

***1,2-Azaphosphetidines
And Related Compounds***

a thesis presented by

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Abstract

The first three chapters review the literature related to the present work. In Chapter One, the synthesis of four membered heterocycles containing one phosphorus and one other heteroatom is reviewed. In Chapter Two an overview of the synthesis and carbon bond-forming reactions of α -diazo phosphono compounds is presented. In Chapter Three, the synthesis of α -amino phosphono compounds is reviewed and the range of biological properties of this and some related classes of organophosphorus compounds is briefly mentioned.

In Chapter Four, synthetic approaches to mono- and bicyclic 2-oxo-1,2-azaphosphetidines are discussed. First, synthesis of precursors for P-N and P-C bond closures and the unsuccessful cyclisation attempts are discussed. Then, an efficient synthesis of precursors for C-C ring closure, α -diazo- β -ketophosphonamidates, and a brief study of their decomposition is described. It is shown that C-H insertion of the carbene generated from some α -diazo phosphonamidates leads to successful C-C ring closure and the formation of 2-oxo-1,2-azaphosphetidines. A crystal structure of this ring system is reported.

In Chapter Five the use of *in situ* generated silyl esters of phosphorous acids for the synthesis of organophosphorus compounds is described. It is shown that although the range of reactive functional groups does not differ for the two reagents, silyl esters of phosphorous acids are superior to the non-silylated phosphorous species in respect of mildness and selectivity. This observation is rationalised in terms of a kinetic enhancement effect in the reactions of silylated phosphorous species towards imines and aldehydes.

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*to my mother
with love*

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Bu	<i>normal</i> Butyl
^t Bu	<i>tertiary</i> Butyl
Bz	Benzoyl
CI	Chemical ionisation
Et	Ethyl
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DMAP	4-N,N-Dimethylaminopyridine
DMF	Dimethylformamide
DMS	Dimethyl sulphide
DMSO	Dimethyl sulphoxide
FAB	Fast atom bombardment
i.r.	Infra red (spectroscopy)
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
Me	Methyl
Ms	Methanesulphonyl
NBA	Nitrobenzylalcohols
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance (spectroscopy)
n. O. e.	Nuclear Overhauser enhancement
ⁱ Pr	<i>iso</i> Propyl
TBAF	Tributylammonium fluoride
TBDMS	tertiary-Butyldimethylsilyl
TEA	Triethylamine
THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	4-Methylphenyl
Ts	4-Methylbenzenesulphonyl

<u>Scheme</u>	<u>Page</u>	<u>Scheme</u>	<u>Page</u>	<u>Scheme</u>	<u>Page</u>	<u>Scheme</u>	<u>Page</u>
1	12	40	33	79	64	118	90
2	13	41	34	80	64	119	91
3	13	42	34	81	65	120	92
4	14	43	35	82	66	121	93
5	14	44	35	83	66	122	93
6	15	45	36	84	67	123	94
7	15	46	37	85	67	124	94
8	15	47	38	86	68	125	95
9	16	48	38	87	69	126	95
10	16	49	39	88	70	127	96
11	17	50	40	89	72	128	97
12	17	51	40	90	73	129	97
13	18	52	41	91	74	130	98
14	18	53	41	92	74	131	98
15	18	54	45	93	75	132	99
16	19	55	46	94	75	133	100
17	19	56	47	95	75	134	100
18	20	57	49	96	77	135	101
19	20	58	49	97	77	136	101
20	21	59	50	98	78	137	102
21	21	60	51	99	78	138	103
22	22	61	51	100	79	139	103
23	23	62	52	101	79	140	105
24	23	63	53	102	80	141	105
25	25	64	54	103	80	142	106
26	25	65	54	104	81	143	106
27	26	66	55	105	82	144	107
28	26	67	55	106	82	145	107
29	27	68	57	107	83	146	107
30	27	69	58	108	83	147	108
31	27	70	58	109	83	148	109
32	28	71	59	110	84	149	109
33	29	72	60	111	84	150	110
34	29	73	60	112	84		
35	30	74	61	113	85	<u>Table</u>	<u>Page</u>
36	30	75	61	114	86	1	71
37	31	76	62	115	86	2	76
38	32	77	63	116	89	3	91
39	32	78	63	117	90	4	99

Nomenclature and stereochemistry

The nomenclature used in this thesis follows the rules laid down by the International Union of Pure and Applied Chemistry (IUPAC).¹ Owing to the diversity of structural types in organophosphorus chemistry, a comprehensive yet simple system for their naming is essential. To avoid confusion, the key features of organophosphorus nomenclature used in this thesis are outlined below:

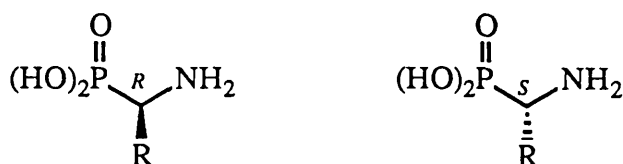
- Structural types are described with the use of a co-ordination number σ and a valency term λ . Hence tetraphenylphosphonium bromide contains a $\sigma^4\lambda^5$ phosphorus atom. In certain cases Roman numerals, e.g. (III) and (IV), have also been used to differentiate valency states.

- Derivatives of phosphorus oxyacids based on the $\sigma^3\lambda^3$ structure are named according to the number of oxygen ligands. Those containing one are referred to as phosphinous, those containing two as phosphonous, and those containing three are called phosphorous acids. Esters are named by replacing the terminal *-ous* (*-orous*) with *-ite*.

- Derivatives of phosphorus oxyacids based on the $\sigma^4\lambda^5$ structure are similarly named. Thus those containing one, two or three oxy ligands, in addition to the oxo ligand, are called respectively phosphinic, phosphonic and phosphoric acids. Esters are named by replacing the terminal *-ic* (*-oric*) with *-ate*.

- When an oxy ligand is replaced by an amino ligand, *-amid-* is inserted before the other suffices.

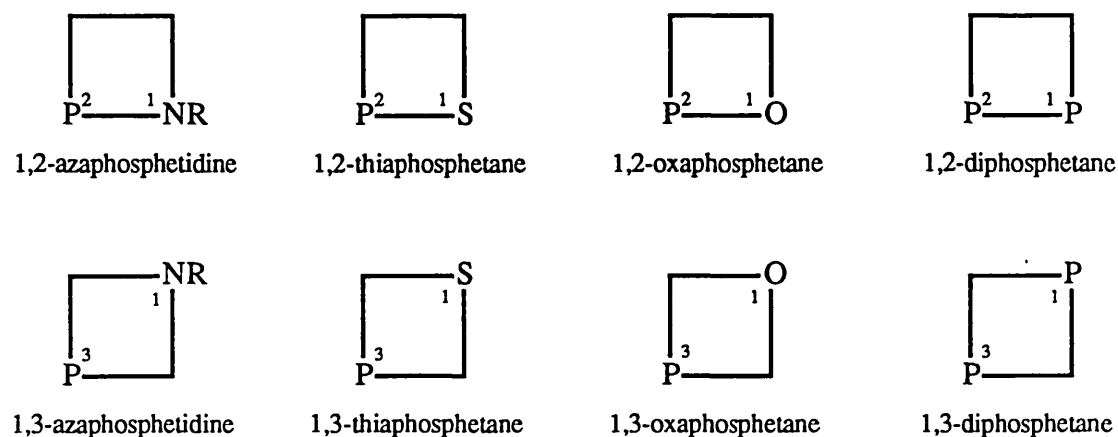
- In accordance with α -aminocarboxylic acids, stereochemistry of the α center in α -amino phosphonic and α -amino phosphinic acids can be distinguished using (*D*) and (*L*) terminology. In this case, stereochemistry is directly related to that of the analogous α -amino carboxylic acid- i.e. the one in which carboxyl group is replaced with phosphonyl or phosphinyl group- and a comparison in terms of structural and conformational relationships within polypeptides is thus made easy. Never the less such designation of chiral centers should be avoided in favour of (*R,S*) system. It should be noted that all natural proteinogenic α -aminocarboxylic acids are *S* at the chiral centre but the stereochemically analogous α -aminophosphoacids are *R*, owing to the priority rules.



Chapter One

*A Review Of Four-membered Heterocycles Containing
One Phosphorus And One Other Heteroatom*

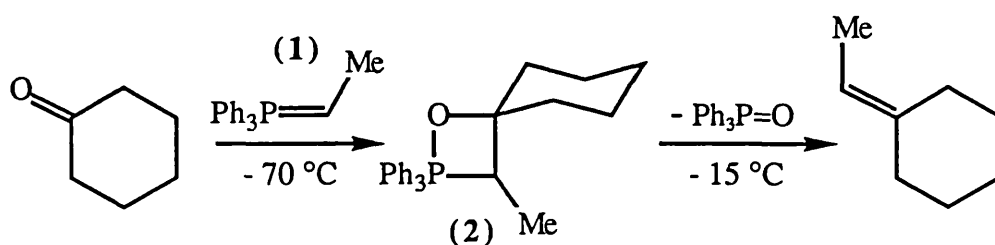
Although in general four-membered saturated phosphorus heterocycles are not sparse, few containing one phosphorus and only one other heteroatom are known. This review addresses the chemistry of the following eight ring systems in which phosphorus shares the ring with two carbon atoms and one of the following : nitrogen, sulfur, oxygen or another phosphorus.



1.1 Synthesis

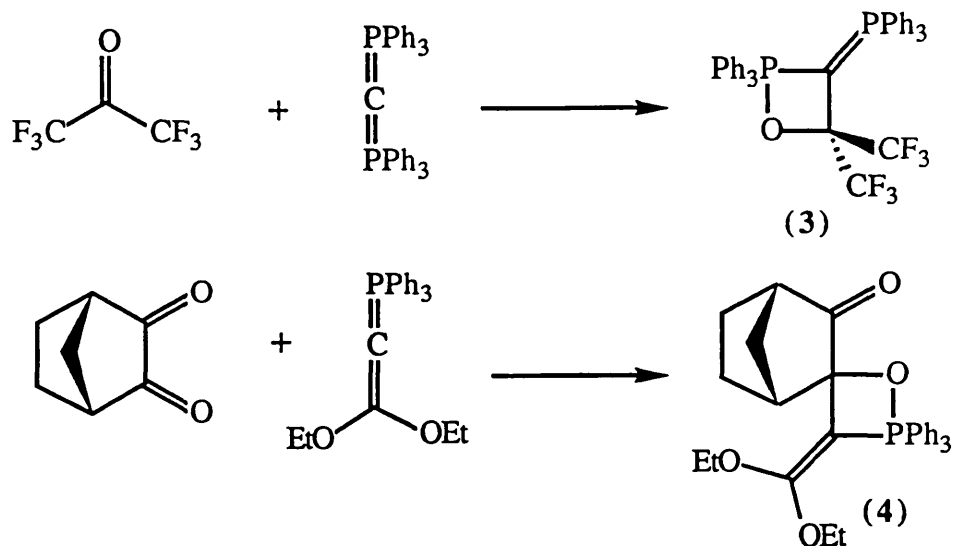
1.1.1 Oxaphosphetanes

1,2-Oxaphosphetanes are best known for their intermediacy in Wittig-Horner and Wadsworth-Emmons reactions. Usually, for these reactions, 1,2-oxaphosphetane intermediates are not isolable at room temperatures, although a good deal of evidence in support of their presence during reactions has been presented.^{2,3} For instance, Vedejs reported that when ylide (1) was treated with cyclohexanone at $-70\text{ }^{\circ}\text{C}$, an initial adduct (2) resulted, which upon warming to $-15\text{ }^{\circ}\text{C}$ broke down to the expected Wittig reaction products, triphenylphosphine oxide and an olefin.² Intermediate (2) was identified by its signal in the ^{31}P NMR spectrum.



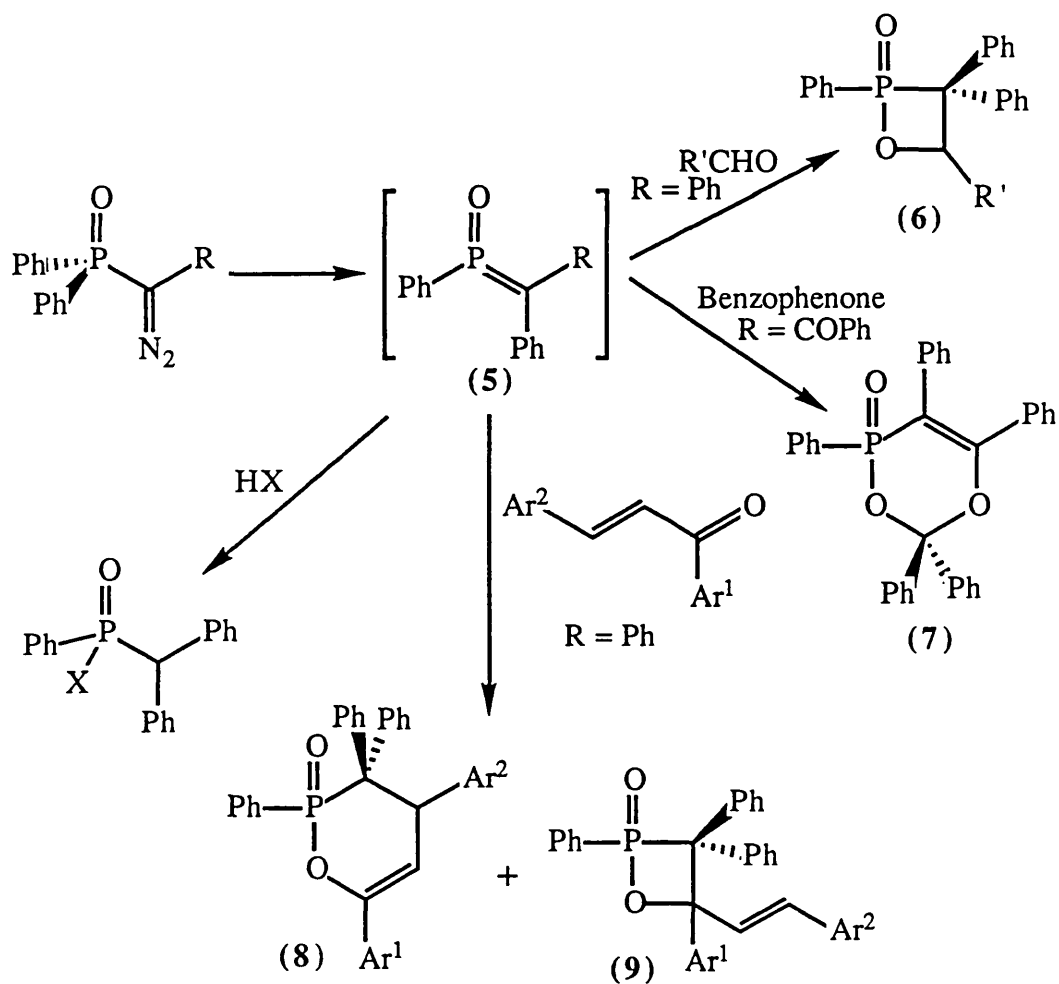
Scheme 1

In some cases, however, the intermediates are stable and do not decompose until much higher temperatures. For example, the two 1,2-oxaphosphetanes (3)⁴ and (4)⁵ are isolable as solids at room temperature.



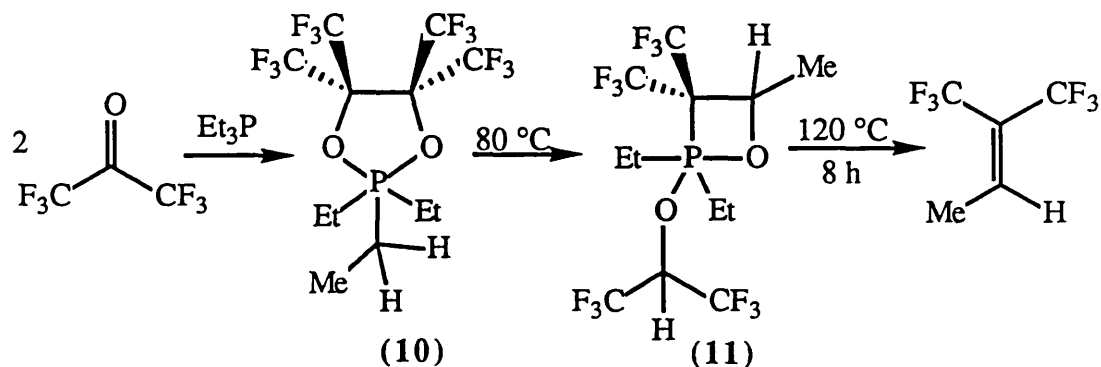
Scheme 2

Regitz has also isolated the 1,2-oxaphosphetanes (6) and (9) by [2+2] addition of reactive intermediate (5, R=Ph), generated from a diazo precursor, to aldehydes and to ketones.⁶ Products (7) and (8) resulting from [2+4] addition reaction are also obtained



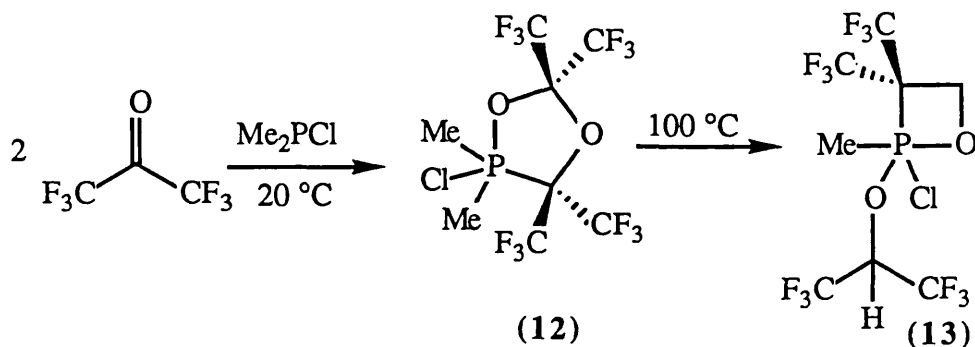
Scheme 3

when intermediate (5) was trapped with α,β -unsaturated carbonyl compounds or when (5, R=COPh) is trapped with benzophenone (Scheme 3). Again all the 1,2-oxaphosphetanes thus obtained decompose in the expected manner to afford olefins and phosphine oxides at elevated temperatures.



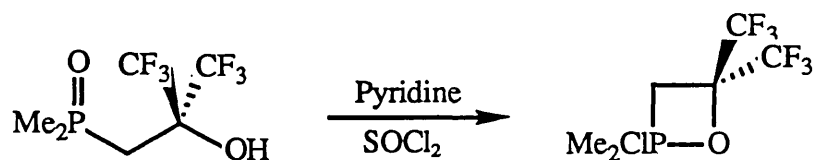
Scheme 4

[2+2] Additions do not represent the only route for the synthesis of stable 1,2-oxaphosphetanes. Ramirez reported a ring contraction from a 1,3,2-dioxaphospholane (10) to an 2-alkoxy-1,2-oxaphosphetane (11) (Scheme 4)⁷ and Gibson reported a similar reaction through a different intermediate (12) (Scheme 5).⁸ In both cases, the *gem* trifluoromethyl substituents at the 4- position appear to contribute strongly to the stability of the ring. Presumably, the effect of two strongly electron withdrawing groups is to prevent decomposition of the ring through a non-concerted retro [2+2] reaction by weakening the developing carbocation character at C-4. In each case the retro [2+2] reaction, the normal mode of decomposition as we have already seen, requires much higher temperatures.



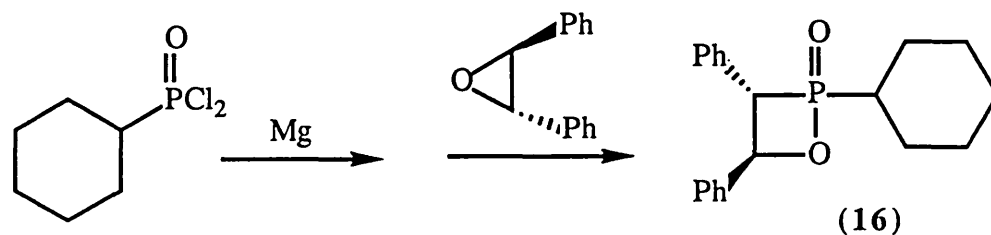
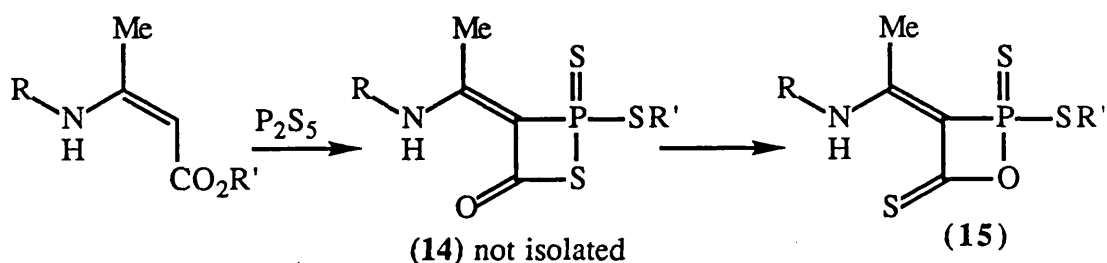
Scheme 5

The following example, Scheme 6, is remarkable since it extends the ring closures utilising the oxygen of P=O as a nucleophile, which is more applicable to five and six membered ring, than to four membered ring formation.⁹



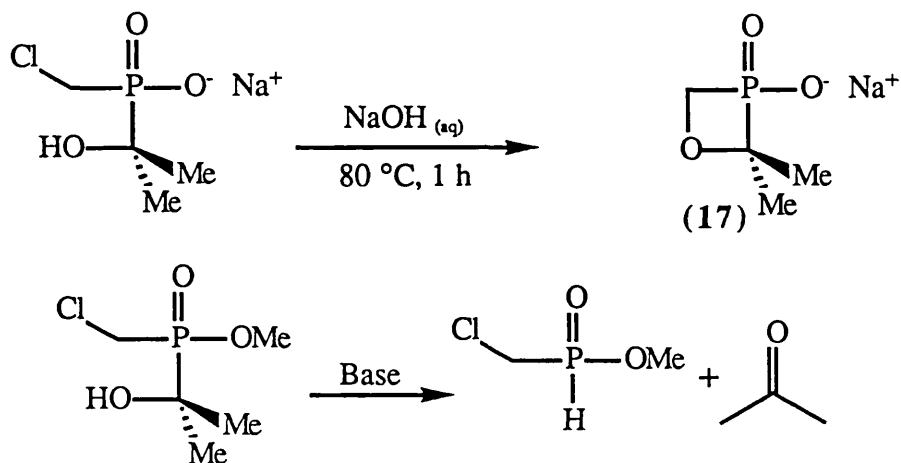
Scheme 6

1,2-Oxaphosphetanes (15)¹⁰ and (16)¹¹ were obtained in the following two reactions although neither route appears to be applicable as a general synthesis of this ring system.



Scheme 7

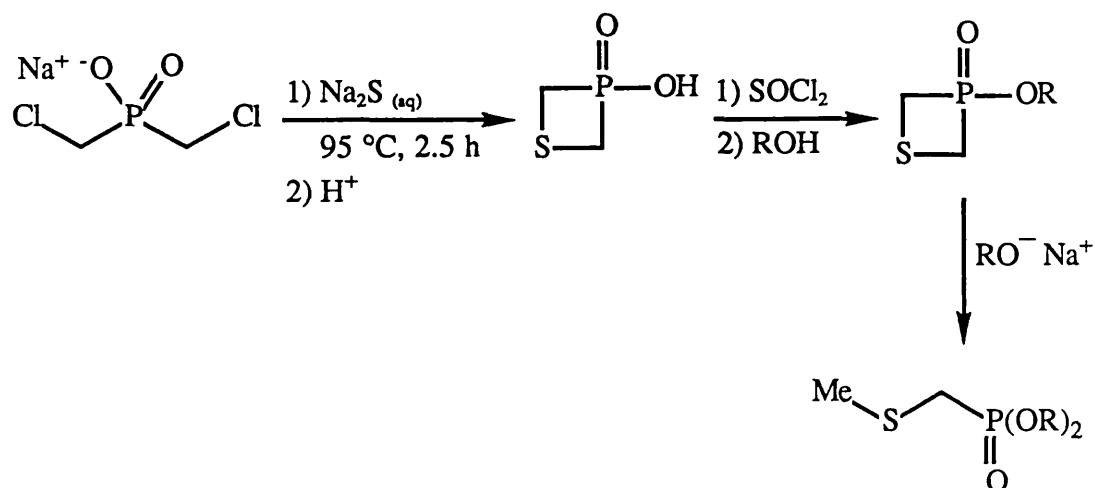
Only a single example of 1,3-oxaphosphetanes is known, namely (17).¹² It can be synthesised (Scheme 8) only as a sodium salt since its acid is unstable. Attempts to prepare the methyl ester by a similar route, and to manipulate the phosphorus functionality failed.



Scheme 8

1.1.2 Thiaphosphetanes

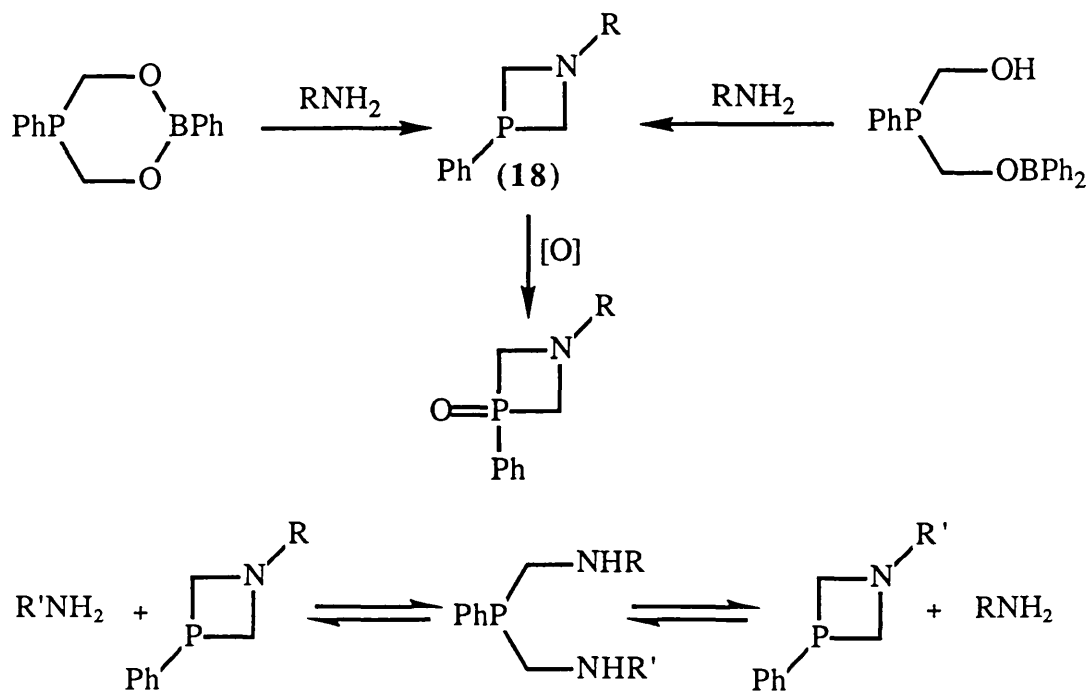
In contrast to oxaphosphetanes, 1,3-thiaphosphetanes, a synthesis of which is outlined below (Scheme 9),¹³ are better known and studied¹⁴ than the isomeric ring system. The single example of a 1,2-thiaphosphetane is the transient intermediate (14) (Scheme 7).



Scheme 9

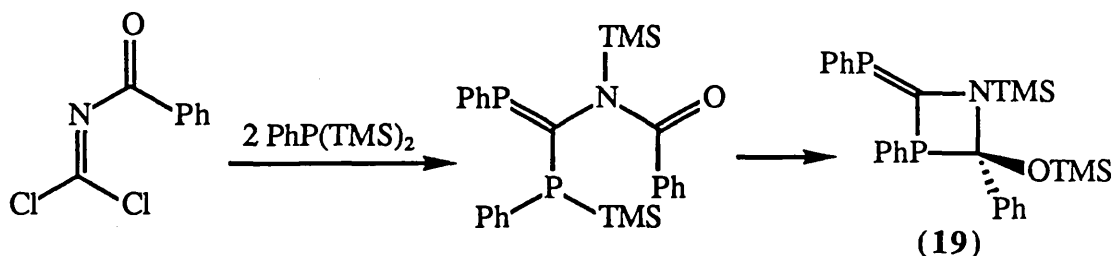
1.1.3 Azaphosphetidines

1,3-Azaphosphetidines (18) were first synthesised by Arbuzov and co-workers. Four membered ring closure was achieved *via* nucleophilic displacement. Arbuzov has shown that the 1,3-azaphosphetidine ring is labile allowing one to be made from another (Scheme 10).¹⁵



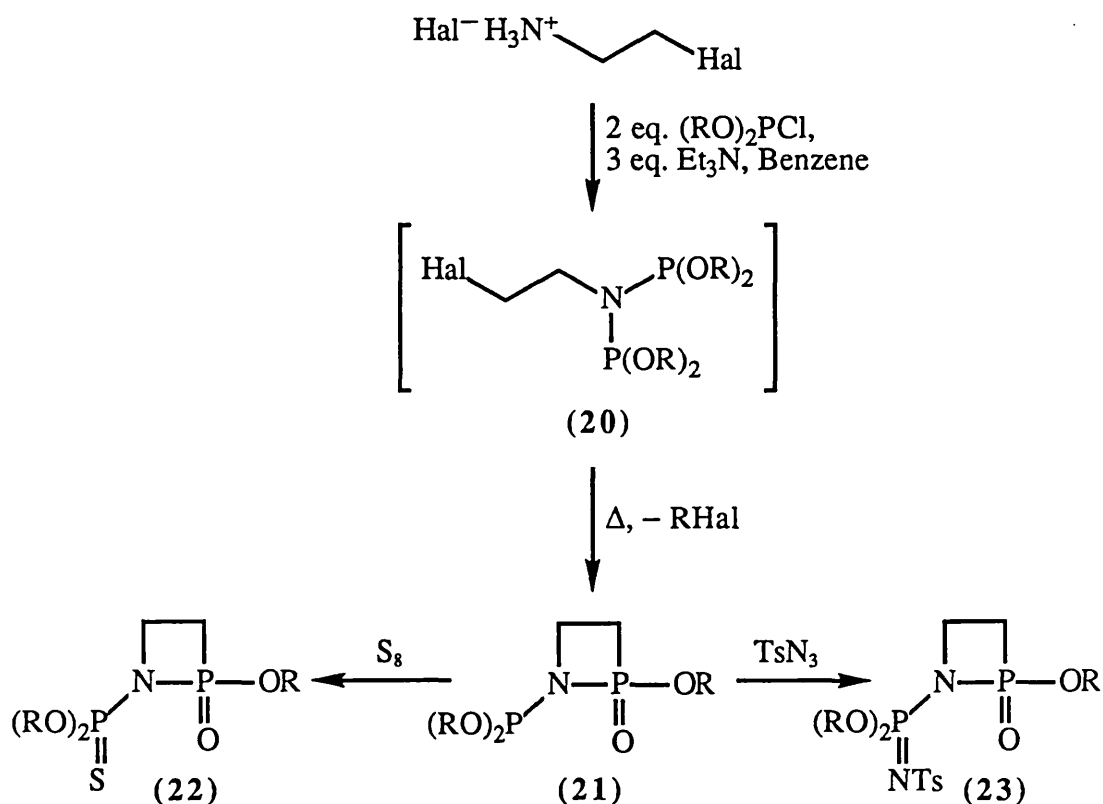
Scheme 10

The only other example of this ring system is (19), the structure of which was confirmed by X-ray crystallography.¹⁶



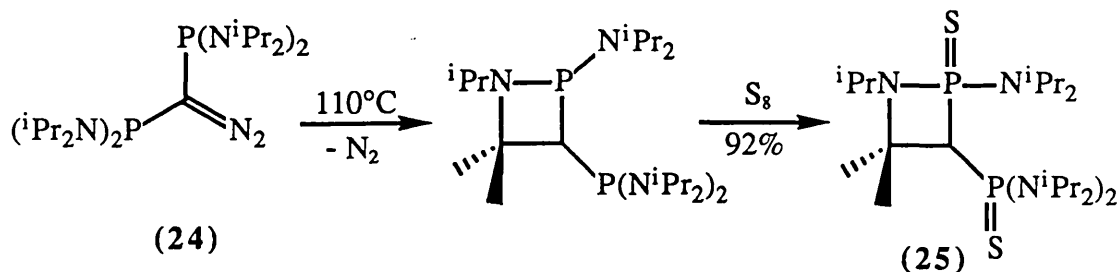
Scheme 11

Gubnitskaya and co-workers have prepared 1,2-azaphosphetidines (22) and (23) by intermolecular Michaelis-Arbuzov reaction. Cyclisation precursors (20) can be prepared from β -haloethylamines (Scheme 12) or aziridines.¹⁷ No examples with substituents on C-3 and C-4 were reported prior to present work.



Scheme 12

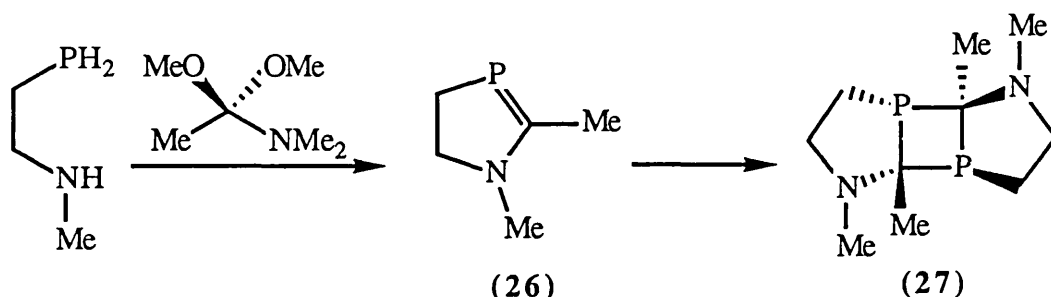
Bertrand also reports a synthesis of 1,2-azaphosphetidine (25) by a carbene CH insertion reaction of the carbene generated from diazo compound (24), but did not provide physical data in support of the assigned structure (Scheme 13).¹⁸



Scheme 13

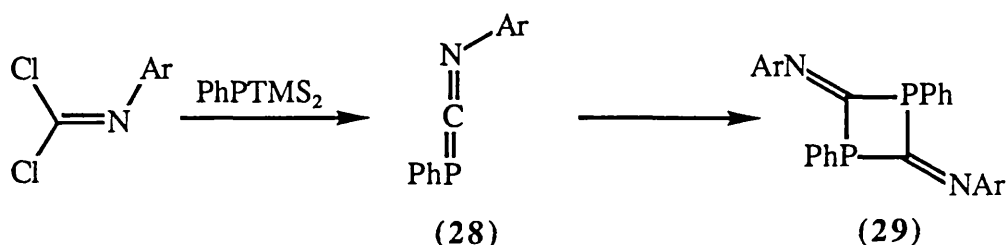
1.1.4 Diphosphetanes

To date, all diphosphetanes reported in the literature have been synthesised by dimerisation of phosphalkene compounds. With the exception of three examples, each with bulky tertiary butyl groups on phosphorus, which yield 1,2-diphosphetanes, all such [2+2] additions result in 1,3-diphosphetanes. For instance, Isseleib serendipitously prepared tricyclic compound (27) when attempting to crystallise (26) after the following reaction sequence.¹⁹



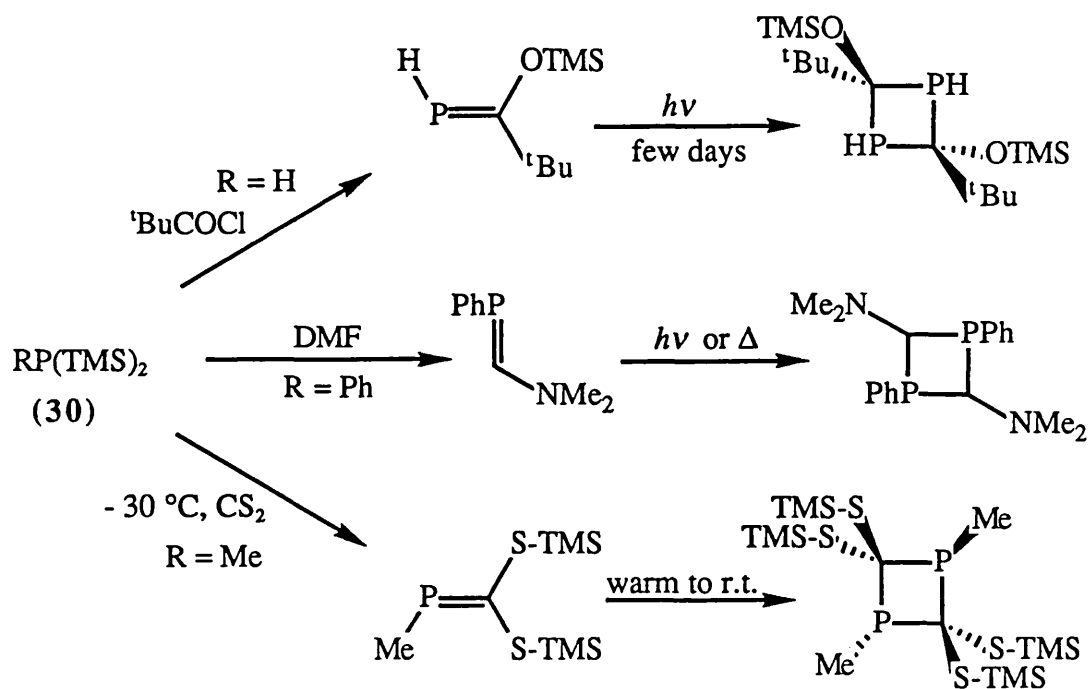
Scheme 14

Addition is often not spontaneous and monomers can be isolated and at least in one case, (28), addition was shown to be reversible. In an extension of Appel's synthesis



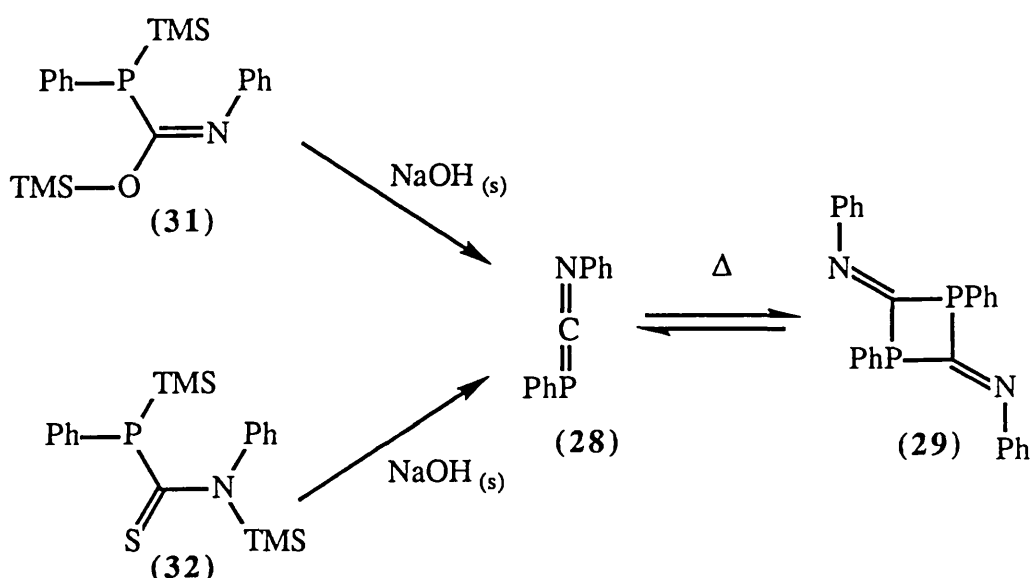
Scheme 15

of (29) (Scheme 15),²⁰ Becker has prepared a range of heterocumulenes from bis(trimethylsilyl)phosphines (30) and other $\delta^3\lambda^3$ phosphorus precursors (Scheme 16) and has shown that some spontaneously dimerise to 1,3-diphosphetanes while the others require heat or light for this transformation.^{21,22,23}



Scheme 16

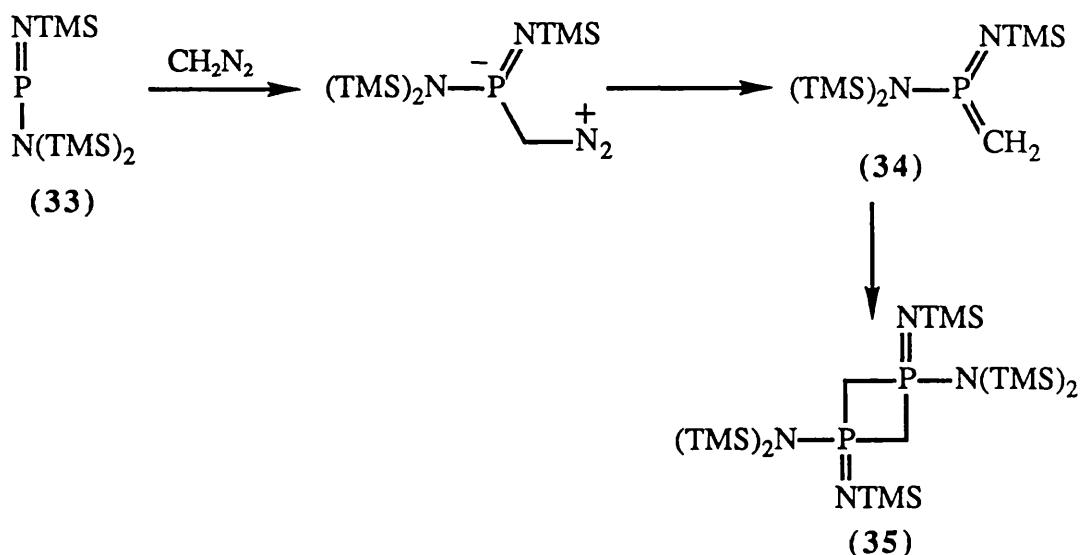
Becker has further shown that Appel's 1,3-diphosphetane (29), prepared from phenyl(bistrimethylsilyl)phosphine (30, $R = Ph$) by treatment with aromatic isocyanates and isothiocyanates to afford (31) and (32) respectively, followed by heating in the presence of a small amount of sodium hydroxide, is in equilibrium with its monomer and that heat drives the equilibrium in favour of monomer (28).²⁴



Scheme 17

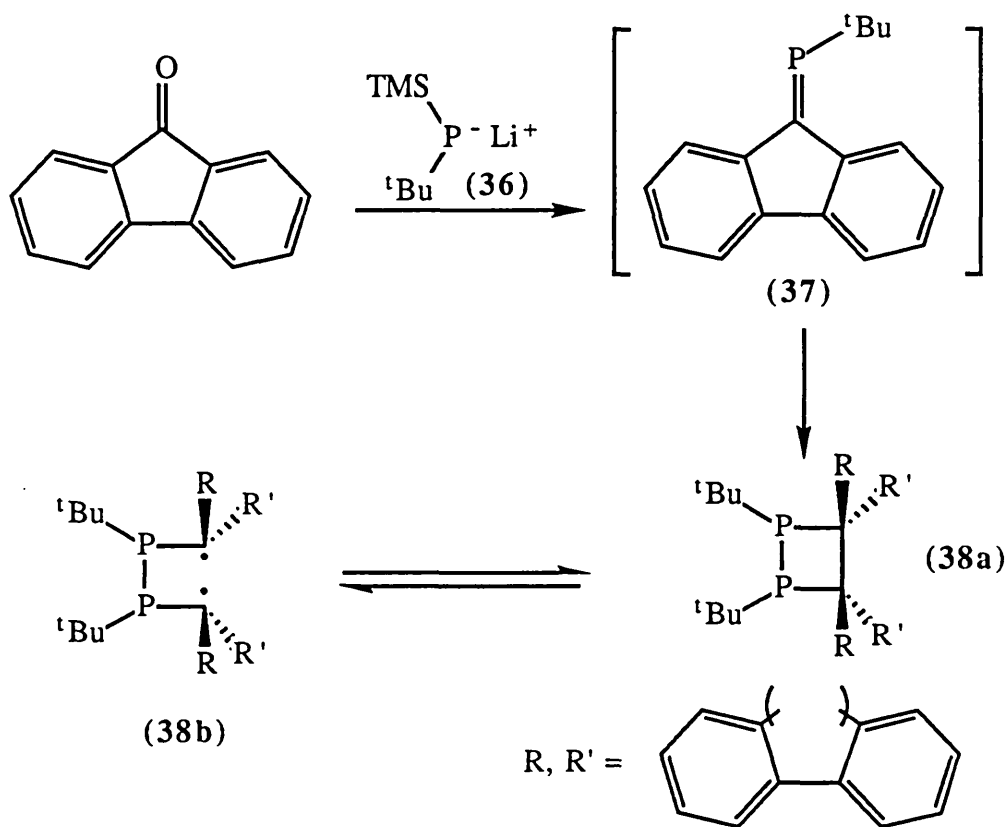
Precursors to diphosphetanes do not necessarily contain $\sigma^3\lambda^3$ phosphorus. For example, when iminomethylenephosphorane (33) was treated with diazomethane, 1,3-

diphosphetane (35) was obtained, presumably through monomer (34) a $\sigma^3\lambda^5$ phosphorus compound.²⁵



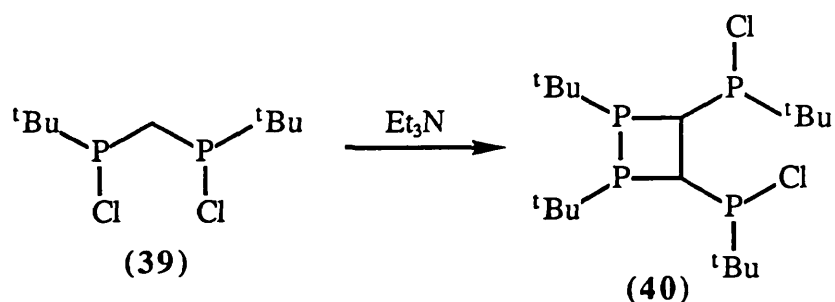
Scheme 18

As was mentioned earlier, in all known examples of 1,2-diphosphetanes, phosphorus bears a *t*butyl substituent. For example, treatment of lithium phosphide (36) with 9-fluorenone gave, through monomer (37), compound (38a). In benzene solution, this compound was in equilibrium with the diradical form (38b) (ESR).²⁶



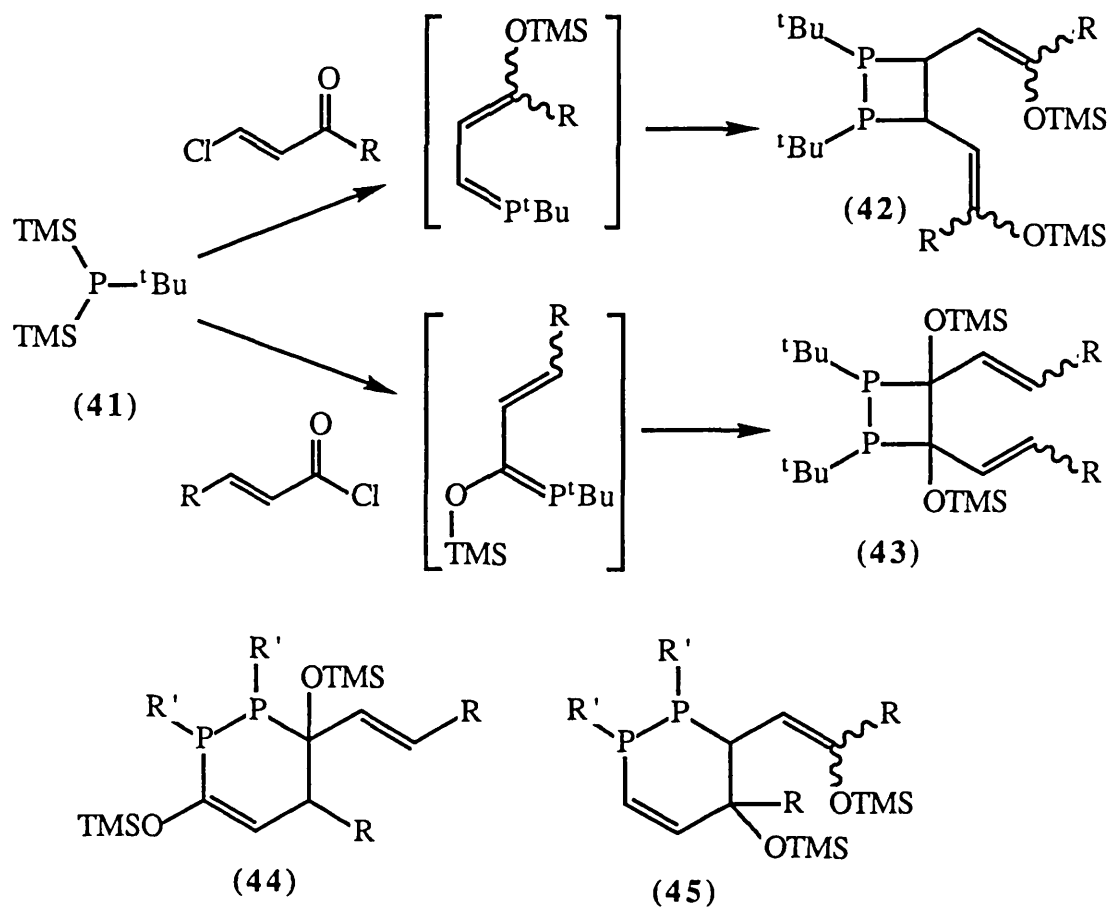
Scheme 19

When compound (39) was treated with triethylamine a 1,2-diphosphetane (40) was obtained.²⁷



Scheme 20

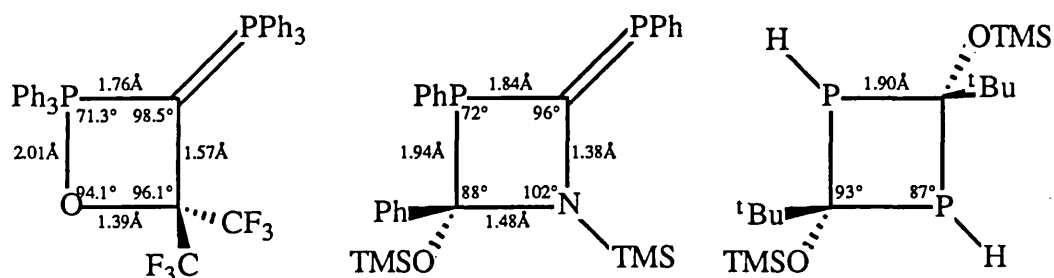
Appel obtained 1,2-diphosphetanes (42) and (43) by the route outlined below (Scheme 21). When the tert-butyl ligand in starting material (41) was replaced with other groups a [4+2] addition occurred instead, to give compounds (44) and (45).²⁸



Scheme 21

1.2 Structure and Spectroscopic Properties

From the available crystal structures,^{4,16,21} it appears that in oxaphosphetanes and azaphosphetidines, the phosphorus within the ring makes an angle of about 70° with adjacent ring atoms, whereas in the 1,3-diphosphetanes, a wider angle of 84-87° is observed. Since all rings that have been studied by X-ray crystallography are shown to be essentially planar, it appears that the ring distortion from a square to a "kite-like" tetragon is predominantly to allow for longer bonds between phosphorus and adjacent atoms. In 1,3-diphosphetanes where the bond lengths within the ring are more or less similar, allowing for unsymmetrical substitutions, such a distortion is unnecessary and is not



Scheme 22

observed. This distortion also means that the four membered ring can accommodate wider bond angles, and ring strain is somewhat reduced. Another way in which the ring strain may be relieved is with the ring phosphorus atom having a near trigonal bipyramidal coordination sphere. This is observed, for instance, for compounds (11) and (13) (see Schemes 4 and 5).

1,3-Thiaphosphetanes have not yet been subject to crystallographic study although extensive spectroscopic studies, infra-red and dipole moment measurements in particular, have been conducted to determine of the ring geometry.¹⁴

1.3 Stability of The Rings

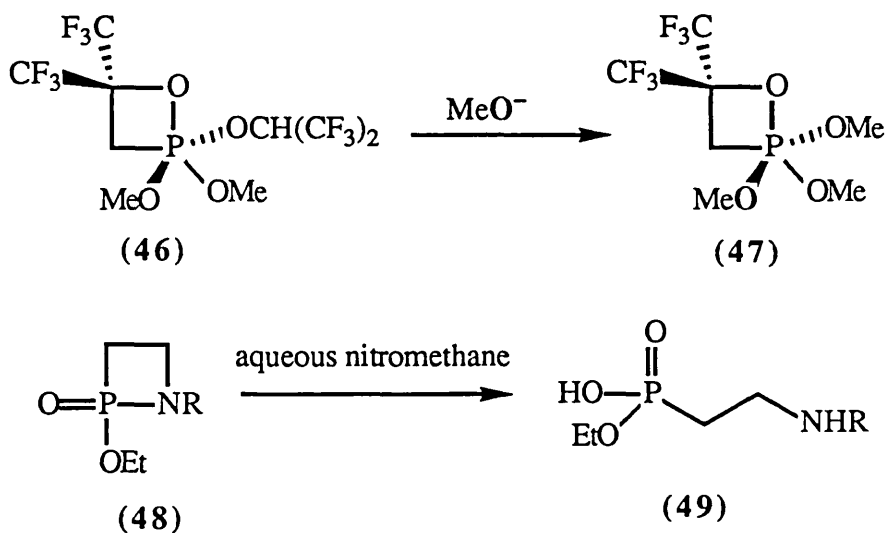
As already mentioned, the principal mode of decomposition is that of retro [2+2] reaction. Different ring systems have different tendencies for this reaction and, as we have seen, ring substituents also play a role.

Although X-ray crystallography has confirmed the existence of covalently bonded rings in the solid phase, ³¹P NMR analysis on the same compounds has revealed that many 1,3-diphosphetanes in solution exist as wholly non-cyclised monomers or in equilibrium with the monomer. This suggests that for these compounds the energy

required for fragmentation of the ring is small, and the inter-atomic forces in the crystalline lattice are enough to overcome the energy barrier for cyclisation.

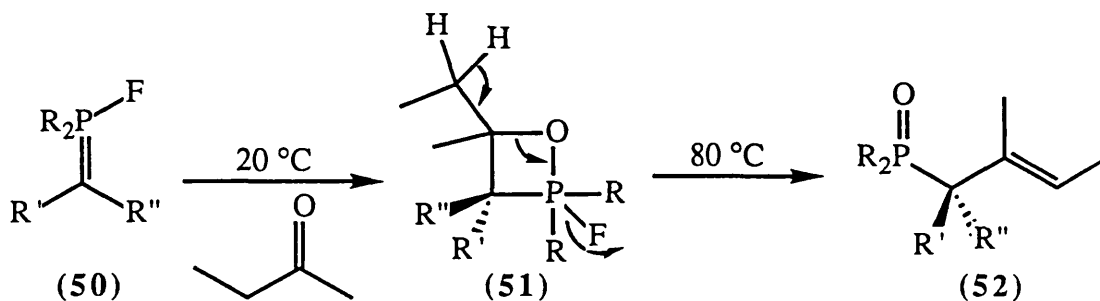
The 1,2-azaphosphetidines and 1,2-oxaphosphetanes are more robust ring systems, though still susceptible to similar decomposition. As we have seen, the presence of electron withdrawing groups such as CF_3 , contributes to the kinetic stability of the ring.

A second, less facile, mode of decomposition is that of ring opening resulting from P-X bond scission. An example has already been encountered in the chemistry of thiaphosphetanes (Scheme 9). Again, depending on ring substituents, ring opening occurs with differing degrees of ease as the following examples show. Oxaphosphetane (46) was robust enough to withstand sodium methoxide,²⁹ whereas 1,2-azaphosphetidine (48) opens readily when dissolved in wet solvents.¹⁷



Scheme 23

Compounds with a fluoro ligand on phosphorus behave differently, as the following example shows.³⁰



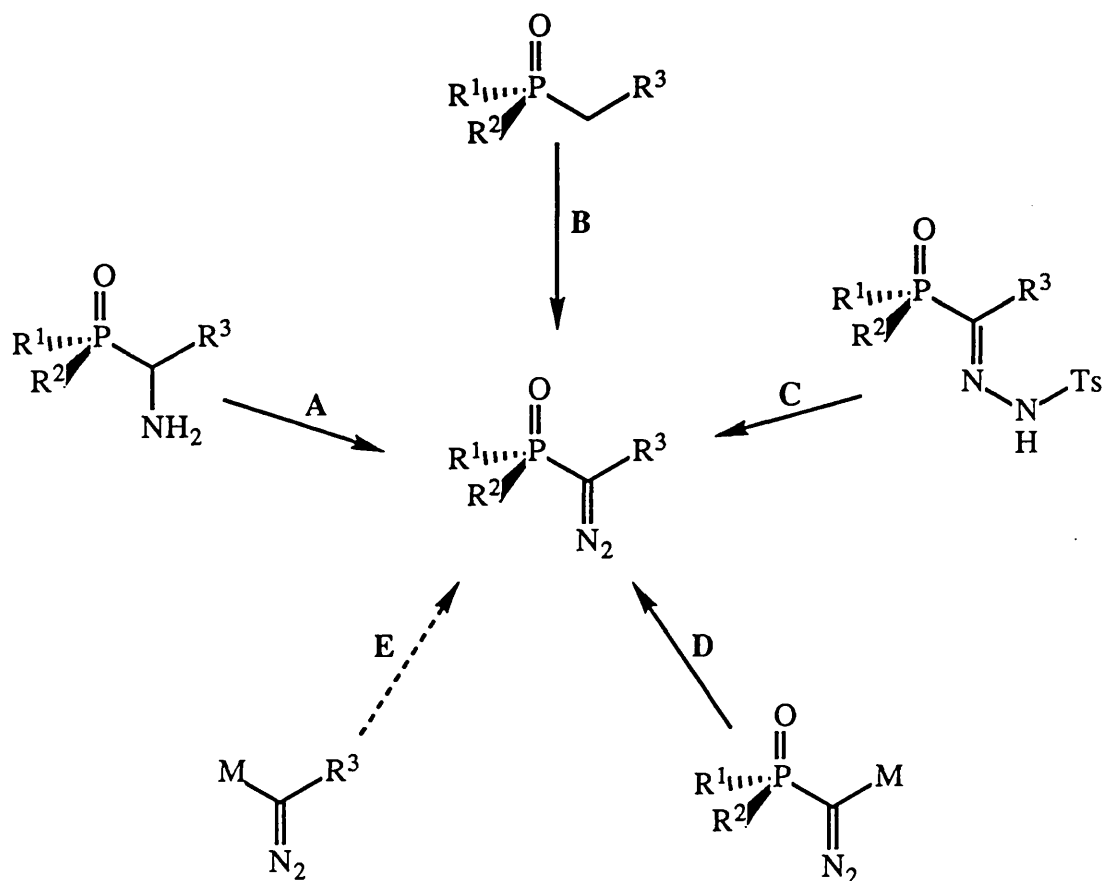
Scheme 24

Chapter Two

*A Review of Synthesis and Carbon-Carbon Bond
Forming Reactions of α -Diazo Phosphonates,
 α -Diazo Phosphinates and α -Diazo Phosphines*

2.1 Synthesis

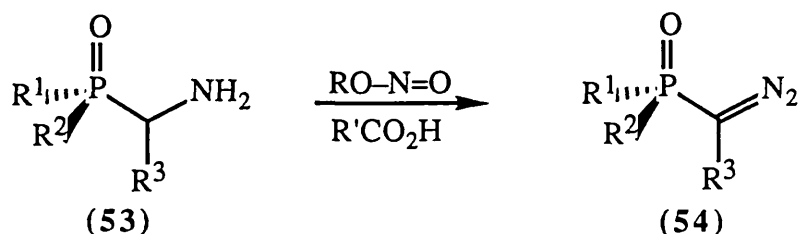
Access to α -diazo phosphono compounds is synthetically limited to routes outlined below (Scheme 25). Each will be considered in turn.



Scheme 25

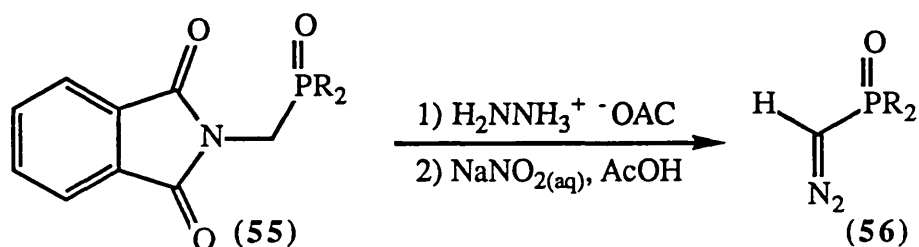
2.1.1. Diazotisation of α -amino phosphono compounds

As with other primary amines, diazotisation of α -amino phosphonates and phosphinates leads to the formation of the corresponding α -diazo compounds. This route requires acid catalysis but since the phosphonyl moiety is not as good an electron-withdrawing group as the carbonyl, protonation at the α position resulting in the decomposition of the α -diazo compound is facile and hence the use of aqueous mineral acids should be avoided in favour of acetic acid.³¹



Scheme 26

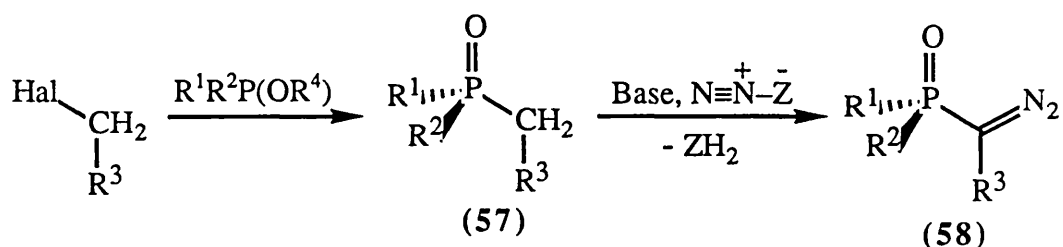
This route is particularly useful for the synthesis of diazomethylphosphonates and phosphinates, e.g. (56),³² which cannot be easily prepared by other means. It should be emphasised that there is no known limitation to the range of substituents, R¹, R² and R³. However since the synthesis of α -amino phosphonates and phosphinates themselves is not so easy, this route has found little favour with workers in the field in recent years.



Scheme 27

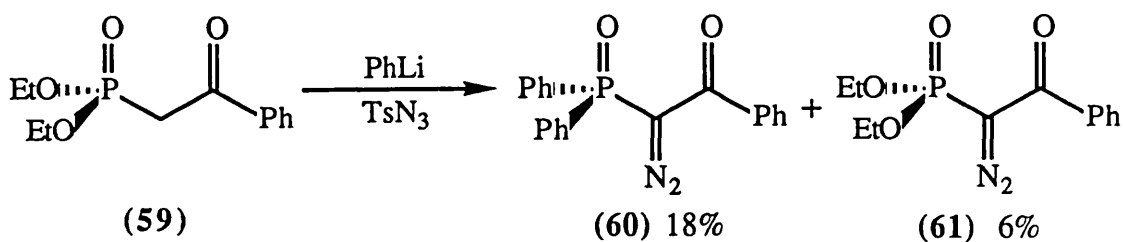
2.1.2. Diazo Transfer

Diazo group transfer reactions have provided preparative routes to a diverse range of α -diazo phosphonyl compounds. The inductive electron withdrawing power of the phosphonyl moiety is expected to be sufficiently strong to activate the adjacent methylene protons towards substitution. However, the number of α -diazo phosphonates and phosphinates prepared by this route which do not bear a further activating group (R³) is small.³³ This is owing to the fact that most easily available α -unsubstituted phosphonates and phosphinates are prepared by Arbuzov reaction which is facilitated with R³ group being electron withdrawing.



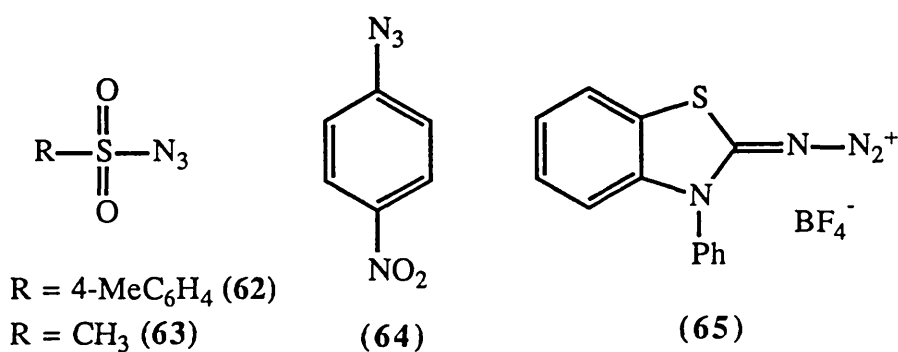
Scheme 28

The choice of base largely depends on this other group (R³). With carbonyl groups which highly activate the adjacent methylene protons, organic amine bases suffice. With less strongly activating groups such as phenyl, potassium ^tbutoxide may be used. The use of organometallic bases such as butyllithium and phenyllithium is not recommended when ligand exchange on phosphorus can occur.³⁴



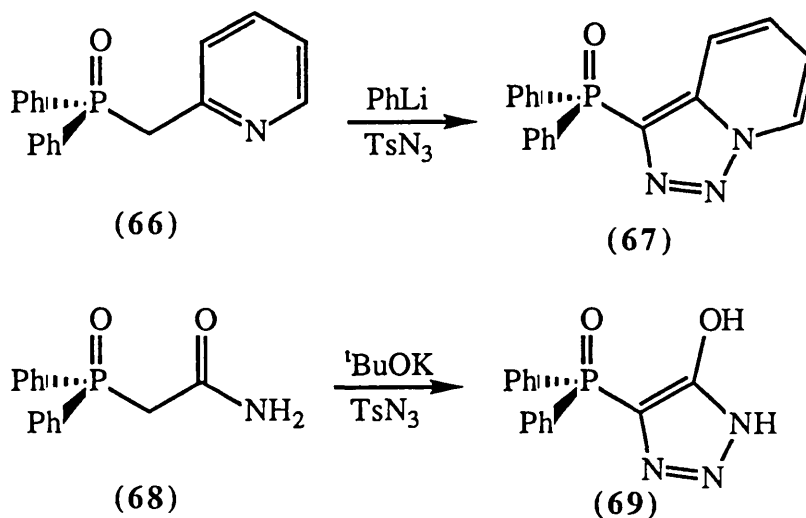
Scheme 29

The diazo transfer reagent is commonly tosyl azide (62)³⁵ although on occasions other reagents such as mesyl azide (63),³⁶ 4-nitrophenylazide (64)³⁷ and (65)³⁸ as well as polymer bound reagents,³⁹ are also used.



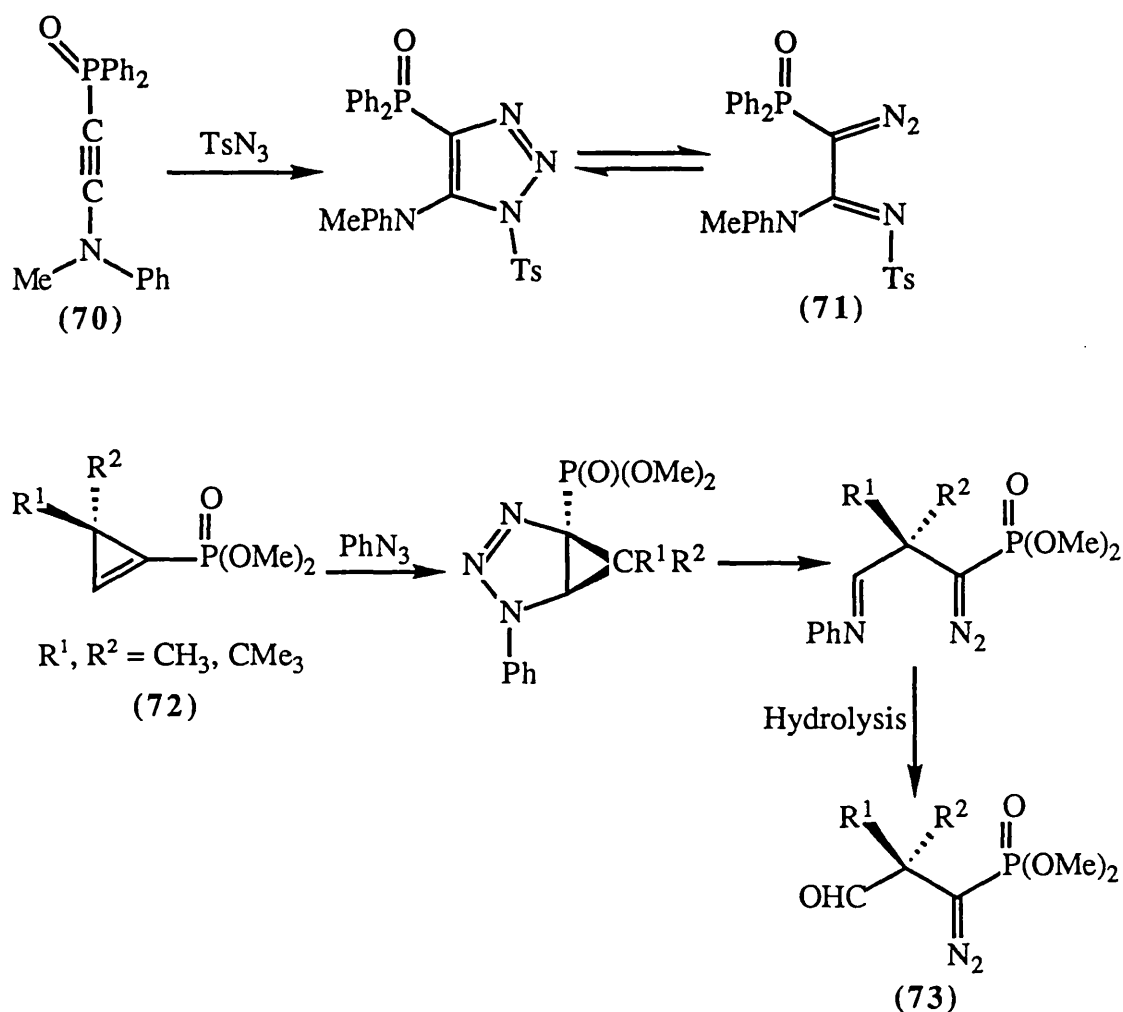
Scheme 30

Diazo group transfer sometimes fails to give the expected α -diazo phosphono compound. This misbehaviour is often due to group R³ and can therefore can be predicted from the chemistry of the parallel α -diazo carbonyl compounds. Thus in the following examples, the presence of nucleophilic groups in R³ which interact with the diazo functions leads to the formation of heterocycles.⁴⁰



Scheme 31

Occasionally, such cyclisations are reversible and are put to good use for synthesis of α -diazo phosphono compounds from precursors which do not have an adjacent methylene group. Ynamine phosphonate (70) and cyclopropene phosphonate (72) are starting materials for the synthesis of diazo phosphonates (71) (the major isomer in solution and the sole isomer in the crystalline state)⁴¹ and (73)⁴² respectively. These reactions are not general and apart from the two reaction types discussed here no other examples are reported to date.

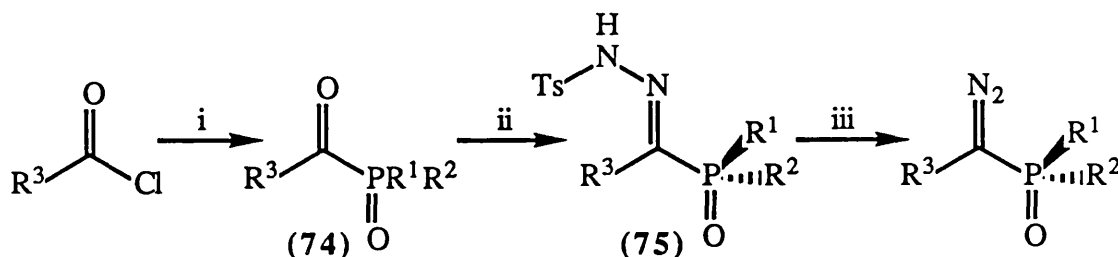


Scheme 32

2.1.3. Bamford-Stevens Reaction

Synthesis of α -diazo phosphonates and phosphinates by the Bamford-Stevens reaction was pioneered by Seyferth (Scheme 33).⁴³ Like the other two methods already discussed, it is not limited in the range of R^1 , R^2 and R^3 , though as before the availability of starting materials has to be taken into account. Thus treatment of phosphorus (III) esters with acid chlorides gives α -oxo phosphono compounds (74). Dehydrative

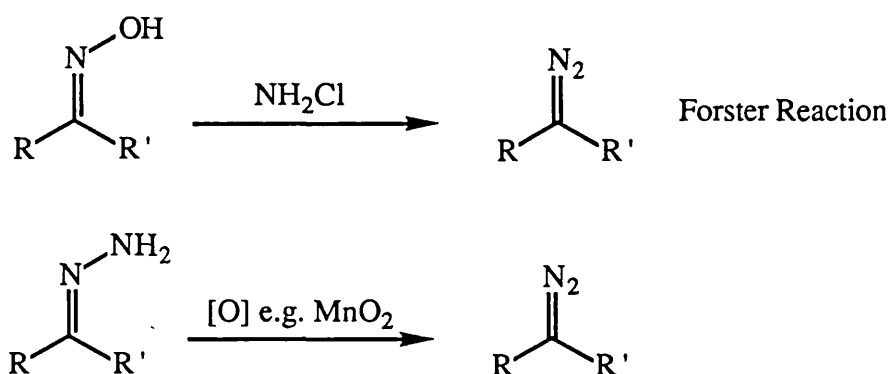
condensation with tosylhydrazine affords tosylhydrazone (75) which upon addition of a base decomposes to yield the diazo compound. Bases used for this step vary in strength, from sodium hydride to aqueous sodium carbonate, depending on substituents.⁴³



i) $R^1R^2P(OR^4)$, Δ ; ii) $TsNHNH_2$, EtOH; iii) Base

Scheme 33

The Forster reaction⁴⁴ (Scheme 34) and oxidation of hydrazones which are both used for the synthesis of α -diazoalkyl carbonyl and sulphonyl compounds⁴⁵ (Scheme 34) have not yet been reported for the synthesis of α -diazo phosphono compounds.

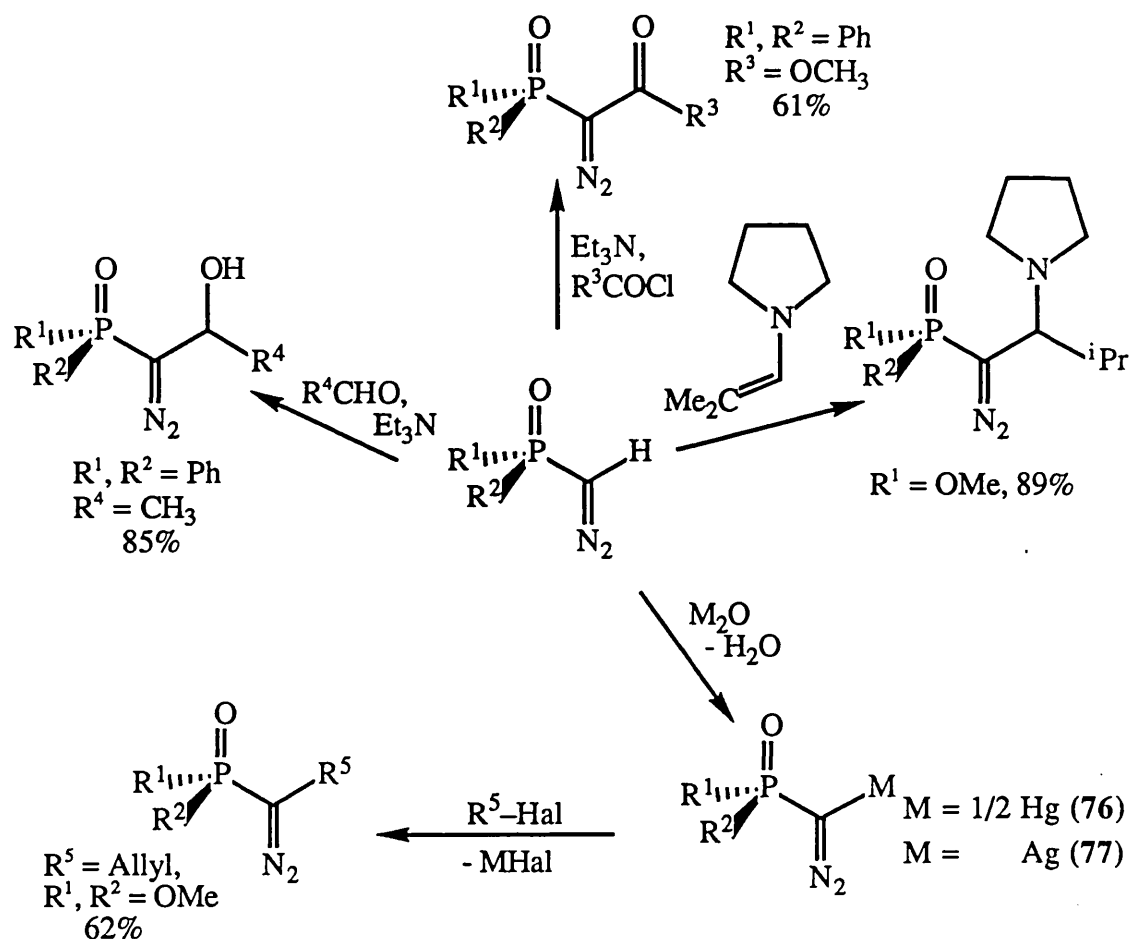


Scheme 34

2.1.4. From Other α -Diazo Phosphono Compounds

Diazomethyl proton is acidic owing to the diazo groups strong anion stabilising effect arising from its electron withdrawing property. In diazomethyl phosphono compounds extra stability to the conjugate anion is provided by the phosphonyl group's dipolar stabilising effect. The result is that α -diazomethylphosphonates and phosphinates can be easily deprotonated and the anion thus formed can react with a range of electrophiles to afford new substituted α -diazo phosphonates. Triethylamine is usually a strong enough base and reactions, usually proceed under mild conditions (Scheme 35).^{46,47,48,49}

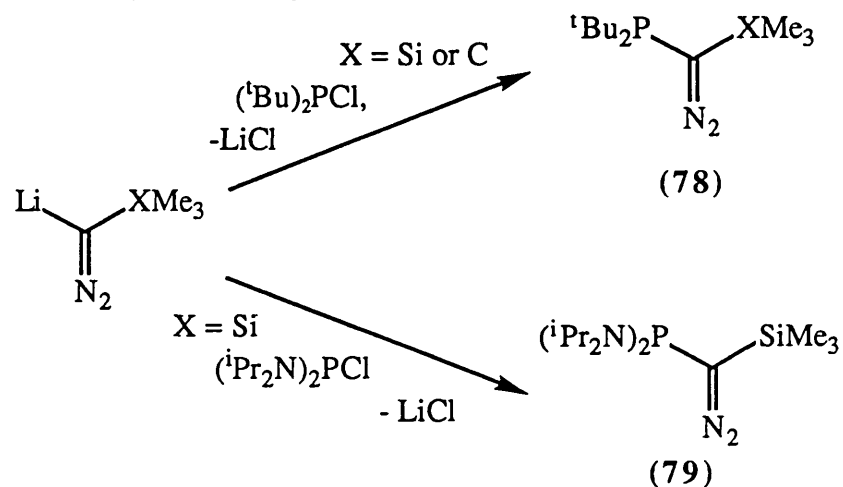
Metallated species are easily generated and some, for instance mercury (76)^{49a} and silver (77)^{49b} derivatives, are stable and isolable.



Scheme 35

2.1.5. From Other α -Diazo Compounds

Diazomethyl carbonyl compounds are also subject to the anion stabilising factors we discussed in the previous section. Surprisingly however, this route has not yet been applied to the synthesis of 1-diazo-2-oxophosphonates though diazo phosphines (78) and (79) have been synthesised by this route (Scheme 36).^{18,50}



Scheme 36

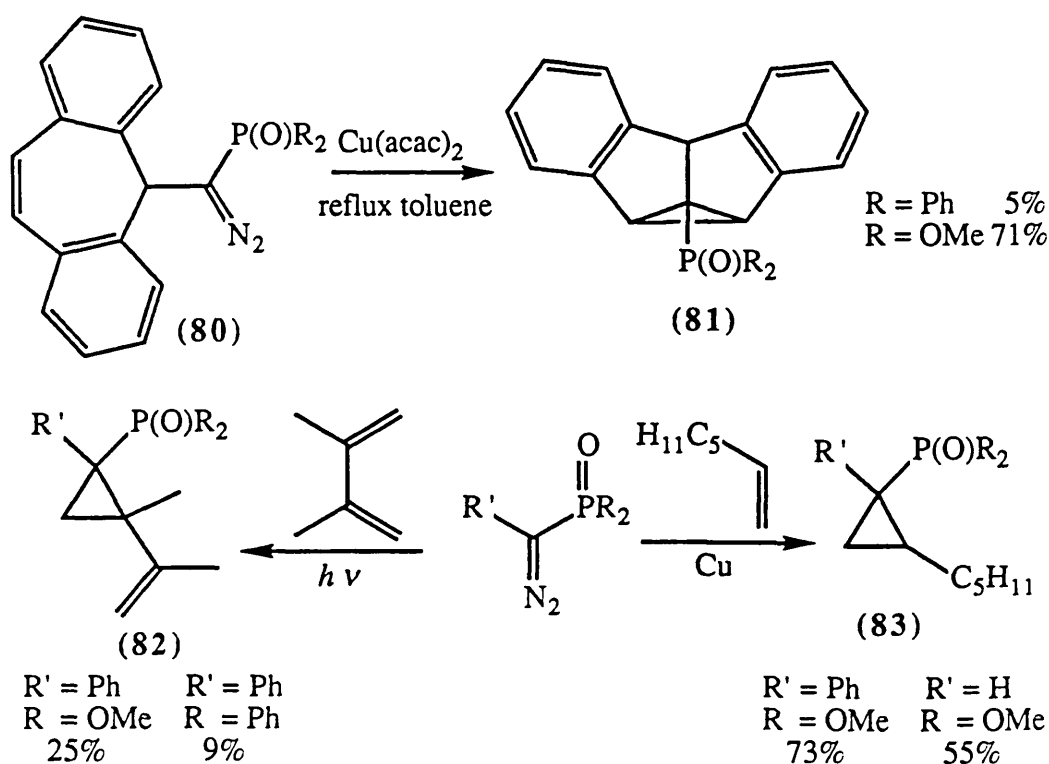
2.2 Carbon-Carbon Bond Forming Reactions

Reactions of α -dialzo phosphonates and α -dialzo phosphinates can be regarded as extension of those observed for other diazo compounds and in this respect they are numerous and diverse. Of these, carbon-carbon bond forming reactions are particularly important as they provide routes to the synthesis of complex organophosphorus compounds which are densely functionalised at the α position. Synthesis of these compounds are particularly challenging as the formation of phosphorus bonds to secondary or tertiary carbon bonds is rarely successful by established methodologies.

In this section, we consider those reactions of α diazo phosphono compounds which lead to carbon-carbon bond formation at the α position. These include addition to C-C π bonds and insertion into C-H and C-C σ bonds as well as molecular rearrangements. The reactivity of diazo compounds, including α -dialzo phosphono compounds, has recently been reviewed which provides a panoramic view of the subject for further reference.³¹

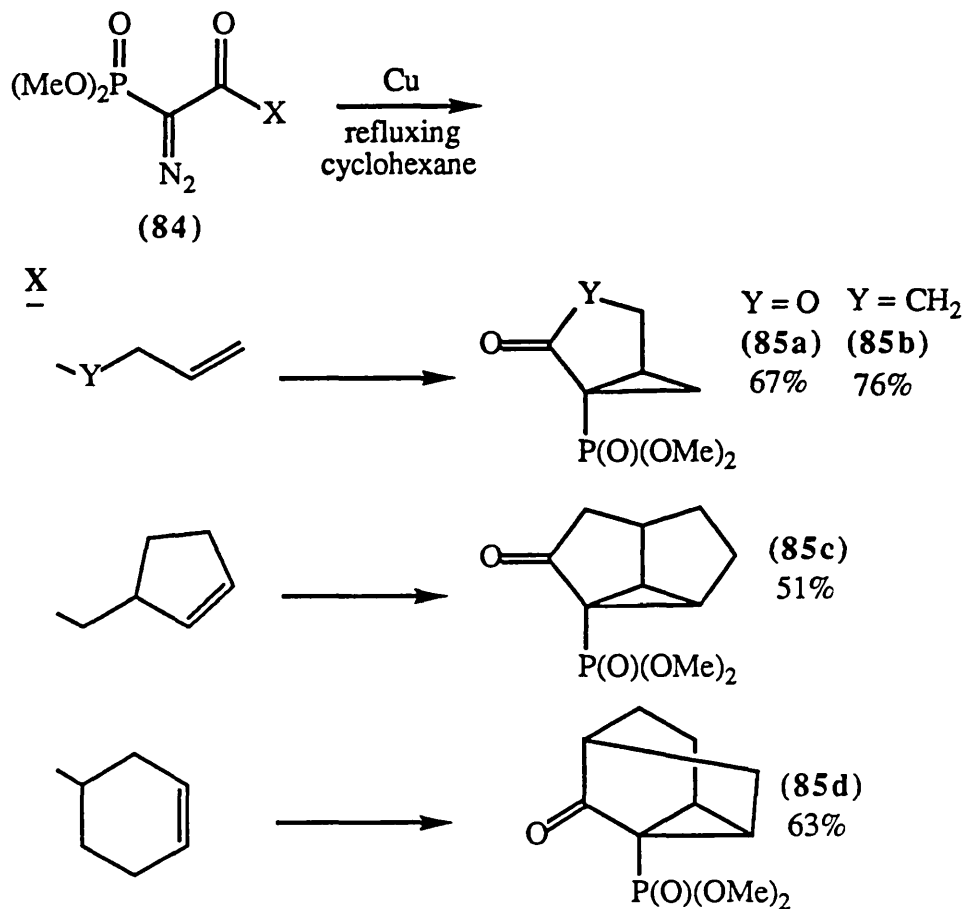
2.2.1 Addition to C-C π Bonds

A number of reports of additions of carbenes generated from α -dialzo phosphono compounds to alkenes, both intramolecular⁵¹ and intermolecular,^{32,52} have appeared. The reaction conditions and yields depend upon the nature of the substituents. (Scheme 37).



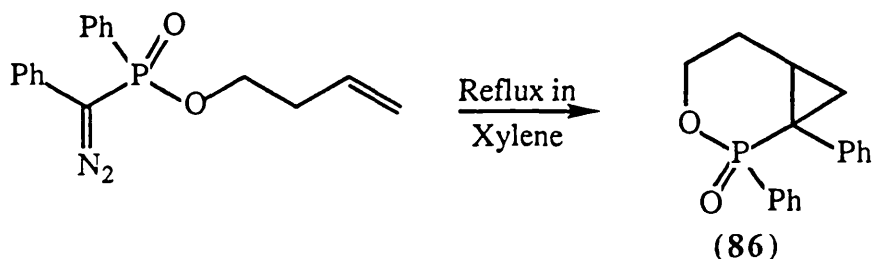
Scheme 37

The addition reactions of β -carbonyl α -diazo phosphonates to $C=C$ have also been investigated and it is shown that a number of strained bicyclic or tricyclic systems can be prepared by this route (Scheme 38).⁵³



Scheme 38

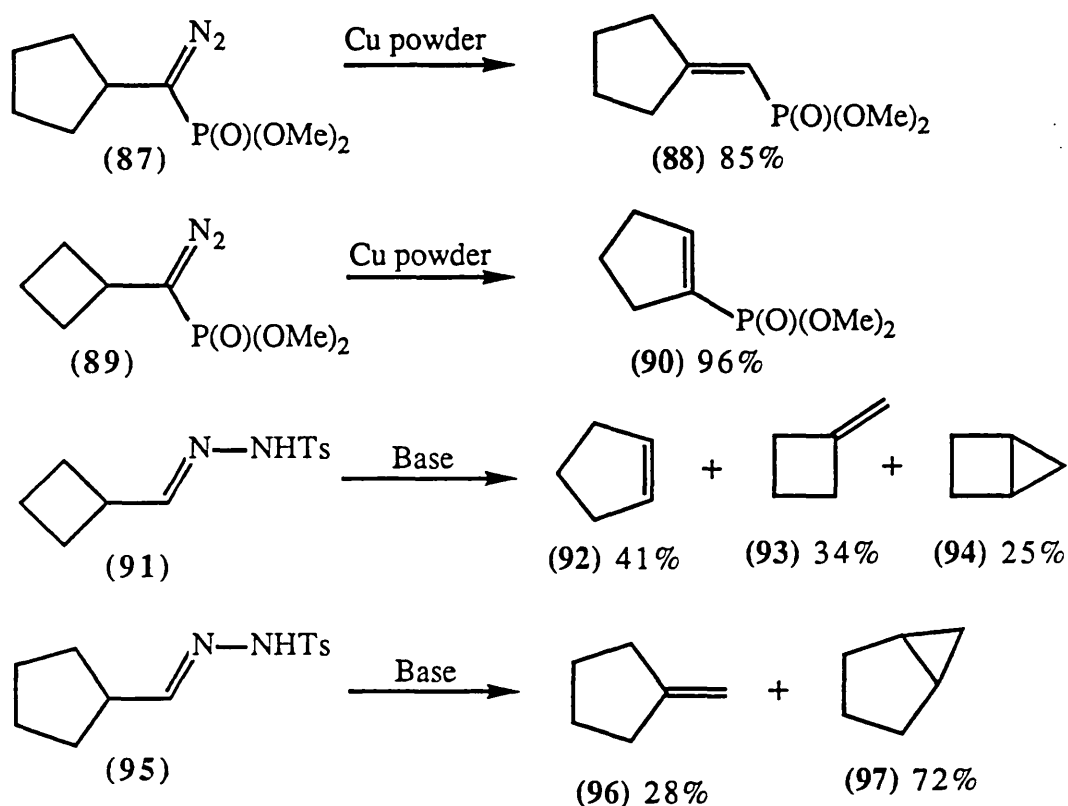
The following reaction is the only one reported in which, addition occurs into a $C=C$ on the phosphorus side chain so that the phosphorous moiety is endocyclic in the product.⁵⁴ The phosphonyl moiety being tetrahedral, conformational analysis of its transition states are more straight forward than for the carbonyl analogues; though unlike the α -diazo carbonyls, no comprehensive study to correlate mode of cyclisations to the conformations of possible transition states has yet been carried out.



Scheme 39

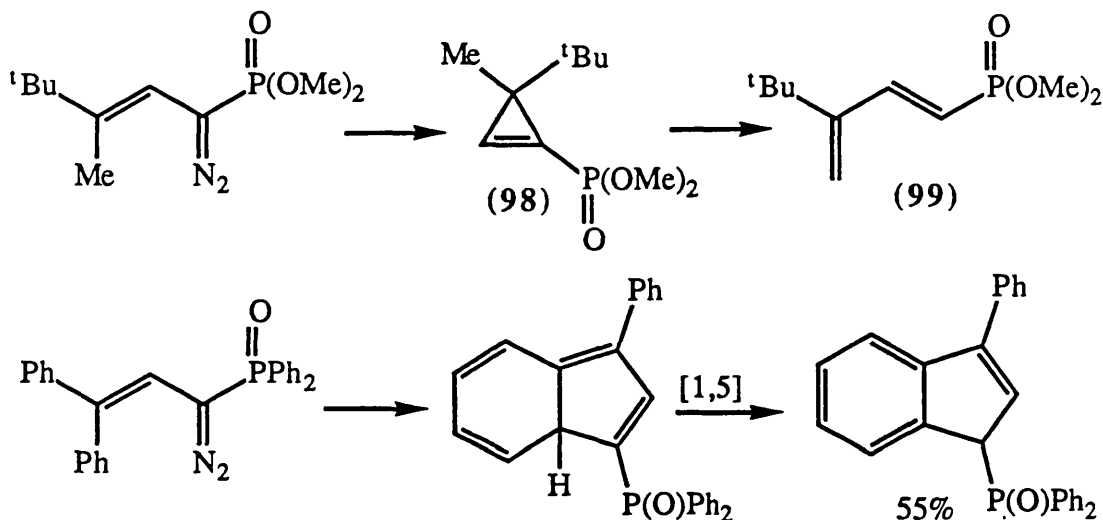
2.2.2 Insertion into C-H Bond

Insertion reactions of carbenes generated from α -diazo phosphonyl compounds into C-H bonds are well studied. Seyferth reported copper catalysed decomposition of α -diazo phosphonyl compounds leading to intramolecular C-H insertion in 1970 and from his results concluded that the introduction of a phosphonyl group adjacent to a carbene has a profound effect on the course of the carbene chemistry observed.⁴³ Most importantly, in the presence of β -protons, the single product of copper catalysed thermal decomposition of (87) is the hydrogen shift product (88), whereas for compound (89) carbon migration leads to (90). In contrast, in the absence of the phosphonyl group, considerable yields of C-H insertion products were obtained (Scheme 40).



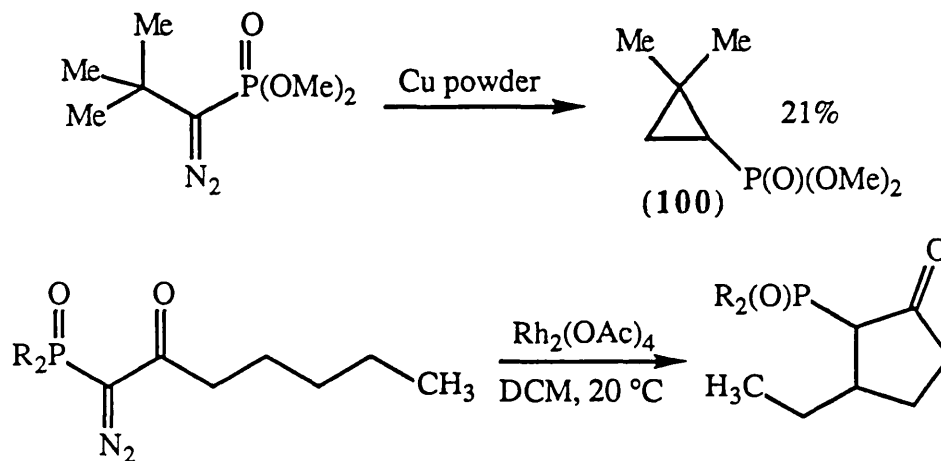
Scheme 40

If the β -proton is vinylic, the outcome of the reaction depends on substituents and reaction conditions. Products that result from a formal hydrogen shift are observed though it is shown that cyclopropene (98) is an isolable intermediate which decomposes to the diene product (99).⁴³ Insertion into aromatic C-H bonds is observed if other decomposition routes are not available (Scheme 41).⁵⁵



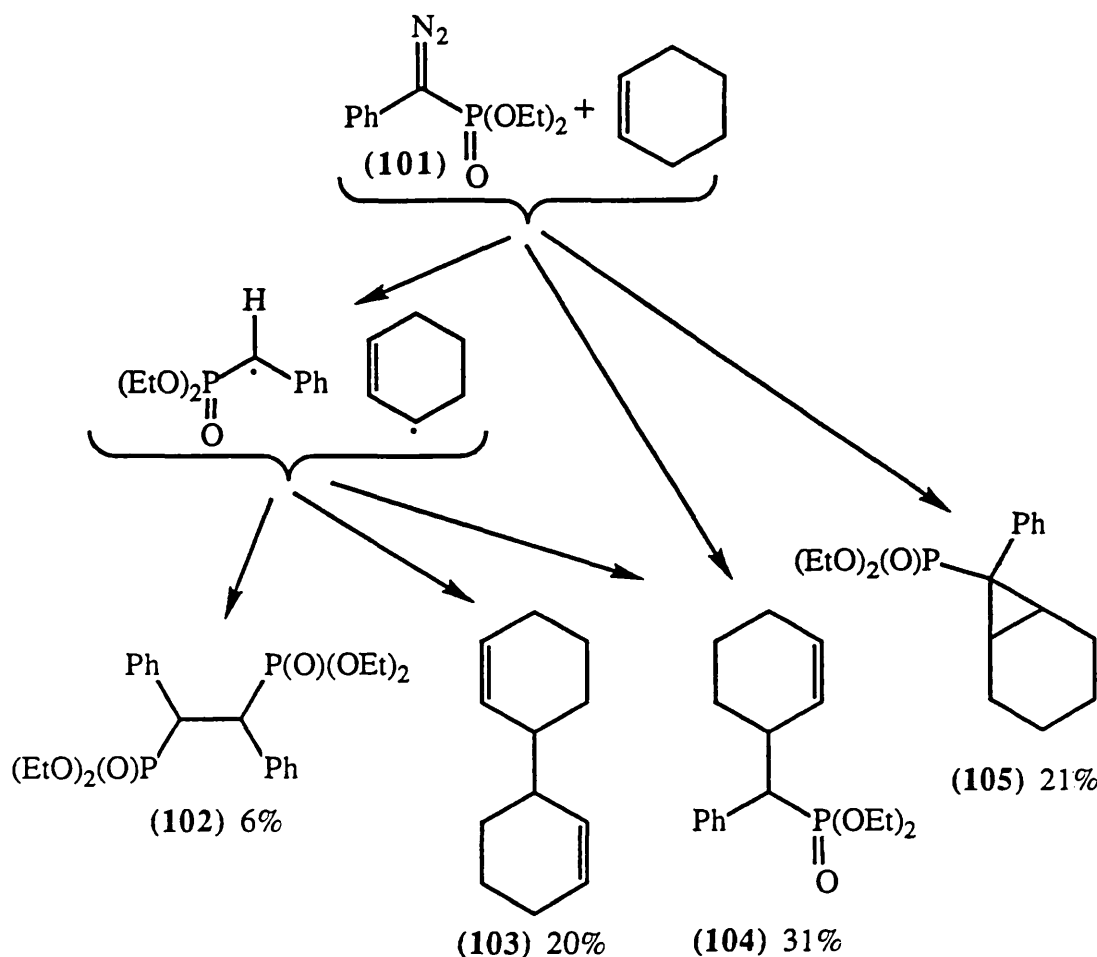
Scheme 41

In the absence of a β -proton, C-H insertions occur in modest yields.⁴³ Again with the introduction of a β -carbonyl, as was the case with C=C addition, intramolecular C-H insertion reactions have been studied (Scheme 42).⁵⁶



Scheme 42

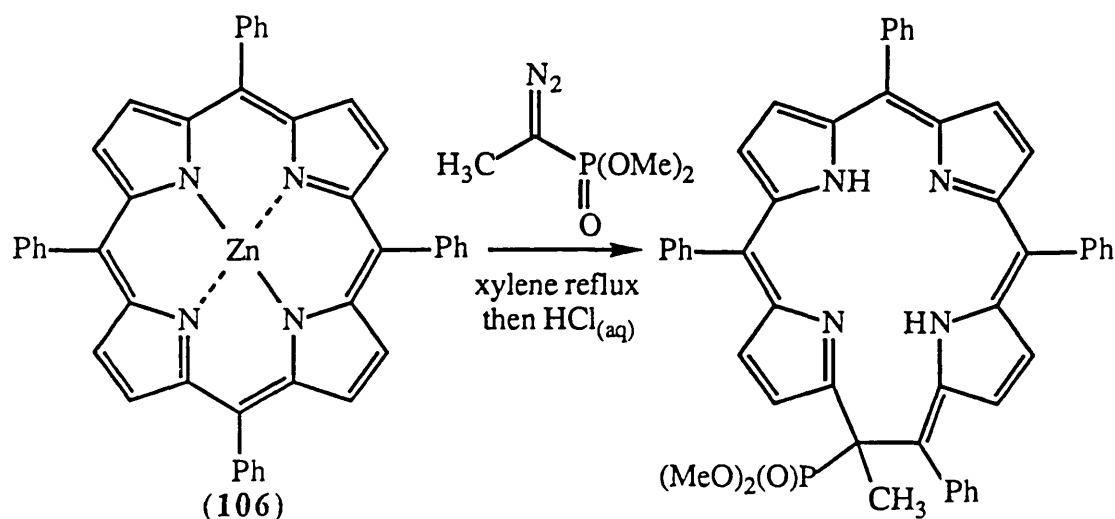
Intermolecular C-H insertions are not as widely reported as their intramolecular counterparts. One interesting example is that outlined in Scheme 43 in which the carbene generated from diazo precursor (101) undergoes addition to C-C π bond and allylic hydrogen abstraction and possibly allylic C-H insertion, to afford products (102) to (105).⁵⁷



Scheme 43

2.2.3 Insertion into C-C σ Bonds

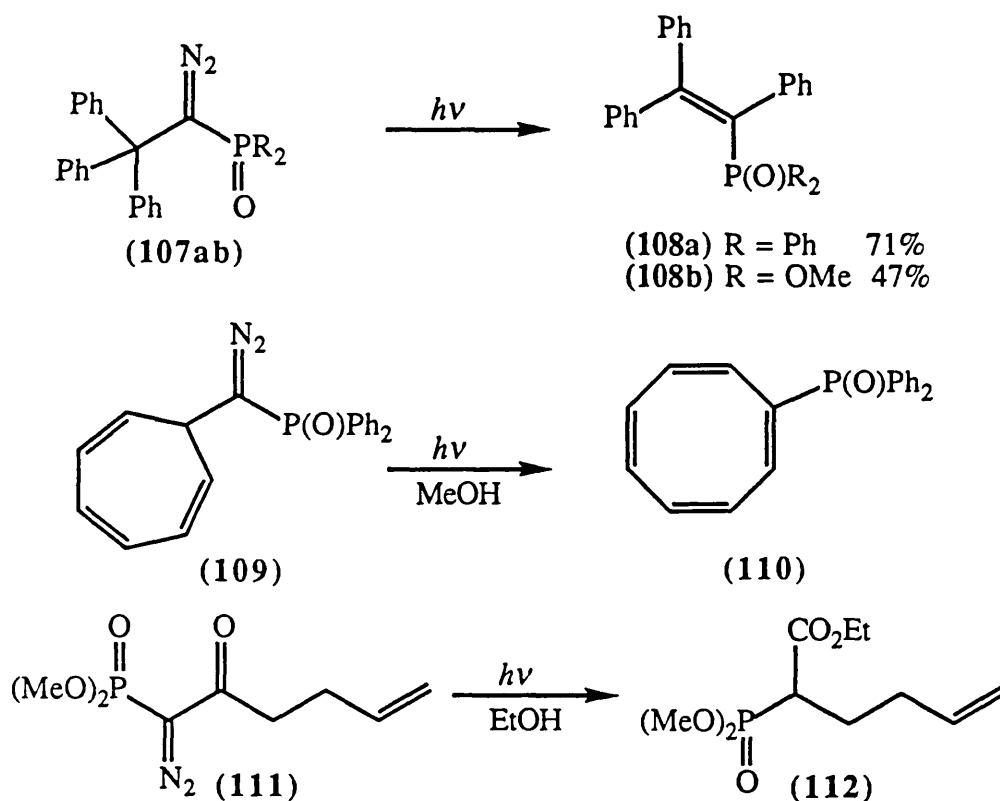
The only example of intermolecular C-C insertion is that observed when the zinc porphyrin complex (106) was used for decomposition of diethyl 1-diazoethane-phosphonate. A similar reaction was not observed for the cobalt complex (Scheme 44).⁵⁸



Scheme 44

2.2.4 Rearrangements

We have already seen examples of rearrangements involving migration of a carbon to a carbene in the formation of compound (90) (Scheme 40) and in Chapter One (Scheme 3) when intermediate (5), generated by a 1,2-phenyl shift, was trapped with benzaldehyde and benzophenone. Although in (5, R = C₆H₅) a phenyl group of the phosphinyl migrated in preference to that of the carbonyl, in compound (107) the phenyls of the phosphinyl group remain intact (Scheme 45).⁵⁹ Also the β-hydrogen shift discussed above does not occur in cases like compound (109) where (110) is formed in place of a strained triene.⁶⁰ The Wolff rearrangement of β-keto phosphonates has also been reported [transformation (111) to (112),⁶¹ Scheme 45].

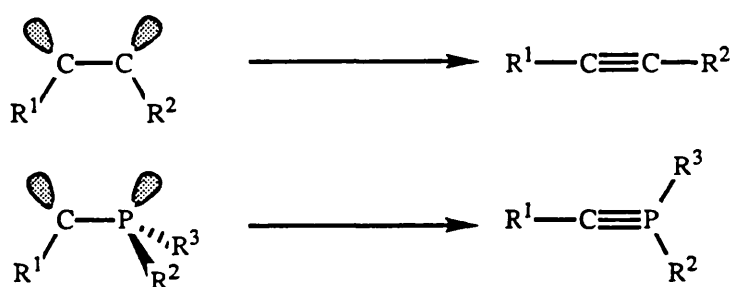
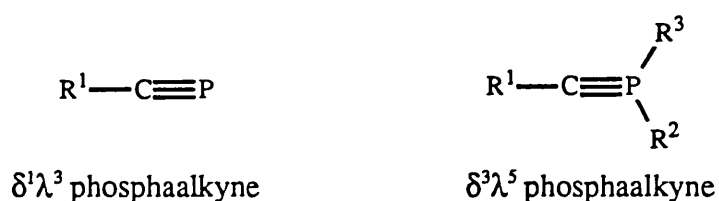


Scheme 45

2.3 α -Diazo Phosphines

An understanding of the chemistry of α -diazo phosphonates will not be complete without consideration of the closely related α -diazo phosphines. Although the two classes of compounds are distinct in their pattern of chemical reactivity, the facile conversion of $\sigma^3\lambda^3$ to $\sigma^4\lambda^5$ phosphorus can present an alternative route for the synthesis of α -diazo phosphonates starting from α -diazo phosphines. Synthesis of α -diazo phosphines has already been discussed (route E).

Originally, the interest in α -diazo phosphines as precursors of phosphinocarbenes was for a different reason. Not only do they represent a rare example of donor substituted diazo compound which alone merits their investigation, but they have also been studied as precursors of $\sigma^3\lambda^5$ phosphalkynes.



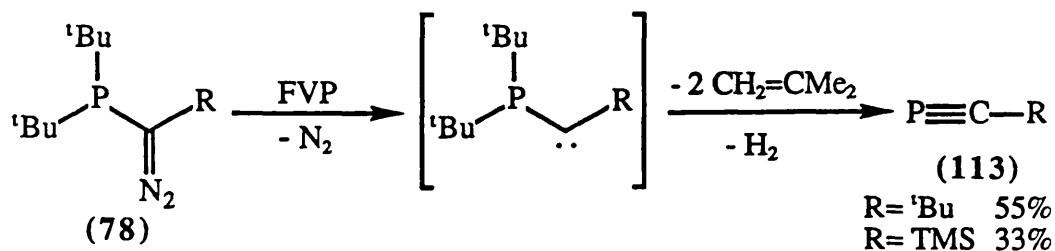
Scheme 46

Phosphaalkynes have been regarded as one of the most exciting new discoveries in organophosphorus chemistry of the past few decades.⁶² These have already opened the way for the synthesis of many interesting new phosphorus containing ring systems and promise to be some of the most valuable synthetic building blocks of organophosphorus chemistry for some years to come.⁶³

$\sigma^1\lambda^3$ Phosphaalkynes have been subject to intense investigation since their discovery in 1961.⁶⁴ However, against a background of an ever increasing number of reported compounds featuring p_π - p_π triple bonds between second and first row elements,⁶⁵ $\sigma^3\lambda^5$ phosphaalkynes remained elusive until a few years ago. Indeed to date a conclusive proof of their existence is lacking.

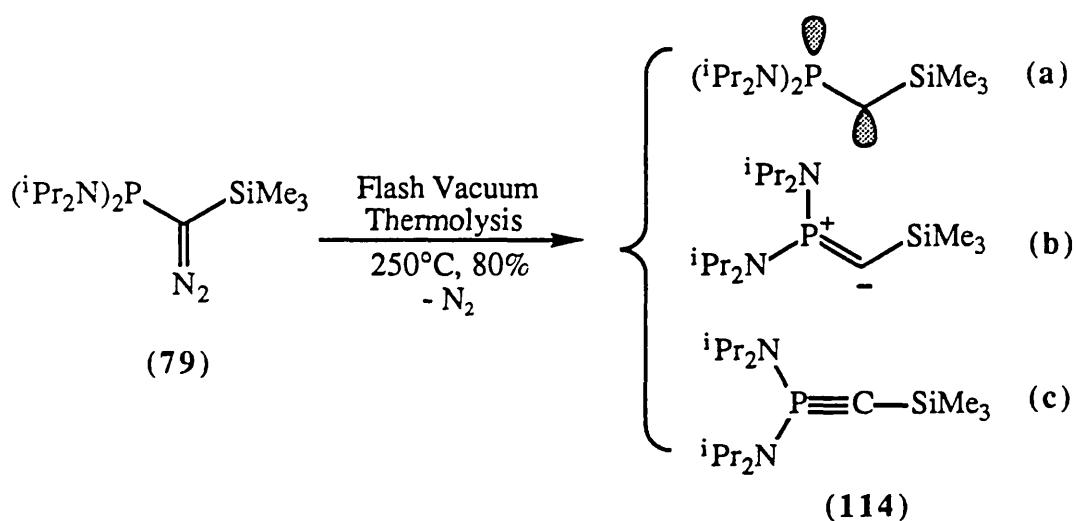
2.3.1 Reactions of α -Diazo Phosphines

Synthesis of α -diazo phosphines (78) and (79) was discussed in Scheme 36. An attempt to prepare a kinetically stable $\sigma^3\lambda^5$ phosphinocarbene through diazo decomposition of (78) failed, producing instead a $\sigma^1\lambda^3$ phosphaaalkyne (113).⁵⁰



Scheme 47

Bertrand prepared [trimethylsilyl bis(diisopropylamino)phosphino]diazomethane (79) and studied the reactivity of this and related compounds in detail.^{18, 65-69} Flash vacuum thermolysis of (79) at 250° C affords another isolable red oil which is assigned as the phosphinocarbene (114). Although thermally stable, (114) reacts with a range of trapping agents to afford the products which were also obtained by photolysis of (79) in the presence of the trap.⁶⁸

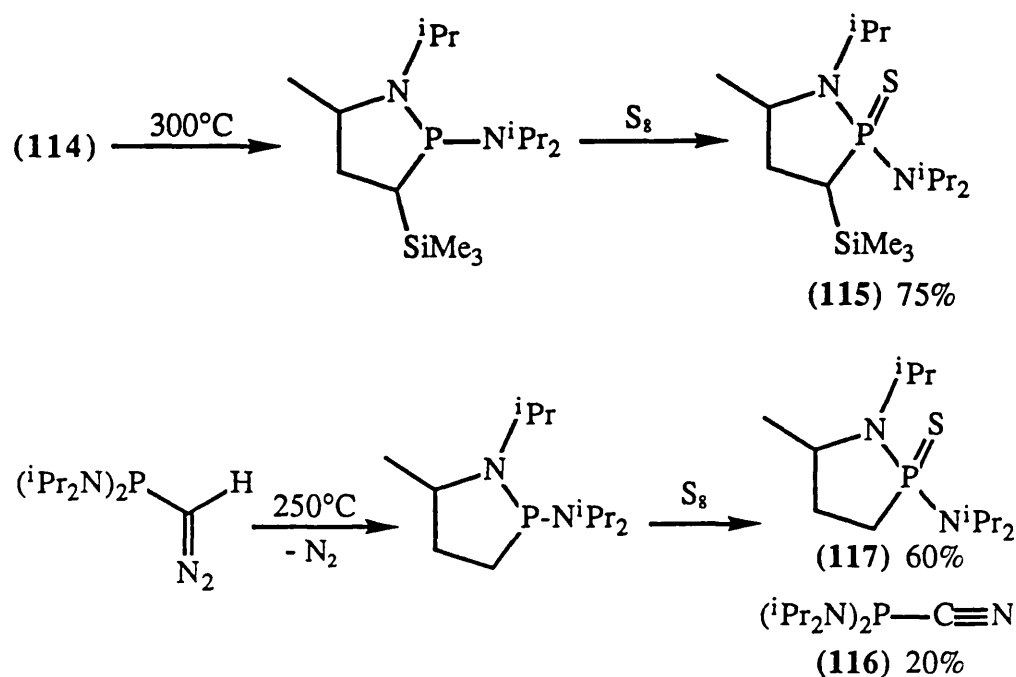


Scheme 48

2.3.1.1 Intramolecular C-H Insertion

The outcome of intramolecular C-H insertion of phosphinocarbenes appears to be governed by its mode of generation and the nature of substituents. Photolysis of (79) does not afford C-H insertion products. Thermolysis of (114) on the other hand leads to insertion into a methyl group instead of the expected methine C-H and after treatment with elemental sulfur affords 1,2-azaphospholidine (115) in unspecified ratio of

diastereomers. If the trimethylsilyl group is replaced by hydrogen then, together with the corresponding 1,2-azaphospholidine (**117**) in 7:3 ratio of diastereomers (unassigned), some (**116**) is also generated.⁶⁸ Bertrand also claims that thermolysis of (**24**) followed by treatment with elemental sulfur leads to 1,2-azaphosphetidine (**25**) but does not provide physical data in support of the assigned structure.¹⁸

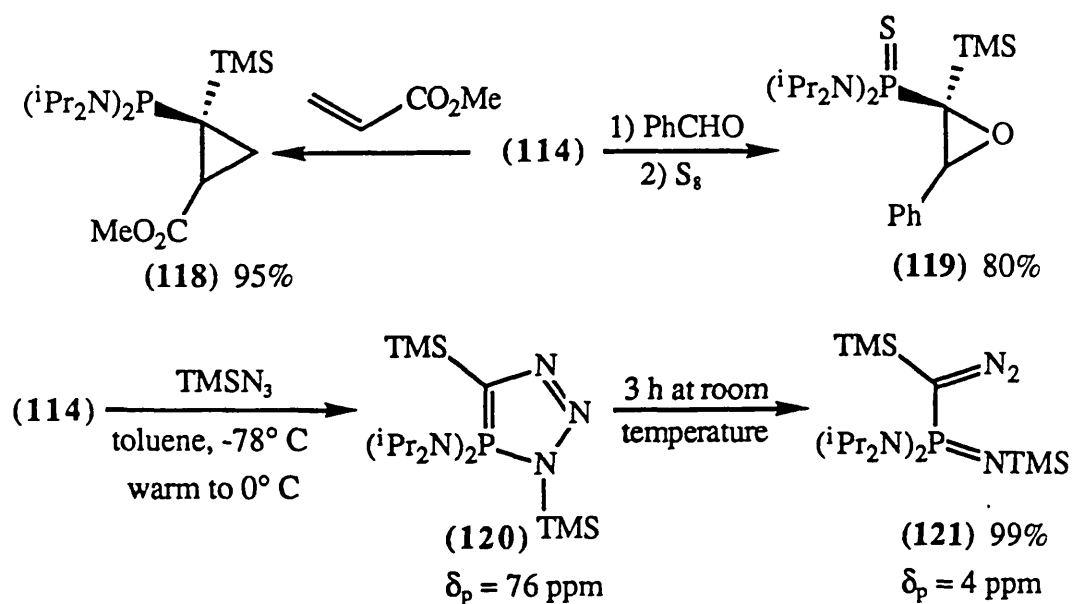


Scheme 49

2.3.1.2 [1,2] and [1,3] Dipolar Additions

The formal [1,2] addition of (**114**) to electron deficient alkenes¹⁸ (but not to cyclohexene or butadiene⁶⁸) and to aldehydes¹⁸ (but not ketones⁶⁸) affords cyclopropanes and oxiranes respectively. The reaction is reported to be diastereoselective with methyl acrylate, and also to result in the thermodynamic product, presumably the trans cyclopropane, being formed from dimethyl fumarate and maleate.¹⁸

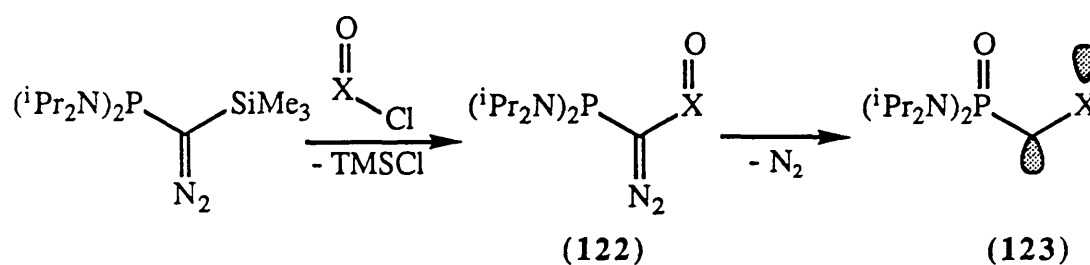
Similarly (**114**) reacts in the cold with trimethylsilylazide to give initially (**120**),⁷⁰ characterised by its ³¹P NMR signal, which upon warming to room temperature changes to open form (**121**).⁶⁸



Scheme 50

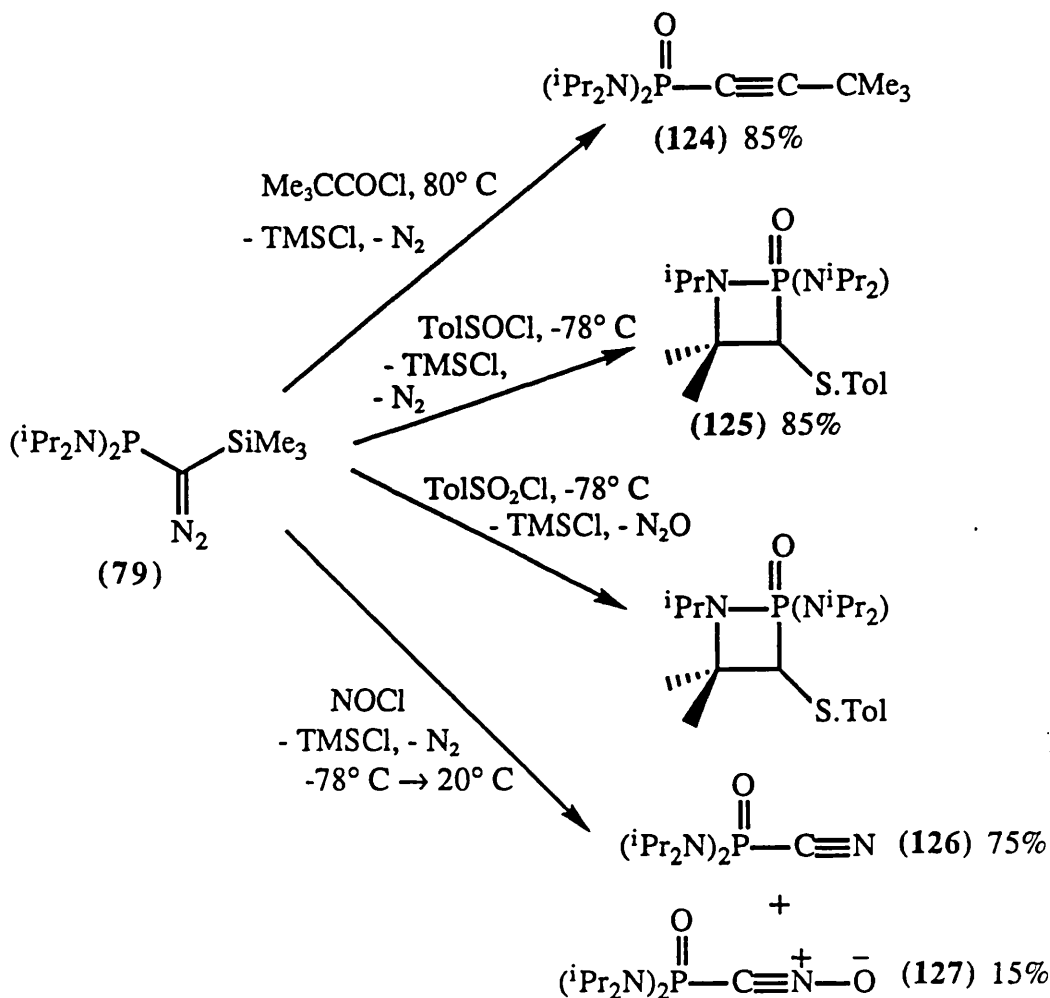
2.3.1.3 Intermolecular Addition to $\text{O}=\text{X}-\text{Cl}$ Functions

Bertrand and co-workers have studied a diverse range of additions of diazophosphines to $\text{X}=\text{O}-\text{Cl}$ functions, in which X is a nitrogen, sulfur, carbon or phosphorus radical.^{18,68} Although the individual chemical products are different depending on X, a general reaction pathway can be clearly inferred. Loss of TMSCl to give a non-isolable intermediate (122), followed by transfer of oxygen from X to phosphorus, resulting in (123) which then undergoes further reaction depending upon the nature of X.



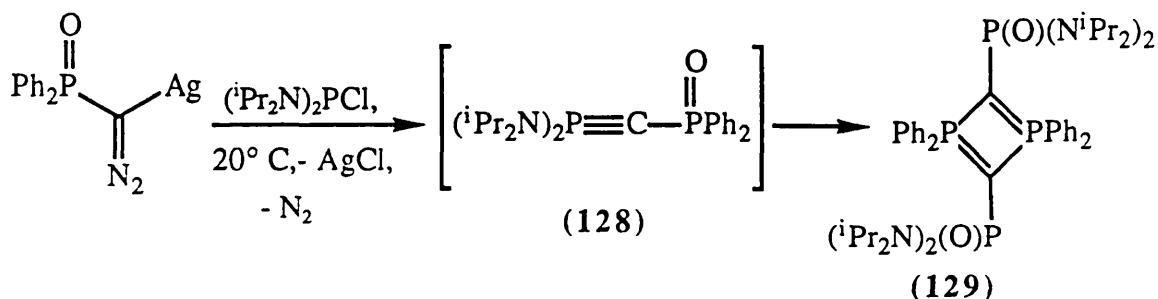
Scheme 51

With X being a carbyne, the product is an alkyne (124), with X being a nitrogen atom, the product is a nitrile (126), and with X being a sulfur atom, the initial product is a ylide which then undergoes a C-H insertion. For instance the addition to toluenesulfonyl chloride affords a product which has been assigned the 1,2-azaphosphetidine structure (125) though no physical data in support of the proposed structure has been provided.



Scheme 52

With X being a phosphonyl group, the oxygen transfer is also observable and in one reported case⁷¹ occurs as expected from the less oxophilic phosphorus bearing phenyl ligands to the more oxophilic one bearing diisopropylamine ligands. The resulting carbene is stabilised by both a $\lambda^3\delta^3$ phosphine and a $\delta^4\lambda^5$ phosphonate as was its precursor. The isolated product, however, is a dimer as confirmed by X-ray crystallography and not a 1,2-azaphosphetidine as reported by Bertrand to be the case with carbene stabilised with a sulfur and $\delta^4\lambda^5$ phosphonate.

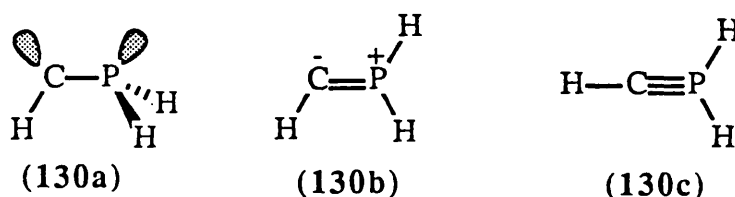


Scheme 53

2.3.2 Electronic Structure of α -Diazo Phosphines

The true nature of (114) is controversial. Bertrand suggests that although each of the three valence tautomers of (114) (Scheme 48) are plausible, on the basis of NMR the molecule must be symmetrical and that (114c) is the true representation of the molecule at least in its metastable form (red oil).

An *ab initio* study of CH_3P molecule does not support this claim.⁷² Linear $\text{H}_2\text{P}\equiv\text{CH}$ (130c) was higher in energy than bent $\text{H}_2\text{P}-\text{CH}$ (130b) in the four basis sets used. Furthermore the singlet phosphinocarbene (130c) was calculated to be 3 kcal/mol lower in energy than the triplet (130a) state, suggesting that (114b) could be the thermodynamically stable species which could transform to (114a) with input of energy. Thus thermolysis or photolysis of compound (79) could generate (114a) with typical carbene reactivity which, in the absence of a trap, transforms to (114b), a distinct chemical entity (the red oil observed by Bertrand) presumably by loss of energy.



It can be argued that, on the basis of the results of this theoretical study alone, a λ^3 -phosphaacetylene structure (114c) cannot be rejected. For instance, allowance has not been made for any delocalisation of electron pairs into empty silicon *d* orbitals and that energy barriers discussed are of sufficiently small magnitude for transformations to be considered true equilibria. On the other hand it has been claimed⁷² that the apparent symmetry of NMR signals is not a result of magnetic equivalence but is derived from the distance of the isopropyl group from the centre of asymmetry and hence the single piece of evidence in favour of the λ^3 -phosphaacetylene structure for (114) is suspect.

Ultimately, physical techniques which directly relate to symmetry of molecules such as Raman and microwave spectroscopy, as NMR was used, are the only methods which can resolve the question regarding the true nature of Bertrand's red oil. Though it is dangerous to draw firm conclusions regarding chemical structure solely based on chemical reactivity, it should be noted that from Bertrand's reports it appears that carbene (114a) is a chemical entity, distinct from isolable red oil, and is generated directly during photolysis or thermolysis of (79) or when the red oil (114bc) is thermolysed. This differentiation is best exemplified in C-H insertion reactivity of (114) under FVP

conditions but lack of reactivity at room temperature. Lack of reactivity of compound (114) towards dimethyl sulphide is another piece of evidence against the carbene character of compound (114). Such a differentiation, however, cannot be easily made between the remaining two valence tautomers. Certainly, compound (114) shows a spectrum of chemical reactivity more consistent with a vinyl ylide structure (114b) than a λ^3 -phosphaacetylene (114c) as indicated by loss of trans isomerism during addition to dimethyl fumarate which indicates a non-concerted reaction.

2.3.3 Conclusions

The choice of a convenient synthesis of an α -diazo phosphono compound ultimately depends on the range of substituents present and the nature of desired reaction. Of the synthetic routes discussed, with the exception of diazotisation route, A, which is useful only for a limited range of compounds, none can claim to have a great advantage over the others; indeed due to difficulties arising in organophosphorus synthesis they are in a sense complementary. Therefore it is expected that their application and utilisation will be further developed in parallel.

From a purely synthetic point of view, α -diazophosphines have proved to be of considerable value. They have paved the way to a variety of highly interesting structures which are not easily available through other known methods. These include cyclopropanes and oxiranes bearing phosphorus functionality on the ring, and 1,2-azaphosphetidines and 1,2-azaphospholidines. However the work so far reported does include some contradictory and inexplicable observations which means that predictable patterns of reactivity cannot yet be established. Furthermore, the only isolable phosphaalkynes/phosphinocarbenes have shown little reactivity towards non-polarised dienes which restricts their use in the construction of heterocyclic rings. Finally, evidence has not yet been presented to suggest a variation in modes of action of carbenes when stabilised by phosphonates or phosphines. The chemistry of phosphinocarbenes needs to be explored more vigorously to supplement the fascinating new perspectives it has presented for organophosphorus chemistry.

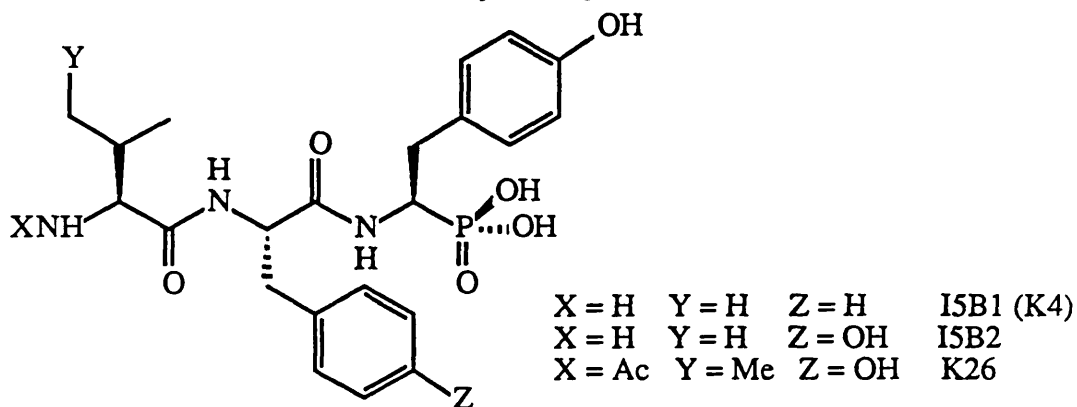
Areas of importance for the future will no doubt include a study of chiral induction from tetra-coordinated phosphorus in the C-H insertion reaction, though this requires the development of synthetic routes to chiral α -diazophosphonates and α -diazophosphinates. A comparison of the stereo and electronic effects influencing the C-H insertion of phosphonyl stabilised diazo compounds *versus* those governing the C-H insertion of carbonyl stabilised diazo compounds would also be extremely useful.

Chapter Three

***A Review of the Synthesis and Properties of
 α -Amino Phosphonic Acids and α -Amino Phosphinic Acids***

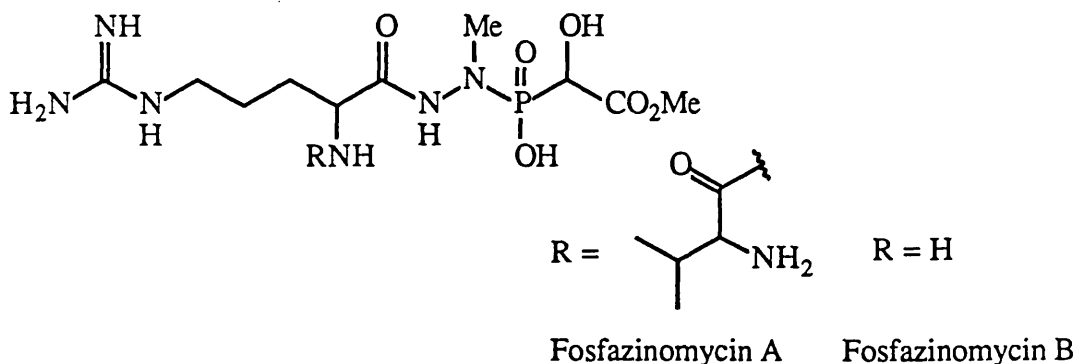
3.1 Natural occurrence

Tyrosine analogue (144) and three peptides of which it is a residue, outlined in Scheme 54, are the reported examples of α -amino phosphonic compounds from Nature. Antibiotic K26, isolated from *Actinomycetes* strain K-26,⁷³ and related antibiotics I5B1 and I5B2, isolated from *Actinomadura spicculospora*,⁷⁴ show mild inhibition of renin.



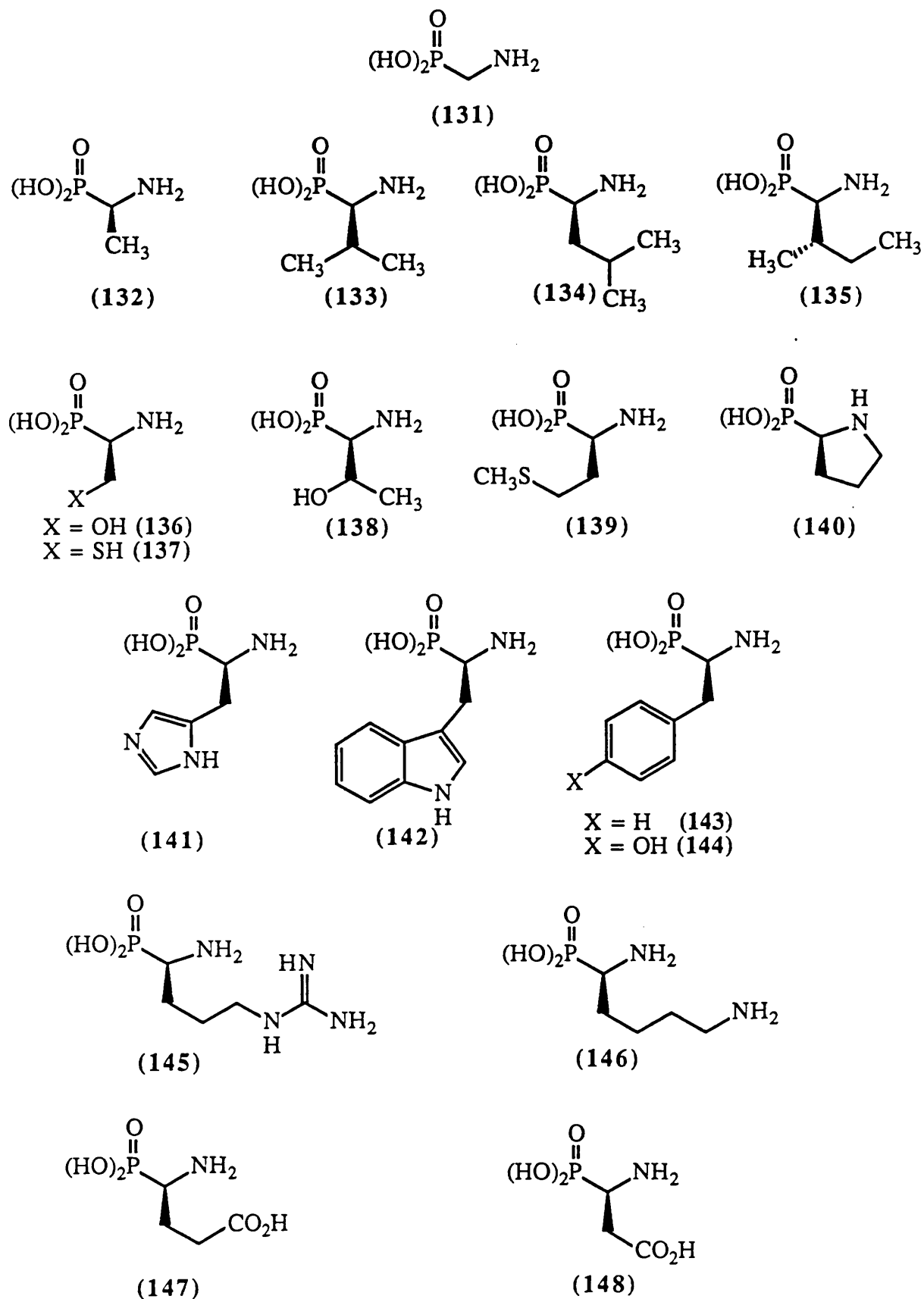
Scheme 54

Although not containing an α -amino phosphonic acid in the strict sense, antifungal antibiotics Fosfazinomycin A and B, isolated from *streptomyces lavendofoliae*,⁷⁵ also deserve a mention as they represent a fascinating example of Nature's adaptation of heteroatoms in building of organic molecules. They contain, in effect, an alanine analogue residue in which not only is the carboxyl replaced by a phosphonyl moiety but the α carbon is also replaced by a nitrogen.



Despite this lack of natural occurrence, many α -aminophenylphosphonic acids and most α -amino phosphonic acids analogues of proteinogenic α -amino carboxylic acids (compounds (131)-(148), Scheme 55) have been synthesised at least in non-optimally pure forms.⁷⁶

The lack of naturally occurring α -amino phosphonic acids should be contrasted with abundance of β -amino phosphonic acid derivatives. The subject of naturally occurring alkylphosphonic acids is similarly diverse and has recently been reviewed.⁷⁷

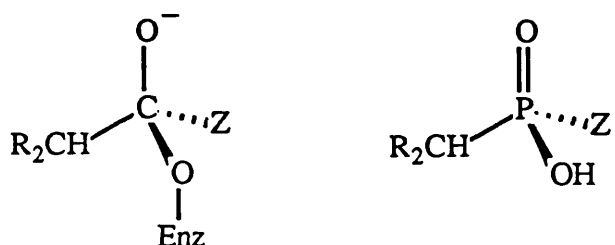


Scheme 55

3.2 Biological Properties

The spectrum of biological activity of organophosphorus compounds is wide. It varies from deadly poisonous to vitally essential to support life. This is mainly a reflection of the diversity of structural types in organophosphorus chemistry

In this section emphasis is put on commercially available α -aminophosphono compounds and some related α -functionalised phosphonates. Commonly the activity of α -amino phosphonic acids is considered to result from their close structural analogy to α -amino carboxylic acids. For instance, when incorporated into a peptide chain they may

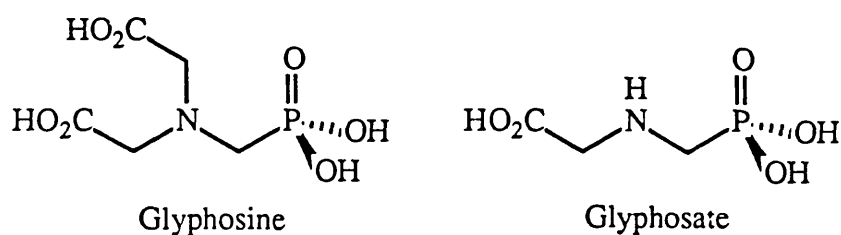


Scheme 56

mimic biologically the transition state involved in hydrolysis of the peptide linkage. So far the number of synthetic α -amino phosphonic compounds has remained relatively small partly as a result of difficulties in synthesis. Since α -aminophosphono compounds are believed to remain untouched by human metabolism, their introduction in the body is not considered to be hazardous, although to date no general study on the toxicity of this class of compounds nor their impact on ecological systems has been published. General biological degradation pathways may be deduced from those of β -aminophosphonates and other non α functionalised phosphonates.⁷⁷

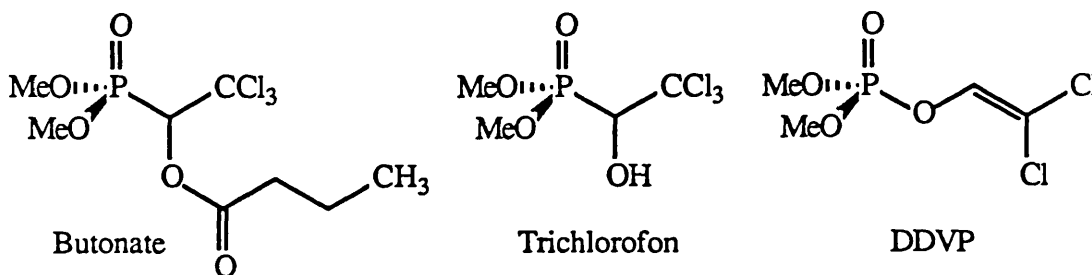
Herbicides

Currently there are a number of post-emergence herbicides containing α -amino phosphonic acid sub-structures in commercial use. The best known is Glyphosate,⁷⁸ the mono triisopropylammonium salt of which is the best selling herbicide, Round-up. Glyphosate was discovered by Monsanto scientists during a routine study of the related compound, Glyphosine,⁷⁹ which enhances sugar production in cane; this exemplifies diversity in the areas in which α -amino phosphonic acids are bioactive.

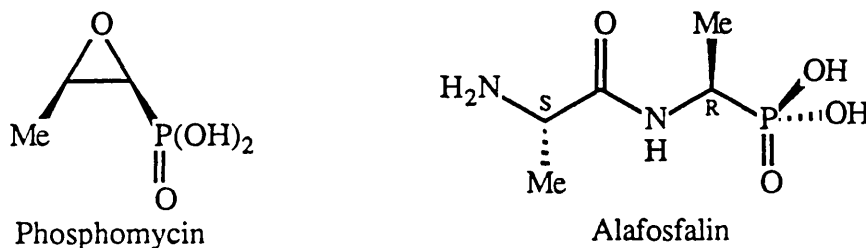


Insecticides

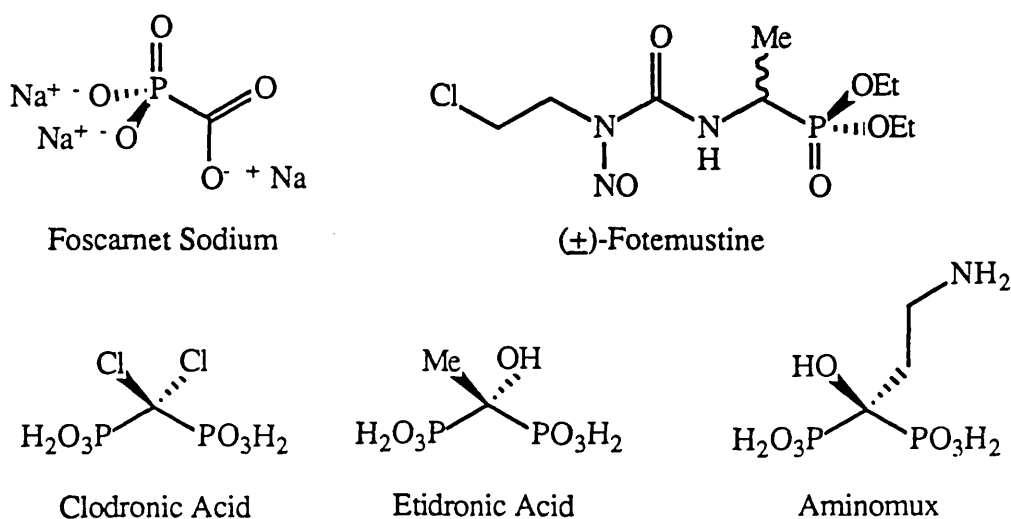
Trichlorofon⁸⁰ and the closely related Butonate⁸¹ are both potent contact insecticides. Though rather unselective and toxic to mammals, they remain in use since they are effective and inexpensive. Their activity results from slow rearrangement to dimethyl dichlorovinyl phosphate (DDVP) which is a poison.

*Bactericides*

The two famous members of this class are Phosphomycin⁸² and Alafosfalin,⁸³ the latter like penicillins interrupts the bacterial cell wall assembly,⁸⁴ though its mode of action is different. The thiirane and aziridine analogues of Phosphomycin have also been synthesised⁸⁵ but are less active.

*Others*

Foscarnet Sodium⁸⁶ is a mild antiviral and Fotemustine (achiral),⁸⁷ is an antineoplastic agent. Aminomux,⁸⁸ as its disodium salt, is a antipagetic agent and both Clodronic acid⁸⁹ and Etidronic acid⁹⁰ are reported to be calcium regulators.



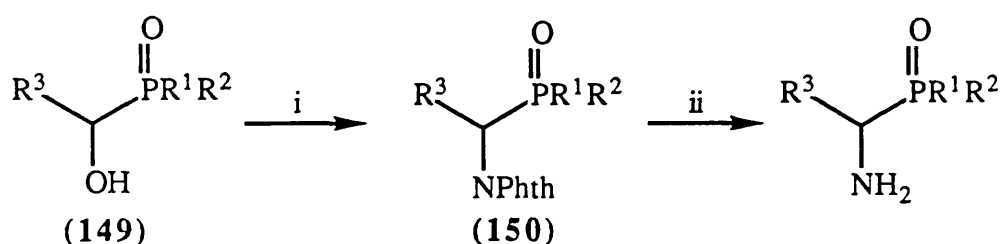
3.3 Synthesis

The first reported synthesis of an α -amino phosphonic acid was that of α -aminomethanephosphonic acid (phosphoglycine) (131) by Chevane in 1948.^{76(a)} Since then phosphorus analogues of all proteinogenic α -amino carboxylic acid have been synthesised at least in non optically active form. The synthetic approaches may be classified as follows:

- By amination at the α position of a phosphonate or phosphinate.
- By addition of $\sigma^3\lambda^3$ phosphorus nucleophiles to imines or related functionalities.
- By addition of $\sigma^3\lambda^3$ phosphorus nucleophiles to α halo amides and related functions.
- By manipulation of other α -amino phosphonic acids or esters.

3.3.1 Amination at the α Position of Phosphonates and Phosphinates

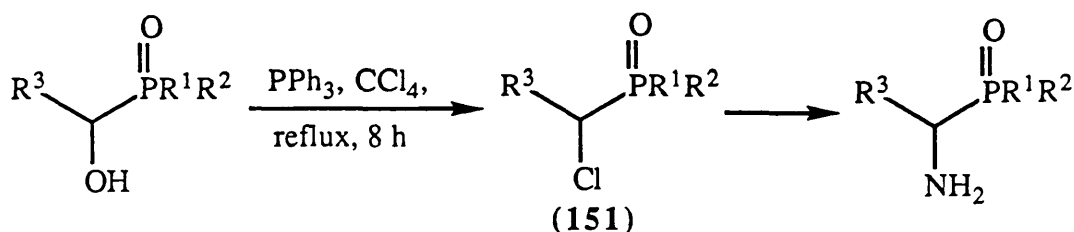
The so called " α substituent effect", comprising the facility of nucleophilic displacement at the positions α to carbonyl functions, is well known and reviewed.⁹¹ The existence of a corresponding effect for phosphonyl compounds, however, remains obscure. It is expected that such an effect would be somewhat subdued for phosphonyl compounds compared to that observed for the more electron withdrawing carbonyls. Nevertheless nucleophilic amination has been used for the synthesis of α -aminophosphonates as the following example shows.⁹²



i) Potassium phthalimide, DCC, reflux; ii) Hydrazine, ethanol

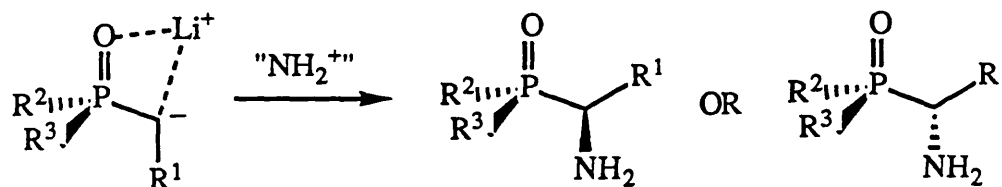
Scheme 57

Nucleophilic displacement of α -chlorophosphonates is also possible,⁹³ though these are themselves prepared from α -hydroxyphosphonates.⁹⁴



Scheme 58

Electrophilic amination for the synthesis of α -aminophosphono compounds has not yet been reported, though it would probably be a successful approach. Interestingly, this methodology has the added advantage that if the phosphorus atom is itself chiral and the ligands are suitable, chiral induction could be used to control the stereochemistry at the α -position.



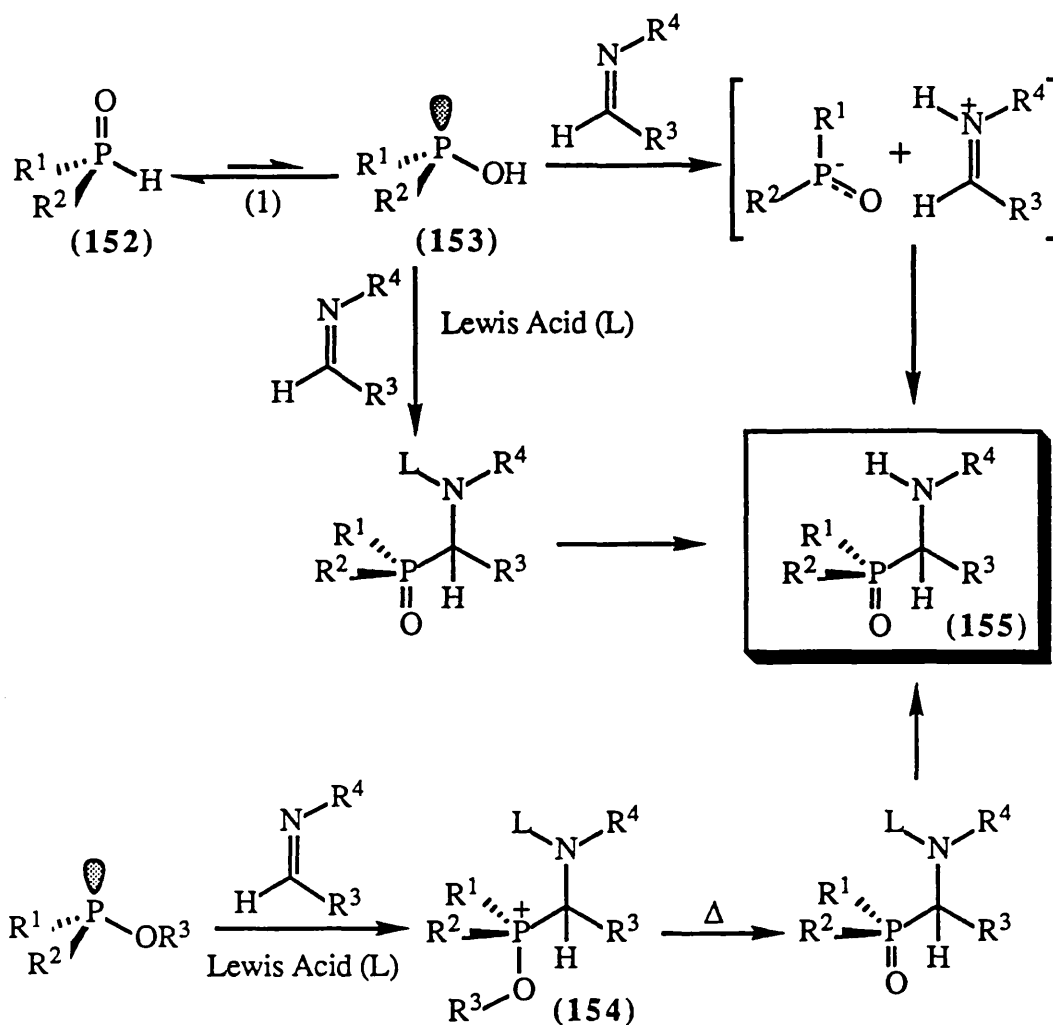
Scheme 59

3.3.2 Addition of Phosphorus Nucleophiles to Imines and Related Functions.

This route is by far the most common for the synthesis of simple α - amino phosphonates and phosphinates. It has proved to be adaptable to a range of phosphorus nucleophiles and to a limited selection of C=N functions including imines, urea derivatives, and nitrones. However traditionally, this synthesis has offered only a limited scope for functional group selectivity.

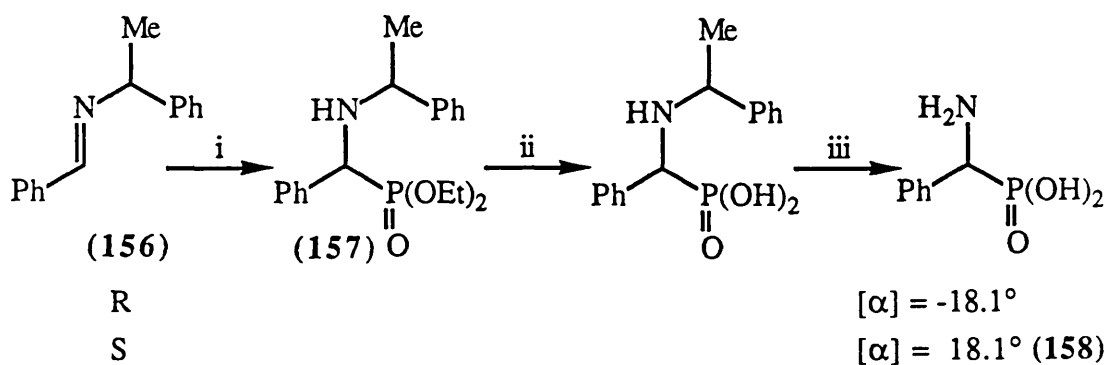
The reactions are usually carried out thermally and/or in presence of protic or Lewis acids. No mechanistic study has yet been performed but it is postulated that catalysis may serve two different purposes. For non-fully esterified phosphites thermal catalysis is required to drive the equilibrium (1) (Scheme 60) from the dominant electrophilic $\sigma^4\lambda^5$ tautomer (**152**) towards the nucleophilic $\sigma^3\lambda^3$ tautomer (**153**)⁹⁵ and hence to promote the reaction. For the fully esterified phosphites where this equilibrium is not applicable, the catalysis probably helps a later stage in the reaction when the phosphonium cation intermediate (**154**) is to be broken down to suppress the reverse reaction and to yield the phosphonate (Scheme 60).

Although he was unable to assign the absolute stereochemistry, Gilmore prepared the first enantiomerically pure α -amino phosphonic acid in 1972 utilising chirally pure α -methylbenzylamines (**156**) as chiral auxiliaries (Scheme 61).⁹⁶ In 1977, Glowiak used X-ray crystallography to show that Gilmore's dextrorotatory phosphono phenylglycine (**158**), that was derived from the *S* imine, had *R* stereochemistry at the α position.⁹⁷ Allowing for the priority rules, this result is in agreement with that obtained by Harada



Scheme 60

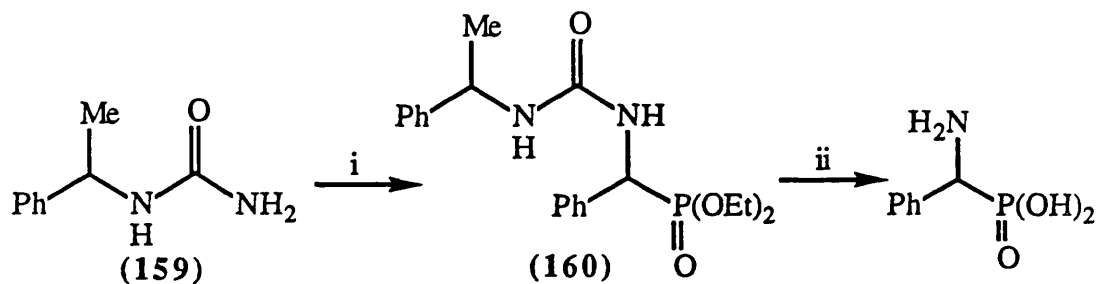
during the study of addition of cyanide ion to imines derived from chirally pure α -methylbenzylamines.⁹⁸ The use of α -methylbenzyl auxiliaries for the synthesis of chirally pure α -aminophosphonates has remained popular ever since. Nevertheless there have been some attempts made to obtain higher yields and/or better chiral purities.



i) $(\text{EtO})_2\text{POH}$, 140°C , 1h; ii) conc. HCl ; iii) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , acetic acid

Scheme 61

For instance, the use of urea derivatives (Scheme 62) by Gilmore⁹⁹ and by Birum;¹⁰⁰ in both cases the chiral purity is worse than in Gilmore's original synthesis, presumably due to the fact that the chiral auxiliary is further removed from the reaction centre.



i) $(\text{EtO})_3\text{P}$, PhCHO , $\text{BF}_3 \cdot \text{OEt}_2$, toluene; ii) conc. HCl , propylene oxide

Scheme 62

Several other chirally pure imines have been used, mostly derived from sugars and camphor, for the preparation of enantiometrically pure α -amino phosphonic acids.¹⁰¹ In contrast the use of chirally pure phosphonic acids has been attempted only once.¹⁰²

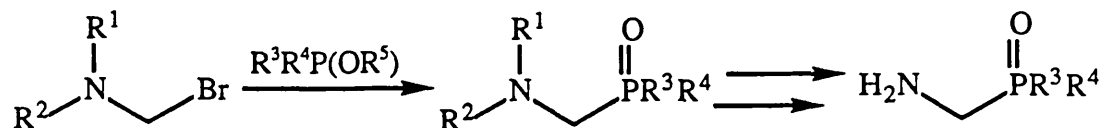
In 1981, Zon reported the use of trimethylsilyl esters of phosphorous acids with Lewis acid catalysis for this reaction. The use of silylated phosphites resulted in the production of silylated phosphonate esters which were easily hydrolysed to afford α -amino phosphonic acids.¹⁰³ Addition of tris(trimethylsilyl) phosphite and Lewis acid to nitrones was also investigated. In this case, a sugar substituent on nitrogen was used as chiral auxiliary which resulted in very impressive enantiomeric excesses.¹⁰⁴

When no Lewis acid catalysis is required, the anion of a dialkyl phosphite or a phosphonite may be used for addition to an imine. The yields vary considerably depending upon the imine and the reaction conditions and therefore this route is not always effective.

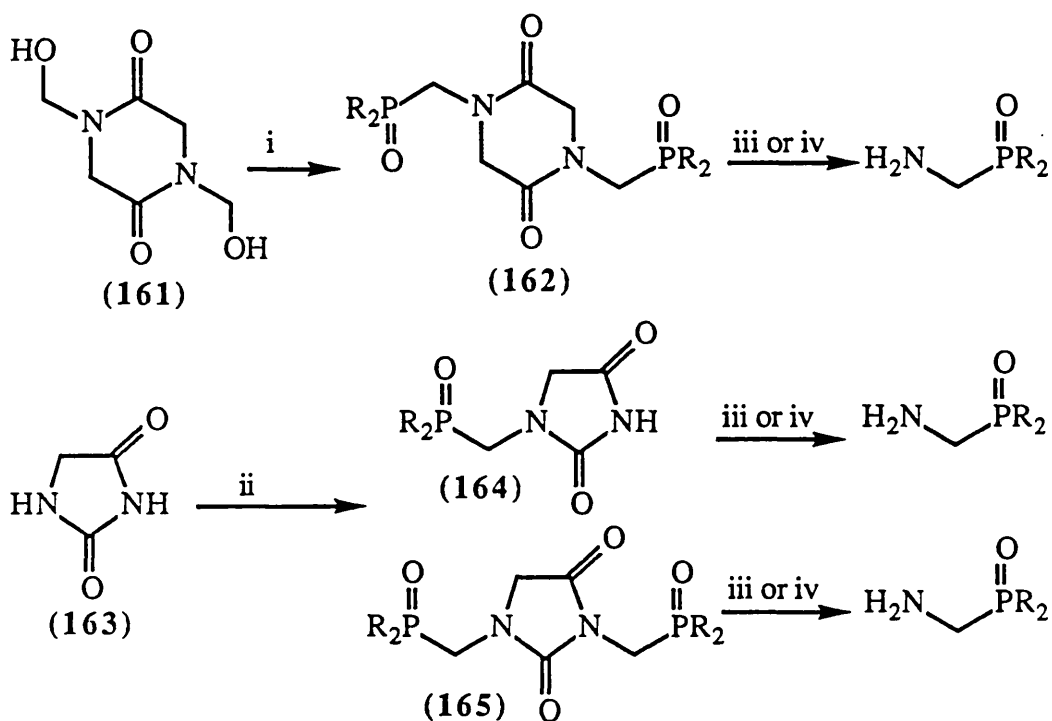
Phosphonites also add to imines to afford α -amino phosphinates. Occasionally, the reaction proceeds with no added base since the phosphorus species is nucleophilic enough, but the use of base catalyst to promote the reaction is recommended.¹⁰⁵

3.3.3 Addition of Phosphorus Nucleophiles to α Halo Amides and Related Functions.

Unlike the other routes, which are general in the sense that a range of α -aminoalkylphosphono compounds can be prepared, this route has found applicability almost exclusively to the synthesis of 1-aminomethanephosphonic acids and 1-aminomethanephosphinic acids. In this respect, this route can be considered complementary to the others since the preparations of these compound is inefficient by other routes.



Although the overall process is analogous to an Arbuzov reaction, the exact mechanistic details of this reaction remain obscure. Generally speaking, the reactions require considerable activation energy (usually provided thermally) as is the case with Arbuzov reactions. An alternative mechanism can be proposed involving iminium cation generated *in situ*. A lowering of the activation energy can be achieved by addition of Lewis acids and in such cases, at least, the intermediacy of an iminium cation is suspected.¹⁰⁶

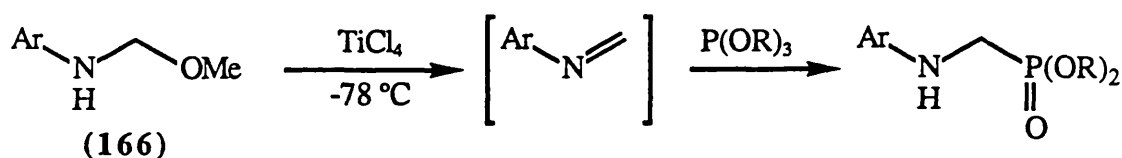


i) $\text{R}_2\text{P}(\text{OR}')$, 140°C ; ii) $(\text{CH}_2\text{O})_n$, $\text{R}_2\text{P}(\text{OR}')$, Co^{II} , 140°C ;
 iii) Phosphodiesterase I, pH 8.8, rt, 8 h; iv) Alkaline Phosphatase, pH 10.4, 6 h.

Scheme 63

Reaction of 1,4-dihydroxymethyl-2,5-piperazinedione (161) with triethyl phosphite and with diethyl methylphosphonite followed by functional group manipulation leads to the preparation of α -aminomethanophosphonic acid and α -(aminomethane)methylphosphonic acid in good overall yield.¹⁰⁶ A variety of other N-hydroxymethyl amides including hydantoin (163) can also be used although in some cases hydroxymethylation has to be carried out *in situ* (Scheme 63).¹⁰⁶ Although no reaction is reported between N-methoxymethyl amides and trialkyl phosphites, N-arylamino-methanophosphonates

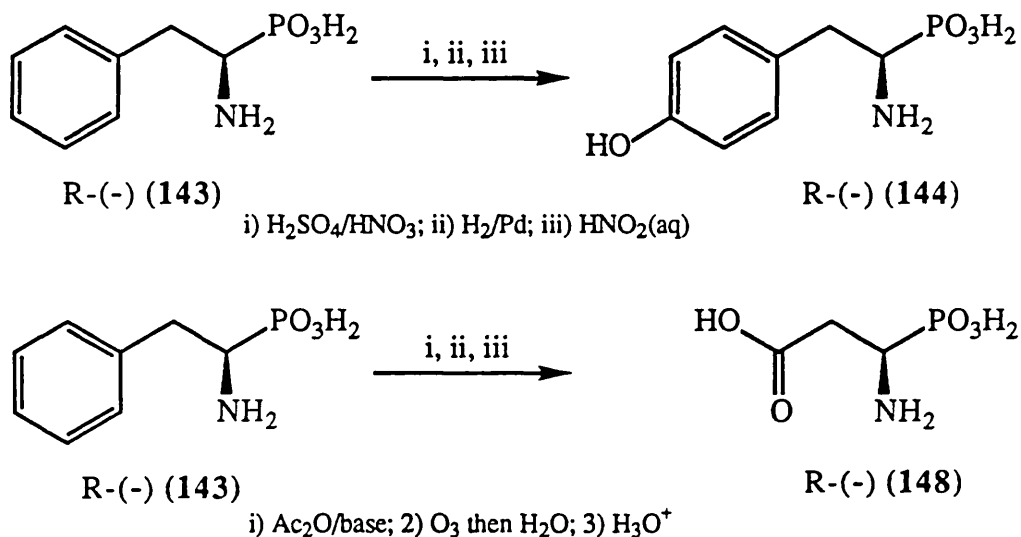
(166) are obtained by treatment of N-(methoxymethyl)arylamine with trialkyl phosphite in the presence of a Lewis acid,¹⁰⁷ or with dialkyl phosphites under mild conditions in the absence of any additive (Scheme 64).¹⁰⁵



Scheme 64

3.3.4 From Other α -Amino Phosphonic Acids.

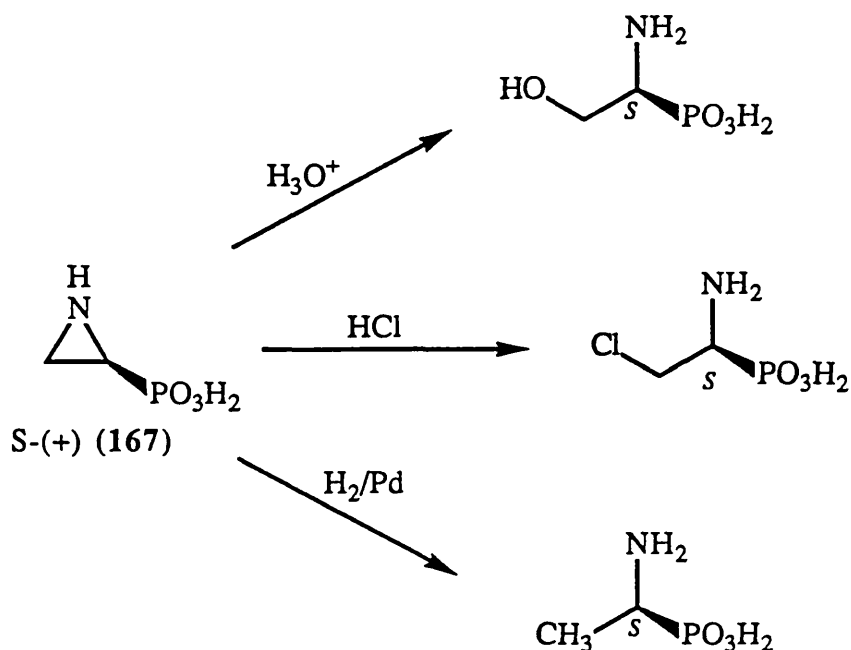
It is difficult to provide a comprehensive overview of this synthetic approach since the subject is so diverse and can potentially include all the relevant functional group manipulations known. We have chosen a selection of those that are of particular significance, either providing efficient and convenient access to compounds that are not easily synthesised through alternative routes, or having good potential for the synthesis of complex, polyfunctional α -aminophosphonates.



Scheme 65

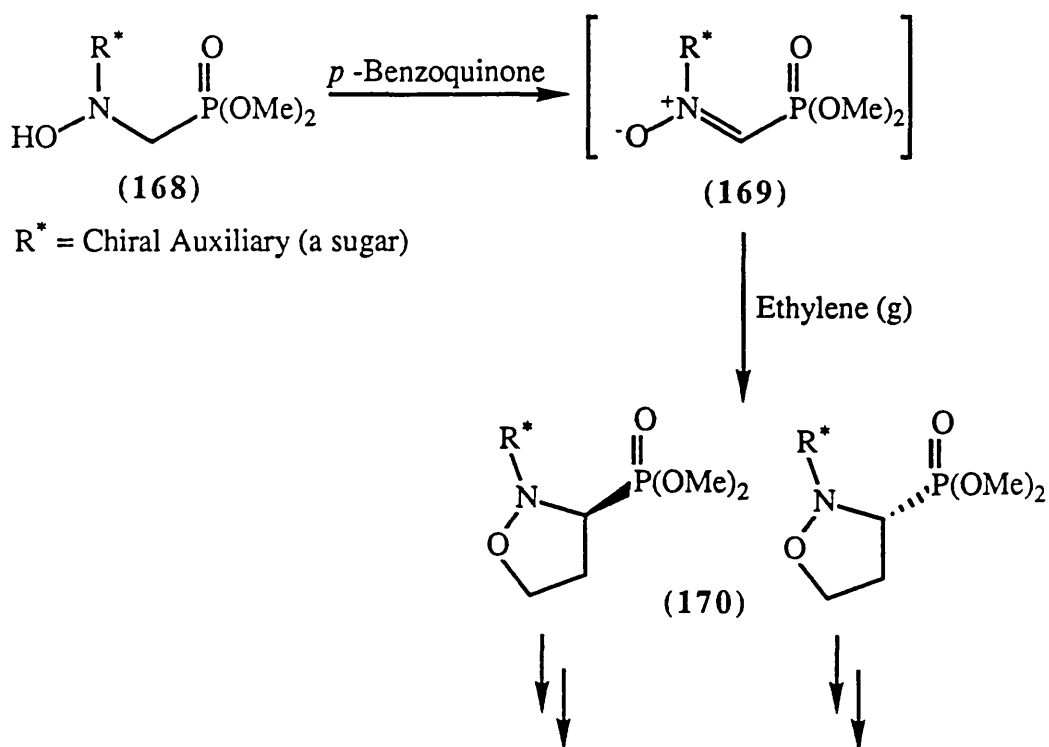
An area in which preparation of new α -amino phosphonic acids by functional group manipulation of the others is particularly useful is where the absolute configuration at the α position cannot be established by X-ray crystallography. For instance, the naturally occurring α -amino phosphonic acid (144), the laevorotatory phosphonic analogue of tyrosine, was shown to have the *R* configuration after the above sequence of reactions starting from the phosphonic analogue of *R*-phenylalanine afforded a laevorotatory compound.¹⁰⁸ Functional group manipulation also provided a route to the phosphonic analogue of *R*-aspartic acid (Scheme 65).¹⁰⁸

Both enantiomers of the chiral aziridine phosphonic acid (**167**) have been prepared and used as starting point for the synthesis of many natural and unnatural α -aminophosphonic acids (Scheme 66).⁹³



Scheme 66

A [3+2] cycloaddition of a nitron (**169**), generated *in situ* from (**168**), to ethylene afforded both diastereomers of (**170**) which were then taken through for the synthesis of homoserine and aspartic acid (Scheme 67).¹⁰⁹



Scheme 67

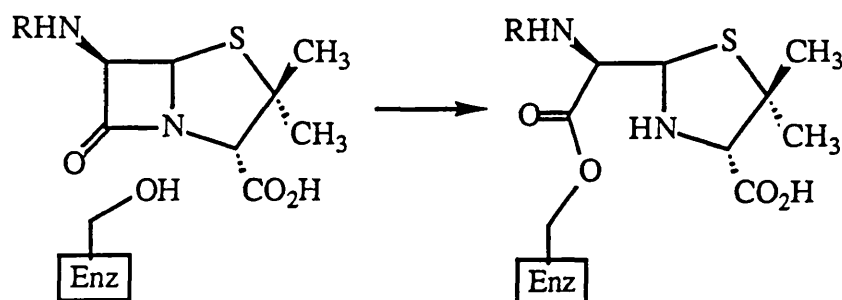
Chapter Four

Synthesis Of 1,2-Azaphosphetidines

4.1 Introduction

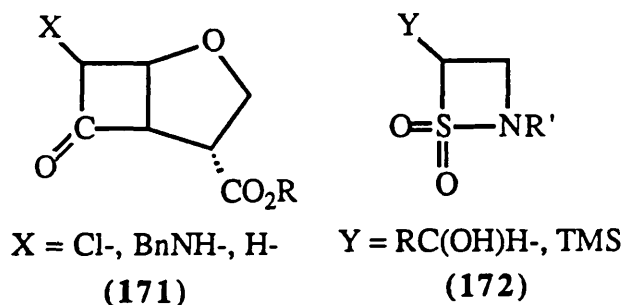
The anti-bacterial action of penicillins and related compounds which is believed to stem solely from presence of the β -lactam ring has been man's most successful weapon against disease to date. This has resulted in the intensive investigation of the β -lactam ring and a diverse range of molecules containing it for many years. The extensive chemical research in this area was originally driven by the need for drugs with a wider spectrum of activity. However the recent discovery of the ability of bacteria to acquire resistance to clinically administered drugs has also spurred scientists to search for newer, more effective substitutes.

Organic chemists have responded to this challenge by preparation of a vast number of synthetic compounds modelled, in the most general sense, on naturally occurring β -lactam containing bactericides. Until recently this endeavour had been solely directed towards synthetic modifications in the periphery of the β -lactam ring. In the past ten years however, attention has also turned to chemical analogues of the β -lactam ring itself.



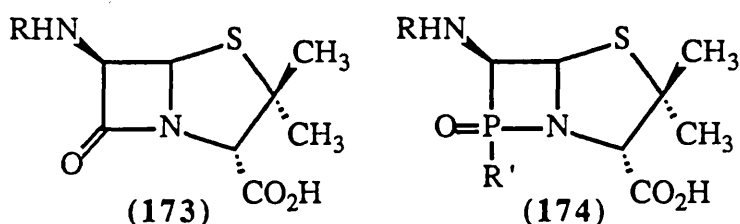
Scheme 68

β -Lactam's biological action is exerted through disabling a peptidase enzyme involved in the assembly of bacterial cell wall.⁸⁴ It is believed that once bound on the enzyme, the β -lactam containing molecule acylates a serine or cysteine residue responsible for the peptidase action (Scheme 68). It is therefore argued that the role of the azetidinone as a capping agent could be mimicked by suitable carbocyclic or heterocyclic rings. Indeed a number of four membered rings, including cyclobutanone (171)^{110,111} and mono-cyclic β -sultam (172),^{112,113} (Scheme 69) has already been synthesised for evaluation of biological activity.



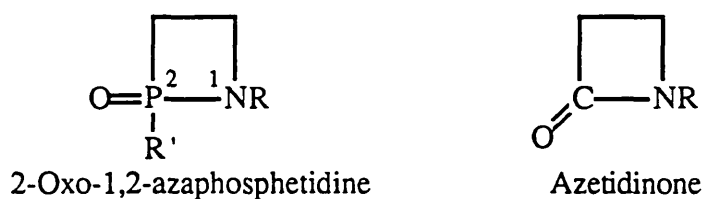
Scheme 69

Our goal has been the synthesis of novel phosphono-penicillin analogues (174) (Scheme 70) which contain a 2-oxo-1,2-azaphosphetidine ring as a direct replacement for the β -lactam (azetidinone) ring. The exertion of bactericidal activity in this ring should result from phosphorylation rather than acylation of the peptidase residue.



Scheme 70

Synthesis of compounds (174), which requires the construction of C-substituted 1,2-azaphosphetidines, represents other challenges and rewards as well. As already discussed in Chapter One, phosphetanes and azaphosphetidines are rarely encountered species and, in particular, no example of a C-substituted or a bicyclic azaphosphetidine is previously reported.

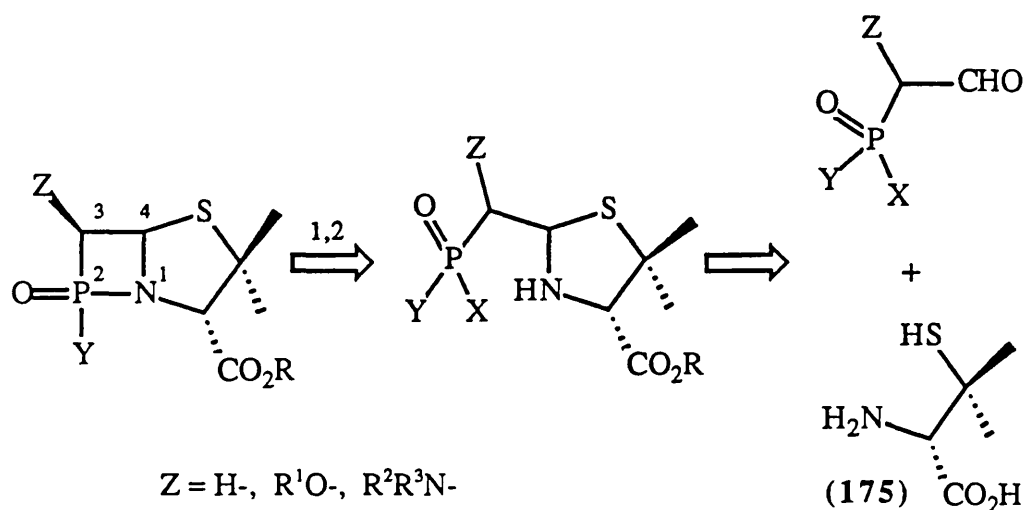


Our approach to the synthesis of 1,2-azaphosphetidines is based on three possible disconnections of this ring. A fourth one, 1,4-disconnection, was not considered to be of imminent usefulness as such a disconnection for the azetidinone ring, which we have considered as a model, is less common.¹¹⁴ In the first part of this chapter, synthesis of precursors for a P-N ring closure and the cyclisation attempts are discussed. Synthetic approaches towards a P-C ring closure are presented in the second part of this chapter and in the third part C-C ring closures are discussed.

4.2 Synthetic Approaches Towards P-N Ring Closure

Our earliest attempted synthesis of phosphopenicillin analogues (**174**) was based on the primary disconnection of the nitrogen-phosphorus bond. Although the analogous disconnection is not very common for the synthesis of β -lactams, it had the advantage of having as the ring closure step a nitrogen-phosphorus bond formation which is generally considered to be easier than the alternative carbon-phosphorus bond formation.

The remaining disconnections are outlined in Scheme 71 and, as can be seen, this route utilises a degradation product of semisynthetic penicillins, (R)-penicillamine, (**175**), to introduce a fixed chiral center into the molecule.

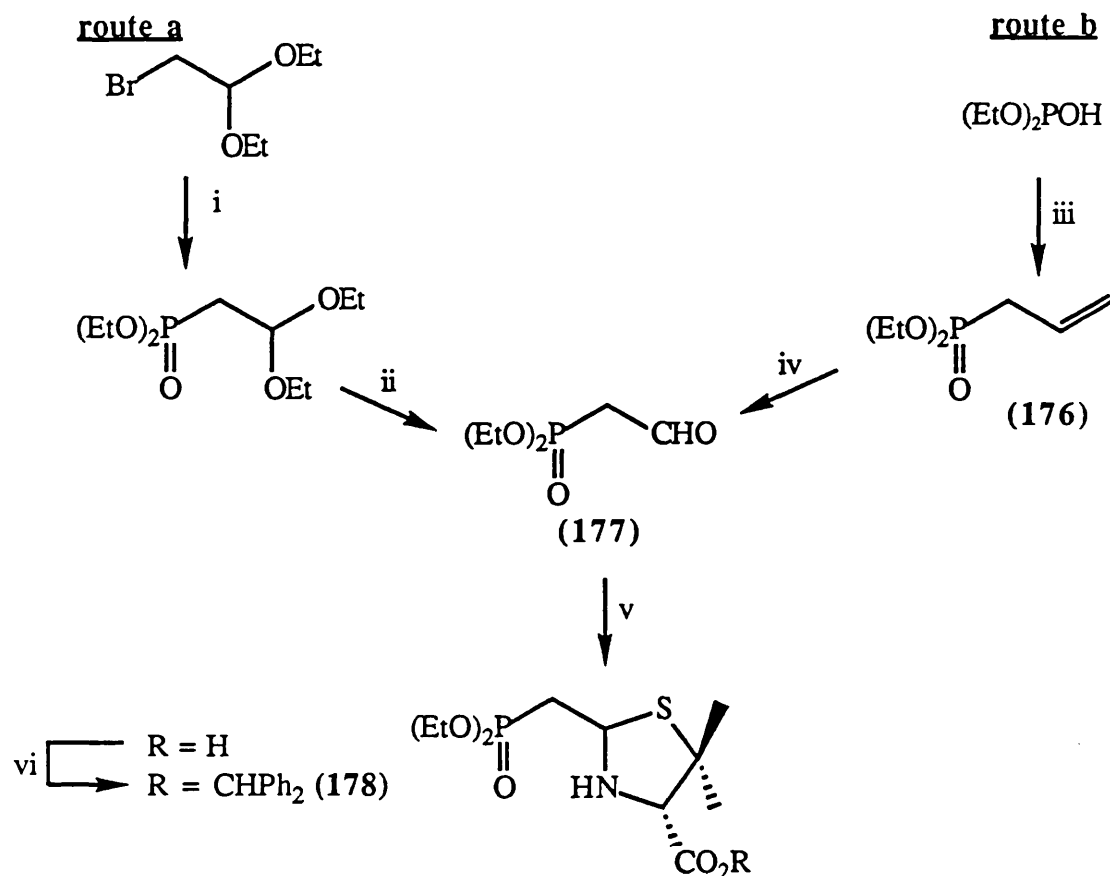


Scheme 71

4.2.1. Synthesis of Cyclisation Precursors

We prepared cyclisation precursors (**178**), with no substituent α to the phosphorus, and (**183**), with an oxy substituent α to the phosphorus, as follows.

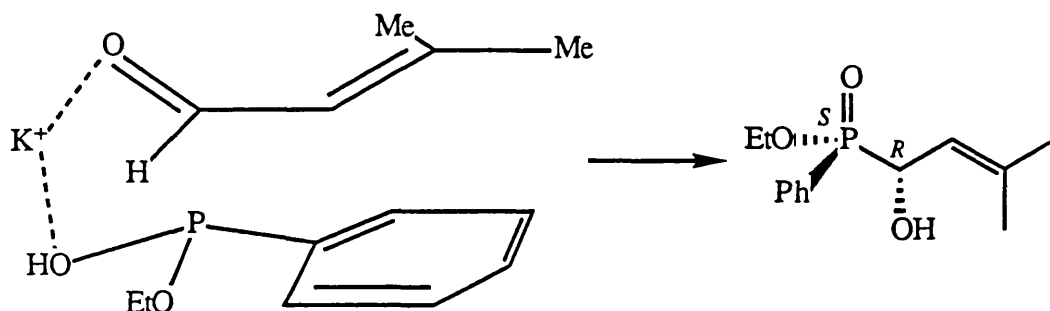
Aldehyde (**177**) is a known compound prepared by route a (Scheme 72); however we opted for an alternative synthesis, route b (Scheme 72) which can be performed on a smaller scale, and is more efficient. Treatment of this aldehyde with (R)-penicillamine followed by esterification with diphenyldiazomethane affords compound (**178**) in good yield as a 4 : 1 ratio of diastereomers which could not be separated by chromatography (Scheme 72).



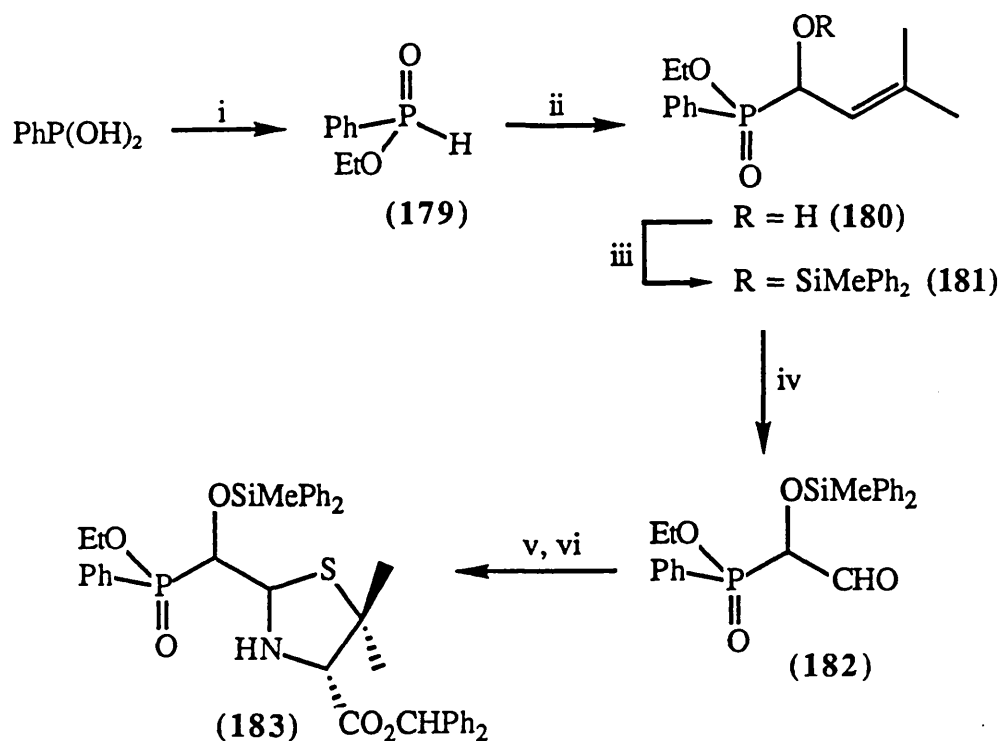
i) $\text{P}(\text{OEt})_3$, Δ ; ii) Conc. aq. HCl ; iii) Na , NH_3 , then allyl bromide; iv) O_3 , -72°C , DCM/MeOH , then Me_2S ; v) (R)-Penicillamine, MeOH ; vi) $\text{Ph}_2\text{C=N}_2$, acetonitrile.

Scheme 72

Phosphonate (180) was prepared as a single diastereomer, the relative stereochemistry of which was not assigned, as outlined in Scheme 74. The origins of this unprecedented diastereoselectivity is not clear but we presume it can be attributed to a preferential stacking of the phenyl group over the double bond of the aldehyde (see Scheme 73) and have therefore tentatively assigned $(S_P, R_C), (R_P, S_C)$ stereochemistry. Compound (183) was prepared by treatment with (R)-penicillamine and esterification.

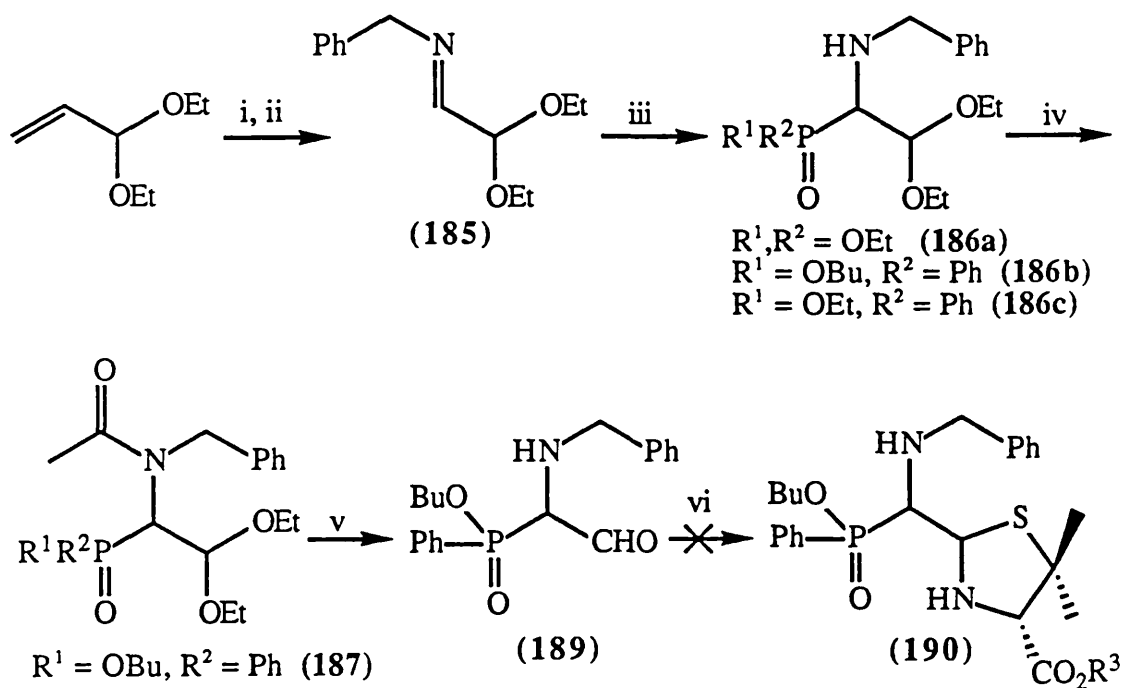


Scheme 73



i) EtOCOCl, Pyridine, CHCl₃; ii) Me₂C=CHCHO, KF; iii) Ph₂MeSiCl, DCM, Et₃N; iv) O₃, -72 °C, DCM/MeOH, then Me₂S; v) (R)-Penicillamine, MeOH; vi) Ph₂C=N₂, acetonitrile.

Scheme 74

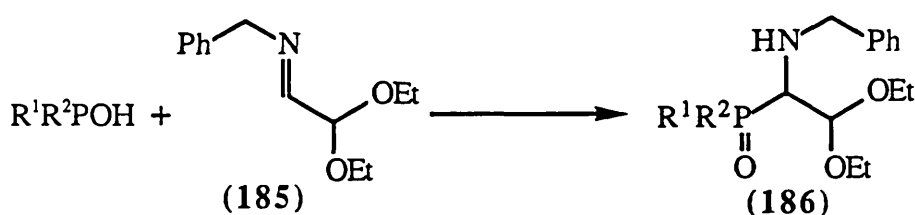


i) O₃, DCM, then Me₂S [to give (184)]; ii) Benzylamine, DCM, K₂CO₃, 4 °C, 15 h; iii) R¹R²POTMS, DCM, 5h, rt; iv) Acetic anhydride, Pyridine, 0 °C, 12 h; v) BBr₃, DCM, -78 °C (inverse addition), then MeOH/K₂CO₃; vi) (R)-Penicillamine, MeOH

Scheme 75

The approach to compound (190), a cyclisation precursor with an amino group at the position α to phosphorus, is outlined in Scheme 75. Imine (185) was prepared in two steps from acrolein diethyl acetal. The thermal addition⁹⁶ of phosphites and the addition of the sodium salt of phosphite (179) to this imine all resulted in complex reactions and the desired products (186) could be isolated only in poor yields (see Section 3.3.2).

This was presumably a result of the delicate nature of the imine and therefore we sought a reaction that proceeded under milder conditions. We found that O-silylation of phosphites prior to the addition to the imine resulted in cleaner reactions and afforded better yields (see Scheme 76). The scope of the addition of silylated phosphites to imines is discussed comprehensively in Chapter Five.

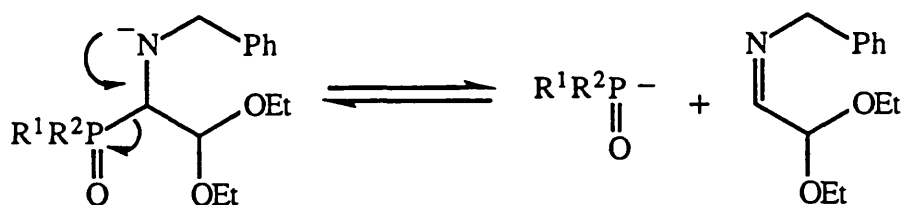


Yields (%) of Addition of Phosphites to Imine (185)

Conditions	Product	(186a)	(186b)	(186c)
		R ¹ = OEt R ² = OEt	R ¹ = O ⁿ Bu R ² = Ph	R ¹ = OEt R ² = Ph
Heat, 90 - 110 °C, 30 min.		55	43	—
TMSCl, Et ₃ N, DCM, 0 °C then add imine, rt, few hours		79	81	83
NaH, THF, 0 °C, then add imine, rt, few hours		—	—	20

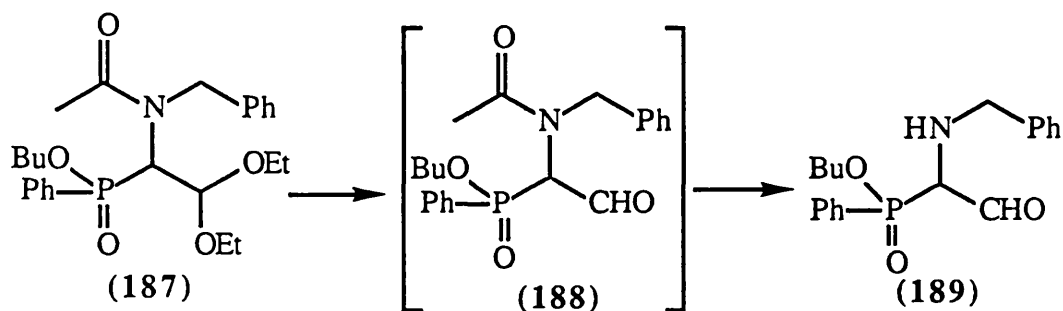
Scheme 76

The next step, hydrolysis of the acetals, proved to be unexpectedly troublesome. Hydrolysis under acidic conditions either gave no aldehyde or resulted in polymeric materials. The aldehyde, if present transiently, could not be trapped with added penicillamine. We suspected the polymeric products to be the result of intermolecular reaction between amine and aldehyde functions that are present in (189) (Scheme 78) and therefore decided to protect the secondary amine in (186) prior to the hydrolysis of the acetal. Although under basic conditions a retro reaction leads to breakup of α -amino phosphonates (Scheme 77) it was possible to protect the secondary amine as an amide (Scheme 75).



Scheme 77

Under all reaction conditions attempted, with the exception of those employing Lewis acid catalysis, hydrolysis of the amide bond in (187) was more facile than hydrolysis of the acetal. With Lewis acid catalysed reactions, analysis of the reaction mixtures prior to hydrolytic work up showed only minor deamidation. In fact after an extensive study, we found that although amide-aldehyde (188) could not be isolated, a methanolic solution of amine-aldehyde (189) could be obtained after a complex work-up procedure. Thus amide-acetal (187) was delivered in the cold to an excess of BBr_3 in DCM. At the end of the reaction, this solution was added slowly to a vigorously stirred mixture of potassium carbonate in dry methanol which transforms the excess of BBr_3 to B(OMe)_3 which is volatile and KBr which is filtered off.



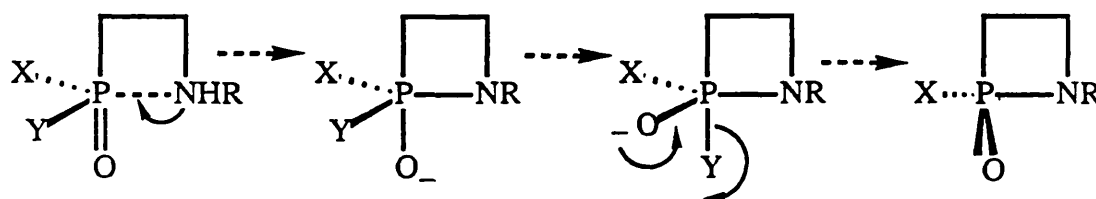
Scheme 78

Unfortunately, treatment of a methanolic solution of (189) with penicillamine did not afford any adduct (190). At this stage, our attempts to cyclise (183) and (178) were also unpromising and we decided to halt the synthetic work towards (190).

4.2.2. Cyclisation Attempts

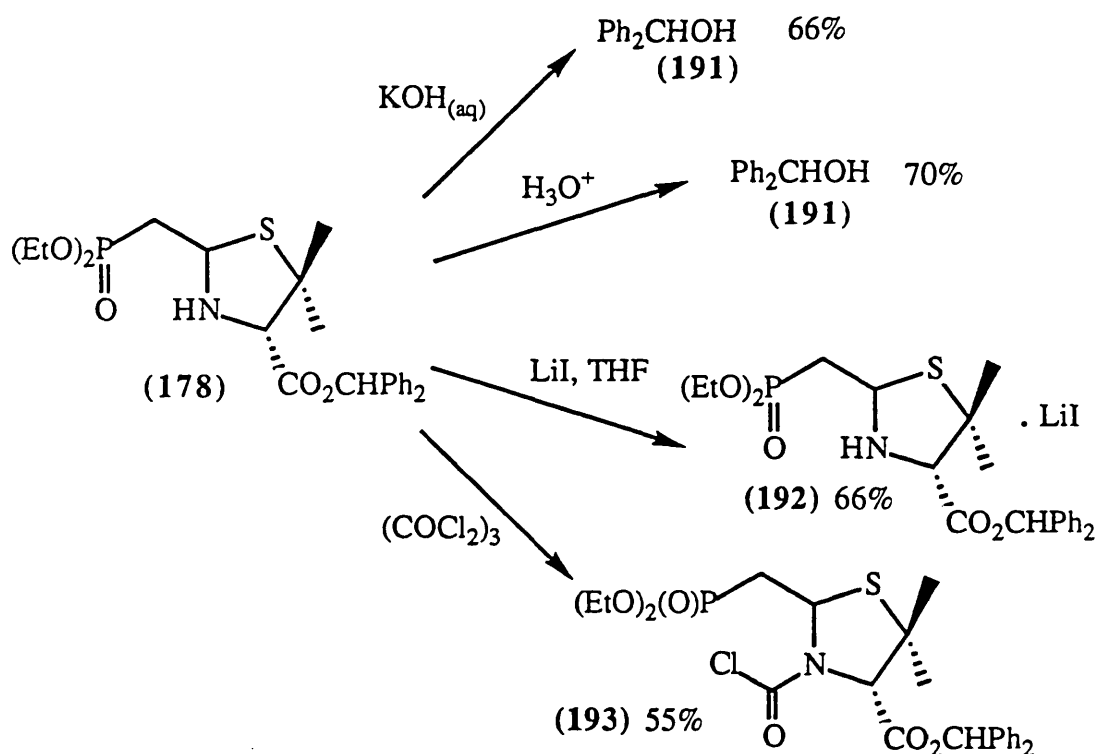
Formation of four-membered rings by nucleophilic displacement ring closures is uncommon. In fact, as we saw in Chapter One, such a cyclisation to form phosphetanes has not yet been observed which further highlights the challenges involved in this synthetic approach. The empirical rules for nucleophilic cyclisations, Baldwin's Rules,¹¹⁵ state that carbocyclic four membered rings are disfavoured as the overlap between the filled orbital of the nucleophile and the empty σ^* orbital at the electrophilic centre is restricted owing to the geometry of the transition state. Nevertheless, such cyclisations do happen and we hoped the fact that the ring to be formed contained a phosphorus atom

would be in our favour. For an intramolecular electrophilic attack at a $\sigma^4\lambda^5$ phosphorus, the angle of approach can be more acute than that on a carbon. This is a result of the ability of phosphorus, to expand its co-ordination number by utilising accessible *d* orbitals to five (trigonal-bipyramidal) and six (octahedral). Furthermore, carbon-phosphorus bonds are longer than carbon-carbon bonds and hence the transition state is not as strained as a carbocyclic analogue (Scheme 79). On the other hand, as a negative point, an oxygen-phosphorus bond was to be broken and a weaker nitrogen-phosphorus bond formed instead, which strongly contributes to the enthalpy of the reaction.



Scheme 79

Formation of the naked anion at nitrogen, by treatment of (178) with sodium hydride in dimethylformamide and LDA in THF did not result in any cyclisation and in both cases the starting material was recovered.



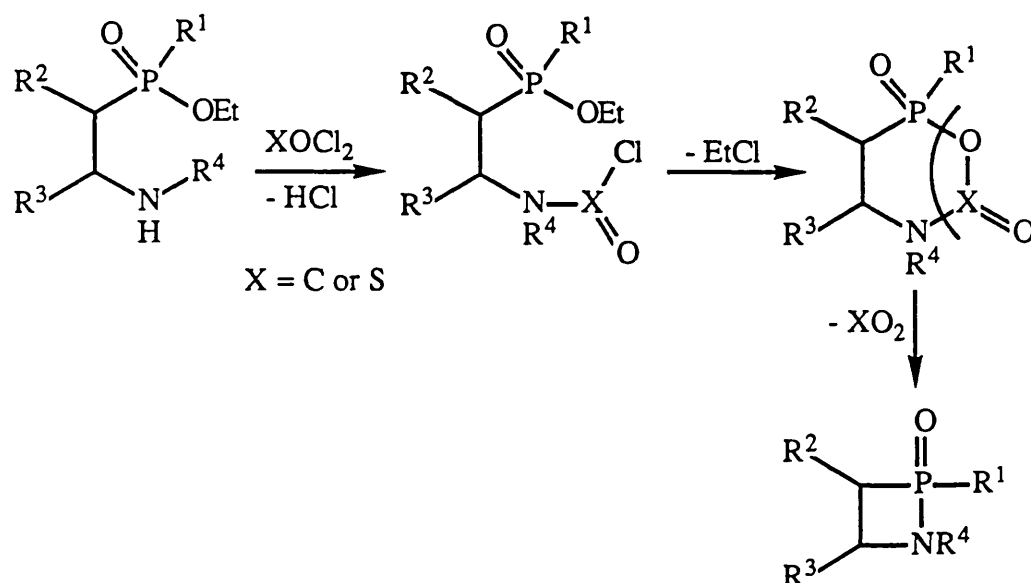
Scheme 80

We also attempted to replace the OEt group with better leaving groups but for both (178) and (183) treatment with phosphorus pentachloride or phosphorus oxychloride did not afford any identifiable product. From acid or base hydrolysis of

(178), benzhydrol (191) was the only identifiable product isolated. Mono de-esterification of dialkyl phosphonates with LiI has been reported¹¹⁶ but treatment of (178) with LiI afforded (192), a curious 1:1 complex of (178) and LiI, only (Scheme 80).

Thermal elimination of ethanol from (178) and (183) was not successful. Both compounds are stable in refluxing toluene for 48 hours though (183) decomposed to unidentifiable material after a few hours reflux in xylene. Compound (178) remained unchanged after reflux in toluene in the presence of tosic acid but in toluene at room temperature both (178) and (183) decomposed rapidly with release of hydrogen sulphide in the presence of Lewis acid (BF₃ etherate).

One solution that we hoped would solve the problems already mentioned was to achieve ring closures *via* extrusion of thermodynamically stable units such as CO₂ or SO₂ (Scheme 81). Although this approach has already been used for formation of non-cyclic amides, no example of cyclic amide formation is yet reported. Elimination of such thermodynamically stable units helps the energetics of N-P bond formation versus O-P bond cleavage which was mentioned before. It would also be an irreversible process.

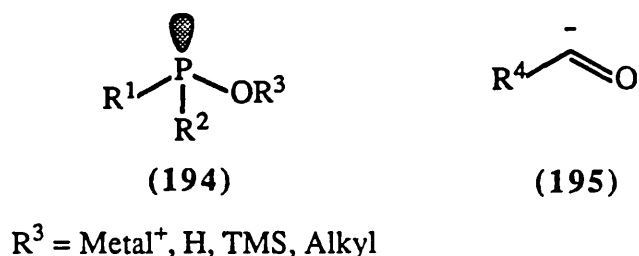


Scheme 81

Treatment of (178) with triphosgene did afford the carbamoyl chloride (193) (Scheme 80) but all our attempts at the elimination of EtCl failed. Treatment of (178) with thionyl chloride gave the starting material back after hydrolytic work-up.

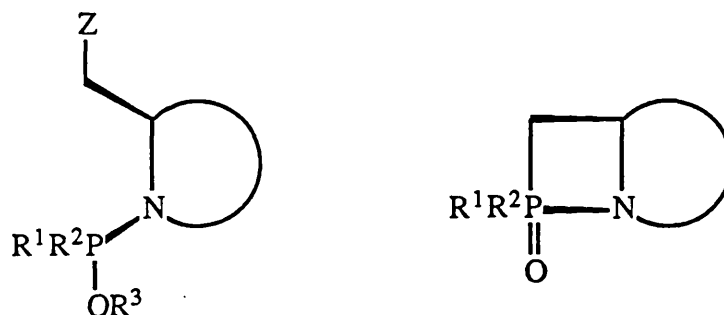
4.3 Synthetic Approaches Towards Precursors for P-C Ring Closure

In the synthetic chemistry of azetidiones, a 1,2-disconnection approach (note that owing to ring numbering system this corresponds to a 2,3-disconnection in azaphosphetidines) is rare. However, the equivalent disconnection for azaphosphetidines is plausible. This dissimilarity stems from the existence of nucleophilic synthons (such as (194)) for phosphonyl group in organophosphorus chemistry whereas a corresponding carbon synthon, an umpolung carbonyl (195), is less common (Scheme 82).



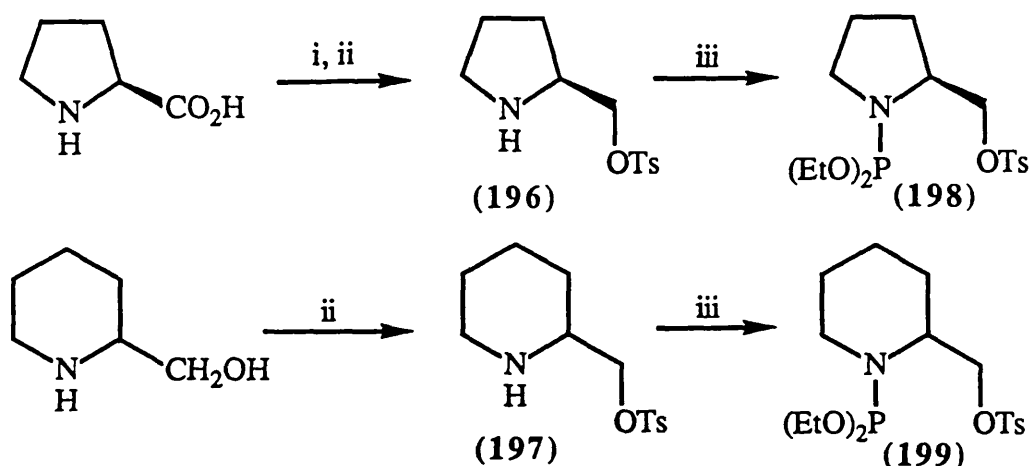
Scheme 82

The first reported synthesis of a 1,2-azaphosphetidine employed a ring closure corresponding to a primary 2,3-disconnection (Scheme 12, Chapter One) and we studied the extension of such ring closures to the formation of bicyclic systems (Scheme 83). It should be noted that for such intramolecular Arbuzov reactions, the *cis* relationship between ring substituents is essential.



Scheme 83

Cyclisation precursors (198) and (199) were prepared as outlined in Scheme 84 for an initial study. We expected that inversion at nitrogen would allow the phosphorus group to flip between both faces of the five-membered ring and, although under equilibrium conditions the majority of molecules would adopt *trans* configuration of the two ring substituents, there would be enough *cis* molecules to sustain a ring closure reaction. In the event, no cyclisation resulted under various conditions (heat in toluene, heat in benzene with KBr and 18-crown-6, heat neat or impregnated on silica).

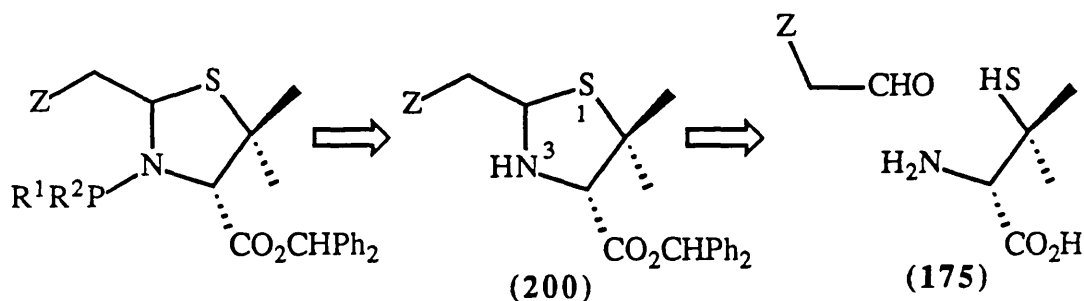


i) LiAlH_4 , THF, reflux; ii) Tosyl Chloride, Et_3N , DCM, room temperature;
iii) $(\text{EtO})_2\text{PCl}$, Et_3N , toluene

Scheme 84

Furthermore, we did not observe any evidence in favour of a *cis-trans* isomeric mixture by NMR, at least at ambient temperatures. The phosphorus signal of (198) is a singlet and similarly the proton NMR points to the lack of isomerism. The inversion may be too fast to be observed on the NMR time scale and therefore it was not clear if the lack of cyclisation could be attributed to the rigid *trans* isomerism of the two ring substituents.

Although these initial model studies were unpromising, in order to investigate systems that are closer to our synthetic targets we proceeded to prepare compounds of type (200), where Z is a good leaving group. We have already seen that an efficient construction of the thiazolidine ring can be achieved by treatment of a suitable aldehyde with (R)-penicillamine (175) (Scheme 85).

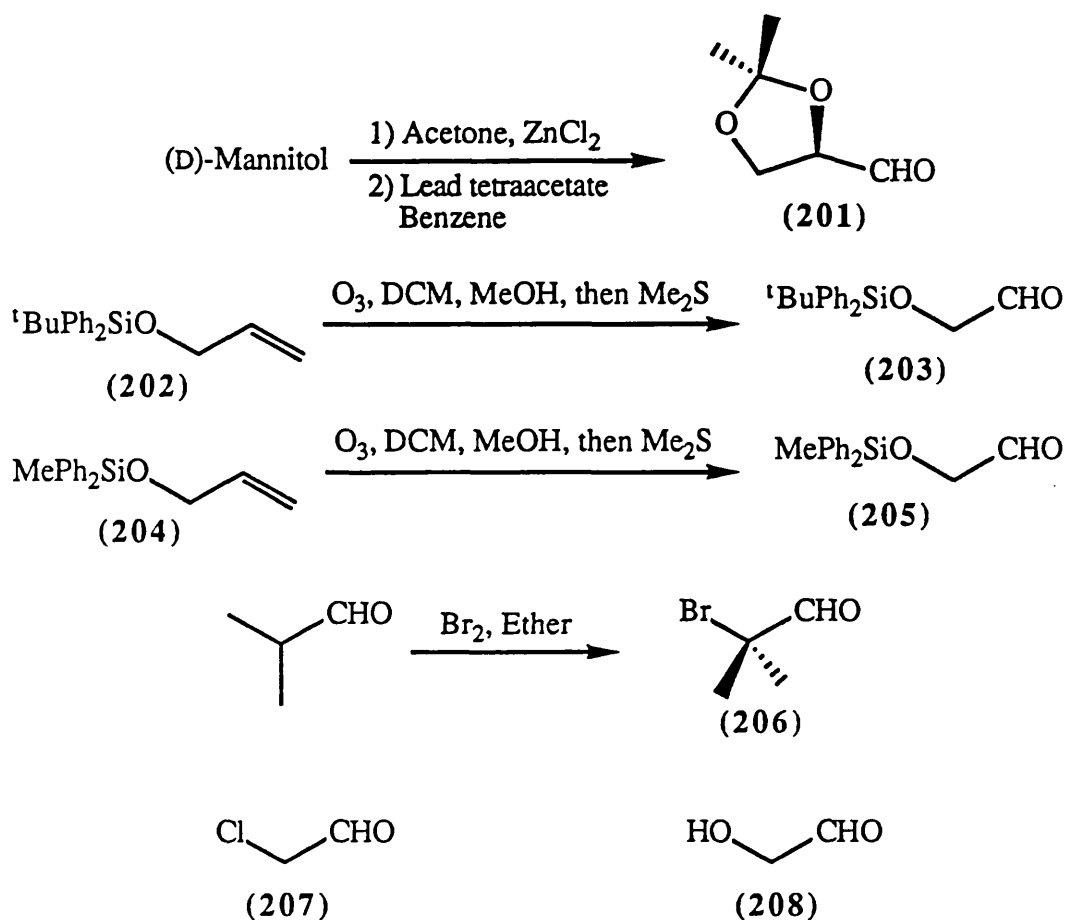


Scheme 85

A selection of commercially and synthetically available aldehydes (Scheme 86) were used and thiazolidines were isolated as acids or, after esterification with diphenyldiazomethane, as benzhydryl esters (Scheme 87).

Our earliest studies showed that direct treatment of (175) with aldehydes with a good leaving group, Z, at the α position results in a complex reaction and does not afford

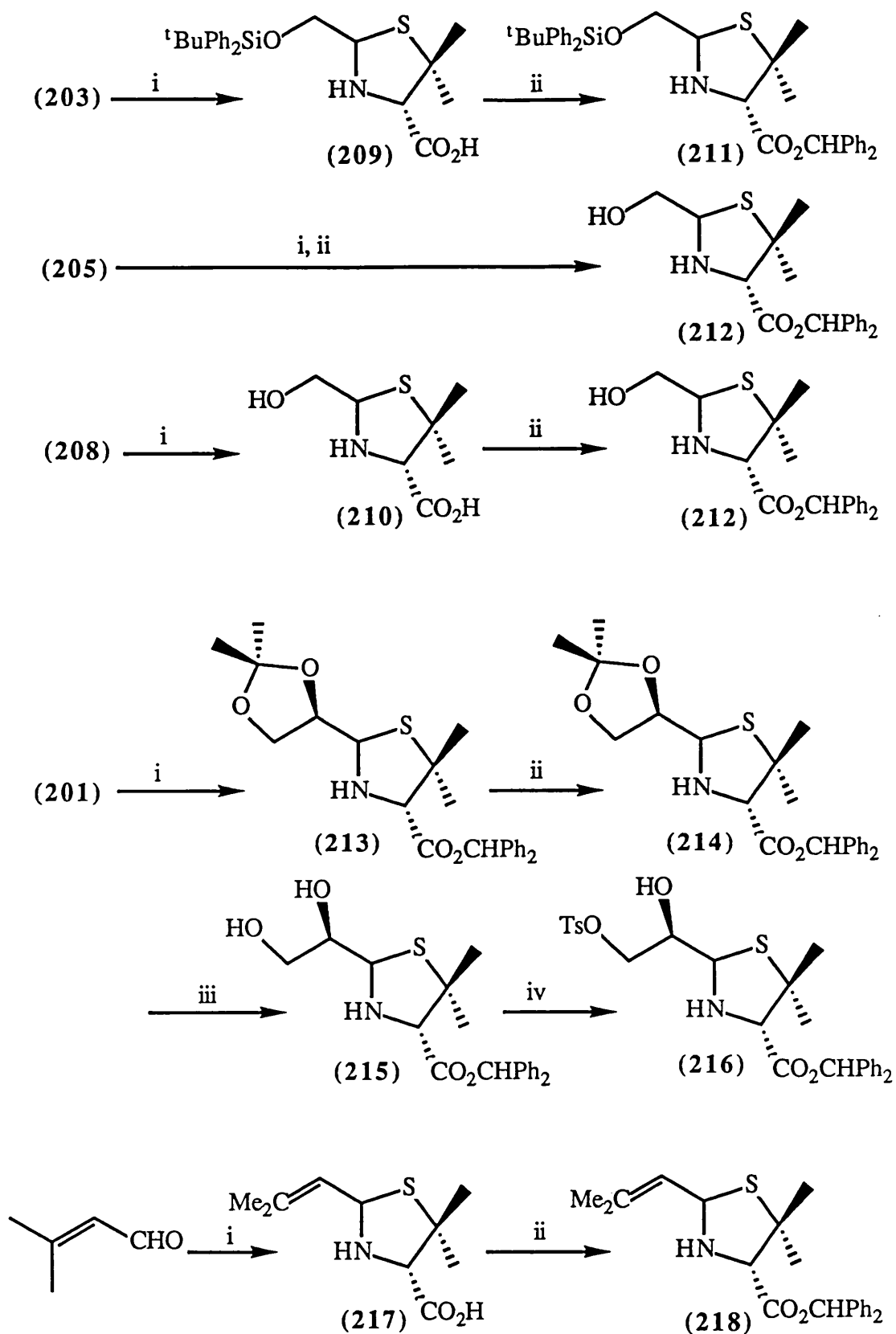
thiazolidines. This was not helped by introduction of steric hindrance at the α position to suppress reactivity of this center and hence both aldehydes (206) and (207) failed to give thiazolidines. Therefore, we pursued a study of the synthesis of (200) with Z being a function that, although not a good leaving group itself, can be converted to one synthetically. One obvious choice is the hydroxyl group.



Scheme 86

Aldehyde (203) was condensed with (175) to afford the thiazolidine (209). Removal of the bulky silyl protection could not be achieved even under forcing conditions (hydrofluoric acid or TBAF at 67 °C). We attributed this stability to the bulkiness of the silicon substituents and indeed when aldehyde (205), in which a methyl group has replaced tBu , was added to a methanolic solution of (175), alcohol (210) was the sole product after esterification. Presumably the acidity of penicillamine or the thiazolidine product is enough to remove this acid labile group. This compound could also be prepared directly from glycolaldehyde (208) (Scheme 87).

Standard synthetic methods were also used for the synthesis of diol (215) and for a non-hydroxyl containing side chain we synthesised alkene (218) (Scheme 87).



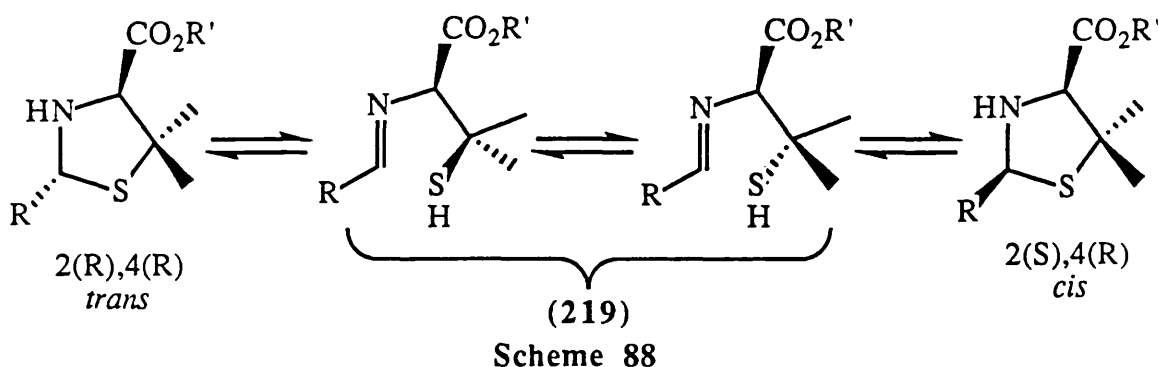
i) (R)-Penicillamine, MeOH, 24 hours; ii) $\text{Ph}_2\text{C}=\text{N}_2$, acetone; iii) 2M aq HCl in acetonitrile 1:9 v/v; iv) 1.1 equivalent tosyl chloride (freshly recrystallised), pyridine, DCM

Scheme 87

During these synthetic studies we also made interesting observations regarding the configurational lability of the synthesised thiazolidines at the C-2 position.

All isolated acids were shown to be single diastereomers by NMR; however, since these are obtained after crystallisation and only in moderate yields, it is not possible to comment on the diastereoselection. Furthermore the stereochemical purity of the acids does not alter in solution with time, as confirmed by proton and occasionally carbon-13 NMR.

The esters (211) and (218) were obtained in around 80-90% *d.e.* The NMR of solutions of these compounds showed that this diastereomeric ratio does not alter with time. However, the NMR of the freshly prepared acetonide (214) was found to have an excess of one diastereomer which slowly equilibrated to afford a diastereomeric mixture of near 1:1 ratio. The progression of this conversion for acetonide (214) in chloroform solution is shown in Diagram 1 (See Appendix 1). A similar but slower process is observed for the diol (215) (Diagram 2, Appendix 1); however, for this compound the anomerisation is reversible. After its synthesis from a diastereomeric mixture of (214), diol (215) is crystallised into a single diastereomer from chloroform/petroleum ether solution. If this diol is redissolved in chloroform, it equilibrates slowly with a second diastereomer; however, slow crystallisation by addition of petroleum ether gave back the original single diastereomeric ester. We attribute these observations to configurational lability at the thiazolidine C-2 position. The chiral center at the C-4 position of thiazolidines is fixed since single enantiomeric penicillamine was used for construction of this ring (Scheme 88).



By matching the NMR signals, we have assigned similar configurations to the major diastereomers of (211) and (218) and the starting diastereomers of (214) and (215) (see Table 1).

Comparison of the diastereomers of compound (200)^a

Compound	NMR Signal of the β -Me (ppm) ^b		NMR Signal of the α -Me (ppm) ^b	
	Major diastereomer	Minor diastereomer	Major diastereomer	Minor diastereomer
(211)	1.65	Not Seen	1.12	Not Seen
(212)	1.65	1.61	1.01	1.03
(214) ^c	1.64	1.60	1.10	1.04
(215) ^c	1.65	1.61	1.01	1.03
(216) ^d	1.63	1.57	0.98	0.98
(218)	1.64	Not Seen	1.04	Not Seen

^aReferenced to tetramethylsilane signal at 0.00 ppm. ^bIn CDCl₃. ^cMajor diastereomer is the starting diastereomer. ^dThe two diastereomers are in equal ratios.

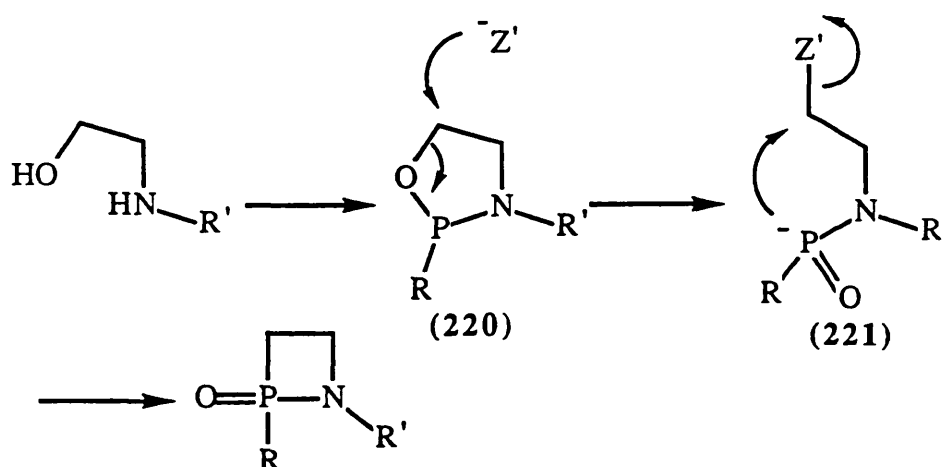
Table 1

N. O. e. experiments involving irradiation of the two ring protons and the methyl groups failed to unequivocally solve the configuration of the compounds and therefore the absolute stereochemistry at C-2 could not be assigned for any of diastereomers.

As far as we know, such diastereoselective ring closures have not been reported. Cyclisation of intermediate (219) can afford both the *cis* and *trans* diastereomers. If the cyclisation of (219) is compared to intermolecular nucleophilic addition to chiral imines one would expect diastereoselection in favour of the [2(*S*),4(*R*)], the *cis* isomer, on kinetic grounds, according to observations made by Harada⁹⁸ and allowing for the priority rules. Thermodynamically, however, the *trans* diastereomer is preferred.

Treatment of alcohol (212) with mesyl chloride and tosyl chloride in presence of base, appeared to form the O- derivatives as suggested by NMR of the crude reaction mixture. They were stable only in solution at 0 °C and we were unable to isolate them. Similarly attempted replacement of the hydroxyl group with bromine or iodine failed. On the other hand mono tosylation of the primary hydroxyl group of (215) gave the stable product (216); if a large excess of tosyl chloride was added in order to tosylate the other hydroxyl, only base line material was observed by tlc analysis.

Since access to compounds of type (200) with Z being a good leaving group that would suit our synthetic purposes was proving difficult it was decided try a close alternative in which Z' is a good nucleophile/leaving group and is used for *in situ* generation of cyclisation precursor (221) from a 1,3,2-oxazaphospholidine (220) (Scheme 89).



Scheme 89

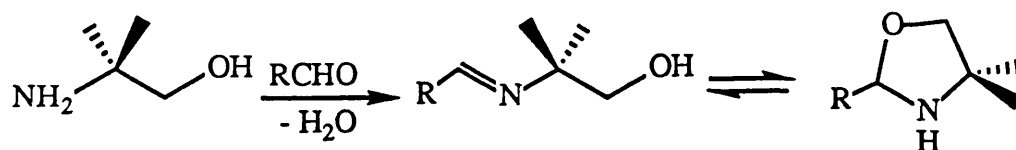
1,3,2-Oxazaphospholidines belong to a rare class of fully saturated heterocycles in which three heteroatoms are contiguous. Thermodynamic instability of these ring systems results from strong electron repulsion between *p* orbitals on the heteroatoms. With variable ease, all such ring systems are prone to ring fragmentation and in some cases, recombination to give thermodynamically more stable rings. We therefore hoped to see thermal rearrangements, without the help of an external nucleophile, as well.

Examples of rearrangements involving this fascinating class of heterocycles, which is not restricted to the realm of organophosphorus chemistry, include that of 1,2,3-trioxolane to 1,2,4-trioxolane during ozonolysis reaction as well as the rearrangement mentioned in Chapter One, of a dioxaphospholidine (10) to oxaphosphetane (11) (Scheme 4, Chapter One).

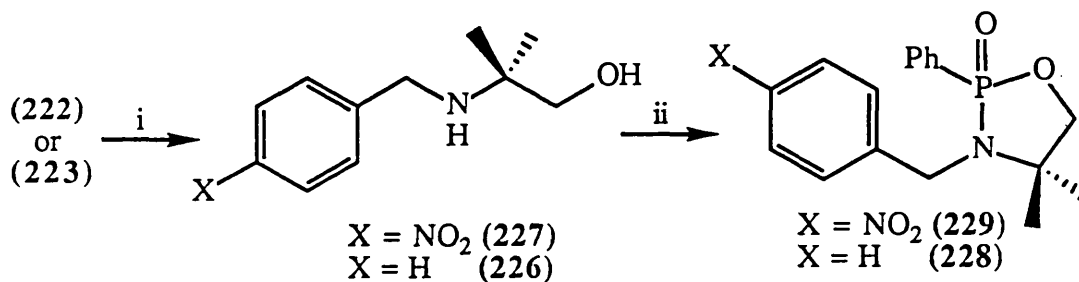
Oxazaphospholidines are rare species and their synthesis has not yet been explored. Our preliminary efforts in this area, which we could not pursue further owing to lack of time, show that these species are highly prone to oxidation and difficult to isolate in the non-oxidised form. Amine-alcohols (226) and (227) were prepared as outlined (Scheme 90). The intermediate imine-alcohols exist in equilibrium with the closed oxazolidine form. The position of this equilibrium depends on the electronic nature of aromatic ring and as expected the ratio of oxazolidine to imine decreases with electron release into the aromatic ring. With acetaldehyde, only the oxazolidine form was observed.

When (226) and (227) were treated with one equivalent of dichlorophenyl phosphine and base under argon, analysis of the reaction mixture at different intervals showed that no tri-coordinated phosphorus species, apart from starting material, was present. Instead the major phosphorus containing products were the oxidised products

(228) and (229) which are isolated at the end of reaction. Structure of (229) was confirmed by X-ray crystallography (Appendix 3).



	R	Imine : Oxazolidine
(222)	4-(O ₂ N)C ₆ H ₄	4 : 1
(223)	C ₆ H ₅	2 : 1
(224)	4-(MeO)C ₆ H ₄	1 : 1
(225)	CH ₃	Oxazolidine only



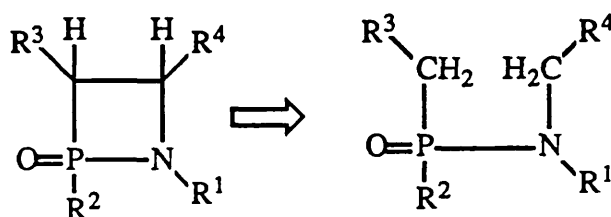
i) NaBH₄, MeOH; ii) PhPCl₂, Et₃N, Benzene

Scheme 90

4.4 Synthesis of Azaphosphetidines via C-C Ring Closures

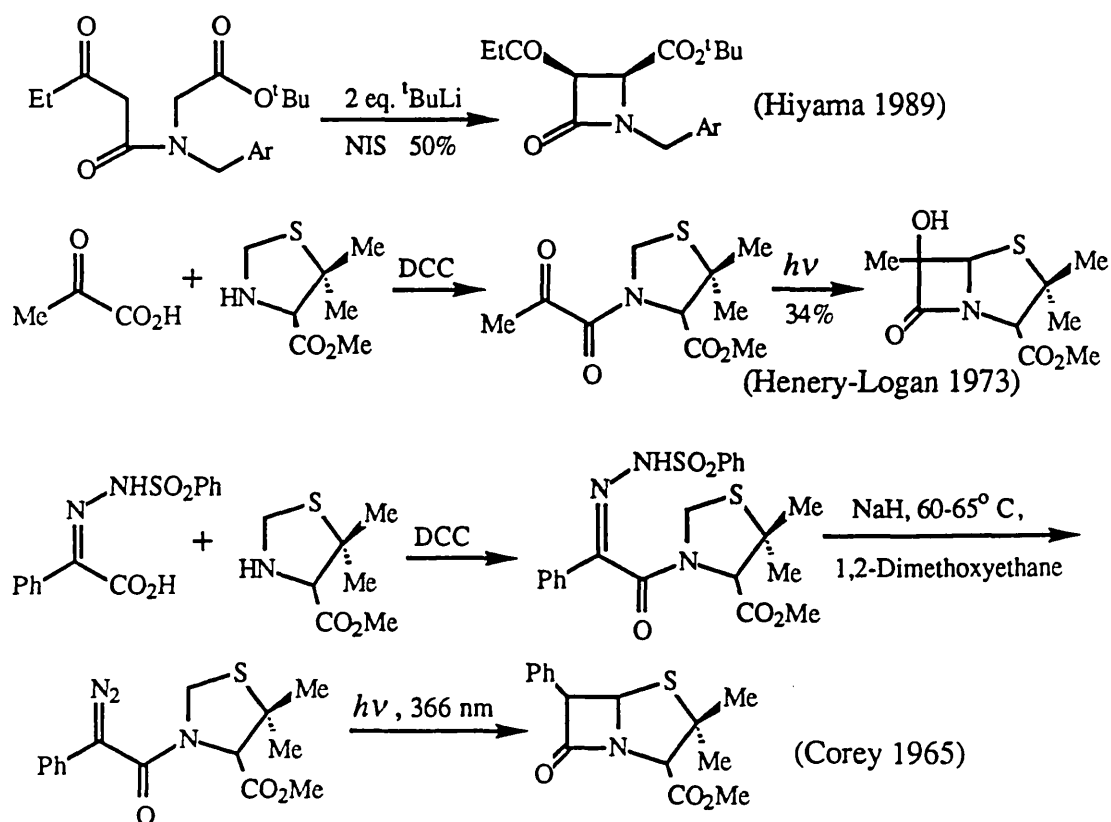
4.4.1 Introduction

The third disconnection of the 1,2-azaphosphetidine ring differs from the previous ones as in the cyclisation step a carbon-carbon rather than a phosphorus-carbon or a phosphorus-nitrogen bond is formed (Scheme 91). Therefore, ring closures that are based on this disconnection rely on methodologies that may not be specific to organophosphorus chemistry. However, one expects that a successful approach would take the presence of phosphorus functionality into account, and ideally take advantage of it.



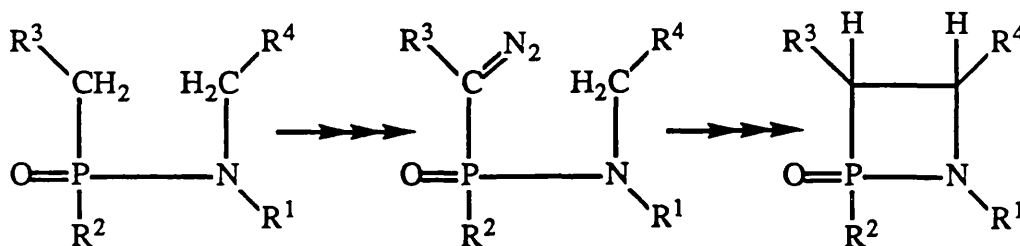
Scheme 91

The formation of the azetidiones by such ring closures is preceded; oxidative coupling,¹¹⁷ a Norrish type II reaction,¹¹⁸ and C-H insertion reaction of carbenes¹¹⁹ have all been used (Scheme 92).



Scheme 92

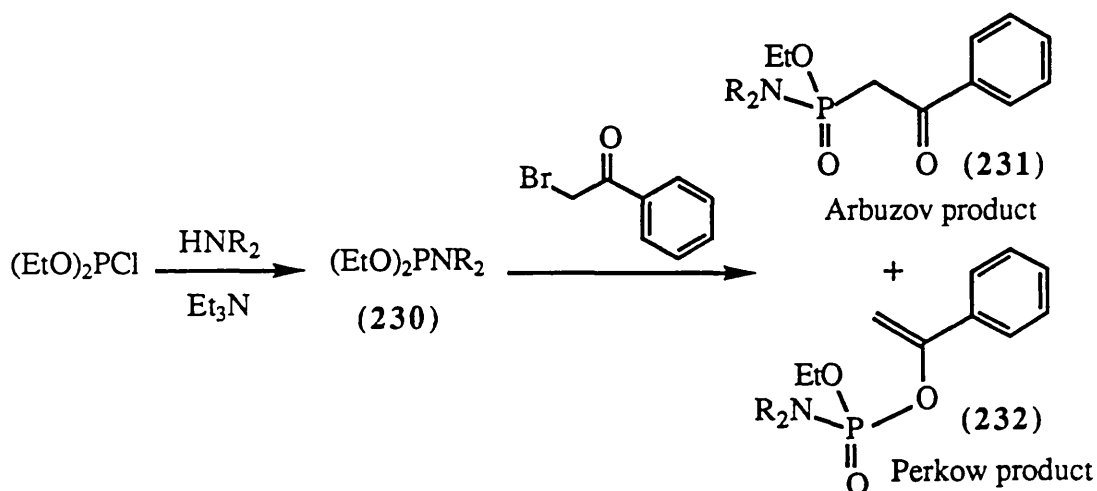
Although we considered each of these routes, our main effort was concentrated on the carbene C-H insertion route (Scheme 93). In Chapter Two, the synthetic chemistry of α -diazo phosphonate and α -diazo phosphinates and their carbon-carbon bond forming reactions was reviewed.



Scheme 93

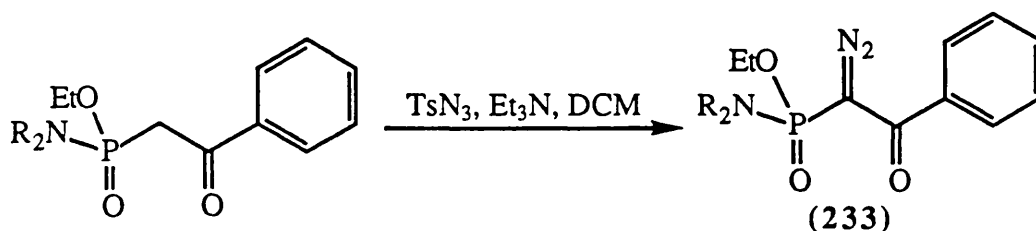
4.4.2 Synthesis of Phosphonamidates and α -Diazo Phosphonamidates

We found that 2-oxo-1-diazoethylphosphonamidates, such as (233) can be efficiently assembled in a three step synthesis (Scheme 94 and 95). Carbon-phosphorus bond formation is achieved through an Arbuzov reaction of the diethyl phosphoramidite (230) itself obtained from amidation of diethyl phosphorochloridate. Although the Arbuzov reaction is well known for formation of phosphonates and phosphinates, synthesis of phosphonamidates by this reaction had not been systematically studied prior to our work.

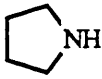
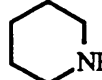
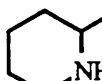
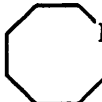
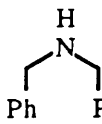
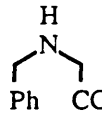
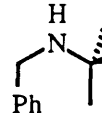
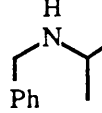
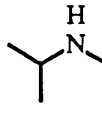
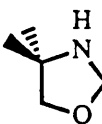


Scheme 94

Diazotisation of the active methylene group of compound (231) then afforded diazo phosphonamidate (233) (Chapter Two and Scheme 95).



Scheme 95

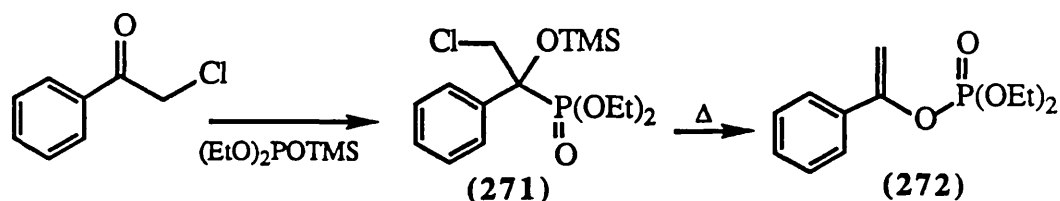
	R^1R^2NH	$R^1R^2N-P(OEt)_2$	$R^1R^2N-P(OEt)(O)CH_2C(=O)Ph$	$R^1R^2N-P(OEt)(O)OCH=C(Ph)CH_2$	$R^1R^2N-P(OEt)(O)N_2C(=O)Ph$
1		(234)	(244) ^a 20%	(254) ^a 26%	(261) 75%
2		(235)	(245) 24%	(255) 20%	(262) 75%
3		(236)	(246) ^b 22%	(256) 20%	(263) ^b 80%
4		(237)	(247) 50%	(257) 14%	(264) 75%
5		(238)	(248) 53%	— 0%	(265) 100%
6		(239)	(249) 50%	— 0%	—
7		(240)	(250) 24%	— 0%	(266) 100%
8		(241)	(251) 50%	(258) 5%	(267) 87%
9		(242)	(252) 67%	(259) 2%	(268) 98%
10		(243)	(253) ^b 36%	(260) ^c 5%	(269) + (270) 96%

^a 4-Bromophenacyl bromide was used. ^b As diastereomeric mixture. ^c As the diethylphosphonate.

Table 2

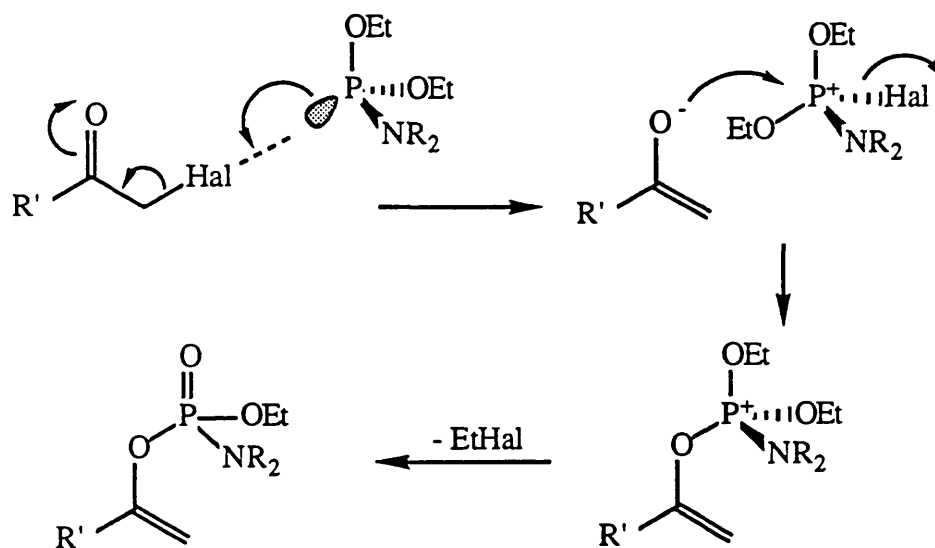
Formation of diethyl phosphoroamidites (234)-(243) proceeded smoothly in near quantitative yield (based on isolated triethylammonium hydrochloride and checked by ³¹P NMR). These may be isolated though for most cases, we used them direct. The yields of the second step are modest (Table 2) mainly due to the presence of a second,

unwanted product resulting from a Perkow reaction (Scheme 94). It is known that Arbuzov and Perkow products are commonly formed together in such reactions, though the factors which decrease the yield of one in favour of the other are not yet fully understood.



Scheme 96

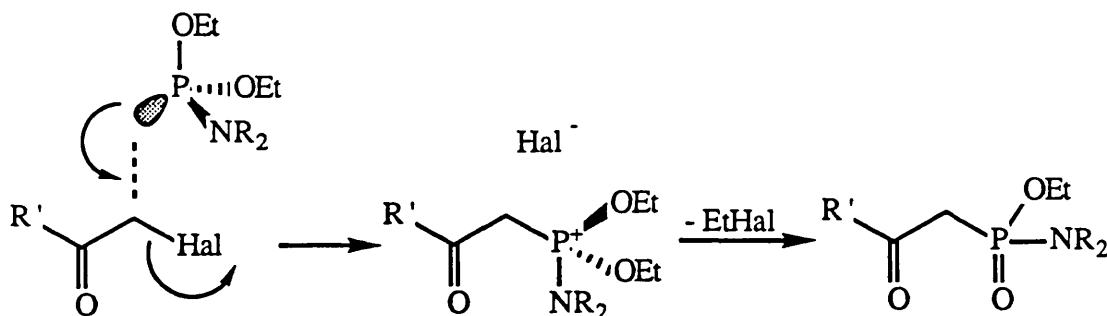
Mechanism of the Perkow reaction has been the subject of much study. Sekine has suggested that for addition of silylated phosphites at least, the Perkow product results from an initial attack of phosphorus nucleophile on the carbonyl followed by a 1,2-phosphonyl migration.¹²⁰ Thus intermediate (271) was prepared by independent synthesis and was shown to rearrange thermally to afford Perkow product (272) (Scheme 96). An alternative mechanism, which is not particular to silylated phosphites has also been suggested in which halogen abstraction is followed by combination of the enolate ion and the phosphonium cation (Scheme 97).¹²¹



Scheme 97

Mechanism for formation of the Arbuzov product is shown in Scheme 98.

We observed a trend based on the isolated yields of the two products. Analysis of crude reaction mixtures by $^{31}\text{P}\{\text{H}\}$ NMR, which is used in other parts of this thesis, could not be used for quantitative comparisons as the two product structures vary considerably and the relative concentration of the compounds do not correlate to the strength of the signal under irradiation.



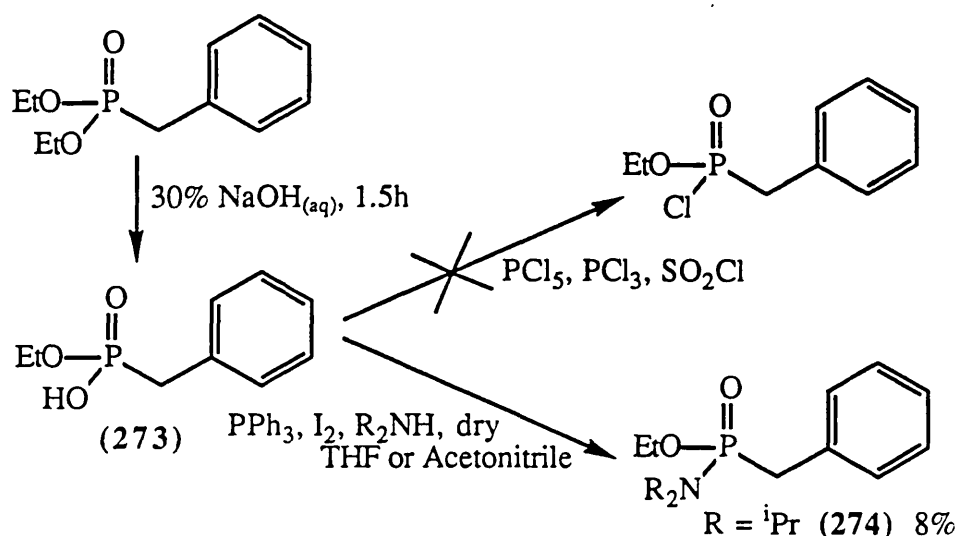
Scheme 98

As can be seen from Table 2, the ratio of Perkow product to Arbuzov product steadily falls as the size of the cyclic amine ring increases (entries 1, 2 and 4, Table 2). For non-cyclic amines, and particularly those with a benzyl substituent, the Perkow products were obtained in very small, almost negligible yields.

We also showed that Arbuzov products (244) and (245) are stable under the reaction conditions (reflux in toluene) and do not isomerise to the corresponding Perkow products. Furthermore, none of the corresponding Arbuzov products were observed during thermal decomposition of Perkow products (254) and (255). These observations imply that the two products do not interconvert under the reaction conditions.

Both steric and electronic factors can account for the trend in the ratio of the two products. On one hand, it can be argued that with smaller ring diethyl phosphoramidites, the greater steric congestion around phosphorus restricts the nucleophilicity at phosphorus and promotes halogen abstraction which is less sterically demanding.

Similarly it may be argued that with diethyl benzylphosphoramidites, the phosphorus is a "harder" atom, as is the adjacent nitrogen by virtue of the benzyl substituent, and therefore prefers nucleophilic addition more than attack at the "soft" bromine atom.

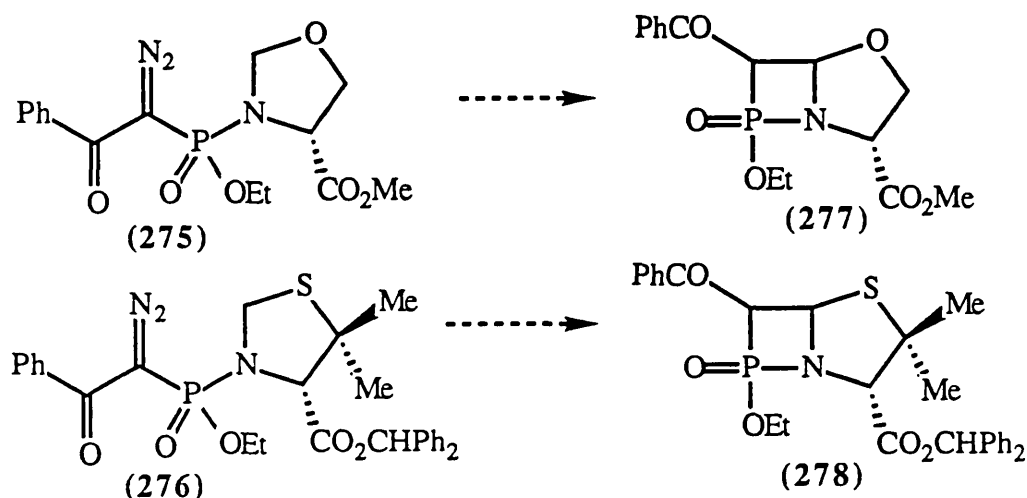


Scheme 99

We also attempted to prepare phosphoramidates from diethyl benzylphosphonate but we were unsuccessful in transforming the mono acid (273) to the mono acid chloride. Dehydrative coupling of the mono acid to the amine afforded phosphoramidates, e.g. (274) only in poor yield (Scheme 99).

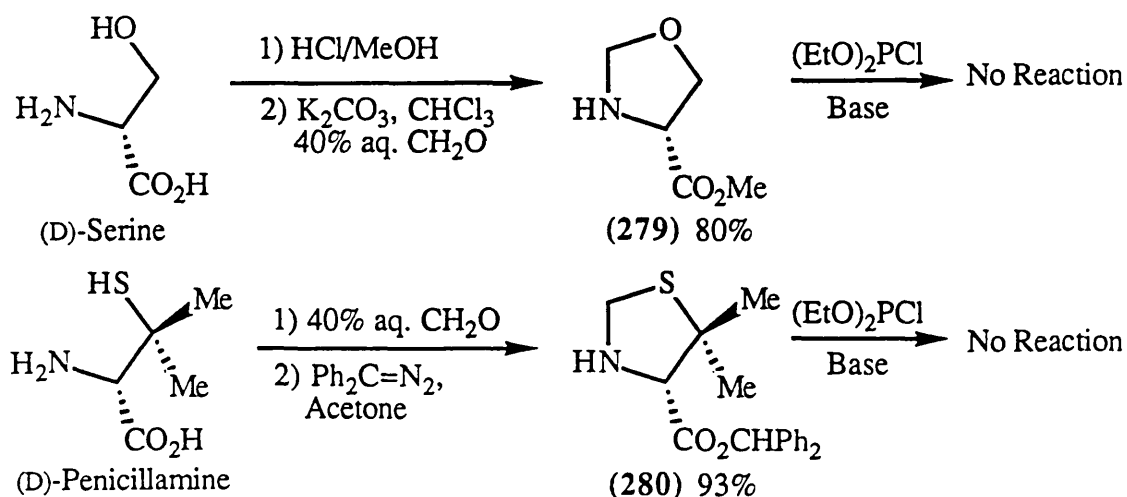
Diazo transfer to the active methylene groups all proceeded in excellent yields with triethylamine as base and tosyl azide as diazo transfer reagent (Table 2, Scheme 96).

We also attempted the synthesis of diazo compounds (275) and (276) which by the expected C-H insertion reaction would afford bicyclic rings (277) and (278) (Scheme 100). In each, a fixed chiral center has been introduced into the molecule and separation of diastereomers would provide a single enantiomer for the cyclisation attempt.



Scheme 100

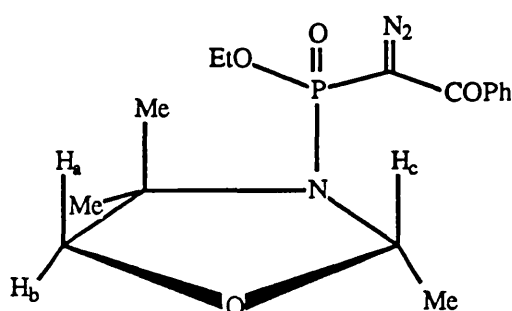
Cyclic amines (279) and (280) were prepared (Scheme 101) but the usual treatment failed to afford the required products. Although one equivalent of triethylamine hydrochloride was isolated from the first step, ³¹P NMR revealed that the main product of



Scheme 101

the reaction is diethyl phosphite, a hydrolysis product of diethyl chlorophosphite. The use of other bases, sodium hydride and DMAP, also failed to give any addition product.

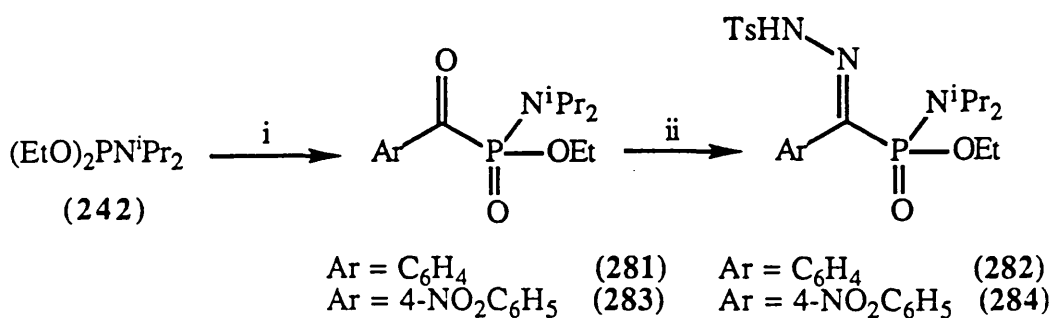
In contrast, cyclic amine (225) (see Scheme 90) after the normal reaction sequence, did yield the expected phosphonamidate as a 1:1 diastereomeric mixture. Chromatographic separation of the diastereomers was possible and the relative stereochemistry of one of them was assigned based on n. O. e. The signal due to proton (a) is distinguished from that due to proton (b) owing to the stronger coupling of proton (a) to ^{31}P which is on the same face of the ring. Proton (c) exhibited stronger n. O. e. to proton (a) and hence it was concluded that this proton must be on the same face of the five membered ring as proton (a) and hence *cis* to the phosphonyl group (Scheme 102).



Relative stereochemistry of (270)

Scheme 102

Although the route in Scheme 94 allowed access to range of β -keto phosphonamidates, similar treatment of diethyl phosphoramidite (230) (Scheme 94) with benzyl halides afforded unacceptably low yields of Arbuzov adduct. For preparation of these we used a route similar to that employed by Seyferth (Scheme 33, Chapter Two). Thus, diethyl diisopropylphosphoramidite (242) was treated with acid chloride to give ketophosphonamidates (281) and (283) which were transformed to their tosylhydrazones (282) and (284) in preparation for direct and indirect (i.e. *via* the diazo compound) carbene generation (Scheme 103).



i) ArCOCl , toluene, Δ , 5 h; ii) TsNHNH_2 , ethanol

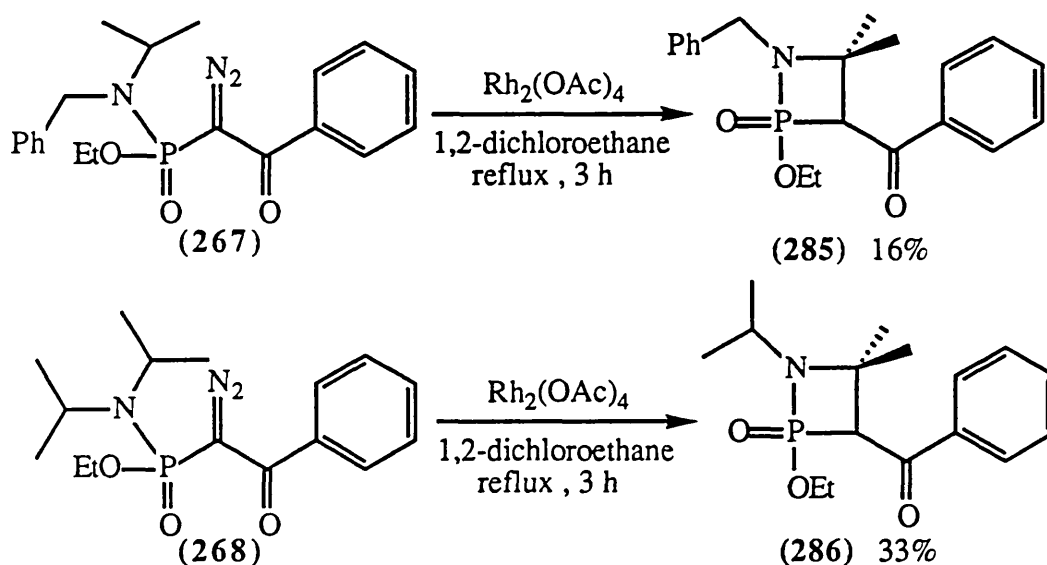
Scheme 103

4.4.3 Catalysed Thermal Decomposition of α -Diazo Phosphonamidates

These reactions were carried out in dry solvents. A 10% mol ratio of catalyst (dirhodium tetracetate,¹²² copper acetylacetonate) was used for reactions of a typical concentrations of 0.05 molar.

In general most diazo compounds mentioned showed considerable thermal endurance in the absence of the catalyst, not decomposing in toluene at reflux (110 °C). Although Seyferth reported that metallic copper in refluxing hydrocarbon solvents is an efficient catalyst for decomposition of α -diazo phosphonates we did not observe any reaction for diazo piperidylphosphonamidate (267) (Table 2) with metallic copper in refluxing cyclohexane even with sonication.

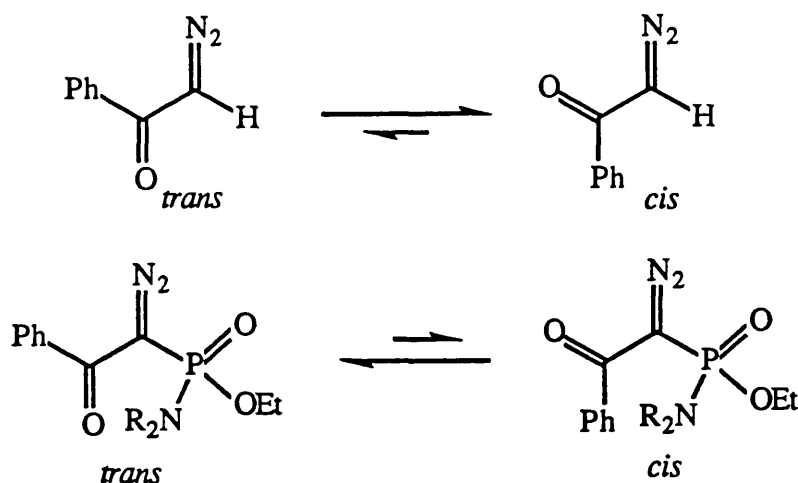
Insertion into the methine bond was observed for compound (267) and (268) in a relatively clean reaction to afford azaphosphetidine (285) and (286) (Scheme 105). Structure of (286) was confirmed by X-ray crystallography (Appendix 2). Both compounds decompose *in vacuo* within a few days.



Scheme 104

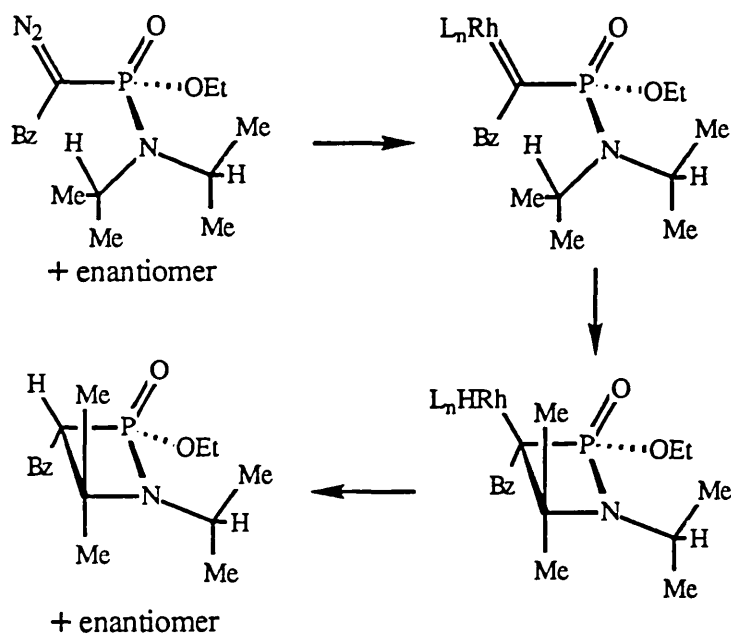
Both compounds were formed diastereoselectively and for (286) the major diastereomer (90%) was shown to be ($S_P R_C$, $R_P S_C$) from its X-ray crystal structure.

This diastereomer is not notably more stable than the other so it is unlikely that it results from equilibration after ring closure. The origin of this diastereoselection is probably in the conformation of the diazo compound (268). The *cis-trans* isomerism for α -diazomethylketones has been established and the dominance of *cis* isomer is rationalised in terms of preferential interactions between the dipoles of the $\text{C}=\text{O}$ and $\text{C}-\text{N}_2$ bonds.¹²³ For phosphonamidates however the *trans* isomer is expected to be dominant.



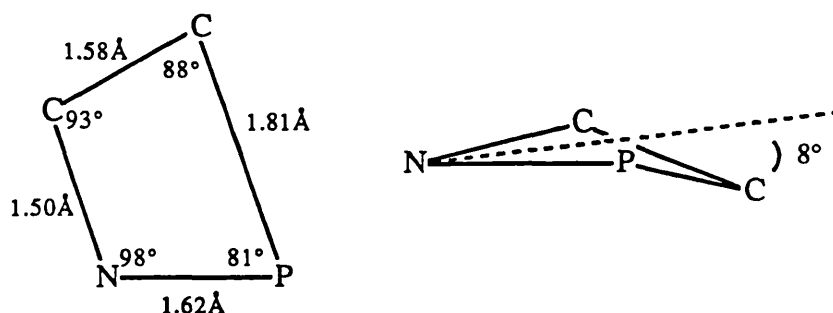
Scheme 105

The dipole of the C–N₂ bond can then interact favourably with the dipole of the P=O bond and the phenyl group is not forced to sterically crowd the phosphorus group (Scheme 105). On this basis we propose that the following mechanism applies (Scheme 106).



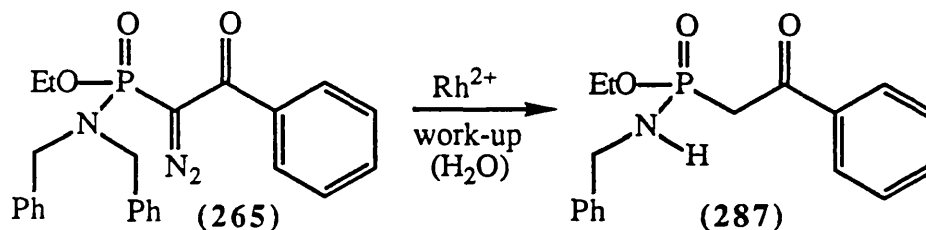
Scheme 106

The crystal structure of compound (286) is the first obtained for a 1,2-azaphosphetidine ring. It has revealed some striking features about this particular ring system (Scheme 107). One is that the nitrogen atom is planar and that the P–N bond is shortened from its expected range of 1.65–1.67 Å to 1.623 Å (Appendix 2). This suggests delocalization of the nitrogen lone pair into an empty phosphorus *d* orbital. This double-bonded character is expected to contribute to the stability of this ring. Secondly, the ring is almost flat (torsion angle of 8°) and trapezium shaped as befits a long (1.8 Å) P–C bond.



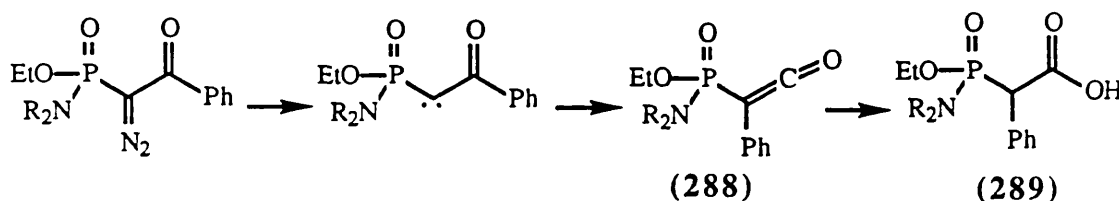
Scheme 107

For N-benzyl phosphonamidate (265), the decomposition reaction was complex though one of the products which we managed to partly characterise was (287) (Scheme 108) formed presumably by loss of an N-benzyl group as benzaldehyde, though this compound was not detected in the reaction mixture.

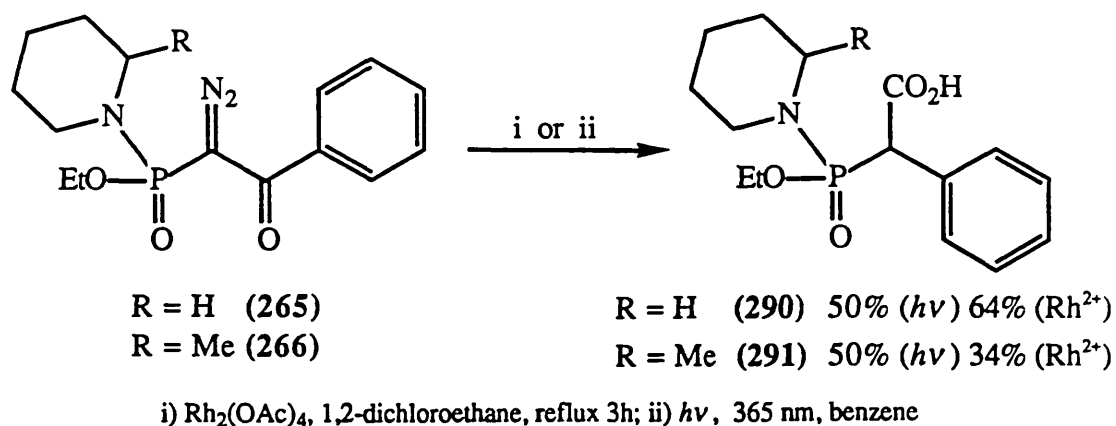


Scheme 108

As with photolysis reactions (see later), dirhodium tetraacetate-catalysed thermal decomposition of diazo compounds afforded substantial Wolff rearrangement products [e.g. compound (288) Scheme 109] in every case which upon hydrolysis afford acids of type (289) (Scheme 109). α -Diazo phosphonamidates with cyclic amines were particularly susceptible to this and with compounds (261) and (262), Wolff rearrangement products (290) and (291) were the only products (Scheme 110).

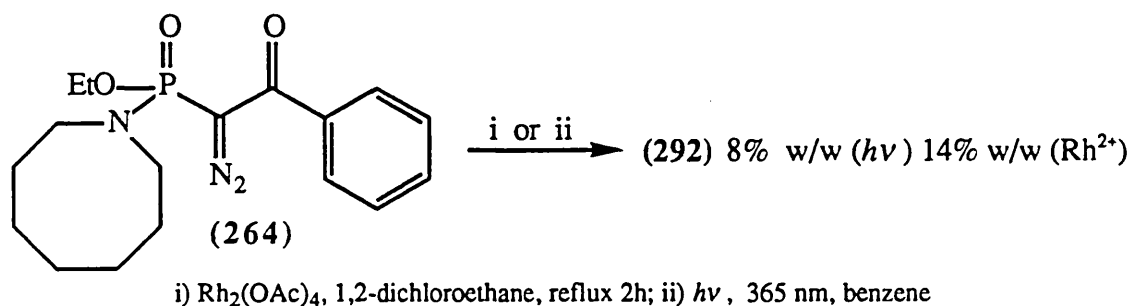


Scheme 109



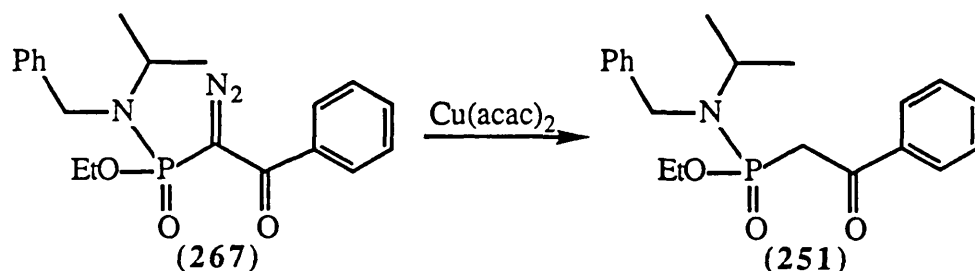
Scheme 110

As well as the Wolff product, we repeatedly observed the formation of a non-polar non-phosphorus containing product in variable yields of between 3-14% (w/w). With compound (264), this constituted the only other product. Although we were able to isolate this compound, (292) (Scheme 111) in a pure state, we are unable to assign a structure.



Scheme 111

Rhodium acetate is known to be a particularly good catalyst for insertion into X-H bonds; nevertheless, other catalysts have also been used and shown to play a critical role in the yield of reaction as well as limiting the range of byproducts. Owing to shortage of time, however, we tried only one other catalyst. In the $\text{Cu}(\text{acac})_2$ catalysed decomposition of (267) only the dediazotised compound (251) was obtained (Scheme 112).

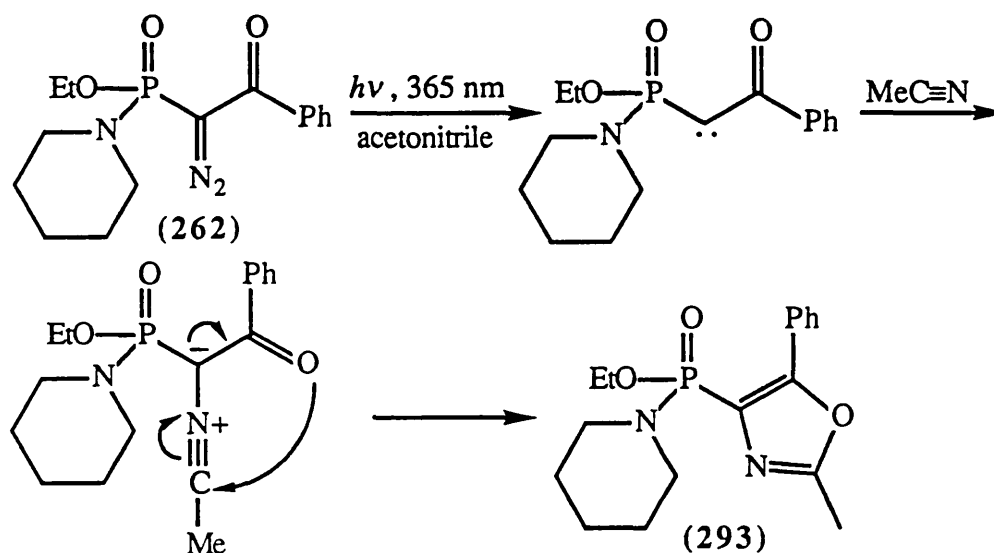


Scheme 112

4.4.4 Photolysis of α -Diazo Phosphonamidates

Photolyses were carried out at room temperature in dry benzene, with dry argon sparging through the solution. Solutions were usually made up to a concentration of 0.02-0.03 molar and were irradiated with UV light from a RUL-3500Å lamp in a Rayonet reactor. This lamp provided a sharp peak at 365 nm (Δw ca. 5 nm) and a less intense (75% of the other) broad band at 355 nm (Δw ca. 45 nm).

To confirm that diazo compounds are decomposed to carbenes under these conditions, a reaction was conducted with (262) in acetonitrile under otherwise similar conditions and the expected product (293) was isolated in good yield (Scheme 113).¹²⁴



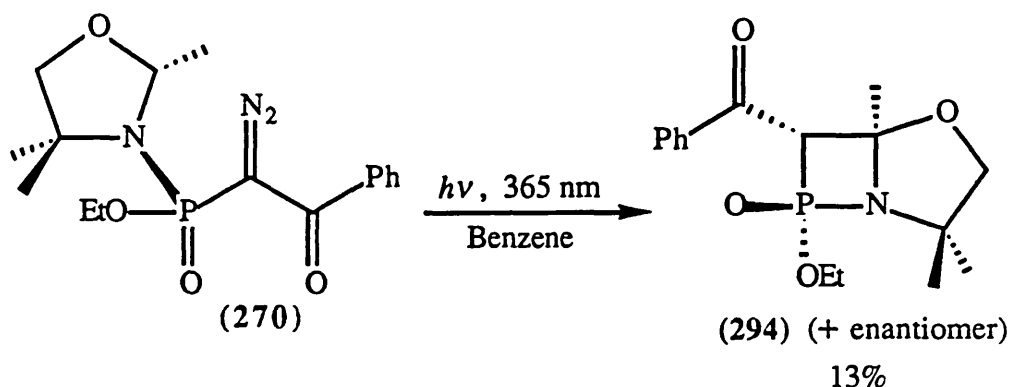
Scheme 113

Reactions of diazo compounds (261)-(270) (Table 2) were generally complex and afforded more than one product. In every case, the Wolff rearrangement product was observed and as with rhodium catalysed decompositions for compounds (262) and (263), these constituted the only products, (290) and (291) (Scheme 110).

Compound (290) has two chiral centres and compound (291) has three, therefore we expected to see multiplet signals in the phosphorus NMR owing to diastereomerism. However, for both compounds, only singlets were observed for the crude product and similarly, proton, phosphorus and carbon NMR's of the isolated products suggested that in each case products are single diastereomers. The origins of this diastereoselection is not clear.

As with rhodium catalysed thermal decomposition of these compounds, a complex reaction mixture was obtained in the photolysis of both diastereomers (269) and (270) which contained the Wolff products as the major component. The pattern was slightly different for compound (270), as an initial product was obtained which showed

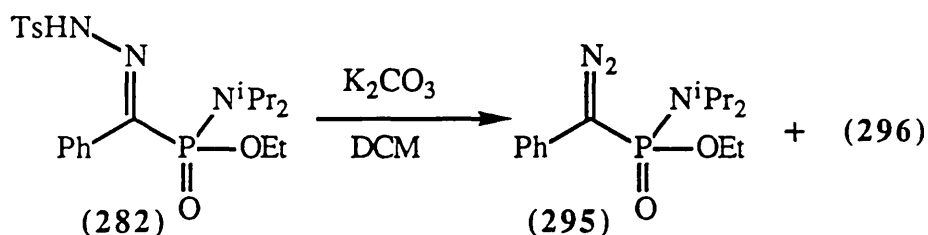
strong UV absorption at 360 nm. However upon exposure to silica, this decomposed within half an hour to a lower more polar (lower R_f) compound and base line material (Scheme 114). Thus chromatography afforded a product the NMR of which was consistent with the 4,5-bicyclic system (294).



Scheme 114

4.4.5 Miscellaneous

Treatment of a dichloromethane solution of tosylhydrazone (284) with potassium carbonate at reflux or at room temperature afforded only modest yields of the expected diazo compound (295) in spite of all the starting material being used up. The phosphorus NMR analysis of the reaction mixture revealed that (295) is not the major phosphorus containing product of this reaction but that it is accompanied by a second product, (296) (Scheme 115). All our attempts to isolate this product were unsuccessful.



Scheme 115

4.5 Summary and Conclusions

A range of synthetic approaches towards mono-cyclic and bicyclic 1,2-azaphosphetidines were investigated.

A diastereoselective synthesis of 1,2-azaphosphetidines *via* carbene C-H insertion to form the C(3)-C(4) bond was achieved. Formation of bicyclic systems by such an approach was possible in one case only, failures mostly being due to the predominance of the Wolff rearrangement.

The first X-ray crystal structure of a 1,2-azaphosphetidine ring system was obtained.

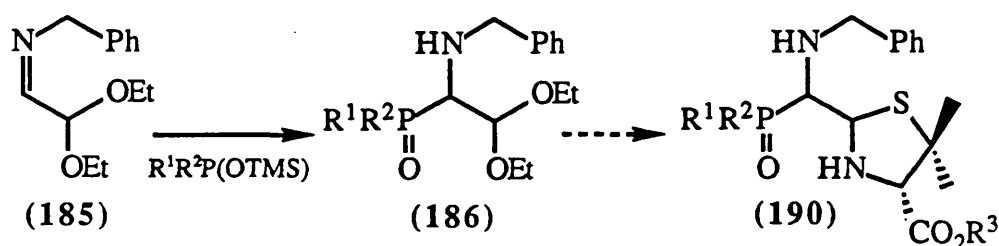
Owing to lack of time, a comprehensive study of the insertion reactions was not possible, though we conclude that this particular approach is a successful one which promises eventual access to a wide range of mono and bicyclic azaphosphetidines. One limitation is that all the insertions observed were into methine C-H bonds (which is known to be easier than insertion into methyl or methylene C-H). This limits the method to 4,4-disubstituted azaphosphetidines but it is hoped that development of this reaction, including the wider use of organometallic catalysts would enhance its scope further.

Chapter Five

***The Application of in situ Generated Silylated
Esters of Phosphorous Acids to the Synthesis
of Organophosphorus Compounds***

5.1 Introduction

As part of our synthetic studies towards (190) (Scheme 116), we required a mild and efficient synthesis of (186). All but one of our syntheses proved to be undesirably unclean and low yielding. The exception, the one in which 2,2-diethoxyacetaldehyde N-benzylimine (185) was treated with *in situ* generated mixed alkyl/trimethylsilyl esters of phosphorous acids, was of particular interest to us as it was



Scheme 116

clean and proceeded under very mild conditions i. e. in dichloromethane at 0 °C and in the absence of Lewis acid additives (see Scheme 76, Chapter Four). Such use of silylated phosphorus nucleophiles for preparation of α -oxyphosphonates is as old as the species themselves; however, as Engle pointed out in a recent review: "The use of silyl reagents [referring to silylated phosphites] for the synthesis of this category of compound [α -aminophosphonates] has been neither as extensive nor as successful as for α -oxyphosphonate. Rather, variable yields are reported for the relatively few syntheses performed with silyl reagents."¹²⁵ This was reflected in another review on the subject of silylated phosphorous species which devoted only a short section to addition to the C=N functional groups.¹²⁶

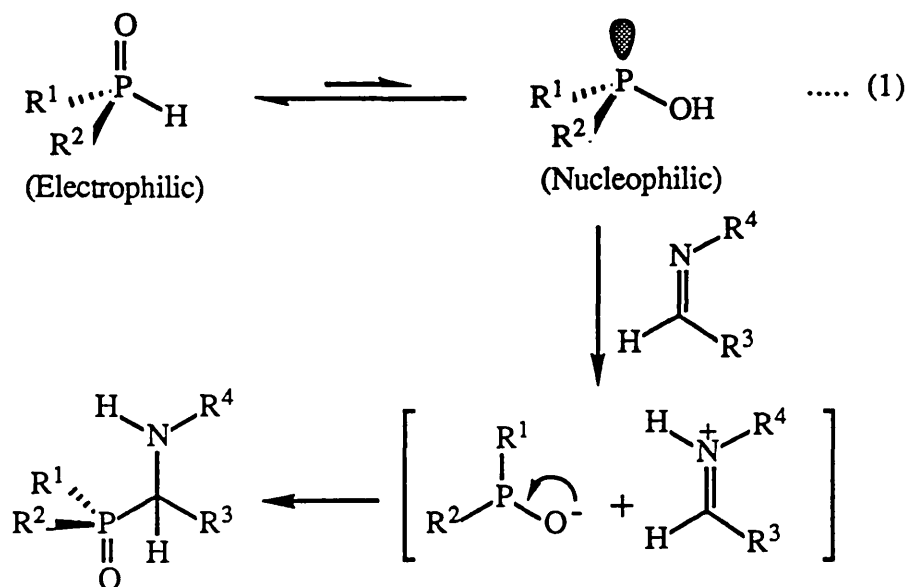
In view of the importance that α -aminophosphono compounds have assumed in recent years (see Chapter Three), we felt that investigating the scope and limitation of this reaction would be useful.

Primarily we aimed to acquire a better understanding of electronic and steric factors that decide the course of this reaction. Furthermore by carrying out reactions at lower temperatures, at which activation barriers and conformational energy barriers are less easily overcome, we hoped to attain total or partial chemo- and stereo- selectivity.

5.2 Silylated $\sigma^3\lambda^3$ Phosphorous and Phosphinous Esters

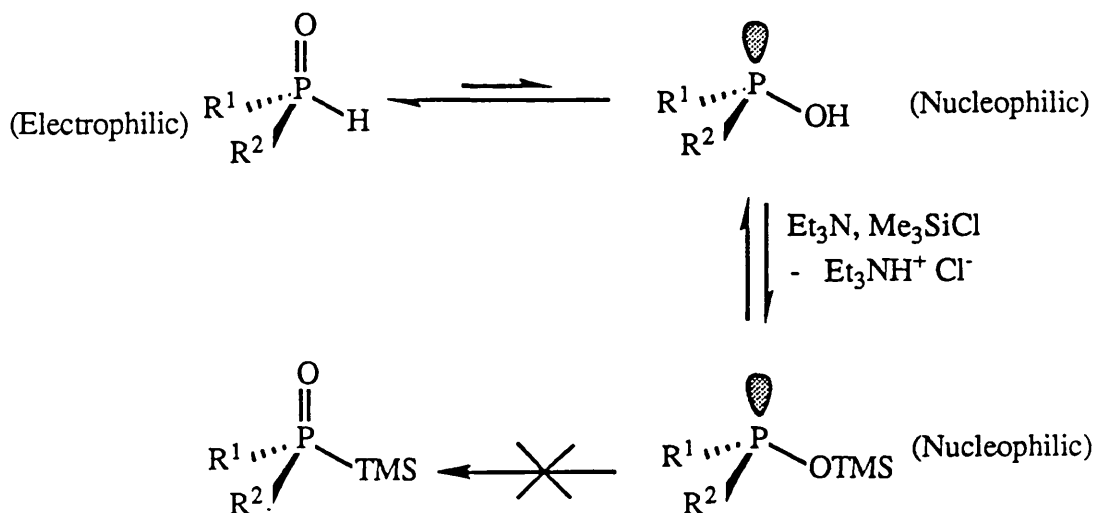
Thermally induced addition of trivalent phosphorus acids or esters to imines as a route to α -aminophosphonic acids was discussed in Chapter One. This thermal promotion is required for all $\lambda^3\sigma^3$ phosphorus acids and esters. It is known that partially esterified

$\lambda^3\sigma^3$ phosphorus species which are nucleophilic, are in equilibrium with $\lambda^4\sigma^5$ phosphorus compounds, which are electrophilic, commonly with the equilibrium heavily in favour of the latter.¹²⁷ Thermal energy is required to drive this equilibrium forward and hence to promote the nucleophilic reaction (Scheme 117).¹²⁸



Scheme 117

The phosphorus species however can be "frozen" in its tricordinated form if it is O-silylated. The strong Si-O bond and weak P-Si bond presumably deter migration of silicon from oxygen to phosphorus and therefore suppress the equilibrium (1) (Scheme 117), leaving the molecules exclusively in nucleophilic form (Scheme 118).¹²⁶ We reasoned that under these circumstances, addition reactions to imines would be kinetically enhanced and hence proceed at or below room temperature.



Scheme 118

Silylated phosphites are isolable compounds and a number have been characterised.¹²⁶ As synthetic reagents, they have gained prominence only recently

though they have been known for some time. Although in theory silylated phosphites can also be used as oxygen abstraction reagents, it is as nucleophilic reagents that they have often been used in recent literature reports. Since the silylated phosphorous species are themselves prepared only in modest yield and are hydrolytically highly sensitive, we opted for their *in situ* generation¹²⁹ prior to addition to imines which provided for a much more convenient and efficient route.

All silyl esters were generated *in situ* with chlorosilane and triethylamine in a chlorinated solvent (usually dichloromethane) at 0 °C and the complete formation of the tri-coordinated phosphorus species was established by ³¹P NMR (see Table 1).

³¹P NMR Signals of R¹R²P-OR³

	R ¹	R ²	R ³	ppm ^a
(297)	Ph	Ph	SiMe ₃	95.3 ^b
(298)	EtO	EtO	Si ^t BuMe ₂	125.7 ^c
(299)	EtO	EtO	SiMePh ₂	126.1 ^c
(300)	EtO	EtO	SiMe ₃	128.4 ^b , 126.7 ^c
(301)	Ph	Me ₃ SiO	SiMe ₃	141.9 ^b
(302)	Ph	EtO	SiMe ₃	147.0 ^b

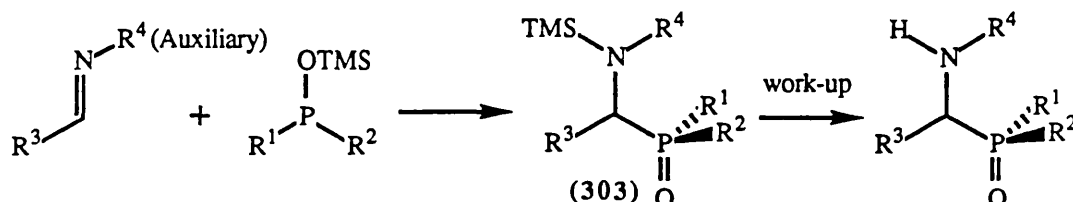
^aReferenced externally to diethyl phosphite in deuteriochloroform at 6.5 ppm

^bIn deuterodichloromethane

^cIn deuteriochloroform

Table 3

Formation of the trimethylsilylated phosphites was more rapid than those of the other silyl esters, though in every case a complete transformation had occurred within a few minutes. Silylated phosphites are stable to gentle heat but are air and moisture sensitive. When exposed to the atmosphere, they revert to the phosphite quantitatively.

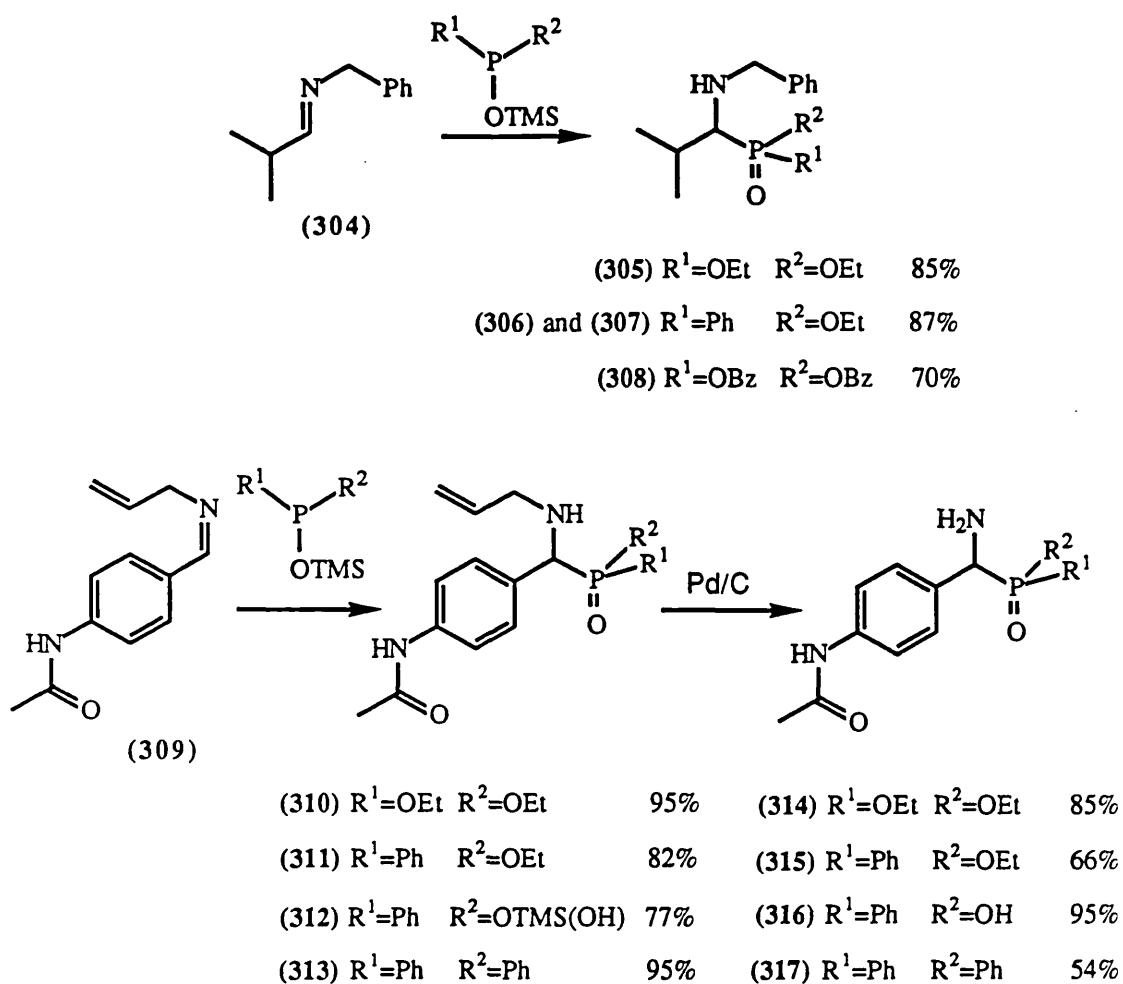


Scheme 119

The initial product of the addition is, we presume, an N-silylated species (303) (Scheme 119). Although we have been able to isolate O-silylated species during the addition to aldehydes, we never isolated N-silylated species from addition to imines, probably because the N-silylated compounds were too labile to survive the hydrolytic work-up.

5.3 Addition to Imines

In order to establish the influence exerted by the substituents on phosphorus, an alkyimine (304) and an arylimine (309) were treated with a selection of phosphonites and phosphites. The results (Scheme 120) show that the addition products were all formed in good to excellent, optimised yields.

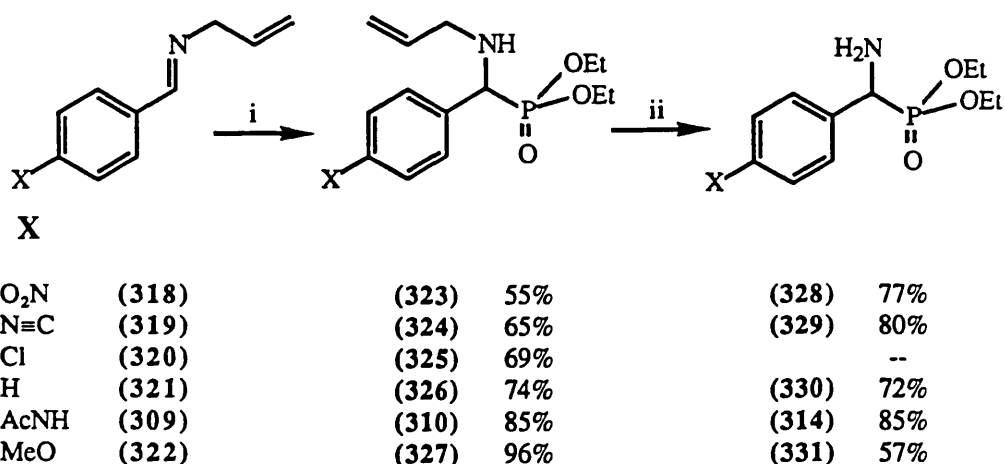


Scheme 120

In the reaction of benzaldimines, where subsequent N-debenzylation would not be unambiguous,¹³⁰ we employed N-allyl rather than N-benzyl as the auxiliary group; this was readily removed from the addition product by treatment with palladium on charcoal¹³¹ in a suitable boiling protic solvent.

This removal of the allyl group is general and works well not only with a range of substituents on phosphorus (Scheme 120) but with various *para* substituents on the benzene ring (Scheme 121).

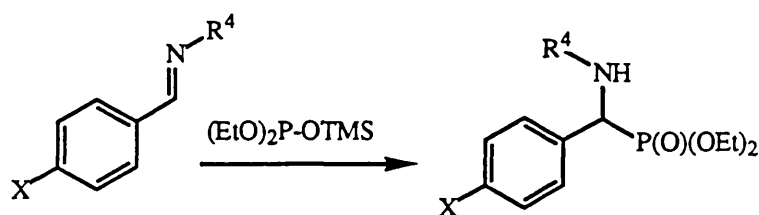
Addition of acids, or other proton sources such as ammonium formate did not improve the yield of de-allylation reaction, though the use of a protic solvent is essential.



i) (EtO)₂P-OTMS (300), DCM, 0°C, 15 h
 ii) Pd/C (10%), EtOH, reflux

Scheme 121

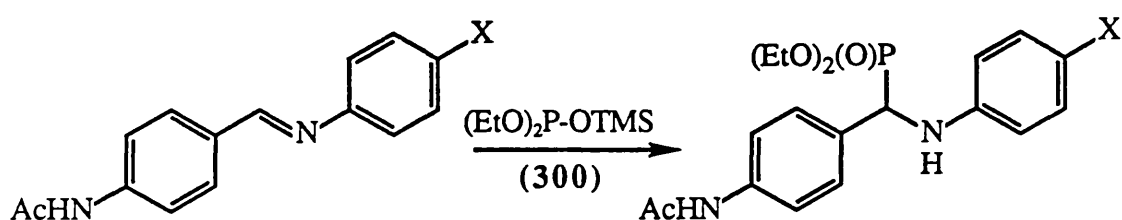
The influence of the imine substituent R³ (see Scheme 119) proved to be quite interesting. For a series of N-allylimines derived from 4-substituted benzaldehydes, we found that with electron-withdrawing substituents, treatment with diethyl trimethylsilyl phosphite (300) under a standard set of conditions leads to lower reaction yields (Scheme 121). This was found to be the result of a dramatic rate deceleration, and that the effect of electron withdrawing groups can be compensated for by an increase in the reaction time or temperature, to afford a nearly quantitative yield in every case.



X = O ₂ N-	Imine	Product	Yield (%)
R ⁴ = CH ₂ .CH=CH ₂	(318)	(323)	55
R ⁴ = CH ₂ CH ₂ CH ₂ Br	(332)	(337)	68
R ⁴ = C(CH ₃) ₃	(333)	(338)	53
R ⁴ = Ph	(334)	(339)	62
R ⁴ = NHPh	(335)	No Reaction	
R ⁴ = OBz	(336)	No Reaction	
X = AcNH-	Imine	Product	Yield (%)
R ⁴ = CH ₂ .CH=CH ₂	(309)	(310)	85
R ⁴ = C ₆ H ₄ .OMe- <i>p</i>	(340)	(344)	92
R ⁴ = Ph	(341)	(345)	84
R ⁴ = C ₆ H ₄ .NO ₂ - <i>p</i>	(342)	(346)	74
R ⁴ = OBz	(343)	No Reaction	

Scheme 122

A similar decelerating effect is observed with electron withdrawing groups on the imine nitrogen substituent (Scheme 122). Initial rate determination, by aid of ^{31}P NMR monitoring of the reaction, enabled us to estimate quantitatively the size of this effect for N-aryl imines (340) - (342) (Scheme 123). Based on the three measurements made, and by means of a Hammet plot, we estimate a reaction constant (ρ) of *ca.* -2.5 (See Appendix 2). The the sign of this reaction constant suggests that in the rate determining step the imine is under electrophilic attack, itself acting as a nucleophile. This substituent dependence rate profile is paralled in the acidic hydrolysis of imines¹³² and we have taken this into account when considering the reaction mechanism (see Section 5.5).

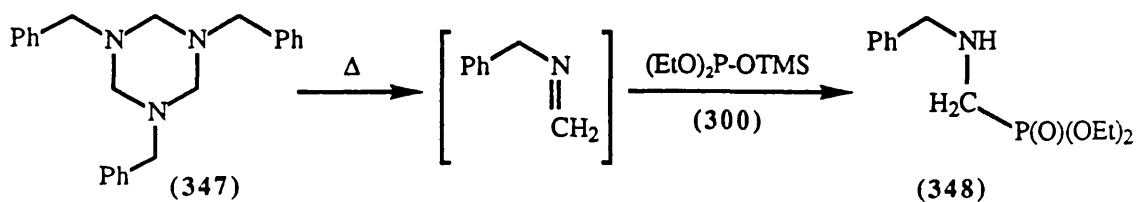


X \ Yield	10%	25%	33%	50%	85%
- OMe	-	-	-	2 min ^E	10 min
- H	0.4 min ^E	0.6 min	1 min	6 min	60 min
- NO ₂	110 min	400 min	-	-	-

^E Estimated by assuming uniform rate prior to the first reading

Scheme 123

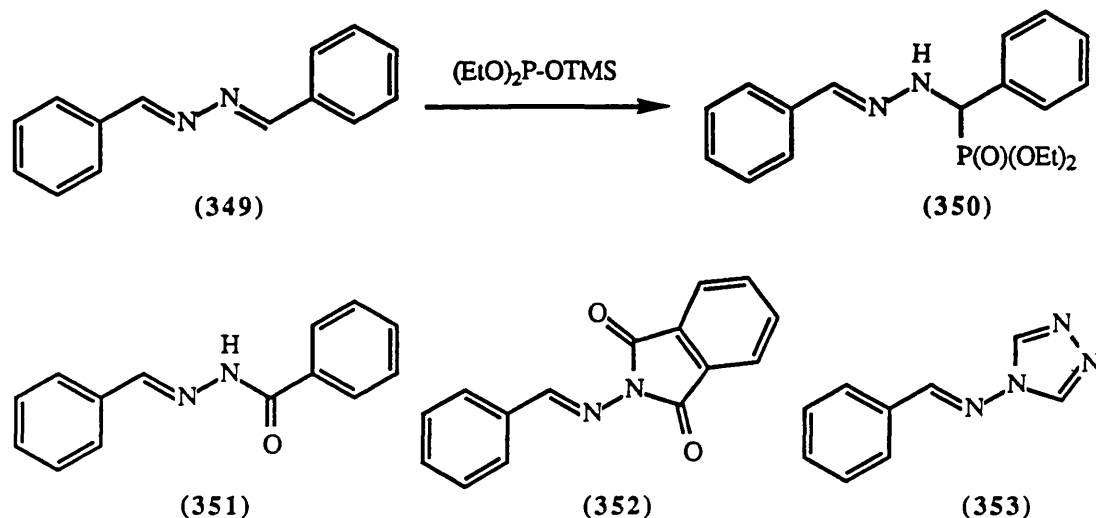
Interestingly, 1,3,5-tribenzylhexahydro-1,3,5-triazine (347), a precursor of N-benzylmethanalimine, reacts with (300) only in boiling 1,2-dichloroethane, and then at the same rate as with diethyl phosphite itself, the rate determining step for the reaction presumably being the fragmentation of the triazine (Scheme 124).



Scheme 124

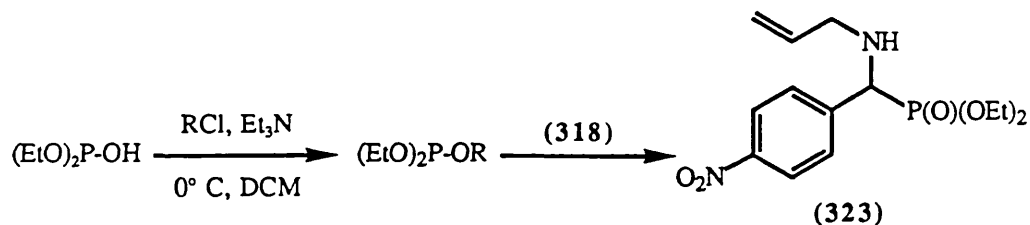
Although electron rich imines all underwent rapid nucleophilic addition of the phosphorus (III) reagents, oxime ethers and hydrazones were inert (Scheme 122). For

example, diethyl trimethylsilyl phosphite (**300**) adds to benzaldehyde azine (**349**) to afford a mono adduct (**350**), which being a hydrazone, does not undergo further reaction. An exactly similar behaviour towards oximes and hydrazones was observed with non silylated compound, diethyl phosphite. No reaction was observed even with compounds in which the hydrazone nitrogen was substituted with electron withdrawing groups, (**351**), (**352**), and (**353**) (Scheme 125).



Scheme 125

We also carried out a brief investigation into the influence of the silylating agent RCl (Scheme 126) on the reaction between diethyl phosphite and 4-nitrobenzaldehyde *N*-allylimine (**318**). This imine was chosen since the expected decelerated rates would magnify any differences in yields of isolated product (**323**) which might result from a change of group R .



RCl	Reaction time (hours)	Yield (%)
Me_3SiCl	15	55
Me_3SiCl	60	85
Me_3SiCl	12 ^a	65
$^t\text{BuMe}_2\text{SiCl}$	120	81
MePh_2SiCl	110	66
$^t\text{BuPh}_2\text{SiCl}$	112	24
MeSO_2Cl	112	28

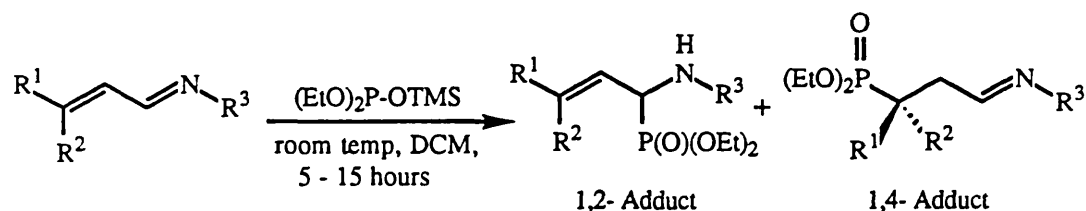
^a at reflux

Scheme 126

We found, not surprisingly, that bulkier silyl groups, R, retarded both the formation of the silicon-phosphorus species and the addition reaction (Scheme 126). With chloro-*t*-butyldiphenylsilane and methanesulphonyl chloride as RCl, no new phosphorus species is generated during reaction as evident by ^{31}P NMR; however, with much longer reaction time, small yields of adduct (323) is obtained. For these, reaction probably results from addition of diethyl phosphite anion, generated in small concentration by triethylamine, to imine (318). To show that this behaviour is not general we carried out similar reactions with benzaldehyde *N*-allylimine (321) and showed that no adduct results.

5.4 Addition to α,β -Unsaturated Imines

In order to establish the influence of electronic and steric effects on regioselectivity in the addition to α,β -unsaturated imines, we treated a range of α,β -unsaturated imines with diethyl trimethylsilyl phosphite (300). We found that electronic as well as steric factors influence the outcome of the reaction. For instance, addition to α,β -unsaturated imines when an aryl substituent is present at the 1- or 4- positions is exclusively 1,2- rather than 1,4-, as verified by ^{31}P NMR on crude reaction mixtures,



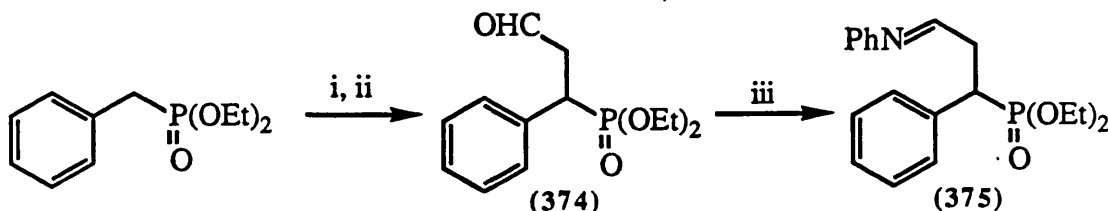
	R ¹	R ²	R ³	Imine	1,2-Adduct	Yield ^a (%)
1	C ₆ H ₅	H	4-MeOC ₆ H ₄	(354)	(364)	77
2	C ₆ H ₅	H	C ₆ H ₅	(355)	(365)	91
3	C ₆ H ₅	H	4-O ₂ NC ₆ H ₄	(356)	(366)	70
4	C ₆ H ₅	H	2,4,6-Me ₃ C ₆ H ₂	(357)	(367)	37
5	CH ₃	H	4-MeOC ₆ H ₄	(358)	(368)	57
6	CH ₃	H	C ₆ H ₄	(359)	(369)	55
7	CH ₃	CH ₃	4-MeOC ₆ H ₄	(360)	(370)	80
8	C ₆ H ₅	H	C ₄ H ₉	(361)	(371)	83
9	C ₆ H ₅	H	(CH ₃) ₂ CH	(362)	(372)	85
10	C ₆ H ₅	H	(CH ₃) ₃ C	(363)	(373)	57

^a Pure isolated 1,2- addition product.

Scheme 127

regardless of the electronic nature or the steric bulk of the N-aryl substituent (Scheme 127).

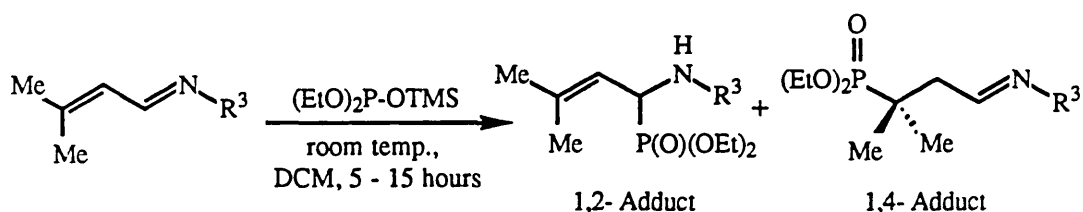
With aromatic electron poor α,β - unsaturated imines or those with bulky groups at nitrogen (entries 3,4 and 10), addition is slower and does not proceed to completion, and again no 1,4- (conjugate) adduct is formed. An authentic 1,4- adduct was prepared (Scheme 128) for comparison in the NMR.



i) THF, $-78\text{ }^{\circ}\text{C}$, BuLi, then allyl bromide; ii) O_3 , DCM/MeOH, then Me_2S ; iii) PhNH_2 , DCM, K_2CO_3 , rt, 24 h

Scheme 128

Only when no 1- or 4- aryl substituent on the 1-azadiene system is present can the steric bulk of the nitrogen substituent promote 1,4- addition. Then the ratio of 1,4- to 1,2- adduct increased with bulk of nitrogen substituents even if the 4-position is sterically crowded (Scheme 129). The 'butylimine was hydrolysed during chromatography and hence compound (381) was isolated as the aldehyde.



	R^3	1,2- : 1,4-	Imine	Yield (Adduct) (%)
11	C_4H_9	95 : 5	(376)	15% (379) ^a
12	$(\text{CH}_3)_2\text{CH}$	95 : 5	(377)	85% (380) ^a
13	$(\text{CH}_3)_3\text{C}$	35 : 65	(378)	50% (381) ^b

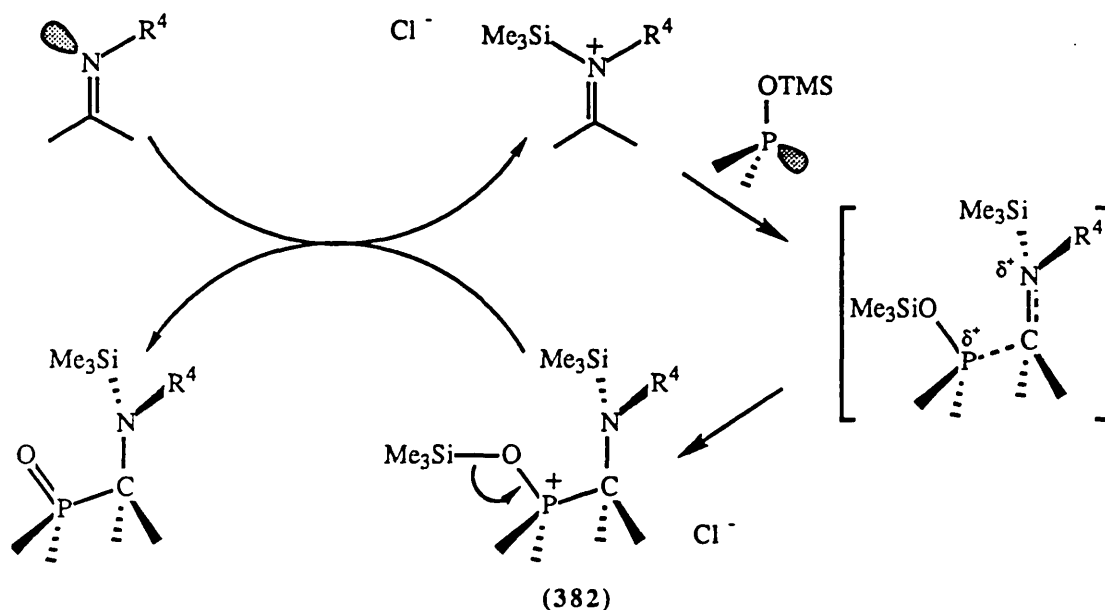
^a 1,2- addition product. ^b 1,4- addition product as the aldehyde.

Scheme 129

This behaviour is in accordance of the earlier findings that addition of silylated phosphites to cinnamaldehydes is predominantly 1,2-¹²⁶ but should be contrasted to the addition of trialkylphosphites to α,β - unsaturated imines under acid catalysis, which is predominantly in the conjugate fashion.¹³³

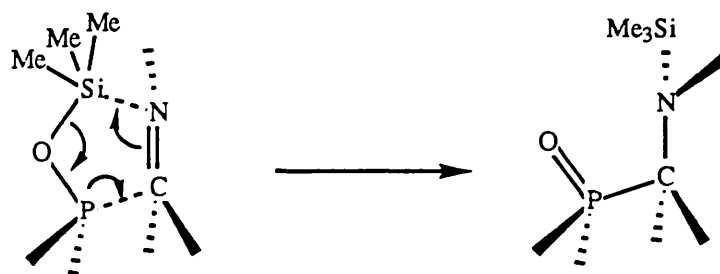
5.5 Mechanism of the Addition to Imines

To provide a mechanism that can successfully accommodate and rationalise the facts regarding this reaction would require a more detailed kinetic study. However, based on our observations to date, we can propose two closely related mechanisms. One is a stepwise mechanism illustrated in Scheme 130. This is supported by the observed electronic demand of the imine bond which suggests that the rate determining step incorporates nucleophilic attack by the imine nitrogen on an electrophilic species; this is presumably a silane in the form of excess chlorotrimethylsilane or (382), to form an iminium cation. Addition of the silyloxy P(III) species to this cation, accompanied by valence expansion at phosphorus, gives the N-silylated product and "TMS⁺" either as regenerated chlorotrimethylsilane or by (382) itself acting as a silylating agent. Hydrolytic work up cleaves the N-silyl group and affords the product.



Scheme 130

Alternatively a concerted [3+2] mechanism, analogous to that suggested by Evans for addition to aldehydes,¹³⁴ could be operating (Scheme 131). This mechanism is a limiting version of the one above where the chronology of events is such that the formation of the P-C bond occurs almost simultaneously with the Si-N bond formation.



Scheme 131

Based on this mechanism, diastereoselectivity in the addition of prochiral silylated phosphites to imines could be rationalised and be predicted (see 5.7). If this mechanism is correct, then the transition state formation would presumably be unsymmetrical with silicon-nitrogen bond formation more advanced than carbon-phosphorus bond formation.

Molecular mechanics calculations were performed on the geometry of the transition state for addition of dimethyl trimethylsilyl phosphite to formimine ($\text{CH}_2=\text{NH}$). Indeed it revealed that the nitrogen-silicon distance is close to a typical N-Si bond length whereas phosphorus-carbon distance is much longer than the expected P-C bond (Table 4). In this minimum energy geometry, phosphorus is approaching the carbon at an angle of 86° to the C-N axis, and silicon is docking by the side of nitrogen in the direction of the non bonding electron pair. Phosphorus-oxygen and silicon-oxygen bonds are almost unchanged. A more detailed structural analysis of this minimum energy geometry is provided in Appendix 3.

	Normal Bond Length ¹³⁵ (Å)	Interatomic Distance (Å)
Si-O	1.66	1.76
O-P	1.64	1.67
P-C	1.85	2.49
C=N	1.33	1.29
N-Si	1.75	2.02

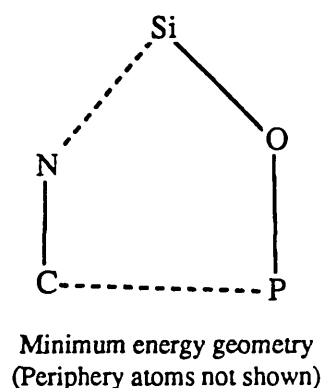
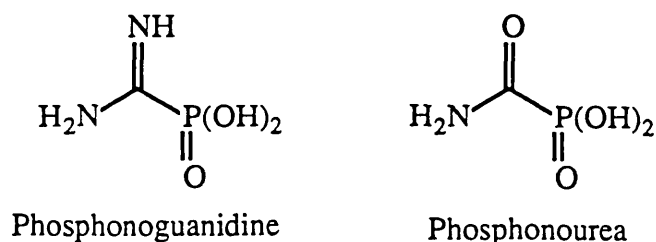


Table 4

Although on its own this result would not prove or disprove either mechanism, it supports the suggestion of a concerted one.

5.6 Addition to Carbodiimides and Isocyanates

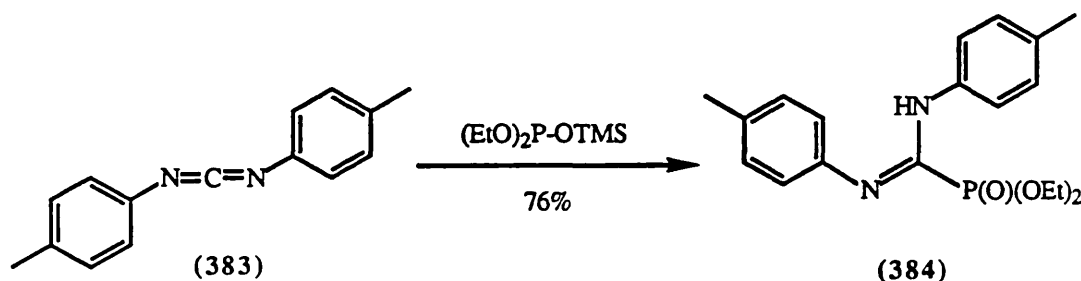
Of the other functional groups related to imines, carbodiimides and isocyanates are potentially the most interesting as they could afford phosphonoguanidines¹³⁶ and phosphonoureas¹³⁷ respectively, analogues of two biologically important groups. Since



Scheme 132

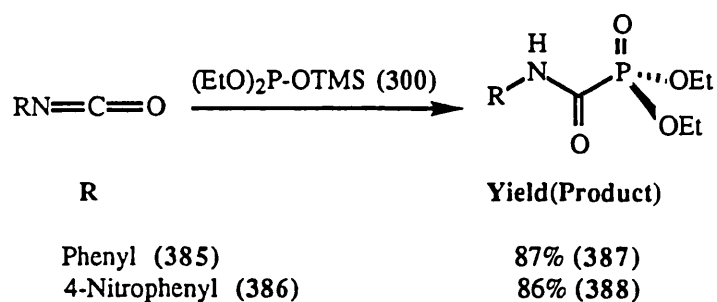
in both cases the imine is connected to another double bond, C=N for diimides and C=O for isocyanates, with the π systems orthogonal, we were interested to see if the electronic demand of the imine remains similar.

Addition to carbodiimides was observed only with the aromatic compound (383) which afforded phosphonoguanidine (384). Surprisingly, there was no reaction with dicyclohexylcarbodiimide (DCC) nor bis(trimethylsilyl)carbodiimide (Scheme 133).



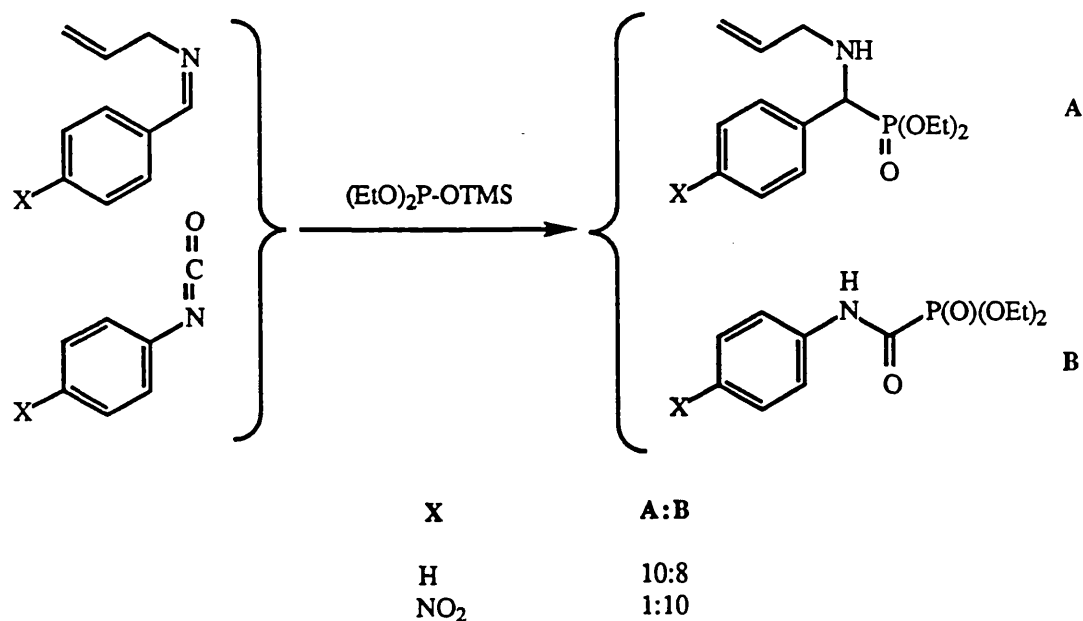
Scheme 133

Addition to aromatic isocyanates proceeded smoothly to give the adducts in good yields (Scheme 134). Competition experiments showed that the reactivity of the isocyanates, unlike that of imines, is enhanced by the presence of a powerfully electron withdrawing group, i.e 4-nitrophenyl isocyanate (386) reacts faster than does the phenyl isocyanate (385) (Scheme 135). Furthermore, when an equimolar mixture of phenyl isocyanate (385) and benzaldehyde N-allylimine (321) was added to a solution of one



Scheme 134

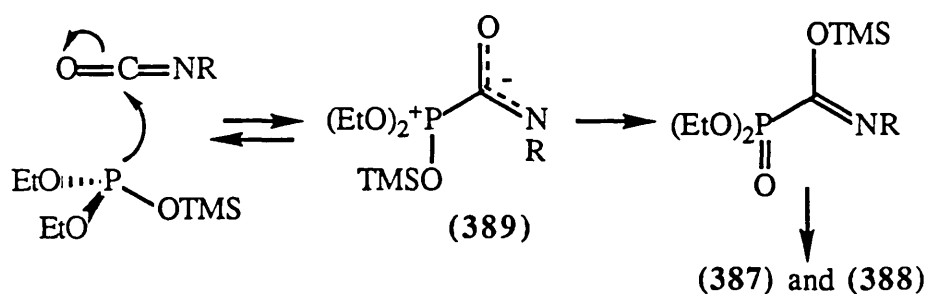
mole equivalent of trimethylsilyl diethyl phosphite (300), addition to the isocyanate slightly predominated. However in a similar experiment with 4-nitrophenyl isocyanate (386) and 4-nitrobenzaldehyde N-allylimine (318), the ratio of the two products was inverted, to be much in favour of the adduct to imine. The results show that reactions with imines and isocyanates, when no substituent is placed on the aromatic rings, have relatively similar rates. Introduction of an electron withdrawing group on the aromatic ring increases the rate of addition to isocyanates and at the same time reduces the rate of addition to imine.



Scheme 135

The difference in the substituent dependent rate profile points to a different reaction mechanism for addition of silylated phosphites to carbodiimides and isocyanates than to imines.

In the addition to isocyanates the reaction probably proceeds by direct nucleophilic attack of the silylated phosphite to highly electrophilic carbon (Scheme 136). Isocyanates being strong electrophiles, this route is expected to be lower in energy than O- or N-silylation which is retarded anyway by electron withdrawal of the C=O group.



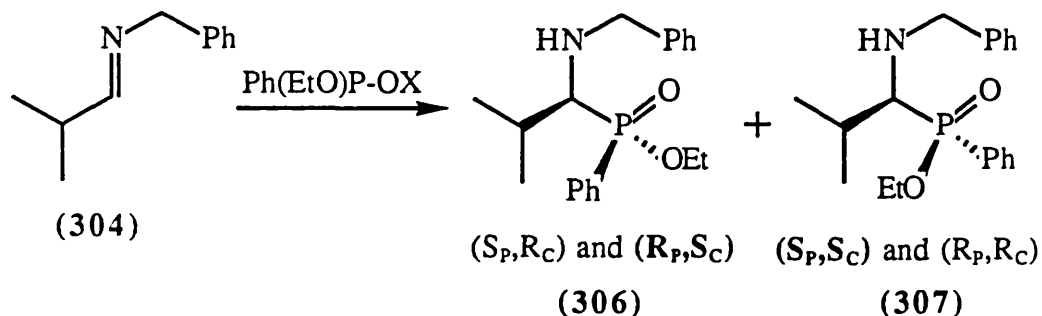
Scheme 136

This mechanism also explains the unexpected lack of reactivity towards DCC and bis(trimethylsilyl)carbodiimide. The rate determining step for these reactions is that of addition of nucleophile to the N=C=N system which is accompanied by a build up of negative charge on nitrogen. This process is assisted for biaryl carbodiimides where the negative charge can delocalise into the adjacent aromatic ring.

5.7 Diastereoselectivity in Addition to Imines

There has been a great deal of effort invested in the chiral synthesis of α -aminophosphonic acids mainly by employment of chiral auxiliaries on nitrogen or by resolution (see Chapter Three). However diastereoselectivity in reactions where the phosphorus group itself is prochiral has not as yet been investigated. A better understanding of the steric and electronic influences on diastereoselectivity in additions of silylated phosphites would not only be synthetically useful but, since these are non-aggregated nucleophiles, is also extremely helpful for a better understanding of nucleophilic additions generally.

We found that addition of silylated phosphites to imines proceeds with a modest diastereoselectivity which is absent from the addition of non silylated phosphites or phosphite anions. The following example (Scheme 137) demonstrates this effect. Compounds (306) and (307) are enantiomeric mixtures and the absolute stereochemistry of the diastereomeric pair shown are highlighted. In this case we were able to isolate the minor diastereomer, compound (306), as crystals and assign its relative stereochemistry by X-ray crystallography (see Appendix 2).

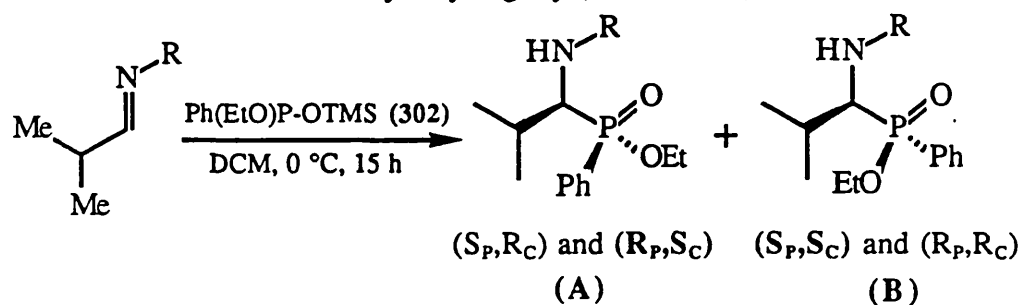


Conditions	Combined Yield (%)	Ratio	
		(306)	(307)
X = TMS (302)			
20°C, 15 h	84	34	66
-70°C, 8 h	70	28	72
-90°C, 10 h	43	26	74
X = H			
130°C, neat, 15 min	55	44	56
110°C, toluene, 13 h	62	48	52
X = Li			
THF, -72°C, 5 h	33	46	54
THF, TMEDA, -72°C, 5 h	33	46	54

Scheme 137

Our further study of diastereoselectivity was restricted since assignment of relative stereochemistry in individual molecules other than by crystallography is difficult. We were, however, able to pursue this investigation by studying reactions of the same phosphite with a range of very closely related imines. In this way we were able to assign the relative stereochemistry by direct comparison of proton and phosphorus NMR's.

Thus it was found that addition of silylated phosphite (302) to the imines (390) - (392) alters the diastereoselectivity only slightly (Scheme 138).

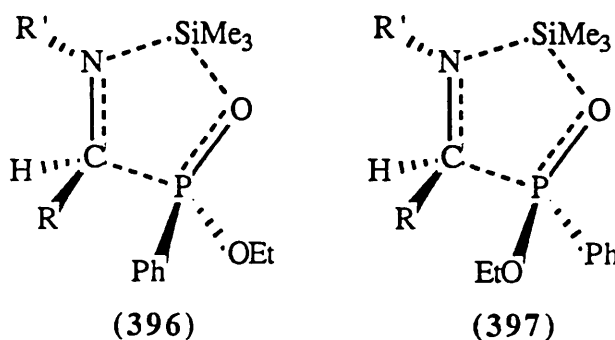


	Imine	R	Yield (%)	Product	Ratio A : B
1	(304)	-CH ₂ Ph	84	(306)/(307)	34 : 66
2	(390)	<i>R</i> -CH(Me)Ph	85	(393) ^a	33 and 8 : 44 and 15
3	(391)	<i>S</i> -CH(Me)Ph	83	(394) ^a	35 and 6 : 47 and 12
4	(392)	-CPh ₃	57	(395) ^b	39 : 61

^a Mixture of four diastereomers, ^b Mixture of two diastereomers

Scheme 138

To rationalise the origins of this diastereoselectivity we propose the following model in which the reaction is taken to proceed *via* a concerted mechanism involving a five membered transition state. The *E* geometry for the imine bonds is assumed. It should be noted that additions are all carried out in an organic solvent at or below room temperature and earlier studies have shown that under such conditions, the imine *E* or *anti* geometric isomer overwhelmingly predominates.¹³⁸



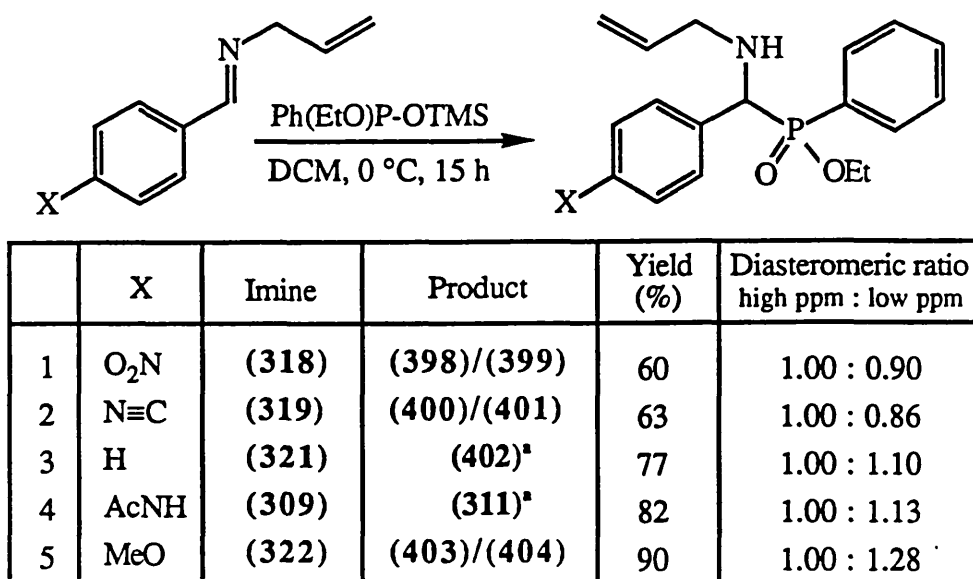
Scheme 139

As can be seen, there are two transition states, (396, R=*i*Pr) and (397, R=*i*Pr). On grounds of greater steric congestion, the former, in which the bulky substituent on phosphorus (Ph) is *cis* to the bulky substituent on carbon (*i*Pr), is disfavoured compared to the latter, in which the same substituents have a *trans* relationship. The minor diastereomer (306) results from the disfavoured transition state (396, R=*i*Pr) and the major diastereomer (307) results from the favoured transition state (397, R=*i*Pr). The original geometry of the imine bond dictates that the nitrogen substituent adopts a *cis* relationship with the phosphorus bulky substituent. It is clear therefore that steric bulk in the nitrogen substituent contributes more to the enthalpy of the transition state (397, R=*i*Pr) and thus in effect promotes the formation of transition state (396, R=*i*Pr), resulting in a lowering of preference for the diastereomer (307). Hence a slight lowering of diastereomeric excess was observed with imines with bulkier nitrogen substituent, (390)-(392).

Since the rigidity of the substituents in the periphery of the five-membered transition state is not clear, the influence of chirality of the nitrogen substituent in this model is difficult to evaluate. It can be seen from entry 2 and 3 (Scheme 138) that two of the four diastereomers are formed in larger excess. Clearly, chirality of the nitrogen substituent does have a strong influence on the transition state. Earlier studies had shown that α -methylbenzyl on the imine transfers chirality to the imine carbon in bond forming reactions. Allowing for the priority rules, with phosphorus nucleophiles, *S* chirality of the nitrogen substituent promotes *R* chirality at carbon and *vice versa* (Scheme 61, Chapter Three). Therefore, though we cannot be certain it is likely that the two major diastereomers of (393) and (394) are the (*R,S,S_p*) and the (*S,R,R_p*) respectively.

As already mentioned, electron withdrawal from the imine bond decelerates the addition of silylated phosphite markedly. For a concerted mechanism, this means a considerable distortion in the transition state which may be reflected in the diastereomeric ratios. We therefore added phosphite (302) to a series of *para* substituted benzaldimines. Since the 4-position of the benzene ring is too far from the reaction center, a progression in the diastereoselection could only be attributed to electronic factors.

In fact addition of (302) to 4-substituted benzaldimines affords a much less pronounced diastereoselection (Scheme 140). This probably results from an increase in energy of transition state (396, R=*i*Pr) in which the two phenyl rings, the phosphorus substituent and the imine carbon substituent, are stacked. Although we have observed a slight shift from one diastereomer to the other as the electronic nature of aldimine phenyl ring is changed, the effect is too small for deductions to be safely made.



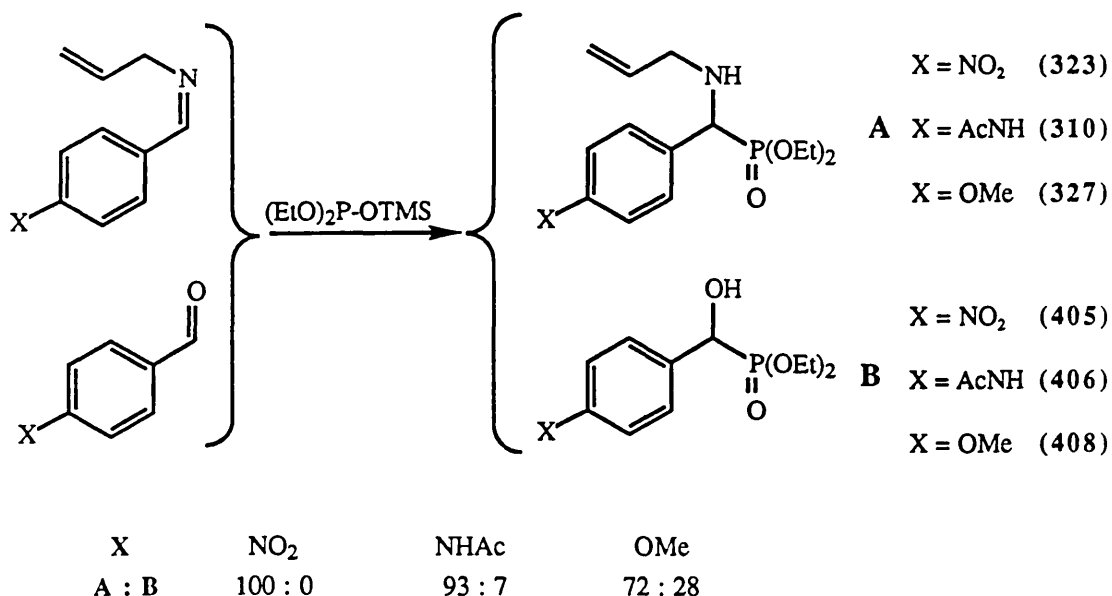
^aDiastereomeric mixture.

Scheme 140

5.8 Addition to Aldehydes and Ketones

As was mentioned earlier in this chapter, chemical reactions that proceed under mild conditions, although providing for experimentally convenient procedures, are best exploited to their limit if used to allow for chemoselectivity.

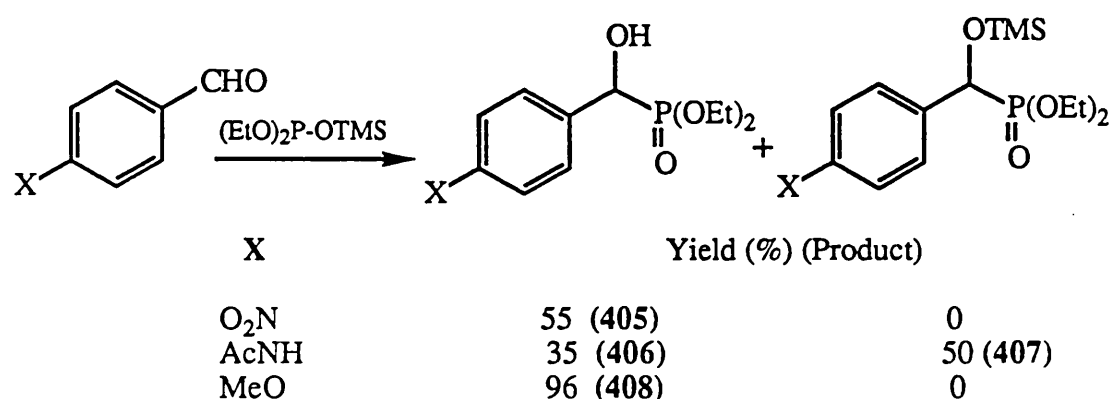
We made a comparison of the reactivity of diethyl trimethylsilyl phosphite (300) towards the C=O functionalities, aldehydes and ketones. We found that the addition of (300) to imines is considerably faster than addition to the parent aldehyde,¹³⁹ and in competition experiments with equimolar amounts of reactant, addition occurred predominantly to the imine (Scheme 141).



Scheme 141

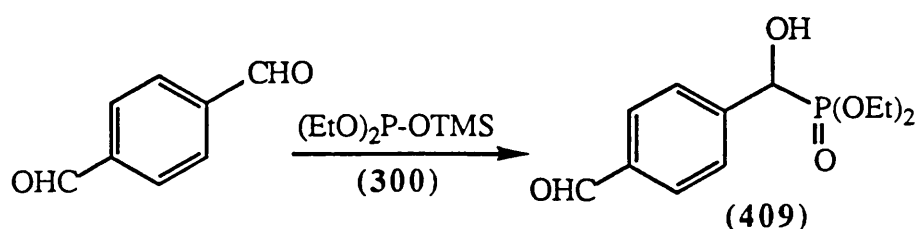
With the electron withdrawing nitro group at the *para* positions, no adduct to aldehyde was observed but with the mildly electron donating acetamido group where addition is faster and less discriminating, to both functions, some adduct to aldehyde was observed. The levelling effect also leads to some aldehyde adduct formed with a methoxy *para* substituent.

The aldehyde adducts were synthesised and characterised for comparison, as outlined in Scheme 142. For 4-acetamidobenzaldehyde, the major product was the O-silylated product (407), which crystallised from the reaction mixture. Chromatography affords the α -oxy phosphonates which are then resilylated *in situ* for NMR study.



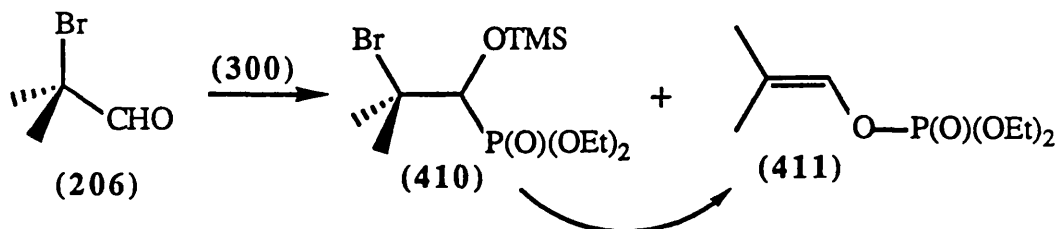
Scheme 142

Interestingly, in the addition to benzene-1,4-dicarboxaldehyde only the mono-adduct (409) could be isolated even with an excess of silylated phosphite reagent. Analysis of the reaction mixture with ³¹P NMR shows only two peaks: one corresponding to the starting material (diethyl phosphite) and one corresponding to the isolated product, mono-adduct (409) (Scheme 143). We were unable to prepare the bis-adduct by independent synthesis or by further reaction of (409) with (300) and therefore cannot refute formation of the bis-adduct conclusively. In view of the fact that the bis-adduct would be a mixture of diastereomers and consequently should give rise to a pair of peaks in the ³¹P NMR we have ruled out the possibility of co-incidence of the ³¹P NMR signals of the adducts.



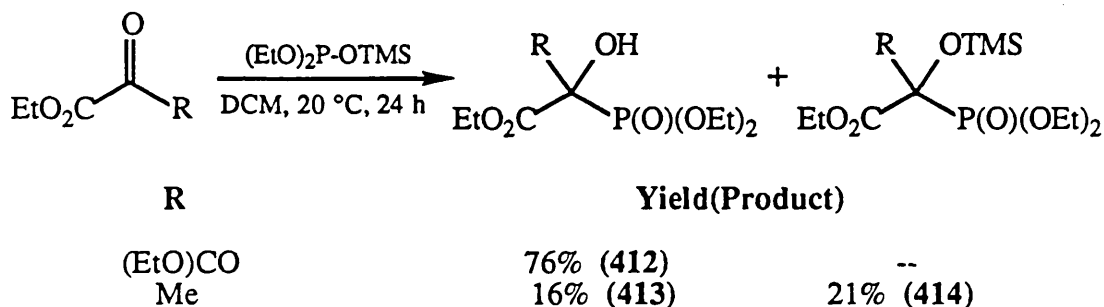
Scheme 143

With 1-bromo-1-methylpropanal (**206**), the Perkow product (**411**) was isolated as well as the carbonyl addition product (**410**). In agreement with Sekine's earlier results,¹²⁰ we found that (**410**) slowly rearranges to (**411**) at room temperature (Scheme 144).



Scheme 144

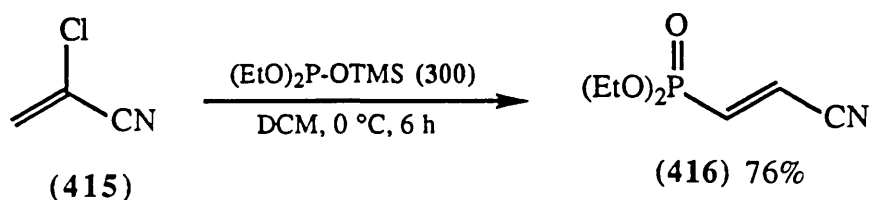
Addition of reagent (300) to ketones is much slower than to aldehydes and only proceeds when there is strong electron withdrawal from the carbonyl group (Scheme 145). There was no reaction with 2-propanone, acetophenone, or benzophenone.



Scheme 145

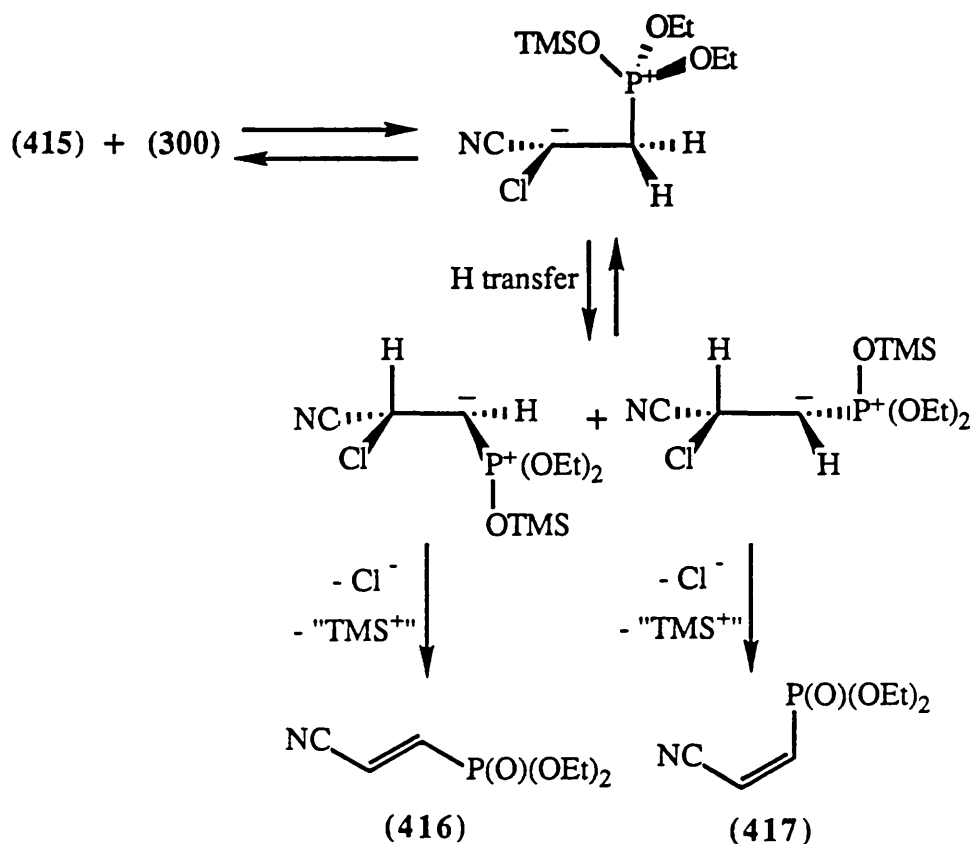
5.9 Addition to Other Functions

There was no addition of reagent (300) to aliphatic or aromatic nitriles, R-CN, where R is methyl, (4-nitrophenyl)methyl, ethoxycarbonyl, phenyl, 4-nitrophenyl and 4-methoxyphenyl. However, 2-chloroacrylonitrile (**415**) underwent a reaction with (300) to afford a product which is the adduct of (300) and (**415**) with loss of TMSCl, and is obtained as single geometric isomer. No reaction occurred when diethyl phosphite and (**415**) are refluxed together. This observation is similar to the reported reactivity of triethyl phosphite and the lack of reactivity of diethyl phosphite towards methyl 2-chloroacrylate.¹⁴⁰ Based on physical data, we have assigned the structure (**416**) to this



Scheme 146

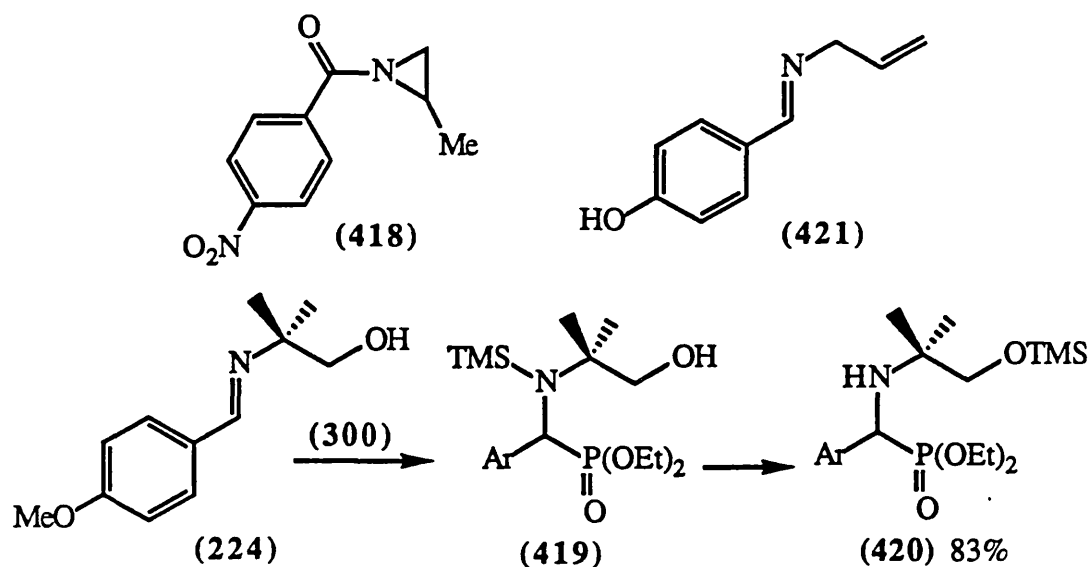
compound (Scheme 146). The *trans* geometry of the alkene is deduced from the large (18 Hz) proton-proton coupling. A mechanism for this reaction is proposed in Scheme 147, involving a Michael addition followed by 1,2- proton shift to afford a ylide, and elimination of chloride. As can be seen, provided there are no rotational restrictions, both the *cis* and *trans* isomers could be formed. The selectivity possibly arises from rotation prior to proton transfer to give preferentially the rotamer in which the two electron withdrawing groups, cyano and the phosphonate are *anti*, allowing minimum dipole repulsion (Scheme 147).



Scheme 147

We made a brief study of the reactivity of silylated phosphite (300) towards a selection of other functionalities. This was not meant to be comprehensive, rather to provide a general guide to the extent of functional group tolerance.

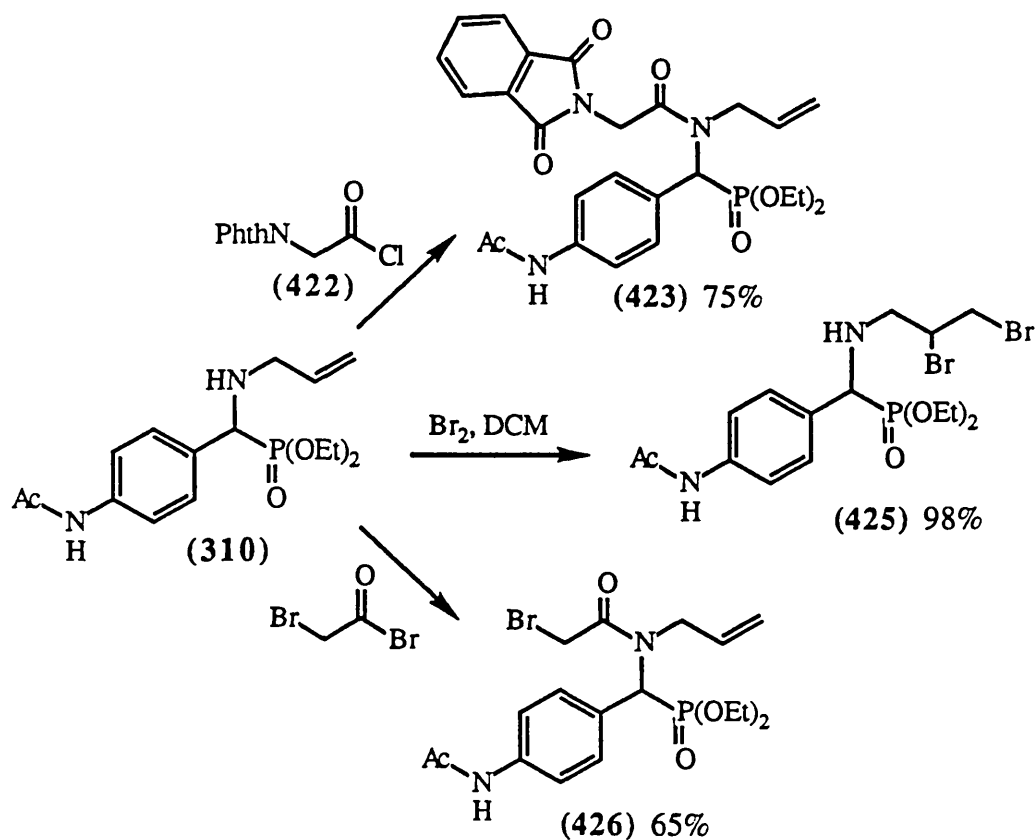
Aziridine (418) remained untouched by silylated phosphite (300). Addition to imine (224) which contains an unprotected hydroxyl group did not pose any problem; the O-silylated adduct (420) was obtained probably by silicon transfer from nitrogen to oxygen in (419). However with imine (421) a very complex reaction resulted. We have already seen that addition to an imine with an unactivated bromo group proceeds smoothly (Scheme 122, imine 332).



Scheme 148

5.10 Reactions of α -Amino Phosphonates

All α -amino phosphonates are prone to retro reaction to afford the starting imine and phosphite when treated with strong base (see Scheme 77, Chapter Four). However, nitrogen could be acylated without any difficulty in triethylamine. The olefin in the allyl group underwent bromine addition but is not readily dihydroxylated or epoxidised (Scheme 149).



Scheme 149

5.11 Conclusions

The kinetic enhancement in their nucleophilic reactivity, which results from O-silylation, of phosphorus (III) acids, allows these species to be used to access a range of organophosphorus compounds under *mild* conditions. Differences in reactivities of functional groups are magnified and hence modest, sometimes significant, selectivities are encountered. In addition to functional group selectivity, preferential steric and electronic interaction is also obtained in the form of modest diastereoselection. Furthermore, these selectivities can be rationalised in terms of stereoelectronic concepts.

Though the role of silylation is mainly to cause a kinetic enhancement for additions, it should not be assumed that the pattern of reactivity of the silylated and non-silylated species are always similar. Occasionally differences in reactivity or pattern of products are encountered.

One aspect of the value of silylated phosphites in synthesis has already been encountered. The combination of better yields and cleaner, more selective reactions should in future provide convenient routes to more complex organophosphorus compounds.

Chapter Six

Experimental

6.1 Introduction

Apparatus. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^1H N.m.r spectra were obtained on a Jeol GSX300 spectrometer operating at 270 MHz or Bruker AM500 operating at 500 MHz. ^{13}C N.m.r. spectra were obtained on a Jeol GSX300 operating at 68 MHz or a Bruker AM500 operating at 125 MHz. ^{31}P N.m.r spectra were obtained on a Jeol FXQ90 spectrometer operating at 36 MHz. All chemical shifts are reported in ppm with positive values being downfield from the standard. For proton nmr, the signal of tetramethylsilane or solvents' residual proton (7.26 ppm for CHCl_3 and 2.50 ppm for DMSO) were used as internal reference. For carbon nmr, the signal of CDCl_3 (at 77.0 ppm) was used as internal reference. For phosphorus nmr, a 0.1M solution of diethyl phosphite in CDCl_3 was used as an external reference (δ_{p} 6.50 ppm). Multiplicity of the signals are described as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants are reported in Hz. Infra-red spectra were measured on a Perkin-Elmer 1710 FTIR spectrometer. Mass spectra were obtained on an AE1 MS12 or a VG Micromass 7070B or a VG Analytical ZAB-E mass spectrometer (courtesy of SERC mass spectroscopy centre at Swansea) using electron impact, chemical ionisation or fast atom bombardment techniques. Ozonolysis was carried out by ozone generated from a commercial ozoniser. The amount of ozone was calibrated at 40 lh^{-1} flow of oxygen against the applied voltage as follows: 1.2% v/v at 100 v, 2.8% v/v at 120 v and 3.5% v/v at 150 v.

Materials. Commercially available compounds were purified where necessary. Dichloromethane and 1,2-dichloroethane were distilled from P_2O_5 and triethylamine was distilled from potassium hydroxide under an inert atmosphere prior to use. Chlorotrimethylsilane was distilled and stored under argon. Ethyl acetate and petroleum ether b.p. 40-60 $^{\circ}\text{C}$ (light petroleum) for chromatography and recrystallisations were distilled before use. Tetrahydrofuran was distilled from potassium/sodium amalgam and dimethylformamide was distilled at reduced pressure from alumina after drying over barium oxide. Benzene was dried over sodium wire, distilled from P_2O_5 , and stored over molecular sieves. Acetonitrile was dried over, and distilled from, calcium hydride and was stored over molecular sieves. Concentrations of butyllithium solutions were established by double titrations.^{141a}

Chromatography. Thin layer chromatography was performed on Merck Kieselgel 60 GF₂₅₄ aluminium-backed plates. Visualisation was by viewing under UV light (245 nm or 360 nm), or by immersion in a solution of ammonium molybdate hexahydrate (50g) in sulfuric acid (10%) followed by heat, or in an iodine tank. For thiazolidines, a sulfur sensitive spray was also used. It was prepared by dissolving sodium azide (3.5 g) in a 0.1N aqueous solution of iodine. Flash chromatography^{141b} was performed on 40-60 mesh silica (Merck Kieselgel 60H or May & Baker Sorbsil 60C) or Brockmann I neutral alumina, as supplied by BDH.

6.2 Experimental For Chapter Four

*Diethyl 2-propenylphosphonate*¹⁴² (**176**). Sodium (1.95 g, 84.8 mmol) was added in six portions to liquid ammonia (250 ml) with vigorous stirring. Freshly distilled diethyl phosphite (11.7 g, 84.7 mmol) was added dropwise (allowing up to 10 seconds between drops towards the end of the addition to ensure total consumption of diethyl phosphite) until the blue colour of solution had discharged. Freshly dried and distilled allyl bromide (12.5 g, 100 mmol) was added at such a rate as to maintain a gentle reflux and the colourless solution was left for 2 h. Evaporation of ammonia, accompanied by addition of ether (150 ml every 30 min) and removal of solid salt at the end afforded a colourless ethereal solution of the required product. Evaporation of ether followed by bulb-to-bulb distillation of the residue (120 °C, 40 mmHg) afforded the required compound as a colourless liquid (12.92 g, 88%) with a pungent smell. Physical data were in accordance of that published in literature.¹⁴² $\delta_{\text{P}}\{\text{H}\}$ (36.2 MHz, CDCl_3) 26.2 ppm.

Diethyl formylmethylphosphonate (**177**). Diethyl 2-propenylphosphonate (**176**) (3.75 g, 20 mmol) in dichloromethane (40 ml) / methanol (10 ml) solution was ozonised (flow of oxygen: 40 lh^{-1} ; voltage 120 v) for 3 h at -72 °C. Argon was then bubbled through this solution for 10 min and dimethylsulphide was added and the solution was brought to room temperature overnight. The residue, after evaporation of solvent, was subjected to slow bulb-to-bulb distillation to afford DMSO as a forerun (30 °C at 0.38 mmHg) and the title compound (80 °C at 0.38 mmHg) as a colourless oil (3.10 g, 82%); ν_{max} . (film) 3371, 2986, 2912, 1724 (C=O), 1633, 1618, 1445, 1395, 1250, 1165, 1027, 974, 789 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.28 (6H, t, J 7 Hz, 2 x CH_3), 3.02 (2H, ddd, J_{HH} 3.2 Hz, 0.9 Hz, J_{HP} 22 Hz, CH_2P), 4.05-4.15 (4H, m, CH_2O), 9.59 (1H, t, J 0.9 Hz, CHO); $\delta_{\text{C}}\{\text{H}\}$ (68 MHz, CDCl_3) 16.25 (d, J_{CP} 6Hz, CH_3), 43 (d, J_{CP} 128Hz, CH_2P), 62.63 (d, J_{CP} 7.4 Hz, CH_2O), 193 (d, J_{CP} 6Hz, CHO); $\delta_{\text{P}}\{\text{H}\}$ (36.2 MHz, CDCl_3) 18.1 ppm; m/z (70eV, 140 °C) 181 (M^+ , 1), 125 (100), 97 (77), 81 (56), 107 (55), 80 (33), 96 (32) and 27 (32). 2,4-Dinitrophenylhydrazone derivative m.p. 109-110 °C (Lit.¹⁴³ 111-112 °C).

Diphenylmethyl 2(R,S)-(diethylphosphonomethyl)-5,5-dimethyl-1,3-thiazolidine-4(R)-carboxylate (**178**). Diethyl formylmethylphosphonate (**177**) (2.0 g, 11mmol) was added to a stirred suspension of (R)-penicillamine in methanol (50 ml). After 2 h at room temperature all the solid had dissolved but stirring was continued for 12 h. 2(R,S)-(Diethylphosphonomethyl)-5,5-dimethyl-1,3-thiazolidine-4(R)-carboxylic acid could

be crystallised over a 24 h period from the reaction mixture by reducing the volume of solvent by two-thirds and cooling the methanolic solution. For convenience, the solvent was totally removed under vacuum and the residue was dissolved in the minimum acetonitrile and diphenyldiazomethane (2.2 g, 11.3 mmol) was added in small portions ensuring total discharge of pink colour of diazo before the next addition. At the end of addition, the solvent was evaporated and the residue was chromatographed to give the *title compound* as a colourless gummy oil (4.51 g, 86% from (177)) in 18:82 ratio of diastereomers. (Found: C, 60.2; H, 6.8; N, 3.0. $C_{24}H_{32}NO_5PS$ requires C, 60.4; H, 6.75; N 2.9%); ν_{\max} . (film) 3276, 3064, 3033, 2978, 2929, 1741 (C=O), 1496, 1455, 1391, 1369, 1245 (P=O), 1165, 1099, 1028, 966, 875, 808, 760, 702, 647, 607 and 531 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.02 (3H, s, 5- CH_3), 1.32 (6H, t, J 7 Hz, 2 x ester CH_3), 1.63 (s, 3H, s, 5- CH_3), 2.30 (1H, dd, J 11 Hz, 6.5 Hz, 1'-H), 2.36 (1H, dd, J 11 Hz, 6.5 Hz, 1'-H), 3.72 (1H, bm, 4-H), 4.07-4.20 (4H, m, 2 x CH_2O), 4.85 (1H, bm, 2-H), 6.98 (1H, s, Ph_2CH), 7.30-7.4 (10H, m, aromatic H); $\delta_p\{H\}$ (36.2 MHz, $CDCl_3$) 25.5 (major) and 24.9 (minor) ppm; $\delta_C\{H\}$ (68 MHz, $CDCl_3$) 16.4 (d, J_{CP} 6Hz, CH_3), 28.2 (5-Me), 29.2 (5-Me), 33.0 (d, J_{CP} 140Hz, CH_2P), 59.7 (5-C), 61.4 (4-C), 61.6 (d, J_{CP} 7 Hz, ester methylene), 61.7 (d, J_{CP} 7 Hz, ester methylene), 77.9 (Ph_2C), 126.9-128.6 (aromatic C's), 139.3 (carbonyl C); m/z (70 eV, 140 °C) 477 (M^+ , 0.1), 310 (M^+ - Ph_2CH , 48), 266 (M^+ - Ph_2CH - CO_2 , 38), 167 (Ph_2CH , 100), 111 (23), 94 (24), 83 (23), 79 (32) and 65 (19); m/z (FAB, pNBA) 478 (MH^+ , 15), 310 (6), 266 (6), 168 (16), 167 (100) and 77 (7).

*Ethyl phenylphosphonite*¹⁴⁴ (179). Pyridine (3.2 ml) was carefully added to a vigorously stirred solution of freshly distilled ethyl chloroformate (4.0 ml) and phenylphosphinous acid (5.6 g, 40 mmol) in chloroform (175 ml) at room temperature. Once the effervesence had stopped, the solution was left to stir in a 40 °C water bath for 15 min and then the solution was poured into 0.1M hydrochloric acid (30 ml) and the organic layer was separated. After washing with water (50 ml) and drying (Na_2SO_4) the solvent was evaporated thoroughly to yield the required product as a colourless oil (6.8 g, quantitative). Physical data were in accordance of that published in literature.¹⁴⁴ $\delta_p\{H\}$ (36.2 MHz, $CDCl_3$) 23.8.

Ethyl (1-hydroxy-3-methylbut-2-enyl)phenylphosphonate (180). Ethyl phenylphosphonite (5.1 g, 30 mmol) and 2-methylbut-2-enal (2.52 g, 30 mmol) were added to KF (10 g) and the mixture was stirred for 1 h until solidified. Dichloromethane

(60 ml) was added and stirring was resumed for a further 5 min. Filtration of solid and evaporation of solvent affords an oil which was recrystallised from dichloromethane /petroleum to afford the *title compound* as white crystals (4.8 g, 63%); m.p.113-115 °C (Found: C, 61.4; H, 7.6; P, 12.5. C₁₃H₁₉O₃P requires C, 61.4; H, 7.5; P 12.2%); ν_{\max} . (nujol) 3273 (OH), 1440, 1226, 1211, 1163, 1121, 1051, 1021, 954, 857, 771, 740, 712, 698, 662, 574 and 532 cm⁻¹; δ_{H} (270MHz, CDCl₃) 1.35 (3H, t, *J* 7 Hz, CH₃), 1.48 (3H, dd, *J* 1.2 Hz, 3.2 Hz, CH_{3(c)}MeC=), 1.69 (3 H, dd, *J* 1.2 Hz, 4.4 Hz, CH_{3(t)}MeC=), 3.79 (t, 1H), 3.98-4.30 (2H, m, CH₂), 4.73 (1H, dt, *J*_P 10 Hz, *J*_H 6 Hz, 1-H), 5.15 (1H, m, 2-H), 7.40-7.84 (5H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36.2 MHz, CDCl₃) 38.2 ppm; *m/z* (70eV, 150 °C) 254 (*M*⁺, 4), 170 (87), 142 (100), 125 (32), 84 (62), 78 (98), 56 (41) and 51 (43).

Ethyl (1-diphenylmethylsilyloxy-3-methylbut-2-enyl) phenylphosphonate (181). Pyridine (0.3 ml) was added to a solution of ethyl (1-hydroxy-3-methylbut-2-enyl)phenylphosphonate (**180**) (254 mg, 1 mmol) and chlorodiphenylmethylsilane (250 mg, 11 mmol) in dry THF (10 ml). After 30 min water (10 ml) was added and the organic products were extracted with ether (2 x 50 ml). The ethereal layer was washed with saturated CuSO₄ (15 ml) and then water (2 x 15 ml) and dried (MgSO₄). Evaporation of solvent and chromatography of the residue afforded the *title compound (187)* as a colourless oil (410 mg, 91%) (Found: C, 68.2; H, 7.0. C₂₅H₃₁O₃PSi requires C, 68.5; H, 7.1%); ν_{\max} . (film) 2978, 1439, 1429, 1240 (P=O), 1216, 1161, 1121, 1068, 1035, 954, 838, 793, 766, 740, 721, 698, 663, 558 and 531 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 0.63 (3H, s, SiCH₃), 1.25 (3H, dd, *J* 0.8 Hz, 3 Hz, CH₃MeC=), 1.43 (3H t, *J* 7 Hz, ester CH₃), 1.73 (3H, d, *J* 4Hz, CH₃MeC=), 4.1-4.3 (2H, m, CH₂), 4.77 (1H, dd, *J* 10 Hz, 7 Hz, 1-H), 5.33-5.38 (1H, m, CH=), 7.32-7.64 (8H, m, aromatic H), 7.82-7.95 (2H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36.2 MHz, CDCl₃) 36.9 ppm; *m/z* (70eV, 150 °C) 367 (10), 366 (34), 365 (11), 282 (21), 281 (81), 198 (Ph₂SiO⁺, 19), 197 (100) and 137 (26).

Ethyl (1-diphenylmethylsilyloxy)formylmethanephenylphosphonate (182). Ethyl (1-diphenylmethylsilyloxy-3-methylbut-2-enyl) phenylphosphonate (**181**) (875 mg, 20 mmol) in dichloromethane (40 ml) / methanol (10 ml) solution was ozonised (flow of oxygen: 40 lh⁻¹; voltage 120 v) for 3 h at -72 °C. Argon was then bubbled through this solution for 10 min and dimethylsulphide was added and the solution was brought to room temperature overnight. The residue, after evaporation of solvent, was subjected to

chromatography to afford the *title compound* as a colourless oil (686 mg, 82%), (Found: M^+ , 412.1260. $C_{22}H_{25}O_4PSi$ requires 412.1260); ν_{max} . (film) 2980, 1732, 1240 (P=O), 1211, 1121, 1068, 1036, 954, 838, 793, 766, 741, 721, 676, 660, 560 and 512 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 0.60 (3H, s, $SiCH_3$), 1.43 (3H, t, J 7 Hz, ester CH_3), 4.12-4.28 (2H, m, CH_2), 5.33 (1H, dd, J 16 Hz, 3 Hz, 1-H), 7.30-7.64 (8H, m, aromatic H), 7.80-7.95 (2H, m, aromatic H), 9.38 (1H, m, $CH=O$); $\delta_P\{H\}$ (36.2 MHz, $CDCl_3$) 37.0 ppm; m/z (CI, NH_3) 412 (33), 198 (100).

Diphenylmethyl 2(R,S)-[1-diphenylmethylsilyoxy)-1(R,S)-butylphenylphosphono methyl]-5,5-dimethyl-1,3-thiazolidine-4(R)-carboxylate (183). Aldehyde (**182**) (420 mg, 1 mmol) was added to a stirred solution of (R)-penicillamine (150 mg, 1 mmol) in methanol (10 ml). After 24 h, solvent was removed and a solution of diphenyl diazomethane (500 mg) in acetone (10 ml) was added. After decolourisation (30-40 min) the solvent was removed and the residue was chromatographed to afford the *title compound* as a foam (diastereomeric mixture); ν_{max} . ($CHCl_3$ solution) 2980, 2931, 1740 (C=O), 1496, 1455, 1439, 1391, 1370, 1266, 1186, 1123, 1033, 961, 871, 739, 698, 647 and 604 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 0.9-1.60 (12H, m, 3 x CH_3), 3.60-4.27 (4H, m, CH_2O and H-4), 5.00-5.27 (2H, m, CHP and H-2), 6.91, 6.96, 6.97 and 7.01 (1H, s, $CHPh_2$), 7.26-7.62 (14H, m, aromatic H), 7.75-7.95 (2H, m, aromatic H); $\delta_P\{H\}$ (36.2 MHz, $CDCl_3$) 34.2 (32%), 35.7 (34%), 36.9 (18%) and 38.3 (16%) ppm; m/z (FAB, Thiodiglycol) 722 (MH^+ , 0.1), 579 (0.4), 526 (5), 170 (2), 168 (15), 167 (100), 165 (4), 141 (4) and 104 (12).

2,2-Diethoxyethanal N-benzylimine (185). Ozone from a commercial ozoniser (150 v, 40 lh^{-1} oxygen flow) was passed through a solution of acrolein diethylacetal (1.30 g, 10 mmol) in 9:1 dichloromethane/methanol (50 ml) at $-72^\circ C$ for 2h until the solution is deep blue. The ozone flow was stopped and nitrogen was passed through the solution for 5 min before dimethyl sulphide (0.9 ml) was added. The solution was brought to room temperature and stirred for 15 h. Evaporation of the solvent followed by distillation (60 $^\circ C$, 4 mmHg) afforded 2,2-diethoxyacetaldehyde (**184**) as a colourless oil (0.8 g, 60%), ν_{max} . 1744 cm^{-1} (Lit.¹⁴⁵ 1740 cm^{-1}); δ_H (90MHz, $CDCl_3$) 1.25 (6H, t, J 7 Hz, 2 x Me), 3.7 (4H, m, 2 x OCH_2), 4.6 (s, 1H, CH), 8.15 (s, 1H, CHO). 2,2-Diethoxyethanal (5.02 g, 38 mmol) was dissolved in dry dichloromethane (50 ml) and benzylamine (4.50 g, 40 mmol) was added dropwise over 5 min with cooling. The mixture was left for 15 min and potassium carbonate (5 g) was added. After standing for 15 h at $4^\circ C$ under a dry

atmosphere of argon, the solid was filtered off and the solvent was evaporated to leave a yellowish oil which on distillation (b.p. 125 °C at 1.2 mmHg) afforded the *title compound* as a colourless liquid (8.05 g, 96%), R_f 0.6 (silica gel, ether); (Found: MH^+ 222.1494. $C_{13}H_{20}NO_2$ requires 222.1494); $\nu_{max.}$ (film) 3064, 3030, 2977, 2878, 1678 (C=N), 1497, 1454, 1374, 1291, 1123, 1062, 1028, 736 and 699 cm^{-1} ; δ_H (90 MHz, $CDCl_3$) 1.23 (6H, t, J 7Hz, 2 x CH_3), 3.64 (4H, m, 2 x CH_2 acetal), 4.62 (2H, s, $PhCH_2$), 4.83 (1H, d, J 5Hz, CH), 7.28 (5H, m, aromatic H) and 7.62 (1H, d, J 5Hz, CH=N); m/z (70 eV, 170 °C) 177 (14), 103 (100), 91 (65) and 75 (46); m/z (CI, NH_3) 222 (MH^+ , 100), 196 (65) and 103 (59).

Diethyl 1-(benzylamino)-2,2-(diethoxy)ethanephosphonate (186a).

Chlorotrimethylsilane (0.35 ml, 1.1 eq) was delivered to a stirring solution of diethyl phosphite (0.35 g, 2.53 mmol) and triethylamine (0.39 ml, 1.1 eq) in dichloromethane (50 ml) maintained at 0 °C and under an atmosphere of argon. Imine (**185**) (0.56 g, 2.53 mmol) was added after 15 min and the solution was brought to room temperature. After 5 h, the reaction mixture was poured into water (50 ml) and organic products were extracted with dichloromethane (2 x 75 ml). Combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed to afford the *title compound* as a colourless oil (720 mg, 79%), (Found: C, 57.0; H, 8.5; N, 4.1. $C_{17}H_{29}NO_5P$ requires C, 57.0; H, 8.2; N, 3.9%); $\nu_{max.}$ (film) 2979, 2905, 1455, 1392, 1373, 1343, 1245, 1109, 1029, 966, 734, 700 and 666 cm^{-1} ; δ_H (270MHz, $CDCl_3$) 1.17 (6H, t, J 7Hz, acetal CH_3), 1.29 (6H, dt, J 5Hz, 7Hz), 2.00 (1H, s, NH), 3.07 (1H, dd, J_P 15Hz, J_H 4Hz, 1-H), 3.36-3.70 (4H, m, CH_2 's), 3.98 (2H, d, J 3 Hz), 4.0-4.2 (4H, m, CH_2 's), 4.76 (1H, t, J 4Hz, 2-H), 7.2-7.4 (5H,m); δ_C (68MHz, $CDCl_3$) 15.2 (q, acetal Me), 15.3 (q, acetal Me), 16.5 (dq, J 6 Hz, ester Me), 16.6 (dq, J 6 Hz, ester Me), 52.8 (t, acetal methylene), 52.9 (t, acetal methylene), 56.9 (dd, J 156 Hz, 1-C), 62.2 (dt., J 41 Hz, ester methylene), 62.3 (dt, J 51 Hz, ester methylene), 63.7 (dt, J 18 Hz, NCH_2), 102.2 (dd, J 10 Hz, 2-C), 127 (d, 2 x aromatic C), 128.2 (d, 2 x aromatic C), 128.6 (d, aromatic C) and 139 (s, aromatic C); δ_P (36MHz, $CDCl_3$) 23.9 ppm; m/z (70 eV, 100 °C) 359 (M^+ , 3), 313 (14), 256 (10), 110 (25), 103 (89), 91 (100) and 83 (24).

Thermal addition of diethyl phosphite to imine (185). Imine (**185**) (0.55 g, 25 mmol) was added to diethyl phosphite (0.34 g, 25 mmol) and the resulting solution was heated at 110 °C for 10 min. The cooled residue was chromatographed (silica gel, ether) to afford (**186a**) as a pale yellow oil (0.50 g, 55%). Physical data were in accordance with that reported above.

Butyl [1-(benzylamino)-2,2-(diethoxy)ethane]phenylphosphinate (186b).

Chlorotrimethylsilane (0.35 ml, 1.1 eq) was delivered to a stirring solution of n-butyl phenylphosphinate (0.51 g, 2.53 mmol) and triethylamine (0.39 ml, 1.1 eq) in dichloromethane (50 ml) maintained at 0 °C and under an atmosphere of argon. Imine (185) (0.56 g, 2.53 mmol) was added after 15 min and the solution was brought to room temperature. After 5 h, the reaction mixture was poured into water (50 ml) and organic products were extracted with dichloromethane (2 x 75 ml). Combined organic extracts were dried (Na₂SO₄) and evaporated. The residue was chromatographed to afford the *title compound* as a colourless oil, yield 81%, (Found M^+ 419.2227. C₂₁H₃₀NO₄P requires 419.2225); ν_{\max} . (film) 2973, 2932, 2874, 1455, 1440, 1373, 1341, 1226, 1120, 1063, 1024, 975, 894, 734, 698 and 666 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 0.95 (3H, t, J 7 Hz, acetal Me), 1.05 (3H, t, J 7 Hz, acetal Me), 1.2 (3H, t, J 7 Hz, ester Me), 1.34-1.4 (2H, sextet, J 7 Hz, CH₂Me), 1.6-1.75 (2H, quintet, J 7 Hz, CH₂CH₂Me), 2.15 (bs, 1H, NH), 3.2 (1H, dd, J 5 Hz, 14 Hz, 1-H), 3.20-4.15 (8H, m, 4 x CH₂), 4.80 (1H, t, J 5 Hz, 2-H), 7.20-7.25 (5 H, m, aromatic H), 7.40-7.60 (3H, m, aromatic H), 7.75-7.90 (2H, m, aromatic H), m/z (70 eV, 100 °C) 419 (M^+ , 0.6), 373 (M^+ - EtO, 64), 345 (M^+ - BuO, 22), 344 (31), 143 (46), 103 (30), 91 (tropolium ion, 100), 86 (30) and 84 (45).

Thermal addition of butyl phenylphosphinate to imine (185): Imine (185) (0.55 g, 25 mmol) was added to n-butyl phenylphosphinate (0.50, 25 mmol) and the mixture was heated to 70 °C for 20 min. The cooled residue was directly chromatographed to afford (186b) as a pale yellow oil (0.45 g, 43%). Physical data were in accordance with that reported above.

Ethyl [1-(benzylamino)-2,2-(diethoxy)ethane]phenylphosphinate (186c).

Chlorotrimethylsilane (0.35 ml, 1.1 eq) was delivered to a stirring solution of ethyl phenylphosphinate (179) (0.43 g, 2.53 mmol) and triethylamine (0.39 ml, 1.1 eq) in dichloromethane (50 ml) maintained at 0 °C and under an atmosphere of argon. Imine (185) (0.56 g, 2.53 mmol) was added after 15 min and the solution was brought to room temperature. After 15 h, the reaction mixture was poured into water (50 ml) and organic products were extracted with dichloromethane (2 x 75 ml). Combined organic extracts were dried (Na₂SO₄) and evaporated. The residue was chromatographed to afford the *title compound* as a colourless oil, (828 mg, 83%), (Found: C, 64.7; H, 8.0; N, 3.6. C₂₁H₃₀NO₄P requires C, 64.4; H, 7.7; N, 3.6%); ν_{\max} . (film) 3509, 3061, 3028, 2977,

2899, 2331, 1778, 1592, 1455, 1440, 1373, 1342, 1227, 1120, 1062, 952, 750, 698, 556 and 510 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) (* refers to the distinguishable signals of the minor diastereomer) 1.00 and 1.02* (3H, t, J 7Hz, ester Me), 1.16* and 1.18 (3H, t, J 7Hz, acetal Me), 1.29 and 1.30* (3H, t, J 7Hz, acetal Me), 2.08 (1H, bs, NH), 3.19* and 3.24 (2H, dd, J 15 Hz, 4 Hz, NCH_2), 3.36-4.20 (7H, m, 1-H and 3 x CH_2), 4.76* and 4.84 (1H, t, J 4 Hz, 2-H), 7.18-7.25 (5H, m), 7.39-7.54 (3H, m), 7.78-7.88 (2H, m); δ_{P} (36 MHz, CDCl_3) 40 (66%) and 39 (34%) ppm; m/z (70 eV, 150 °C) 391 (M^+ , 2), 345 (M^+ - EtO, 64), 318 (11), 317 (56), 288 (9), 116 (26), 222 (42), 176 (24) and 103 (100).

Addition of anion of (179) to imine (185): n -Butyllithium (1.0 ml, 1.58M) was delivered to a stirred solution of (179) (270 mg, 1.59 mmol) in THF (35 ml) at -72 °C under an atmosphere of dry argon. After 15 min, imine (185) (360 mg, 1.62 mmol) was delivered as a THF solution. The solution was allowed to come to room temperature after 30 min and after 3 h total reaction time, saturated ammonium chloride was added. Extraction of organic products by ether (3 x 100 ml) followed by drying (MgSO_4) and evaporation of solvent afforded an oil which was chromatographed to afford non-reacted imine (140 mg, 40% recovery) (186c) as an oil (133 mg, 20% based on starting phosphite). Physical data were in accordance with that reported above.

Butyl 1-(N-acetyl-N-benzylamino)-2,2-diethoxyethylphenylphosphinate (187). Acetic anhydride (2.00 g, 5.4 eq.) was added to a stirred solution of butyl 1-benzylamino-2,2-diethoxyethylphenylphosphinate (186b) (1.50 g, 3.58 mmol) and pyridine (1.60 g, 5.5 eq.) in dichloromethane (20 ml) at 0 °C under a dry nitrogen atmosphere. The solution was brought to room temperature and left stirring for 15 h. Dichloromethane (50 ml) and water (30 ml) were added and the organic and aqueous layers were separated. The dichloromethane extract was washed with water (10 ml), saturated CuSO_4 solution (20 ml), and then water again (10 ml), and dried over MgSO_4 . The original aqueous layer was further extracted with ether (50 ml) and the ethereal layer was shaken with sat. sodium bicarbonate solution (10 ml) and then saturated CuSO_4 solution (20 ml), washed with water (10 ml) and brine (10 ml), and added to the other organic extracts for drying. Evaporation of solvent afforded a pale yellow oil from which pyridine was thoroughly removed under high vacuum. The remaining oil was chromatographed on silica gel to afford the *title compound* as a colourless oil (1.27 g, 77%), R_f 0.45 (ethyl acetate); ν_{max} . (film) 3061, 2962, 2933, 1661, 1456, 1440, 1407,

1373, 1351, 1226, 1120, 1062, 1027, 976, 734 and 698 cm^{-1} ; δ_{H} (90 MHz, CDCl_3) 0.88 (6H, tm, J 7 Hz, ester and acetal CH_3), 1.2 (3H, t, J 7 Hz, acetal CH_3), 1.4 (2H, m, CH_2Me), 1.6 (2H, m, $\text{CH}_2\text{CH}_2\text{Me}$), 2.05 (3H, s, acetate CH_3), 3.2-4.2 (9H, m, H-1 and CH_2N and 3 x CH_2O), 4.9 (1H, t, J 5 Hz, H-2), 7.2-7.9 (10H, m, aromatic H); m/z (70 eV, 180 °C) 461 (M^+ , 2.2), 415 (4), 387 (20), 143 (33), 103 (100), 91 (67), 75 (26).

Hydrolysis of acetal (187). To a stirred solution of acetal (187) (460 mg, 1.0 mmol) in DCM under argon at -78 °C was added a DCM solution of BBr_3 (2M, 5 ml) and the resulting colourless solution was left stirring for 2 h. Under inert atmosphere of argon, the solution was added dropwise to a mixture of K_2CO_3 (3 g) in methanol (15 ml) at -78 °C and the mixture was then brought to room temperature over 30 min. Filtration afforded a colourless solution which on evaporation of solvent afforded an orange oil. Chromatography (0-10% methanol in ether, silica) afforded a red oil (37 mg, 11%) which was identified as aldehyde (189) on the basis of NMR. δ_{H} (270 MHz, CDCl_3) 0.8 (3H, t, J 7 Hz, ester CH_3), 1.1-1.6 (4H, m, MeCH_2CH_2), 5.8-4.05 (4H, m, CH_2O and CH_2N), 5.75 (1H, dt, J Hz, 1H), 7.1-7.55 (m, 10H, aromatic H), 7.55 (1H, dd, J Hz, CHO); $\delta_{\text{C}}\{\text{H}\}$ (68 MHz, CDCl_3) 13.6 (CH_3), 18.8 (CH_2Me), 32.4 (d, J_p 7Hz, OCH_2CH_2), 56.1 (d, J_p 2.5 Hz, CH_2Ph), 64.7 (d, J_p 6Hz, OCH_2), 118.4 (d, J_p 141Hz, CP), 128-137 (m, aromatic H), 140.5 (d, J_p 10Hz, CHO).

Treatment of (178) with lithium iodide. Lithium iodide (67 mg, 0.5 mmol) was added to a solution of compound (178) (238 mg, 0.5 mmol) in dry THF (5 ml) and the mixture was stirred for 10 min until all the solid had dissolved. The solution was cooled down and after 24 h at 4 °C crystals of (192) had precipitated (190 mg, 66%), m.p. 132 °C (Found: C, 47.1; H, 5.6; N, 2.1. $\text{C}_{24}\text{H}_{32}\text{NO}_5\text{PS}\cdot\text{LiI}$ requires C, 47.15; H, 5.3; N, 2.3%); ν_{max} (nujol) 3451 (NH), 1727 (C=O), 1609 (C=C), 1496, 1334, 1275, 1223, 1204 (P=O), 1158, 1119, 1054, 1016, 913, 846, 814, 757, 740, 705, 639, 606 and 538 cm^{-1} ; δ_{H} (270 MHz, DMSO-d_6) 1.00 and 1.01 (3H, s, 5- CH_3), 1.13 and 1.21 (6H, t, J 7 Hz, and dt, J 1.5 Hz, 7 Hz, ester CH_3), 1.55 and 1.56 (3H, s, 5- CH_3), 2.1-2.4 (2H, m, CH_2P), 3.76 and 4.43 (s and dd, J 8 Hz, 11 Hz, 4-H), 3.86-4.04 (4H, m, OCH_2), 4.67 and 4.91 (dheptet, J 2 Hz, 8 Hz and pentet, J 8 Hz, 2-H), 6.92 and 6.93 (1H, s, CHPh_2), 7.23-7.48 (10H, m, aromatic H); δ_{p} (36 MHz, CDCl_3) 30.6 ppm; m/z (70 eV, 230 °C) 168 (20), 167 (100), 166 (23), 165 (137), 156 (87), 152 (11), 127 (13) and 63 (6); m/z (FAB, Thiodiglycol) 484 (MLi^+ , 25).

Diphenylmethyl 2(R,S)-(diethylphosphonomethyl)-5,5-dimethyl-1,3-thiazolidine-3-carbamoylchloride-4(R)-carboxylate (193). Compound (178) (238 mg, 0.5 mmol) was dissolved in CCl_4 (5 ml) and imidazole (34 mg, 0.5 mmol) and triphosgene (50 mg, 0.5 mmol) were added. The solution was refluxed for 3 h and then left to cool. The solvent was removed at reduced pressure and the residue was chromatographed to afford the title compound as an oil (142 mg, 55%), (Found: C, 54.7; H, 5.75; N, 2.65; S, 6.3. $\text{C}_{25}\text{H}_{31}\text{NO}_6\text{PSCl}$ requires C, 55.65; H, 5.8; N, 2.6; S, 5.9%), [Found: $M-(\text{CHPh}_2)^+$ 372.0435. $\text{C}_{25}\text{H}_{31}\text{NO}_6\text{PSCl}$ requires 372.0437), ν_{max} . (film) 2981, 2932, 1746 (C=O's), 1496, 1456, 1392, 1373, 1305, 1251, 1179, 1129, 1098, 1029, 969, 804, 758, 736, 701, 647, 600 and 509 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.27 (3H, s, 5- CH_3), 1.30 (6H, t, J 7 Hz, ester CH_3), 1.57 (3H, s, 5- CH_3), 2.50 (1H, ddd, J 11 Hz, 2 Hz, 18 Hz), 3.06 (1H, ddd, J 2 Hz, 5 Hz, 22 Hz, HCP), 4.00-4.12 (4H, m, CH_2O), 4.79 (1H, d, J 2 Hz, 3-H), 5.35 (1H, ddd, J 2 Hz, 5 Hz, 11 Hz, 2-H), 6.96 (1H, s, CHPh_2), 7.28-7.35 (10H, m, aromatic H); δ_{p} (36 MHz, CDCl_3) 23.88 (78%) and 23.53 (22%) ppm; m/z (70 eV, 230 °C) 372 (7), 168 (17), 167 (100), 166 (17), 165 (32), 138 (13), 64 (13), 36 (22) and 29 (16).

Hydrolysis of (178). Compound (178) (200 mg, 0.42 mmol) was dissolved in ethanol (5 ml) and aqueous sodium hydroxide was added (15%, 5ml, ca. 4.5 equivalent). This solution was stirred at room temperature for thirty-five days at which point tlc analysis of the reaction mixture showed all the starting material was consumed. Addition of acid to neutralise the solution was followed by precipitation of benzhydrol which was filtered and dried (54 mg, 70%) m. p. 66 °C, Lit.¹⁴⁶ m. p. 67 °C. Evaporation of solvent left a residue which when analysed by ^{31}P nmr showed a major peak at 22.5 ppm (D_2O).

2-(Toluenesulphonatehydroxymethyl)pyrrolidine (196). Tosyl chloride (1.91 g, 10 mmol) was added in five equal portions to a cold, stirred solution of prolinol¹⁴⁷ (1.0 g, 10 mmol) and triethylamine (1.38 ml, 10 mmol) in DCM (50 ml) (Caution! Exothermic reaction). After addition was complete the solution was left at room temperature for 1 hour after which water (50 ml) was added and the organic products were extracted with DCM (2 x 150 ml). Drying followed by evaporation of solvent gave an oil which was chromatographed to afford the required compound as a white solid (2.2 g, 87%), ν_{max} . (nujol) 3534 (NH), 1595, 1337, 1291, 1200, 1156, 1092, 1037, 1011, 997, 821, 768, 723, 710, 683, 668, 647, 609, 591 and 552 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.39-1.51 and 1.63-1.84 (4H, m, $-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{N}$), 2.44 (3H, s, ArCH_3), 2.78 (1H, dd, J 7 Hz, 5

Hz, NCHRR'), 3.26 (1H, dt, J 10 Hz, 7 Hz, CHHOTs), 3.45 (1H, dt, J 10 Hz, 5 Hz, CHHOTs), 3.60-3.72 (2H, m, CH₂N), 7.33 (2H, dd, J 9 Hz, 0.5 Hz, aromatic H), 7.73 (2H, d, J 9 Hz, aromatic H); m/z (70 eV, 100 °C) 255 (M^+ , 1), 226 (6), 225 (13), 224 (100), 155 (37), 92 (96), 91 (63), 65 (10) and 41 (7).

Diethyl [2-(toluenesulphonatehydroxymethyl)pyrrolidine]phosphoramidite (197). A solution of prolinol O-tosylate (196) (2.54 g, 10 mmol) in triethyl amine (1.4 ml, 10 mmol) was added to a stirred solution of diethyl phosphochlororidate (1.3 ml, 11 mmol) in toluene (250 ml). After 17 hours, the precipitated triethylammonium chloride was filtered, dried, and weighed (1.36 g, 99%) and solvent was removed from the filtrate at reduced pressure. The residue was dissolved in petroleum ether (40-60 °C b.p. fraction) and quickly passed through a pad (6.5 cm diameter, 5 cm depth) of neutral alumina. Removal of solvent affords the *title compound* as an oil (3.0 g, 80%) which decomposed upon distillation attempt, v_{\max} . (film) 2977, 2880, 2446, 2387, 2348, 2306, 1201, 1161, 1094, 1024, 917, 817, 741, 666, 608, 588 and 551 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.28 (6H, t, J 7 Hz, CH₃), 1.56 (2H, m, NCH₂CH₂CH₂), 1.81-1.93 (2H, m, NCH₂CH₂CH₂), 2.43 (3H, s, ArCH₃), 3.05-3.14 (1H, m, CHHOTs), 3.43 (1H, m, CHHOTs), 3.68-3.78 (2H, m, CH₂N), 3.89 (4H, pentet, $J_H = J_P$ 7 Hz, CH₂O), 4.04 [1H, t, J 7 Hz, NCH(CH₂OTs)], 7.31 (2H, dd, J_H 9 Hz, J_P 1 Hz, aromatic H), 7.73 (2H, d, J_H 9 Hz, aromatic H); δ_P (36 MHz, CDCl₃) 138 ppm; m/z (70 eV, 120 °C) 375 (M^+ , 5), 253 (20), 155 (13), 121 [(EtO)₂P, 100], 83 (15), 43 (45) and 39 (22).

2-(Toluenesulphonatehydroxymethyl)piperidine (198). Tosyl chloride (1.91 g, 10 mmol) was added in five equal portions to a cold, stirred solution of 2-(hydroxymethyl)piperidine (1.14 g, 10 mmol) and triethylamine (1.38 ml, 10 mmol) in DCM (50 ml) (Caution! Exothermic reaction). After addition was complete the solution was left at room temperature for 1 hour after which water (50 ml) was added and the organic products were extracted with DCM (2 x 150 ml). Drying followed by evaporation of solvent gave an oil which was chromatographed to afford the required compound as a white solid (2.4 g, 90%), m.p. 79 °C, v_{\max} . (nujol) 3544 (NH), 1595, 1319, 1304, 1213, 1189, 1154, 1090, 1065, 1032, 993, 929, 894, 818, 735, 659, 600, 562, 548, 519 and 504 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.14-1.62 (6H, m, CH₂-CH₂-CH₂-CH₂N), 2.18 (1H, bs, NH), 2.44 (3H, s, ArCH₃), 3.10 (1H, dt, J 7 Hz, 2 Hz, NCHRR'), 3.50-4.07 (4h, m, CH₂N and CH₂OTs), 7.33 (2H, d, J 9 Hz, aromatic H), 7.72 (2H, d, J 9 Hz, aromatic H).

Diethyl [2-(toluenesulphonatehydroxymethyl)piperidine]phosphoramidite (199). A solution of compound (198) (2.68 g, 10 mmol) in triethyl amine (1.4 ml, 10 mmol) was added to a stirred solution of diethyl phosphochlororidate (1.3 ml, 11 mmol) in toluene (250 ml). After 17 hours, the precipitated triethylammonium chloride was filtered, dried, and weighed (1.34 g, 98%) and solvent was removed from the filtrate at reduced pressure. Removal of solvent affords the *title compound* as an oil (3.0 g, 80%) which decomposed upon distillation or chromatography attempts, ν_{\max} . (film) 2990, 2883, 1449, 1201, 1261, 1104, 1024, 817, 741, 677, 608, 590 and 550 cm^{-1} ; δ_{H} (90 MHz, CDCl_3) 1.59 (6H, t, J 7 Hz, CH_3), 1.60 (6H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.74 (3H, s, ArCH_3), 3.15-3.64 (2H, m, CH_2OTs), 3.70-4.70 (7H, m, $\text{NCHR}_2\text{CH}_2\text{N}$, 2 x CH_2O), 7.63 (2H, dd, J_{H} 9 Hz, aromatic H), 8.10 (2H, d, J_{H} 9 Hz, aromatic H); δ_{P} (36 MHz, CDCl_3) 140 ppm..

*(D)-Glyceraldehyde acetonide*¹⁴⁸ (201). (D)-Mannitol (10 g) was added to a stirred solution freshly dried zinc chloride (60g) in dry acetone (300 ml) and this solution was left stirring overnight. This solution was added slowly to a mixture of ether (300 ml) and aqueous potassium carbonate (70 g in 70 ml water) with constant shaking over 5 minutes. The shaking was continued for an hour and then the solid was filtered off. Evaporation of solvent affords a solid (10.5 g) which was crystallised from ethylacetate (30 ml) and petroleum ether (570 ml, 60-80 °C b.p. fraction) to afford (D)-mannitol diacetonide as fine white needles (10.1 g, 70%), m.p. 120 °C (Lit.¹⁴⁸ 122 °C). Freshly prepared lead tetraacetate¹⁴⁹ (2.65 g), was added to a suspension of (D)-mannitol diacetonide (1.75 g) in dry benzene. After 5 minutes, the mixture was tested with iodine-starch paper and showed all the oxidant had been used up. The clear solution was decanted and benzene and acetic acid were removed by distillation through a Vigreux column. The residue (3 ml) was subjected to bulb-to-bulb distillation (100 °C, 10 mmHg) to afford the *title compound* as a colourless oil (0.60 g, 40%). This yield fell when stale lead tetraacetate was used.

1-¹Butyldiphenylsilyloxyprop-2-ene (202). Chloro¹butyldiphenylsilane (3.00 g, 1.1 mmol) was added to a stirred solution of allyl alcohol (0.60 g, 1.0 mmol) and imidazol (1.5 g, 2.2 mmol) in dichloromethane (25 ml). After 1 hour, the mixture was poured into water (50 ml) and extracted with ether (3 x 100 ml). The combined ethereal extracts were washed with water (100 ml) and then dried over MgSO_4 . Evaporation of solvent afforded an oil (3.09 g, 99%) which on bulb-to bulb distillation (125 °C, 0.2 mmHg) afforded the

title compound as a colourless oil (2.57 g, 83 %), (Found: C, 76.9; H, 8.2. $C_{19}H_{24}OSi$ requires C, 77.0; H, 8.2%); ν_{max} . (film) 3072, 2959, 2932, 2892, 2858, 1473, 1428, 1113, 1078, 1036, 1010, 998, 918, 824, 741, 702 and 617 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.08 [9H, s, $(CH_3)_3C$], 4.23 (2H, dt, J 4.4 Hz, 3.8 Hz, CH_2O), 5.13 (1H, ddd, J 10.5 Hz, 3.8 Hz, 2 Hz, terminal $H_C=C=$), 5.39 (1H, ddd, J 17 Hz, 3.8 Hz, 2 Hz, terminal $H_C=C=$), 5.94 (1H, ddd, J 17 Hz, 10.5 Hz, 4.4 Hz, $CH=CH_2$), 7.35-7.47 and 7.67-7.74 (10H, m, aromatic H); m/z (70 eV, 100 °C) 296 (M^+ , 3), 240 (22), 239 ($M^+ - ^tBu$, 100), 221 (9), 199 (23), 183 (18), 161 ($M^+ - ^tBu - Ph$, 47), 68 (13) and 41 (9).

^tButyldiphenylsilyloxyacetaldehyde (203). Ozone (generated from a commercial ozoniser at 120 v and oxygen flow rate of 40 lh^{-1}) was passed through a solution of *t*-butyldiphenylsilyloxyprop-2-ene (202) (2.00 g, 6.75 mmol) in methanol (25 ml) and dichloromethane (25 ml) at -72 °C for 75 min until the reaction was shown to be complete by tlc analysis. Nitrogen was passed through the solution for 5 minutes to remove the excess ozone and then dimethylsulfide (0.75 ml, 1.15 equiv.) was added and the solution was allowed to warm to ambient temperature over a few hours. Removal of solvent followed by bulb-to-bulb distillation of the residue (125 °C, 0.15 mmHg) afforded *t*-butyldiphenylsilyloxyacetaldehyde as a colourless oil (1.8 g, 89%), ν_{max} . (film) 3072, 3050, 2932, 2892, 2858, 1738 (C=O stretch), 1473, 1428, 1392, 1362, 1114, 1009, 999, 900, 824, 742, 703 and 611 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.10 [9H, s, $(CH_3)_3C$], 4.21 (2H, d, J 0.7 Hz, OCH_2), 7.35-7.5 (6H, m, aromatic H), 7.65-7.85 (m, 4H, m, aromatic H), 9.72 (1H, t, J 0.7 Hz, CHO); m/z (70 eV, 140 °C) 242 (18), 241 (85), 223 (25), 200 (18), 199 (100), 183 (21), 163 (91) and 105 (17).

Methyldiphenylsilyloxyprop-2-ene (204). Chlorodiphenylmethylsilane (2.56 g, 1.1 mmol) was added to a stirred solution of allyl alcohol (0.60 g, 1.0 mmol) and imidazole (1.5 g, 2.2 mmol) in dichloromethane (25 ml). After 1 hour, the mixture was poured into water (50 ml) and extracted with ether (3 x 100 ml). The combined ethereal extracts were washed with water (100 ml) and then dried over $MgSO_4$. Evaporation of solvent afforded an oil which on bulb-to bulb distillation (120 °C, 0.8 mmHg) afforded the title compound as a colourless oil (2.23 g, 88 %). (Found: C, 73.5; H, 7.0. $C_{16}H_{18}OSi$ requires C, 75.5; H, 7.1%); ν_{max} . (film) 3070, 3050, 3013, 2960, 2859, 1429, 1404, 1255, 1120, 1076, 1035, 998, 919, 831, 792, 767, 738, 722, 700 and 666 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 0.67 (3H, s, CH_3Si), 4.26 (2H, apparent t, J 2 Hz, OCH_2), 5.12 and 5.32 (2H, dm, J 11 Hz, $=CH_2$), 5.96 (1H, m, $CCH=$), 7.36-7.63 (10H, m, aromatic H); m/z (70 eV, 100

°C) 254 (M^+ , 6), 239 (M^+ - Me, 34), 198 (63), 193 (34), 176 (80), 161 (69), 137 (34), 58 (34) and 57 (100).

Methyldiphenylsilyloxyacetaldehyde (205). Ozone (generated from a commercial ozoniser at 120 v and oxygen flow rate of 40 lh^{-1}) was passed through a solution of methyldiphenylsilyloxyprop-2-ene (204) (1.00 g, 3.95 mmol) in methanol (25 ml) and dichloromethane (25 ml) at -72°C for 65 min until the reaction was shown to be complete by tlc analysis. Argon was passed through the solution for 5 minutes to remove the excess ozone and then dimethylsulfide (0.45 ml, 1.2 equiv.) was added and the solution was allowed to warm to ambient temperature over a few hours. Removal of solvent afforded a residue which could not be further purified by distillation or chromatography and was used for the next step directly, ν_{max} (film) 2932, 2890, 1740 (C=O stretch), 1470, 1430, 1407, 1377, 1124, 1009, 1000, 900, 812 and 742 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 0.63 (3H, s, SiCH₃), 3.41 (2H, s, CH₂O), 7.35-7.59 (10H, m, aromatic H).

2-Bromo-2-methylpropanal¹⁵⁰ (206). Bromine (38 g) was added dropwise over a period of 5 hours to a cold solution of 2-methylpropanal (19g) in dry ether (100 ml) containing dry dioxan (0.9 ml). At the end of the addition, the orange solution was poured into aqueous saturated sodium carbonate solution and was extracted with DCM (2 x 250). Evaporation of solvent followed by distillation through a vigroux column afforded (206) (13 g, 40%). Physical data in accordance with that reported in literature¹⁵⁰, δ_{H} (90 MHz, CDCl_3) 1.81 (6H, s, 2 x CH₃), 9.37 (1H, CH=O); ν_{max} (film) 1733 (C=N).

2-(¹Butyldiphenylsilyloxomethyl)-5,5-dimethyl-1,3-thiazolidine-4(R)-carboxylic acid (209). ¹Butyldiphenylsilyloxyacetaldehyde (203) (1.5 g, 5.0 mmol) was added to a stirred suspension of (R)-penicillamine (0.75 g, 5.0 mmol) in methanol (30 ml). A homogenous solution is obtained after 2.5 hours and Tlc analysis showed the reaction to be complete after a further 12h. Evaporation of solvent to complete dryness from this solution afforded the *title compound* (209) in quantitative yield (2.15g) and pure enough for the use in the next stage directly. An analytically pure sample may be obtained by reducing the volume of solvent by more than half by evaporation under vacuum at room temperature and inducing crystallisation by cooling this solution to -4°C (1.38 g, 64%). m.p. 171-172 °C; (Found: C, 64.4; H, 7.3; N, 3.1; S, 7.35. C₂₃H₃₁NO₃SSi requires C, 64.3; H, 7.3; N, 3.1; S, 7.45%); ν_{max} (nujol) 3263 (N-H), 1427, 1317, 1268, 1244, 1188, 1141, 1112, 1093, 1018, 994, 958, 936, 903, 824, 764, 745, 703, 690, 667 and 612 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.07 (9H, s, (CH₃)₃C], 1.33 (3H, s, 5-CH₃), 1.66 (s,

3H, 5-CH₃), 3.76 (1H, s, 4-H), 3.79 (1H, dd, *J* 11 Hz, 3 Hz, methylene H), 3.91 (1H, dd, *J* 11 Hz, 3 Hz, methylene H), 4.82 (1H, t, *J* 3 Hz, 2-H), 6.33 (2H, bs, NH and OH), 7.35-7.43 (4H, m, aromatic H), 7.66-7.75 (6H, m, aromatic H); *m/z* (70 eV, 170 °C) 372 (*M*⁺ - ^tBu, 15), 326 (*M*⁺ - ^tBu - CO₂, 9), 294 (*M*⁺ - ^tBu - Ph, 7), 199 (23), 162 (9), 160 (thiazolidine, 100), 135 (7), 128 (10) and 114 (10).

Diphenylmethyl 2-(^tbutyldiphenylsilyloxomethyl)-5,5-dimethyl-1,3-thiazolidine carboxylate (211). Compound (209) (107 mg, 0.25 mmol) was dissolved in acetone (5 ml) and diphenyldiazomethane¹⁵¹ (95 mg, 0.5 mmol) was added and the reaction mixture was left overnight. Evaporation of solvent followed by chromatography (silica, 10% ether in petrol) afforded the *title compound* as a gummy oil (137 mg, 92 %) (Found: C, 72.2; H, 6.9; N, 2.5. C₃₆H₄₁NO₃SSi requires C, 72.6; H, 6.9; N, 2.35%); *v*_{max}. (film) 2960, 2931, 2858, 1741 (C=O), 1589, 1496, 1456, 1428, 1368, 1252, 1187, 1157, 1113, 1008, 823, 759, 743, 701, 641, 608 and 505 cm⁻¹; *δ*_H (270 MHz, CDCl₃) 1.07 (3H, s, (CH₃)₃C], 1.12 (3H, s, 5-CH₃), 1.65 (3H, s, 5-CH₃), 3.63 (1H, d, *J* 12 Hz, H-1'), 3.72-3.98 (2H, m, H-1' and H-4), 4.78 (1H, dm, H-2), 7.02 (1H, s, Ph₂CH), 7.28-7.46 (20H, m, aromatic H), 7.68-7.75 (m, 4H); *m/z* (14 eV, 220 °C) 538 (*M*⁺ - ^tBu, 1), 328 (5), 327 (15), 326 (53), 294 (5), 201 (5), 200 (19), 199 (100), 168 (8) and 167 (Ph₂CH, 31).

1-Hydroxymethyl-5,5-dimethyl-1,3-thiazolidine-4(R)-carboxylic acid (210).

Glycolaldehyde dimer (208) (600 mg, 5 mmol) was add to a stirred suspension of (R)-penicillamine (1.49 g, 10 mmol) in dry methanol (50 ml). After 15 hours, the volume of the solvent was reduced to about 5 ml at which point the *title compound* separated as crystals, m. p. 160 °C (dec.), (Found: C, 44.1; H, 6.9; N, 7.2. C₇H₁₃NO₃S requires C, 44.0; H, 6.85; N 7.3%); *v*_{max}. (nujol) 1537, 1527, 1397, 1337, 1281, 1164, 1131, 1098, 1055, 1023, 871, 782, 757, 723, 677, 578, 547 and 504 cm⁻¹; *δ*_H (270 MHz, DMSO-d₆) 1.18 (3H, s, 5-CH₃), 1.52 (3H, s, 5-CH₃), 3.16 (1H, dd, *J* 11 Hz, 6 Hz, 1'-H), 3.43 (1H, dd, *J* 11 Hz, 7 Hz, 1'-H), 3.49 (1H, s, 4-H), 4.57 (1H, dd, *J* 7 Hz, 6 Hz, 2-H); *m/z* (70 eV, 150 °C) 160 (*M*⁺ - CH₂OH, 31), 114 (11), 87 (6), 75 (100), 74 (6), 70 (9), 57 (12) and 41 (24).

Diphenylmethyl 1-hydroxymethyl-5,5-dimethyl-1,3-thiazolidine-4(R)-carboxylic acid (212). Acid (211) (190 mg, 1 mmol) was dissolved in methanol (5 ml) and diphenyl diazomethane (1.05 g, 5.5 mmol) was added in five equal portions. Solvent was removed and residue was chromatographed to afford the *title compound* as an oil (302 mg, 85%),

(Found: C, 67.25; H, 6.4; N, 3.85. $C_{20}H_{23}NO_3S$ requires C, 67.2; H, 6.5; N, 3.9%); ν_{\max} . ($CHCl_3$) 3033 (OH), 2966, 2929, 2867, 1738 (C=O), 1587, 1496, 1455, 1370, 1321, 1249, 1183, 1152, 1080, 1030, 956, 914, 872, 759, 743, 700, 648 and 607 cm^{-1} ; δ_H (270 MHz, DMSO- d_6) (* refers to the distinguishable peak of the minor diastereomer) 0.96* and 0.98 (3H, s, 5-Me), 1.55* and 1.60 (3H, s, 5-Me), 3.12 (2H, bs, NH and OH), 3.33-3.81 (3H, m, CH_2O) and H-4), 4.63* and 4.75 (1H, dd, J^* 9 Hz, 5 Hz, J 5 Hz, 2 Hz, H-2), 6.94* and 6.95 (1H, s, $CHPh_2$), 7.20-7.38 (10H, m, aromatic H); m/z (70 eV, 240° C) 326 (7), 168 (17), 167 (100), 166 (10), 165 (20), 152 (8), 128 (5) and 59 (4).

5,5-Dimethyl-2-(2',2'-dimethyldioxolidin-4'-yl)-1,3-thiazolidine-4-carboxylic acid (213). (R)-Penicillamine (372 mg, 2.50 mmol) was added to a solution of 2,3-O-isopropylidenglyceraldehyde (329 mg, 2.49 mmol) in methanol (10 ml) and acetonitrile (1 ml) and the resulting solution was left stirring overnight. Evaporation of solvent under reduced pressure afforded *5,5-dimethyl-2-(2',2'-dimethyldioxolidin-4'-yl)-1,3-thiazolidine-4-carboxylic acid* as a powdery solid, δ_H (270 MHz, $CDCl_3$) 1.25 (3H, s, 5- CH_3), 1.35 (3H, s, isopropylidene CH_3), 1.45 (3H, s, isopropylidene CH_3), 1.63 (s, 3H, s, 5- CH_3), 3.5 (1H, s, 4-H), 3.79 (1H, dd, J 9 Hz, 5.5 Hz, 4'-H), 4.12 (1H, dd, J 9 Hz, 7 Hz, 5'-H), 4.33 (1H, dd, J 9 Hz, 7 Hz, 5'-H), 4.58 (1H, d, J 5.5 Hz, 2-H), 5.97 (2H, s, NH and OH); δ_C (68 MHz, $CDCl_3$) 25.5 (q), 26.5 (q), 28 (q), 28.5 (q), 67.5 (d), 68 (t), 76.5 (d), 78 (d), 110 (s), 170 (s).

Diphenylmethyl 5,5-dimethyl-2-(1'(R),2'-dihydroxyethyl)-1,3-thiazolidine-4(R)-carboxylate (215), Acid (213) was dissolved in acetonitrile (5 ml) and diphenyldiazomethane (0.5 g, 2.5 mmol) was added in small portion over a period of 2 h and the resulting mixture was left stirring for overnight. Evaporation of solvent followed by chromatography afforded *diphenylmethyl 5,5-dimethyl-2-(2',2'-dimethyldioxolidin-4'-yl)-1,3-thiazolidine-4-carboxylate* (214) as a gummy oil (0.87 g). δ_H (270 MHz, $CDCl_3$) (of 1:1 diastereomeric mixture) 1.10 and 1.04 (3H, s, 5- CH_3), 1.34 and 1.35 (3H, s, 2'- CH_3), 1.42 and 1.44 (3H, s, 2'- CH_3), 1.60 and 1.64 (3H, s, 5- CH_3), 3.61 and 3.81 (1H, dd, J 8 Hz, 6 Hz, 4'-H), 3.74 and 3.84 (1H, s, 4-H), 4.03-4.33 (2H, m, 4'-H and 5'-H), 4.60 and 4.71* (1H, dd, J 8 Hz, 5 Hz*, H-2), 6.97 and 6.99 (1H, s, $CHPh_2$), 7.28-7.40 (10H, m, aromatic H); δ_C (68 MHz, $CDCl_3$) 25.4 (q), 26.2 (q), 27.5 (q), 28.7 (q), 67.7 (t), 69 (d), 73.2 (d), 77 (d), 78 (d), 110 (s), 126-129 (m), 139 (s); m/z (14 eV, 100 °C) 198 (41), 142 (36), 141 (100), 78 (5), 77 (53), 65 (17) 51 (20) and

47 (21). This gummy oil was dissolved in acetonitrile (9 ml) and 1M hydrochloric acid (1 ml). After 3 days at room temperature, the reaction mixture was neutralised with saturated sodium bicarbonate and the organic products were extracted with ether (3 X 35 ml). Evaporation of solvent after drying (MgSO_4) afforded the *title compound* (215) as a 3:2 ratio of diastereomers. The gummy oil thus obtained may be recrystallised from chloroform-petroleum as fibrous needles to afford pure *diphenylmethyl 5,5-dimethyl-2(S)-(1,2(R)-dihydroxyethyl)-1,3-thiazolidine-4(R)-carboxylate*, R_f 0.15 (ether, silica gel), m.p. 131-132 °C, (Found: C, 65.0; H, 6.4; N, 3.5. $\text{C}_{21}\text{H}_{25}\text{NO}_4\text{S}$ requires C, 65.1; H, 6.5; N 3.6%); ν_{max} . (CDCl_3 solution) 3458, 3344, 2970, 2931, 1738 (C=O), 1496, 1456, 1390, 1371, 1323, 1299, 1250, 1184 (C-O), 1153, 1134, 1081, 1041, 992, 954, 877 and 701 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.01 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.7-2.3 (bs, 3H, 2 OH and NH), 3.52 (1H, dd, J 11 Hz, 6.5 Hz, 2'-H), 3.61 (1H, dd, J 11 Hz, 4.5 Hz, 2'-H), 3.71 (1H, s, 5-H), 4.01 (1H, ddd, J 6.5 Hz, 4.5 Hz, 2.2 Hz, 1'-H), 4.82 (1H, d, J 2.2 Hz, H-2), 6.99 (1H, s, CHPh_2), 7.28-7.38 (10H, m, aromatic H); δ_{C} (68 MHz, CDCl_3) 27.1 (q), 27.8 (q), 59.7 (s), 62.7 (t), 66.5 (d), 71.3 (d), 74.5 (d), 78.2 (d), 126-129 (m), 168.4 (s); m/z (FAB, Glycerol) 388 (M^+ , 9), 277 (2), 222 (2), 185 (21), 168 (16), 167 (Ph_2CH , 100) and 152 (2); m/z (70 eV, 180 °C) 388 (M^+ , 2), 326 (17), 167 (100), 105 (10), 77 (5).

Diphenylmethyl 5,5-dimethyl-2-[1'(R)-hydroxy-2'-(4"-methylphenylsulphonate)ethyl]-1,3-thiazolidine-4(R)-carboxylate (216). The diol (215) (4.0 mg, 10 μmol) was dissolved in DCM (2 ml) and tosyl chloride (2 mg, 10 μmol) followed by triethylamine (1.45 μl , 10 μmol) were added. The resulting solution was stirred for 4 hours and then it was poured into water (10 ml) and was extracted with DCM (2 x 10 ml). Drying followed by removal of solvent left a residue that was chromatographed to afford the required compound as a foam (5 mg, 90%), (Found: C, 62.15; H, 5.7; N, 2.5. $\text{C}_{28}\text{H}_{31}\text{NO}_6\text{S}_2$ requires C, 62.1; H, 5.8; N 2.6%); ν_{max} . (CDCl_3 solution) 3350 (OH and NH), 2965, 1742 (C=O), 1599, 1496, 1456, 1364, 1177, 1124, 1034, 1010, 910, 816, 757, 701, 684, 569 and 555 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) (1:1 ratio of diastereomers) 0.98 (3H, s, 5-Me), 1.57 and 1.63 (3H, s, 5-Me), 2.44 and 2.45 (3H, s, 4"-Me), 3.58-4.22 (4H, m, CH_2O , H-1' and H-4), 4.60 and 4.79* (1H, dd, J 18 Hz, 8 Hz, J^* 4 Hz, 2 Hz, H-2), 6.95 and 6.97 (1H, s, CHPh_2), 7.26-7.36 (12H, m, aromatic H), 7.77-7.81 (2H, m, aromatic H); m/z (70 eV, 140 °C) 388 (21), 167 (100), 166 (8), 164 (18), 152 (8), 90 (9), 44 (20), 43 (14) and 32 (12).

5,5-Dimethyl-2-(prop-2'-enyl)-1,3-thiazolidine-4(R)-carboxylate (217).

3-Methylbut-2-enal (840 mg, 10 mmol) was added to a stirred suspension of (R)-penicillamine (1.49 g, 10 mmol) in dry methanol (50 ml). After 10 hours, the volume of the solvent was reduced to about 5 ml at which point the *title compound* separated as crystals (240 mg 11%), m. p. 140 °C (dec.), major diastereomer δ_{H} (270MHz, DMSO- d_6) 1.21 (3H, s, 5-CH₃), 1.56 (3H, s, 5-CH₃), 1.61 (3H, d, *J* 1 Hz, CH₃C=), 1.67 (3H, d, *J* 1 Hz, CH₃C=), 3.46 (1H, s, H-4), 5.22 (1H, dm, *J* 10 Hz, H-2), 5.38 (1H, dm, *J* 10 Hz, CH=CMe₂); *m/z* (FAB, Glycerol) 216 (*MH*⁺, 100), 116 (16), 84 (21) and 70 (17).

Diphenylmethyl 5,5-dimethyl-2-(prop-2'-enyl)-1,3-thiazolidine-4(R)-carboxylate (218).

The above procedure was repeated but at the end of the reaction, methanol was removed to complete dryness and the residue was taken up in acetone (10 ml). Diphenyldiazomethane (2.0 g, 11 mmol) was added and the solution was stirred for 2 h. The solvent was removed at reduced pressure and the residue was chromatographed to afford the *title compound* as an oil (1.27 g, 33%), (Found: *M*⁺ 381.1763. C₂₃H₂₇NO₂S requires 381.1762); ν_{max} . (CHCl₃ solution) 3312 (NH), 2970, 2928, 1741 (C=O), 1496, 1455, 1369, 1341, 1300, 1271, 1229, 1177, 1152, 1115, 1080, 983, 954, 854, 758, 700, 648, 607 and 539 cm⁻¹; δ_{H} (270MHz, CDCl₃) 1.04 (3H, s, 5-CH₃), 1.64 (3H, s, 5-CH₃), 1.69 (3H, d, *J* 1 Hz, CH₃C=), 1.73 (3H, d, *J* 1.5 Hz, CH₃C=), 2.93 (1H, bs, NH), 3.62 (1H, s, H-5), 5.22 (1H, d, *J* 10 Hz, 1.5 Hz, CH=CMe₂), 5.38 (1H, d, *J* 10 Hz, H-2), 7.00 (1H, s, CHPh₂), 7.30-7.37 (10H, m, aromatic H); *m/z* (70eV, 110 °C) 381 (*M*⁺, 4), 214 (16), 184 (12), 183 (38), 168 (17), 167 (100), 165 (18), 105 (16) and 43 (11).

The following compounds were prepared by dehydrative condensation of the relevant aldehyde (20 mmol) and 2-amino-2-methylpropanol (1.80 g) in dichloromethane.

5,5-Dimethyl-2-(4-nitrophenyl)-1,3-oxazolidine / 4-nitrobenzaldehyde N-2,2-dimethylethanoline (222). This compound was purified by crystallisation after removal of the solvent and other volatile material, yield 88%, m. p. 59-60 °C (DCM/light petroleum), (Found: C, 59.4; H, 6.3; N, 12.6. C₁₁H₁₄N₂O₃ requires C, 59.45; H, 6.35; N, 12.6%); ν_{max} . (nujol) 3284, 1604, 1514, 1344, 1259, 1212, 1096, 1031, 1005, 965, 941, 927, 870, 853, 806, 750, 708 and 651 cm⁻¹; δ_{H} (270 MHz, CDCl₃) Imine 1.28 (6H, s, CH₃), 3.57 (2H, s, CH₂), 7.92 (2H, dd, *J* 9 Hz, aromatic H), 8.27 (2H, d, *J* 9 Hz,

aromatic H), 8.40 (1H, s, CH=N); Oxazolidine 1.28 (3H, s, 4-CH₃), 1.33 (3H, s, 4-CH₃), 3.59 (1H, d, *J* 8 Hz, 5-H), 3.74 (1H, d, *J* 8 Hz, 5-H), 5.64 (1H, s, H-2), 7.68 (2H, d, *J* 9 Hz, aromatic H), 8.22 (2H, d, *J* 9 Hz, aromatic H); *m/z* (70 eV, 120 °C) 222 (*M*⁺, 10), 221 (44), 207 (*M*⁺ - Me, 45), 192 (56), 191 (*M*⁺ - "CH₂O", 100), 145 (26), 100 (25), 56 (23) and 55 (15).

5,5-Dimethyl-2-phenyl-1,3-oxazolidine / benzaldehyde N-2,2-dimethylethanolimine (223). This compound was purified by distillation after removal of the solvent and other volatile material, yield 80%, b. p. 150 °C/ 0.3 mmHg, m. p. 60-61 °C, (Found: C, 73.2; H, 8.4; N, 7.7. C₁₁H₁₅NO requires C, 74.5; H, 8.5; N, 7.9%); *v*_{max.} (nujol) 3240, 1636 (C=N), 1579, 1379, 1353, 1316, 1294, 1271, 1209, 1184, 1161, 1072, 1011, 963, 905, 760, 696 and 512 cm⁻¹; *δ*_H (270 MHz, CDCl₃) Imine 1.31 (6H, s, CH₃), 3.52 (2H, s, CH₂), 7.31-7.52 (5H, m, aromatic H), 8.33 (1H, s, CH=N); Oxazolidine 1.27 (3H, s, 4-CH₃), 1.31 (3H, s, 4-CH₃), 3.58 (1H, d, *J* 8 Hz, 5-H), 3.72 (1H, d, *J* 8 Hz, 5-H), 5.55 (1H, s, H-2), 7.31-7.52 (5H, m, aromatic H); *m/z* (70 eV, 100 °C) 177 (*M*⁺, 7), 176 (28), 162 (*M*⁺ - Me, 7), 147 (22), 146 (*M*⁺ - "CH₂O", 100), 104 (10), 100 (12), 91 (tropylium ion, 16) and 77 (phenyl, 10).

2-(4-Methoxyphenyl)-4,4-dimethyl-1,3-oxazolidine / 4-methoxybenzaldehyde N-(1,1-dimethylethanol)imine (224). This compound was purified by crystallisation after removal of the solvent and other volatile material, m.p. 51 °C (DCM/ light petroleum), (Found: C, 69.8; H, 8.3; N, 6.65. C₁₂H₁₇NO₂ requires C, 69.5; H, 8.3; N, 6.8%); *v*_{max.} (nujol) 3154, 1640, 1608, 1515, 1381, 1353, 1303, 1267, 1171, 1108, 1063, 1028, 985, 920, 864, 827, 736, 589, 571 and 517 cm⁻¹; *δ*_H (270 MHz, CDCl₃) Imine form: 1.24 (6H, s, 2 x CH₃), 3.50 (2H, s, CH₂O), 2.26 (1H, bs, OH), 3.84 (3H, s, CH₃O), 6.93 (2H, d, *J* 9 Hz, aromatic H), 7.69 (2H, d, *J* 9 Hz, aromatic H), 8.26 (1H, s, CH=N); Oxazoline form: 1.30 (3H, s, 4-CH₃), 1.31 (3H, s, 4-CH₃), 2.17 (1H, s, NH), 2.57 (1H, d, *J* 7.5 Hz, 5-H), 3.71 (1H, d, *J* 7.5 Hz, 5-H), 3.80 (3H, s, CH₃O), 5.49 (1H, s, 2-H), 6.89 (2H, d, *J* 9 Hz, aromatic H), 7.40 (2H, d, *J* 9 Hz, aromatic H); *m/z* (70 eV, 130 °C) 207 (*M*⁺, 11), 206 (35), 177 (16), 176 (*M*⁺ - "CH₂O", 100), 135 (10), 134 (14), 121 (24) and 77 (8).

2,4,4-Trimethyl-1,3-oxazoline (225). After removal of the solvent and excess acetaldehyde, this compound was not purified, *v*_{max.} (film) 3284, 2971, 2932, 2871, 1466, 1391, 1370, 1231, 1155, 1116, 1072, 1030, 990, 907, 822, 662 and 604 cm⁻¹; *δ*_H (270 MHz, CDCl₃) 1.17 (3H, s, 4-CH₃), 1.25 (3H, s, 4-CH₃), 1.34 (3H, d, *J* 5.2 Hz,

2-CH₃), 3.40 (1H, d, *J* 7.6 Hz, H-5), 3.47 (1H, d, *J* 7.6 Hz, H-5), 4.60 (1H, quartet, *J* 5.2 Hz, H-2); *m/z* (70 eV, 140 °C) 116 (*M*⁺, 25), 110 (68), 100 (*M*⁺ - Me, 85), 85 (39), 84 (100), 58 (70), 55 (47), 42 (47) and 41 (52).

2-(4-Nitrobenzylamino)-2-methylpropan-1-ol (226). Sodium borohydride (0.81 g, 30 mmol) was added to a stirred cold solution of compound (222) (2.22 g, 10 mmol) in ethanol (50 ml) in five equal portions at 10 min intervals. After 5 h total reaction time, water (25 ml) was added slowly with vigorous stirring and then a few drops of concentrated hydrochloric acid was added until the solution was clear. This solution was extracted with chloroform (4 x 100 ml) and organic extracts were washed with water (2 x 100 ml) and dried (Na₂SO₄). Evaporation of solvent to complete dryness followed by crystallisation from petroleum ether (b. p. fraction 60-80 °C, 120 ml per gram) afforded the *title compound* as a pale yellow solid (2.02 g, 82%), m.p. 80 °C, (Found: C, 58.7; H, 7.2; N, 12.5. C₁₁H₁₆N₂O₃ requires C, 58.9; H, 7.2; N, 12.5%); *v*_{max.} (nujol) 3261, 1604, 1515, 1379, 1318, 1281, 1232, 1190, 1112, 1064, 1043, 1005, 924, 852, 819, 775, 742 and 695 cm⁻¹; *δ*_H (270 MHz, CDCl₃) 1.16 (6H, s, 2 x CH₃), 3.39 (2H, s, CH₂O), 3.81 (2H, s, CH₂N), 7.53 (2H, d, *J* 8 Hz, aromatic H), 8.18 (2H, d, *J* 8 Hz, aromatic H); *m/z* (70 eV, 130 °C) 194 (*M*⁺ - "CH₂O", 12), 193 (100), 147 (8), 136 (20) 106 (BzNH, 15), 90 (10), 89 (7) and 78 (7).

2-(Benzylamino)-2-methylpropan-1-ol (227). Sodium borohydride (0.54 g, 20 mmol) was added to a stirred cold solution of compound (223) (1.76 g, 10 mmol) in ethanol (50 ml) in five equal portions at 10 min intervals. After 5 h total reaction time, water (25 ml) was added slowly with vigorous stirring and then concentrated hydrochloric acid (1 ml) was added until the solution was clear. This solution was extracted with chloroform (5 x 100 ml) and organic extracts were washed with water (2 x 100 ml) and dried (Na₂SO₄). Evaporation of solvent to complete dryness followed by crystallisation from petroleum ether (b. p. fraction 60-80 °C, 100 ml per gram) afforded the *title compound* as a white solid (1.34 g, 76%), m.p. 53-54 °C (Petroleum ether), (Found: C, 73.7; H, 9.7; N, 7.8. C₁₁H₁₇NO requires C, 73.7; H, 9.6; N, 7.8%); *v*_{max.} (nujol) 3294, 1331, 1274, 1227, 1192, 1074, 1025, 989, 948, 843, 804, 771, 734, 697, 596, 566 and 515 cm⁻¹; *δ*_H (270 MHz, CDCl₃) 1.13 (6H, s, 2 x CH₃), 2.69 (2H, bs, NH and OH), 3.34 (2H, s, CH₂O), 3.67 (2H, s, CH₂N) and 7.27-7.32 (5H, m, aromatic H); *m/z* (70 eV, 140 °C) 162 (*M*⁺ - OH, 2), 149 (7), 148 (*M*⁺ - "CH₂O", 65), 106 (BzNH, 2), 92 (8), 91 (tropylium ion, 100), 77 (2), 65 (7), 58 (2) and 42 (2).

4,4-Dimethyl-2-oxo-3-(4-nitrophenylmethyl)-2-phenyloxazaphospholidine (228).

A solution of dichlorophenylphosphine (1.3 ml, 9.6 mmol) in benzene was added dropwise over a period of 3 h to a stirring solution of amine-alcohol (226) (2.24 g, 10 mmol) and triethylamine (2.8 ml, 20 mmol) in benzene (250 ml) under an argon atmosphere and maintained at 0 °C. After addition was complete, stirring was continued for a further hour before the solid was filtered off. Evaporation of solvent followed by chromatography afforded the title compound as a pale yellow solid, m.p. 90-94 °C (DCM/Petroleum ether), (Found: C, 58.9; H, 5.5; N, 8.1. $C_{17}H_{19}N_2O_4P$ requires C, 59.0; H, 5.5; N, 8.1%); ν_{\max} . ($CHCl_3$ solution) 2997, 1524, 1440, 1372, 1348, 1327, 1245, 1208, 1126, 1023, 901, 834, 728, 694, 666, 599, 569, 519 and 505 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.29 (3H, s, 4- CH_3), 1.31 (3H, s, 4- CH_3), 4.16 (2H, d, J_P 13 Hz, $ArCH_2$), 4.22 (1H, dd, J_H 10.5 Hz, J_P 9 Hz, OCH_2), 4.30 (1H, dd, J_H 10.5 Hz, J_P 8 Hz, OCH_2), 7.33- 7.72 (7H, m, aromatic H), 7.99 (2H, d, J 9 Hz, aromatic H); δ_C {H} (68 MHz, $CDCl_3$) 25.2 (dq, 4-Me), 25.5 (q, 4-Me), 43.6 (dt, 5-C), 59.5 (d, 4-C), 78.4 (s, $ArCH_2$), 123.4 (d, 2 x 4-nitro aromatic C), 128.4 (dd, J_P 15 Hz, 2 x phosphonyl aromatic C), 129.3 (d, 2 x 4-nitro aromatic C), 131 (s, 4-nitro aromatic C), 132.1 (dd, J_P 11 Hz, 2 x phosphonyl aromatic C), 132.3 (d, J_P 2 Hz, phosphonyl aromatic C), 145.9 (d, J 2 Hz, phosphonyl aromatic C), 147.2 (s, 4-nitro aromatic C); δ_P {H} (36 MHz, $CDCl_3$) 34.0 ppm; m/z (70 eV, 160 °C) 346 (M^+ , 3), 332 (14), 331 ($M^+ -O$, 100), 136 (25), 106 (15), 90 (7), 78 (9), 77 (8), 70 (19)

4,4-Dimethyl-2-oxo-3-(phenylmethyl)-2-phenyloxazaphospholidine (229).

A solution of dichlorophenylphosphine (1.3 ml, 9.6 mmol) in benzene was added dropwise over a period of 3 h to a stirring solution of amine-alcohol (227) (1.78 g, 10 mmol) and triethylamine (2.8 ml, 20 mmol) in benzene (250 ml) under an argon atmosphere and maintained at 0 °C. After addition was complete, stirring was continued for a further hour before the solid was filtered off. Evaporation of solvent followed by chromatography afforded the title compound as a pale yellow oil, (Found: M^+ 301.1231. $C_{17}H_{20}NO_2P$ requires 301.1232); ν_{\max} . (film) 2988, 1449, 1348, 1317, 1288, 1245, 1208, 1199, 1025, 901, 834, 729, 694, 601, 569 and 515 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.29 (3 H, s, 4- CH_3), 1.32 (3H, s, 4- CH_3), 4.20-4.32 (4H, m, CH_2), 7.25-8.20 (10H, m, aromatic H); δ_P {H} (36 MHz, $CDCl_3$) 34 ppm; m/z (70 eV, 200 °C) 301 (M^+ , 5), 285 ($M^+ -O$, 100), 174 (34), 106 (15), 90 (7), 78 (6), 77 (18), 70 (9)

General procedure for the synthesis of 2-oxo-2-phenylethanephosphonamidates. The corresponding amine (1.4 mmol) was dissolved in dry triethylamine (1.95 ml, 14 mmol) and this solution was delivered over 2 min to a stirred solution of freshly distilled diethyl phosphochloridate (2 ml, 13.8 mmol) in toluene (200 ml) under an argon atmosphere at room temperature. After 12 h the precipitated triethylammonium chloride was filtered off (1.85-1.90 g, near quantitative) and to the clear filtrate was added phenacyl bromide (2.75 g, 13.8 mmol). After this solution was refluxed for 5 h, solvent was removed at reduced pressure and the residue was chromatographed (silica gel, 150-200 g) to afford the products.

General procedure for the synthesis of 1-diazo-2-oxo-2-phenylethanephosphonamidates. Tosyl azide¹⁵² (2.00 g, 10 mmol) was added to a stirred solution of the corresponding 2-oxo-2-phenylethanephosphonamidates (10 mmol) in dichloromethane (5 ml) and triethylamine (5 ml, 36 mmol) under an argon atmosphere at room temperature. The reaction mixture was monitored by tlc and when all the starting material had been consumed (typical reaction time of 1 week, but if a large excess of tosyl azide is used, reaction was complete within 24 h), the reaction mixture was poured into water (100 ml) and was extracted with dichloromethane (100 ml then 2 x 50 ml). The combined DCM extracts were washed with 5% aqueous sodium hydroxide (2 x 50 ml), water (2 x 50 ml) and brine (30 ml). Drying (Na₂SO₄) followed by evaporation of solvent left a residue that was chromatographed (silica gel, 100-150 g) to afford the product.

The physical data for compounds prepared are as follows:

Ethyl P-2-oxo-2-(4-bromophenyl)ethane(N,N-tetramethylene)phosphonamidate (244), yield 20%, oil (Found: C, 46.4; H, 5.3; N, 3.7. C₁₄H₁₉NO₃PBr requires C, 46.7; H, 5.3; N 3.9%); ν_{\max} . (film) 2976, 2872, 1677 (C=O), 1586, 1276 (P=O), 1240, 1099, 1070, 1037, 1001, 954, 798, 595, 525 and 510 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.28 (3H, t, *J* 7Hz, CH₃), 1.83 (4H, m, 2 x ring CH₂), 3.10 and 3.22 (4H, m, 2 x CH₂N), 3.50 (1H, dd, *J* 21Hz, 13 Hz, 1-H), 3.62 (1H, dd, *J* 21Hz, 13 Hz, 1-H), 3.88-4.17 (2H, m, CH₂O), 7.61 (2H, d, *J* 9Hz, aromatic H), 7.95 (2H, d, *J* 9Hz, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl₃) 20.7 ppm; *m/z* (70 eV, 150 °C) 361 (*M*⁺, 3), 359 (3), 207 (7), 162 (*M*⁺ - CH₂COAr, 8), 161 (11), 150 (13), 134 (7), 133 (6), 71(7), 70 (pyrrolidinium, 100) and 42 (6).

Ethyl P-2-oxo-2-phenylethane(N,N-pentamethylene)phosphonamidate (245), yield 24%, oil (Found: C, 60.7; H, 7.5; N, 4.5. $C_{15}H_{22}NO_3P$ requires C, 61.0; H, 7.5; N 4.7%); ν_{\max} . (film) 2980, 2936, 2853, 1677 (C=O), 1599, 1450, 1382, 1339, 1277, 1241 (P=O), 1165, 1120, 1072, 1040, 1004, 962, 764, 689, 584 and 505 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.26 (3 H, t, J 7Hz, CH_3), 1.45-1.56 (6 H, m, 3 x ring CH_2), 2.95-3.18 (4H, m, 2 x CH_2N), 3.49 (1 H, dd, J_P 21Hz, J_H 13 Hz, 1-H), 3.67 (1 H, dd, J_P 21Hz, J_H 13 Hz, 1-H), 3.89-4.17 (2 H, m, CH_2O), 7.43-7.60 (3 H, m, aromatic H), 8.00-8.09 (2 H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 21.9 ppm; m/z (70 eV, 100 °C) 295 (M^+ , 22), 176 (M^+ - $CH_2CO.Ph$, 20), 175 (21), 113 (8), 105 ($PhC\equiv O^+$, 22), 84 (piperidinyl, 100), 83 (49) and 77 (16).

Ethyl P-2-oxo-2-phenylethane[(2-methyl)piperidine]phosphonamidate (246), yield 22% (of 1:1 diastereomeric mixture), oil (Found: C, ; H, ; N, . $C_{16}H_{24}NO_3P$ requires C, 62.1; H, 7.8; N 4.5%); ν_{\max} . (film) 2976, 2936, 1678 (C=O), 1449, 1391, 1304, 1277, 1242 (P=O), 1197, 1161, 1141, 1087, 1039, 1004, 971, 951, 916, 760, 689, 587 and 531 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.08 and 1.17 (3 H, d, J 7 Hz, ring substituted CH_3), 1.18 and 1.19 (3 H, t, J 7 Hz, ester CH_3), 1.23-1.60 (6 H, m, 3 x ring CH_2), 2.89-3.17 (4H, m, 2 x CH_2N), 3.52 (1 H, m, $PhCOCH_2$), 3.75-4.13 (3 H, m, and C(Me)HN and CH_2O), 7.39-7.55 (3 H, m, aromatic H), 8.02-8.06 (2 H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 21.2 and 21.6 ppm; m/z (70 eV, 150 °C) 309 (M^+ , 1), 235 (9), 221 (11), 220 (100), 192 (14), 164 (35), 98 (17), 56 (6) and 32 (12).

Ethyl P-2-oxo-2-phenylethane(N,N-heptamethylene)phosphonamidate (247), yield 50%, oil (Found: C, ; H, ; N, . $C_{16}H_{24}NO_3P$ requires C, 62.1; H, 7.8; N 4.5%); ν_{\max} . (film) 2927, 2855, 1677 (C=O), 1599, 1449, 1391, 1275, 1240 (P=O), 1133, 1039, 1003, 907, 872, 759, 690, 583 and 515 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.22 (3 H, t, J 7Hz, CH_3), 1.57 (10 H, m, 3 x ring CH_2), 2.92-3.17 (4H, m, 2 x CH_2N), 3.51 (1 H, dd, J_P 22 Hz, J_H 13 Hz, 1-H), 3.63 (1 H, dd, J_P 22 Hz, J_H 13 Hz, 1-H), 3.90-4.17 (2 H, m, CH_2O), 7.41-7.57 (3 H, m, aromatic H), 8.02-8.06 (2 H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 24.3 ppm; m/z (70 eV, 150 °C) 323 (M^+ , 3), 206 (59), 192 (69), 166 (62), 112 (heptamethyleneimine, 100), 111 (73), 110 (48), 83 (68) and 65 (54).

Ethyl P-2-oxo-2-phenylethane(N,N-dibenzyl)phosphonamidate (248), yield 53%, oil (Found: C, 70.7; H, 6.6; N, 3.5. $C_{24}H_{26}NO_3P$ requires C, 70.75; H, 6.4; N 3.4%); ν_{\max} . (film) 3029, 2981, 1680 (C=O), 1599, 1495, 1450, 1373, 1296, 1240 (P=O),

1205, 1103, 1064, 1038, 1004, 952, 791, 751, 701, 609 and 583 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.16 (3 H, t, J 7Hz, CH_3), 3.58 (1 H, dd, J_{P} 21Hz, J_{H} 14 Hz, 1-H), 3.65 (1 H, dd, J_{P} 21Hz, J_{H} 14 Hz, 1-H), 3.84 and 4.13 (2 H, dq, J_{P} 10Hz, J_{H} 7 Hz, CH_2O), 4.16 (4 H, dd, J 10Hz, 1 Hz, 2 x CH_2N), 7.23-7.35 (10 H, m, aromatic H), 7.43-7.60 (3 H, m, aromatic H), 8.01-8.05 (2 H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 23.7 ppm; m/z (70 eV, 170 $^{\circ}\text{C}$) 407 (M^+ , 1), 317 (21), 316 (M^+ - PhCH_2 , 100), 211 [M^+ - (PhCH_2)₂N, 56], 183 (16), 106 (65), 105 ($\text{PhC}\equiv\text{O}^+$, 22), 103 (PhCH_2N , 21) and 91 (PhCH_2 , 70).

Ethyl P-2-oxo-2-phenylethane(N-benzyl-N-ethylacetate)phosphonamidate (249), yield 50%, oil (Found: C, 62.4; H, 6.75; N, 3.6. $\text{C}_{21}\text{H}_{26}\text{NO}_5\text{P}$ requires C, 62.5; H, 6.5; N 3.5%); ν_{max} . (film) 2982, 1742 (ester C=O), 1681 (benzoyl C=O), 1449, 1371, 1275, 1244 (P=O), 1202, 1163, 1105, 1073, 1030, 1005, 952, 792, 739 and 699 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.19 (3 H, t, J 7Hz, phosphonate ester CH_3), 1.23 (3 H, t, J 7Hz, carboxylate ester CH_3), 3.63-4.32 (8 H, m, 4 x CH_2), 7.25-8.09 (10 H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 24.1 ppm; m/z (70 eV, 160 $^{\circ}\text{C}$) 403 (M^+ , 7), 316 (M^+ - PhCH_2 , 37), 211 (M^+ - $\text{EtO}_2\text{CCH}_2\text{NCH}_2\text{Ph}$, 46), 192 ($\text{EtO}_2\text{CCH}_2\text{NCH}_2\text{Ph}$, 36), 120 (29), 105 ($\text{PhC}\equiv\text{O}^+$, 22), 103 (PhCH_2N , 17), 91 (PhCH_2 , 100) and 77 (15).

Ethyl P-2-oxo-2-phenylethane(N-benzyl-N-^tbutyl)phosphonamidate (250), yield 24%, oil (Found: C, 67.8; H, 7.6; N, 3.65. $\text{C}_{21}\text{H}_{28}\text{NO}_3\text{P}$ requires C, 67.5; H, 7.6; N 3.75%); ν_{max} . (film) 2977, 1678 (C=O), 1450, 1367, 1276, 1252 (P=O), 1234, 1193, 1103, 1036, 1006, 953, 926, 880, 813, 733, 701, 579, 530 and 510 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.04 (3 H, t, J 7Hz, CH_3), 1.39 [9H, s, (CH_3)₃C], 3.59 (1 H, dd, J_{P} 21Hz, J_{H} 13 Hz, 1-H), 3.75 (1 H, dd, J_{P} 21Hz, J_{H} 13 Hz, 1-H), 3.86 and 4.09 (2 H, dq, J 10Hz, 7 Hz, CH_2O), 4.33 (2 H, dd, J 12Hz, 2 Hz, CH_2N), 7.20-7.60 (8 H, m, aromatic H), 8.04-8.08 (2 H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 24.3 ppm; m/z (70 eV, 180 $^{\circ}\text{C}$) 373 (M^+ , 2), 316 (M^+ - ^tBu, 100), 211 (M^+ - ^tBuNCH₂Ph, 56), 148 (41), 106 (57), 105 ($\text{PhC}\equiv\text{O}^+$, 29), 103 (PhCH_2N , 23), 91 (PhCH_2 , 86) and 77 (Ph, 21).

Ethyl P-2-oxo-2-phenylethane(N-benzyl-N-ⁱpropyl)phosphonamidate (251), yield 50%, oil (Found: C, 66.7; H, 7.45; N, 4.1. $\text{C}_{20}\text{H}_{26}\text{NO}_3\text{P}$ requires C, 66.8; H, 7.3; N 3.9%); ν_{max} . (film) 2977, 2934, 1678 (C=O), 1599, 1450, 1402, 1276 (P=O), 1240, 1207, 1171, 1035, 1005, 952, 874, 770, 710, 690, 581 and 520 cm^{-1} ; δ_{H} (270 MHz,

CDCl₃) 1.02 (3H, d, *J* 7Hz, CH₃ of isopropyl), 1.16 (3H, d, *J* 7Hz, CH₃ of isopropyl), 1.18 (3H, t, *J* 7Hz, CH₃), 3.53 (1H, dd, *J_P* 21Hz, *J_H* 14 Hz, 1-H), 3.62 (1H, dd, *J_P* 21Hz, *J_H* 14 Hz, 1-H), 3.74 (1H, d, *J_P* 12Hz, *J_H* 7 Hz, Me₂CH), 3.92 (1H, dq, *J_P* 10Hz, *J_H* 7 Hz, one of CH₂O), 4.07-4.30 (3H, m, 2 x CH₂N and one of CH₂O), 7.17-7.58 (13H, m, aromatic H), 8.03-8.08 (2H, m, aromatic H); δ_P{H} (36 MHz, CDCl₃) 24.0 ppm; *m/z* (70 eV, 160 °C) 359 (*M*⁺, 2), 316 (*M*⁺ - ^{*i*}PrN, 37), 270 (19), 211 (*M*⁺ - ^{*i*}PrNCH₂Ph, 33), 134 (, 20), 106 (23), 105 (PhC≡O⁺, 31), 91 (PhCH₂, 100) and 77 (Ph, 22).

Ethyl P-2-oxo-2-phenylethane(N,N-bis isopropyl)phosphonamidate (252) yield 67%, oil, (Found: *MH*⁺ 312.1729. C₁₆H₂₆NO₃P requires 312.1729); *v*_{max.} (film) 2971, 1678 (C=O), 1449, 1407, 1368, 1277, 1244 (P=O), 1206, 1185, 1160, 1127, 1041, 999, 949, 759, 691, 583, 553 and 526 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.20 (3H, t, *J* 7Hz, ethoxy CH₃), 1.24 [6H, d, *J* 7Hz, (CH₃)₂C], 1.26 [6H, d, *J* 7Hz, (CH₃)₂C], 3.39 (1H, hept, *J* 7Hz, Me₂CH), 3.46 (1H, hept, *J* 7Hz, Me₂CH), 3.57 (1H, d, *J* 3Hz, H-1), 3.49 (1H, d, *J* 2 Hz, H-1), 3.82-4.05 (2H, m, CH₂O), 7.43-7.59 (3H, m, aromatic H), 8.10-8.15 (2H, m, aromatic H); δ_P{H} (36 MHz, CDCl₃) 21.9 ppm; *m/z* (70 eV, 150 °C) 311 (*M*⁺, 8), 222 (*M*⁺ - OEt - ^{*i*}Pr, 100), 211 (*M*⁺ - ^{*i*}Pr₂N, 38), 180 (85), 152 (32), 145 (31), 124 (40), 87 (44) and 86 (41).

Ethyl P-2-oxo-2-phenylethane(2,4,4-trimethyloxazolidinyl)phosphonamidate (253) yield 36% (of 1:1 diastereomeric mixture), oil, (Found: C, 59.05; H, 7.1; N, 4.3. C₁₆H₂₄NO₄P requires C, 59.1; H, 7.3; N 4.1%); *v*_{max.} (film) 2981, 2934, 2870, 1678 (C=O), 1449, 1391, 1368, 1320, 1275, 1245 (P=O), 1186, 1137, 1029, 1005, 955, 759, 691, 586, 549 and 488 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.22 and 1.47 (3H, dd, *J* 7Hz, 6 Hz ring substituted CH₃), 1.33 and 1.32 (3H, t, *J* 7Hz, ester CH₃), 3.44-4.24 (8H, overlapping m, 4 x CH₂), 5.08 and 5.21 (1H, dq, *J_P* 2 Hz, *J_H* 6 Hz, CHMe), 7.53-7.59 (3H, m, aromatic H), 8.06-8.13 (2H, m, aromatic H); δ_P{H} (36 MHz, CDCl₃) 16.6 ppm; *m/z* (70 eV, 170 °C) 325 (*M*⁺, 5), 211 (99), 205 (86), 114 (38), 105 (100), 103 (57), 100 (63), 91 (40), 77 (66), 42 (42).

Ethyl 1-(4-bromophenyl)ethene (N,N-tetramethylene) phosphoramidate (254), yield 26%, oil (Found: C, 46.6; H, 5.3; N, 3.9. C₁₄H₁₉NO₃PBr requires C, 46.7; H, 5.3; N 3.9%); *v*_{max.} (film) 2978, 2873, 1631 (C=C-O), 1488, 1393, 1270 (P=O), 1207, 1165, 1097, 1044, 994, 967, 824, 762 and 559 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.35 (3H, t,

J 7 Hz, CH₃), 1.83 (4H, m, 2 x ring CH₂), 3.24 (4H, m, 2 x CH₂N), 4.16 (2H, pentet, J 7 Hz, CH₂O), 5.23 (2H, m, CH₂), 7.47 (4H, d, J 1 Hz, aromatic H); $\delta_{\text{p}}\{\text{H}\}$ (36 MHz, CDCl₃) 1.9 ppm; m/z (70 eV, 120 °C) 361/359 (M^+ , 18), 185/183 (CH₂COAr, 26), 161 (M^+ - CH₂COAr, 100), 155 (18), 150 (25), 134 (37), 133 (31), 111 (19) and 70 (pyrrolidinium, 40).

Ethyl 1-phenylethene (N,N-pentamethylene) phosphoramidate (255). This compound was obtained contaminated with another product of reaction from which it could not be separated by chromatography. Therefore it was not fully characterised. Yield 20% (based on nmr), oil, ν_{max} . (film) 2980, 1630 (C=C-O), 1449, 1275, 1207, 1098, 1066, 1045, 970, 864, 823, 780, 706, 585 and 558 cm⁻¹; $\delta_{\text{p}}\{\text{H}\}$ (36 MHz, CDCl₃) 2.0 ppm.

Ethyl 1-phenylethene [(2-methyl)piperidine] phosphoramidate (256), yield 20%, oil, (Found: M^+ 309.1494. C₁₄H₂₀NO₃P requires 309.1494); ν_{max} . (film) 2977, 1631 (C=C-O), 1449, 1367, 1274 (P=O), 1207, 1100, 1080, 1045, 992, 980, 864, 830, 780, 706, 610, 558 and 510 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.30 (3H, t, J_{H} 7 Hz, ester CH₃), 1.80 [6H, m, ring CH₃ and -(CH₂)₃-], 3.10 [2H, m, (CH₂)₂N], 4.17 [3H, m, CH₂O and NCH(Me)], 5.22-5.24 (2H, m, CH₂=), 7.28-7.61 (5H, m, aromatics); $\delta_{\text{p}}\{\text{H}\}$ (36 MHz, CDCl₃) 2.1 ppm; m/z (70 eV, 180 °C) 309 (1), 204 (13), 205 (66), 160 (11), 105 (100), 98 (23), 91 (9), and 77 (56).

Ethyl 1-phenylethene (N,N-heptamethylene) phosphoramidate (257), yield 14%, oil, (Found: C, 59.9; H, 6.9; N, 5.0. C₁₄H₂₀NO₃P requires C, 59.8; H, 7.2; N, 5.0%); ν_{max} . (film) 2977, 2360, 1631 (C=C-O), 1447, 1274, 1207, 1098, 1077, 1045, 992, 966, 864, 823, 775, 706, 585, 558, 519 and 510 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.35 (3H, dt, J_{H} 7 Hz, J_{P} 1 Hz, CH₃), 1.81 [4H, m, -(CH₂)₂-], 3.24 [4H, dt, J 7 Hz, 3 Hz, (CH₂)₂N], 4.17 (2H, m, dquartet, J_{H} 7 Hz, J_{P} 0.7 Hz, CH₂O), 5.22 (2H, d, J 2.2 Hz, CH₂=), 7.28-7.61 (5H, m, aromatics); $\delta_{\text{p}}\{\text{H}\}$ (36 MHz, CDCl₃) 1.9 ppm; m/z (70 eV, 100 °C) 281 (2), 175 (13), 161 (14), 160 (100), 105 (23), 98 (23), 91 (9), 77 (16) and 70 (9).

*Ethyl 1-phenylethene (N-benzyl-N-*i*-propyl) phosphoramidate (258)*, yield 5%, oil, (Found: M^+ 359.1651. C₂₀H₂₆NO₃P requires 359.1650); ν_{max} . (film) 2980, 1632 (C=C-O), 1495, 1447, 1410, 1260 (P=O), 1209, 1190, 1172, 1101, 1030, 959, 887,

820, 775, 713, 707, 665 and 515 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.23 [6H, d, J 6.8 Hz, $(\text{CH}_3)_2\text{C}$], 1.30 (3H, dt, J 7 Hz, 1 Hz, CH_3), 3.54 (1H, hept, J 7Hz, Me_2CH), 4.05-4.42 (4H, m, CH_2O and CH_2N), 5.27 (1H, dd, J_{H} 2 Hz, J_{P} 4 Hz, $\text{CH}=\text{}$), 5.38 (1H, dd, J_{H} 2 Hz, J_{P} 3 Hz, $\text{CH}=\text{}$), 7.36-7.60 (10H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 2.0 ppm; m/z (70 eV, 150 $^\circ\text{C}$) 359 (M^+ , 2), 345 (11), 268 (45), 259 (36), 254 (100), 148 (23), 126 (16), 105 (98), and 91 (23).

Ethyl 1-phenylethene (N,N-bis isopropyl) phosphoramidate (259), yield 2%, oil (Found: $M\text{H}^+$ 312.1729. $\text{C}_{16}\text{H}_{26}\text{NO}_3\text{P}$ requires 312. 1729); ν_{max} . (film) 2972, 1633 ($\text{C}=\text{C}-\text{O}$), 1495, 1447, 1410, 1368, 1261 ($\text{P}=\text{O}$), 1209, 1187, 1162, 1111, 1046, 991, 959, 887, 859, 819, 773, 713, 691, 661 and 559 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.23 [6H, d, J 7Hz, $(\text{CH}_3)_2\text{C}$], 1.26 [6H, d, J 7Hz, $(\text{CH}_3)_2\text{C}$], 1.34 (3H, dt, J 7Hz, 1 Hz, CH_3), 3.47 (1H, hept, J 7Hz, Me_2CH), 3.54 (1H, hept, J 7Hz, Me_2CH), 4.05-4.21 (2H, m, CH_2O), 5.22 (1H, dd, J_{H} 2 Hz, J_{P} 2.5 Hz, $\text{CH}=\text{}$), 5.34 (1H, dd, J_{H} 2Hz, J_{P} 3Hz, $\text{CH}=\text{}$), 7.30-7.38 (3H, m, aromatic H), 7.56-7.60 (2H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 1.9 ppm; m/z (70 eV, 150 $^\circ\text{C}$) 311 (M^+ , 6), 296 ($M^+ - \text{Me}$, 31), 194 (67), 152 (55), 124 (23), 105 ($\text{PhC}\equiv\text{O}^+$, 100), 77 (Ph, 56) and 51 (15).

Diethyl 1-phenylethene phosphate (260), yield 5%, oil, ν_{max} . (film) 2983, 2934, 1635, 1495, 1447, 1392, 1370, 1273 ($\text{P}=\text{O}$), 1166, 1143, 1100, 1029, 838, 774, 707 and 505 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.26 (3H, dt, J 7 Hz, 1 Hz, ester), 4.13 (dq, J 2 Hz, 7 Hz, 1 Hz, CH_2O), 5.15 (1H, dd, J 2 Hz, 3 Hz, $\text{CH}_2=\text{}$), 5.21 (1H, dd, J 3 Hz, $\text{CH}_2=\text{}$), 7.30-7.40 (3H, m, aromatic H), 7.48-7.54 (2H, m, aromatic H); δ_{P} (36 MHz, CDCl_3) -7.2 ppm; m/z (70 eV, 170 $^\circ\text{C}$) 325 (M^+ , 0.3), 130 (67), 127 (20), 105 (56), 103 (36), 102 (100), 91 (22), 81 (20) and 77 (36).

Ethyl P-1-diazo-2-oxo-2-(4-bromophenyl)ethane(N,N-tetramethylene) phosphonamidate (261) yield 80%, oil, ν_{max} . (film) 2980, 2857, 2099 ($\text{N}=\text{N}$), 1677 ($\text{C}=\text{O}$), 1590, 1267 ($\text{P}=\text{O}$), 1242, 1099, 1070, 1037, 901, 856, 810, 595 and 525 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.29 (3H, t, J 7 Hz, CH_3), 1.90 (4 H, m, 2 x ring CH_2), 3.08 and 3.22 (4H, m, 2 x CH_2N), 3.88-4.17 (2H, m, CH_2O), 7.61 (2H, d, J 8 Hz, aromatic H), 7.95 (2H, d, J 8 Hz, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 12.0 ppm; m/z (70 eV, 150 $^\circ\text{C}$) 359 ($M^+ - \text{N}_2$, 3), 207 (7), 161 (30), 150 (13), 134 (8), 133 (6), 71(7), 70 (pyrrolidinium, 100) and 42 (56).

Ethyl P-1-diazo-2-oxo-2-phenylethane(N,N-pentamethylene)phosphonamidate (262), m. p. 48 °C, (Found: C, 56.1; H, 6.3; N, 12.8. $C_{15}H_{20}N_3O_3P$ requires C, 56.1; H, 6.3; N, 13.1%); ν_{\max} . (film) 2987, 2936, 2851, 2126 (N=N), 1623 (C=O), 1578, 1464, 1446, 1339, 1276, 1241 (P=O), 1165, 1117, 1023, 964, 780, 717, 694, 677, 574, 553, 530 and 515 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.33 (3H, dt, J 7 Hz, 0.5 Hz, *estre* CH_3), 1.30-1.52 (6H, m, ring CH_2), 2.85-3.08 [4H, m, $(CH_2)_2N$], 4.04-4.21 (2H, m, CH_2O), 7.42-7.56 (3H, m, aromatic H), 7.73-7.77 (2H, m, aromatic H).

Ethyl P-1-diazo-2-oxo-2-phenylethane(2-methylpiperidine)phosphonamidate (263), yield 80% (1:1 diastomeric mixture), gummy oil, (Found: C, 57.1; H, 6.8; N, 12.4. $C_{16}H_{22}N_3O_3P$ requires C, 57.3; H, 6.6; N, 12.5%); ν_{\max} . (film) 2977, 2937, 2864, 2098 (N=N), 1631 (C=O), 1579, 1447, 1391, 1278 (P=O), 1214, 1163, 1139, 1089, 1067, 1029, 956, 916, 786, 715, 676, 602 and 558 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.12 and 1.13 (3H, 2 x t, J_H 7 Hz, pyrrolidine ring CH_3), 1.30 and 1.32 (3H, 2 x dt, J_H 7 Hz, J_P 0.5 Hz, ester CH_3), 1.40- 1.58 [6H, m, ring $-(CH_2)_3-$] 2.89 (1H, m, 6'-H of $-CH_2N$), 3.39 (1H, m, 6'-H of $-CH_2N$), 3.84-4.19 [3H, m, CH_2O and $C(Me)HN$], 7.42-7.56 (3H, m, aromatic H), 7.72-7.81 (2H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 12.2 and 11.6 ppm; m/z (70 eV, 200 °C) 307 ($M^+ - N_2$, 42), 292 (100), 110 (77), 105 ($PhC\equiv O^+$, 85), 98 (2-methylpyrrolidinyl, 48), 89 (44), 84 (84), 77 (53) and 55 (44).

Ethyl P-1-diazo-2-oxo-2-phenylethane(N,N-heptamethylene)phosphonamidate (264), yield 75%, oil (Found: C, 58.0; H, 7.1; N, 11.9. $C_{17}H_{24}N_3O_3P$ requires C, 58.4; H, 7.1; N 12.0%); ν_{\max} . (film) 2926, 2855, 2098, 1631 (C=O), 1447, 1278 (P=O), 1240, 1150, 1128, 1088, 1033, 1008, 961, 784, 713, 671, 559 and 509 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.27 (3H, t, J 7Hz, CH_3), 1.55 [10H, m, ring $-(CH_2)_5-$], 4.85-3.12 (4H, m, 2 x CH_2N), 4.02-4.20 (2H, m, CH_2O), 7.28-7.49 (3H, m, aromatic H), 7.58-7.71 (2H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 15.3 ppm; m/z (70 eV, 180 °C) 321 ($M^+ - N_2$, 85), 181 (27), 112 (heptamethyleneimine, 100), 110 (68), 105 ($PhC\equiv O^+$, 61), 89 (26), 77 (Ph, 31), 55 (32) and 41 (32).

Ethyl P-1-diazo-2-oxo-2-phenylethane(N,N-dibenzyl)phosphonamidate (265), yield 100%, oil (Found: C, 66.7; H, 5.8; N, 9.7. $C_{24}H_{24}N_3O_3P$ requires C, 66.5; H, 5.6; N 9.7%); ν_{\max} . (film) 3030, 2983, 2103 (N=N), 1632 (C=O), 1495, 1455, 1319, 1288, 1243 (P=O), 1207, 1162, 1103, 1029, 953, 802, 748, 700, 611, 592 and 539 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.33 (3 H, dt, J 7Hz, 1 Hz, CH_3), 4.07-4.20 (4 H, m, CH_2O),

4.13 (2 H, dd, J 16Hz, 12 Hz, CH₂N), 4.39 (2 H, dd, J 15Hz, 10 Hz, CH₂N), 7.23-7.55 (15 H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl₃) 14.3 ppm; m/z (18 eV, 200°C) 406 (11), 405 ($M^+ - \text{N}_2$, 33), 314 ($M^+ - \text{N}_2 - \text{PhCH}_2$, 33), 300 ($M^+ - \text{N}_2 - \text{PhCH}_2\text{N}$, 19), 297 (11), 270 (12), 243 (13), 242 (100) and 91 (PhCH₂, 17).

Ethyl P-1-diazo-2-oxo-2-phenylethane(N-^tbutyl-N-benzyl)phosphonamidate (266), yield 100%, m.p. 106-107 °C (Found: C, 63.1; H, 6.6; N, 10.4. C₂₁H₂₆N₃O₃P requires C, 63.15; H, 6.6; N 10.5%); ν_{max} . (nujol) 2087 (N=N), 1632 (C=O), 1319, 1302, 1286, 1256 (P=O), 1213, 1116, 1018, 959, 884, 816, 781, 718, 703 and 544 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.19 (3 H, dt, J 7Hz, 1 Hz, CH₃), 1.36 [9H, s, (CH₃)₃C], 4.00-4.17 (2 H, m, CH₂O), 4.31 (1 H, dd, J_{P} 18Hz, J_{H} 16 Hz, benzylic H), 4.80 (1 H, dd, J_{P} 18Hz, J_{H} 11 Hz, benzylic H), 7.20-7.62 (10 H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl₃) 12.8 ppm; m/z (70 eV, 180 °C) 371 ($M^+ - \text{N}_2$, 5), 315 ($M^+ - \text{N}_2 - ^t\text{Bu}$, 37), 148 (13), 106 (13), 105 (PhC≡O⁺, 35), 92 (14), 91 (PhCH₂, 100), 77 (15) and 57 (21).

Ethyl P-1-diazo-2-oxo-2-phenylethane(N-benzyl-N-ⁱpropyl)phosphonamidate (267) yield 100%, oil (Found: C, ; H, ; N, . C₁₆H₂₄N₃O₃P requires C, 57.0; H, 7.2; N 12.5%); ν_{max} . (film) 2979, 2100 (N=N), 1635 (C=O), 1579, 1447, 1393, 1368, 1288, 1245 (P=O), 1207, 1169, 1126, 1027, 938, 866, 784, 713, 673, 604 and 563 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.04 (3H, d, J 6.5 Hz, CH₃), 1.10 (3H, d, J 6.5 Hz, CH₃), 1.33 (3H, dt, J 7 Hz, 1 Hz, ester CH₃), 3.92 (1H, d, J_{P} 7 Hz, J_{H} 6.5 Hz, Me₂CH), 4.19 (2H, m, J 7 Hz, CH₂O), 4.31 (2H, dd, J_{P} 13 Hz, 2 Hz, PhCH₂), 7.24-7.70 (10H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl₃) 13.9 ppm; m/z (70 eV, 170 °C) 357 ($M^+ - \text{N}_2$, 7), 314 ($M^+ - \text{N}_2 - ^i\text{Pr}$, 19), 177 (10), 146 (PhCH₂NⁱPr, 15), 134 (21), 106 (14), 105 (PhC≡O⁺, 45), 91 (tropylium ion, 100) and 77 (25).

Ethyl P-1-diazo-2-oxo-2-phenylethane(N,N-bis ⁱpropyl)phosphonamidate (268), yield 98%, oil (Found: C, 56.8; H, 7.2; N, 12.4. C₁₆H₂₄N₃O₃P requires C, 57.0; H, 7.2; N 12.5%); ν_{max} . (film) 2973, 2934, 2098 (N=N), 1636 (C=O), 1579, 1448, 1408, 1368, 1318, 1284, 1246, 1204, 1182, 1159, 1123, 1029, 1000, 958, 785, 714, 680, 659, 564 and 504 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.13 [6H, d, J 7Hz, (CH₃)₂C], 1.22 [6H, d, J 7Hz, (CH₃)₂C], 1.26 (3H, dt, J 7Hz, 1 Hz, ethoxy CH₃), 3.52 (1H, heptet, J 7Hz, Me₂CH), 3.59 (1H, heptet, J 7Hz, Me₂CH), 4.04 and 4.07 (2H, 2 x quartet, J 7Hz, CH₂O), 7.36-7.51 (3H, m, aromatic H), 7.65-7.68 (2H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl₃) 12.5 ppm; m/z (70 eV, 120°C) 309 ($M^+ - \text{N}_2$, 8), 294 ($M^+ - \text{N}_2 - \text{Me}$, 28), 105 (PhC≡O⁺, 39), 77 (26), 44 (35), 43 (22), 42 (27), 41 (25), 28 (N₂⁺, 100).

Ethyl P-1-diazo-2-oxo-2-phenylethane(2,4,4-trimethyloxazolidinyl)phosphoramidate diastereomer (269), oil, yield 47%, R_f 0.33 (ether), (Found: C, 54.9; H, 6.3; N, 11.8. $C_{16}H_{22}N_3O_4P$ requires C, 54.7; H, 6.3; N, 12.0%); ν_{max} . (film) 2981, 2933, 2098 (N=N), 1636 (C=O), 1448, 1388, 1368, 1319, 1274 (P=O), 1185, 1138, 1025, 959, 786, 714, 677, 624, 594 and 555 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.31 (3H, t, J_H 7 Hz, J_P 1 Hz, ester CH_3), 1.34 (3H, s, 4'- CH_3), 1.41 (3H, s, 4'- CH_3), 1.49 (3H, dt, J_H 5 Hz, ring substituted CH_3), 3.52 (1H, dd, J_H 8 Hz, J_P 1 Hz, 3'-H), 3.71 (1H, d, J_H 8 Hz, 3'-H), 3.98-4.25 (2H, m, ester CH_2O), 5.21 (1H, dq, J_H 5 Hz, J_P 2 Hz, 2'-H), 7.40-7.52 (3H, m, aromatic H), 7.67-7.70 (2H, m, aromatic H); δ_P {H} (36 MHz, $CDCl_3$) 6.3 ppm; *diastereomer (270)*, m.p. 156-158 °C, yield 49%, R_f 0.36 (ether), (Found: C, 55.1; H, 6.3; N, 11.6. $C_{16}H_{22}N_3O_4P$ requires C, 54.7; H, 6.3; N, 12.0%); ν_{max} . ($CHCl_3$ solution) 2980, 2931, 2100 (N=N), 1635 (C=O), 1447, 1368, 1318, 1289 (P=O), 1186, 1141, 1027, 955, 931, 784, 711, 629, 590, 553 and 539 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.31 (3H, t, J_H 7 Hz, J_P 1 Hz, ester CH_3), 1.42 (3H, dt, J_H 5 Hz, ring substituted CH_3), 1.43 (3H, s, 4'- CH_3), 1.44 (3H, s, 4'- CH_3), 3.57 (1H, dd, J_H 8 Hz, J_P 1 Hz, 3'-H), 3.57 (1H, d, J_H 8 Hz, 3'-H), 4.00-4.20 (2H, m, ester CH_2O), 5.50 (1H, dq, J_H 5 Hz, J_P 2 Hz, 2'-H), 7.42-7.65 (5H, m, aromatic H); δ_P {H} (36 MHz, $CDCl_3$) 6.2 ppm; m/z (70 eV, 140 °C) 323 ($M^+ - N_2$, 26), 308 (27), 237 (14), 236 (100), 172 (18), 105 ($PhC\equiv O^+$, 13), 99 (40), and 98 (12).

Ethyl phenylmethanephosphonate (273). Diethyl phenylmethanephosphonate (7.8 g, 30 mmol) was refluxed in aqueous sodium hydroxide (10%, 75 ml) for 1.5 h. After the solution had cooled down, concentrated hydrochloric acid was added (specific gravity 1.18, 15 ml). Extraction with chloroform (3 x 250 ml) followed by evaporation of solvent afforded a gum which solidified on standing. Crystallisation from petroleum ether affords white needles (6.4 g, 93%), m.p. 64 °C (Lit.¹⁵² 63-65 °C), δ_P {H} (36 MHz, $CDCl_3$) 28.25 ppm; m/z (70 eV, 140 °C) 200 (M^+ , 25).

Ethyl P-benzyl(N,N-bis i-propyl)phosphoramidate (274). Iodine (127 mg, 0.5 mmol) was added to a stirred solution of triphenylphosphine (130 mg, 0.5 mmol), acid (273) (100 mg, 5 mmol) and diisopropylamine (0.14 ml, 10 mmol) in dry THF (10 ml), at 0 °C and under an argon atmosphere. After 20 min, the reaction mixture was poured into water and extracted with ether (3 x 50 ml). The combined extracts were dried ($MgSO_4$). Removal of solvent followed by chromatography afforded the title compound as an oil (12 mg, 8%, impure), oil, ν_{max} . (film) 2973, 2932, 1493, 1452, 1408, 1366,

1207, 1180, 1156, 1087, 1029, 1000, 952, 886, 788, 699, 661 and 560 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.15 [3H, d, J_{H} 6.8 Hz, $(\text{CH}_3)_2\text{C}$], 1.16 (3H, t, J 7 Hz, ester CH_3), 1.24 [3H, d, J_{H} 6.8 Hz, $(\text{CH}_3)_2\text{C}$], 3.32-3.52 [3H, m, 2 x Me_2CH and $\text{CH}(\text{H})\text{O}$], 3.81-3.97 [2H, m, $\text{CH}(\text{H})\text{Ph}$ and $\text{CH}(\text{H})\text{O}$], 4.84 [1H, d, J 10 Hz, $\text{CH}(\text{H})\text{Ph}$], 7.26-7.37 (3H, m, aromatic H), 7.46-7.50 (2H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 25.4 ppm; m/z (70 eV, 150 °C) 284 (MH^+ , 3), 193 (97), 192 (47), 178 (58), 164 (82), 122 (63), 86 (100) and 77 (40).

Methyl 1,3-oxazolidine-4-carboxylate (279). Methyl (D)-serine hydrochloride (1.6 g, 10.3 mmol) was dissolved in aqueous potassium carbonate solution (g in 2ml) and when the effervescence had ceased, formalin (2 ml) was added. Chloroform (10 ml) was added and the two phase mixture was vigorously stirred for 24 h. The organic layer was separated and the aqueous layer was washed with more chloroform (2 x 10 ml). Combined organic extracts were dried (Na_2SO_4) and evaporation of solvent afforded the *title compound* as an oil (1.35 g, 100%), (Found: C, 46.1; H, 6.7; N, 10.75. $\text{C}_5\text{H}_9\text{NO}_3$ requires C, 45.8; H, 6.9; N, 10.7%); ν_{max} . (film) 2955, 2889, 1742 (C=O), 1439, 1379, 1287, 1206, 1106, 1020, 929, 757, 667 and 506 cm^{-1} ; δ_{H} (90 MHz, CDCl_3) 3.68 (3H, s, ester CH_3), 2.50-3.80 (5H, m, CH and 2 x CH_2); m/z (70 eV, 140 °C) 130 (M^+ , 30), 116 (57), 59 (45) and 45 (100) and 31 (22).

Diphenylmethyl 5,5-dimethyl-1,3-thiazolidine-4(R)-carboxylate (280). Formaldehyde as an aqueous solution (38-40%, 0.1ml, ca 1.3 eq) was added to a suspension of (D)-penicillamine (149 mg, 1.0 mmol) in methanol (10 ml) and the mixture was stirred to a homogenous solution in 0.5 h. The solution was left overnight. Evaporation of the solvent and complete removal of all volatile matter from the residue to constant weight afforded *5,5-dimethyl-1,3-thiazolidine-4(R)-carboxylic acid* as a white powdery solid (160 mg, quantitative yield), m.p. 205 °C (dec.)(Lit.¹⁵³ 197 °C); Found C, 45.0%; H, 6.85%; N, 8.8%; S, 19.0%. Calculated for $\text{C}_6\text{H}_{11}\text{NSO}_2$: C, 44.7%; H, 6.9%; N, 8.7%; S, 19.9%. δ_{H} (270 MHz, DMSO-d_6) 1.19 (3H, s, 5- CH_3), 1.56 (3H, s, 5- CH_3), 3.32 (1H, s, 4-H), 4.05 (1H, d, J 9 Hz, 2-H), 4.25 (1H, d, J 9 Hz, 2-H); m/z (FAB, glycerol matrix) 254 (MH^+ + glycerol, 12), 185 (23), 162 (MH^+ , 100), 115 (28), 93 (glycerol, 56), 75 (17), 57 (15), 45 (13). This acid (453 mg, 3 mmol) was suspended in acetone and diphenyldiazomethane (602 mg, 3.1 mmol) was added. After stirring for 15 h the solvent was removed and residue was chromatographed to obtain a white solid which on recrystallisation affords *diphenylmethyl 5,5-dimethyl-1,3-thiazolidine-4(R)-carboxylate* as a crystalline compound, m.p.112 °C (Found: C, 70.2; H, 6.5; N, 4.25.

$C_{19}H_{21}NO_3S$ requires C, 69.7; H, 6.5; N, 4.3%); ν_{\max} . ($CHCl_3$ solution) 3327 (NH), 3033, 2974, 2884, 1739 (C=O), 1497, 1456, 1345, 1299, 1230, 1175 (C-O), 1147, 1130, 999, 955, 856, 792, 701 and 668 cm^{-1} ; δ_H (270MHz, $CDCl_3$) 1.02 (3H, s, 5- CH_3), 1.67 (3H, s, 5- CH_3), 3.11 (1H, bs, NH), 3.62 (1H, s, H-5), 4.23 (1H, d, J 9.8 Hz, H-2), 4.34 (1H, d, J 9.8 Hz, H-2), 7.00 (1H, s, $CHPh_2$), 7.27-7.40 (10H, m, aromatic H); δ_C (68 MHz, $CDCl_3$) 27.8 (q, Me-5), 29.1 (q, Me-5), 52.2 (t, C-2), 58.1 (s, C-4), 74.4 (d, C-5), 77.94 (d, CPh_2), 127.0 (d), 127.7 (d), 128.1 (d), 128.6 (d), 139.4 (s), 139.42 (s, aromatic C's), 168.67 (s, carboxyl C); m/z (70 eV, 110 °C) 326 (M^+ , 1), 168 (16), 167 (100), 166 (9), 165 (22), 160 (49), 152 (10), 116 (70).

*Ethyl P-1-oxo-1-phenylmethane(N,N-bis *i*propyl)phosphonamidate tosyl hydrazone (282)*. Diisopropylamine (2.0 ml, 14 mmol) was dissolved in dry triethylamine (1.95 ml, 14 mmol) and this solution was delivered over 2 min to a stirred solution of freshly distilled diethyl phosphochloridate (2 ml, 13.8 mmol) in toluene (200 ml) under an argon atmosphere at room temperature. After 12 h the precipitated triethylammonium chloride was filtered off (1.89 g, quantitative) and to the clear filtrate was added benzoyl chloride (1.94 g, 13.8 mmol). After this solution was refluxed for 5 h, solvent was removed at reduced pressure and the residue was chromatographed to afford *ethyl P-1-oxo-1-phenylmethane(N,N-bis *i*propyl)phosphonamidate (281)* as a gummy oil (2.79 g, 68%), (Found: C, 59.3; H, 8.1; N, 4.5. $C_{15}H_{24}NO_3P$ requires C, 60.6; H, 8.1; N, 4.7%); ν_{\max} . (film) 2973, 2935, 1654 (C=O), 1595, 1449, 1408, 1368, 1240 (P=O), 1204, 1181, 1159, 1127, 1030, 1002, 962, 928, 783, 691, 638 and 568 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.13 (3H, t, J 6.8 Hz, CH_3 of *i*Pr), 1.18 (3H, d, J 6.8 Hz, CH_3 of *i*Pr), 1.31 (3H, d, J 7 Hz, CH_3 of OEt), 3.42 (2H, d, J_P 19 Hz, J_H 6.8 Hz, $CHMe_2$), 4.04 (1H, dq, J_P 10 Hz, J_H 7 Hz, CH_2O), 4.16 (1H, quintet, J_P 10 Hz, J_H 7 Hz, CH_2O), 7.34-7.52 (3H, m, aromatic H), 8.27-8.30 (2H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 7.4 ppm; m/z (70 eV, 150 °C) 297 (M^+ , 11), 192 (72), 164 (70), 122 (54), 105 ($PhC\equiv O^+$, 100), 80 (11), 77 (39), 58 (12) and 43 (11). To a stirred solution of compound (281) (2.67 g, 9.0 mmol) in ethanol (100 ml), tosyl hydrazide (1.67 g, 9.0 mmol) was added. After eight days at room temperature, solvent was removed and the residue was chromatographed to afford the *title compound* as a solid, (4.0 g, 95%) m.p 133-135 °C, (Found: C, 56.3; H, 6.9; N, 9.4. $C_{22}H_{32}N_3O_4PS$ requires C, 56.7; H, 6.9; N, 9.3%); ν_{\max} . ($CHCl_3$ solution) 2974, 1408, 1368, 1339, 1224 (P=O), 1204, 1167, 1094, 1030, 1001, 955, 863, 815, 769, 717, 700, 667, 592, 569, 549 and 504 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.01 (3H, t, J 6.8 Hz, CH_3 of *i*Pr), 1.17 (3H, d, J 7 Hz, CH_3 of

OEt), 1.17 (3H, d, J 6.8 Hz, CH₃ of *i*Pr), 2.42 (3H, d, J 5 Hz, ArCH₃), 3.33 (2H, dseptet, J_P 19 Hz, J_H 6.8 Hz, CHMe₂), 3.93 (2H, dq, J_P 1 Hz, J_H 7 Hz, CH₂O), 7.27-7.43 (3H, m, aromatic H), 7.72-7.76 (2H, m, aromatic H), 8.13 (1H, bs, NH); $\delta_p\{H\}$ (36 MHz, CDCl₃) 13.2 ppm.

*Ethyl P-1-oxo-1-(4-nitrophenyl)methane(N,N-bis *i*propyl)phosphonamidate tosyl hydrazone (284)*. Diisopropylamine (2.0 ml, 14 mmol) was dissolved in dry triethylamine (1.95 ml, 14 mmol) and this solution was delivered over 2 min to a stirred solution of freshly distilled diethyl phosphochloridate (2 ml, 13.8 mmol) in toluene (200 ml) under an argon atmosphere at room temperature. After 12 h the precipitated triethylammonium chloride was filtered off (1.89 g, quantitative) and to the clear filtrate was added 4-nitrobenzoyl chloride (2.56 g, 13.8 mmol). After this solution was refluxed for 2 h, solvent and other volatile materials were removed and the residue was taken up in ether and filtered through a short pad (5 cm) of silica gel. Removal of solvent afforded *ethyl P-1-oxo-1-(4-nitrophenyl)methane(N,N-bis *i*propyl)phosphonamidate (283)* as an orange gum. The residue was hydrolytically too sensitive to be purified by chromatography and hence it was not possible to be fully characterized. This orange gum was taken up in ethanol (100 ml) and tosyl hydrazide (1.67 g, 9.0 mmol) was added. After five days at room temperature, solvent was removed and the residue was chromatographed to afford the *title compound* as a solid (2.1 g, 29% over two steps), m.p. 112-114 °C, [Found: ($M - TsH$)⁺ 354.1456. C₁₅H₂₃N₄O₄P requires 354.1456]; ν_{max} . (nujol) 3410 (NH), 1599, 1520 (C=N), 1411, 1348, 1221, 1203, 1163, 1018, 958, 882, 858, 816, 759, 724, 698, 673, 657, 613, 585 and 550 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.07 (3H, d, J 6.6 Hz, CH₃ of *i*Pr), 1.21 (6H, d, J 6.6 Hz, 2 x CH₃ of *i*Pr), 1.23 (3H, d, J 7 Hz, CH₃ of OEt), 1.28 (3H, t, J 6.6 Hz, CH₃ of *i*Pr), 2.45 (3H, s, ArCH₃), 3.31-3.58 (2H, m, 2 x CHMe₂), 3.95-4.32 (2H, m, CH₂O), 7.55 (2H, dd, J 9 Hz, 1 Hz, 4-nitroPhH), 8.30 (4H, m, 4-MePhH), 8.53 (2H, d, J 8 Hz, 4-nitroPhH); $\delta_p\{H\}$ (36 MHz, CDCl₃) 12.6 ppm; m/z (70 eV, 200 °C) 354 [(M^+ - TsH), 6], 192 (48), 191 (53), 176 (31), 164 (42), 149 (100), 122 (32) and 120 (38); m/z (CI, NH₃) 355 [(M^+ - Ts), 50].

2-Ethoxy-3-benzoyl-1-benzyl-4,4-dimethyl-2-oxo-1,2-azaphosphetidine (285). Diazo compound (267) (308 mg, 8.0 mmol) was dissolved in freshly redistilled, dry 1,2-dichloroethane and dirhodium tetracetate (30 mg, 0.7 mmol) was added. This solution was refluxed under argon for 4 h and then was left to cool. Removal of solvent followed

by chromatography of the residue afforded an oil (70 mg). This oil contained 80% of the title compound (based on nmr) and the rest unidentified impurities. Crystallisation and other purification attempts were unsuccessful. ν_{\max} . (CH_2Cl_2) 2975, 2950, 2885, 1682 ($\text{C}=\text{O}$), 1449, 1391, 1385, 1273, 1241 ($\text{P}=\text{O}$), 1208, 1170, 1130, 1028, 997, 944, 815, 758, 692, 580 and 550 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.29 (3H, t, J 7 Hz, CH_3 of OEt), 2.01 (3H, d, J 1 Hz, 3- CH_3), 2.20 (3H, d, J 1 Hz, 3- CH_3), 3.68-4.40 (4H, m, CH_2O and CH_2Ph), 4.40 (1H, d, J_{P} 13 Hz, 3-H), 7.12-7.65 (8H, m, aromatic H) and 7.88-7.94 (2H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 19.9 ppm; m/z (70 eV, $180\text{ }^\circ\text{C}$) 281 (2), 175 (13), 161 (14), 160 (100), 105 (23), 98 (23), 91 (9), 77 (16) and 70 (9).

2-Ethoxy-3-benzoyl-1-isopropyl-4,4-dimethyl-2-oxo-1,2-azaphosphetidine (286).

Diazo compound (268) (405 mg, 1.2 mmol) was dissolved in freshly redistilled, dry 1,2-dichloroethane and dirhodiumtetracetate (53 mg, 0.12 mmol) was added. This solution was refluxed under argon for 4 h and then was left to cool. Removal of solvent followed by chromatography of the residue afforded the title compound as a white solid (110 mg, 29%), m.p. $125\text{-}126\text{ }^\circ\text{C}$, (Found: C, 62.1; H, 7.9; N, 4.6. $\text{C}_{16}\text{H}_{24}\text{NO}_3\text{P}$ requires C, 62.1; H, 7.8; N, 4.5%); ν_{\max} . (KBr disk) 2974, 2931, 2878, 1682 ($\text{C}=\text{O}$), 1598, 1449, 1391, 1370, 1273, 1241 ($\text{P}=\text{O}$), 1208, 1161, 1130, 1030, 997, 944, 758, 692, 647, 580 and 522 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.01 (3H, t, J 7 Hz, CH_3 of OEt), 1.28 (3H, d, J 6.6 Hz, CH_3 of $i\text{Pr}$), 1.29 (3H, d, J 6.6 Hz, CH_3 of $i\text{Pr}$), 1.53 (6H, s, 2 x 3- CH_3), 3.26 (1H, d, J_{P} 20 Hz, J_{H} 6.6 Hz, CHMe_2), 3.68-3.77 and 3.90-4.03 (2H, m, CH_2O), 4.44 (1H, d, J_{P} 23 Hz, 3-H), 7.46-7.61 (3H, m, aromatic H) and 8.02-8.04 (2H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 19.2 ppm; m/z (70 eV, $140\text{ }^\circ\text{C}$) 309 (M^+ , 6), 294 ($M^+ - \text{O}$, 79), 105 ($\text{PhC}\equiv\text{O}^+$, 73), 84 (57), 77 (Ph, 39), 44 [$(i\text{Pr} + \text{H})^+$, 100], 42 [$(i\text{Pr} - \text{H})^+$, 92] and 41 (31).

Ethyl P-2-oxo-2-phenylethane(N-benzyl)phosphonamidate (287). Diazo compound (265) (215 mg, 5 mmol) was dissolved in dry 1,2-dichloroethane (20 ml) and dirhodiumdiacetate (22 mg, 0.5 mmol) was added. This solution was refluxed under argon while the progress of reaction was monitored by ir. After 4 h, the ir peak due to the diazo function had almost disappeared and the heating was stopped. Removal of solvent followed by chromatography of the residue afforded an oil (20 mg, 12%), δ_{H} (270 MHz, CDCl_3) 1.29 (3H, dt, J 15 Hz, 7 Hz, ester CH_3), 3.95 (1H, d, J 13 Hz, PCH_2HBz), 4.03-4.24 (4H, m, CH_2O , CH_2N), 4.93 (1H, d, J 13 Hz, PCH_2HBz), 7.26-7.51 (10H, m, aromatics); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 20.9 ppm.

Photolysis of diazo compounds (262) and (263): The diazo compounds (20-30 mmol) were dissolved in benzene (50-80 ml) and transferred into a quartz long tube (diameter 2 cm, length: 45 cm). Dry argon gas was bubbled through the solution through a cannula needle for 15 min and then the tube was installed in the apparatus and photolysed. When the analysis of the reaction mixture (tlc or ir) indicated the completion of the reaction, the photolysis was stopped and the volume of the reaction mixture was reduced (to about 5 ml). The residue was left exposed to atmosphere. After 15-48 hours, the precipitated Wolff rearrangement products were collected and the filtrate was analysed for other products. If these were present, the solvent was removed and the residue was chromatographed.

The physical data for the prepared compounds are as follows:

(Ethyl piperidinephosphonamidyl)(phenyl)ethanoic acid (290) yield 50%, m.p. 193 °C (Found: MH^+ 312.1364. $C_{15}H_{22}NO_4P$ requires 312.1365); ν_{max} . (KBr disk) 2943, 1679 (C=O), 1631, 1597, 1449, 1302, 1240 (P=O), 1164, 1087, 1048, 950, 734 and 691 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.00 (3H, d, J 7Hz, CH_3), 1.30-1.96 [6H, m, $-(CH_2)_3-$], 3.10-4.20 (6H, m, 2 x CH_2N and CH_2O), 6.12 (1H, d, J_p 21 Hz, H-1), 7.50 (2H, t, J 7Hz, *meta* aromatic H), 7.59 (1H, d, J 7Hz, *para* aromatic H), 8.22 (2H, d, J 7Hz, *ortho* aromatic H); $\delta_p\{H\}$ (36 MHz, $CDCl_3$) 1.2 ppm; m/z (FAB, o-NBA) 623 ($2M^+ + H$, 13), 312 (MH^+ , 82), 202 (100), 105 (8), 86 (11), 77 (15) and 65 (7).

[Ethyl (2-methylpiperidine)phosphonamidyl](phenyl)ethanoic acid (291) yield 50%, m.p. 183-185 °C (Found: MH^+ 326.1521. $C_{16}H_{24}NO_4P$ requires 326.1521); ν_{max} . (KBr disk) 2980, 2945, 1675 (C=O), 1449, 1246 (P=O), 1188, 1162, 1087, 1047, 999, 965, 947, 864, 753, 690, 585, 548 and 524 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 0.95 (3H, d, J 7Hz, ester CH_3), 1.24 (3H, d, J 6Hz, 1'- CH_3), 1.45-2.09 [6H, m, $-(CH_2)_3-$], 3.39-3.91 (4H, m, CH_2N and CH_2O), 4.55 (1H, d, J 6Hz, NCHMe), 6.10 (1H, d, J_p 23 Hz, H-1), 7.41-7.55 (3H, m, aromatic H), 8.21 (2H, d, J 7Hz, *ortho* aromatic H), 10.8 (1H, bs, OH); $\delta_p\{H\}$ (36 MHz, $CDCl_3$) 1.2 ppm; m/z (FAB, o-NBA) 651 ($2M^+ + H$, 10), 326 (MH^+ , 26), 216 (100) and 105 (15).

Unknown (292) m. p. 98-100 °C, (Found: C, 60.7; H, 7.3; N, 9.0.); ν_{max} . ($CHCl_3$ solution) 2974, 2932, 1684 (C=O), 1598, 1581, 1449, 1390, 1370, 1273, 1236, 1206, 1038, 991, 954, 901, 872, 826, 762, 695, 651, 580 and 510 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 1.46-1.48 (4H, m), 1.59-1.61 (3H, m), 1.75-1.80 (4H, m), 2.39 (3H, s), 3.42 (2H, t,

falls to singlet when irradiated at 1.78), 3.52 (2H, t, falls to singlet when irradiated at 1.78), 7.26 (2H, dd, J 8 Hz, 0.5 Hz), 7.76 (2H, d, J 8 Hz), 8.18 (1H, s); $\delta_{\text{C}}\{\text{H}\}$ (68 MHz, CDCl_3) 21.54 (t), 24.45 (t), 24.9 (t), 25.46 (t), 26.25 (t), 47.47 (t), 54.08 (t), 126.39 (d), 129.34 (d), 142.29 (s), 158.84 (d); m/z (FAB, m-NBA) 296 (100), 112 (26), 91 (36), 82 18, 70 (36), 57 (30), 55 (47) and 41 (31).

4-[Ethyl (piperidinyl)phosphonamidyl]-2-methyl-5-phenyl-1,3-oxazole (293). The above procedure was followed with the exception of using dry acetonitrile in place of benzene as solvent. At the end of reaction, solvent was removed and the title compound was purified by chromatography, m.p. 107-109 °C, (Found: C, 61.1; H, 7.1; N, 7.7. $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_3\text{P}$ requires C, 61.0; H, 6.9; N 8.4%); ν_{max} . (CHCl_3 solution) 2997, 2854, 1666, 1491, 1445, 1378, 1330, 1241 (P=O), 1187, 1118, 1101, 1037, 969, 945, 870, 803, 694, 666 and 546 cm^{-1} ; δ_{H} (250 MHz, CDCl_3) 1.41 (3H, t, J 7 Hz, ester CH_3), 1.45 [6H, m, $-(\text{CH})_3$ -], 2.31 (3H, s, 1-Me), 2.89-2.96 [4H, m, $(\text{CH}_2)_2\text{N}$], 4.21 (2H, pentet, $J_{\text{H}}=J_{\text{P}}$ 7 Hz, CH_2O), 7.53-7.42 (3H, m, aromatic H), 7.70-7.77 (2H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) -2.30 ppm; $\delta_{\text{C}}\{\text{H}\}$ (125 MHz, CDCl_3) 16.68 (dq, J_{P} 6 Hz, ester Me), 23.00 (dq, J_{P} 11 Hz, 1-Me), 23.67 (t, 3'- CH_2), 26.12 (t, 2'- CH_2), 53.06 (1'- CH_2), 61.82 (dt, J_{P} 6 Hz, CH_2O), 124.91 (d, J_{P} 151 Hz, C-2), 128.00 (d, 2''-C), 128.31 (d, 3''-C), 129.48 (d, 4''-C), 132.79 (d, J_{P} 9 Hz, 1''-C), 154.42 (d, J_{P} 6 Hz, 3-C), 163.25 (d, J_{P} 5 Hz, C-1); m/z (70 eV, 160 °C) 334 (M^+ , 9), 294 (14), 293 (M^+ - $\text{C}\equiv\text{N}$, 82), 149 (11), 148 (13), 105 ($\text{PhC}\equiv\text{O}^+$, 100), 96 (61), 84 (piperidinyl, 21) and 77 (Ph, 34).

(5S, 6R, 7S) 6-Benzoyl-5-ethoxy-5-oxo-3,3,7-trimethyl-1,4,5-bicyclo-[3.2.0]-oxazaphosphapane (294). Diazo compound (270) (350 mg, 10 mmol) was dissolved in dry benzene (80ml) and subjected to photolysis as above. After 3 h, tlc analysis showed that all the starting material had been consumed and then, reaction mixture was reduced in volume (to about 5 ml) and was left under argon at room temperature for a week. The remaining solvent was removed and the residue was chromatographed on silica gel to give an oil (45 mg). Removal of solvent followed by crystallisation (2 ml ether/5 ml petroleum ether) afforded the title compound as white crystals (42 mg, 13%), m.p. °C, (Found: C, ; H, ; N, . $\text{C}_{16}\text{H}_{22}\text{NO}_4\text{P}$ requires C, 59.4; H, 6.9; N, 4.3%); ν_{max} . (CH_2Cl_2 solution) 2977, 1682 (C=O), 1598, 1581, 1449, 1392, 1372, 1286, 1196 (P=O), 1163, 1107, 1021, 908, 822, 776, 690, 631, 518 and 504 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) [* refers to the distinguishable signal of the (5S, 6S, 7S)

diastereomer] 1.18 [6H, s, (CH₃)₂C], 1.20 (3H, t, *J* 7 Hz, ester CH₃), 1.42 and 1.40* (3H, s, 7-CH₃), 3.68* and 3.95 (2H, m, ester CH₂O), 4.09 and 4.06* (1H, dd, *J_P* 17 Hz, *J_H* 11 Hz, 2-H), 4.22 and 4.44* (1H, dd, *J_P* 2Hz, *J_H* 11 Hz, 2-H), 5.25* and 5.29 (1H, d, *J_P* 13 Hz, H-6), 7.49 (2H, t, *J* 7 Hz, aromatic H), 7.60 (1H, t, *J* 7 Hz, aromatic H), 8.00* and 8.14 (2H, d, *J* 7 Hz, aromatic H); δ_C{H} (125 MHz, CDCl₃) 16.21 (dq, *J_P* 4.5 Hz, ester Me), 22.40 (q, Me), 25.48 (q, Me), 49.70 (d, *J_P* 6.0 Hz, C-3), 57.53 (dd, *J_P* 13 Hz, C-6), 62.92 (dt, *J_P* 6.3 Hz, ester methylene), 128.63 (d, 2 x aromatic C), 129.21 (d, 2 x aromatic C), 134.16 (d, aromatic C), 134.95 (s, aromatic C), 192.19 (s, C-7); δ_P{H} (36 MHz, CDCl₃) 3.78 (80%) and 9.06* (20%) ppm; *m/z* (70 eV, 150 °C) 323 (*M*⁺, 1), 297 (12), 192 (76), 149 (15), 105 (100), 82 (15), 77 (27), 56 (10) and 55 (14).

Ethyl P-phenyldiazomethane(N,N-bis i-propyl)phosphonamidate (295). Tosyl hydrazone (282) (1.00 g, 2.15 mmol) was dissolved in DCM (25 ml) and dry potassium carbonate (5 g) was added. The mixture was refluxed for a total of 3 h and then was left to cool. The solid was removed by filtration. Phosphorus nmr analysis on the filtrate showed that it contained two products. One gave a signal at 19.65 ppm (20%) and the other gave a signal at 16.92 ppm (80%). Removal of the solvent followed by chromatography afforded toluenesulphonic acid as a solid (340 mg, quantitative) and *the title compound* as an orange oil (133 mg, 20%) (Found: C, 58.1; H, 8.0; N, 13.5. C₁₅H₂₄N₃O₂P requires C, 58.2; H, 7.8; N, 13.6%); ν_{max}. (film) 2972, 2935, 2066 (N=N), 1598, 1497, 1368, 1295, 1241 (P=O), 1205, 1181, 1030, 999, 960, 752, 689, 658 and 578 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.15 (3H, t, *J* 6.6 Hz, CH₃ of *i*Pr), 1.21 (3H, d, *J* 6.6 Hz, CH₃ of *i*Pr), 1.34 (3H, d, *J* 7 Hz, CH₃ of OEt), 3.46 (2H, d, *J_P* 19 Hz, *J_H* 7 Hz, CHMe₂), 4.16 (2H, quintet, *J_P* = *J_H* 7 Hz, CH₂O), 7.31 (5H, m, aromatic H); δ_P{H} (36 MHz, CDCl₃) 19.65 ppm; *m/z* (70 eV, 140 °C) 309 (*M*⁺, 6), 176 (9), 146 (47), 106 (7), 105 (PhC≡O⁺, 16), 104 (100), 77 (10), 43 (12) and 42 (8).

6.2 Experimental for Chapter Five

Unless otherwise stated, the following typical experimental procedures were followed.

Imines were obtained by condensation of the relevant aldehyde and amine in dichloromethane or benzene solution from which water was removed by a Dean-Stark apparatus. They were purified by bulb-to-bulb distillation, crystallisation or chromatography as appropriate.

O-Benzoyloximes were prepared by dehydrative condensation of the aldehyde and *O*-benzylhydroxyammonium chloride in benzene in the presence of poly(4-vinylpyridine).

Typical experimental procedure for the addition of diethyl phosphite to imines and related compounds. Chlorotrimethylsilane (0.35 ml, 1.1 eq) was delivered to a stirring solution of diethyl phosphite (0.35 g, 2.53 mmol) and triethylamine (0.39 ml, 1.1 eq) in dichloromethane (50 ml) maintained at 0 °C and under an atmosphere of argon. The imine (2.53 mmol) was added after 15 min and the solution was brought to room temperature. If refluxing was required it was carried out under argon. The reaction mixture was poured into water (50 ml) and organic products were extracted with dichloromethane (2 X 75 ml). Combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed to afford the required compounds.

Similar experimental procedure was used for the addition of other phosphites to the imines.

Removal of N-allyl groups. The *N*-allyl compound (300 mg) was dissolved in ethanol (10 ml) and palladium on charcoal (10%, 100 mg) was added. The mixture was refluxed until the reaction was complete, as detected by tlc analysis. The solid was filtered off and the ethanol was removed at reduced pressure. The residue was chromatographed on alumina directly to afford the required compounds.

The physical data for compounds prepared are as follows:

2-Methylpropanaldehyde N-benzylimine (304),¹⁵⁵ b.p. 105 °C/4 mmHg, ν_{\max} . 1671 (C=N) cm^{-1} ; δ_{H} (90 MHz, CDCl_3) 1.39 [6 H, d, J 6 Hz, $(\text{CH}_3)_2\text{C}$], 2.75 (1 H, m, CH), 4.80 (2 H, d, J 1 Hz, CH_2), 7.45-7.60 (5 H, m, aromatic H) and 7.90 (1 H, dt, J 5 Hz, 1 Hz, CH=N).

4-Acetamidobenzaldehyde N-allylimine (309), m.p. 141-142 °C, (DCM / diethylether) (Found: C, 71.1; H, 6.9; N, 13.7. $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$ requires C, 71.3; H, 7.0; N, 13.85%); ν_{\max} . (nujol) 3288, 3252, 2955, 1665 (C=N), 1606 (C=O), 1551, 1512, 1408, 1326, 915, 839 and 529 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 2.18 (3H, s, CH_3CO), 4.24 (2H, m, allylic H), 5.15 (1H, dm, J_{cis} 10 Hz, C= CH_{cis}), 5.23 (1H, dm, J_{trans} 17 Hz, C= CH_{trans}), 6.05 (1H, ddm, J_{trans} 17 Hz, J_{cis} 10 Hz, -CH=), 7.57 (2H, d, J 8.5 Hz, aromatic H), 7.68 (1H, s, NH), 7.70 (2H, d, J 8.5 Hz, aromatic H), 8.24 (1H, bs, CH=N); m/z (70 eV, 140 °C) 202 (M^+ , 100), 201 (84), 159 (64), 107 (82), 106 (79), 84 (64), 49 (85), 43 (84) and 41 (66).

Diethyl 2-methyl-1-(benzylamino)propanephosphonate (305), yield 85%, b.p. 180°C/0.35 mmHg, (Found: C, 60.2; H, 8.9; N, 4.7. $\text{C}_{15}\text{H}_{26}\text{NO}_3\text{P}$ requires C, 60.2; H, 8.75; N, 4.7%); ν_{\max} . (film) 3475, 2978, 2932, 2906, 1455, 1391, 1245, 1164, 1055, 1029, 960, 795, 741, and 701 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.00 [3H, d, J 7 Hz, $(\text{CH}_3)_2\text{C}$], 1.01 (3H, dd, J 7 Hz, 1 Hz, $^i\text{Pr CH}_3$), 1.33 (6H, dt, J 7 Hz, 1 Hz, 2 x CH_3 of EtO), 1.8 (1H, bs, NH), 2.14 (1H, m, Me_2CH), 2.73 (1H, dd, J 15 Hz, 4 Hz, $\alpha\text{-H}$), 3.83 (1H, dd, J 13 Hz, 2 Hz, benzylic H), 4.03 (1H, dd, J 13 Hz, 1 Hz), 4.06-4.21 (4H, m, CH_2 's), 7.2-7.66 (5H, m, aromatic H), $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 27.9 ppm, m/z (70 eV, 140 °C) 299 (M^+ , 1), 162 (45), 161 (17), 111 (18), 92 (17), 91 (100), 83 (17), 65 (13) and 45 (5).

Ethyl [2-methyl-1-(benzylamino)propane]phenylphosphinate, yield 87% of a 2:1 diastereomeric mixture the minor diastereomer (306) of which was obtained crystalline: m. p. 103-105 °C (Found: C, 68.6; H, 8.0; N, 4.2. $\text{C}_{19}\text{H}_{26}\text{NO}_2\text{P}$ requires C, 68.9; H, 7.9; N, 4.2%); ν_{\max} . (nujol) 3283, 1437, 1220, 1117, 1032, 941, 767, 746, 732, 699, 564 and 516 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 0.93 (3H, dd, J 7 Hz, 1 Hz, CH_3), 0.95 (3H, d, J 7 Hz, CH_3), 1.33 (3H, t, J 7 Hz, CH_3 of EtO), 1.88 (1H, bm, NH), 2.86 (2H, dd, J 10 Hz, 3 Hz, CH_2Ph), 3.77-3.99 (2H, m, CH_2Me), 4.14 (1H, dhept, J 10 Hz, 7 Hz, CH), 7.21-7.31 (5H, m, benzylic aromatic H), 7.43-7.58 (3H, m, aromatic H) and 7.78-7.85 (2H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 43.5 ppm; m/z (70 eV, 210 °C) 331

(M^+ , 0.1), 162 (43), 142 (11), 141 (11), 92 (16), 91 (100), 79 (12), 78 (16) and 77 (14).

Dibenzyl 2-methyl-1-(benzylamino)propanephosphonate (308), yield 70%, oil, (Found: C, 70.7; H, 7.3; N, 3.3. $C_{25}H_{30}NO_3P$ requires C, 70.9; H, 7.1; N, 3.0%); ν_{\max} . (film) 3064, 3032, 2960, 2890, 1497, 1456, 1381, 1245, 1081, 996, 919, 866, 798, 736, 698, 599, 548 and 494 cm^{-1} ; δ_H (270MHz, $CDCl_3$) 0.98 (3H, d, J 7 Hz, 2 Hz, CH_3), 1.00 (3H, dd, J 7Hz, 2Hz, CH_3), 1.75 (1H, bs, NH), 2.17 (1H, dhept, J 16 Hz, 7 Hz, H-2), 2.80 (2H, dd, J 14 Hz, 4 Hz, H-1), 3.79 (1H, dd, J 23 Hz, 2 Hz, benzylic H), 3.98 (1H, dd, J 13 Hz, 2 Hz, benzylic H), 4.92-5.14 (4H, m, CH_2Me), 7.2-7.39 (5H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 28.8 ppm; m/z (70 eV, 170 °C) 423 (M^+ , 0.1), 180 (9), 171 (36), 163 (25), 162 (10), 107 (13), 92 (14), 91 (100) and 65 (11).

Diethyl (4-acetamidophenyl)allylaminomethanephosphonate (310), yield 95%, m.p. 141-142 °C (DCM/ diethyl ether) (Found: C, 56.55; H, 7.5; N, 8.1. $C_{16}H_{25}N_2O_4P$ requires C, 56.5; H, 7.4; N, 8.2%); ν_{\max} . (nujol) 3306, 3256, 3190, 3121, 3069, 1684, 1603, 1544, 1514, 1415, 1317, 1230, 1183, 1163, 1101, 1030, 960, 910, 875, 850, 795, 754, and 578 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.17 (3 H, t, J 7Hz, CH_3 of EtO), 1.31 (3 H, t, J 7Hz, CH_3 of EtO), 1.34 (1 H, bs, NH), 2.17 (3 H, s, CH_3CO), 3.00 (1H, dd, J 6Hz, J 14Hz, allylic H), 3.21 (1H, dd, J 6Hz, J 1Hz, allylic H), 3.80-4.17 (5 H, m, CH_2 's and PhCH), 5.07 and 5.13 (2 H, m, $=CH_2$), 5.73-5.87 (1 H, m, $-CH=$), 7.28 (2 H, dd, J_H 8Hz, J_P 2 Hz, aromatic H), 7.47 (2 H, d, J 8 Hz, aromatic H) and 8.77 (1 H, bs, AcNH); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 22.75 ppm; m/z (70 eV, 160 °C) 340 (M^+ , 2), 203 (100), 202 (70), 201 (60), 111 (70), 83 (75), 65 (60), 43 (54), and 41 (53).

Ethyl [(4-acetamidophenyl)allylaminomethane]phenylphosphinate (311), yield 82% (of diastereomeric mixture), m.p. 55-65 °C (Found: C, 64.4; H, 6.8; N, 7.5. $C_{20}H_{25}N_2O_3P$ requires C, 64.5; H, 6.8; N, 7.5%); ν_{\max} . (nujol) 3261, 1689, 1603, 1542, 1510, 1411, 1315, 1264, 1214, 1035, 957, 722, 694, 569 and 548; δ_H (270 MHz, $CDCl_3$) (* refers to the distinguishable signals of the minor diastereomer) 1.18* and 1.32 (3 H, t, J 7Hz, CH_3), 1.97 (1H, bs, NH), 2.13* and 2.16 (3 H, s, $COCH_3$), 2.91* and 2.98 (1 H, dd, J 7Hz, 15 Hz, allylic H), 3.17* and 3.23 (1 H, ddm, J 5 Hz, 16 Hz, allylic H), 3.85-4.20 (3H, m, CH_2 and PhCH), 4.94-5.07 (2 H, m, $=CH_2$), 5.55-5.83 (1H, m, $-CH=$), 7.01-7.75 (9H, m, aromatic H), 8.83 and 9.07* (1H, bs, AcNH);

$\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 38.8 (major) and 38.0 (minor) ppm; m/z (70 eV, 150 °C) 372 (M^+ , 1), 203 (65), 202 (67), 170 (62), 142 (79), 141 (64), 79 (70), 78 (100) and 77 (87).

[(4-Acetamidophenyl)allylaminomethane]phenylphosphinic acid (**312**), yield 77%, m.p. 217 °C (water/ ethanol) (Found: C, 61.3; H, 6.2; N, 8.0. $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_3\text{P}\cdot\frac{1}{2}\text{H}_2\text{O}$ requires C, 61.2; H, 6.3; N, 7.9%); ν_{max} . (nujol) 3301, 3256, 2726, 2618, 1667, 1600, 1538, 1417, 1330, 1199, 1130, 1044, 1025, 947, 861, 836, 757, 720, 698, and 554 cm^{-1} ; δ_{H} (270 MHz, DMSO-d_6) 2.00 (3 H, s, CH_3), 3.19 (1H, dd, J 13 Hz, J 9 Hz, allylic H), 3.50 (1H, bd, J 14 Hz, allylic H), 4.13 (1H, d, J 11 Hz, CH), 5.13 (2 H, m, $=\text{CH}_2$), 6.10 (1 H, m, $-\text{CH}=\text{)$, 7.16-7.50 (9 H, m, aromatic H) and 9.25 (1 H, bs, AcNH); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, D_2O) 30.8 ppm; m/z (FAB, Glycerol) 345 (MH^+ , 9), 289 (4), 204 (16), 203 (100), 185 (16), 163 (14), 75 (24), 57 (22) and 45 (20).

[(4-Acetamidophenyl)allylaminomethyl]diphenylphosphine oxide (**313**), yield 95%, m.p. 211-214 °C (Found: C, 71.4; H, 6.3; N, 6.95. $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_2\text{P}$ requires C, 71.3; H, 6.2; N, 6.9%); ν_{max} . (nujol) 1680, 1603, 1542, 1510, 1415, 1317, 1267, 1175, 1117, 722, 698, 561, 530 and 514 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 2.13 (3 H, s, CH_3), 2.99 (1H, dd, J 13 Hz, J 7 Hz, allylic H), 3.26 (1H, dd, J 14 Hz, J 5 Hz, allylic H), 4.25 (1H, d, J 11 Hz, CH), 5.00-5.10 (2 H, m, $=\text{CH}_2$), 5.75 (1 H, m, $-\text{CH}=\text{)$, 7.25 (2 H, dd, J_{H} 9 Hz, J_{P} 2 Hz, aromatic H), 7.30-7.64 and 7.81-7.89 (12 H, m, aromatic H), and 8.50 (1 H, bs, AcNH); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 30.6 ppm; m/z (70 eV, 210 °C) 202 (54), 201 (100), 159 (19), 132 (15), 124 (22), 78 (21), 77 (27), 51 (18), and 43 (54); m/z (FAB, 3-Nitrobenzylalcohol) 405 (MH^+ , 5), 203 (93), 107 (32), 90 (25), 89 (28) and 77 (35).

Diethyl (4-acetamidophenyl)aminomethanephosphonate (**314**), yield 85%, m.p. 105-108 °C (chloroform/ ether), (Found: C, 52.05; H, 7.0; N, 9.15. $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_4\text{P}$ requires C, 52.0; H, 7.05; N, 9.3%); ν_{max} . (nujol) 3259, 3191, 3123, 1687 (C=O), 1605, 1543, 1515, 1414, 1319, 1268, 1224, 1049, 1019, 962, 847, 787, 580 and 553 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.20 (3 H, t, J 7 Hz, CH_3), 1.29 (3 H, t, J 7 Hz, CH_3), 1.78 (2H, bs, NH_2), 2.16 (3 H, s, COCH_3), 3.80-4.09 (4 H, m, CH_2 's), 4.23 (1H, d, J 16 Hz, CH), 7.33 (2H, d, J_{H} 8 Hz, J_{P} 2 Hz, aromatic H), 7.47 (2H, d, J 8 Hz, aromatic H) and 8.29 (1H, bs, NHAc); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 23.8 ppm; m/z (70 eV, 180 °C) 300 (M^+ , 1), 164 (10), 163 (100), 121 (22), 120 (14), 119 (11), 94 (7), 83 (8) and 43 (10).

Ethyl [(4-acetamidophenyl)aminomethane]phenylphosphinate (315), yield 66%, (Found: MH^+ 333.1368. $C_{17}H_{22}N_2O_3P$ requires 333.1368); ν_{max} . (film) 3256, 3187, 3118, 3058, 2984, 1674, 1605, 1540, 1515, 1439, 1412, 1372, 1319, 1268, 1207, 1121, 1035, 958, 845, 721, 697 and 549 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) (* refers to the distinguishable signals of the minor diastereomer) 1.23* and 1.33 (3 H, t, J 7Hz, CH_3), 1.81 (2H, bs, NH_2), 2.12* and 2.15 (3 H, s, $COCH_3$), 3.85-4.20 (2H, m, CH_2), 3.39 and 4.36* (1H, d, J 11 Hz, J 13 Hz*, benzylic H), 7.01-7.75 (9H, m, aromatic H), 9.09 and 9.29* (1H, bs, AcNH); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 39.35 (major) and 39.15 (minor) ppm; m/z (FAB, oNBA) 333 (MH^+ , 7).

[(4-Acetamidophenyl)aminomethane]phenylphosphinic acid (316), yield 95%, m.p. 212-213 °C (water/ ethanol), (Found: C, 55.95; H, 6.1; N, 8.6. $C_{15}H_{17}N_2O_3P \cdot H_2O$ requires C, 55.9; H, 5.9; N, 8.7%); ν_{max} . (nujol) 1667, 1599, 1520, 1418, 1323, 1271, 1173, 1130, 1044, 1021, 843, 748, 719, 692, 629, 550 and 509 cm^{-1} ; δ_H (270 MHz, D_2O) 1.97 (3H, s, $COCH_3$), 4.32 (1H, d, J_P 12Hz, CH), 7.00-7.43 (10H, m, aromatic H); δ_P (36 MHz, D_2O) 24.0 ppm; m/z (70 eV, 240 °C) 148 (18), 121 (100), 120 (24), 119 (23), 106 (64), 94 (20), 78 (21), 77 (20) and 43 (39).

[(4-Acetamidophenyl)aminomethyl]diphenylphosphine oxide (317), yield 55%, m.p. 127-130°C (Found: 201.0469. $C_{10}H_{10}OP$ requires 201.0469); ν_{max} . (film) 3253, 3186, 3115, 3059, 1683, 1603, 1549, 1513, 1438, 1413, 1371, 1318, 1271, 1178, 1120, 1100, 1072, 999, 911, 846, 726, 696 and 647 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 2.09 (3 H, s, $COCH_3$), 6.75 (1H, d, J 10 Hz), 7.22-7.77 (14H, m, aromatic H), 9.78 (1H, bs, AcNH); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 31.3 ppm; m/z (70 eV, 110 °C) 201 ($Ph_2P=O^+$, 100), 77 (45) and 45 (13).

4-Nitrobenzaldehyde N-allylimine (318),¹⁵⁶ m.p. 55-56 °C, (DCM / light petroleum) (Found: C, 63.15; H, 5.2; N, 14.8. Calc. for $C_{10}H_{10}N_2O_2$: C, 62.85; H, 5.3; N, 14.7%); ν_{max} . (nujol) 1647 (C=N), 1598, 1515, 1344, 1290, 1104, 1027, 983, 933, 858, 832 and 749 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 4.33 (2H, m, allylic H), 5.21(1H, dm, J_{cis} 10 Hz, $C=CH_{cis}$), 5.26 (1H, dm, J_{trans} 17 Hz, $C=CH_{trans}$), 6.08 (1H, ddm, J_{trans} 17 Hz, J_{cis} 10 Hz, -CH=), 7.92 (2H, d, J 8 Hz, aromatic H), 8.28 (2H, d, J 8 Hz, aromatic H), 8.39 (1H, bs, CH=N); m/z (70 eV, 130 °C) 190 (M^+ , 39), 189 (47), 173 (45), 143 (29), 116 (37), 89 (35), 41 (100) and 39 (32).

4-Cyanobenzaldehyde *N*-allylimine (319),¹⁵⁶ m.p. 25 °C; b.p. 125 °C/1 mmHg (Found: C, 77.5; H, 6.0; N, 16.5. Calc. for C₁₁H₁₀N₂ : C, 77.6; H, 5.9; N, 16.5%); ν_{\max} . (film) 2879, 2228 (C=N), 1650 (C=N), 1413, 1372, 1303, 1287, 1021, 994, 921, 833 and 554 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 4.29 (2H, dm, allylic H), 5.17 (1H, dm, *J*_{cis} 10 Hz, C=CH_{cis}), 5.23 (1H, dm, *J*_{trans} 17 Hz, C=CH_{trans}), 6.05 (1H, ddm, *J*_{trans} 17 Hz, *J*_{cis} 10 Hz, -CH=), 7.69 (2H, d, *J* 8 Hz, aromatic H), 7.84 (2H, d, *J* 8 Hz, aromatic H), 8.31 (1H, bs, CH=N); *m/z* (70 eV, 100 °C) 170 (*M*⁺, 80), 169 (100), 142 (75), 129 (30), 116 (30), 115 (40), 41 (70) and 39 (33).

4-Chlorobenzaldehyde *N*-allylimine (320), b.p. 100°C/0.05 mmHg (Found: C, 67.2; H, 5.5; N, 7.7. C₁₀H₁₀NCl requires C, 66.9; H, 5.6; N, 7.8%); ν_{\max} . (film) 2845, 1650 (C=N), 1596, 1573, 1490, 1407, 1297, 1088, 1015, 994, 920, 850, 822 and 505 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 4.25 (2H, m, allylic H), 5.16 (1H, dm, *J*_{cis} 10 Hz, C=CH_{cis}), 5.23 (1H, dm, *J*_{trans} 17 Hz, C=CH_{trans}), 6.06 (1H, ddm, *J*_{trans} 17 Hz, *J*_{cis} 10 Hz, -CH=), 7.38 (2H, d, *J* 8 Hz, aromatic H), 7.69 (2H, d, *J* 8 Hz, aromatic H), 8.25 (1H, bs, CH=N); *m/z* (70 eV, 120 °C) 180 (39), 179 (*M*⁺, 66), 178 (100), 151 (45), 138 (34), 125 (33), 89 (36) and 41 (75)

Benzaldehyde *N*-allylimine (321),¹⁵⁶ b.p. 60 °C/1mmHg (Found: C, 82.8; H, 7.8; N, 9.8. Calc. for C₁₀H₁₁N : C, 82.7; H, 7.6; N, 9.65%); ν_{\max} . (film) 3063, 2843, 1650 (C=N), 1451, 1418, 1376, 1309, 1293, 1025, 993, 920, 755 and 694 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 4.27 (2H, m, allylic H), 5.16 (1H, dm, *J*_{cis} 10 Hz, C=CH_{cis}), 5.24 (1H, dm, *J*_{trans} 17 Hz, C=CH_{trans}), 6.08 (1H, ddm, *J*_{trans} 17 Hz, *J*_{cis} 10 Hz, -CH=), 7.40-7.43 (3H, m, aromatic H), 7.74-7.77 (2H, m, aromatic H), 8.30 (1H, bs, CH=N); *m/z* (70 eV, 70 °C) 145 (*M*⁺, 69), 144 (100), 117 (39), 104 (34), 91 (31), 90 (30), 41 (45) and 39 (23).

4-Methoxybenzaldehyde *N*-allylimine (322),¹⁵⁶ b.p. 100 °C/0.07 mmHg (Found: C, 75.4; H, 7.6; N, 7.9. Calc. for C₁₁H₁₃NO : C, 75.4; H, 7.5; N, 8.0%); ν_{\max} . (film) 2837, 1650 (C=N), 1607, 1579, 1512, 1306, 1252, 1167, 1033, 919, 832, and 529 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 3.84 (3H, s, CH₃O), 4.22 (2H, m, allylic H), 5.14 (1H, dm, *J*_{cis} 10 Hz, C=CH_{cis}), 5.22 (1H, dm, *J*_{trans} 17 Hz, C=CH_{trans}), 6.06 (1H, ddm, *J*_{trans} 17 Hz, *J*_{cis} 10 Hz, -CH=), 6.92 (2H, d, *J* 9 Hz, aromatic H), 7.70 (2H, d, *J* 9 Hz, aromatic H), 8.22 (1H, bs, CH=N); *m/z* (70 eV, 100 °C) 175 (*M*⁺, 75), 174 (100), 147 (17), 134 (29), 133 (19), 121 (30), 77 (18), 41 (44) and 39 (18).

Diethyl allylamino(4-nitrophenyl)methanephosphonate (323), yield 50%, m.p. 50-51 °C (Found: C, 51.1; H, 6.5; N, 8.5. $C_{14}H_{21}N_2O_5P$ requires C, 51.2; H, 6.45; N, 8.5%); ν_{\max} . (nujol) 3299, 1520, 1466, 1366, 1348, 1234, 1188, 1109, 1051, 943, 924 and 755 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.20 (3H, t, J 7 Hz, CH_3), 1.27 (3H, t, J 7 Hz, CH_3), 2.07 (1H, bs, NH), 2.99 (1H, dd, J 7 Hz, 14 Hz, allylic H), 3.20 (1H, dd, J 7 Hz, 14 Hz, allylic H), 3.92-4.13 (4H, m, CH_2 's), 4.21 (1H, d, J_P 21 Hz, CH), 5.04-5.12 (2H, m, = CH_2), 5.71-5.86 (1H, m, -CH=), 7.59 (2H, dd, J_H 8.5 Hz, J_P 2.2 Hz, aromatic H) and 8.20 (2H, d, J_H 8.5 Hz, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 21.0 ppm; m/z (70 eV, 140 °C) 328 (M^+ , 2), 192 (12), 191 (100), 190 (3), 179 (6), 145 (8), 117 (2), 56 (4) and 41 (30).

Diethyl allylamino(4-cyanophenyl)methanephosphonate (324), yield 65%, m.p. 39-40 °C (Found: C, 58.7; H, 6.85; N, 9.1. $C_{15}H_{21}N_2O_3P$ requires C, 58.4; H, 6.9; N, 9.1%); ν_{\max} . (film) 2983, 2229, 1608, 1392, 1247, 1164, 1099, 1025, 970, 872, 788, 754, 578, and 489 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.18 (3H, t, J 7 Hz, CH_3), 1.26 (3H, t, J 7 Hz, CH_3), 2.03 (1H, bs, NH), 2.97 (1H, dd, J 7 Hz, 14 Hz, allylic H), 3.20 (1H, dd, J 6 Hz, 16 Hz, allylic H), 3.88-4.11 (4H, m, CH_2 's), 4.14 (1H, d, J_{HP} 21 Hz, CH), 5.06 (1H, dm, J 9.5 Hz, = CH_2), 5.11 (1H, bs, = CH_2), 5.70-5.85 (1H, m, -CH=), 7.52 (2H, dd, J_H 8 Hz, J_P 2 Hz, aromatic H) and 7.625 (2H, d, J_H 8 Hz, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 21.2 ppm; m/z (70 eV, 100° °C) 308 (M^+ , 3), 172 (13), 171 (100), 111 (18), 99 (10), 83 (17), 65 (14), 41 (37), and 29 (10).

Diethyl allylamino(4-chlorophenyl)methanephosphonate (325), yield 69%, m.p. 15 °C (Found: C, 52.9; H, 6.7; N, 4.4. $C_{14}H_{21}NO_3P$ requires C, 52.75; H, 6.7; N, 4.3%); ν_{\max} . (film) 2982, 2908, 1490, 1445, 1408, 1392, 1244, 1164, 1093, 1025, 966, 868, 836, 787, 754 and 569 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.17 (3H, dt, J_H 7 Hz, J_P 0.5 Hz, CH_3), 1.27 (3H, dt, J_H 7 Hz, J_P 0.5 Hz, CH_3), 1.95 (1H, bs, NH), 2.98 (1H, ddm, J 7 Hz, 14 Hz, allylic H), 3.21 (1H, ddm, J 5 Hz, 14 Hz, allylic H), 3.845-4.12 (4H, m, CH_2 's), 4.06 (1H, d, J_P 21 Hz, CH), 5.05-5.12 (2H, m, = CH_2), 5.72-5.86 (1H, m, -CH=), 7.33 (4H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 22.2 ppm; m/z (70 eV, 120 °C) 319 (2), 317 (M^+ , 5), 182 (33), 181 (13), 180 (100), 179 (7), 178 (6), 125 (5), 41 (17) and 32 (11).

Diethyl allylamino(phenyl)methanephosphonate (326), yield 74%, oil (Found: M^+ 283.1342. $C_{14}H_{22}NO_3P$ requires 283.1337); ν_{\max} . (film) 2981, 2908, 1494, 1455,

1392, 1244, 1164, 1099, 1028, 967, 789, 701 and 568 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.14 (3 H, t, J 7 Hz, CH_3), 1.285 (3 H, t, J 7 Hz, CH_3), 1.99 (1 H, bs, NH), 3.03 (1H, ddm, J 6 Hz, J 14 Hz, allylic H), 3.22 (1H, ddm, J 6 Hz, J 15 Hz, allylic H), 3.79-4.14 (5 H, m, CH_2 's and PhCH), 5.08 and 5.13 (1 H, m, $=\text{CH}_2$), 5.76-5.90 (1 H, m, $-\text{CH}=\text{}$), 7.28-7.43 (5H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 22.75 ppm; m/z (70 eV, 140 °C) 283 (M^+ , 2), 147 (11), 146 (100), 145 (5), 144 (8), 104 (7), 91 (9) and 41 (18).

Diethyl allylamino(4-methoxyphenyl)methanephosphonate (327), yield 96%, m.p. 35 °C (Found: C, 57.3; H, 7.8; N, 4.4. $\text{C}_{15}\text{H}_{24}\text{NO}_4\text{P}$ requires C, 57.5; H, 7.7; N, 4.5%); ν_{max} . (film) 2981, 2908, 1610, 1511, 1462, 1304, 1250, 1178, 1098, 1029, 965, 841, 789, 753, 563 and 488 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.16 (3 H, t, J 7 Hz, CH_3), 1.28 (3 H, t, J 7 Hz, CH_3), 1.83 (1H, bs, NH), 3.01 (1 H, ddm, J 7 Hz, 14 Hz, allylic H), 3.23 (1 H, ddm, J 5 Hz, 14 Hz, allylic H), 3.81 (3 H, s, OCH_3), 3.80-4.13 (5H, m, CH_2 's and CH), 5.06-5.14 (2 H, m, $=\text{CH}_2$), 5.74-5.89 (1H, m, $-\text{CH}=\text{}$), 6.88 (2H, dd, J_{H} 9 Hz, J_{P} 1 Hz, aromatic H) and 7.32 (2H, dd, J_{H} 9 Hz, J_{P} 2 Hz, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36MHz, CDCl_3) 22.8 ppm; m/z (70 eV, 150 °C) 313 (M^+ , 3), 176 (100), 175 (56), 174 (87), 134 (30), 121 (31), 83 (62), 65 (49) and 41 (52).

Diethyl (4-nitrophenyl)aminomethanephosphonate (328), yield 77%, oil, (Found: $M\text{H}^+$ 289.0953. $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_5\text{P}$ requires 289.0953); ν_{max} . (film) 3382, 2983, 2929, 1605, 1521, 1348, 1241, 1164, 1099, 1051, 1024, 970, 860, 795, 659, 564 and 505 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.20 (3 H, dt, J 7 Hz, 0.5 Hz, CH_3), 1.24 (3 H, dt, J 7 Hz, 0.5 Hz, CH_3), 2.04 (2H, bs, NH_2), 3.95-4.10 (4 H, m, CH_2 's), 4.38 (1H, d, J 19 Hz, CH), 7.62 (2H, d, J_{H} 8 Hz, J_{P} 2.5 Hz, aromatic H), 8.17 (2H, d, J 8 Hz, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 22.0 ppm; m/z (FAB, oNBA) 289 ($M\text{H}^+$, 3) and 151 ($M^+ - (\text{EtO})_2\text{P}=\text{O}$, 16).

Diethyl (4-cyanophenyl)aminomethanephosphonate (329), yield 80%, oil, (Found: C, 53.5; H, 6.5; N, 10.2. $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_3\text{P}$ requires C, 53.7; H, 6.4; N, 10.4%); ν_{max} . (film) 3294, 2983, 2229 ($\text{C}\equiv\text{N}$), 1670, 1609, 1542, 1505, 1444, 1392, 1240 ($\text{P}=\text{O}$), 1164, 1050, 1024, 971, 855, 797 and 746 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.22 (3 H, dt, J 7 Hz, 0.5 Hz, CH_3), 1.27 (3 H, t, J 7Hz, CH_3), 1.83 (2H, bs, NH_2), 3.92-4.11 (4 H, m, CH_2 's), 4.34 (1H, d, J 19 Hz, CH), 7.56-7.66 (4H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 22.3 ppm; m/z (70 eV, 160°C) 268 (M^+ , 3), 132 (10), 131 ($M^+ - (\text{EtO})_2\text{P}=\text{O}$, 100), 130 (7), 129 (10), 128 (7), 111 (9), 83 (8) and 82 (7).

Diethyl phenylaminomethanephosphonate (330), oil, physical data in agreement with that published in literature;¹⁵⁷ ν_{\max} . (film) 3300, 2928, 1642, 1339, 1245, 1160, 1121, 1008, 837, 677 and 560 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.08 (3 H, t, J 7 Hz, ester CH_3), 1.17 (3 H, t, J 7 Hz, ester CH_3), 2.20 (2H, bs, NH_2), 3.85-4.15 (5 H, m, CH and 2 x CH_2O), 4.22 (1H, d, J 17 Hz, CH), 7.26-7.34 (5H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 23.8 ppm (Lit.¹⁵⁷ 24.0 ppm in CD_2Cl_2); m/z (70 eV, 150 °C) 243 (M^+ , 1).

Diethyl (4-methoxyphenyl)aminomethanephosphonate (331), oil, (Found MH^+ 274.1208. $\text{C}_{12}\text{H}_{21}\text{NO}_4\text{P}$ requires 274.1425); ν_{\max} . (neat) 3300, 2928, 1640, 1330, 1250, 1160, 1063, 1028, 837, 860, 794 and 560 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.20 (3 H, t, J 7 Hz, ester CH_3), 1.24 (3 H, t, J 7 Hz, ester CH_3), 2.10 (2H, bs, NH_2), 3.85-4.05 (4 H, m, CH_2 's), 4.22 (1H, d, J 17 Hz, CH), 7.62 (2H, d, J_{H} 8 Hz, J_{P} 2 Hz, aromatic H), 8.17 (2H, d, J 8 Hz, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 24.0 ppm; m/z (FAB, oNBA) 274 (MH^+ , 1).

4-Nitrobenzaldehyde N-(3-bromopropyl)imine (332), m.p. 103 °C, (Found: C, 44.9; H, 3.8; N, 10.2. $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_2\text{Br}$ requires C, 44.3; H, 4.1; N, 10.3%); ν_{\max} . (nujol) 1706 (C=N), 1434, 1398, 1380, 1288, 1171, 1069, 1036, 850, 805, 723 and 506 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 2.29 (2H, quintet, J 6 Hz, C- CH_2 -C), 3.51 (2H, t, J 6 Hz, CH_2Br), 3.82 (2H, dt, J 6 Hz, 1.5 Hz, CH_2N), 7.90 (2H, d, J 9 Hz, aromatic H), 8.27 (2H, J 9 Hz, aromatic H), 8.43 (1H, d, J 1.5 Hz, CH=N); m/z (70 eV, 110°C) 272/270 (M^+ , 1), 165 (10), 164 (100), 163 (45), 147 (12), 117 (41), 90 (18), 89 (10) and 41 (16).

4-Nitrobenzaldehyde N-^tbutylimine (333), m.p. 74 °C (Found: C, 63.9; H, 6.9; N, 13.5. $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ requires C, 64.0; H, 6.8; N, 13.6%); ν_{\max} . (nujol) 1640, 1598, 1526, 1347, 1230, 1201, 1105, 1010, 958, 855, 835 and 751 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.315 (9 H, s, $(\text{CH}_3)_3\text{C}$), 7.91 (2 H, d, J 8.8 Hz, aromatic H), 8.26 (2 H, d, J 8.8 Hz, aromatic H) and 8.33 (1 H, s, CH=N); m/z (70 eV, 140 °C) 206 (M^+ , 5), 192 (7), 191 (60), 145 (14), 58 (5), 57 (100), 56 (4), 41 (16) and 39 (4).

4-Nitrobenzaldehyde N-phenylimine (334), m.p. 90-91 °C (Lit.¹⁵⁸ 93 °C) (Found: C, 69.2; H, 4.3; N, 12.5. Calc. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2$: C, 69.0; H, 4.5; N, 12.4%); ν_{\max} . (nujol) 1599, 1516, 1465, 1356, 1316, 1096, 1072, 976, 853, 771, 746, 701 and 687 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.24 (3 H, m, aromatic H), 7.40-7.47 (2 H, m, aromatic H), 8.08

(2H, d, J 9 Hz, 4-NO₂ aromatic H), 8.33 (2H, d, J 9 Hz, 4-NO₂ aromatic H) and 8.56 (1H, s, CH=N); m/z (70 eV, 100 °C) 227 (15), 226 (M^+ , 100), 225 (29), 180 (6), 179 (33), 104 (15), 77 (36), 51 (11) and 49 (31).

4-Nitrobenzaldehyde O-benzoyloxime (336),¹⁵⁹ m.p. 118-119 °C, (DCM/ light petroleum) (Found: C, 65.5; H, 4.6; N, 10.9. Calc. for C₁₄H₁₂N₂O₃: C, 65.6; H, 4.7; N, 10.9%); ν_{\max} . (nujol) 3030, 1588, 1456, 1343, 1105, 1080, 1027, 937, 853, 837, 750 and 688 cm⁻¹; δ_H (270 MHz, CDCl₃) 5.27 (2H, s, CH₂), 7.34-7.44 (5 H, m, aromatic H), 7.74 (2H, d, J 9.5 Hz, 4-NO₂ aromatic H), 8.18 (1H, s, CH=N) and 8.22 (2H, d, J 9.5 Hz, 4-NO₂ aromatic H); m/z (70 eV, 140 °C) 256 (M^+ , 1), 92 (9), 91 (100), 77 (4), 76 (2), 65 (5), 63 (2), 51 (3) and 50 (2).

Diethyl (4-nitrophenyl)(3'-bromopropyl-1'-amino)methanephosphonate (337), yield 68%, m.p. 41 °C, (Found: C, 41.3; H, 5.5; N, 6.8. C₁₄H₂₂N₂O₅PBr requires C, 41.1; H, 5.4; N, 6.8%); ν_{\max} . (nujol) 2982, 1606, 1521, 1392, 1348, 1245 (P=O), 1163, 1100, 1025, 971, 862 and 696 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.19 (3 H, t, J 7 Hz, CH₃), 1.28 (3H, t, J 7 Hz, CH₃), 2.00 (2H, dq, J 3 Hz, 6 Hz, 2'-CH₂), 2.63 (2H, t, J 6 Hz, 1'-CH₂), 3.47 (2H, t, J 6 Hz, 3'-CH₂), 3.90-4.14 (4 H, m, ester CH₂'s), 4.16 (1H, d, J 21 Hz, 1-H), 7.61 (2H, d, J_H 9 Hz, J_P 2 Hz, aromatic H), 8.21 (2H, dd, J_H 9 Hz, J_P 0.5 Hz, aromatic H); δ_P {H} (36 MHz, CDCl₃) 20.5 ppm; m/z (14 eV, 100 °C) 410 and 408 (M^+ , 2), 274 and 272 (12), 273 and 271 (M^+ - (EtO)₂P=O, 100), 227 (17), 192 (8), 191 (44), 164 (15) and 111 (8).

Diethyl ^tbutylamino(4-nitrophenyl)methanephosphonate (338), yield 57%, m.p. 96-97 °C (Found: M^+ 344.1501. C₁₅H₂₅N₂O₅P requires 344.1501); ν_{\max} . (nujol) 3311, 1519, 1456, 1365, 1344, 1239, 1108, 1060, 961, 772, 734, and 573 cm⁻¹; δ_H (270 MHz, CDCl₃) 0.98 [9H, s, (CH₃)₃C], 1.16 (3 H, t, J 7 Hz, CH₃), 1.28 (3 H, t, J 7 Hz, CH₃), 1.84 (1H, bs, NH), 3.81-4.14 (4H, m, CH₂'s), 4.28 (1 H, d, J_P 26 Hz, CH), 7.66 (2H, dd, J_H 9 Hz, J_P 2 Hz, aromatic H) and 8.17 (2H, dd, J_H 9 Hz, J_P 1 Hz, aromatic H); δ_P {H} (36 MHz, CDCl₃) 22.0 ppm; m/z (70 eV, 100 °C) 344 (M^+ , 5), 208 (12), 207 (100), 191 (24), 152 (7), 151 (81), 105 (11), 57 (36), and 41 (11).

Diethyl (4-nitrophenyl)(phenylamino)methanephosphonate (339), yield 62%, m.p. 150 °C (Found: C, 56.0; H, 5.9; N, 7.6. C₁₇H₂₁N₂O₅P requires C, 56.0; H, 5.8; N, 7.7%); ν_{\max} . (nujol) 1603, 1510, 1467, 1347, 1307, 1276, 1234, 1101, 1034, 964, 862,

749, 694 and 589 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.19 (3 H, t, J 7 Hz, CH_3), 1.30 (3 H, t, J 7 Hz, CH_3), 3.83-4.21 (4 H, m, CH_2 's), 4.8-4.9 (2H, m, NH and CH), 6.53 (2H, dm, J 9 Hz, aromatic H), 6.74 (1H, t, 8 Hz, aromatic H), 7.12 (2H, ddm, J 9 Hz and 8 Hz, aromatic H), 7.66 (2H, dd, J_{H} 9 Hz, J_{P} 2 Hz, aromatic H), 8.20 (2H, dd, J_{H} 9 Hz, J_{P} 1 Hz, aromatic H); δ_{P} {H} (36 MHz, CDCl_3) 20.0 ppm; m/z (70 eV, 150 °C) 364 (M^+ , 7), 228 (15), 227 (100), 226 (6), 225 (4), 181 (15), 180 (5), 179 (4) and 77 (8).

4-Acetamidobenzaldehyde N-(4-methoxyphenyl)imine (340), m.p. 184 °C (DCM/ light petroleum) (Found: C, 71.4; H, 5.9; N, 10.4. $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ requires: C, 71.6; H, 6.0; N, 10.4%); ν_{max} . (nujol) 3279, 1665, 1624, 1607, 1587, 1542, 1510, 1413, 1316, 1251, 1031 and 839 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 2.21 (3 H, s, CH_3CO), 3.83 (3H, s, OCH_3), 6.93 (2H, d, J 9 Hz, aromatic H), 7.22 (2H, d, J 9 Hz, aromatic H), 7.39 (1H, bs, NHAc), 7.62 (2H, d, J 8.5 Hz, aromatic H), 7.85 (2H, d, J 8.5 Hz, aromatic H) and 8.42 (1H, bs, $\text{CH}=\text{N}$); m/z (70 eV, 160 °C) 269 (19), 268 (M^+ , 100), 253 (21), 226 (16), 212 (10), 211 (51), 107 (11), 92 (12) and 43 (18).

4-Acetamidobenzaldehyde N-phenylimine (341), m.p. 137-141 °C (DCM/ diethylether) (Found: C, 75.5; H, 5.9; N, 11.6. $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$ requires C, 75.6; H, 5.9; N, 11.7%); ν_{max} . (nujol) 3245, 1662, 1624, 1593, 1533, 1410, 1321, 1264, 1170, 841, 761, 721, 698 and 545 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 2.12 (3 H, s, CH_3CO), 7.18-7.25 (2 H, m, aromatic H), 7.36-7.44 (3 H, m, aromatic H and NHAc), 7.64 (2 H, d, J 9 Hz, aromatic H), 7.87 (2 H, d, J 9 Hz, aromatic H) and 8.40 (1 H, s, $\text{CH}=\text{N}$); m/z (70 eV, 140 °C) 239 (17) , 238 (M^+ , 100), 197 (11), 196 (76), 195 (75), 107 (11), 77 (30), 51 (11) and 43 (19).

4-Acetamidobenzaldehyde N-(4-nitrophenyl)imine (342), m.p. 231-232 °C (DCM/ light petroleum) (Found M^+ 283.0957. $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_3$ requires 283.0957); ν_{max} . (nujol) 3309, 3187, 1676, 1598, 1582, 1530, 1510, 1412, 1342, 1324, 1268 and 1168 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 2.23 (3 H, s, CH_3CO), 7.24 (2 H, d, J 9Hz, aromatic H), 7.40 (1H, bs, NHAc), 7.68 (2 H, d, J 9 Hz, aromatic H), 7.89 (2 H, d, J 9 Hz, aromatic H) and 8.26 (2 H, d, J 9 Hz, aromatic H) and 8.36 (1 H, s, $\text{CH}=\text{N}$) ; m/z (70 eV, 180 °C) 283 (M^+ , 10), 241 (11), 163 (50), 121 (71), 120 (100), 92 (18), 65 (21) and 43 (54).

4-Acetamidobenzaldehyde O-benzylloxime (343), m.p. 105-115 °C (Found: C, 71.5; H, 5.9; N, 10.35. $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ requires C, 71.6; H, 6.0; N, 10.4%); ν_{max} . (nujol) 3244,

1665, 1596, 1538, 1515, 1455, 1408, 1370, 1322, 1271, 1038, 932 and 745 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 2.18 (3H, s, CH_3CO), 5.20 (2H, s, CH_2), 7.31-7.44 (5 H, m, aromatic H and NHAc), 7.53 (4 H, m, aromatic H), and 8.09 (1 H, s, $\text{CH}=\text{N}$); m/z (70 eV, 200 °C) 268 (M^+ , 21), 119 (7), 118 (14), 91 (100), 77 (8), 65 (8) and 43 (16).

Diethyl (4-acetamidophenyl)-(4-methoxyphenylamino)methanephosphonate (344), yield 86%, m.p. 157°C (Found: C, 51.3; H, 6.8; N, 6.9. $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_5\text{P}$ requires C, 51.1; H, 6.7; N, 6.9%); ν_{max} . (nujol) 3352, 3301, 3259, 3192, 3123, 1682, 1604, 1543, 1514, 1321, 1275, 1223, 1054, 1023, 971, 580 and 554 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.14 (3 H, t, J 7 Hz, CH_3), 1.29 (3 H, t, J 7 Hz, CH_3), 2.16 (3 H, s, COCH_3), 3.68 (3 H, s, OCH_3), 3.68-4.18 (4 H, m, CH_2 's), 4.65 (1H, d, J_{P} 24, CH), 6.52 (2H, d, J_{H} 9 Hz, aromatic H), 6.68 (2H, d, J_{H} 9 Hz, aromatic H), 7.36 (2H, dd, J_{H} 8.5 Hz, J_{P} 2 Hz, aromatic H), 7.47 (2H, d, J_{H} 8.5 Hz, aromatic H) and 7.65 (1H, bs, NHAc); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 21.8 ppm; m/z (70 eV, 170 °C) 406 (M^+ , 7), 270 (17), 269 (100), 268 (42), 253 (9), 211 (12), 111 (12), 83 (13), 65 (11) and 43 (9).

Diethyl (4-acetamidophenyl)(phenylamino)methanephosphonate (345), yield 84%, m.p. 151-153 °C (Found: C, 60.5; H, 6.7; N, 7.45. $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_4\text{P}$ requires C, 60.6; H, 6.7; N, 7.4%); ν_{max} . (nujol) 3333, 1677, 1604, 1544, 1509, 1415, 1318, 1282, 1240, 1052, 1026, 975, 753, 570 and 504; δ_{H} (270 MHz, CDCl_3) 1.14 (3 H, t, J 7 Hz, CH_3), 1.28 (3H, t, J 7 Hz, CH_3), 2.16 (3H, s, CH_3CO), 3.68-3.78 and 3.91-4.18 (4H, m, CH_2 's), 4.73 (1H, d, J_{P} 24, CH), 6.57 (2H, dd, J_{H} 8.0 Hz, J_{P} 0.8 Hz, aromatic H), 6.69 (1H, t, 7Hz, aromatic H), 7.10 (2H, d, J_{H} 8 Hz, J_{P} 7.5 Hz, aromatic H), 7.385 (2H, d, J_{H} 9 Hz, J_{P} 2 Hz, aromatic H), 7.47 (2H, d, J_{H} 9 Hz, aromatic H) and 7.53 (1H, bs, NHAc); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 21.6 ppm; m/z (70 eV, 160 °C) 376 (M^+ , 2), 240 (18), 239 (100), 238 (13), 197 (8), 196 (14), 195 (13), 104 (5) and 43 (6).

Diethyl (4-acetamidophenyl)-(4-nitrophenylamino)methanephosphonate (346), yield 74%, m.p. 209-210 °C (Found: C, 53.9; H, 5.8; N, 10.05. $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_6\text{P}$ requires C, 54.2; H, 5.7; N, 10.0%); ν_{max} . (nujol) 3347, 3256, 3192, 1684, 1601, 1544, 1513, 1330, 1290, 1272, 1234, 1115, 1016, 982 and 576 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.11 (3H, t, J 7 Hz, CH_3), 1.29 (3 H, t, J 7 Hz, CH_3), 2.16 (3 H, s, COCH_3), 3.62-3.96 and 4.06-4.20 (4 H, m, CH_2 's), 4.79 (1H, dd, J_{H} 8 Hz, J_{P} 24 Hz, CH), 6.61 (2H, d, J_{H} 9 Hz, aromatic H), 6.8 (1H, t, 8 Hz, ArNH), 7.33 (2H, d, J_{H} 9 Hz, aromatic H), 7.48 (2H, d, J_{H} 9 Hz, aromatic H), 7.99 (2H, d, J_{H} 9 Hz, aromatic H) and 8.37 (1H,

bs, NHAc); $\delta_{\text{p}}\{\text{H}\}$ (36 MHz, CDCl_3) 20.1 ppm; m/z (70 eV, 160 °C) 421 (M^+ , 3), 285 (17), 284 (100), 242 (8), 241 (8), 196 (6), 111 (7), 83 (7), 65 (6), and 43 (12).

Determination of the rate of addition of diethyl trimethylsilyl phosphites (300) to imines (341) and (342): Diethyl phosphite (14 mg) was dissolved in CDCl_3 (1 ml) and the solution transferred to a NMR tube and kept under argon atmosphere. Triethylamine (140 μl) and then chlorotrimethylsilane (130 μl) were added and the tube was shaken to ensure complete mixing. One equivalent of the corresponding imine was dissolved in CDCl_3 (1 ml) and delivered to the NMR tube. The NMR was recorded at appropriate time intervals. Similar procedure could not be performed for imine (340) as by the time of the first reading, the rate of reaction had already reached a plateau.

Determination of the rate of addition of diethyl trimethylsilyl phosphites (300) to imine (340): A normal reaction was set up for the addition to imine (340) in CDCl_3 in place of the DCM. The imine was added as a CDCl_3 solution. Aliquots (1ml) were withdrawn from this reaction mixture at 30 second intervals and squirted into water (1ml) to quench. NMR analysis was carried on this mixture.

1,3,5-Tribenzyltrihydro-1,3,5-triazine (347). Formalin (40% aqueous, 46 ml) was delivered to stirred, cooled benzylamine (49 g, 0.46 mmol) over a period of 1 hour at such a rate as to keep the temperature below 12 °C. After 10 minutes, a solution of sodium hydroxide (6.0 g) in water (50 ml) was added whilst vigorous stirring was maintained. The solution thus obtained was extracted with ether (3 x 150 ml) and the combined ethereal extracts were dried over MgSO_4 . Removal of solvent followed by crystallisation from ethanol (45 ml) and water (3 ml) afforded the desired product (347) (18g, 30%) m. p. 48 °C (Lit.¹⁶⁰ 48-49 °C)

Diethyl N-benzylaminomethanephosphonate (348). Triazine (347) (120 mg, 1mmol) was added to a solution of (300), prepared in the usual manner from diethyl phosphite (414 mg, 3 mmol), in refluxing 1,2-dichloroethane (5 ml) under argon. After 5 hours, heat was removed and solvent was removed at reduced pressure to leave a residue that was chromatographed on silica to afford a yellow oil, (175 mg, 30%), physical data in agreement with literature;¹⁶¹ δ_{H} (90 MHz, CDCl_3) 1.40 (6H, J 7 Hz, ester CH_3), 3.65 (2H, d, J 12 Hz, CH_2P), 4.28 (4H, m, CH_2O), 4.81 (2H, s, PhCH_2), 7.50-7.63 (5H, m, aromatic H).

Benzaldehyde azine adduct (350), yield 91%, m.p. 98-100 °C (Found: C, 62.1; H, 6.7; N, 7.9. $C_{18}H_{23}N_2O_3P$ requires C, 62.4; H, 6.7; N 8.1%); ν_{max} . (nujol) 3221, 1494, 1242, 1094, 1058, 1019, 976, 820, 754, 731, 691 and 562 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.13 (3 H, t, J 7 Hz, CH_3), 1.30 (3 H, t, J 7 Hz, CH_3), 3.74-4.20 (4 H, m, CH_2 's), 4.92 (1H, d, J_P 21 Hz, J_H 7 Hz, CH), 6.22 (1 H, bs, NH), 7.23-7.38 and 7.45-7.48 (10H, m, aromatic H) and 7.64 (1 H, s, HC=N); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 20.8 ppm; m/z (70 eV, 150 °C) 346 (M^+ , 5), 210 (16), 209 (100), 208 (7), 131 (9), 106 (9), 104 (11), 91 (8), and 77 (15).

Benzaldimines (351), m.p. 204 °C (Lit.¹⁶² 206 °C), *(352)*, m.p. 163 °C (Lit.¹⁶³ m.p. 166 °C) and *(353)* m.p. 170 °C (Lit.¹⁶⁴ m.p. 169-170 °C) were prepared from benzaldehyde and the relevant amine in refluxing ethanol and were recrystallized from ethanol.

Cinnamaldehyde N-(4-methoxyphenyl)imine (354),¹⁶⁵ m.p. 120 °C, (DCM / light petroleum) (Found: C, 80.7; H, 6.3; N, 5.9. Calc. for $C_{16}H_{15}NO$: C, 81.0; H, 6.4; N, 5.9%); ν_{max} . (nujol) 1629, 1605, 1575, 1505, 1288, 1250, 1179, 1164, 1154, 1111, 1032, 988, 960, 838, 759, 747 and 695 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.92 (2H, d, J 9 Hz, 4-MeO aromatic H), 7.21 (2H, d, J 9 Hz, 4-MeO aromatic H), 7.34-7.43 (3H, m, aromatic H), 7.11 (1H, d, J 4 Hz), 7.12 (1H, d, J 5 Hz), 7.52-7.55 (2H, m, aromatic H), 8.30 (1H, dd, J 4 Hz, 5 Hz, $CH=N$); m/z (70 eV, 120 °C) 238 (10), 237 (M^+ , 59), 236 (100), 122 (4), 115 (23), 92 (4), 77 (6) and 64 (4).

Cinnamaldehyde N-phenylimine (355),¹⁶⁵ m.p. 107 °C, (DCM / light petroleum) (Found: C, 86.7; H, 6.1; N, 6.6. Calc. for $C_{15}H_{13}N$: C, 86.9; H, 6.3; N, 6.8%); ν_{max} . (nujol) 1623, 1599, 1573 (C=N), 1303, 1148, 1074, 995, 959, 914, 770, 750, 688 and 635 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 7.10-7.21 (5H, m, aromatic and vinylic H), 7.32-7.40 (5H, m, aromatic H), 7.48 (2H, m, aromatic H), 8.24 (1H, dd, J 6 Hz, 2 Hz, $CH=N$); m/z (70 eV, 100 °C) 207 (42), 206 (M^+ , 100), 115 (6) and 77 (18).

Cinnamaldehyde N-(4-nitrophenyl)imine (356),¹⁶⁶ m.p. 115 °C, (DCM / light petroleum) (Found: C, 71.6; H, 4.9; N, 11.2. Calc. for $C_{15}H_{12}N_2O_2$: C, 71.4; H, 4.8; N, 11.1%); ν_{max} . (nujol) 1630, 1597, 1578, 1513, 1337, 1207, 1159, 1105, 989, 964, 872, 856, 844, 753, 696, 667, 633, 530 and 513 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 6.85 (1H, dd, J 9 Hz, 12 Hz, 1-H), 7.22 (2H, d, J 9 Hz, 4- NO_2 aromatic H), 7.27 (1H, d, J 12

Hz, 2-H), 7.40-7.45 (3H, m, aromatic H), 7.55-7.59 (2H, m, aromatic H), 8.23 (1H, d, J 9 Hz, CH=N), 8.26 (2H, d, J 9 Hz, 4-NO₂ aromatic H); m/z (70 eV, 150 °C) 252 (M^+ , 44), 251 (100), 206 (8), 205 (45), 204 (12), 115 (16), 103 (7) and 76 (9).

Cinnamaldehyde N-(2,4,6-trimethylphenyl)imine (357), b.p. 200 °C/1 mmHg, m.p. 82 °C, (Found: C, 87.2; H, 7.8; N, 5.5. C₁₈H₁₉N requires: C, 86.7; H, 7.7; N, 5.6%); ν_{\max} . (film) 3026, 2915, 2857, 1681, 1632 (C=N), 1479, 1450, 1255, 1206, 1161, 1141, 1031, 991, 962, 854, 792, 750, 690, 585, and 510 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 2.13 (6H, s, 2 x ArCH₃), 2.29 (3H, s, ArCH₃), 6.89 (2H, s, Me₃Ph aromatic H), 7.06 (1H, d, J 16 Hz, 2-H), 7.27 (1H, dd, J 16 Hz, 8 Hz, 1-H), 7.32-7.46 (3H, m, aromatic H), 7.54-7.58 (2H, m, aromatic H), 7.96 (1H, d, J 8 Hz, CH=N); m/z (70 eV, 140 °C) 250 (13), 249 (M^+ , 73), 248 (100), 234 (7), 158 (7), 146 (8), 145 (11), 91 (11) and 77 (7).

Crotonaldehyde N-phenylimine (358) and *crotonaldehyde N-(4-methoxyphenyl)imine (359)* were unstable and were therefore distilled directly into the reaction vessel for the next step.

3-Methylbutenal N-(4-methoxyphenyl)imine (360), oil, b. p. 150 °C/0.5 mmHg, (Found: C, 75.9; H, 8.2; N, 7.8. C₁₂H₁₆NO requires C, 76.2; H, 8.0; N, 7.4%); ν_{\max} . (film) 2997, 2910, 2835, 1646, 1607, 1505, 1441, 1377, 1293, 1245, 1217, 1181, 1166, 1107, 1036, 833, 748 and 550 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.94 (3H, d, J 1 Hz, =CCH₃), 1.99 (3H, d, J 1 Hz, =CCH₃), 3.79 (3H, s, OCH₃), 6.19 (1H, d, J 9 Hz, 1 Hz, -CH=), 6.87 (2H, d, J 9 Hz, aromatic H), 7.10 (2H, d, J 9 Hz, aromatic H), 8.37 (1H, d, J 1 Hz, -CH=N); m/z (70 eV, 150 °C) 189 (M^+ , 2), 124 (7), 123 (78), 109 (8), 108 (100), 80 (36), 65 (7), 53 (13), 52 (10) and 39 (7).

Cinamaldehyde N-nbutylimine (361), oil, b. p. 80 °C/0.22 mmHg, (Found: C, 83.4; H, 9.4; N, 7.6. C₁₃H₁₇N requires C, 83.4; H, 9.15; N, 7.5%); ν_{\max} . (film) 2958, 2930, 2872, 2833, 1636, 1620, 1450, 1377, 1339, 1166, 986, 964, 749 and 691 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 0.94 (3H, d, J 7 Hz, CH₃), 1.37 (2H, hextet, J 7 Hz, MeCH₂), 1.65 (2H, pentet, J 7 Hz, CH₂), 3.51 (2H, dt, J 7 Hz, 1 Hz, CH₂N), 6.90 (1H, d, J 2 Hz, vinylic H), 6.91 (1H, d, J 3 Hz, vinylic H), 7.30-7.49 (5H, m, aromatic H), 8.01 (1H, m, J 7 Hz, 1 Hz, CH=N); m/z (70 eV, 100 °C) 187 (M^+ , 79), 186 (63), 145 (29), 144 (91), 130 (56), 118 (41), 115 (100) and 91 (59).

Cinamaldehyde Nⁱpropylimine (362), oil, b. p. 100 °C/0.4 mmHg, (Found: C, 83.2; H, 8.9; N, 8.1. C₁₂H₁₅N requires C, 83.2; H, 8.7; N, 8.1%); ν_{\max} . (film) 3027, 2967, 2928, 2838, 1635, 1619, 1450, 1381, 1361, 1326, 1301, 1150, 980, 957, 750, 691, 557, 512 and 501 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.15 [6H, d, *J* 7 Hz, (CH₃)₂C], 3.31 (1H, d, septet, *J* 7 Hz, 1 Hz, Me₂CH), 6.81 (1H, dd, *J* 1 Hz, vinylic H), 6.82 (1H, d, *J* 7 Hz, vinylic H), 7.18-7.38 (5H, m, aromatic H), 7.92 (1H, dd, *J* 7 Hz, 1 Hz, CH=N); *m/z* (70 eV, 150 °C) 173 (78), 172 (M⁺, 87), 158 (80), 130 (82), 117 (26), 116 (20), 115 (100), 91 (91), 77 (21) and 32 (22).

Cinamaldehyde N^tbutylimine (363), oil, b. p. 100 °C/0.3 mmHg, (Found: MH⁺ 187.1361. C₁₃H₁₇N requires 187.1361); ν_{\max} . (film) 3027, 2968, 1635, 1619, 1494, 1474, 1450, 1359, 1293, 1215, 1150, 978, 956, 750, 691 and 512 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.23 [9H, s, (CH₃)₃C], 6.90 (1H, dd, *J* 6 Hz, vinylic H), 6.91 (1H, d, *J* 2 Hz, vinylic H), 7.23-7.45 (5H, m, aromatic H), 8.00 (1H, dd, *J* 6 Hz, 2 Hz, CH=N); *m/z* (70 eV, 150 °C) 187 (M⁺, 27), 172 (100), 132 (31), 131 (49), 130 (90), 115 (54), 103 (26), 77 (22) and 57 (45).

Diethyl 1-(4-methoxyphenylamino)-3-phenylprop-2-enephosphonate (364), yield 77%, m.p. 98 °C (Found: C, 64.0; H, 7.0; N, 3.8. C₂₀H₂₆NO₄P requires C, 64.0; H, 7.0; N, 3.7%); ν_{\max} . (nujol) 3290, 1527, 1506, 1265, 1225, 1161, 1042, 1016, 970, 943, 818 and 749 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.30 (6 H, t, *J* 7 Hz, CH₃'s), 1.63 (1H, bs, NH), 3.73 (3H, s, OCH₃), 4.08-4.24 (4 H, m, CH₂'s), 4.38 (1H, dd, *J* 25 Hz, 7 Hz, allylic H-1), 6.25 (1H, ddd, *J* 16 Hz, 6 Hz, 5 Hz, vinylic H-2), 6.66 (2H, d, *J* 9 Hz, aromatic H), 6.73 (1H, overlapping ddd, vinylic H-3), 6.77 (2H, d, *J* 9 Hz, aromatic H), 7.22-7.37 (5H, m, aromatic H); δ_{P} {H} (36 MHz, CDCl₃) 21.8 ppm; *m/z* (70 eV, 120 °C) 375 (M⁺, 7), 239 (11), 238 (66), 237 (59), 236 (100), 115 (23), 111 (18), 83 (17) and 65 (12).

Diethyl 3-phenyl-1-(phenylamino)prop-2-enephosphonate (365), yield 91%, m.p. 87 °C (Found: C, 65.9; H, 7.2; N, 4.1. C₁₉H₂₄NO₃P requires C, 66.1; H, 7.0; N, 4.1%); ν_{\max} . (film) 3300, 2982, 1603, 1499, 1236, 1098, 1053, 1024, 970, 751, 694 and 547 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.26 (3 H, t, *J* 7 Hz, CH₃), 1.28 (3 H, t, *J* 7 Hz, CH₃), 4.07-4.22 (4 H, m, CH₂'s), 4.35 (1H, m, H-1), 6.25 (1H, ddd, *J* 25 Hz, 6 Hz, 5 Hz, vinylic H-2), 6.65-6.75 and 7.10-7.35 (11H, m, aromatic H and vinylic H-3); δ_{P} {H} (36 MHz, CDCl₃) 21.5 ppm; *m/z* (70 eV, 100 °C) 345 (M⁺, 9), 209 (17), 208 (100), 207 (6), 206 (15), 115 (8), 91 (4), 77 (8) and 43 (14).

Diethyl 1-(4-nitrophenylamino)-3-phenylprop-2-enephosphonate (366), yield 70%, m.p. 104 °C (Found: C, 58.45; H, 5.9; N, 7.1. C₁₉H₂₃N₂O₅P requires C, 58.5; H, 5.9; N, 7.2%); ν_{\max} . (nujol) 3237, 1599, 1552, 1307, 1228, 1183, 1113, 1047, 1024, 963, 834, 757, 725, 695 and 562 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.31 (3 H, t, *J* 7 Hz, CH₃), 1.33 (3 H, t, *J* 7 Hz, CH₃), 4.08-4.26 (4 H, m, CH₂'s), 4.53 (1H, ddd, *J* 25 Hz, 8 Hz, 6 Hz, H-1), 4.53 (1H, dd, *J* 16 Hz, 8 Hz, H-3), 6.23 (1H, dd, *J* 16 Hz, 6 Hz, H-2), 6.67 (2H, d, *J* 9 Hz, aromatic H), 7.25-7.36 (5H, m, aromatic H), 8.09 (2H, d, *J* 9 Hz, aromatic H); δ_{P} {H} (36 MHz, CDCl₃) 20.2 ppm; *m/z* (70 eV, 150 °C) 390 (*M*⁺, 11), 254 (17), 253 (100), 251 (15), 205 (7), 130 (8), 115 (9), 84 (6) and 49 (9).

Diethyl 1-(2,4,6-trimethylphenylamino)-3-phenylprop-2-enephosphonate (367), yield 37%, m.p. 80-82 °C (Found: C, 68.1; H, 7.9; N, 3.6. C₂₂H₃₀NO₃P requires C, 68.2; H, 7.8; N, 3.6%); ν_{\max} . (nujol) 2980, 2927, 2863, 1485, 1448, 1392, 1245, 1162, 1098, 1025, 969, 855, 791, 752, 694, 565, 529 and 504 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.32 (3 H, t, *J* 7 Hz, ester CH₃), 1.42 (3 H, t, *J* 7 Hz, CH₃), 2.31 (3H, s, PhCH₃), 2.38 (6H, s, 2 x PhCH₃), 3.28 (1H, bs, NH), 4.09-4.31 (4H, m, 1-H and OCH₂), 6.43 (1H, dt, *J*_d (*J*_{trans}) 16 Hz, *J*_{triplet} (*J*_H = *J*_P) 6 Hz, H-2), 6.72 (1H, dd, *J*_{trans} 16 Hz, *J*_P 3 Hz, H-3), 6.89 (2H, s, Me₃PhH), 7.33-7.47 (5H, m, aromatic H); δ_{P} {H} (36 MHz, CDCl₃) 23.5 ppm; *m/z* (70 eV, 150 °C) 387 (*M*⁺, 5), 250 (68), 249 (75), 248 (100), 134 (29), 111 (27), 83 (7), 57 (28) and 43 (24).

Diethyl 1-(4-methoxyphenylamino)but-2-enephosphonate (368), yield 57%, oil (Found: C, 57.2; H, 7.7; N, 4.7. C₁₅H₂₄NO₄P requires C, 57.5; H, 7.7; N, 4.5%); ν_{\max} . (film) 3304, 2983, 2833, 1619, 1511, 1443, 1392, 1237, 1179, 1097, 1028, 969, 823, 793 and 510 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.28 (3 H, t, *J* 7 Hz, 0.5 Hz, CH₃), 1.31 (3 H, t, *J* 7 Hz, 0.5 Hz, CH₃), 1.71 (3 H, tm, *J* 5 Hz, CH₃C=), 3.73 (3 H, s, OCH₃), 4.08-4.22 (5 H, m, CH₂'s and CH), 5.44-5.54 (1H, m, H-3), 5.74-5.84 (1H, m, H-2), 6.61 (2H, d, *J* 9 Hz, aromatic H), 6.76 (2H, d, *J* 9 Hz, aromatic H); δ_{P} {H} (36 MHz, CDCl₃) 22.6 ppm; *m/z* (70 eV, 120 °C) 313 (*M*⁺, 10), 177 (12), 176 (100), 175 (21), 160 (14), 111 (31), 83 (27) and 65 (19).

Diethyl 1-(4-phenylamino)but-2-enephosphonate (369), yield 54%, m.p. 48 °C (Found: C, 59.4; H, 7.9; N, 4.9. C₁₄H₂₂NO₃P requires C, 59.35; H, 7.8; N, 4.9%); ν_{\max} . (nujol) 3292, 1602, 1532, 1499, 1306, 1235, 1155, 1058, 1029, 966, 803, 746, 691 and 590 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.27 (3 H, t, *J* 7 Hz, CH₃), 1.31 (3 H, t, *J*

Hz, CH₃), 1.71 (3 H, apparent t, *J* 6Hz, C=CCH₃), 4.07-4.32 (5H, m, CH₂'s and CH), 5.46-5.86 (1H, m, H-3), 5.74-5.86 (1H, m, H-2), 6.64 (2H, d, *J* 8 Hz, aromatic H), 6.72 (1H, t, *J* 7 Hz, aromatic H), 7.16 (2H, dd, *J* 9 Hz, 8Hz, aromatic H); δ_p{H} (36 MHz, CDCl₃) 22.4 ppm; *m/z* (70 eV, 160 °C) 283 (*M*⁺, 5), 149 (40), 147 (11), 146 (100), 145 (19), 144 (23), 111 (10), 83 (11) and 77 (21).

Diethyl 1-(4-methoxyphenylamino)-3-methylbut-2-enphosphonate (370), yield 80%, m. p. 98-100°C, (Found: C, 58.7; H, 8.2; N, 4.1. C₁₆H₂₆NO₄P requires C, 58.7; H, 8.0; N, 4.3%); ν_{max.} (film) 2982, 2932, 2910, 1739, 1511, 1444, 1391, 1375, 1239 (P=O), 1180, 1165, 1098, 1034, 969, 822, 761, 736 and 569 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.27 (6H, dt, *J* 7 Hz, 4 Hz, ester CH₃), 1.74 [6H, m, (CH₃)₂C=], 3.71 (3H, s, OCH₃), 4.09-4.20 (4 H, m, 2 x CH₂), 4.32 (1H, dd, *J* 21 Hz, 10 Hz, H-1), 5.07 (1H, dm, *J* 10 Hz, H-2), 6.58 (2H, d, *J* 9 Hz, aromatic H), 6.74 (2H, d, *J* 9 Hz, aromatic H); δ_p{H} (36 MHz, CDCl₃) 23.6 ppm; *m/z* (70 eV, 150 °C) 327 (*M*⁺, 6), 190 (100), 189 (62), 174 (24), 149 (18), 111 (30), 83 (32), 65 (26) and 41 (19).

Diethyl 1-(ⁿbutylamino)-3-phenylprop-2-enphosphonate (371), yield 83%, oil, (Found: C, 62.55; H, 8.6; N, 4.2. C₁₇H₂₈NO₃P requires C, 62.75; H, 8.7; N, 4.3%); ν_{max.} (film) 3026, 2959, 2931, 2872, 1739, 1496, 1449, 1391, 1244 (P=O), 1164, 1099, 1029, 966, 789, 752, 694 and 574 cm⁻¹; δ_H (270 MHz, CDCl₃) 0.86 (3 H, d, *J* 7Hz, CH₃), 1.28 (3H, t, *J* 7 Hz, ester CH₃), 1.29 (3 H, t, *J* 7 Hz, ester CH₃), 1.31 (2 H, m, CH₂), 1.42 (2H, m, CH₂), 2.51 and 2.71 (2H, 2 x dt, *J* 11Hz, 7 Hz, CH₂N), 3.62 (1H, ddd, *J* 19 Hz, 8.5 Hz, 1 Hz, H-1), 4.07-4.20 (4 H, m, CH₂'s), 6.09 (1H, ddd, *J*_t 16 Hz, 8.5 Hz, 4.6 Hz, H-2), 6.60 (1H, dd, *J*_t 16 Hz, 4.6 Hz, H-3), 7.20-7.38 (5H, m, aromatic H); δ_p{H} (36 MHz, CDCl₃) 23.0 ppm; *m/z* (70 eV, 150 °C) 325 (*M*⁺, 1), 188 (100), 187 (21), 144 (25), 115 (34), 111 (37), 91 (21), 83 (39) and 65 (29).

Diethyl 1-(ⁱpropylamino)-3-phenylprop-2-enphosphonate (372), yield 82%, oil, (Found: C, 61.8; H, 8.5; N, 4.4. C₁₆H₂₆NO₃P requires C, 61.7; H, 8.4; N, 4.5%); ν_{max.} (film) 3288, 2967, 2931, 1496, 1448, 1391, 1368, 1244 (P=O), 1166, 1098, 1028, 968, 801, 753, 695 and 570 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.00 (3 H, d, *J* 7Hz, ⁱPr CH₃), 1.07 (3 H, d, *J* 7Hz, ⁱPr CH₃), 1.29 (3H, t, *J* 7Hz, CH₃), 1.31 (3 H, t, *J* 7Hz, CH₃), 2.93 (1H, heptet, Me₂CH), 3.75 (1H, ddd, *J* 22 Hz, 8.5 Hz, 1 Hz, H-1), 4.10-4.21 (4 H, m, CH₂'s), 6.25 (1H, ddd, *J*_t 16 Hz, 8.5 Hz, 5.5 Hz, H-2), 6.73 (1H, dd,

J_t , 16 Hz, 1 Hz, H-3), 7.22-7.39 (5H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 21.8 ppm; m/z (70 eV, 120 °C) 375 (M^+ , 7), 239 (11), 238 (66), 237 (59), 236 (100), 115 (23), 111 (18), 83 (17) and 65 (12).

*Diethyl 1-(*t*-butylamino)-3-phenylprop-2-enphosphonate (373)*, yield 57%, m.p. 65-67 °C, (Found: C, 62.6; H, 8.8; N, 4.3. $C_{17}H_{28}NO_3P$ requires C, 62.75; H, 8.7; N, 4.3%); ν_{max} . (film) 3026 (NH), 2974, 2907, 2869, 1496, 1477, 1448, 1391, 1365, 1244 (P=O), 1165, 1099, 1029, 968, 787, 752, 695 and 572 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.09 [9H, s, $(CH_3)_3C$], 1.26 (3H, t, J 7 Hz, CH_3), 1.30 (3H, t, J 7 Hz, CH_3), 3.84 (1H, dd, J_H 8 Hz, J_P 25 Hz, H-1), 4.07-4.22 (4H, m, 2 x CH_2 's), 6.18 (1H, ddd, J_t 16 Hz, 8 Hz, 6 Hz, H-2), 6.60 (1H, dd, J_t 16 Hz, 6 Hz, H-3) and 7.20-7.37 (5H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 23.4 ppm; m/z (70 eV, 200 °C) 325 (M^+ , 1), 188 (27), 187 (26), 172 (100), 130 (100), 115 (63), 110 (51), 83 (52), 65 (41) and 57 (53).

3-Diethylphosphonyl-3-phenylpropanal (374). *n*-Butyllithium (2 ml, 1.55M) was delivered to a stirred solution of diethyl phenylmethanephosphonate (680 mg, 2.98 mmol) in dry THF (60 ml) at -72 °C under an atmosphere of argon. After 30 minutes, allyl bromide (1ml, 12 mmol) was added and the reaction mixture was left for an hour before it was brought to room temperature over a period of an hour. Stirring was continued for a further 2 hours and then the solution was poured into water (30 ml). The organic products were extracted with ether (3 x 100 ml) and dried (magnesium sulphate). Removal of solvent followed by chromatography on the residue afforded diethyl 1-phenylprop-3-enephosphonate as a colourless oil (620 mg, 78%), ν_{max} . (film) 2981, 2907, 1642, 1455, 1248, 1164, 1098, 1028, 1164, 1098, 1028, 964, 843, 793, 737, 701, 619, 594, 556, 520 and 505 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.10 (3H, t, J 7 Hz, ester CH_3), 1.28 (3H, t, J 7 Hz, ester CH_3), 2.6-2.9 (1H, m, allylic H), 3.08 (1H, ddd, J 4.4 Hz, 9 Hz, 22 Hz, allylic H), 3.65-4.12 (5H, m, 2 x CH_2O and $CHPh$), 4.91 (1H, dm, J 10 Hz, $=CH_cH_i$), 4.99 (1H, dm, J 17 Hz, $=CH_cH_i$), 5.61 (1H, m, $CH=$), 7.29-7.31 (5H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 27.34 ppm; m/z (70 eV, 180 °C) 268 (M^+ , 28), 158 (11), 131 (48), 130 (100), 129 (27), 128 (10), 115 (11) and 91 (70). This oil was dissolved in DCM and was subjected to ozonolysis followed by dimethylsulphide work-up. Chromatography of the residue after removal of solvent afforded the title compound as a pale yellow oil (560 mg, 90%), (Found: C, 61.7; H, 8.0. $C_{13}H_{19}O_4P$ requires C, 57.8; H, 7.1%), ν_{max} . (film) 2981, 2931, 2908, 1730 (C=O), 1499, 1447, 1392, 1240 (P=O), 1163, 1097, 1024, 961, 915, 799, 761, 699, 619 and 570 cm^{-1} ; δ_H (270 MHz, $CDCl_3$)

1.12 (3H, t, J 7 Hz, ester CH₃), 1.26 (3H, t, J 7 Hz, ester CH₃), 3.45-4.12 (7H, m, 2 x CH₂O and CHPh and CH₂CHO), 7.27-7.31 (3H, m, aromatic H), 7.43-7.54 (2H, m, aromatic H), 8.8 (1H, t, J 4 Hz, CHO); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl₃) 29.1 ppm; m/z (70 eV, 160 °C) 270 (M^+ , 8), 228 (80), 138 (20), 133 (60), 132 (100), 131 (12), 91 (10) and 42 (90).

3-Diethylphosphonyl-3-phenylpropanal N-phenylimine (375). Potassium carbonate (5 g) was added to a solution of aldehyde (374) (540 mg, 20 mmol) and aniline (190 mg, 20.5 mmol) in DCM (10 ml). The mixture was stored at room temperature for two days before solid was filtered off and washed with DCM. The filtrate and washings were combined and were stripped of solvent in vacuo. The residue was chromatographed to afford the desired compound as an oil (352 mg, 51%), (Found: M^+ 345.1494. C₁₉H₂₄NO₃P requires 345.1494), ν_{max} . (film) 2981, 2931, 2855, 1737 (C=O), 1630, 1610, 1489, 1402, 1242 (P=O), 1163, 1107, 1024, 962, 915, 799, 761, 712, 699, 610 and 573 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.12 (3H, t, J 7 Hz, ester CH₃), 1.16 (3H, t, J 7 Hz, ester CH₃), 3.46-4.10 (7H, m, 2 x CH₂O and CHPh and CH₂CHO), 7.27-7.43 (8H, m, aromatic H), 7.48-7.54 (2H, m, aromatic H), 9.1 (1H, m, CH=N); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl₃) 30.0 ppm; m/z (CI, NH₃) 345 (M^+ , 100), 228 (80), 132 (10) and 117 (25).

Imines (376)-(378) rapidly polymerise at room temperatures. They were prepared as other imines but were flash distilled and used promptly.

3-Methylbut-2-enal N-nbutylimine (376) oil, (Found: C, 75.1; H, 12.1; N, 9.8. C₉H₁₇N requires C, 77.6; H, 12.3; N, 10.1%); ν_{max} . (film) 2959, 2931, 2862, 1657 (C=N), 1619 (C=C), 1446, 1378, 1341, 1204, 1116, 1048, 985, 854, 740 and 539 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 0.86 (3H, t, J 7 Hz, CH₃), 1.30 (2H, hexet, J 7 Hz, CH₂Me), 1.54 (2H, pentet, J 7 Hz, CH₂CH₂Me), 1.81 (3H, s, CH₃C=), 1.85 (3H, s, CH₃C=), 3.38 (2H, t, J 7 Hz, NCH₂), 5.93 (1H, dm, J 10Hz, =CH-CH=N), 8.10 (1H, dm, J 10 Hz, =CH-CH=N); m/z (70 eV, 140 °C) 140 (45), 139 (M^+ , 32), 96 (55), 84 (52), 82 (71), 57 (68), 42 (38), 41 (100) and 39 (34).

3-Methylbut-2-enal N-i-propylimine (377), b.p. 120 °C, ν_{max} . (film) 2968, 2930, 2865, 1657 (C=N), 1615 (C=C), 1447, 1380, 1331, 1210, 1145, 1047, 984, 946, 854 and 506 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.21 [6H, d, J 6 Hz, (CH₃)₂C], 1.89 (3H, s, CH₃C=), 1.94 (3H, s, CH₃C=), 3.36 (1H, heptet, J 6 Hz, Me₂CH), 6.01 (1H, d, J 8 Hz, =CH-CH=N), 8.22 (1H, d, J 8 Hz, =CH-CH=N).

3-Methylbut-2-enal N-'butylimine(378), b. p. 100 °C/0.7 mmHg, ν_{\max} . (film) 2968, 2932, 1650 (C=N), 1615 (C=C), 1446, 1376, 1359, 1218, 1149, 1051, 984, 909, 855 and 515 cm^{-1} ; δ_{H} (90 MHz, CDCl_3) 1.21 [9H, s, $(\text{CH}_3)_3\text{C}$], 1.87 (3H, s, $\text{CH}_3\text{C}=\text{}$), 1.92 (3H, m, $\text{CH}_3\text{C}=\text{}$), 6.02 (1H, dm, J 9 Hz, $\text{C}=\text{CHCH}=\text{N}$), 8.19 (1H, dm, J 9 Hz, $\text{C}=\text{CHCH}=\text{N}$); m/z (70 eV, 100 °C) 139 (M^+ , 51), 124 (46), 83 (100), 82 (49), 68 (47), 57 (86), 43 (35), 42 (35) and 41 (73).

Diethyl 3-methyl-2-(i-propylamino)but-2-enephosphonate (379), yield 85%, 125 °C/1.1 mmHg, (Found: C, ; H, ; N, . $\text{C}_{12}\text{H}_{26}\text{NO}_3\text{P}$ requires C, 54.7; H, 9.9; N, 5.3%), ν_{\max} . (film) 2970, 2932, 2870, 2657, 1445, 1381, 1339, 1230 (P=O), 1166, 1029, 967, 802, 749, 569 and 515 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 0.84 [3H, d, J 7 Hz, $(\text{CH}_3)\text{HMe}$], 0.91 [3H, d, J 7 Hz, $(\text{CH}_3)\text{CHMe}$], 1.13 (3H, d, J 7 Hz, ester CH_3), 1.16 (3H, d, J 7 Hz, ester CH_3), 1.56 [3H, dd, J 4 Hz, 1 Hz, $\text{Me}(\text{CH}_3)\text{C}=\text{}$], 1.64 [3H, dd, J 5 Hz, 1 Hz, $\text{Me}(\text{CH}_3)\text{C}=\text{}$], 2.74 (1H, heptet, J 7 Hz, Me_2CH), 3.66 (1H, dd, J 20 Hz, 9 Hz, H-1), 3.94-4.11 (4H, m, CH_2O), 4.90 (1H, m, $\text{CH}=\text{CMe}_2$); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 24.5 ppm; m/z (70 eV, 120 °C) 126 (M^+ - $(\text{EtO})_2\text{P}=\text{O}$, 41), 111 (59), 110 (67), 84 (69), 83 (100), 68 (58), 67 (48) and 65 (45).

Diethyl 3-methyl-2-(butylamino)but-2-enephosphonate (380), yield 55%, b.p. 150 °C/ 1 mmHg, ν_{\max} . (film) 2960, 2932, 2873, 1446, 1392, 1251 (P=O), 1165, 1055, 971, 789, 551 and 503 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.10-1.32 [11H, m, 3 x CH_3 and CH_2Me], 1.56 [3H, dd, J 3 Hz, 2 Hz, $\text{Me}(\text{CH}_3)\text{C}=\text{}$], 1.65 [3H, dd, J 4 Hz, 2 Hz, $\text{Me}(\text{CH}_3)\text{C}=\text{}$], 3.10 (2H, m, CH_2Et), 3.37 (1H, m, NCHH-CH_2), 3.51 (1H, m, NCHH-CH_2), 3.58 (1H, dd, J 20 Hz, 9 Hz, H-1), 3.94-4.11 (4H, m, CH_2O), 4.93 (1H, m, $\text{CH}=\text{CMe}_2$); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 24.8 ppm; m/z (70 eV, 170 °C) 140 (M^+ - $(\text{EtO})_2\text{P}=\text{O}$, 100), 111 (69), 100 (32), 96 (51), 83 (72) 82 (49), 65 (53) and 41 (34).

Diethyl 2-formyl-1,1-dimethylethanphosphonate (381), yield 50%, oil, (Found: C, 48.65; H, 8.8. $\text{C}_9\text{H}_{19}\text{O}_4\text{P}$ requires C, 48.65; H, 8.6%); ν_{\max} . (film) 2981, 1722 (C=O), 1392, 1234 (P=O), 1165, 1098, 1055, 1029, 963, 791, 659 and 504 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.30 (3H, s, 2- CH_3), 1.33 (6H, t, J 7 Hz, ester CH_3), 1.36 (3H, s, 2- CH_3), 2.52 (2h, dd, J_{P} 16 Hz, J_{H} 3 Hz, CH_2CO), 4.14 (4H, quintet, $J_{\text{H}} = J_{\text{P}}$ 7 Hz, OCH_2), 9.86 (1H, dt, J_{P} 1 Hz, J_{H} 3 Hz, $\text{CH}=\text{O}$); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 32.5 ppm; m/z (70 eV, 140°C) 222 (M^+ , 1), 194 (41), 138 (100), 111 (62), 110 (25), 83 (23), 82 (43), 56 (24) and 41 (26).

Diethyl 4-methylphenylamino-(4-methylphenylimino)methanephosphonate (384), yield 76%, m.p. 88 °C (Found: C, 63.1; H, 7.0; N, 7.7. $C_{19}H_{25}N_2O_3P$ requires C, 63.3; H, 7.0; N 7.8%); ν_{\max} . (nujol) 3283, 1596, 1505, 1316, 1251, 1163, 1109, 1028, 967, 923, 822, 768, 735, 683, 646, 602, 553 and 504 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.22 (6 H, bt, J 7Hz, CH_3 's), 2.30 (6 H, t, J 7Hz, $ArCH_3$'s), 3.96 (4 H, bm, CH_2 's), 6.75-6.8 (2H, bm, aromatic H), 7.04-7.62 (4H, bm, aromatic H), 7.6-7.62 (2H, bm, aromatic H), 7.77-7.78 (1 H, bs, NH); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 3.1 ppm; m/z (70 eV, 160 °C) 360 (M^+ , 43), 255 (14), 254 (100), 223 (13), 222 (16), 198 (12), 118 (20), 109 (9) and 91 (19).

Diethyl (N-phenylcarbamoyl)phosphonate (387), yield 87%, oil (Found: C, 51.3; H, 6.3; N, 5.4. $C_{11}H_{16}NO_4P$ requires C, 51.4; H, 6.3; N, 5.5%); ν_{\max} . (nujol) 3240, 2985, 1662, 1601, 1542, 1499, 1445, 1319, 1264, 1228, 1164, 1025, 980, 800, 758, 693, and 537 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.40 (6 H, t, J 7Hz, CH_3 's), 4.19-4.39 (4 H, m, CH_2 's), 7.18 (1H, t, J 7.5Hz, aromatic H), 7.33 (2H, d, J 7.5 Hz, aromatic H), 7.66 (2H, d, J 7.5 Hz, aromatic H) and 9.07 (1H, bs, NH); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) -2.6 ppm; m/z (70 eV, 140°C) 257 (M^+ , 18), 138 (100), 111 (75), 110 (21), 109 (18), 83 (25), 82 (50) and 65 (16).

Diethyl (N-4-nitrophenylcarbamoyl)phosphonate (388), yield 86%, m.p. 142 °C (Found: C, 43.7; H, 4.8; N, 9.3. $C_{11}H_{15}N_2O_6P$ requires C, 43.7; H, 5.0; N, 9.3%); ν_{\max} . (nujol) 3199, 1677, 1597, 1556, 1505, 1338, 1305, 1263, 1228, 1180, 1111, 1049, 1028, 986, 957, 861, 754, 652, and 571 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.43 (6 H, t, J 7Hz, CH_3 's), 4.25-4.40 (4 H, m, CH_2 's), 7.97 (2H, d, J 9 Hz, aromatic H), 8.24 (2H, d, J 9 Hz, aromatic H) and 10.12 (1H, bs, NH); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) -4.2 ppm; m/z (70 eV, 140 °C) 302 (M^+ , 14), 138 (100), 111 (74), 109 (43), 91 (28), 84 (36), 83 (45), 82 (36) and 65 (31).

Competition reaction between addition to (321) and (385). To a stirred solution of diethyl phosphite (350 mg, 2.53 mmol) and triethylamine (0.38 ml, 2.73 mmol) in dichloromethane (40 ml) under an argon atmosphere and maintained at 0 °C was delivered chlorotrimethylsilane (0.35 ml, 2.76 mmol) in one portion. After 15 min a solution of imine (293) (367 mg, 2.53 mmol) and phenylisocyanate (385) (300 mg, 2.52 mmol) in dichloromethane (2ml) was added. After 5 h a 2ml aliquot was withdrawn. Solvent was evaporated under a flow of moist argon gas and the residue was analysed by ^{31}P NMR.

The following peaks were obtained (in ppm): -3.7 (5%), -2.6 (isocyanate adduct, 36%), 20.6 (45%) and 22.66 (imine adduct, 14%).

Competition reaction between addition to (318) and (386): To a stirred solution of diethyl phosphite (350 mg, 2.53 mmol) and triethylamine (0.38 ml, 2.73 mmol) in dichloromethane (40 ml) under an argon atmosphere and maintained at 0 °C was delivered chlorotrimethylsilane (0.35 ml, 2.76 mmol) in one portion. After 15 min a solution of imine (318) (482 mg, 2.53 mmol) and 4-nitrophenylisocyanate (386) (416 mg, 2.53 mmol) in dichloromethane (2ml) was added. After 5 h a 2ml aliquot was withdrawn. Solvent was evaporated under a flow of moist argon gas and the residue was analysed by ³¹P NMR. The following peaks were obtained (in ppm): -5.8 (12%), -4.4 (isocyanate adduct, 80%) and 20.7 (imine adduct, 8%).

*2-Methylpropanal N-(R)- α -methylbenzylimine*⁹⁷ (390) and *2-methylpropanal N-(S)- α -methylbenzylimine*⁹⁷ (392) had similar physical data and in accordance to that reported in the literature: b. p. 100 °C/0.4 mmHg, ν_{\max} . (film) 1669 (C=N) cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.10 [3H, d, *J* 7 Hz, (CH₃)₂C], 1.11 [3H, d, *J* 7 Hz, (CH₃)₂C], 1.50 (3H, *J* 7 Hz, CH₃CHN), 2.49 (1H, heptet, *J* 7 Hz, Me₂CH), 4.30 (1H, q, *J* 7Hz, CH₃CHN), 7.20-7.40 (5H, m, aromatic H), 7.63 (1H, d, *J* 5 Hz, CH=N); *m/z* (70 eV, 190 °C) 175 (*M*⁺, 11), 150 (6), 106 (16), 105 (100), 104 (8), 79 (11), 77 (11) and 59 (9).

Ethyl 2-methyl-1-[1(R)-phenylethylamino]propanephosphonate (391), after chromatography, the major diastereomeric pair were isolated together with the minor diastereomeric pair, oil, (Found: C, ; H, ; N, . C₂₀H₂₈NO₂P requires C, 69.5; H, 8.2; N, 4.05%); ν_{\max} . (film) 2970, 1439, 1211, 1120, 1034, 947, 815, 764, 702, 581, 561 and 516 cm⁻¹; δ_{H} (270 MHz, CDCl₃) (* Refers to the distinguishable signals of the minor diastereomer of the major diastereomeric pair. Signals of the minor diastereomeric pair are omitted) 0.69* and 0.87 [3H, d, *J* 7 Hz, (CH₃)₂C], 0.80* and 0.95 [3H, d, *J* 7 Hz, (CH₃)₂C], 1.12* and 1.40 [3H, d, *J* 7 Hz, (CH₃)CHN], 1.25* and 1.30 (3H, t, *J* 7 Hz, ester CH₃), 2.07 (1H, bs, NH), 2.70 and 2.74* (1H, dt, *J* 3 Hz, H-1), 3.60-4.34 (4H, m, OCH₂, Ph(CH₃)CHN, Me₂CH), 6.95-7.87 (10H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl₃) 45.3 (33%), 43.3 (8%), 41.75 (44%), 41.2 (15%) ppm; *m/z* (70 eV, 200 °C) 176 (49), 140 (12), 106 (50), 105 (100), 104 (12), 79 (15), 78 (14), 77 (20) and 72 (28).

Ethyl 2-methyl-1-[1(S)-phenylethylamino]propanephosphonate (393), after chromatography, the major diastereomeric pair were isolated, oil, (Found: C, ; H, ; N, . $C_{20}H_{28}NO_2P$ requires C, 69.5; H, 8.2; N, 4.05%); ν_{\max} . (film) 2970, 1439, 1212, 1118, 1033, 947, 764, 702, 581, 560 and 515 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) (* Refers to the distinguishable signals of the minor diastereomer of the major diastereomeric pair.) 0.70* and 0.84 [3H, d, J 7 Hz, $(CH_3)_2C$], 0.81* and 0.93 [3H, d, J 7 Hz, $(CH_3)_2C$], 1.11* and 1.36 [3H, d, J 7 Hz, $(CH_3)CHN$], 1.25* and 1.28 (3H, t, J 7 Hz, ester CH_3), 1.87 (1H, bs, NH), 2.69 and 2.72* (1H, dt, J 3 Hz, H-1), 3.60-4.34 (4H, m, OCH_2 , $(CH_3)CHN$, Me_2CH), 6.95-7.87 (10H, m, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 45.5 (minor) and 41.87 (major) ppm; m/z (70 eV, 170 °C) 345 (M^+ , 1), 176 (49), 140 (12), 106 (12), 105 (100), 79 (15), 78 (14), 77 (20) and 72 (26).

Ethyl 2-triphenylmethylamino-3-methylpropanephosphinic acid (395), yield 57%, m.p. 173 °C (Found: C, 76.7; H, 7.2; N, 3.0. $C_{31}H_{34}NO_2P$ requires C, 77.0; H, 7.1; N, 2.9%); ν_{\max} . ($CHCl_3$ solution) 3058, 2977, 1594, 1490, 1439, 1391, 1368, 1216, 1159, 1119, 1034, 949, 762, 732, 705, 642, 584, 564 and 515 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.25 (3 H, t, J 7Hz, CH_3), 1.28 (3 H, t, J 7Hz, CH_3), 4.02-4.16 (4 H, m, CH_2 's), 5.16 (1H, dd, J_{HP} 12 J_{HH} 5Hz, CH), 7.66 (2H, d, J_{HH} 8 Hz, J_{HP} 2 Hz, aromatic H) and 8.22 (2H, d, J 9 Hz, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 42.21 (minor) and 41.06 (major) ppm; m/z (70 eV, 180 °C) 243 (9), 183 (15), 182 (100), 165 (8), 128 (7), 105 (9), 104 (20) and 77 (16).

Ethyl [(4-nitrophenyl)allylaminomethane]phenylphosphinate, yield 60% (of diastereomeric mixture), diastereomer a (398): m.p. 110-112 °C, (Found: C, 57.55; H, 5.8; N, 7.2. $C_{18}H_{21}N_2O_4P$ requires C, 60.0; H, 5.9; N, 7.8%); ν_{\max} . ($CHCl_3$) 2983, 2903, 2832, 1596, 1520, 1439, 1347, 1223, 1122, 1033, 956, 861, 753, 713, 697, 563 and 515 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.23 (3 H, t, J 7 Hz, CH_3), 2.21 (1H, bs, NH), 2.92 (1 H, dd, J 7 Hz, 14 Hz, allylic H), 3.15 (1 H, dm, J 14 Hz, allylic H), 3.90-4.17 (2H, m, CH_2), 4.30 (1H, d, J 17 Hz, $CHPh$), 4.95-5.08 (2 H, m, $=CH_2$), 5.68 (1H, m, $-CH=$), 7.37-7.65 (7H, m, aromatic H), 8.10 (2H, m, 4- NO_2 aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 36.23 ppm; m/z (70 eV, 140 °C) 360 (M^+ , 1), 192 (11), 191 (100), 170 (11), 142 (16), 141 (18), 78 (15), 77 (17) and 41 (25). diastereomer b (399): oil; ν_{\max} . ($CHCl_3$) 2984, 1684, 1605, 1523, 1439, 1393, 1348, 1220, 1122, 1034, 958, 860, 752, 697, 564 and 506 cm^{-1} ; δ_H (250 MHz, $CDCl_3$) 1.33 (3 H, t, J 7Hz, CH_3), 3.01 (1 H, dd, J 7 Hz, 14 Hz, allylic H), 3.21 (1 H, dm, J 14 Hz, allylic H), 3.93-4.24 (2H, m,

CH₂), 4.39 (1H, d, *J* 18 Hz, CHPh), 5.01-5.12 (2 H, m, =CH₂), 5.79 (1H, m, -CH=), 7.29-7.50 (7H, m, aromatic H), 8.02 (2H, m, 4-NO₂ aromatic H); δ_p{H} (36 MHz, CDCl₃) 37.67 ppm.

Ethyl [(4-cyanophenyl)allylaminomethane]phenylphosphinate, yield 63% (of diastereomeric mixture), **diastereomer a (400)**: m.p. 122-123 °C (Found: C, 66.9; H, 6.2; N, 8.1. C₁₉H₂₁N₂O₂P requires C, 67.05; H, 6.2; N, 8.2%); ν_{max.} (CHCl₃) 2982, 2228 (C≡N), 1607, 1440, 1222, 1122, 1099, 1034, 998, 957, 866, 751, 735, 697, 575, 546 and 515 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.23 (3 H, t, *J* 7Hz, CH₃), 2.02 (1H, bs, NH), 2.91 (1 H, dd, *J* 7Hz, 13 Hz, allylic H), 3.16 (1 H, dm, *J* 14 Hz, allylic H), 3.89-4.08 (2H, m, CH₂), 4.24 (1H, d, *J* 18 Hz, CHPh), 4.95-5.07 (2 H, m, =CH₂), 5.68 (1H, m, -CH=), 7.32-7.54 (5H, m, aromatic H), 7.52-7.64 (4H, m, aromatic H); δ_p{H} (36 MHz, CDCl₃) 36.4 ppm; *m/z* (70 eV, 180°C) 340 (*M*⁺, 4), 171 (100), 170 (53), 169 (47), 142 (50), 141 (27), 78 (22), 77 (22) and 41 (26); **diastereomer b (401)**: ν_{max.} (film) 2982, 2904, 2228 (C≡N), 1680, 1644, 1607, 1504, 1439, 1413, 1392, 1224, 1112, 1035, 957, 866, 752, 697, 574 and 519 cm⁻¹; δ_H (270 MHz, CDCl₃) 1.32 (3 H, t, *J* 7Hz, CH₃), 2.12 (1H, bs, NH), 2.96 (1 H, dd, *J* 7Hz, 14 Hz, allylic H), 3.19 (1 H, dd, *J* 5 Hz, 14 Hz, allylic H), 3.94-4.10 and 4.13-4.24 (2H, m, OCH₂), 4.27 (1H, d, *J* 18 Hz, CHPh), 5.00-5.10 (2 H, m, =CH₂), 5.75 (1H, m, -CH=), 7.21-7.52 (10H, m, aromatic H); δ_p{H} (36 MHz, CDCl₃) 37.8 ppm.

Ethyl (phenylallylaminomethane)phenylphosphinate (402), obtained as a diastereomeric mixture, oil, (Found: C, ; H, ; N, . C₁₈H₂₂NO₃P requires C, 65.25; H, 6.7; N, 4.2%); ν_{max.} (CHCl₃) 3061 (NH), 2980, 2927, 1455, 1439, 1392, 1223, 1161, 1122, 1035, 998, 955, 855, 802, 753, 698, 613 and 560 cm⁻¹; δ_H (250 MHz, CDCl₃) (* refers to the distinguishable signals of the minor diastereomer) 1.17 and 1.30* (3 H, t, *J* 7Hz, CH₃), 2.30 (1H, bs, NH), 2.93 (1 H, dd, *J* 7 Hz, 14 Hz, allylic H), 3.18 (1 H, ddm, *J* 5Hz, 14 Hz, allylic H), 3.91 (2H, m, OCH₂), 4.13 and 4.18* (1H, d, *J* 15 Hz, PhCH), 4.94-5.02 (2 H, m, =CH₂), 5.69 (1H, m, -CH=), 7.30-7.67 (10H, m, aromatic H); δ_p{H} (36 MHz, CDCl₃) 37.38 ppm; *m/z* (70 eV, 150 °C) 315 (*M*⁺, 1), 170 (40), 146 (9100), 144 (78), 142 (45), 141 (41), 79 (36), 78 (52) and 77 (56).

Ethyl [(4-methoxyphenyl)allylaminomethane]phenylphosphinate, yield 90% (of diastereomeric mixture), **diastereomer a (403)**: m.p. 66-68 °C (Found: C, 66.4; H, 7.2; N, 3.9. C₁₉H₂₄NO₃P requires C, 66.1; H, 7.0; N, 4.05%); ν_{max.} (CHCl₃) 2980, 2837,

1610, 1511, 1440, 1251 (P=O), 1221, 1179, 1122, 1035, 955, 839, 751, 733, 697, 559 and 505 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.20 (3 H, t, J 7Hz, CH_3), 2.05 (1H, bs, NH), 2.94 (1 H, dd, J 7Hz, 14 Hz, allylic H), 3.18 (1 H, ddm, J 5Hz, 14 Hz, allylic H), 3.79 (3H, s, CH_3O), 3.93 (2H, pentet, $J_{\text{H}}=J_{\text{P}}$ 7 Hz, CH_2), 4.09 (1H, d, J 14 Hz, PhCH), 4.98-5.03 (2 H, m, $=\text{CH}_2$), 5.04 (1H, m, $-\text{CH}=\text{}$), 6.80 (2H, d, J_{H} 9 Hz, 4-methoxy aromatic H), 7.21 (2H, d, J_{H} 9 Hz, J_{P} 2.5 Hz, 4-methoxy aromatic H), 7.38-7.68 (5H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 37.6 ppm; m/z (70 eV, 170 °C) 345 (M^+ , 1), 170 (51), 142 (76), 141 (66), 79 (71), 78 (100), 77 (90) and 51 (43); diastereomer b: (404) ν_{max} . (CHCl_3) 2981, 2837, 1610, 1511, 1440, 1251 (P=O), 1223, 1179, 1122, 1035, 955, 751, 697, 558, 515 and 505 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.20 (3 H, t, J 7Hz, CH_3), 2.50 (1H, bs, NH), 2.99 (1 H, dd, J 7 Hz, 14 Hz, allylic H), 3.12 (1 H, ddm, J 5 Hz, 14 Hz, allylic H), 3.63 (3H, s, CH_3O), 3.85 and 4.04 (2H, 2 x m, OCH_2), 4.04 (1H, d, J 17 Hz, PhCH), 4.92-4.97 (2 H, m, $=\text{CH}_2$), 5.68 (1H, m, $-\text{CH}=\text{}$), 6.62 (2H, d, J_{H} 9 Hz, 4-methoxy aromatic H), 6.92 (2H, d, J_{H} 9 Hz, J_{P} 2.5 Hz, 4-methoxy aromatic H), 7.17-7.40 (5H, m, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 39.2 ppm

Diethyl hydroxy-(4-nitrophenyl)methanephosphonate (405), yield 55%, m.p. 89 °C (Found: C, 45.65; H, 5.5; N, 4.8. $\text{C}_{11}\text{H}_{16}\text{NO}_6\text{P}$ requires C, 45.7; H, 5.6; N, 4.8%); ν_{max} . (nujol) 3235, 1598, 1520, 1349, 1263, 1238, 1208, 1160, 1105, 1030, 977, 875, 864, 815, 801, 777, 699 and 559 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.25 (3 H, t, J 7Hz, CH_3), 1.28 (3 H, t, J 7Hz, CH_3), 4.02-4.16 (4 H, m, CH_2 's), 5.16 (1H, dd, J_{HP} 12 J_{HH} 5Hz, CH), 7.66 (2H, d, J_{HH} 8 Hz, J_{HP} 2 Hz, aromatic H) and 8.22 (2H, d, J 9 Hz, aromatic H); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 18.9 ppm; m/z (70 eV, 120°C) 289 (M^+ , 1), 151 (58), 150 (46), 138 (63), 111 (100), 83 (79), 82 (36), 77 (40) and 65 (59).

Diethyl (4-acetamidophenyl)hydroxymethanephosphonate (406), yield 35%, m.p. 153-154°C (Found: C, 51.6; H, 6.6; N, 4.7. $\text{C}_{13}\text{H}_{20}\text{NO}_5\text{P}$ requires C, 51.8; H, 6.7; N, 4.65%); ν_{max} . (nujol) 3310, 1693 (C=O), 1604, 1537, 1511, 1408, 1313, 1275, 1255, 1189, 1059, 1021, 974, 849, 577 and 549 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.21 (3 H, t, J 7Hz, CH_3), 1.28 (3 H, t, J 7Hz, CH_3), 1.71 (1 H, bs, OH), 2.16 (3 H, s, COCH_3), 3.88-4.13 (4 H, m, CH_2 's), 4.94 (1H, dd, J_{HP} 12 Hz, J_{HH} 5Hz, CH), 7.34 (2H, d, J_{HH} 8 Hz, J_{HP} 2 Hz, aromatic H), 7.44 (2H, d, J 8 Hz, aromatic H) and 8.08 (1H, bs, NHAc); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 20.4 ppm; m/z (70 eV, 170 °C) 163 (55), 121 (69), 120 (100), 111 (66), 93 (21), 83 (67), 65 (53), 45 (22) and 43 (56).

Diethyl (4-acetamidophenyl)trimethylsilyloxymethanephosphonate (407), yield 50%, m.p. 144 °C (Found: C, 51.35; H, 7.7; N, 3.5. $C_{16}H_{28}NO_5PSi$ requires C, 51.5; H, 7.6; N, 3.75%); ν_{max} . (nujol) 3259, 31192, 3125, 1687 (C=O), 1604, 1547, 1511, 1416, 1317, 1252, 1216, 1190, 1029, 967, 882, 849, 756 and 574 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 0.06 [9H, s, $(CH_3)_3Si$] 1.20 (3 H, t, J 7Hz, CH_3), 1.28 (3 H, t, J 7Hz, CH_3), 2.16 (3 H, s, $COCH_3$), 3.80-4.20 (4 H, m, CH_2 's), 4.90 (1H, d, J_{HP} 14 Hz, CH), 7.29 (2H, d, J_{HH} 9 Hz, J_{HP} 2 Hz, aromatic H), 7.42 (2H, d, J 9 Hz, aromatic H) and 8.93 (1H, bs, NHAc); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 19.7 ppm; m/z (70 eV, 130°C) 373 (4), 238 (5), 237 (19), 236 (100), 210 (14), 147 (30), 120 (8), 75 (8), 73 (45) and 43 (8).

Diethyl hydroxy-(4-methoxyphenyl)methanephosphonate (408), yield 96%, m.p. 116°C (Found: C, 52.4; H, 6.9. $C_{12}H_{19}O_5P$ requires C, 52.55; H, 7.0%); ν_{max} . (nujol) 3251, 1614, 1586, 1330, 1302, 1251, 1196, 1171, 1108, 1065, 1029, 964, 838, 797, 757, 669, 597 and 558 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.21 (3 H, t, J 7Hz, CH_3), 1.27 (3 H, t, J 7Hz, CH_3), 3.80 (3 H, s, OCH_3), 3.90-4.10 (4 H, m, CH_2 's), 4.05 (1H, d, J_{HP} 12 Hz, J_{HH} 7Hz, CH), 6.89 (2H, d, J_{HH} 8 Hz, aromatic H) and 7.40 (2H, d, J 9 Hz, 2 Hz, aromatic H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 20.9 ppm; m/z (70 eV, 100°C) 274 (M^+ , 1), 136 (71), 135 (100), 111 (46), 92 (18), 83 (48), 77 (25), 65 (38) and 45 (16).

Competition reaction between addition to imine (318) and 4-nitrobenzaldehyde: To a stirred solution of diethyl phosphite (350 mg, 2.53 mmol) and triethylamine (0.38 ml, 2.73 mmol) in dichloromethane (50 ml) under an argon atmosphere and maintained at 0 °C was delivered chlorotrimethylsilane (0.35 ml, 2.76 mmol) in one portion. After 15 min a solution of imine (318) (482 mg, 2.51 mmol) and 4-nitrobenzaldehyde (381 mg, 2.52 mmol) in dichloromethane (2ml) was added. After 15 h a 2ml aliquot was withdrawn. Solvent was evaporated under a flow of moist argon gas and the residue was analysed by ^{31}P NMR. The following peaks were obtained (in ppm): -10.0 (42%), -2.8 (7%), -2.7 (3%), -1.4 (13%) and 20.65 (imine adduct, 37%).

Competition reaction between addition to imine (322) and 4-methoxybenzaldehyde: To a stirred solution of diethyl phosphite (350 mg, 2.53 mmol) and triethylamine (0.38 ml, 2.73 mmol) in dichloromethane (50 ml) under an argon atmosphere and maintained at 0 °C was delivered chlorotrimethylsilane (0.35 ml, 2.76 mmol) in one portion. After 15 min a solution of imine (322) (444 mg, 2.53 mmol) and 4-methoxybenzaldehyde (345 mg, 2.53 mmol) in dichloromethane (2ml) was added. After 15 h a 2ml aliquot was

withdrawn. Solvent was evaporated under a flow of moist argon gas and the residue was analysed by ^{31}P NMR. The following peaks were obtained (in ppm): 6.5 (unreacted diethyl phosphite, 15%), 6.9 (15%), 20.7 (aldehyde adduct, 20%) and 22.7 (imine adduct, 50%).

Competition reaction between addition to imine (310) and 4-acetamidobenzaldehyde:

To a stirred solution of diethyl phosphite (355 mg, 2.57 mmol) and triethylamine (0.38 ml, 2.73 mmol) in dichloromethane (50 ml) under an argon atmosphere and maintained at 0 °C was delivered chlorotrimethylsilane (0.35 ml, 2.76 mmol) in one portion. After 15 min a solution of imine (310) (520 mg, 2.57 mmol) and 4-acetamidobenzaldehyde (420 mg, 2.57 mmol) in dichloromethane (2ml) was added. After 15 h a 2ml aliquot was withdrawn. Solvent was evaporated under a flow of moist argon gas and the residue was analysed by ^{31}P NMR. The following peaks were obtained (in ppm): 6.5 (unreacted diethyl phosphite, 4%), 19.5 (silylated aldehyde adduct, 9%) and 22.7 (imine adduct, 87%).

Diethyl (4-carboxaldehydophenyl)hydroxymethanephosphonate (409), yield 66%, m. p. 90°C, (Found: M^+ 272.0814. $\text{C}_{12}\text{H}_{17}\text{O}_5\text{P}$ requires 272.0814); ν_{max} . (nujol) 3216, 1698 (C=O), 1606, 1577, 1417, 1304, 1207, 1024, 966, 854, 843, 800, 759, 710, 642, 630, 567, 537 and 509 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.23 (3H, dt, J_{H} 7 Hz, J_{P} 0.5 Hz, CH_3), 1.26 (3H, t, J_{H} 7 Hz, CH_3), 4.02-4.14 (4H, m, CH_2O), 5.14 (1H, d, J_{P} 12 Hz, CHPh), 5.48 (2H, bs, OH), 7.65 (2H, dd, J_{H} 8 Hz, J_{P} 2 Hz, aromatic H), 7.86 (2H, d, J_{H} 8 Hz, aromatic H), 10.0 (1h, s, $\text{CH}=\text{O}$); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 18.1 ppm; m/z (70 eV, 150°C) 272 (M^+ , 16), 138 (100), 134 (42), 133 (43), 111 (89), 99 (52), 83 (49), 82 (59) and 77 (50).

Diethyl 2-bromo-1-hydroxy-2,2-dimethylethanephosphonate (410), yield 20%, oil (Found: C, 33.1; H, 6.25. $\text{C}_8\text{H}_{18}\text{O}_4\text{PBr}$ requires C, 33.2; H, 6.3%); ν_{max} . (film) 3273, 2982, 2934, 1445, 1392, 1370, 1295, 1224 (P=O), 1166, 1024, 971, 852, 798, 762, 646 and 525 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.36 (6H, t, J 7Hz, ester CH_3 's), 1.94 (3H, s, 2- CH_3), 2.00 (3H, s, 2- CH_3), 3.38 (1H, bs, OH), 4.05 (1H, d, J 13 Hz, H-1), 4.22 (4H, dq, J 7 Hz, 3Hz, CH_2 's); $\delta_{\text{P}}\{\text{H}\}$ (36 MHz, CDCl_3) 17.5 ppm; m/z (70 eV, 140°C) 291 and 289 (M^+ , 0.2), 209 (M^+ - HBr, 61), 138 (100), 111 (82), 83 (54), 82 (82), 81 (27), 71 (56) and 65 (39).

Diethyl 2-methyl-2-propene phosphate (411), yield 31%, oil (Found: C, 46.3; H, 8.5. Calculated for $C_8H_{17}O_4P$: C, 64.15; H, 8.3%); ν_{max} . (film) 2982, 2918, 1692, 1447, 1394, 1271 (P=O), 1133, 1098, 967, 893, 806 and 573 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.36 (6H, dt, J 7Hz, 1 Hz, CH_3 's), 1.61 [3H, d, J 1.5 Hz, =C CH_3], 1.67 [3H, s, =C CH_3], 4.16 (4H, quintet, J 7 Hz, CH_2 's), 6.24 (1H, heptet, J 1.5 Hz, H-2); δ_P {H} (36 MHz, $CDCl_3$) -5.00 ppm; m/z (70 eV, 160°C) 209 (M^+ , 49), 152 (56), 151 (35), 127 (20), 99 (100), 81 (29), 71 ($Me_2C=CHCO^+$, 39) and 54 (34). All data in accordance with that reported in literature.¹⁶⁷

Diethyl 1,1-bis(ethoxycarbonyl)-1-hydroxymethanephosphate (412), yield 76%, oil (Found: C, 42.5; H, 6.8. $C_{11}H_{21}O_8P$ requires C, 42.3; H, 6.8%); ν_{max} . (film) 2987, 2941, 1752, 1448, 1396, 1372, 1274, 1185, 1123, 1030, 971, 916, 849, 762 and 489 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.30 (6H, t, J 7Hz, carboxylate CH_3 's), 1.34 (6H, dt, J 7Hz, 1 Hz, phosphonate CH_3 's), 4.19 (4 H, quartet, carboxylate CH_2 's), 4.28 (4H, dqintet, J 9 Hz, 3Hz, phosphonate CH_2 's) and 5.28 (1H, d, J 10 Hz, CH); δ_P {H} (36 MHz, $CDCl_3$) -3.0 ppm; m/z (70 eV, 180 °C) 312 (M^+ , 5), 240 (55), 213 (32), 155 (100), 138 (68), 127 (68), 109 (35), 99 (91) and 81 (45).

Diethyl 1-(ethoxycarbonyl)-1-hydroxyethanephosphate (413), yield 16%, oil (Found MH^+ 255.0998. $C_9H_{20}O_6P$ requires 255.0998); (Found: C, 42.7; H, 7.7. $C_9H_{19}O_6P$ requires C, 58.5; H, 5.9; N, 7.2%); ν_{max} . (film) 3294, 2985, 2938, 1735, 1447, 1393, 1370, 1251, 1152, 1023, 975, 863, 797, 602 and 504 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.30 (3H, t, J 7Hz, carboxylate CH_3 's), 1.306 (3H, dt, J 7Hz, 0.5 Hz, phosphonate CH_3 's), 1.31 (3H, dt, J 7Hz, 0.5 Hz, phosphonate CH_3 's), 1.61 (3H, d, J 16 Hz, 2-Me), 4.11-4.27 (4 H, m, phosphonate CH_2 's), 4.29 (2 H, dqartet, J 7 Hz, 2 Hz, carboxylate CH_2 's); δ_P {H} (36 MHz, $CDCl_3$) 17.3 ppm; m/z (70 eV, 140 °C) 111 (86), 93 (28), 83 (100), 81 (27), 67 (26), 65 (70), 45 (35) and 43 (93); m/z (CI/ NH_3) 255 (MH^+ , 100).

Diethyl 1-(ethoxycarbonyl)-1-trimethylsilyloxyethanephosphate (414), yield 21%, oil (Found: C, 44.1; H, 8.2. $C_{12}H_{27}O_6PSi$ requires C, 44.2; H, 8.3%); ν_{max} . (film) 2985, 1746, 1447, 1392, 1371, 1252, 1174, 1127, 1028, 847, 759 and 584 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 0.14 [9H, s, $(CH_3)_3Si$], 1.27 (3H, t, J 7Hz, carboxylate CH_3 's), 1.28 (6H, tm, J 7Hz, phosphonate CH_3 's), 1.66 (3H, d, J 16 Hz, 2-Me), 4.08-4.23 (6H, m, CH_2 's); δ_P {H} (36 MHz, $CDCl_3$) 16.9 ppm; m/z (70 eV, 140°C) 210 (32), 181 (68), 153 (22), 125 (36), 109 (24), 75 (42), 73 (27), 45 (27) and 43 (100).

(Diethyl phosphonyl)acrylonitrile (416), yield 76%, b.p. 130 °C/0.5 mmHg, (Found: C, 44.1; H, 6.2; N, 7.0. $C_7H_{12}NO_3P$ requires C, 44.4; H, 6.4; N, 7.4%), ν_{max} . (film) 2986, 2935, 2230 ($C\equiv N$), 1603 ($C=C$), 1479, 1446, 1395, 1371, 1258 ($P=O$), 1165, 1099, 1024, 975, 841, 790, 747, 572 and 521 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.33 (6H, dt, J 7 Hz, J_P 0.5 Hz, CH_3), 4.13 (4H, ddq, J_P 8 Hz, 7 Hz, 1 Hz, CH_2O), 6.30 (1H, dd, J 18 Hz, J_P 21 Hz, 1-H), 6.72 (dd, J 18 Hz, J_P 15 Hz, 2-H); δ_P {H} (36 MHz, $CDCl_3$) 10.2 ppm; m/z (70 eV, 170 °C) 188 [($M-H$)⁺, 2], 162 (17), 161 (48), 144 (14), 134 (100), 116 (52), 81 (23), 65 (22) and 47 (16).

1-(4-Nitrobenzoyl)-2-methylaziridine (418): 2-Methylaziridine was added slowly to a cold stirred solution of 4-nitrobenzoylchloride in DCM over a period of 30 min and stirring was continued for a further h. The solution was poured into water and extracted with DCM. Removal of solvent followed by crystallisation afforded the title compound as a pale yellow solid. yield 54%, m.p. 79 °C (Found: C, 58.1; H, 4.8; N, 13.5. $C_{10}H_{10}N_2O_3$ requires C, 58.25; H, 4.9; N, 13.6%); ν_{max} . (nujol) 1666 ($C=O$), 1605, 1522, 1407, 1323, 1106, 869, 855 and 717 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 1.43 (3H, d, J 5 Hz, 2- CH_3), 2.24 (1H, d, J 4 Hz, 3-H), 2.61 (1H, d, J 6 Hz, 3-H), 2.69 (1H, ddq, J 4 Hz, 5 Hz, 6 Hz, 2-H), 8.19 (2H, d, J 9 Hz, aromatic H), 8.31 (2H, J 9 Hz, aromatic H); m/z (70 eV, 130 °C) 206 (M^+ , 3), 162 (5), 140 (28), 120 (6), 104 (15), 76 (12), 56 (100), 50 (6) and 32 (8).

Diethyl (4-methoxyphenyl)[1',1'-dimethyl-2'-(trimethylsilyloxy)ethylamino] methanephosphonate (420), yield 88%, oil, (Found: C, 54.6; H, 8.5; N, 3.4. $C_{19}H_{36}NO_5PSi$ requires C, 54.65; H, 8.7; N, 3.35%); ν_{max} . (film) 3469, 2963, 2906, 1611, 1511, 1466, 1391, 1303, 1251, 1178, 1096, 1058, 1030, 965, 876, 843, 790, 750 and 580 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 0.03 [9H, s, (CH_3)₃C], 0.8 (3H, s, 1'- CH_3), 0.95 (3H, s, 1'- CH_3), 1.10 (3H, t, J 7 Hz, ester CH_3), 1.27 (3H, t, J 7 Hz, ester CH_3), 3.16 (2H, dd, J_{HH} 17.5 Hz, J_{HP} 8.5 Hz, CH_2OSi), 3.70-4.15 (5H, m, CH_2 's and CH), 3.78 (3H, s, OCH_3), 6.83 (2H, dd, J_{HH} 9 Hz, J_{HP} 1 Hz, aromatic H), 7.33 (2H, dd, J_{HH} 9 Hz, J_{HP} 2.5 Hz, aromatic H); δ_P {H} (36 MHz, $CDCl_3$) 23.6 ppm; m/z (70 eV, 200°C) 177 (13), 176 (100), 111 (10), 83 (11), 75 (7), 73 (10) and 65 (8).

4-Hydroxybenzaldehyde *N*-allylimine (421), m. p. 108-118 °C (Found: C, 74.4; H, 6.8; N, 8.6. $C_{10}H_{11}NO$ requires C, 74.5; H, 6.9; N, 8.7%); ν_{max} . (nujol) 2954, 2752, 2683, 2605, 2494, 1646, 1633, 1606, 1520, 1459, 1308, 1283, 1250, 1224, 1170,

1026, 929,839 and 531 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 4.22 (2H, dm, J 6 Hz, NCH_2), 5.21 (1H, dm, J 10 Hz, $=\text{CH}_{\text{cis}}$), 5.14 (1H, dm, J 17 Hz, $=\text{CH}_{\text{trans}}$), 6.02 (1H, ddt, J 17 Hz, 10 Hz, 6Hz, $-\text{CH}=\text{)$, 6.71 (2H, d, J 8 Hz, aromatic H), 7.52 (2H, J 8 Hz, aromatic H), 8.18 (1H, s, $\text{CH}=\text{N}$); m/z (70 eV, 120°C) 161 (M^+ , 64), 160 (100), 133 (32), 120 (31), 107 (31), 106 (20), 41 (46) and 39 (25).

N-Phthalamidoglycinate chloride. (422) A mixture of *N*-phthalamidoglycine (1.90 g) and thionyl chloride (10 ml) was refluxed for 30 minutes. A homogeneous solution was obtained from which the excess of thionyl chloride was removed at reduced pressure. The residue was recrystallised from petroleum ether (b.p. fraction 60-80 °C), yield 1.60 g (72 %), m.p. 83 °C (Lit.¹⁶⁸ 83-85 °C).

*Diethyl (4-acetamidophenyl)*N*-allyl-*N*-(phthalamido)glycinamidomethanephosphonate (423).* Acid chloride (422) (280 mg, 1.25 mmol) was added to a stirred solution of (310) (340 mg, 1 mmol) in DCM (5 ml) under an atmosphere of dry argon at 0 °C. Pyridine (0.1 ml, 1.25 mmol) was added and solution was brought to room temperature. After 10 min, water (10 ml) was added and the organic products were extracted with DCM (2 x 20 ml). The DCM extracts were washed with water (10 ml), saturated copper sulphate solution (10 ml) and water (10 ml) again. Drying (magnesium sulphate), removal of solvent followed by chromatography (EtOAc as elutant) afforded the *title compound* as a white solid, yield 410 mg (75%), m. p. 206 °C (Ethanol) (Found: C, 59.2; H, 5.8; N, 8.0. $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_7\text{P}$ requires C, 59.2; H, 5.7; N, 8.0%); ν_{max} . (nujol) 3351 (NH), 1775, 1726, 1689, 1636, 1598, 1530, 1466, 1440, 1414, 1391, 1316, 1257, 1236, 1193, 1113, 1035, 980, 950, 928, 743, 727 and 566 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 1.15 (3H, t, J 7 Hz, ester CH_3), 1.37 (3H, t, J 7 Hz, CH_3), 2.11 (3H, s, CH_3CO), 3.92-4.58 (8H, m, 4 x CH_2), 5.02-5.08 (2H, m, $=\text{CH}_2$), 5.40 (1H, m, $-\text{CH}=\text{)$, 6.24 (1H, d, J 22 Hz, PhCH), 7.49 (4-acetamidophenyl aromatic H), 7.71 (2H, dd, J 6 Hz, 3 Hz, phthalimide aromatic H), 7.85 (2H, dd, J 6 Hz, 3 Hz, phthalimide aromatic H), 8.26 (1H, s, NHAc); δ_{P} (36 MHz, CDCl_3) 19.2 ppm; m/z (70 eV, 220°C) 527 (M^+ , 10), 299 (28), 203 (27), 161 (40), 160 (100), 69 (29), 57 (42), 55 (34), 43 (32) and 41 (30).

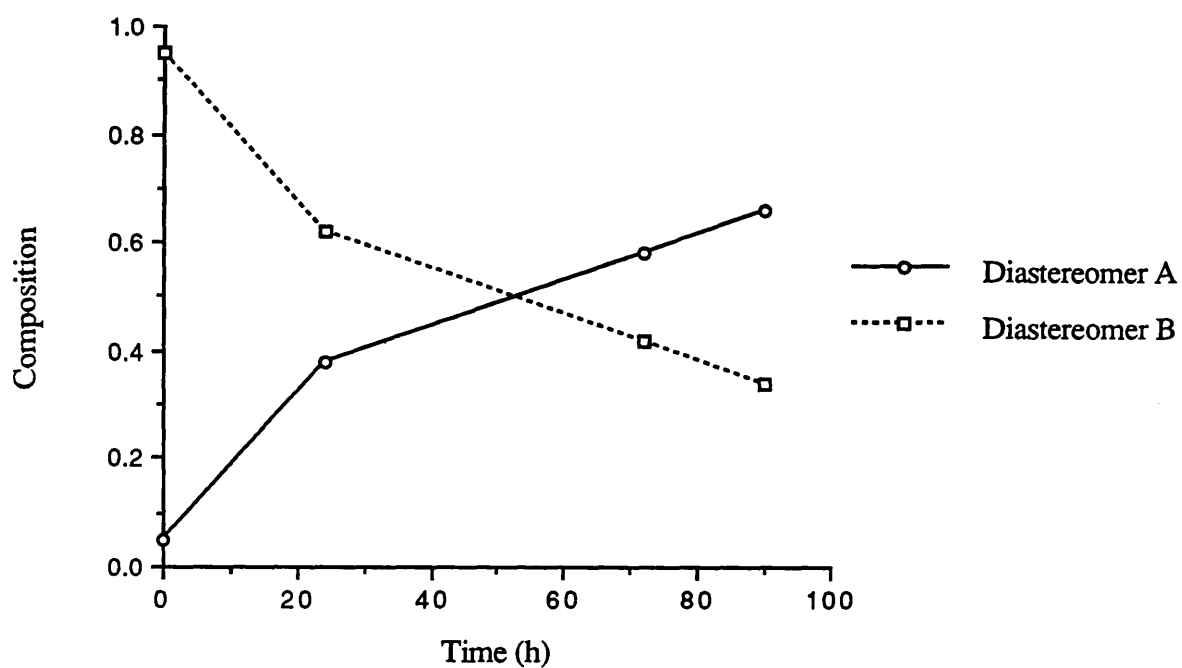
Diethyl (4-acetamidophenyl)(2',3'-dibromopropylaminomethanephosphonate (424). Bromine (10 ml of 0.1 molar solution in CCl_4) was added in ten portions to a stirred solution of (310) (340 mg) in CCl_4 (40 ml) over a period of 90 minutes. The solution was poured into DCM (200 ml) and washed with water (100 ml). The organic extracts were dried over magnesium sulphate. Removal of solvent followed by crystallisation

afforded the *title compound* as a pale yellow solid, yield 490 mg (98%), m.p.127-129 °C (DCM/Ether 1:4), (Found: C, 38.5; H, 5.1; N, 5.3. C₁₆H₂₅N₂O₄PBr₂ requires C, 38.4; H, 5.0; N, 5.6%); ν_{\max} . (nujol) 3265, 1694, 1674, 1603, 1545, 1515, 1414, 1319, 1270, 1231, 1182, 1055, 1025, 974, 860, 766 and 561 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.17 and 1.19 (3H, *J* 7 Hz, ester CH₃), 1.32 and 1.33 (3H, *J* 7 Hz, ester CH₃), 2.19 (3H, s, CH₃CO), 2.91-3.15 (2H, m, NCH₂), 3.74 (8 Hz, m, 2 x CH₂O, ArCH, CH₂Br, CHBr), 7.32 (2H, m, aromatic H), 7.49 (2H, d, *J* 8 Hz, aromatic H), 8.14 and 8.17 (1H, bs, NH); δ_{P} (36 MHz, CDCl₃) 21.5 and 21.7 ppm; *m/z* (70 eV, 160°C) 420/418 (*M*⁺ - HBr, 1), 283 (100), 281 (100), 203 (36), 202 (45), 201 (43), 175 (32), 149 (40) and 133 (35).

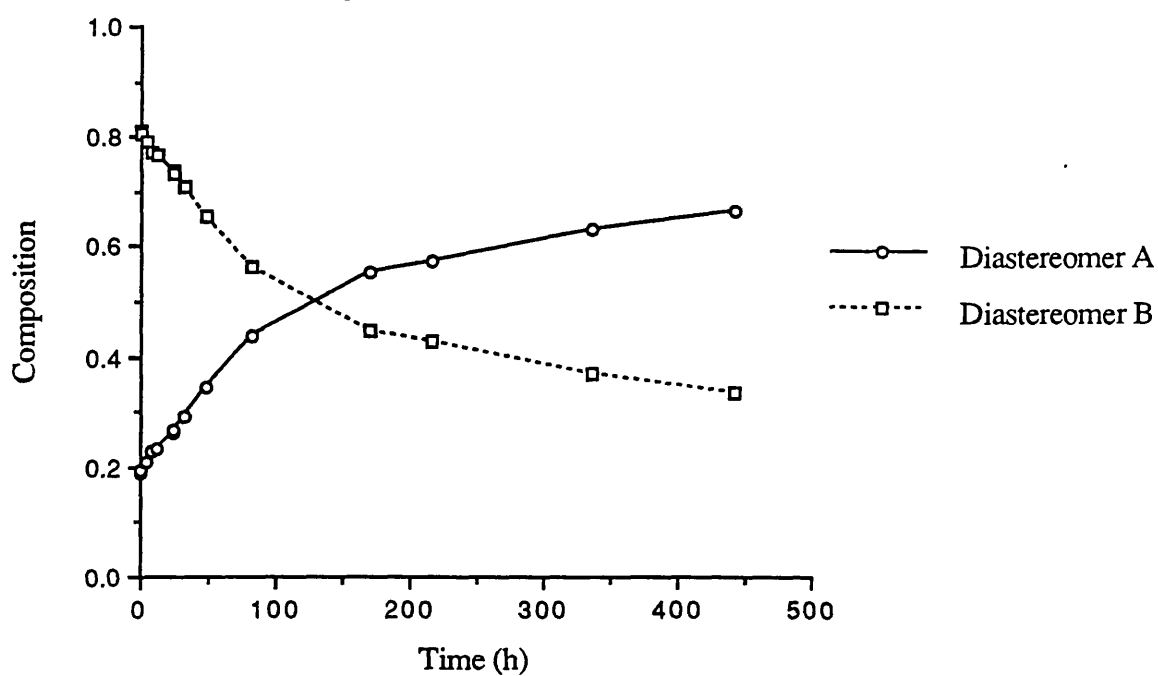
Diethyl (4-acetamidophenyl)N-allyl-N-(bromo)glycinamidomethanephosphonate (425). Bromoacetyl bromide (0.05 ml, 0.57 mmol) was added to a stirred solution of (310) (170 mg, 0.5 mmol) in DCM (5 ml) under an atmosphere of dry argon at 0 °C. Pyridine (0.05 ml, 0.62 mmol) was added and solution was brought to room temperature. After 5 h, water (10 ml) was added and the organic products were extracted with DCM (2 x 20 ml). The DCM extracts were washed with water (10 ml), saturated copper sulphate solution (2 x 10 ml) and water (10 ml) again. Drying (magnesium sulphate), removal of solvent followed by chromatography (EtOAc as elutant) afforded the *title compound* as a white solid, yield 150 mg (65%), m. p. 112-114 °C(Ether/DCM/Petrol 1:1:1), (Found: C, 46.9; H, 5.6; N, 6.0. C₁₈H₂₆N₂O₅PBr requires C, 46.9; H, 5.7; N, 6.1%); ν_{\max} . (nujol) 3319 (NH), 1700, 1625, 1602, 1537, 1514, 1410, 1316, 1298, 1248, 1031, 977, 927, 743 and 551 cm⁻¹; δ_{H} (270 MHz, CDCl₃) 1.14 (3H, t, *J* 7 Hz, ester CH₃), 1.32 (3H, t, *J* 7 Hz, CH₃), 2.13 (3H, s, CH₃CO), 3.80-4.34 (8H, m, 4 x CH₂), 5.26-5.38 (2H, m, =CH₂), 4.92 (1H, m, -CH=), 6.18 (1H, d, *J* 22 Hz, PhCH), 7.47 (4-acetamidophenyl aromatic H), 8.69 (1H, s, NHAc); δ_{C} (68 MHz, CDCl₃) 16.2 (dq, *J*_P 6 Hz, ester Me), 16.5 (dq, *J*_P 6 Hz, ester Me), 24.4 (q, CH₃CO), 26.5 (t, CH₂N), 48.5 (t, CH₂Br), 53.2 (dd, *J*_P 159 Hz, PhCH), 62.9 (dt, *J*_P 7 Hz, CH₂O), 63.3 (dt, *J*_P 7 Hz, CH₂O), 117 (t, =CH₂), 120 (d, -CH=), 127.8 (d, *J*_P 4 Hz, 1-C), 130.9 (dd, *J*_P 8 Hz, 2-C), 133.9 (d, C-3), 139.1 (s, 4-C), 167.8 (d, *J*_P 4 Hz, BrCH₂CO), 169.0 (s, ArNHCO); *m/z* (70 eV, 200°C) 462/460 (*M*⁺, 5), 325/323 (48), 299 (41), 245 (100), 243 (31), 203 (80), 201 (33), 161 (25) and 106 (22).

Appendix 1

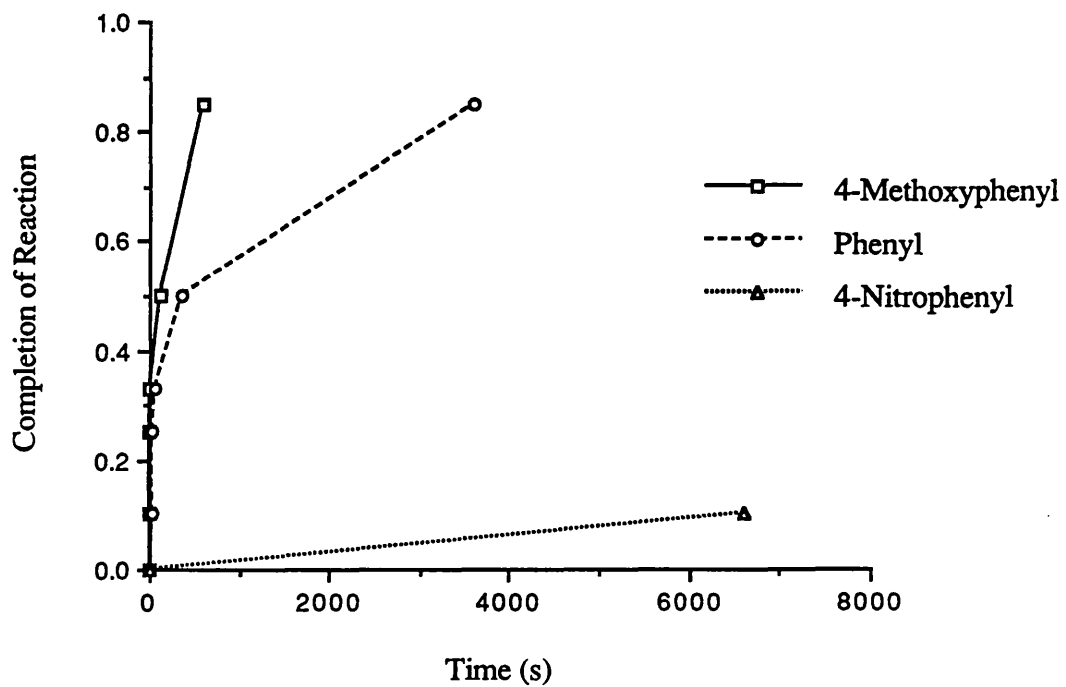
Time Dependent Change in the Diastereomeric Composition of Acetonide (214) in Chloroform



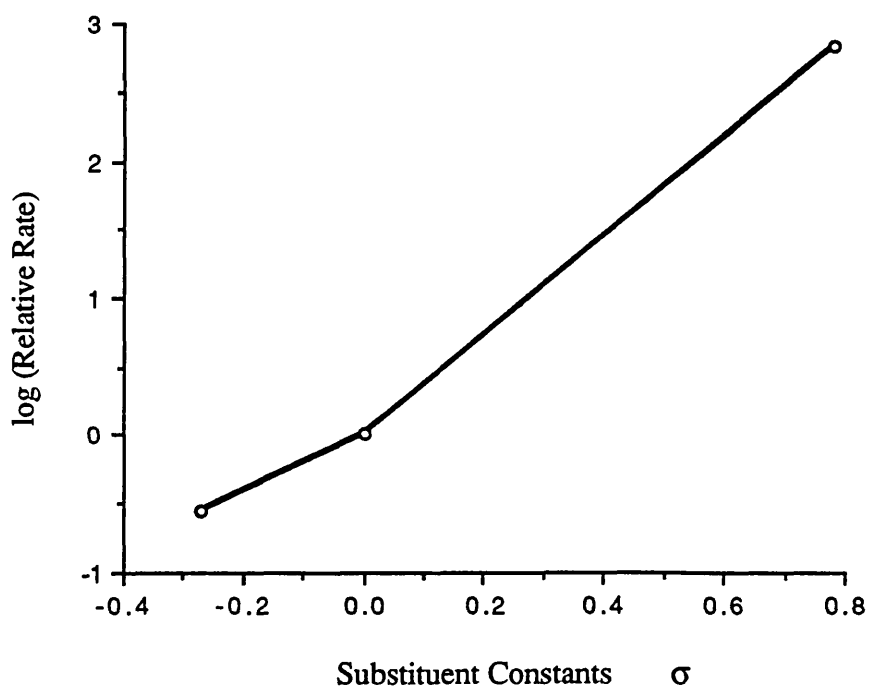
Time Dependent Change in The Diastereomeric Composition of Diol (215) in Chloroform



Rates of Reactions of 4-Acetamidobenzaldimines



Hammet Plot



Appendix 2

X-Ray Crystallography of (228)

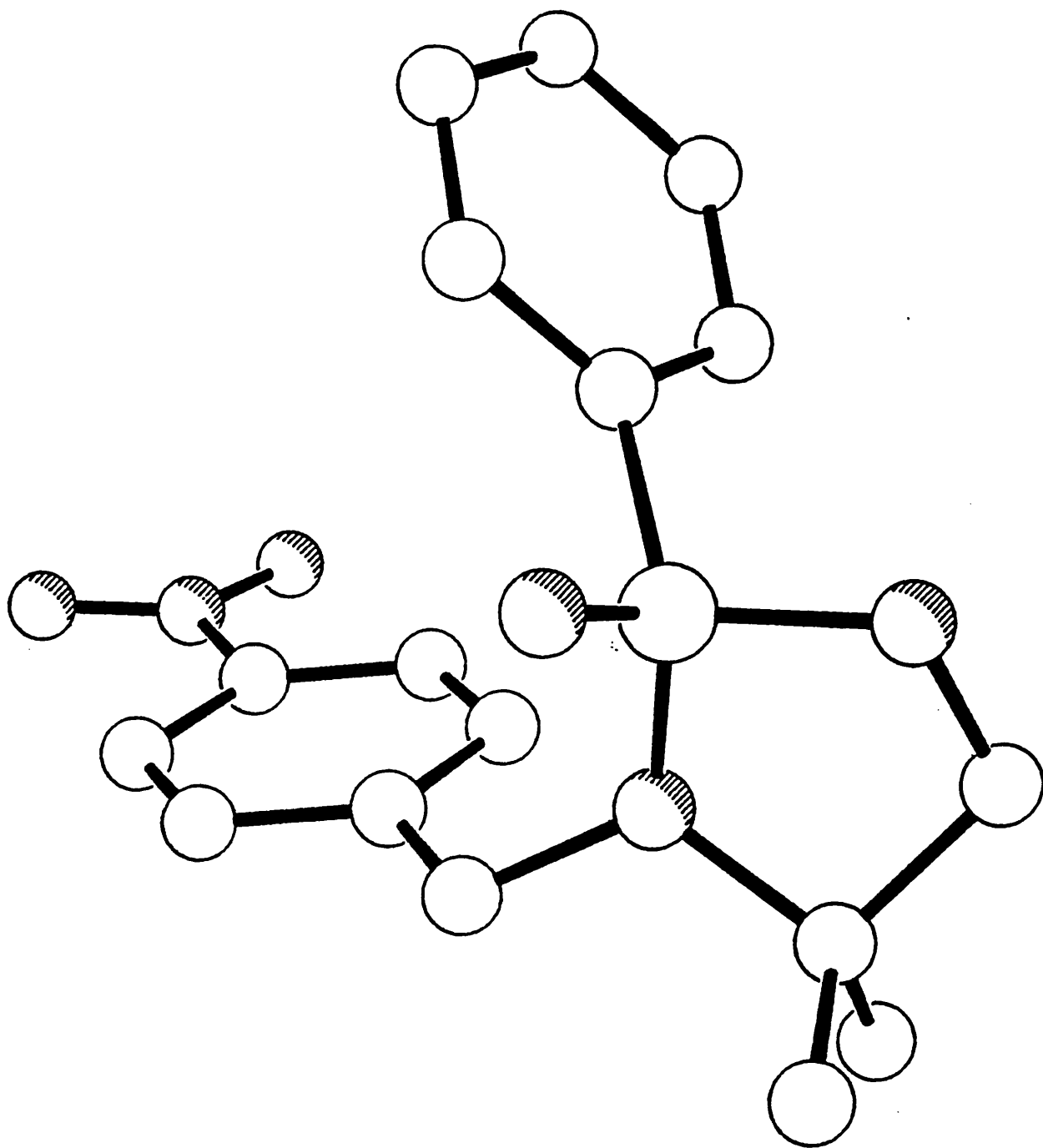
Crystal data: $C_{17}H_{19}N_2O_4P$, $M = 346.3$, monoclinic, $a = 6.153(1)$, $b = 22.644(4)$, $c = 12.262(2)$ Å, $\beta = 95.36(1)^\circ$, $V = 1701$ Å³, space group $P2_1/n$, $Z = 4$, $D_c = 1.35$ gcm⁻³, Cu radiation, $\lambda = 1.54178$ Å, $\mu(\text{Cu-K}\alpha) = 16$ cm⁻¹, $F(000) = 728$. Data were measured on a Nicolet R3m diffractometer with Cu-K α radiation (graphite monochromator) using ω scans. A crystal of dimensions 0.10x0.12x0.33 mm was used. 1203 Independent reflections ($2\theta \leq 116^\circ$) were measured, of which 1875, had $|F_o| > 3\sigma(|F_o|)$, and were considered to be observed. The data were corrected for Lorenz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were located on a ΔF map and their position were idealised, C-H = 0.96 Å, assigned isotropic thermal parameters, $U(H) = 1.2 U_{eq}(C)$, and allowed to ride on their parent atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full-matrix least-squares to $R = 0.044$, $R_w = 0.044$ [$w^{-1} = \sigma^2(F) + 0.00032F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.18 and -0.21 eÅ⁻³ respectively. The mean and maximum shift/error in the final refinement were 0.008 and 0.035 respectively. Computations were carried out on an Eclipse S140 computer using a SHELXTL program system.

Bond lengths (Å) with e.s.d.'s in parentheses:

N(1)-P(2)	1.653(2)	N(1)-C(5)	1.496(3)	N(1)-C(8)	1.468(3)
P(2)-O(2)	1.464(2)	P(2)-O(3)	1.583(2)	P(2)-C(15)	1.791(3)
C(3)-C(4)	1.3439(4)	C(4)-C(5)	1.513(4)	C(5)-C(6)	1.517(4)
C(5)-C(7)	1.516(4)	C(8)-C(9)	1.511(4)	C(9)-C(10)	1.383(4)
C(9)-C(14)	1.384(4)	C(10)-C(11)	1.371(5)	C(11)-C(12)	1.370(5)
C(12)-C(13)	1.371(4)	C(12)-N(12)	1.475(4)	C(13)-C(14)	1.377(4)
N(12)-O(121)	1.230(4)	N(12)-O(122)	1.226(5)	C(15)-C(16)	1.382(4)
C(15)-C(20)	1.388(4)	C(16)-C(17)	1.374(5)	C(17)-C(18)	1.373(5)
C(18)-C(19)	1.376(5)	C(19)-C(20)	1.382(5)		

Bond angles (°) with e.s.d.'s in parentheses:

P(2)-N(1)-C(5)	110.0(2)	P(2)-N(1)-C(8)	120.2(2)
C(5)-N(1)-C(8)	120.0(2)	N(1)-P(2)-O(2)	118.9(1)
N(1)-P(2)-O(3)	95.5(1)	O(2)-P(2)-O(3)	114.3(1)
N(1)-P(2)-C(15)	110.6(1)	O(2)-P(2)-C(15)	109.6(1)
O(3)-P(2)-C(15)	106.8(1)	P(2)-O(3)-C(4)	112.4(2)
O(3)-C(4)-C(5)	108.1(2)	N(1)-C(5)-C(4)	100.3(2)
N(1)-C(5)-C(6)	111.3(2)	C(4)-C(5)-C(6)	112.2(2)
N(1)-C(5)-C(7)	111.4(2)	C(4)-C(5)-C(7)	110.6(3)
C(6)-C(5)-C(7)	110.7(2)	N(1)-C(8)-C(9)	114.0(2)
C(8)-C(9)-C(10)	119.0(3)	C(8)-C(9)-C(14)	122.6(2)
P(10)-C(9)-C(14)	118.4(3)	C(9)-C(10)-C(11)	121.2(3)
C(10)-C(11)-C(12)	119.0(3)	C(11)-C(12)-C(13)	121.5(3)
C(11)-C(12)-N(12)	119.7(3)	C(13)-C(12)-N(12)	118.8(3)
C(12)-C(13)-C(14)	118.9(3)	C(9)-C(14)-C(13)	121.0(3)
C(12)-N(12)-O(121)	117.7(3)	C(12)-N(12)-O(122)	118.1(3)
O(121)-N(12)-O(122)	124.2(3)	P(2)-C(15)-C(16)	118.9(2)
P(2)-C(15)-C(20)	121.9(2)	C(16)-C(15)-C(20)	119.0(3)
C(15)-C(16)-C(17)	120.7(3)	C(16)-C(17)-C(18)	120.0(3)
C(17)-C(18)-C(19)	120.2(3)	C(18)-C(19)-C(20)	119.9(3)
C(15)-C(20)-C(10)	120.2(3)		



X-Ray Crystallography of (286)

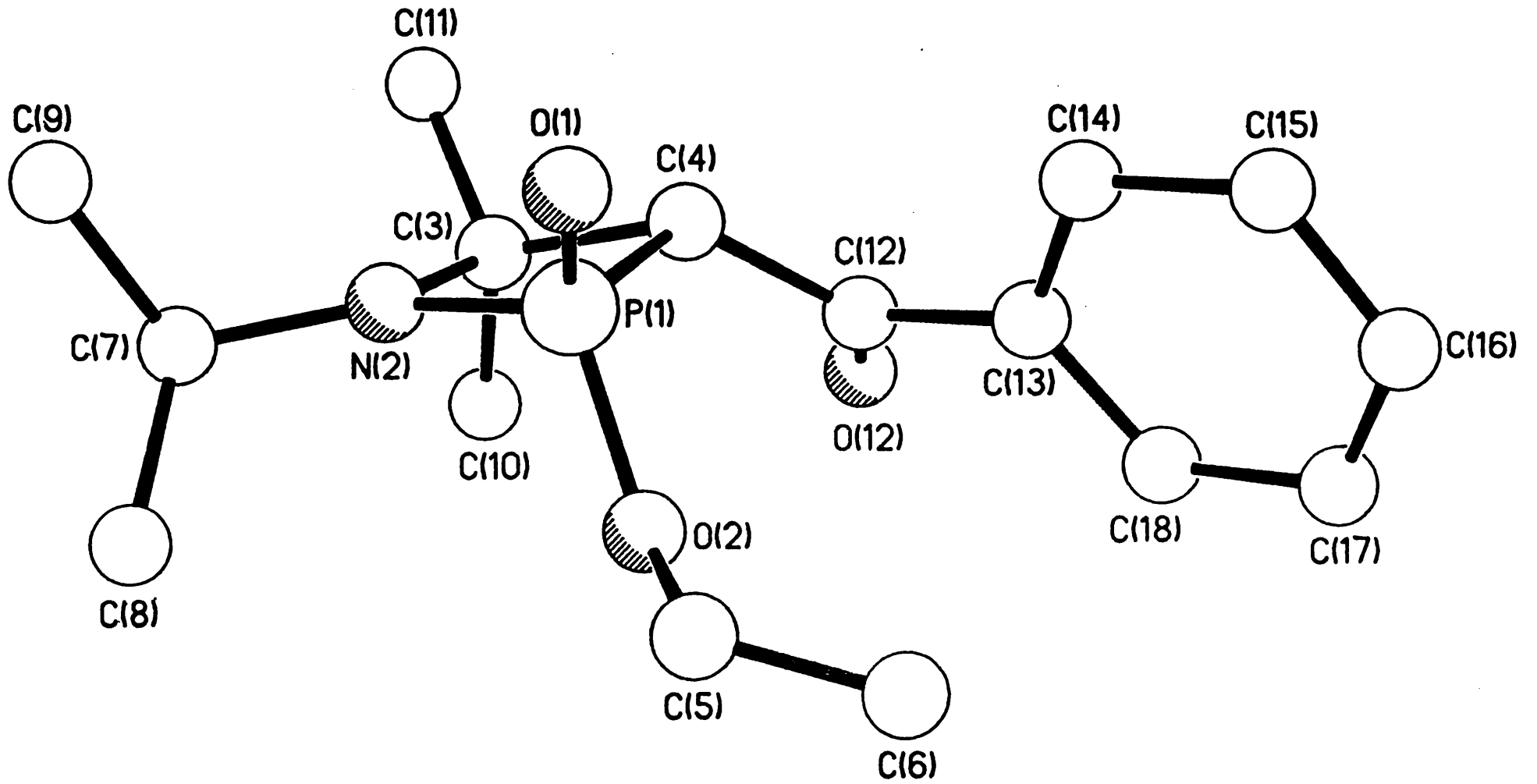
Crystal data: $C_{16}H_{24}NO_3P$, $M = 309.3$, orthorhombic, $a = 8.030(2)$, $b = 11.426(4)$, $c = 18.493(6)$ Å, $V = 1697$ Å³, space group $P2_12_12_1$, $Z = 4$, $D_c = 1.21$ gcm⁻³, Cu radiation, $\lambda = 1.54178$ Å, $\mu(\text{Cu-K}\alpha) = 15$ cm⁻¹, $F(000) = 664$. Data were measured on a Nicolet R3m diffractometer with Cu-K α radiation (graphite monochromator) using ω scans. A crystal of dimensions 0.17x0.27x0.50 mm was used. 1338 Independent reflections ($2\theta \leq 116^\circ$) were measured, of which 1256, had $|F_o| > 3\sigma(|F_o|)$, and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The proton on C(4) was located from a ΔF map and refined isotropically subject to C-H distance constraint. The position of the remaining hydrogen atoms were idealised, C-H = 0.96 Å, assigned isotropic thermal parameters, $U(H) = 1.2 U_{eq}(C)$, and allowed to ride on their parent atoms. The methyl groups were refined as rigid bodies. The absolute configuration chirality of the molecule could not be determined unambiguously. Refinement was by block-cascade full-matrix least-squares to $R = 0.045$, $R_w = 0.050$ [$w^{-1} = \sigma^2(F) + 0.00205F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.27 and -0.25 eÅ⁻³ respectively. The mean and maximum shift/error in the final refinement were 0.022 and 0.171 respectively. Computations were carried out on an Eclipse S140 computer using a SHELXTL program system.

Bond lengths (Å) with e.s.d.'s in parentheses:

P(1)-N(2)	1.623(3)	P(1)-C(4)	1.814(4)	P(1)-O(1)	1.463(3)
P(1)-O(2)	1.574(3)	N(2)-C(3)	1.498(5)	N(2)-C(7)	1.451(6)
C(3)-C(4)	1.581(5)	C(3)-C(10)	1.521(5)	C(3)-C(11)	1.507(7)
C(4)-C(12)	1.509(5)	O(2)-C(5)	1.457(6)	C(5)-C(6)	1.358(9)
C(7)-C(8)	1.504(8)	C(7)-C(9)	1.516(7)	C(12)-O(12)	1.220(5)
C(12)-C(13)	1.465(5)	C(13)-C(14)	1.382(5)	C(13)-C(18)	1.396(6)
C(14)-C(15)	1.400(6)	C(15)-C(16)	1.361(7)	C(16)-C(17)	1.379(7)
C(17)-C(18)	1.378(7)				

Bond angles (°) with e.s.d.'s in parentheses:

N(2)-P(1)-C(4)	81.0(2)	C(4)-P(1)-O(1)	123.6(2)
C(4)-P(1)-O(2)	106.5(2)	P(1)-N(2)-C(3)	97.8(2)
C(3)-N(2)-C(7)	126.0(3)	N(2)-C(3)-C(10)	110.1(4)
N(2)-C(3)-C(11)	112.1(3)	C(10)-(C3)-C(11)	109.8(4)
P(1)-C(4)-C(12)	120.1(3)	P(1)-O(2)-C(5)	123.4(3)
N(2)-C(7)-C(8)	111.6(4)	C(8)-C(7)-C(9)	110.5(5)
C(4)-C(12)-C(13)	117.4(3)	C(12)-C(13)-C(14)	123.1(4)
C(14)-C(13)-C(18)	118.3(4)	C(14)-C(15)-C(16)	102.2(4)
C(16)-C(17)-C(18)	120.2(4)	N(2)-P(1)-O(1)	120.6(2)
N(2)-P(1)-O(2)	110.1(2)	O(1)-P(1)-O(2)	111.3(2)
P(1)-N(2)-C(7)	136.0(3)	N(2)-C(3)-C(4)	93.1(3)
C(4)-(C3)-C(10)	117.4(3)	C(4)-(C3)-C(11)	113.3(3)
P(1)-C(4)-C(3)	87.6(2)	C(3)-(C4)-C(12)	122.0(3)
O(2)-(C5)-C(6)	116.1(5)	N(2)-(C7)-C(9)	112.0(4)
C(4)-(C12)-O(12)	121.2(3)	O(12)-(C12)-C(13)	121.3(4)
C(12)-C(13)-C(18)	118.6(4)	C(13)-C(14)-C(15)	120.5(4)
C(15)-C(16)-C(17)	120.0(4)	C(13)-C(18)-C(17)	120.7(4)



X-Ray Crystallography of (306)

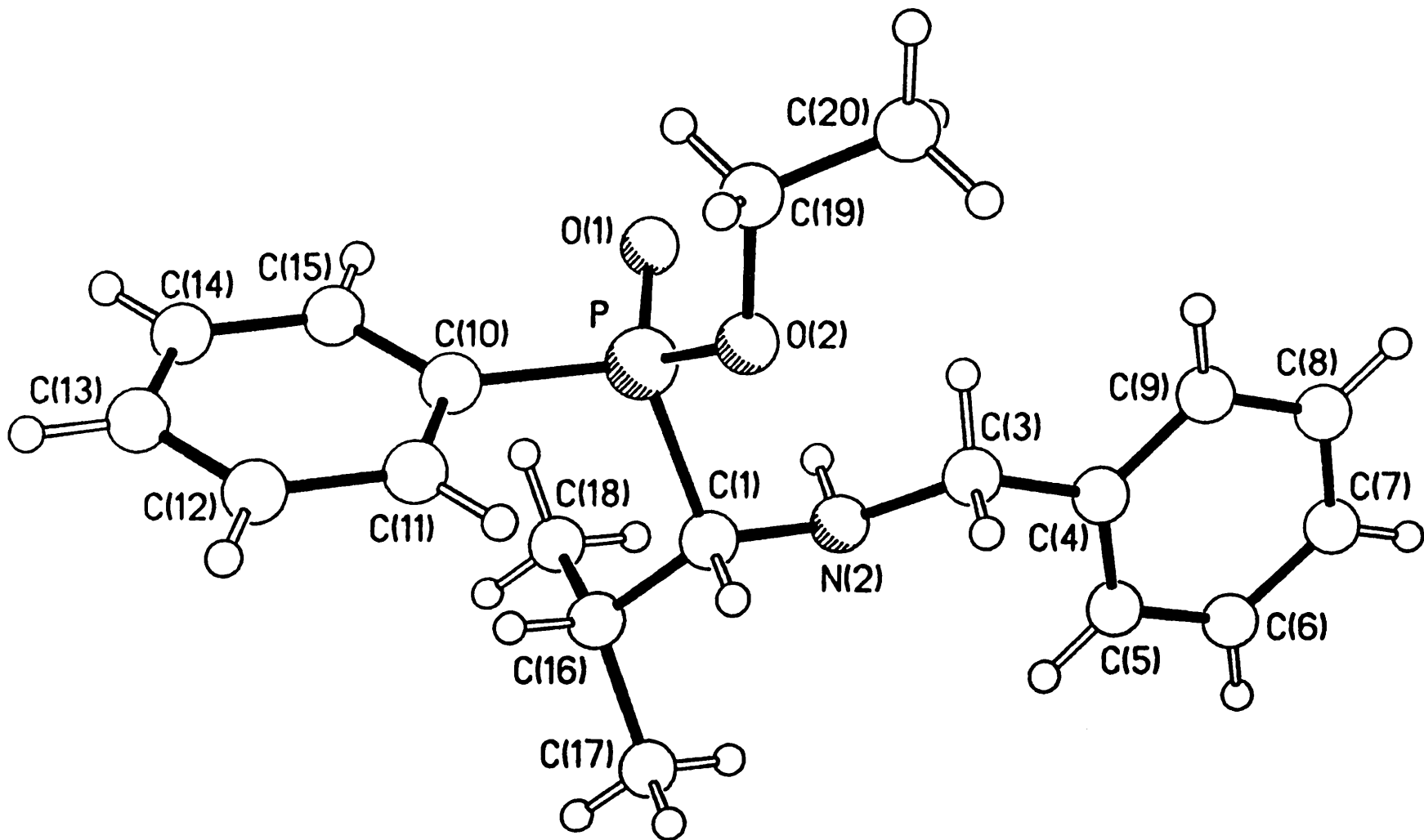
Crystal data: $C_{15}H_{26}NO_2P$, $M = 331.4$, triclinic, $a = 9.812(2)$, $b = 10.012(2)$, $c = 180.871(2)$ Å, $\alpha = 64.92(2)$, $\beta = 88.44(2)$, $\gamma = 75.99(2)^\circ$, $V = 935$ Å³, space group P_1 , $Z = 2$, $D_c = 1.18$ gcm⁻³, Cu radiation, $\lambda = 1.54178$ Å, $\mu(\text{Cu-K}\alpha) = 14$ cm⁻¹, $F(000) = 356$. Data were measured on a Nicolet R3m diffractometer with Cu-K α radiation (graphite monochromator) using ω scans. A crystal of dimensions 0.27x0.27x0.40 mm was used. 2525 Independent reflections ($2\theta \leq 116^\circ$) were measured, of which 2436, had $|F_o| > 3\sigma(|F_o|)$, and were considered to be observed. The data were corrected for Lorenz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The proton on N(2) was located from a ΔF map and refined isotropically subject to N-H distance constraint. The position of the remaining hydrogen atoms were idealised, C-H = 0.96 Å, assigned isotropic thermal parameters, $U(\text{H}) = 1.2 U_{eq}(\text{C})$, and allowed to ride on their parent atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full-matrix least-squares to $R = 0.041$, $R_w = 0.053$ [$w^{-1} = \sigma^2(F) + 0.00048F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.30 and -0.24 eÅ⁻³ respectively. The mean and maximum shift/error in the final refinement were 0.029 and 0.173 respectively. Computations were carried out on an Eclipse S140 computer using a SHELXTL program system.

Bond lengths (Å) with e.s.d.'s in parentheses:

P(1)-O(1)	1.469(1)	P(1)-C(1)	1.839(2)	O(2)-C(19)	1.443(3)
C(1)-C(16)	1.542(2)	C(3)-C(4)	1.510(2)	C(4)-C(9)	1.375(2)
C(6)-C(7)	1.371(2)	C(8)-C(9)	1.383(2)	C(10)-C(15)	1.391(2)
C(12)-C(13)	1.378(3)	C(14)-C(15)	1.375(2)	C(16)-C(18)	1.519(2)
P(1)-O(2)	1.595(1)	P(1)-C(10)	1.801(1)	C(1)-N(2)	1.461(1)
N(2)-C(3)	1.459(2)	C(4)-C(5)	1.385(3)	C(5)-C(6)	1.390(2)
C(7)-C(8)	1.360(3)	C(10)-C(11)	1.388(2)	C(11)-C(12)	1.383(2)
C(13)-C(14)	1.365(2)	C(16)-C(17)	1.521(3)	C(19)-C(20)	1.423(2)

Bond angles (°) with e.s.d.'s in parentheses:

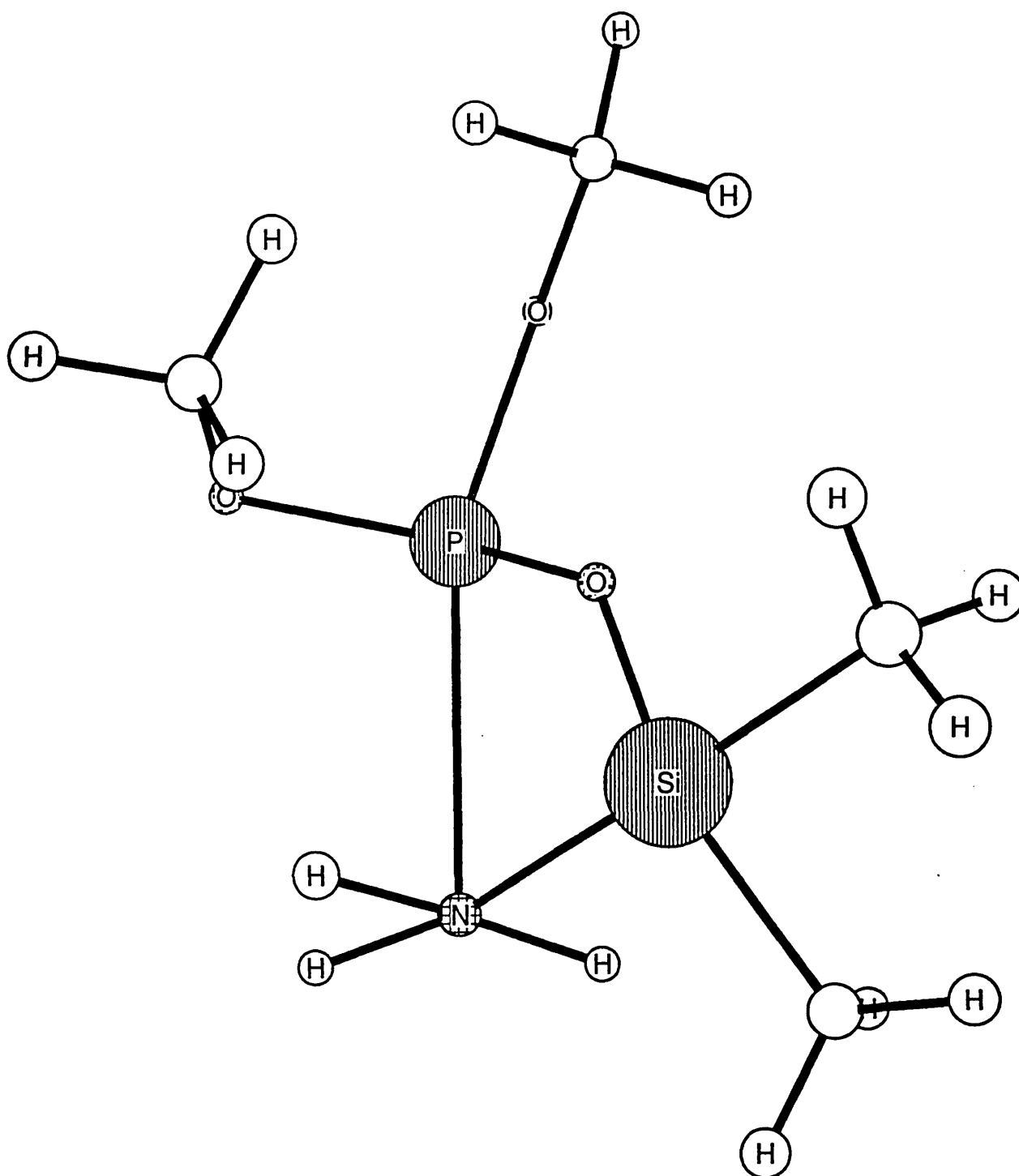
O(1)-P(1)-O(2)	115.3(1)	O(1)-P(1)-C(1)	115.0(1)
O(2)-P(1)-C(1)	99.5(1)	O(1)-P(1)-C(10)	111.6(1)
O(2)-P(1)-C(10)	104.6(1)	C(1)-P(1)-C(10)	109.9(1)
P(1)-O(2)-C(19)	120.9(1)	P(1)-C(1)-N(2)	112.4(1)
P(1)-C(1)-C(16)	113.9(1)	N(2)-C(1)-C(16)	110.8(1)
C(1)-N(2)-C(3)	115.5(1)	N(2)-C(3)-C(4)	112.4(1)
C(3)-C(4)-C(5)	122.2(1)	C(3)-C(4)-C(9)	119.1(2)
C(5)-C(4)-C(9)	118.7(1)	C(4)-C(5)-C(6)	120.1(1)
C(5)-C(6)-C(7)	119.8(2)	C(6)-C(7)-C(8)	120.6(1)
C(7)-C(8)-C(9)	119.7(2)	C(4)-C(9)-C(8)	121.1(2)
P(1)-C(10)-C(11)	120.8(1)	P(1)-C(10)-C(15)	120.0(1)
C(11)-C(10)-C(15)	119.2(1)	C(10)-C(11)-C(12)	120.0(2)
C(11)-C(12)-C(13)	120.0(1)	C(12)-C(13)-C(14)	120.2(1)
C(13)-C(14)-C(15)	120.5(2)	C(10)-C(15)-C(14)	120.1(1)
C(1)-C(16)-C(17)	110.3(1)	C(1)-C(16)-C(18)	113.1(1)
C(17)-C(16)-C(18)	111.1(1)	O(2)-C(19)-C(20)	110.4(2)



Appendix 3

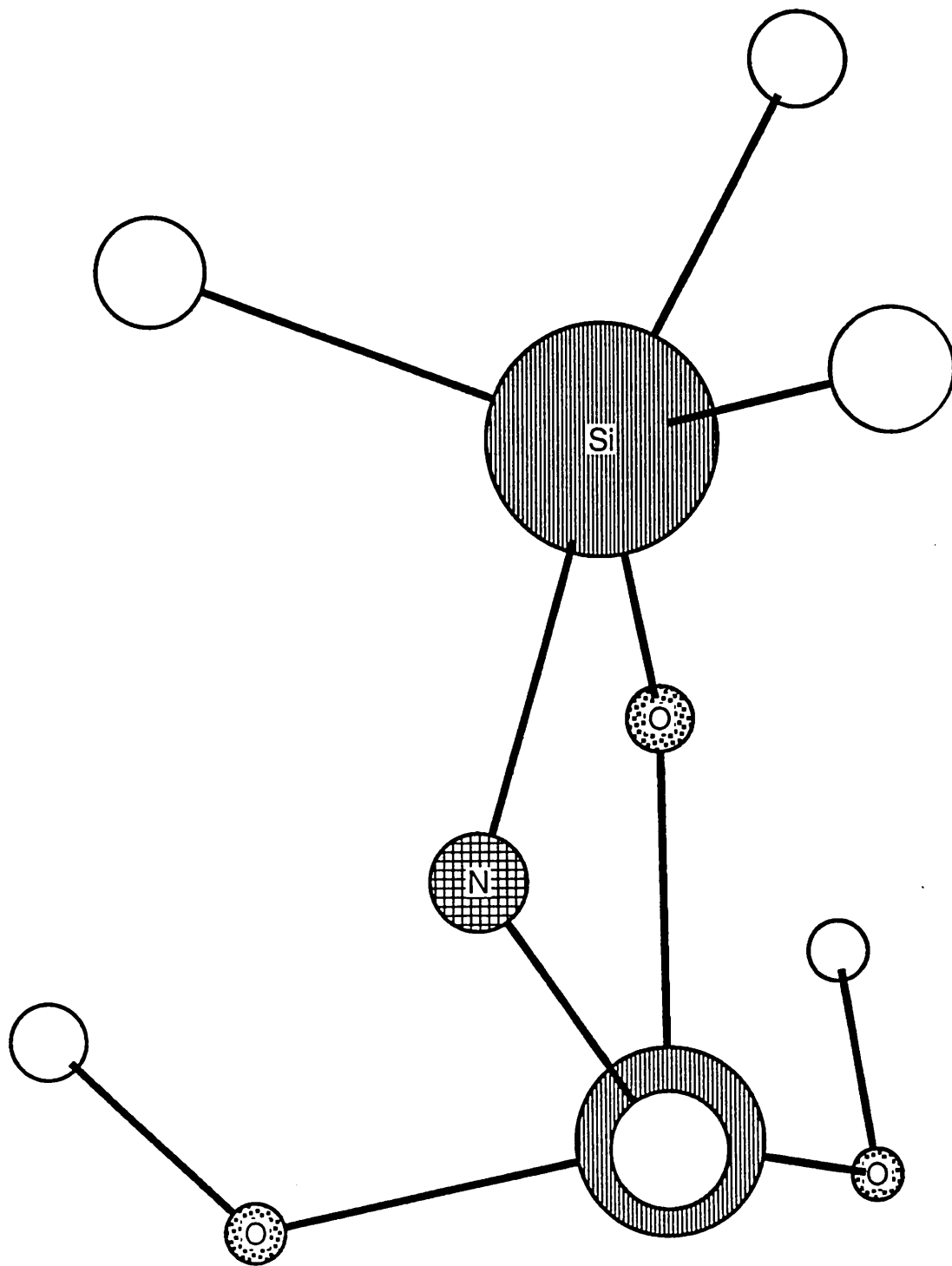
The structure was built on a Tektronix CAChe work-station and minimised using augmented MM2¹⁶⁹ molecular mechanics force fields, with P-C and Si-N distances constrained to 2.40 Å initially. This was then submitted for MOPAC¹⁷⁰ calculation. Geometry was optimised first with bonds constrained as above using precise option and the PM3¹⁷¹ Hamiltonian and the bonds were then optimised with NLLSQ technique. 4000 Cycles were performed on a IBM RS6000 model 530 computer in conjunction with a FPS 146 processor.

In the following pages various "snap-shots" of this transition state are produced.



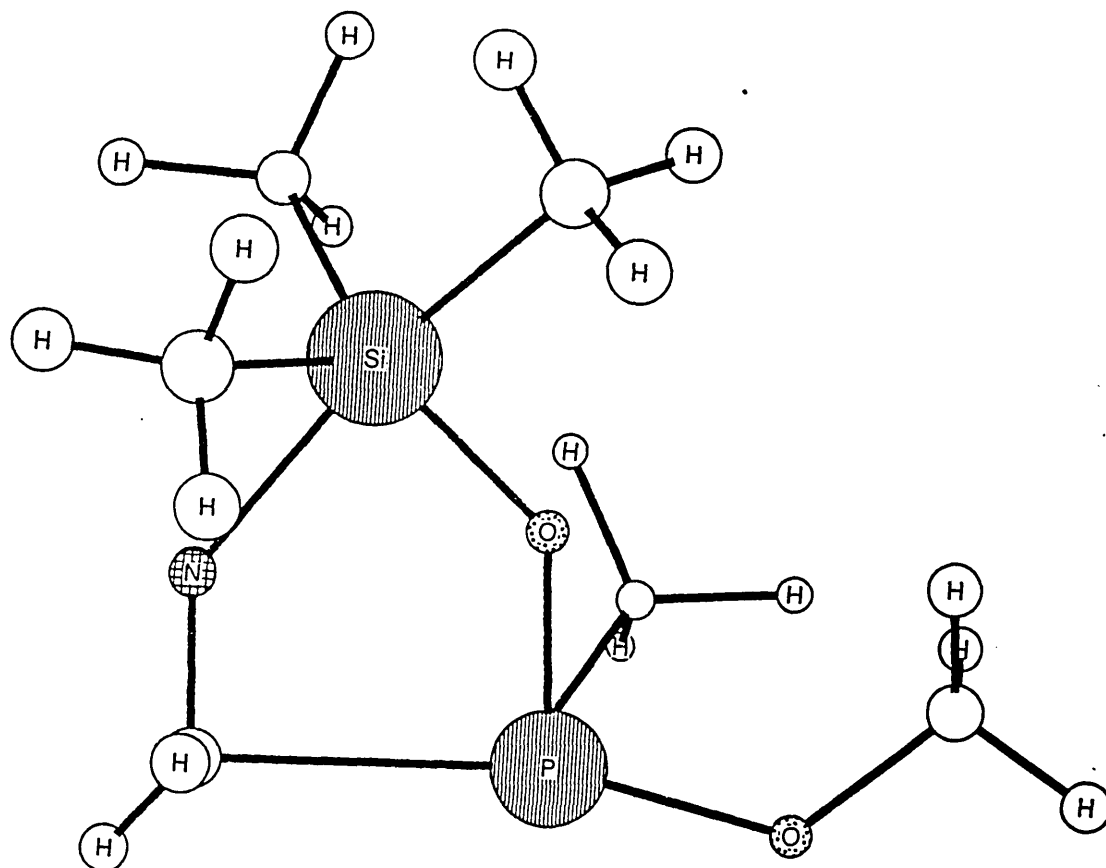
View Alongside the N=C Bond

Carbon atom of the imine bond is covered by the nitrogen atom. One methyl substituent on silicon is omitted.



View Alongside the Partly-Formed P-C Bond

Hydrogen atoms are omitted.



View From the Top of the Transition State

Hydrogen substituent of the nitrogen is covered by this atom.
One of the oxygen substituents of the phosphorus atom is also obscured.

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