60 and 90 min but can vary according to the nucleoside (note the *S*p diastereoisomer always elutes first, see Figure 9.12).
5. Using a trial run, check the separation of the two isomers and if necessary change the gradient (but maintain it isocratic).

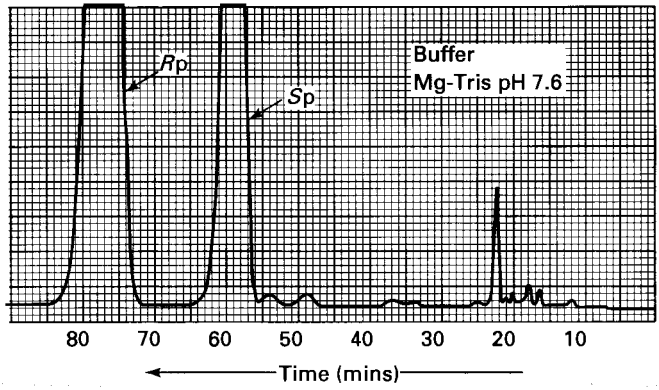

Fig. 9.12 Typical HPLC trace for *S*p and *R*p diastereoisomers of a nucleoside (1-thio)triphosphate using Tris/Mg buffer (see Protocol 22).

Protocol 22. *Continued*

6. Collect the fractions in a round-bottomed flask, and dilute with 0.5 M tetrasodium EDTA (1 mL per 10 mL of fraction).
7. Desalt the fractions using a sepharose weak anion exchange column according to Protocol 23.

Protocol 23.
Desalting nucleoside (1-thio)triphosphate diastereoisomers from Tris/Mg buffer

The following may be used for most triphosphate syntheses up to 0.5 mmol. For purification of other nucleotides, a useful guideline to buffers required is shown in Table 9.1.

Method

1. Make up two solutions buffer A and buffer B: A = 2 L of distilled water containing 2% ethanol; B = 2 L 0.5 M TEAB pH 8.5 containing 2% ethanol.
2. Prepare an MPLC column containing sepharose weak anion exchange resin (diameter 40 mm × 400 mm) packed in solution A.
3. Prepare an MPLC column containing sepharose weak anion exchange resin (diameter 40 mm × 400 mm) packed in solution A and set up to run a gradient between solutions A and B analogously to that described in Protocol 19.
4. Load the sample as described in Protocol 19 and run the following gradient: t = 0 min, 0% B; t = 20 min, 0% B; t = 65 min, 50% B; t = 95 min, 50% B;

t = 105 min, 65% B; t = 135 min, 65% B; t = 160 min, 100% B; using a flow rate of 15 mL/min.

5. The pure, desalted (1-thio)triphosphate generally elutes at about 75% solution B.
6. Remove the buffer using a freeze dryer or rotary evaporator, and check the purity by ^{31}P NMR spectroscopy (see Protocol 12).

Protocol 24.
Conversion of nucleotide triethylammonium salts into sodium salts

Method

1. Dissolve the triethylammonium salt of the nucleotide (50 μmol) in HPLC grade methanol (1 mL) to give a solution of 50 μmol/mL (50 mM).
2. Add the solution in step 1 to 20 mL of a 1 M solution of sodium iodide in HPLC grade acetone in a centrifuge tube. The sodium salt should immediately precipitate.
3. Centrifuge the precipitated sodium salt from step 2.
4. Carefully decant the supernatant solution and wash the nucleotide pellet well with 20 mL of HPLC grade acetone and re-centrifuge.
5. Repeat step 4 two more times and decant the supernatant solution.
6. Redissolve the pellet in distilled water (gentle warming may be required) and obtain the sodium salt by rotary evaporation (below 30°C) or preferably by freeze-drying.

Acknowledgements

The authors would like to thank Dr Sarah Lee, Dr Nathalie Mignet, Dr Jane Grasby and Elaine Frary for providing experimental data and valuable comments on the manuscript.

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