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Recent developments in phosphono-transfer chemistry

Michael C. Mitchell, Terence P. Kee *

School of Chemistry, University of Leeds, Leeds LS2 9JT, UK

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Contents

Abstract

Recent developments in methods for the construction of phosphorus–carbon bonds are reviewed emphasising mechanistic features and stereocontrol in asymmetric variants. © 1997 Elsevier Science S.A.

Keywords: Phosphorus–carbon bonds; Stereocontrol in asymmetric variants

1. Introduction

For over 300 years the study of phosphorus has played a major role in the development of chemical science and to this day continues to contribute significantly

* Corresponding author. Email: terryk@chem.leeds.ac.uk.

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to both a healthy scientific base and economical competitiveness of the global chemical industry [1]. Indeed, the exploitation of phosphorus chemistry in homogeneous asymmetric catalysis, the synthesis of new materials and in the design of new therapeutic drugs emphasises that the study of phosphorus science is of interest to inorganic, organic, biological, organometallic and materials chemists [2].

In many of these applications, there is a fundamental need to be able to fabricate phosphorus compounds with properties which are tailored to specific uses. This in turn requires synthetic methods which combine several important features: (i) energy efficiency; (ii) atom efficiency; (iii) yield; (iv) selectivity; (v) control over the mechanistic pathway. These five process criteria may be considered to be of primary importance and apply to the majority of laboratory-based transformations. In addition to these primary properties, any process which is designed with an industrial application in mind should address certain, secondary features including: (vi) minimising toxicity problems; (vii) optimising purification procedures; (viii) maximising overall financial efficiency. Therefore, the design and subsequent development of any chemical process should be measured against both primary and secondary process criteria.

In this article we review some recent developments in the construction of phosphono molecules by phosphorus–carbon [P–C] bond-forming processes. Coverage is by no means intended to be comprehensive, but in selecting material for inclusion we have been guided by the contributions to mechanistic understanding, product application and process development. As a consequence of this, most of our attention has been drawn to the most recent developments which have predominantly involved asymmetric variants. Furthermore, since the excellent review of Wozniak and Chojnowski [3] summarises the state of the field up to 1989, we have focused on developments in the intervening 6 years.

The types of organophosphorus framework that result from these processes are phosphonate esters, acids and related derivatives (Fig. 1): classes of phosphono molecule that have been found to have broad-based properties in the fields of both biological and materials science.

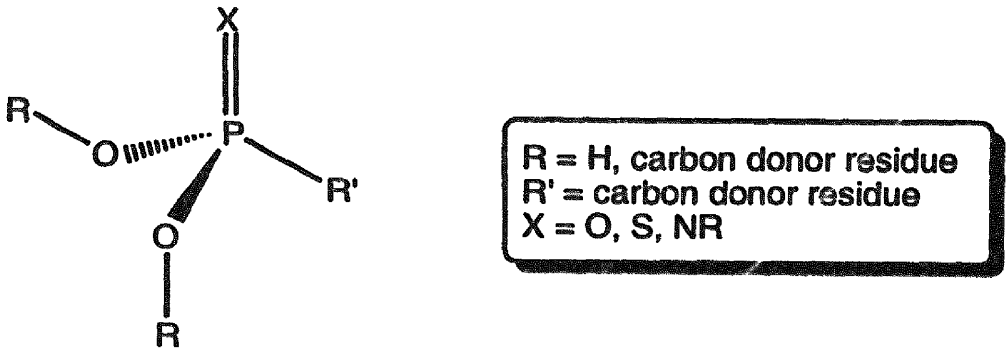


Fig. 1. Phosphonate ester topology.

The most commonly encountered methods of [P–C] bond formation are: (i) nucleophilic attack of a carbon-based nucleophile on an electrophilic phosphorus centre, commonly one which possess at least one effective leaving group such as a halogen, alkoxy or amido function; (ii) attack of a phosphorus-based nucleophile upon an electrophilic carbon-based substrate which may either be chemically saturated or unsaturated. In this article we focus on the latter approach for two major reasons. Firstly, there are distinct mechanistic differences between the two methods; secondly, most of the recent advances in stereoselective [P–C] bond formation have been based on this latter approach. Consequently, it is appropriate at this point to mention the two principal classes of organophosphorus scaffold which are commonly used to achieve [P–C] bond formation via this approach; the $\sigma^3\lambda^3$ ester and the $\sigma^4\lambda^5$ ester (Fig. 2).

As is evident from Fig. 2(a), the $\sigma^3\lambda^3$ ester contains a phosphorus(III) atom and as such is capable of acting as a nucleophile without any preliminary manipulation. However, the $\sigma^4\lambda^5$ ester of Fig. 2(b) contains phosphorus in its highest valence state (V) and consequently is not capable of acting as a nucleophile unless activated by reduction to phosphorus(III). This may be achieved through the equilibrium connecting (b) and (c), but for most systems where R = alkoxy, alkyl and X = O, this equilibrium lies overwhelmingly to the side of the $\sigma^4\lambda^5$ ester (b). However, $\sigma^3\lambda^3$ isomer (c) is consistently favoured when the phosphorus-bound hydrogen atom is replaced by either a silyl function [3] or an electropositive metal such as sodium or lithium [4]. Therefore, common activation pathways for (b) involve reaction with R_3SiCl in the presence of an HCl acceptor, such as pyridine or triethylamine, or deprotonation with NaH or LiN^iPr_2; examples of both of these activation modes will be presented below.

2. The importance of phosphono compounds

Phosphate esters $[(RO)_nO_{3-n}P(O)]^{(3-n)-}$ $(n=1–3)$ are profoundly endogenous chemicals, forming the backbone of many of the most important molecules in life, such as the oligonucleotide polymers DNA and RNA and the phosphorylated

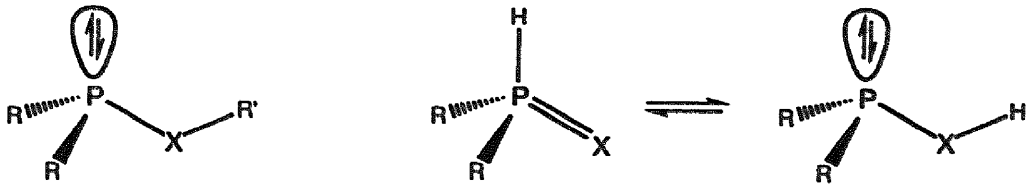


Fig. 2. Common classes of reagent in [P–C] bond-forming reactions.

proteins that control signal transduction, yet studies of their chemistry are often hampered by facile enzyme-mediated hydrolysis. However, replacing a [P–O] bond in a phosphate by a [P–C] moiety to afford a phosphonate ester affords increased stability towards hydrolysis, with the result that phosphonate esters have found important applications as mimics of phosphate esters (see for example Ref. [5]), phospho-transfer enzymes [6], and in antisense oligonucleotide technology (Fig. 3) [7]. These phosphato-mimics express a range of desirable physiological properties as, for example, antibiotics, [8] antiviral agents, [9] pesticides and antitumour agents [5].

α-Functionalised phosphonic acids are among the most important [P–C] derivatives, especially when the functionality possesses hydrogen-bonding capabilities as in α-OH, α-NH_2 and α-F, since it is this extra functionality which is crucial to their abilities to mimic, for example, amino carboxylic acids (for example see Ref. [10]) and kinase and phosphatase enzymes [6]. Consequently, there is a recognised need for the continued development of methods to construct functionalised phosphonate frameworks which combine efficiency, selectivity (both regio and stereo), generality, flexibility and ease of operation.

As well as being a versatile component of biological construction, phosphonate esters and their salts are currently attracting intense interest for their uses in the chemical self-assembly of new materials [11]. In particular, organic phosphonate $[RPO_3]^{2-}$ salts of tetravalent metals such as zirconium possess layered structures in which the organic functions R are disposed within the inter-layer region between quasi-two-dimensional metal–oxygen sheets (Fig. 4). This structural motif appears to be relatively insensitive to the nature of the organic group, which may be selected to promote a particular application such as ion exchange, a catalytic reaction, analyte binding, crystal growth [12] and in the construction of well-defined pillared structures in which the phosphonate superstructure is able to orientate hyperpolarisable molecules such as azo dyes resulting in non-linear optical effects [13].

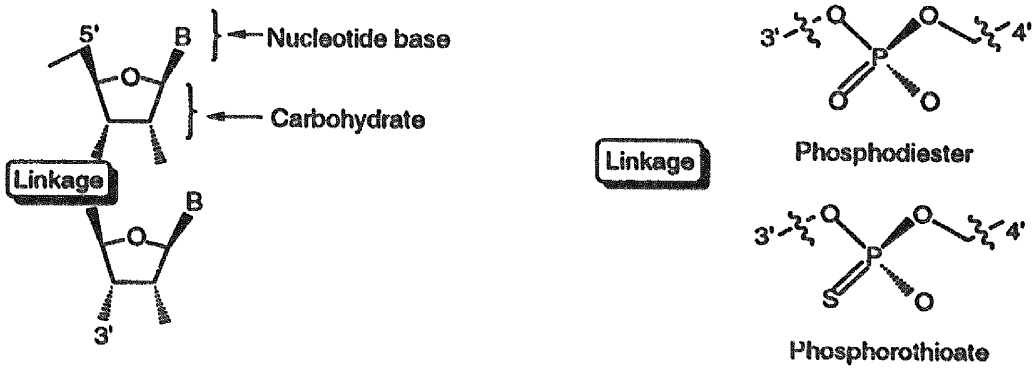


Fig. 3. Modified nucleotides.

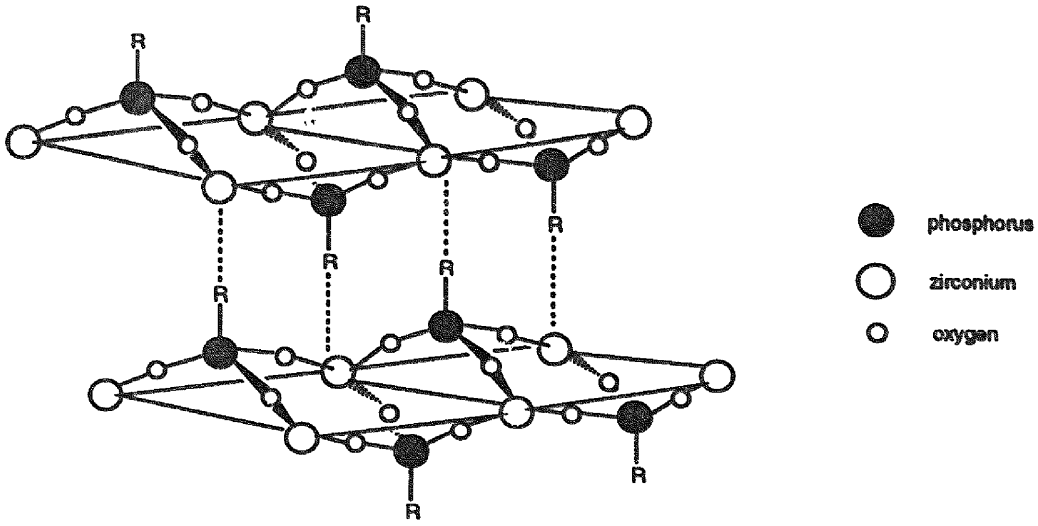
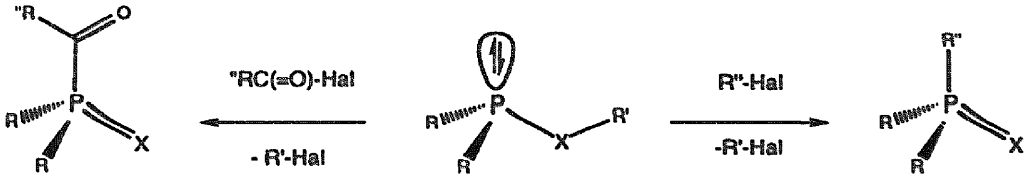


Fig. 4. Lamellar structure of metallophosphonates.

3. Symmetric phosphono-transfer processes

3.1. Transfer to halogenated substrates

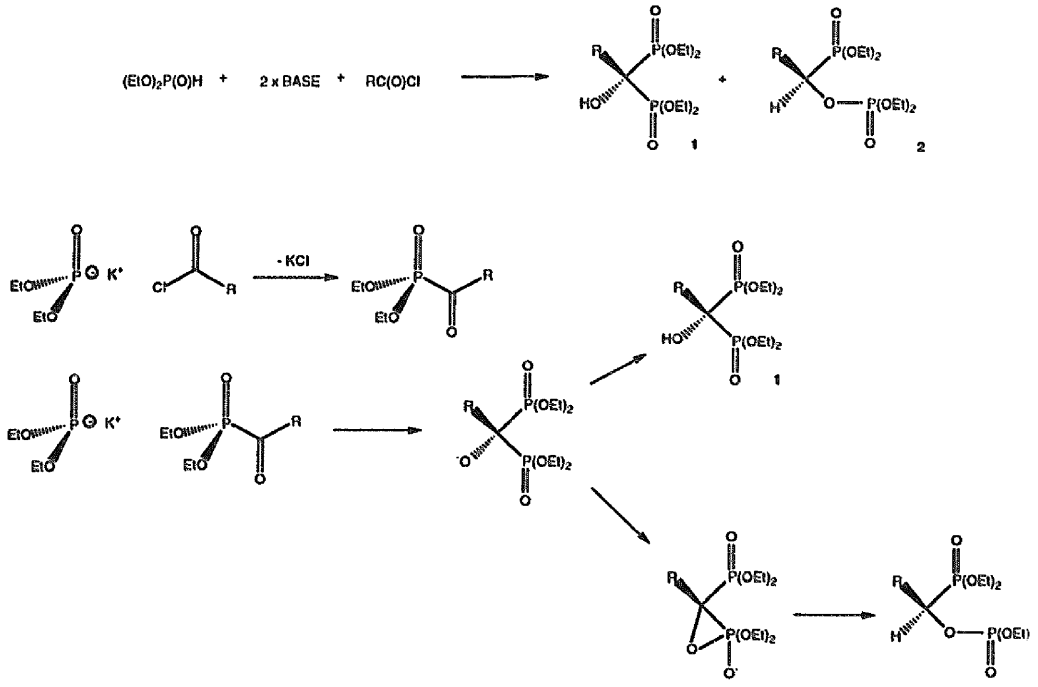
The reaction of a phosphorus nucleophile with alkyl or related organic halides has been known for many years as one of the most versatile [P–C] bond forming reactions; the most common variant being the Michaelis–Arbuzov reaction illustrated in Scheme 1.



Scheme 1. The Michaelis–Arbuzov reaction.

The Michaelis–Arbuzov reaction has been developed as an effective method to both bisphosphonates and hydroxybisphosphonates, classes of organophosphorus compound which have proved highly valuable in the treatment of bone diseases and

calcium metabolism of which osteoporosis is the most common form [14]. Scheme 2 outlines the general form of addition of dialkylphosphito anions to acid chlorides resulting in mixtures of α-hydroxybisphosphonates **1** and the corresponding isomeric phosphate products **2**, the composition of the reaction mixture being strongly influenced by the nature of the base used and the extent of substitution at the α-alkyl function [15]. It is found that lithium amide bases and sterically demanding α-alkyl groups favour formation of **2**, whilst potassium amide bases and small R groups favour bisphosphonates **1**. Further studies [15] revealed that the formation of **2** did not result from rearrangement of **1** under conditions of work-up or purification, but rather resulted from a kinetic preference of alternative pathways influenced by choice of alkali metal cation and acyl halide substitution patterns from potentially common intermediates, as illustrated in Scheme 2.



Scheme 2. Acylation of secondary phosphites and their metal salts.

Other advances in bisphosphonate synthesis have been reported recently, including the ^{13}C- and ^{14}C-labelled derivatives of clodronate, (dichloromethylene)bisphosphonic acid disodium salt tetrahydrate [16], and monophosphonate ester starting materials, such as mixed esters of methylphosphonic acid [17].

Amongst the most important applications of phosphono compounds are phosphono-peptides and phosphono-nucleotides, and consequently there have been extensive synthetic studies in recent years which exploit Michaelis–Arbuzov chemistry. It is not possible within the present article to do justice to these contributions, but introductions to the literature may be achieved by consulting work describing

the synthesis of phosphonamidate, phosphonate and phosphinate analogues of glutamyl-γ-glutamate [18], the synthesis of phosphorus-containing sarcosine derivatives [19], the synthesis of nucleotides containing bridged non-chiral internucleotide 5′- or 3′-phosphoramidate linkages [20], 3′-*S*-phosphorothiolate linkages [21,22], nucleotide analogues related to HPMPA [23], unsaturated phosphonates as acyclic nucleotide analogues [24], *S*-alkylphosphorodichloridothioates [25], diethyl-2,4-dioxoimidazolidine-5-phosphonates [26] and phosphorus-containing glycine and (*E*)-2,3-dehydroamino acid-derivatives from t-butyl-2-t-butyl-3-methyl-4-oxo-1-imidazolidine carboxylate [27].

In addition to the above, Michaelis–Arbuzov chemistry has been used to develop routes to chiral phosphines and phosphine oxides [28], allyldiphenylphosphine oxide via a tandem process promoted by microwave heating [29], (*E*)-enol ethers of protected 4-amino aldehydes [30], an improved synthesis of diethyl bromomethylphosphonate and a new method for the isomerisation of triethyl phosphite to diethyl ethylphosphonate catalysed by diiodomethane [31]. Similarly, the first applications of benzyl phosphites in the Michaelis–Arbuzov reaction have been reported [32,33], and several metal-based processes have been developed which involve the Michaelis–Arbuzov reaction of coordinated trialkyl phosphites [34–36].

Interestingly, a single-crystal X-ray diffraction study has been performed on the intermediate adduct from neopentyl diphenylphosphinite and phenacyl bromide (Fig. 5) which reveals a four-coordinate tetrahedral phosphonium geometry with a non-bonding distance of 4.229 Å between the phosphonium cation and bromide

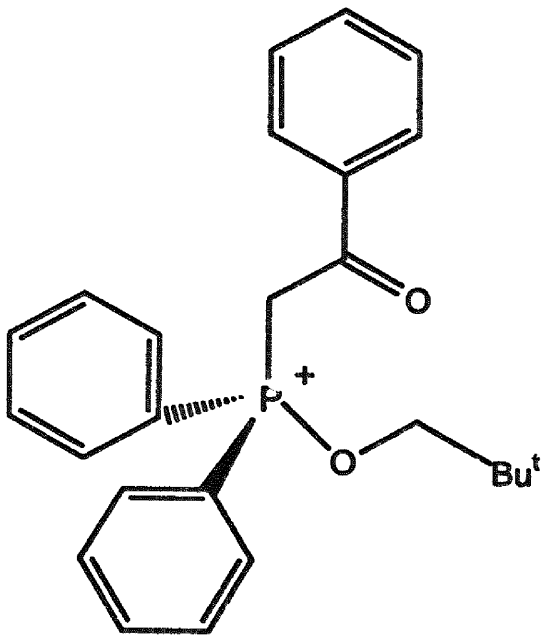
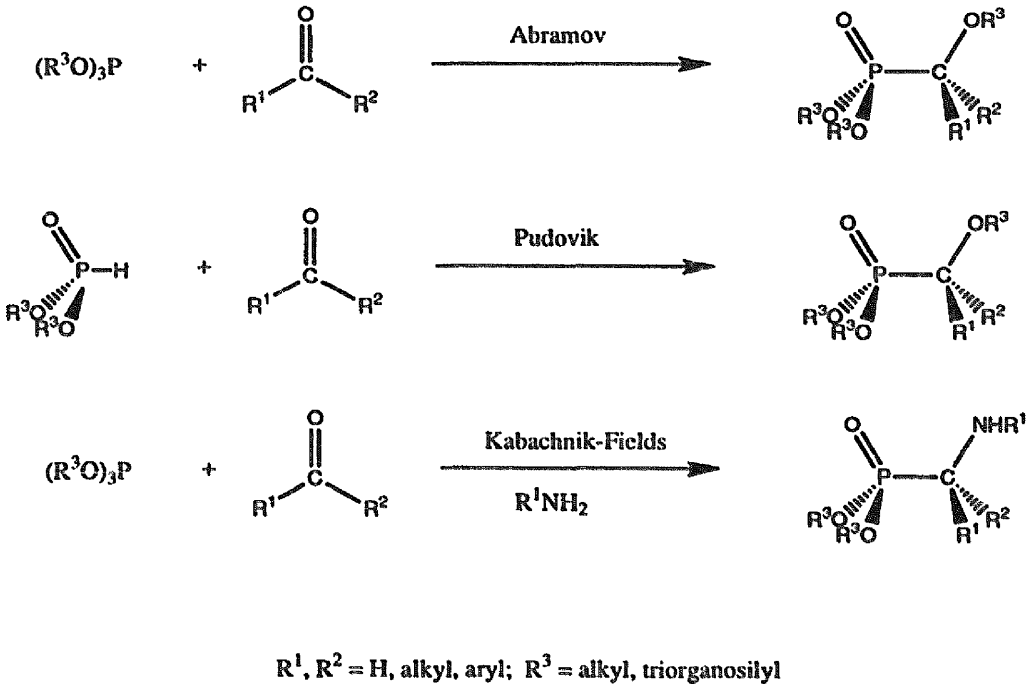


Fig. 5. Stucture of neopentyloxy(phenacyl)diphenylphosphonium bromide (anion omitted for clarity).

anion. The phosphorus–phenyl distances are normal. Although the phosphorus–oxygen bond length of 1.573 Å indicates significant double bond character, the reactivity of intermediates of this type is thought to be controlled mainly by inductive effects. Rearrangement of this intermediate to the vinyloxyphosphonium bromide (the Perkow intermediate) does not occur [37].

3.2. *Transfer to carbonyl and related substrates*

The seminal work in this area has been reviewed comprehensively by Wozniak and Chojnowski in 1989. In the intervening years the emphasis has shifted towards the development of chiral variants (vide infra). In addition to the significant amount of work that has been published on the addition of $\sigma^3\lambda^3$ (the Abramov reaction) and $\sigma^4\lambda^5$ organophosphorus esters (the Pudovik reaction) to carbonyls and α,β-unsaturated carbonyls (vide supra), significant interest has been kindled recently in developing asymmetric variants of these addition reactions with imines (Scheme 3). Although asymmetric work will be described later in this report, a number of achiral studies have been performed on a Strecker-type variant of the Pudovik reaction, which is commonly given the name Kabachnik–Fields. Thus, the addition of dialkylphosphites to preformed imines has been performed under sonochemical conditions and shown to result in significantly reduced reaction times [38]. The evidence from EPR spectroscopy suggested the reaction involved radical species. If, instead of



R^1, R^2 = H, alkyl, aryl; R^3 = alkyl, triorganosilyl

Scheme 3. Three common phophonylation processes of prochiral substrates.

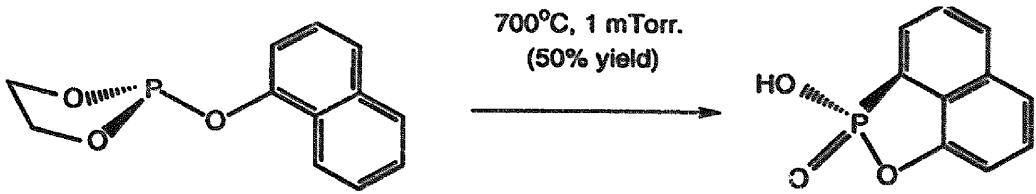
using the $\sigma^4\lambda^5$ dialkylphosphite ester, the $\sigma^3\lambda^3$ phosphonite ester, $(Me_3SiO)_2PH$, is employed, then imine phosphonylation proceeds smoothly at 0 °C in the absence of any ultrasonic activation [39]. This phosphonylation is directly related to the Abramov reaction discussed above.

The more common Kabachnik–Fields protocol involves a three component system of carbonyl, amine (either ammonia or a primary amine) and dialkylphosphite as outlined in Scheme 3.

3.3. *Transfer to other unsaturated substrates*

A number of studies have been reported on the phosphonylation of the aromatic nucleus. Thus, it has been demonstrated that sodium iodide acts as a catalyst (at loadings of 5 mol%) for the photochemically-induced phosphonylation of halobenzenes to phenylphosphonates in tetrahydrofuran–acetonitrile solvent [40]. Along similar lines, it has been reported that aryl phosphonates may be synthesised in good yield from the respective arenes and tri- or dialkylphosphites by either chemical (peroxydisulphate/silver nitrate in acetonitrile/water) or anodic oxidation [41].

As an alternative to the milder routes to [P–C] bond formation, recent reports from Cadogan et al. reveal a high temperature protocol involving the flash vacuum pyrolysis of 2-aryloxy-1,3,2-dioxaphospholanes (Scheme 4): reaction is presumed to proceed via the intermediacy of highly electrophilic metaphosphate ($ArOPO_2$) followed by intramolecular C–H bond insertion [42]. Unfortunately, it did not prove possible to observe the putative metaphosphate in these particular systems; however, ethene is observed to be a co-product of the thermolysis, and, in other work, more stable analogues of metaphosphate have been prepared and studied and shown to be highly electrophilic [43].



Scheme 4. Thermally induced [P–C] bond formation.

4. Stoichiometric asymmetric phosphono-transfer processes

4.1. *The Abramov reaction*

As described above, the Abramov process (Scheme 3) has been developed as a particularly versatile method for the phosphonylation of unsaturated organic compounds [3], a variety of substrates (e.g. aldehydes, ketones, imines, azides, etc.) being compatible with the protocol [44].

The versatility of the Abramov reaction is further illustrated by the fact that protection and deprotection procedures are generally not required during the phosphonylation process. The use of tertiary phosphite reagents as a method of performing phosphonylation reactions thus permits a general and flexible methodology for the synthesis of α-functionalised phosphonates and related classes of organophosphorus compound.

In the development of the asymmetric Abramov reaction, two general approaches have been adopted which differ in the origin of stereochemical control; in the first of these protocols, the seat of stereodifferentiation is located within the carbonyl substrate, whilst in the second it is located within the organophosphorus coordination sphere. Both approaches are highlighted below.

4.1.1. Chirality within the carbonyl substrate

One area of research which highlights the biological significance of phosphonate esters is the synthesis of modified nucleosides. This owes much to the fact that the early drugs exhibiting recognised therapeutic value in the treatment of viral diseases such as HIV were based upon such modified nucleosides, for example 3′-azidothymidine (AZT), dideoxyinosine (DDI) and dideoxycytidine (DDC). However, since the observed toxicity of these compounds continues to be a limiting factor in their usefulness, significant interest is being focused upon the development of less toxic variants. Furthermore, since it is believed that prior to displaying their desirable physiological properties these nucleosides must be phosphorylated, the synthesis of modified nucleosides containing phosphonate groups is of great interest. Methylenephosphonate analogues of 5′- and 3′-phosphates have been known for some time [45], whereas analogues of nucleoside 2′- and 3′-phosphates have only just recently been investigated [46].

The hydrophosphonylation of 2′- and 3′-keto nucleosides would be expected to afford hydroxyphosphonates which are isomeric to nucleoside 2′- and 3′-phosphates. The potential antiviral activity of such compounds has led to the Abramov phosphonylation of 2′-keto derivatives of uridine (**a**) and adenosine (**b**), and of 3′-keto derivatives of uridine (**c**), adenosine (**d**) and 2′-deoxythymidine (**e**) by diethyl phosphite (Fig. 6).

Although mixtures of diastereoisomers were obtained at ambient temperatures in all cases, reduced temperatures allowed the synthesis of single diastereoisomers [46]. Crystallographic data obtained on the 2′-deoxythymidine system at low temperature indicate that phosphite attack took place on the sterically less hindered α-face of the nucleoside, to yield 5′-*O*-trityl-3′-β-hydroxy-3′-α-(diethyl)phosphonothymidine. A variety of related compounds have also been reported to be accessible via a similar Abramov protocol [47].

The biological importance of α-alkyl phosphonic acids has been reflected in a significant amount of research being directed currently towards developing asymmetric synthetic methodology for these compounds [48]. Accordingly, Abramov-based technology has provided a sound platform for the development of these processes. The addition of phosphorus nucleophiles to *N*-glycosyl nitrones has been shown to

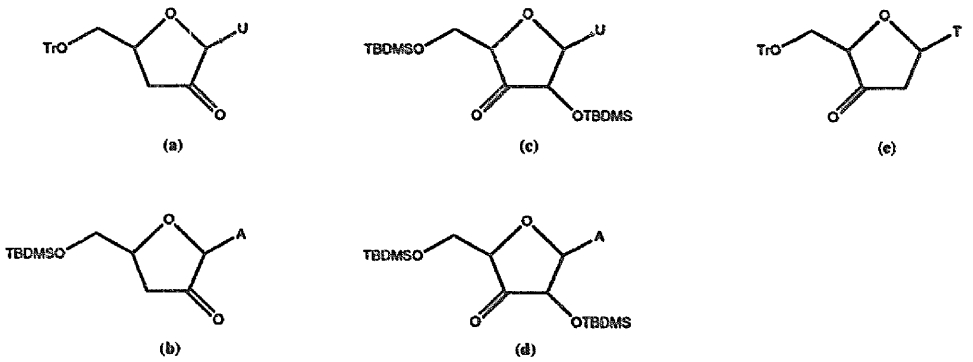
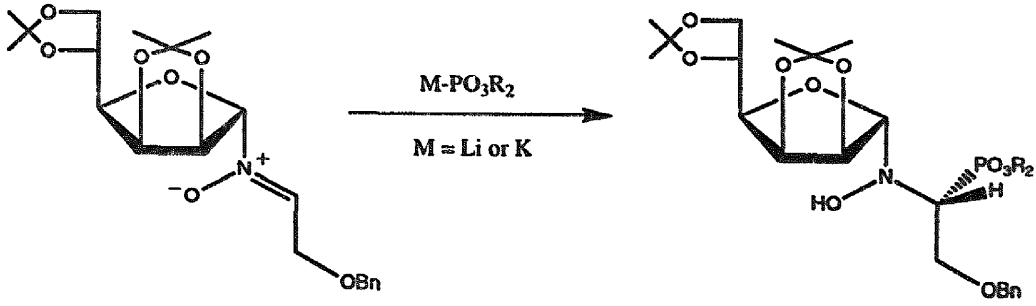


Fig. 6. Derivatives of uridine, adenosine and 2-deoxythymidine.

be an effective route to enantiomerically pure α-aminophosphonic acids via *N*-hydroxy-α-aminaophosphonic acids (Scheme 5) [49].

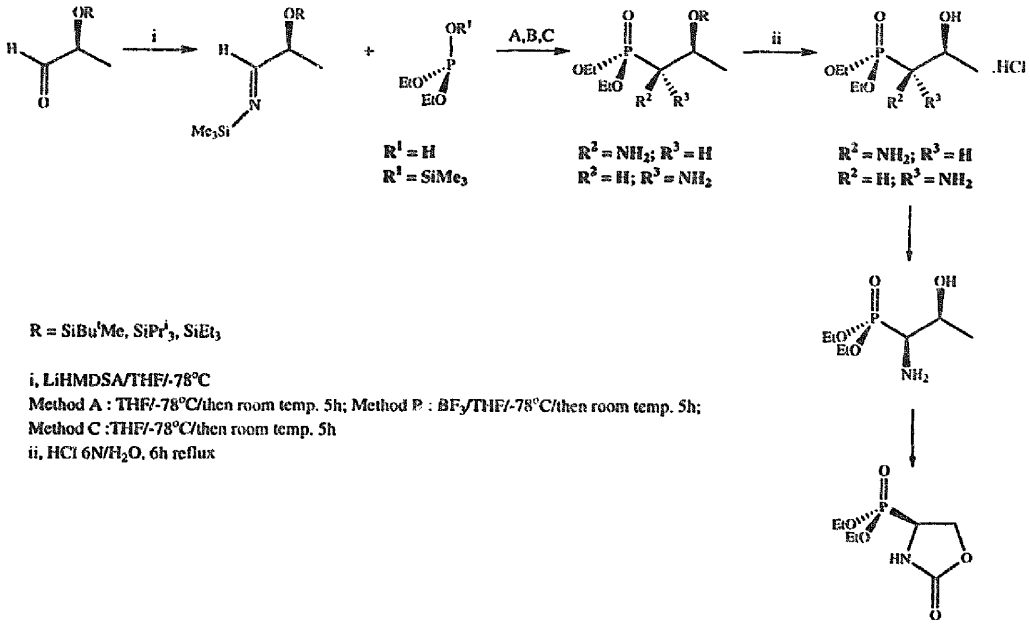


Scheme 5. Phosphonylation of niotrones.

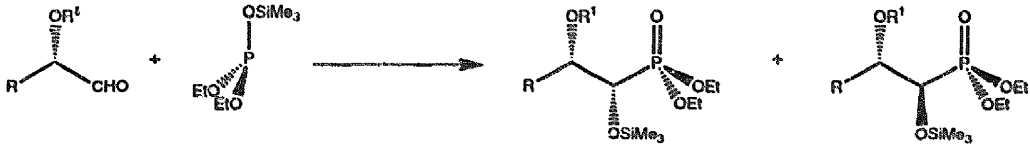
Lithium and potassium dialkylphosphites have both been used to phosphonylate *N*-glycosyl nitrones. The role of the nucleophilic phosphorus reagent in the diastereo-controlling step of reaction is reflected in greater diastereoselectivities (in the range 78–92%) being obtained when lithium reagents are used, whereas the corresponding potassium phosphites exhibit greatly reduced selectivity. This difference is even more pronounced when the phosphites employed are more sterically demanding.

(1*S*,2*S*)-1-amino-2-hydroxy-propane-phosphonic acid has been successfully synthesised from (*S*)-lactic aldehyde (Scheme 6) [50]. Following conversion of the aldehyde to the *N*-trimethylsilylimine, a protected α-amino phosphonate ester may be obtained via the Abramov reaction with a tertiary phosphite. The presence of an alkoxy, rather than hydroxy, group at the β-carbon position of the substrate results in a phosphonylation step which occurs with a selectivity which depends upon steric demand at the β-functionality, as illustrated also in the phosphonylation of α-siloxyaldehydes (Scheme 7) [51].

In such reactions, it is again necessary to bear in mind that one of the major factors governing both stereochemistry and yield is the nucleophilicity of the phosphorus atom in the phosphonylating reagent. *O*-Silylation of the phosphorus reagent



Scheme 6. Phosphonylation of chiral imines.



Scheme 7. Phosphonylation of chiral aldehydes.

leads to an overall increase in stereoselectivity and yield, presumably as a result of the reduced tendency for tautomerisation between the $\sigma^3\lambda^3$ phosphite and $\sigma^4\lambda^5$ phosphonate forms. Consequently, this results in the trivalent nucleophilic species dominating, as opposed to the pentavalent electrophilic form. As expected, the nature of the solvent employed also leads to a degree of control over both rate and stereoselectivity, although this is less pronounced compared with the stereoelectronic parameters described above.

An interesting and highly valuable extension of this work has been the synthesis of the naturally occurring and broad-based antibiotic (1*R*,2*S*)-fosfomycin via chiral α-alkyl phosphonic acids [52].

Mechanistic studies on these stoichiometric systems suggest the possibility of a cyclic (closed) transition state involving both phosphorus–carbon [P–C] bond formation and both silicon–oxygen [Si–O] bond cleavage and formation via a pentacoordinate silicon atom. However, there are still a great many questions which remain unanswered, not least of which are those regarding the potential role of Lewis acids

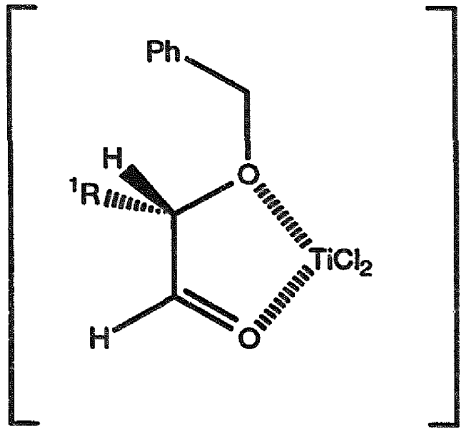
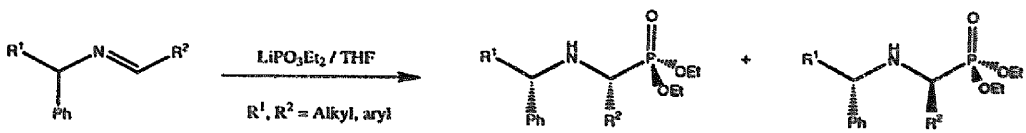


Fig. 7. Proposed Lewis acid activation of functionalised carbonyls via chelate ring formation [53].

in these systems and the precise factors which control the stereochemistry of reaction. For example, work performed on the reaction of α-amino aldehyde [53] and α-benzyloxyaldehydes [54] with phosphorus nucleophiles in the presence of titanium(IV) chloride suggest that chelation control has a significant role to play in the determination of diastereoselectivity. Stereoselectivity is very high in the case of α-benzyloxy aldehydes, possibly as the result of chelate ring formation such as that illustrated in Fig. 7.

Variations in the alkyl group attached to the α-carbon of the substrate and in the alkoxy moiety of the phosphorus nucleophile are seen to affect the diastereoselectivity in a manner generally consistent with the steric demands of the system, although a full rationalisation of the role of these parameters has yet to be realised.

In a similar manner, chelation effects have been proposed to control the phosphonylation of chiral functionalised imines by lithium diethyl phosphite (Scheme 8) [55].



Scheme 8. Phosphonylation of chiral imines.

The diastereoselectivities in the above system were generally very high (96–98% d.e.) and were found to be essentially independent of the nature of R^1. It was also observed that the nature of the phosphite counterion had a significant effect on the reaction; an investigation of the imine for which R^2 = cyclohexyl showed that sodium and potassium salts of diethyl phosphite were ineffective as phosphonylating agents [55]. As a result of these observations, it was proposed that the transition state for the step that has most influence over diastereoselectivity involves a chelate ring system of the type shown in Fig. 8.

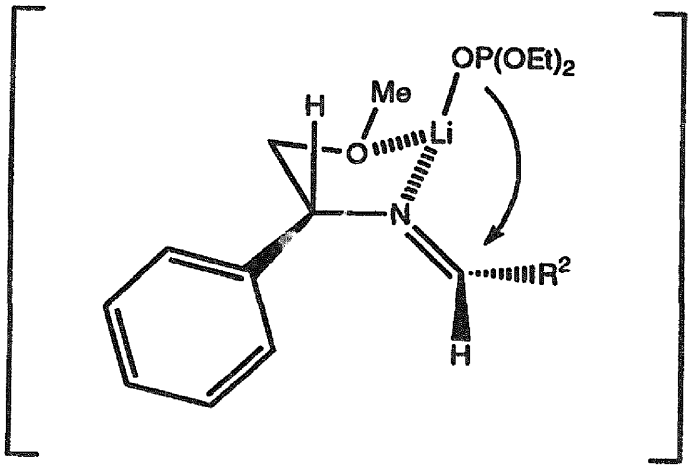
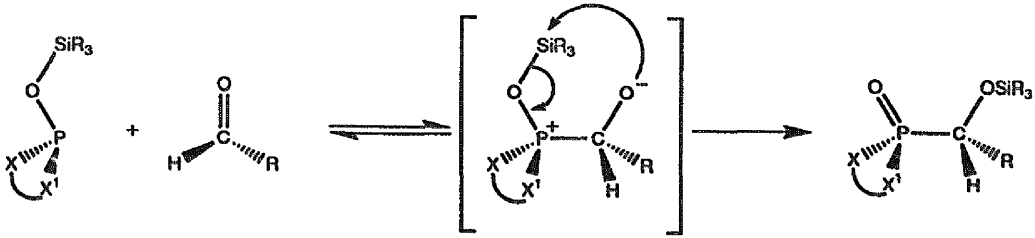


Fig. 8. Proposed intermediate in the asymmetric phosphonylation of chiral chelating functionalised imines [55].

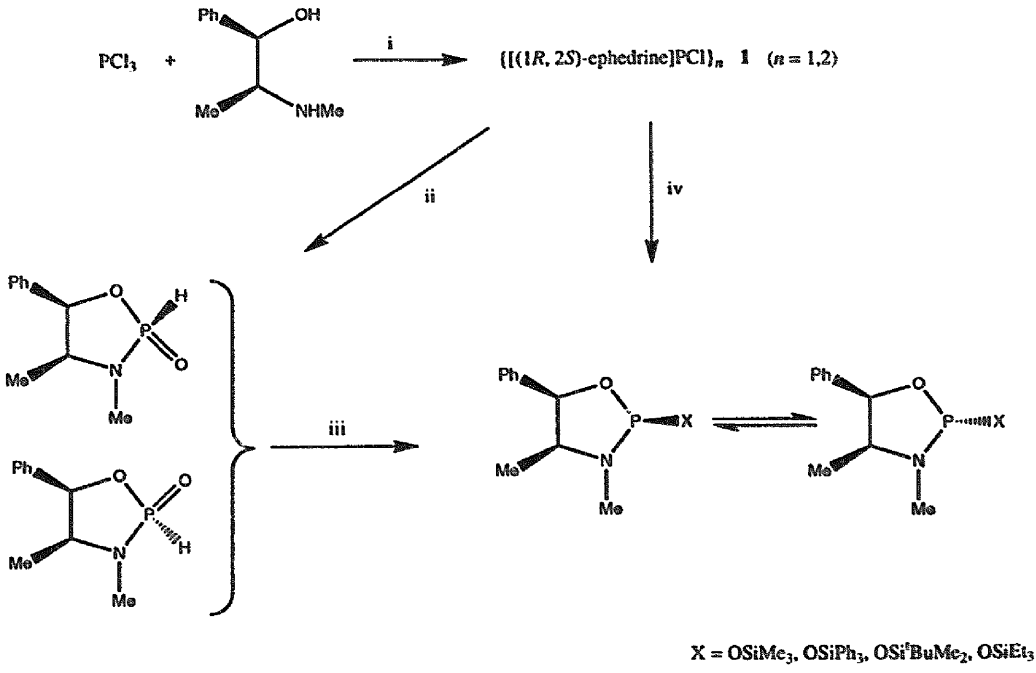
4.1.2. *Chirality within the phosphorus substrate*

A significant amount of research has been performed on the Abramov reaction in which chiral phosphonylating agents employed have contained the source of stereocontrol in the form of a chiral chelating auxiliary. Achiral silyl phosphite esters incorporating the diazaphospholidine moiety have been recognised to be effective and potentially highly versatile phosphonylating agents for the symmetric Abramov reaction [56]. Thus, the use of phosphonylating agents employing auxiliaries such as chiral oxazaphospholidines has led to successful chiral hydrophosphonylation methods. A proposed mechanism for such a mode of Abramov phosphonylation is shown in Scheme 9.



Scheme 9. A proposed mechanism of the asymmetric Abramov reaction.

2-Chloro-1,3,2-oxazaphospholidines derived from (1*R*,2*S*)-ephedrine have provided a route to the chiral 2-triorganosiloxy-1,3,2-oxazaphospholidines, {(1*R*,2*S*)-ephedrine}$POSiR_3$ ($R_3 = Ph_3$, $^tBuMe_2$, Et_3) as a mixture of epimers with diastereoselectivities up to 94% in which, on the basis of derivatisation and analysis of ^1H NMR shift and coupling constant data, the major epimer appears to be that with the siloxo group anti to the ephedrine backbone phenyl and methyl substituents (Scheme 10) [57].



Scheme 10. Syntheses of oxazaphospholidine heterocycles.

These silylated organophosphorus(III) esters undergo the Abramov reaction with aldehydes, such as benzaldehyde and pivalaldehyde, at room temperature to afford a mixture of all four expected diastereoisomeric α-siloxyphosphonate esters {(1*R*,2*S*)-ephedrine}P(=O)*C*HR′(OSiR$_3$)(R′=Ph, ^{t}Bu) in good yields. Although a mixture of products results, one diastereoisomer in each case appears to dominate the products ranging from 61% (R′=^{t}Bu, R$_3$=Ph$_3$) to 86% (R′=^{t}Bu, R$_3$=^{t}BuMe). The absolute configuration at phosphorus can normally be determined with a reasonable degree of accuracy by analysis of ^{1}H chemical shift and coupling constant parameters [57,58], but the absolute configuration at the newly generated α-carbon atom stereocentre is difficult to assay without X-ray crystallographic information which, unfortunately, is not available for these systems [57]. However, results do suggest that the major epimers of the 2-siloxo-1,3,2-oxazaphospholidines react with aldehydes R′CHO with overall retention of configuration at phosphorus.

Interestingly, results suggest that the chiral 2-chloro-1,3,2-oxazaphospholidine produced in the reaction of (1*R*,2*S*)-ephedrine with PCl$_3$ exists as a dimer (**c** and **d**, Fig. 9) [57] rather than a monomer (**a** and **b**, Fig. 9) [59]. Specifically, solution relative molecular mass measurements are more consistent with a dimeric species, and the relative rate of reaction with elemental sulphur, a reaction normally expected to proceed smoothly at ambient temperature, requires prolonged heating at 80 °C to effect significant reaction [57]. To date, definitive X-ray crystallographic evidence is not yet available to distinguish between the proposed most reasonable alternatives (**c** and **d**) shown in Fig. 9.

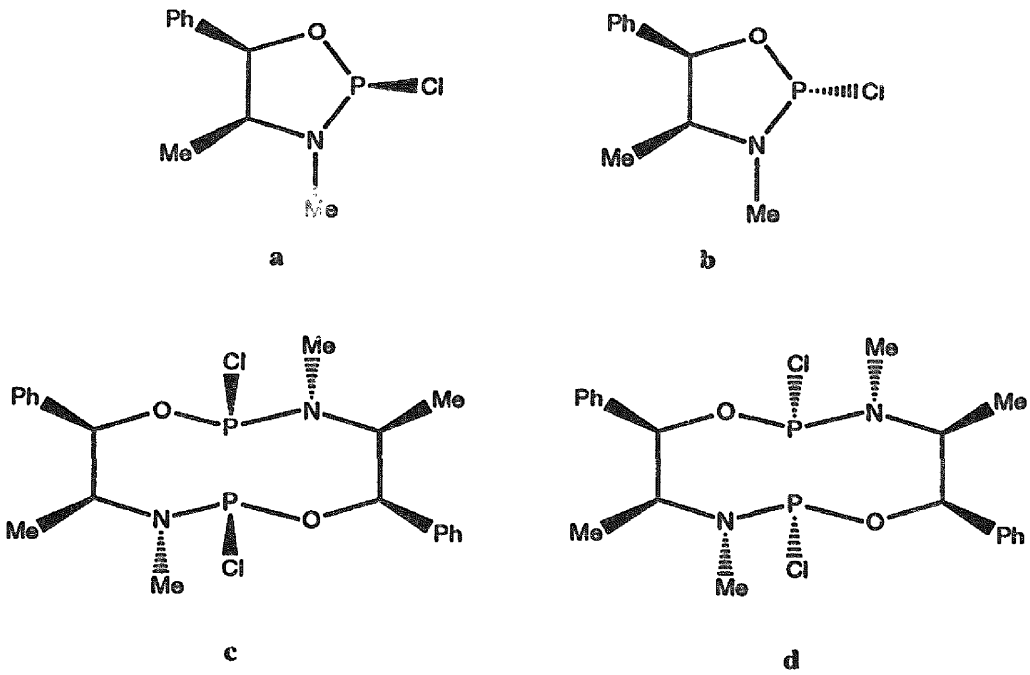
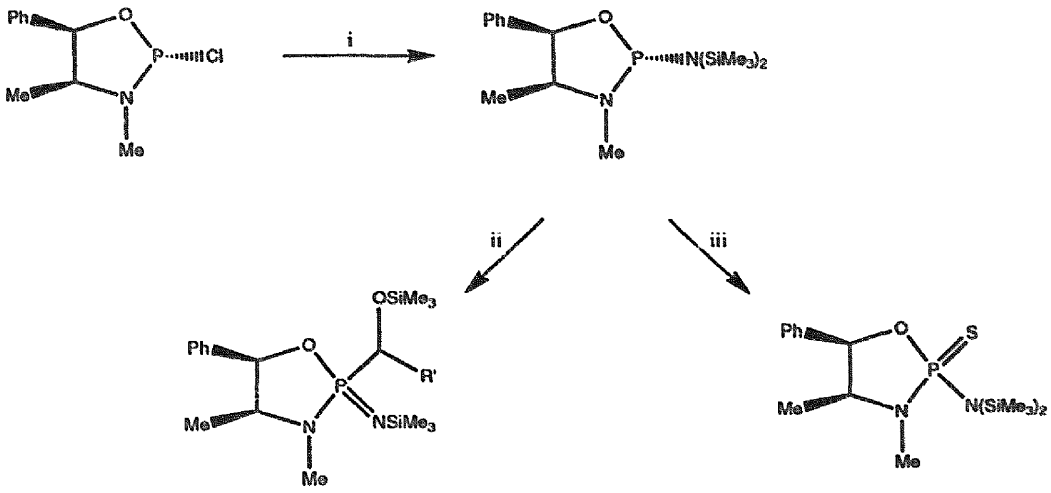


Fig. 9. Possible monomeric and dimeric forms of the chiral 2-chloro-1,3,2-oxazaphospholidine derived from (1*R*,2*S*)-ephedrine.

The phosphorus reagents above containing (1*R*,2*S*)-ephedrine as the chiral chelating auxiliary have the disadvantage that they exist as a mixture of epimers which appear to be in equilibrium (the rate of equilibration appears to be of a similar order to that of aldehyde phosphonylation). A much more satisfactory situation would be to have a phosphonylating reagent that exists in a single stereoisomeric form and would, consequently, give rise to only two epimeric Abramov phosphonate products. One solution to this particular problem has been found in which the siloxo group is replaced by the isoelectronic and isolobal bis(trimethylsilyl)amido (BTSA) function $N(SiMe_3)_2$. The idea is that the more sterically demanding profile of the BTSA group would result in a phosphonylating agent which exists in a one-isomeric form as a result of steric effects. Consequently, the phosphorodiamidite reagent [*N*,*O*-(1*R*,2*S*)-ephedrine]$PN(SiMe_3)_2$ has been synthesised and found to exist in a single isomeric form (to at least greater than 98% by ^1H NMR spectroscopy) and the absolute configuration (as determined by a single-crystal X-ray diffraction study on the corresponding sulphur adduct) is confirmed as being S_P [60]. Subsequently, [*N*,*O*-(1*R*,2*S*)-ephedrine]$PN(SiMe_3)_2$ was found to react readily with aldehydes to afford the ester {*N*,*O*-(1*R*,2*S*)-ephedrine}$P(=NSiMe_3)CHR(OSiMe_3)$ (R = Ph, ^{t}Bu, 2-naphthyl, ^{n}Pr, ^{n}Bu) (Scheme 11) [61].

In such systems, excellent stereoselectivities may be obtained (R = Ph and substituted phenyl 89–94%; R = ^{t}Bu, 96%), and the use of single-crystal X-ray crystallography provides conclusive evidence for the overall retention of configuration at

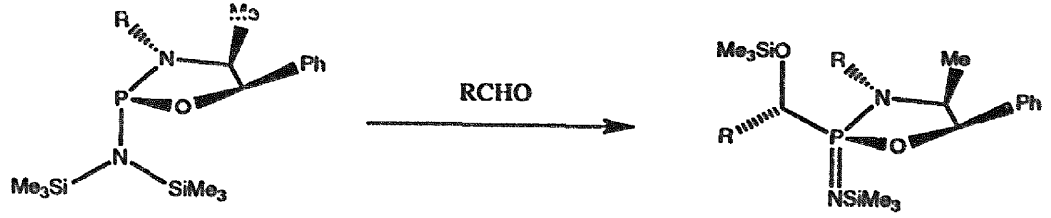


Scheme 11. Synthesis of a chiral 2-(bis-trimethylsilylamido)-1,3,2-oxazaphospholidine derived from (1*R*,2*S*)-ephedrine.

phosphorus. These assignments of configuration at phosphorus are supported by the observed small $^{3}J_{PH}$ coupling (less than 2 Hz) between phosphorus and the PhCHO methine hydrogens for each of the products. These results are in accordance with the proposed and generally accepted mechanism for the Abramov reaction (Scheme 9).

Of course, the above conclusion of overall retention of configuration at phosphorus is strictly valid only for a system containing the [P–N–Si] function. However, several studies, including ^{18}O labelling investigations, have provided evidence for the retention of configuration in the more commonly encountered [P–O–Si] systems [62].

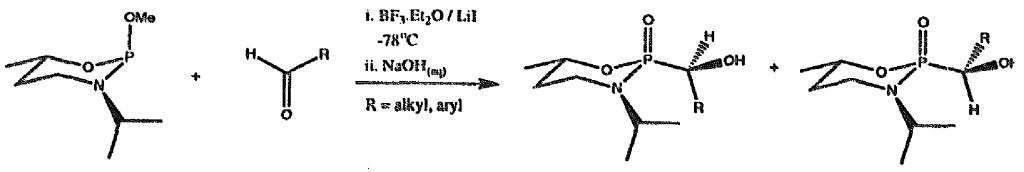
The need to delineate the causes of stereocontrol at the α-carbon atom has prompted further investigation of the stereoelectronic factors involved in the Abramov phosphonylation of aldehydes, particularly those resulting from the use of phosphorodiamidite systems (Scheme 12). A number of sites exist in [*N*,*O*-(1*R*,2*S*)-ephedrine]PN(SiMe$_3$)$_2$ for manipulation, and of these (i) the nature of the ephedrine nitrogen substituent, and (ii) the stereochemistry of the ephedrine backbone carbon atoms are accessible targets [63].



Scheme 12. Abramov phosphonylation of aldehydes via a chiral 2-(bis-trimethylsilylamido)-1,3,2-oxazaphospholidine derived from (1*R*,2*S*)-ephedrine.

A comparison of N–Me– and N–^{i}Pr–(1*R*,2*S*)-ephedrine auxiliaries shows that the latter is a generally less facile phosphonylating agent than the former. This is presumably due to the increased steric requirement of the isopropyl group within the primary coordination sphere of phosphorus. However, there appears to be little difference in diastereoselectivity between the N–Me– and N–^{i}Pr–(1*R*,2*S*)-ephedrine auxiliaries in the phosphonylation of meta- and para-substituted benzaldehydes. When the benzaldehyde substrate is ortho-substituted, however, the presence of N–^{i}Pr–(1*R*,2*S*)-ephedrine as an auxiliary confers a consistently greater preference for (S_P,S_C) stereochemistry in the product. Investigations have not yet advanced to the stage where it is possible to deduce which precise stage of reaction is both rate and stereochemistry determining, but a number of pertinent features have been uncovered concerning the mechanism of reaction [62]. (i) Double crossover experiments reveal that reaction proceeds with intramolecular silyl group transfer. (ii) The product α-siloxoimidophosphonate esters do not revert to starting materials under the ambient conditions used for the reaction, suggesting that reaction is overall kinetically controlled rather than influenced predominantly by product stability. However, upon heating to 80 °C, reversible aldehyde extrusion is observed (which can subsequently be trapped by a second phosphonylating agent) which leads to epimerisation at the α-carbon atom. (iii) Epimerisation also appears to occur in the presence of trace acid (especially prevalent in chlorinated solvents) [62]. Furthermore, studies reveal that the overall rate of reaction with substituted benzaldehydes is strongly dependent upon the electronic nature of the aldehyde substituent, reaction rate increasing as the substituent becomes more electron withdrawing. This suggests that the rate-determining transition state must presumably contain a significant degree of [P–C] bond formation. However, the same experiment reveals that even though the rate of reaction varies by a factor of ten between *p*-$MeOC_6H_4CHO$ (slowest) and *p*-$O_2NC_6H_4CHO$ (fastest), the diastereoselectivity in the two cases is the same. The available evidence points to steric effects as being dominant in determining the stereochemical outcome, since the closer the substituent to the carbonyl carbon atom (for example, in an ortho position), the greater its influence over both rate and stereochemistry. Studies are currently in progress in this laboratory which will hopefully shed light on the precise roles of [P–C] bond formation and silyl group transfer in determining stereocontrol.

The use of a different type of chelating chiral auxiliary bound to phosphorus has been explored by Gordon and Evans in the phosphonylation of aldehyde–boron trifluoride etherates (Scheme 13) [64]. The diastereoselectivities obtained on phosphonylating aliphatic aldehydes with such 2-oxa-1,3,2-oxazaphospholidines are gen-



Scheme 13. Abramov phosphonylation of aldehydes via a chiral 1-methoxy-1,3,2-oxazaphospholidine.

erally modest, even at −78 °C. It is apparent that models of the transition state which consider the steric requirements of both substrates do concur with the observed stereoselectivity and that these transition states are postulated as being of the open (acyclic) type in which [P–C] bond formation is dominant. It seems, however, that the degree of conformational restriction in the transition state is insufficient to produce a significantly increased steric response as the bulk of the carbonyl alkyl group increases.

When the substrate aldehyde is aromatic in nature, the use of Hammett studies have illustrated the significance of electronic effects in the diastereoselectivity of the reaction. It is at least apparent that the more reactive carbonyls are attended by reduced diastereoselectivity during reaction. Presumably the para-substituent influences the timing of the diastereoselective determining step of the reaction with respect to the phosphorus–carbon bond forming step by influencing reactivity of the carbonyl carbon atom [64].

4.2. *The Pudovik process*

The Pudovik reaction is a hydrophosphonylation process and is a close relative of the Abramov reaction. The major difference between the two, as mentioned earlier, is that in the former process the phosphonylating reagent is present as a $\sigma^4\lambda^5$ phosphorus(V) species compared with the Abramov process in which it is a $\sigma^3\lambda^3$ phosphorus(III) species. The equilibrium between an H-phosphonate and its phosphite tautomer may thus influence strongly the procedure of a reaction depending on the conditions used.

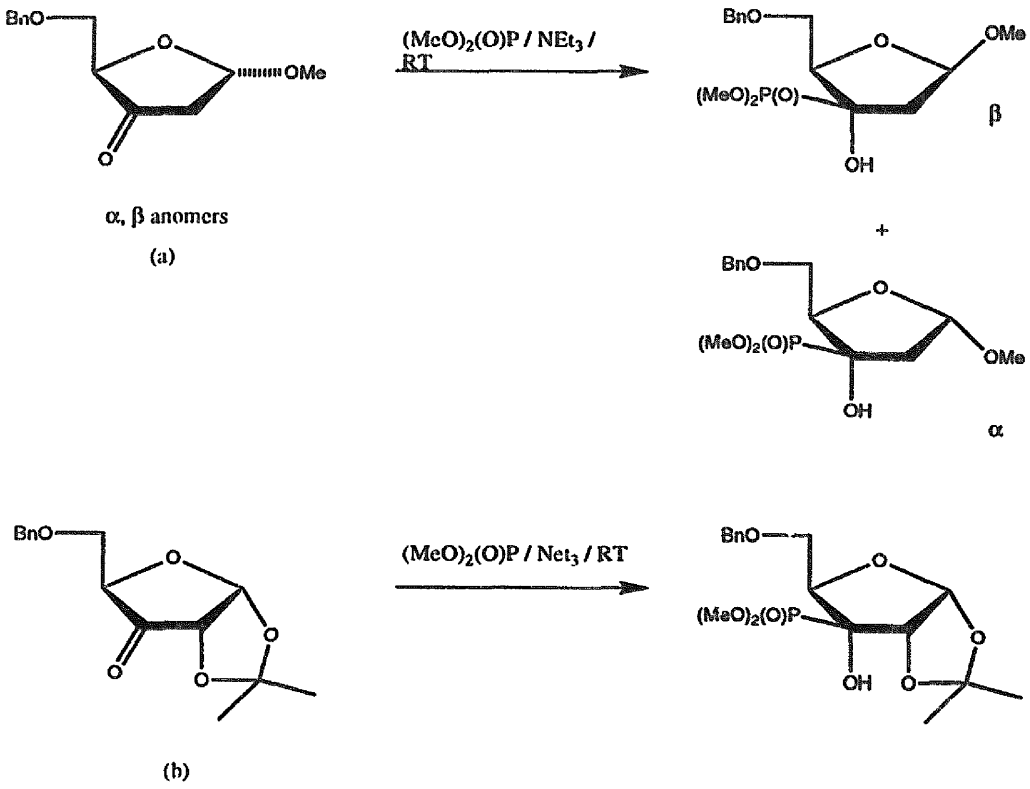
It has already been mentioned above that the phosphonylation of modified nucleosides may be performed under Abramov conditions where the phosphonylating agent is present predominantly as the phosphite tautomer in the form of a stabilised phosphite anion [65]. It is also possible to perform such reactions under conditions which favour the Pudovik process [66]. Thus the synthesis of 3′-phosphono-2′-deoxyribonucleosides may be achieved via the addition of dimethylphosphite to 3′-keto-sugars under basic conditions (Scheme 14).

The enantiopurity of the 3′-nucleotide analogues subsequently obtained depends on two key points in the synthetic procedure: (i) the anomeric effect of the cyclic sugar directing the stereoselectivity of the phosphonylation; (ii) the possibility of epimerisation at the 3′-carbon during reduction of the geminal hydroxyphosphonate moiety to yield the deoxygenated products. The presence of an isopropylidene group in (b) strongly enhances the stereocontrol of these steps, while the methoxy group allows the synthesis of α and β anomers.

5. Catalytic asymmetric phosphono-transfer processes

5.1. *The Abramov process*

One strategy which has been utilised in the development of asymmetric catalytic phosphonylation has involved chiral Lewis acidic catalysts. The design of catalysts

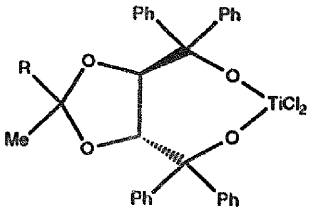


Scheme 14. Phosphonylation of keto-sugars.

which selectively bind and activate one or more of the reaction substrates and then allow phosphonylation to occur in a stereoselective manner has been an area of interest which has seen a dramatic increase in recent years. Enantioselectivity has been achieved using catalysts such as those depicted in Fig. 10 [67].

Enantioselectivies in the range 15–31% are achieved with catalyst (a); this was increased to 53% with the use of the Sharpless catalyst (c) based on a titanium tetraalkoxide. It seems reasonable to assume that displacement of one or more alkoxide moieties plays a significant role in the phosphonylation reaction, as is observed with the production of racemic phosphonate ester (87% yield) in the presence of catalyst (b) (20 mol%). The dependence of yield and diastereoselectivity on the nature of the solvent under conditions of active asymmetric catalysis is supportive of this hypothesis.

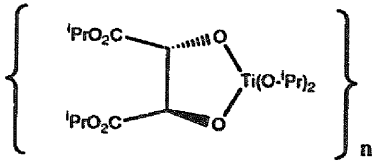
The phosphonylation of aromatic aldehydes with catalyst (d) results in enantioselectivities which depend greatly on the electronic nature of the aldehyde. Hammett plots indicate that coordination of the aldehyde to the Lewis acid is both the rate-determining and stereochemistry determining step of reaction.



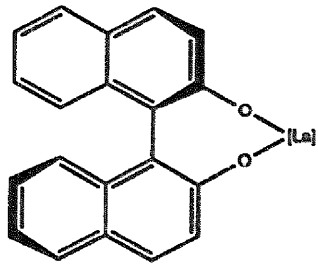
(a)

$Ti(O\text{-}^iPr)_4$

(b)



(c)



(d)

Fig. 10. Metal-based catalysts used in asymmetric variants of the Pudovik reaction.

5.2. *The Pudovik process*

Lewis acids have also found significant use as catalysts for the promotion of the Pudovik reaction, especially those based on the use of lanthanum ions with a chiral chelating binaphthol auxiliary [68].

The base-catalysed hydrophosphonylation of carbonyls with secondary phosphites has been one of the most promising, yet little studied, methods of achieving catalytic enantioselective hydrophosphonylation. One such strategy has explored the use of natural products as chiral bases. For example, alkaloids such as quinine (a) and quinidine (b) (Fig. 11) have been successfully used as chiral catalysts for the Pudovik reaction between *o*-nitrobenzaldehyde and a variety of dialkylphosphites [69].

As could be expected, the steric demands of the phosphorus reagent influence both enantioselectivity and reaction rate; with greater stereoselectivites and slower rates of reaction being obtained with the more sterically demanding dialkylphosphites (^{t}BuO vs. MeO). A most pertinent point is that the presence of the hydroxy functionality within the alkaloid is vital for the production of an optically active product. Attempts to catalyse the reaction with *O*-acetylquinine result in an optically inactive product at a greatly retarded rate of reaction [70].

The action of such alkaloids as chiral catalysts for the Pudovik reaction may thus be explained by the potential of the attendant hydroxy functionality for chelation control of the stereoselective transition state. However, it should be noted that since the degree of stereoselectivity is high for sterically demanding phosphorus reagents,

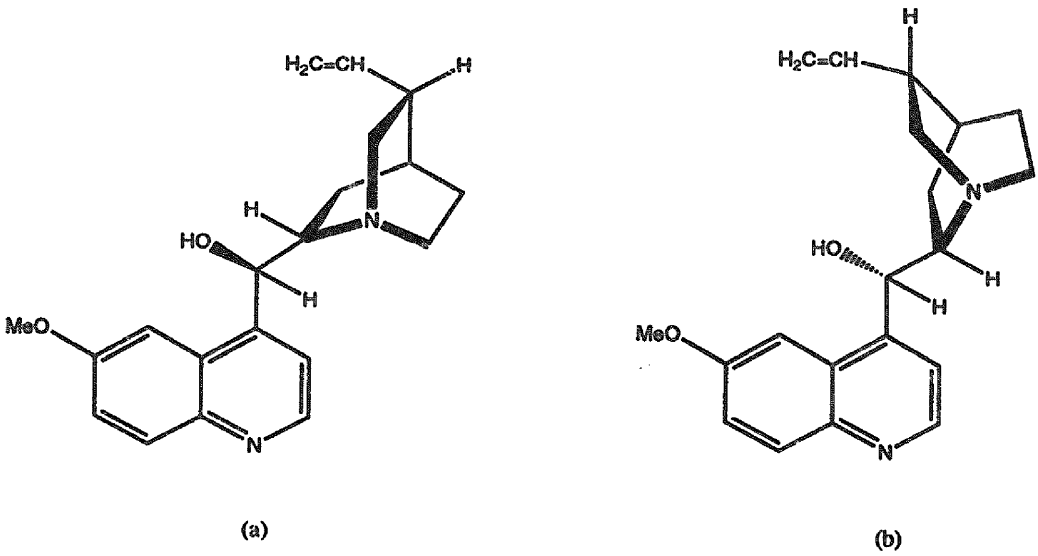


Fig. 11. Non-metal-based catalysts used in asymmetric variants of the Pudovik reaction.

but only at the expense of a severely retarded reaction rate, the degree of chelation interaction may be limited. Supporting studies which may provide further evidence, such as NMR titration studies, to determine binding constants between catalyst and substrate are not available to date. Nevertheless, the important conclusion from these results is that effective hydrophosphonylation catalysis appears to result from a catalyst which possesses both Lewis acidic and Lewis basic properties, i.e. an amphoteric catalyst. This idea has been recognised and exploited in an achiral variant of the Pudovik reaction employing an amphoteric receptor in which hydrogen-bonding sites act as the Lewis acid binding site and endogenous amino functions provide the means of activating the dialkylphosphite substrate towards reaction (Fig. 12) [71]. This amphoteric receptor has been shown, via NMR titration studies, to bind both substrates of the Pudovik reaction with binding constants of $0.34\ mol^{-1}\ dm^3$ (dimethylphosphite) and $0.48\ mol^{-1}\ dm^3$ (benzaldehyde) and to catalyse the Pudovik reaction with second order kinetics at a similar rate to triethylamine. One potential problem with this particular system appears to be product inhibition, which becomes problematic after ca. 15 turnovers. These problems may be overcome by a modified design of receptor which is designed to bind only one of the Pudovik reaction substrates specifically.

Acknowledgements

Portions of the research described above have been performed in this laboratory by several talented and enthusiastic co-workers whose names appear in the appropriate references. We wish to thank the EPSRC, Nuffield Foundation, University of

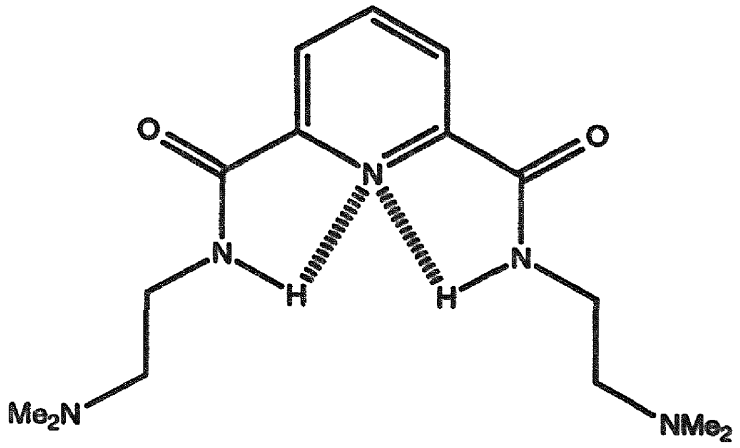


Fig. 12. Amphoteric receptor catalyst for the Pudovik reaction.

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