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Synthesis of Phosphonates by Nucleophilic Substitution at Phosphorus: The S_N P(V) Reaction.

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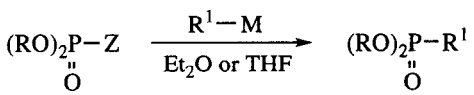
1. Introduction

Historically, the first method for the generation of a carbon-phosphorus bond was described 103 years ago (1897) by Michaelis and Becker.[1] It involved the nucleophilic phosphorylation of a saturated carbon by the salts of dialkylphosphites. One year later Michaelis and Kaehne discovered the nucleophilic phosphorylation of a saturated carbon by reaction of an ester of trivalent phosphorus with an alkyl halide.[2] This latter reaction, the most useful transformation of this type, was explored in depth by Arbuzov[3,4] and is now widely employed for the synthesis of phosphonates. Since 1949, the extensive literature on the Michaelis-Arbuzov reaction has been summarised in several reviews.[5-9] In addition to these two nucleophilic phosphorylation reactions, the addition of trivalent phosphorus to carbonyl groups, under thermal or basic conditions, the Abramov[10-12] and Pudovik[13] reactions, constitutes two other important synthetic procedures for carbon-phosphorus bond formation.

By way of contrast, the use of umpolung[14] (or charge affinity inversion) for generating carbon-phosphorus bonds has only been explored since 1975. The subsequent 25 years have seen tremendous progress in the chemistry of carbanionic displacement reactions at a quinquevalent phosphorus. This approach involves the nucleophilic attack at a relatively electropositive quinquevalent phosphorus center by an anionic species with displacement of a good or moderate leaving group attached to the phosphoryl group. Owing to the synthetic and biological importance of phosphonates, this versatile strategy which allows the introduction of a large variety of phosphorus appendages is especially attractive. The early efforts using organometallics were concerned with control of selective monoalkylation at phosphorus such that substitution of only one of the three substituents occurs. A number of factors which may affect the success of the reaction have been recognised. They include: a) the nature of the nucleophile which can be a stabilised or unstabilised anion, b) the nature and size of the groups attached to the electrophilic phosphorus center, halides, alkoxy or phenoxy function, c) the metal counterion (Li, Mg), d) the solvent (Et_2O, THF), e) the presence or absence of salts or various additives, f) the reaction temperature, and g) the reaction time. However, detailed information in this field is particularly scattered and the purpose of this article is to collect and to examine the evolution of the methodology, thus providing a general overview of the synthetic schemes which have been designed and developed to effect the preparation of phosphonates by nucleophilic substitution at a quinquevalent phosphorus center (S_N P(V) reaction) (Scheme 1). In 1988 a general review, including both trivalent and quinquevalent phosphorus compounds, has appeared summarizing some applications of this reaction and bringing to light the advantages of organometallics for the generation of carbon-phosphorus bonds.[15]



R = alkyl, phenyl
R^1 = alkyl, alkynyl, aryl, heteroaryl
Z = RO, F, Cl
M = Li, Mg

Scheme 1.

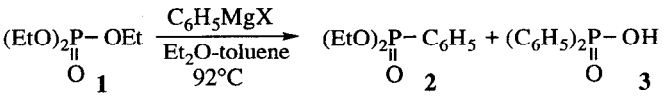
Two distinct periods, "the magnesium period" and "the lithium period", can be distinguished in the generation of carbon-phosphorus bonds by carbanionic displacement reactions at quinquevalent phosphorus centers. From 1929 until around 1960, Grignard reagents were intensively used then progressively replaced by the lithium reagents, which are almost exclusively employed nowadays. This natural division has determined the order of discussion.

2. Reactions of Quinquevalent Phosphorus Esters or Halides with Grignard Reagents

Undoubtedly, Grignard reagents have played an important part in the development of phosphorus chemistry. Numerous results have been recorded on the general topic of nucleophilic displacement reactions at a quinquevalent phosphorus center. Their significance was first covered in reviews in 1957[16] and 1960[17], with the latest reevaluation in 1964.[18a] With the objective of yield optimisation in the synthesis of phosphonates, several investigations have been carried out concerning the effects of reagent concentration, the influence of the leaving group, and the ideal solvent system. However, the major difficulty with Grignard reagents being their high reactivity coupled with low selectivity, their role in the chemistry of phosphonates has remained as one of limited synthetic utility.

2.1. Reactions of Quinquevalent Phosphorus Esters with Grignard Reagents

The preparation of phosphonates *via* the reaction of Grignard reagents with quinquevalent phosphorus esters has seen only limited use. It was quickly recognised that the nature of the leaving group, alkoxy or phenoxy function, the basicity of the nucleophile, and the solvent system were all critical factors for maximum yield of product. Unfortunately, phosphonate syntheses using trialkyl phosphates and Grignard reagents are not selective, and a mixture of compounds containing C-P bonds are generally obtained. A clear illustration of the difficulties of this procedure was provided by the reaction of triethyl phosphate **1** with the phenyl Grignard reagent.[19] At 92°C for 6 h in an Et_2O-toluene mixture, in spite of using a large excess of Grignard reagent, this reaction gave only low yields of diethyl phenylphosphonate **2** (16%) and diphenylphosphinic acid **3** (17%) (Scheme 2).[19]



Scheme 2.

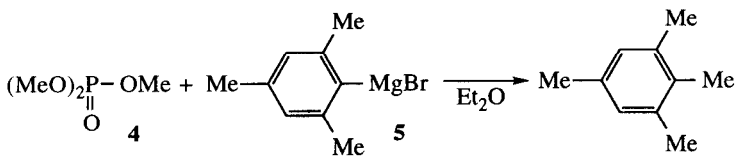
Coordination between the ester and Grignard reagent was suggested to facilitate the nucleophilic attack by the latter at the more electron-deficient phosphorus atom in the complex.[17] For example, if diethyl phenylphosphonate **2** is mixed with $MgBr_2$ prior to addition of the phenylmagnesium bromide, triphenylphosphine oxide **29** could be isolated in 55% yield.[20a] An activated complex was postulated in which the phosphoryl oxygen atom was coordinated with $MgBr_2$. Apparently, through coordination of the oxygen atom, the phosphorus atom of the activated complex becomes more sensitive to nucleophilic attack.[17] The effect of 1 eq. of added magnesium halide on the rate of reaction of phenylmagnesium bromide with diethyl phenylphosphonate **2** was further reinvestigated in THF at 68°C. The isolated yields of triphenylphosphine oxide **29** after 6 h were 55-59% in the absence of magnesium halides and 19-25% in the presence of magnesium

halides. From these results it is readily obvious that, contrary to previous reports, the reaction of diethyl phenylphosphonate with phenylmagnesium bromide is not accelerated but is retarded by the addition of magnesium chloride or bromide.[20b]

Furthermore, displacement of aryloxy groups appears to be facile and total reaction times are shorter than with compounds containing alkoxy groups.[18a] Diphenyl phenylphosphonate in an Et_2O/C_6H_6 solution at 55°C is more receptive to attack by Grignard reagents and yields of greater than 50% of unsymmetrical tertiary phosphine oxides can be obtained. The reactions of a variety of different phosphorus esters with phenylmagnesium bromide were investigated in THF at 68°C. For a structurally similar series of substituted phosphonates the order of reactivity was found to be *p*-ClPhP(O)(OEt)$_2$ > PhP(O)(OEt)$_2$ > *p*-MePhP(O)(OEt)$_2$ > EtP(O)(OEt)$_2$. These results supported the theory that electron-withdrawing substituents increase the susceptibility of the phosphorus atom to nucleophilic attack. On the other hand, in structurally dissimilar phosphorus esters, the order of reactivity was observed to be $Ph_2P(O)OEt$ > PhP(O)(OEt)$_2$ > EtP(O)(OEt)$_2$ > P(O)(OEt)$_3$.[18b]

In further investigations, the reaction of trimethyl phosphate with controlled amount of phenylmagnesium bromide was examined. When trimethyl phosphate was treated with phenylmagnesium bromide in an Et_2O/C_6H_6 solution at 60°C, all products of displacement reaction, namely, dimethyl phenylphosphonate, methyl diphenylphosphinate and triphenylphosphine oxide were not found. Surprisingly, careful investigation of various reaction mixtures have revealed only the presence of methyl diphenylphosphinate and triphenylphosphine oxide **26**. In no case was dimethyl phenylphosphonate detected. The *C*-alkylation product, toluene, was detected in all reaction mixtures.[21a]

Bulky Grignard reagents were shown to direct nucleophilic attack towards the carbon atom rather than to the phosphorus atom in trialkyl phosphates. For example, several relatively hindered Grignard reagents, mesitylmagnesium bromide **5** (Scheme 3) and triphenylmethylmagnesium chloride, were treated with trimethyl phosphate **4** in Et_2O. In both cases tested, nucleophilic attack on carbon atom occured to give the alkylation products with quite satisfactory yields (39.1% and 77% respectively).[21b]



4 5

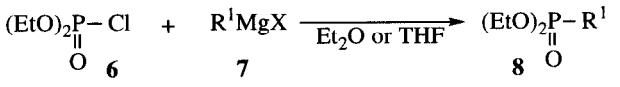
Scheme 3.

Steric hindrance to approach of the Grignard reagent provides an explanation for the chemoselective attack on carbon rather than phosphorus. Moreover, the steric requirements and reactivity of the trialkyl phosphate esters also appear to be important, since tributylphosphate fails to react with the mesitylmagnesium bromide **5** in Et_2O.[21b]

2.2. Reactions of Quinquevalent Phosphorus Halides with Grignard Reagents

Since the quinquevalent phosphorus ester route requires forcing conditions which are incompatible with the selective production of phosphonates in good yields, this technique has largely been supplanted in subsequent years by the dialkyl chlorophosphate route. Dialkyl chlorophosphates, and especially diethyl chlorophosphate **6** which is a commercially available starting material, were frequently employed with success in the synthesis of

aryl-, heteroaryl- and alkynylphosphonates. Historically, the most common and perhaps most generally available reagents which have been developed for the nucleophilic alkylation of chlorophosphates were Grignard reagents (Scheme 4).[22]



R^1 = aryl, heteroaryl, alkynyl, ...

Scheme 4.

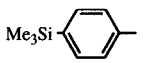
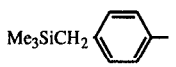
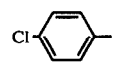
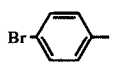
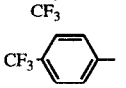
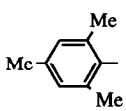
The initial procedure for the synthesis of phosphonates **8** was based upon the normal addition of the diethyl chlorophosphate **6** to a solution of an aryl Grignard reagent **7** (1 or 2 eq.) in Et_2O. This technique appeared to have limited synthetic potential and, owing to competitive displacement of the ester groups, it was generally difficult to prepare selectively diethyl arylphosphonates in high yields, free of side-products. In the absence of an *ortho*-substituent, the normal addition of diethyl chlorophosphate **6** to an arylmagnesium halide **7** caused a reaction which could not be stopped before the triarylphosphine oxide stage was reached. For example, phenylmagnesium bromide **10b** and diethyl chlorophosphate **6** furnished triphenylphosphine oxide. The corresponding aromatic phosphine oxides were obtained in similar fashion from *p*-chlorophenyl-, *p*-tolyl-, *p*-biphenyl-, 2-thienyl- and 2-naphthylmagnesium bromide. It was possible to obtain good yields of the phosphonates **8** only with *ortho*-substituted aryl Grignard reagents.[22]

Finally, it had been shown that diethyl arylphosphonates may be prepared from sterically unhindered arylmagnesium halides using an "inverse" addition. For example, the slow addition of a dilute solution of phenylmagnesium bromide **10b** or its *p*-chloro derivative to a solution of diethyl chlorophosphate **6** in refluxing Et_2O in a 1/1 ratio limits the reaction mainly to the formation of diethyl arylphosphonates by selective displacement of the chloride ion.[22] This bears out the prediction that the ester groups of a dialkyl chlorophosphate have a lower affinity to Grignard reagents than that shown by its chlorine atom. At present, the reverse addition of the Grignard reagent to a dialkyl chlorophosphate is generally preferred for minimisation of side reactions in the preparation of phosphonates.

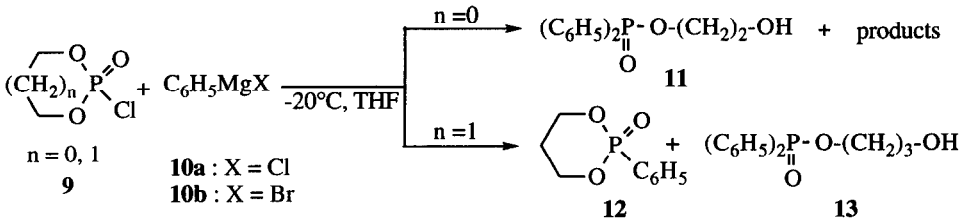
Despite the limited number of investigations, it has been reported that the ester groups of dialkyl (Et, *i*-Pr, *cyclo*-C_6H_{11}) and diaryl fluorophosphates are stable to attack by Grignard reagents, and only the fluorine atom is replaced. The stability of the ester groups in fluorophosphates obviates the necessity for reverse addition, providing a convenient and efficient method with markedly improved results over those obtained with chlorophosphates. However, the synthetic utility of these (toxic) phosphorus reagents remains to be confirmed.[23]

Although acyclic phosphoryl chlorides such as diethyl chlorophosphate **6** are frequently employed in the preparation of phosphonates **8** as exemplified by Scheme 4, displacement reactions using the more reactive cyclic (six- and five-membered ring) phosphoryl chlorides **9** are seldom utilised. The attack at such a phosphorus center by phenylmagnesium bromide **10b** (1, 2 or 3 eq.) is difficult to control and gives, according to the ring size (n value), either the corresponding phenylphosphonate **12** accompanied by some 3-hydroxypropyl diphenylphosphinate **13** (n=1) or a mixture of products from which the 2-hydroxyethyl diphenylphosphinate **11** (n=0) may be isolated (Scheme 5).[24]

Table 1. Synthesis of Diethyl Aryl- and Heteroarylphosphonates.

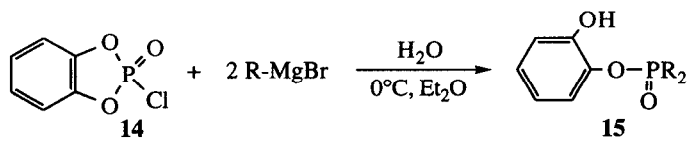
8	R^1	X	Solvent	Yield (%)	Ref.
		Cl	THF	51[a]	24
a		Br	Et_2O	40.5[a]	22
		Br	Et_2O	28[a]	24
b		Br	Et_2O	50.4[a]	22
c		Cl	THF/Et_2O	60[a]	27
d		Cl	THF/Et_2O	60[a]	27
e		Cl	THF/Et_2O	56[a]	28
f		Cl	THF/Et_2O	36[a]	28
g		Br	Et_2O	45[a]	26
h		Br	Et_2O	48[a]	22
i		Br	Et_2O	24[a]	26
		Br	THF	47[a]	29
j		Br	Et_2O	60[a]	30
k		Br	Et_2O	93[a]	30,31
l		Br	Et_2O	31[a]	30
m		Br	THF	41[a]	33
n		I	Et_2O	27.6[b]	32
o		Br	Et_2O	80[a] 75.4[b]	32

[a] Using diethyl chlorophosphate **6**; [b] Using diphenyl chlorophosphate.



Scheme 5.

Similarly, the strain energy present in the five-membered ring of 2-chloro-1,3,2-benzodioxaphosphole-2-oxide **14** has been exploited in ring-opening by both alkyl and aryl Grignard reagents (2 eq.). Only 2-hydroxyphenyl dialkyl- or diarylphosphinates **15** are formed by attack at the phosphorus center (Scheme 6).[25]



R = *n*-Bu, *c*-C_6H_{11}, C_6H_5, 4-$MeOC_6H_4$, mesityl, 1-naphthyl, 2-thienyl...

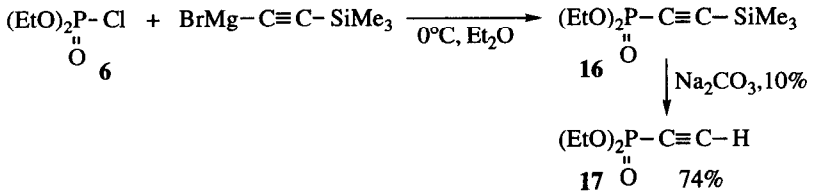
Scheme 6.

Together with its modification, the conversion of diethyl chlorophosphate **6** to phosphonates **8** by Grignard reagents (Scheme 4) is a useful transformation available for the preparation of *o*-, *m*-, and *p*-substituted aryl- and heteroarylphosphonates. Aryl- or heteroarylmagnesium chlorides or bromides **7** can be used and Et_2O is preferred as the reaction solvent. The Grignard reagent **7** is generally added to an ice-cooled Et_2O solution of chlorophosphate (diethyl or diphenyl) or less frequently at lower temperature, with the reagents being in a 1/1 ratio. It presently appears that the dihalobenzene compounds may not be useful for the selective preparation of monomagnesium derivatives by reaction with 1 eq. of magnesium metal.[26] Effectively, only low to moderate yields of the corresponding phosphonates **8** were obtained in that cases (24% for the Grignard from 1,4-dibromobenzene and 45% for the Grignard from 3-bromochlorobenzene) indicating that dihalobenzenes do not survive the reaction conditions necessary for the formation of the monomagnesium derivative and they are particularly prone to form dimagnesium derivatives.[26] Finally, a diverse assortment of *o*-, *m*- and *p*-substituted aryl- and heteroarylphosphonates **8** have been prepared in moderate to excellent yields (24-96%).[22,26-33] The main results are collected in Table 1.

2.3. Reactions of Quinquevalent Phosphorus Halides with Alkynylmagnesiums

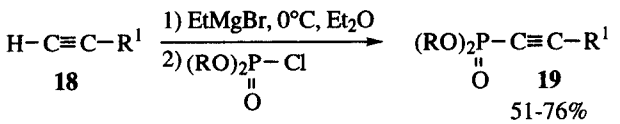
Since metallated terminal acetylenes have been frequently used as acyl anion equivalents, it was of particular interest to develop an efficient preparation of dialkyl 1-alkynylphosphonates **19**. For example, the 1-alkynylphosphonates **19** formed upon reaction of a chlorophosphate with either substituted or unsubstituted acetylenide ions may be readily converted into 2-oxoalkylphosphonates by subsequent hydration. This useful transformation has stimulated a number of publications in the past.[164] Dialkyl ethynylphosphonates were prepared for the first time in 1960 by the reverse addition of ethynylmagnesium bromide in THF to the appropriate dialkyl chlorophosphate in a 1/1 ratio.[34] Unfortunately, the reaction gave very low product yields (12

to 25%),[34,35] presumably arising from side reactions involving the relatively acidic alkynyl proton. The yields can be increased slightly (25 to 35%) by the use of (toxic) dialkyl fluorophosphates.[36] Diethyl ethynylphosphonate **17** was most easily prepared by reaction of trimethylsilylethyne with methylmagnesium bromide in Et_2O,[37] followed by addition to a solution of diethyl chlorophosphate **6**.[38] The resulting diethyl trimethylsilylethynylphosphonate **16** was then deprotected by hydrolysis with 10% Na_2CO_3 to give the parent diethyl ethynylphosphonate **17** in good overall yield of 74% (Scheme 7).[38]



Scheme 7.

The extension of this methodology to higher homologues **19** of diethyl ethynylphosphonate **17** gave superior results.[39] They were readily obtained from dialkyl or diphenyl chlorophosphates and the appropriate terminal alkynylmagnesium bromide, which was prepared in turn from the alkyne **18** and ethylmagnesium bromide in Et_2O (Scheme 8). All of these reactions were carried out at 0°C in Et_2O, and the chloride ion was more easily displaced than either the alkoxide or the phenoxide ion. This approach gave moderate[40] to good yields (51 to 76%) of the desired dialkyl 1-alkynylphosphonates **19** (Table 2).[39]



R = Me, Et, C_6H_5

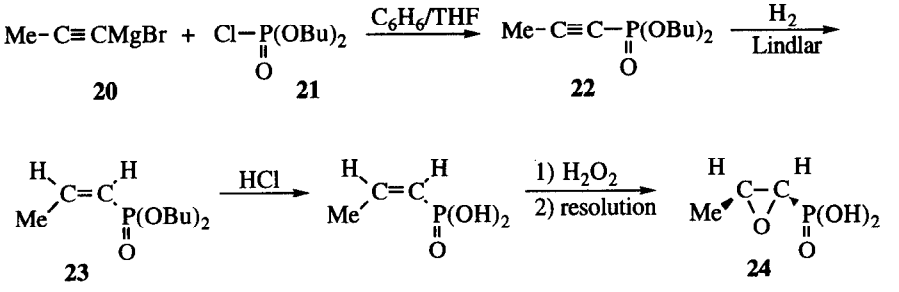
R^1 = *n*-Pr, *n*-Bu, *n*-Hex, C_6H_5, C_5H_9, C_6H_{11}, ...

Scheme 8.

Table 2.[39] Synthesis of Dialkyl 1-Alkynylphosphonates.

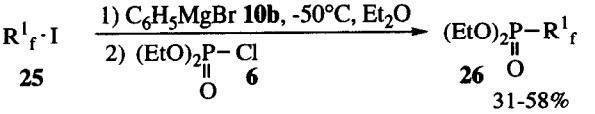
19	R	R^1	Yield (%)	19	R	R^1	Yield (%)
a	Me	*n*-Pr	57	**f**	Et	C_6H_5	53
b	Et	Me	76	**g**	Et	$C_6H_5(CH_2)_2$	60
c	Et	*n*-Pr	59	**h**	Et	*c*-C_6H_{11}	51
d	Et	*n*-Bu	64	**i**	Et	*c*-C_5H_9	70
e	Et	*n*-Hex	52	**k**	C_6H_5	Me	74

The first racemic synthesis of the antibiotic fosfomycin **24** in 1969 was based on the stereospecific reduction, of dibutyl 1-propynylphosphonate **22** into dibutyl (*Z*)-1-propenylphosphonate **23** with Lindlar catalyst. The preparation of **22** was effectively achieved by reaction of the propynylmagnesium bromide **20** with dibutyl chlorophosphate **21** in a C_6H_6/THF solution (Scheme 9).[41]



Scheme 9.

The preparation of perfluoroalkylphosphonates **26** uses perfluoroalkyl Grignard reagents generated from the exchange reaction between perfluoroalkyl iodides **25** and phenylmagnesium bromide **10b**. The addition of diethyl chlorophosphate **6** to perfluoroalkyl Grignard reagents was carried out in Et_2O at -50°C to give moderate yields (31 to 58%) of diethyl perfluoroalkylphosphonates **26** (Scheme 10).[42]



Scheme 10.

3. Reactions of Quinquevalent Phosphorus Esters with Lithiated Reagents

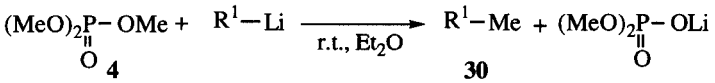
Organolithium compounds are known to behave as more effective carbanions than their corresponding Grignard counterparts. The routine use of these reagents in phosphorus chemistry has completely transformed and diversified phosphonate chemistry resulting in the development of a methodology which has enormously extended the synthetic utility of these reagents. It might be expected that lithium reagents add readily and smoothly to quinquevalent phosphorus compounds at low temperature in a clean and selective manner, thus avoiding or minimizing the problems associated with the obtention a of series of compounds (all in low yield) due to uncomplete or indesired side reactions. Because of these advantages, the electrophilic chemistry of phosphonates extends the nucleophilic route and often succeeds better.

3.1. with Aryllithiums and Bulky Alkyllithiums

In 1957, it was reported that when a tertiary phosphate ester **27** was merely treated with C_6H_5Li **28**, all three alkoxy groups were displaced to give triphenylphosphine oxide **29** in high yield (85%) (Scheme 11).[43] These preliminary observations indicated that aryllithium compounds were more effective than the corresponding Grignard reagents for the replacement of alkoxy by aryl groups in tertiary phosphate esters, but also implied that the reaction appears to be uncontrollable and inappropriate for the synthesis of phosphonates.

Scheme 11.

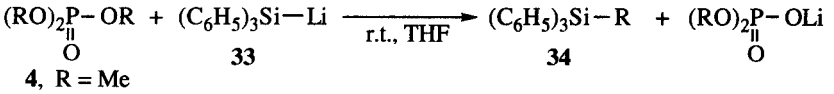
With bulky lithium compounds, alkylation on carbon occurs rather than displacement of an alkoxy group from a trialkyl phosphate. Thus trimethyl phosphate **4**, when treated in Et_2O at room temperature with triphenylmethyllithium, diphenylmethyllithium or 9-phenyl-9-fluorenyllithium in a 1/1 mole ratio, gave the corresponding alkylation products **30** in yields of 77, 88 and 80.5%, respectively (Scheme 12).[21]



$R^1 = (C_6H_5)_3C$, $(C_6H_5)_2CH$, 9-phenyl-9-fluorenyl

Scheme 12.

Similarly, triphenylsilyllithium compounds **33** in THF reacted smoothly and promptly with trimethyl- **4**, tributyl- **31** and tri-*iso*-butyl phosphate **32** in a 1/1 ratio to give the corresponding triphenylalkylsilanes **34** in good to excellent yield (87 to 97%) (Scheme 13).[44]



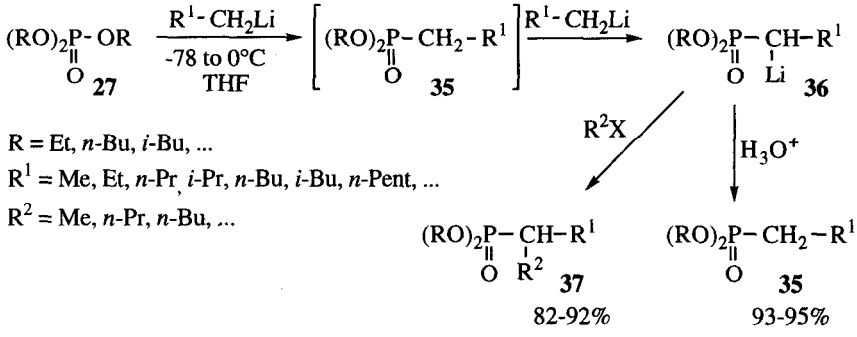
4, R = Me
31, R = *n*-Bu
32, R = *i*-Bu

Scheme 13.

Thus, when the organometallic compound is sufficiently hindered, the large size of the anion precludes attack at the phosphorus atom and the alkylation reaction occurs. In all cases, alkylation reaction is limited to the removal of only one alkyl group from the trialkyl phosphate.

3.2. with Primary Alkyllithiums

Perhaps the most useful transformation involving a trialkyl phosphate **27** and an organolithium reagent is the phosphate-phosphonate conversion which was described in 1987.[45] A relatively general procedure for the conversion of trialkyl phosphates **27** to dialkyl phosphonates **35** using primary alkyllithiums has been developed. This sequence was initiated by the addition at low temperature of a trialkyl phosphate (1 eq.) **27** to a primary alkyllithium in excess (2 eq.) to give on warming, the dialkyl 1-lithioalkylphosphonate **36**. The sequence involves attack of the alkyllithium at the phosphorus center with expulsion of an alkoxide group, followed by deprotonation of the resultant phosphonate **35** in the α position. The reaction is easily controlled by formation of the α-metallated phosphonate **36** such that displacement of only one of the three alkoxide groups occurs. The neutral phosphonate **35** was never observed in the reaction mixture. The overall transformation was rapid, complete and clean. On warming, the dialkyl 1-lithioalkylphosphonate **36** was the only species present in the reaction mixture (Scheme 14).[45,46]



Scheme 14.

The phosphate-phosphonate conversion is salt dependent and the attack at the phosphoryl group is retarded by the presence of lithium salts, especially LiBr, which can be present in ethereal solutions of organolithium reagents. The salt effect is particularly marked with the use of MeLi,[47] whose lower reactivity is probably a consequence of the polymeric nature of the reagent. Although alkyllithiums containing lithium salts do display a lower reactivity than the salt-free alkyllithiums under the same conditions, they are still suitable reagents for the phosphate-phosphonate transformation. The transformation has been applied to different trialkyl phosphates **27** and triethyl-**1**, tributyl- **31** and tri-*iso*-butyl phosphates **32** were specifically and quantitatively converted into the parent phosphonates **35** when treated with two equivalents of primary alkyllithiums. In marked contrast, trimethyl phosphate **4** behave mainly as an alkylating agent. Several primary alkyllithium reagents were employed with the same efficiency : MeLi, EtLi, *n*-PrLi, *n*-BuLi, *i*-BuLi, *n*-$C_5H_{11}Li$, *i*-$C_5H_{11}Li$, *n*-$C_6H_{13}Li$, etc.[48]

One of the major advantages of this procedure is the opportunity either for protonation or for further alkylation of the dialkyl 1-lithioalkylphosphonates **36** to give linear or branched dialkyl alkylphosphonates respectively. Thus the lithiated products **36**, when treated in acidic medium provide linear phosphonates **35** (Table 3)[48] and when alkylated produce the branched phosphonates **37** (Table 4).[48] All of these reactions have been performed on a large scale with excellent yields (82 to 95%).

Table 3.[48] Synthesis of Linear Dialkyl Alkylphosphonates.

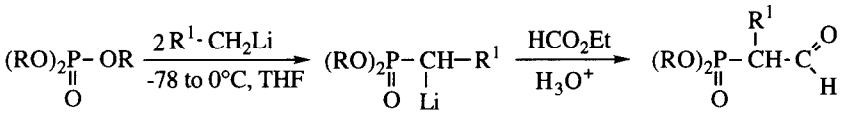
35	R	R^1	Yield (%)
a	Et	Me	95
b	Et	Et	94
c	Et	*i*-Pr	93
d	Et	*n*-Pr	94
e	Et	*i*-Bu	95
f	Et	*n*-Bu	93
g	Et	*n*-Pent	93
h	*n*-Bu	*n*-Pr	94
i	*i*-Bu	*n*-Pr	93

In addition to this methodology for simple nucleophilic alkylation, the phosphoryl carbanions **36** can also react with other electrophiles to produce variously functionalised phosphonates.[49] For example, alkylation of a trialkyl

phosphate **27** at low temperature with a primary alkyllithium followed by addition of ethylformate affords the useful dialkyl 1-formylalkylphosphonates **38** in high yields (45 to 94%) (Scheme 15).[45,50]

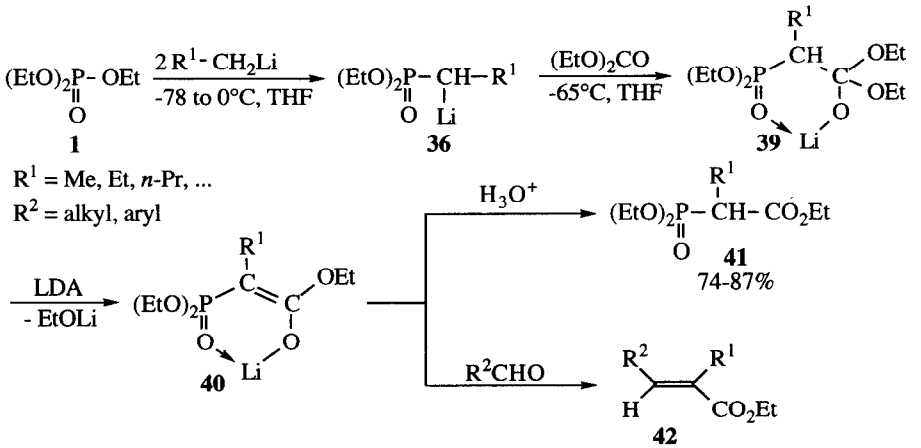
Table 4.[48] Synthesis of Branched Dialkyl Alkylphosphonates.

37	R	R^1	R^2	Yield (%)
a	Et	Me	Me	91
b	Et	Et	Me	89
c	Et	*i*-Pr	Me	92
d	Et	*n*-Pr	Me	88
e	Et	*n*-Pr	*n*-Pr	84
f	Et	*i*-Bu	Me	87
g	Et	*n*-Bu	Me	89
h	Et	*n*-Bu	*n*-Bu	83
i	Et	*n*-Pent	Me	87
j	Et	n-C_7H_{15}	Me	82
k	*n*-Bu	*n*-Pr	Me	87
l	*i*-Bu	*n*-Pr	Me	89



Scheme 15.

The phosphate-phosphonate conversion also offers a useful synthetic route to substituted triethyl phosphonoacetates **41** bearing larger or uncommon R^1 substituents which are not available *via* the Michaelis-Arbuzov reaction.

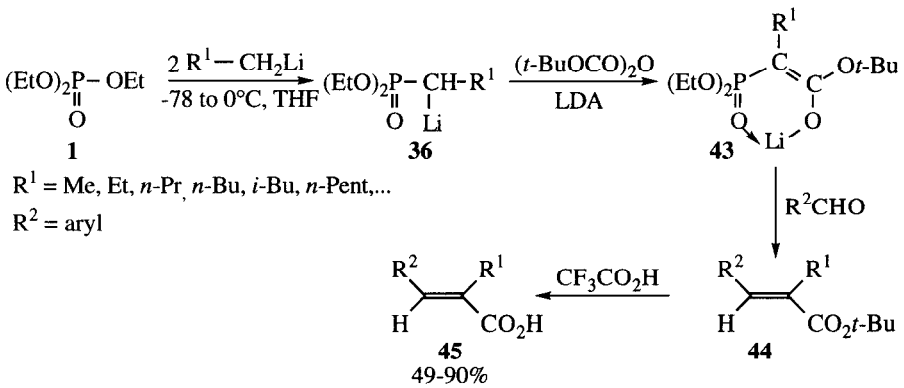


Scheme 16.

Thus, addition of diethyl carbonate to diethyl 1-lithioalkylphosphonates **36**, followed by acidic hydrolysis of the resulting enolate **40** provides a convenient and high yielding route (74 to 87%) to substituted triethyl phosphonoacetates **41** (Scheme 16).[51]

The phosphate-phosphonate conversion can, of course, successfully participate in several useful olefination reactions with carbonyl compounds. Thus, treatment of triethyl phosphate **1** with primary alkyllithiums (2 eq.) at low temperature followed by reaction with diethyl carbonate at -65°C proceeded as mentioned above to give an unstable intermediate **39** which undergoes spontaneous elimination of lithium ethoxide to produce the triethyl phosphonoacetates **41**. In the presence of a base (LDA, 1 eq.), there is concomitant generation of the enolate anion **40** which reacts readily at 0°C with aromatic or aliphatic aldehydes to provide good yields of synthetically useful α-substituted acrylic esters **42** as (*E*) isomers (Scheme 16).[51] Alternatively, the diethyl 1-lithioalkylphosphonates **36** may be treated with BOC-F or DIBOC to produce the enolate **43**. On reaction with a variety of aromatic aldehydes, **43** afforded the protected α-substituted acrylates **44** which can be converted into their corresponding α-substituted acrylic acids **45** by acid-catalysed hydrolysis with trifluoroacetic acid (Scheme 17)[52]. The overall yields obtained by these two procedures with a variety of aldehydes were good to excellent (64 to 95%, Table 5).[52]

These two multi-step procedures are applicable for the construction of a variety of α,β-unsaturated-α-substituted esters **42** (Scheme 16)[51] or acids **45** (Scheme 17),[52] with each of the steps in these reaction sequences being executed in one-pot without isolation of any of intermediates.



Scheme 17.

These two one-pot procedures for the formation of α,β-unsaturated-α-substituted esters **42** or acids **45** are clear illustrations of the synthetic utility provided by the phosphate-phosphonate sequence which may become more widely employed.

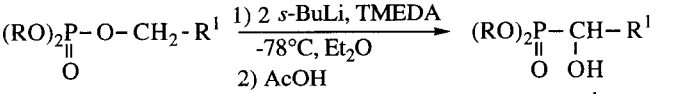
Unfortunately, the phosphate-phosphonate conversion appears to be limited to the use of acyclic trialkyl phosphates **27** since cyclic phosphoryl esters were particularly prone to the complication of ring opening. The addition of 2-ethoxy-, 2-thioethyl- or 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane to *n*-BuLi (2 eq.) at low temperature in THF did not give a clean, single reaction. Although the results do depend on the nature of the leaving group (EtO, EtS, Cl), the formation of mixtures, in which the expected phosphorylated carbanion was present, was always observed.[53]

Table 5.[52] Synthesis of α-Substituted Acrylic Acids.

45	R^1	R^2	Yield (%)
a	Me	C_6H_5	81
b	Me	4-MeO-C_6H_4	75
c	Me	4,5-(OCH_2O)-C_6H_3	90
d	Et	C_6H_5	60
e	Et	4-Me-C_6H_4	66
f	*n*-Pr	C_6H_5	77
g	*n*-Pr	4-Me-C_6H_4	68
h	*n*-Bu	C_6H_5	58
i	*n*-Bu	4,5-(OCH_2O)-C_6H_3	49
j	*i*-Bu	C_6H_5	81
k	*n*-Pent	C_6H_5	66

3.3. with Secondary Alkyllithiums

Recently, the deprotonation of symmetrical trialkyl phosphates derived from primary alcohols by secondary alkyllithiums has been investigated (Scheme 18).[54] The first phosphate subjected to deprotonation was triethyl phosphate **1**, which was treated with *s*-BuLi (2 eq.)/TMEDA in Et_2O at low temperature for 3h. Work-up gave a crude product containing almost exclusively the desired diethyl α-hydroxyethylphosphonate **47** which was isolated in 41% yield. Similarly, the tripropyl phosphate **46** was rearranged under the same conditions to give the dipropyl α-hydroxypropylphosphonate **48** in 66% yield. However, tributyl phosphate **31** furnished the isomeric phosphonate **49** in 53% yield contaminated with 30% of starting material **31**. The best result (55%) was obtained in THF as solvent and no starting phosphate **31** could be detected in the crude product.[54]



1, R=Et, R^1=Me — **47**, R=Et, R^1=Me
46, R=*n*-Pr, R^1=Et — **48**, R=*n*-Pr, R^1=Et
31, R=*n*-Bu, R^1=*n*-Pr — **49**, R=*n*-Bu, R^1=*n*-Pr

Scheme 18.

These results indicate that trialkyl phosphates derived from primary alcohols can be deprotonated in Et_2O or THF at -78°C using *s*-BuLi in combination with TMEDA to give the phosphoryloxy substituted carbanions which probably isomerised to α-hydroxyalkylphosphonates (*vide infra*, Chapter 5, Scheme 48).[54] As expected, there was no displacement of an alkoxy group from the trialkyl phosphate by the hindered secondary alkyllithium. The first reaction step was the complexation of lithium to the oxygen of the P=O function,[55] thus inductively increasing the electrophilicity of the phosphorus and the acidity of the hydrogen atoms on the carbon α to oxygen. Furthermore, the complexation of lithium to the oxygen atom of the P=O function may well have increased the basicity of the lithium reagent and hence favoured deprotonation.

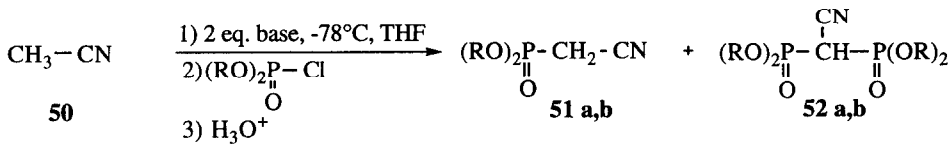
4. Reactions of Dialkyl Chlorophosphates with Lithiated Reagents

In addition to the preceding method, and perhaps the most powerful transformation of this type, there is the preparation of phosphonate reagents by nucleophilic substitution-functionalization of dialkyl chlorophosphates in the presence of a base (LDA or LiHMDS). The application of this technique is of significant synthetic importance for generating the lithiated phosphonate coupling-partners used in olefination reactions. Each step of these reaction sequences may be executed in one-pot without the isolation of intermediates.

4.1. with α-Lithiated Nitriles

The first route to dialkyl cyanoalkylphosphonates based on the nucleophilic attack at a phosphoryl chloride by a metallated acetonitrile and higher homologues was described in 1975.[56] It was the first example of a general strategy for the phosphorylation of a functional group through the intermediacy of an appropriate metallated partner and perhaps the most useful approach for the olefination of carbonyl compounds by the Horner-Wadsworth-Emmons reaction.

The α-cyano carbanions were quantitatively generated on large scale in THF at low temperature by action of strong bases (*n*-BuLi or LDA) on acetonitrile or other aliphatic nitriles, and reacted with bis(dimethylamino) chlorophosphate to give the corresponding cyanoalkylphosphonates in high yields (Scheme 20).[57] In the optimum situation, the method requires the use of two equivalents of base per equivalent of nitrile to guarantee the success of the reaction.[58] The first equivalent effects the deprotonation of the nitrile to give the derived anion which attacks the phosphoryl chloride to produce the desired cyanoalkylphosphonate. The phosphonate product, being more acidic than the starting nitrile, owing to the presence of the phosphoryl group, then undergoes deprotonation by the second equivalent of base to provide finally the dialkyl 1-lithio-1-cyanoalkylphosphonate **54**.[57] Recent improvements in this synthetic procedure have shown that lithiation of nitriles is dependent upon the nature of the lithium reagent.[59] In contrast to previously reported results using LDA (2 eq.) as base with acetonitrile **50**,[60-62] the LiHMDS (2 eq.) was found to be the preferred reagent in terms of giving the best yields of dialkyl cyanomethylphosphonate **51**.[59] LDA generates side reactions resulting in the competitive formation of dialkyl cyanomethylenediphosphonate **52** (Scheme 19).[59]



$(RO)_2 = (EtO)_2$, **a**;  **b**

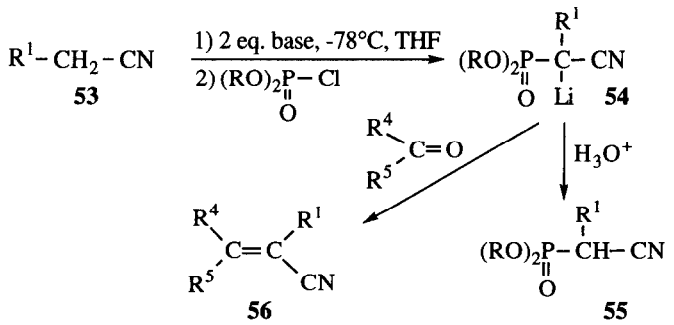
LDA :	65%	35%
LiHMDS :	100%	0%

Scheme 19.

In marked contrast, when the carbanions of higher nitriles are generated with LDA (2 eq.), the more sterically hindered lithium derivatives of cyanoalkylphosphonates **54** are obtained in high yields and without trace amounts of by-products.[59-62] LiHMDS, being not sufficiently basic, is not recommended for the metallation of higher homologues **53** of acetonitrile.[59] The dialkyl cyanoalkylphosphonates **55** were isolated in good to excellent

yields (47 to 95%) after mild acidic work-up of the solution.[56,57,59-62] By judicious variation of the nitriles and the phosphorus halides, this convenient, one-pot procedure is advantageous for the construction of dialkyl cyanoalkylphosphonates bearing widely varied alkyl appendages at phosphorus and in the α-position to phosphorus (Scheme 20). When the α-cyano carbanion was generated in the presence of only one equivalent of base, on addition of the chlorophosphate the phosphonate product liberates free nitrile, which then reacts with the α-cyano carbanion to give either self-condensation or quenching of the reaction.[58]

An added and valuable advantage found in this attractive and mild approach to dialkyl cyanoalkylphosphonates **55** is that this method generates quantitatively and *in situ* the dialkyl 1-lithio-1-cyanoalkylphosphonates intermediates **54**, which are useful precursors to α,β-unsaturated nitriles **56** (Horner-Wadsworth-Emmons reaction[63]) (Scheme 20).[64-71] In general, they undergo reactions with both aldehydes or ketones to give the corresponding α-substituted ($R^1 \neq H$) or nonsubstituted ($R^1 = H$) α,β-unsaturated nitriles **56**, the yields being somewhat higher for aldehydes. The reported olefination reactions are not highly stereoselective and mixtures of (*E*) and (*Z*) isomers are frequently obtained from which the predominant (*E*) isomer is isolated by column chromatography. While some described procedures involve the isolation of the dialkyl cyanoalkylphosphonates **55** prior to olefination,[62,71] most of the reaction sequences are executed in one-pot without the isolation of intermediates.[64-68]



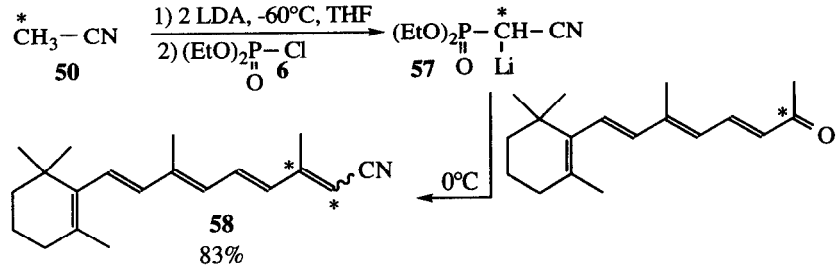
base = *n*-BuLi, LDA, LiHMDS

RO = EtO, Me_2N

R^1 = H, Me, Et, $CH_2CH{=}CH_2$, CH_2OMe, $(CH_2)_2C(OMe)_2$, $(CH_2)_4CN$, $(CH_2)_5CN$, C_6H_5, ...

Scheme 20.

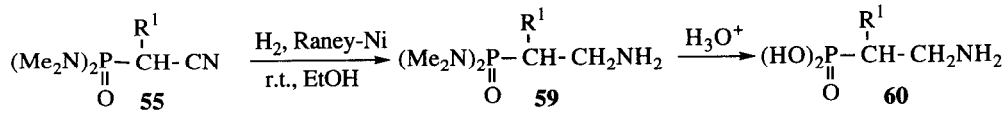
Perhaps the most useful illustration of this technique is the development of a synthetic programme around chemically modified retinals.[64-68] Several innovations have significantly extended the scope and utility of the process. A great variety of cyanophosphonate synthons were prepared in their deprotonated form from the corresponding nitriles and diethyl chlorophosphate **6** at -60°C in the presence of LDA (2 eq.).[64,66,67] Moreover, an interesting variant of the procedure has been described for the preparation of specifically enriched retinal **58** using the anion of (2-^{13}C) diethyl cyanomethylphosphonate **57**, itself effectively obtained from (2-^{13}C) labeled acetonitrile **50**, diethyl chlorophosphate **6** and LDA (2 eq.) (Scheme 21).[65] Based on the same method, during the synthesis of (+)-cleomeolide, the phosphoryl group was introduced in preparation for macrocyclization *via* the condensation of an α-cyano carbanion with the diethyl chlorophosphate **6** (86%).[69,70]



Scheme 21.

A recently reported synthesis of β-carotene and retinoid derivatives involved the use of acetonitrile **50** labelled with (1-^{14}C). This one was prepared from sodium cyanide ^{14}C and dimethyl sulfate, then reacted in Et_2O at -60°C with diethyl chlorophosphate **6** (1 eq.) in the presence of LDA (1.35 eq.).[71]

The bis(dimethylamino)cyanoalkylphosphonates **55** were also precursors of great synthetic utility for the preparation of aminoalkylphosphonic acids **60**. Once the bis(dimethylamino)cyanoalkylphosphonates **55** are in hand, they may be easily converted to bis(dimethylamino)aminoalkylphosphonates **59** by hydrogenation using Raney-Ni as catalyst and then hydrolysed with 6N HCl to produce β-aminoalkylphosphonic acids **60** (Scheme 22).[57]

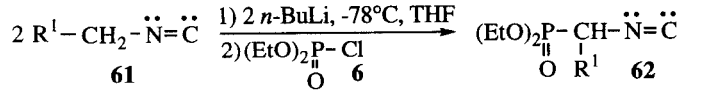


R^1 = H, Me, Et, *n*-Bu, $C_6H_5CH_2$, ...

Scheme 22.

4.2. with α-Lithiated Isonitriles

The diethyl isocyanomethyl- and isocyanobenzylphosphonates **62** have been respectively prepared by condensation of the corresponding lithiated α-isonitrile carbanions with diethyl chlorophosphate **6** in THF at low temperature (Scheme 23).[72] The presence of α-isonitrile carbanions in excess (2 eq.) was crucial to the success of the reactions, in order to achieve complete consumption of the chlorophosphate **6** and to promote the deprotonation of the isocyanophosphonate products **62**. The isocyanophosphonates **62** may be metallated to give the corresponding carbanions that add readily to aldehydes and ketones to give α,β-unsaturated isonitriles, hydrolysis of which should give aldehydes containing an additional carbon atom.[72,73] The isocyanophosphonates **62** are also useful intermediates in the asymmetric synthesis of 1-aminoalkylphosphonic acids *via* palladium catalysed hydrogenolysis of 4-oxazolinephosphonates, themselves obtained in high yield by aldol condensation between **62** and aldehydes in the presence of gold(I) catalysts.[74]

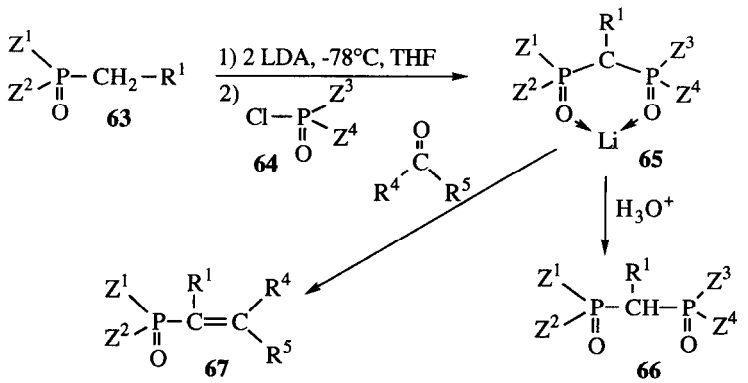


R^1 = H (62%), C_6H_5 (54%)

Scheme 23.

4.3. with α-Lithiated Phosphonates

The diphosphonates play an important role as precursors of vinylphosphonates in organic synthesis and as drugs, in the acid form, for prophylaxis and therapy of abnormal calcium phosphate metabolism and for diagnosis of bone pathologies.[75] The first method of generating diphosphonates *via* electrophilic phosphorylation was described in 1982.[76] Using diisopropyl methylphosphonate as starting material, it involved alternate deprotonation by *n*-BuLi and phosphorylation by chlorophosphates **64** using a decreasing quantity of each reagent for efficient consumption of the starting material.[76,77] The method using LDA (2 eq.) described independently in 1984 and 1985 was found to be preferable for preparing tetraalkyl diphosphonates **66** in high yields and without by-products.[78,79] Dialkyl alkylphosphonates (1 eq.) **63** were metallated with LDA (2 eq.) at low temperature and the resulting α-phosphorylated carbanions trapped at the same temperature by dialkyl chlorophosphates (1 eq.) **64** to produce quantitatively the tetraalkyl lithiomethylenediphosphonates **65** which are thermally stable (Scheme 24).[79,80] The use of this procedure has allowed extension of the reaction to the synthesis of a large variety of symmetrical and unsymmetrical diphosphonates **66**.[80] Moreover, the procedure is particularly well suited to the preparation of elaborated diphosphonates, especially those bearing substituents such as alkyl and aryl groups or halogen atoms, fluorine or chlorine, on the methylene group.[80-90] Varying reaction conditions can lead to low yields of diphosphonates **66**,[91-93] for example when the reaction is accomplished with one equivalent of LDA the yields are not higher than 40% (Table 6, entry **ad**).



Scheme 24.

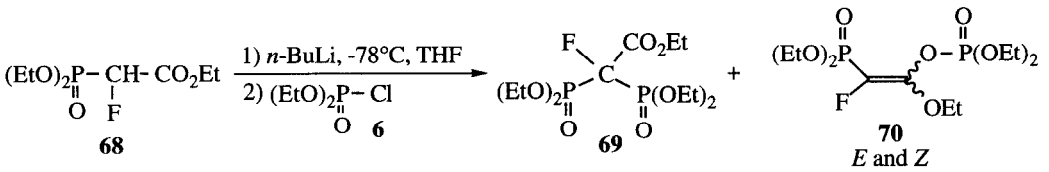
The successful application of the LDA process to the synthesis of diphosphonates **66** has confirmed its efficiency by giving access to compounds bearing widely varied alkyl appendages generally in good to excellent yields (as outlined in Table 6). The tetraalkyl lithiomethylenediphosphonates **65** generated *in situ* undergo reactions with both aliphatic and aromatic aldehydes to give dialkyl (*E*)-vinylphosphonates **67** with a considerable degree of stereoselectivity.[79,80,84,89]

Table 6. Synthesis of Tetraalkyl Methylenediphosphonates.

66	Z^1	Z^2	Z^3	Z^4	R^1	Yield (%)	Ref.
a	MeO	MeO	EtO	EtO	H	67	80
b	MeO	MeO	EtO	Oct_2N	H	81	90
c	MeO	*i*-PrO	MeO	Bu_2N	H	55	90
d	EtO	EtO	MeO	MeO	H	86	83
e	MeO	MeO	*i*-PrO	*i*-PrO	H	94	83
f	MeO	MeO	C_6H_5O	C_6H_5O	H	47	83
g	CH_2=$CHCH_2O$	MeO	MeO	MeO	H	60	83
h	*i*-PrO	MeO	MeO	MeO	H	86	83
i	HexO	MeO	MeO	MeO	H	97	83
j	EtO	EtO	EtO	EtO	H	83	80
k	EtO	EtO	*i*-PrO	*i*-PrO	H	85	83
l	*i*-PrO	*i*-PrO	EtO	EtO	H	87	80
m	EtO	EtO	*t*-BuO	*t*-BuO	H	75	83
n	*n*-BuO	*n*-BuO	*i*-PrO	*i*-PrO	H	85	83
o	HexO	HexO	*i*-PrO	*i*-PrO	H	90	83
p	*i*-PrO	MeO	*i*-PrO	*i*-PrO	H	82	83
q	*i*-PrO	*i*-PrO	HexO	*t*-BuO	H	75	83
r	*i*-PrO	*i*-PrO	OctadecO	*t*-BuO	H	60	83
s	BnO	BnO	C_6H_5O	C_6H_5O	H	43	83
t	Et_2N	Et_2N	MeO	MeO	H	99	90
u	Et_2N	Et_2N	EtO	Et_2N	H	98	90
v	Et_2N	MeO	MeO	MeO	H	99	90
w	Et_2N	MeO	EtO	Et_2N	H	95	90
x	Et_2N	*i*-PrO	MeO	MeO	H	97	90
y	EtO	EtO	EtO	EtO	Me	81	80
z	EtO	EtO	EtO	EtO	Et	69	80
aa	EtO	EtO	EtO	EtO	*n*-Pr	77	80
ab	EtO	EtO	EtO	EtO	Allyl	100	82
ac	EtO	EtO	EtO	EtO	*n*-Bu	78	80
ad	*i*-PrO	*i*-PrO	EtO	EtO	F	37*	92
ae	EtO	EtO	EtO	EtO	Cl	81	80
af	EtO	EtO	EtO	EtO	MeO	87	81
ag	EtO	EtO	EtO	EtO	*n*-BuO	87	81
ah	EtO	EtO	EtO	EtO	MeS	88	81
ai	EtO	EtO	EtO	EtO	C_6H_5S	78	81
aj	EtO	EtO	EtO	EtO	C_6H_5	74	80
ak	$OCH_2CMe_2CH_2O$		EtO	EtO	H	52	80
al	$OCH_2CMe_2CH_2O$		EtO	EtO	Cl	51	80
am	EtO	EtO	Me_2N	Me_2N	H	73	80
an	EtO	EtO	Me_2N	Me_2N	Me	82	80
ao	EtO	EtO	Me_2N	Me_2N	Et	72	80
ap	EtO	EtO	Me_2N	Me_2N	Cl	53	80

* The conjugate base of phosphonate **63ad** acts as deprotonating agent

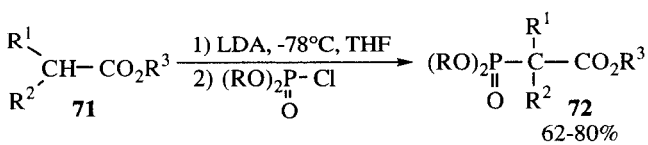
The lithiated anion derived from triethyl 2-fluoro-2-phosphonoacetate **68** reacted with acid halides such as benzoyl chloride, acetyl chloride and ethyl chloroformate to produce the respective *C*-acylated phosphonates. In marked contrast, treatment of the lithiated anion with diethyl chlorophosphate **6** led to a mixture of *C*- **69** and *O*- **70** phosphorylated products in an approximately 25/37 ratio (Scheme 25).[94]



Scheme 25.

4.4. with α-Lithiated Carboxylates and Carboxamides

Phosphonocarboxylates,[95,96] phosphonopyruvates[97], phosphonoacetoacetates[98] and phosphonocarboxamides[99] constitute the family of compounds under discussion but the area is not well explored. The α-carbanions of esters of α-branched and straight-chain acids (isobutyric, hexanoic and acetic acid) **71** were prepared at low temperature by metallation with LDA (1 eq.). Since the obvious difficulties which mitigate against the success of the electrophilic phosphorylation are self-condensation reactions, all the α-carbanions were employed to test the general applicability of the condensation reactions. Isobutyrates, on reaction with chlorophosphates at low temperature gave good yields of the expected trialkyl phosphonoacetates **72b,c,d** (Scheme 26).[95] The same reaction attempted with methyl hexanoate and ethyl acetate failed to give the expected phosphonates. The anion of *t*-butyl acetate on condensation with diethyl chlorophosphate **6** gave 65% of the desired phosphonate **72a** indicating the advantages of using hindered esters to avoid self-condensation products (Table 7). The relative success of esters which are sterically hindered on the α-carbon or on the ester group indicates that the Claisen condensation and/or oxygen alkylation may be two important side-reactions.[95]



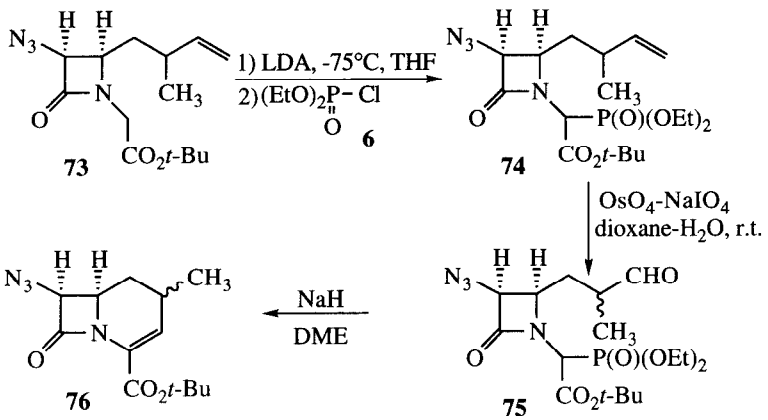
Scheme 26.

Table 7.[95] Synthesis of Trialkyl Phosphonoacetates.

72	R	R^1	R^2	R^3	Yield (%)
a	Et	H	H	*t*-Bu	65
b	Me	Me	Me	Me	62
c	Me	Me	Me	Et	64
d	Et	Me	Me	Et	80

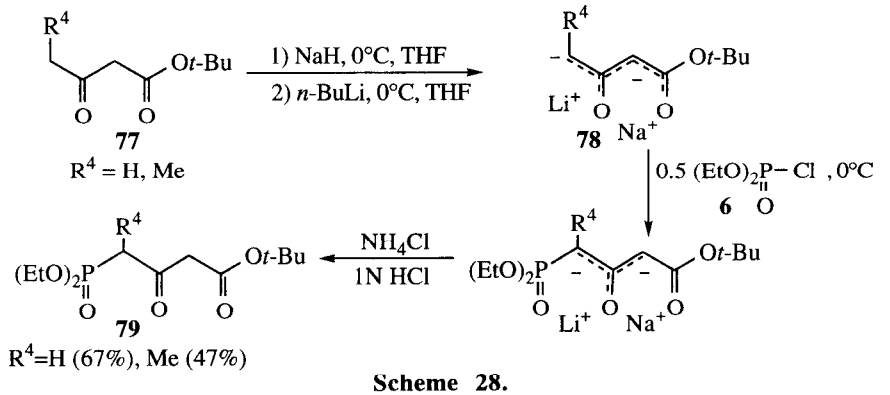
The synthesis of the 2α-CH_3- and 2β-CH_3-3*H*-1-carbacephem derivatives **76** was achieved by intramolecular Horner-Wadsworth-Emmons reaction of a phosphorylated azetidinone acetate **74**. This one was obtained by deprotonation of the α-carbon of the ester group of (±)-*tert*-butyl-2-[*cis*-4-(2-methyl-3-butenyl)-3-azido-2-

oxoazetidin-1-yl]acetate **73** with LDA followed by reaction of the resulting enolate with diethyl chlorophosphate **6** at low temperature in the presence of HMPA. The *cis* phosphorylated isomer **74** was oxidatively cleaved according to Lemieux-Johnson reaction to give an unstable aldehyde **75**. The subsequent NaH-catalysed intramolecular cyclisation gave rise to the 3*H*-carbacephem compound **76** as a mixture of isomers in the ratio of 4 to 1 (Scheme 27).[96]



Scheme 27.

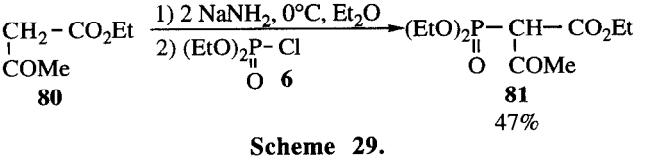
The phosphonopyruvates **79** were prepared by *C*-phosphorylation of the dianions of β-keto esters **78** (Scheme 28).[97] The β-keto esters **77** were first reacted with NaH in THF at 0°C then with *n*-BuLi at the same temperature to give the dianions **78** (1 eq.) which were condensed with diethyl chlorophosphate **6** (0.5 eq.). The dianions **78** act both as reagents in reactions with the diethyl chlorophosphate **6** and as deprotonation agents with respect to phosphonopyruvates **79**. The yields are moderate to good, 67% for R^4 = H and 47% for R^4 = Me.[97]



Scheme 28.

Several reactions between diethyl chlorophosphate **6** and either diethyl malonate or ethyl acetoacetate *via* their sodium or magnesium salts have been described. For example, ethyl acetoacetate **80** (1 eq.) may be readily metallated by treatment with sodium amide (2 eq.) in Et_2O and the resulting carbanion condensed with diethyl

chlorophosphate **6** to give, after work-up, the triethyl phosphonoacetate **81** in moderate yield (47%) (Scheme 29).[98]

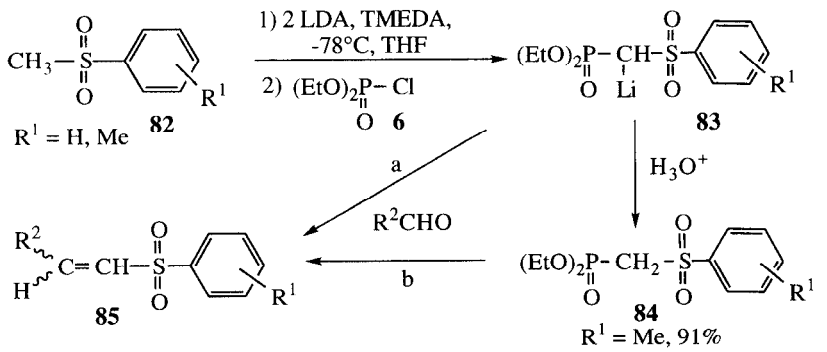


Scheme 29.

Electrophilic phosphorylation has been found to be the method of choice for preparing phosphonocarboxamides from α-carbanions of acyclic and cyclic secondary or tertiary amides.[99] These compounds being more stable than the corresponding α-carbanions of esters, are well suited to the preparation of phosphonocarboxamides by nucleophilic substitution at phosphorus. The metallation of amides was carried out at 0°C in THF with LDA (2 eq. with tertiary amides or 3 eq. with secondary amides), followed by addition of diethyl chlorophosphate **6** at room temperature to give the diethyl phosphonocarboxamides in good yields (64-69%).[99] Finally, this method of generating phosphonoacetate derivatives was found to be preferable to the use of traditional approaches and resulted generally in good yields. Further extension of the scope and synthetic utility of electrophilic phosphorylation would certainly be of interest.

4.5. with α-Lithiated Methyl Sulfones and Sulfonates

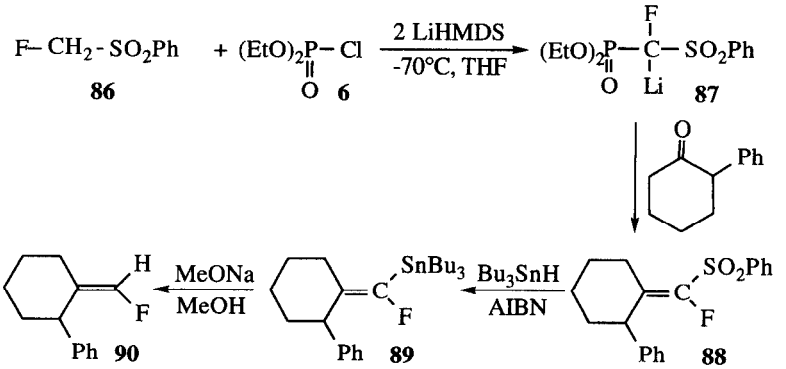
The *C*-phosphorylation of a methyl sulfone based upon nucleophilic substitution at phosphorus was first reported in 1975.[100] The lithium salt of the methyl trifluoromethylsulfone has been found to react slowly on heating in THF with diethyl chlorophosphate **6** to give the diethyl trifluorosulfonylmethylphosphonate after hydrolysis with HCl.[100] More recently, the phosphorylated derivatives of phenyl- and *p*-tolylsulfonylmethane have been prepared from their lithium salts **83** and successfully subjected to Horner-Wadsworth-Emmons reaction for the olefination of aldehydes in generally good to excellent yields.[101,102] The phosphonate coupling partner **84** was generated, either *in situ* or in a separate step (91%) (Scheme 30), by phosphorylation of the corresponding lithiated sulfones produced by metallation at low temperature of **82** with LDA (2 eq.) in THF and TMEDA.[102] Using either a one-pot (a) or two-pot (b) procedure, with 2-benzyloxyethanal as a model aldehyde, the corresponding α,β-unsaturated sulfones **85** were obtained independently as a (*Z*)/(*E*) mixture with both the same purity and yield (90%).[102] More elaborated sulfones such as (*E*)-9-(phenylsulfonyl)-1,3-nonadiene and (*E*)-8-(phenylsulfonyl)-1,3-octadiene were also available for the metallation reaction.[103,104]



Scheme 30.

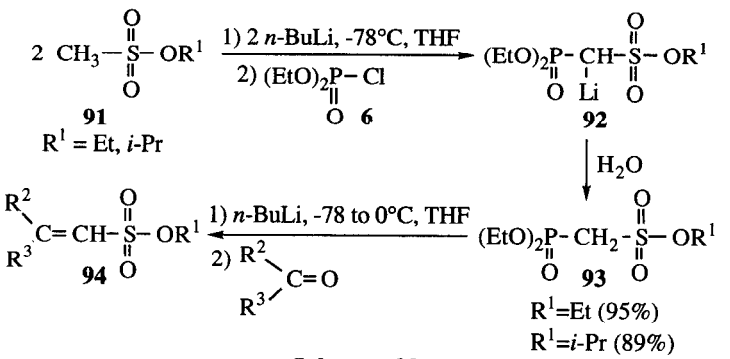
Similarly, the lithiation of *S*-methyl-*S*-phenyl-*N*-(*p*-tolylsulfonyl)sulfoximine with *n*-BuLi (1 eq.) in THF at -78°C followed by the addition of one equivalent of *t*-BuOK as an auxiliary base prior to treatment with diethyl chlorophosphate **6** led to *in situ* generation of the anion of the sulfoximine-substituted phosphonate. Usually, the sulfoximine-substituted phosphonate, being much too sensitive to a proton quench, was not isolated, but reacted directly with an aldehyde to give the alkene product.[105,106]

Another attractive method has also been recently reported for the preparation of 1-fluoroalkene product **90** using *C*-phosphorylation of lithiated fluoromethyl phenylsulfone **86**.[107-111] The olefination of the carbonyl group into the (*E*)- and (*Z*)-fluoroalkenes **90**, *via* the lithiated anion of 1-fluoro-1-(phenylsulfonyl)methylphosphonate **87**, is based on the discovery that fluorovinyl sulfones **88** are converted in excellent yields into fluorovinylstannanes **89** by a subsequent treatment with two equivalents of tributyltin hydride on heating in C_6H_6 in the presence of catalytic amount of AIBN. Conversion of fluorovinylstannanes **89** to 1-fluoro olefines **90** is a stereospecific reaction and provides a general method to (*E*) and (*Z*) fluoro olefines (Scheme 31).[108-110]



Scheme 31.

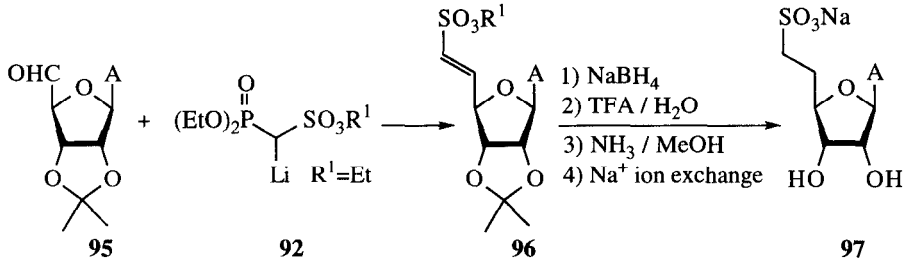
The intermediate diethyl phosphonomethanesulfonate **93**, prepared by nucleophilic addition of the metallated alkyl methanesulfonate (2 eq.) to diethyl chlorophosphate **6** (1 eq.), can be used for the synthesis of α,β-unsaturated sulfonates **94**.[112] In spite of an excess of starting alkyl methanesulfonate **91** (2 eq.), acting both as reagent and as transmetallation agent, phosphorylated esters **93** (R^1=Et, *i*-Pr) were isolated in high yields, 95% and 89%, respectively.



Scheme 32.

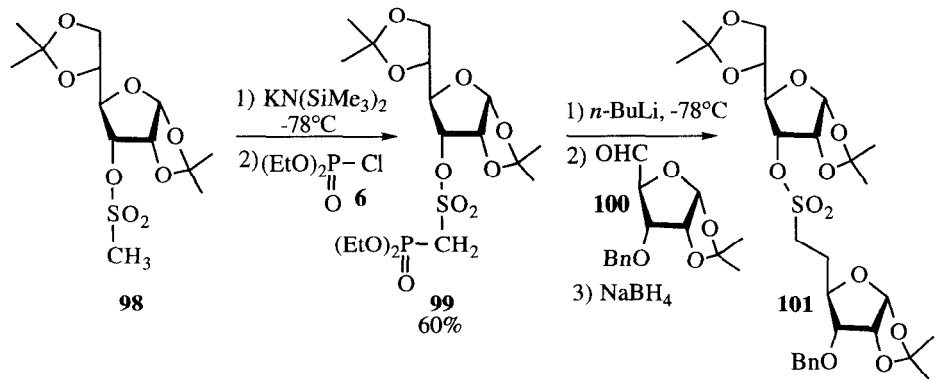
The phosphonomethanesulfonates **93** were subjected to the conditions of the Horner-Wadsworth-Emmons reaction. The lithium salts reacted readily with aliphatic and conjugated aldehydes, but with difficulty towards ketones, to provide excellent yields of α,β-unsaturated sulfonate esters **94** (88 to 99%) as mixtures of (*E*) and (*Z*) isomers in which the (*E*) isomer predominates (Scheme 32).[112]

This efficient technique for the preparation of α,β-unsaturated sulfones and sulfonates has proven to be an attractive and facile method for the synthesis of 3'-, or 5'-sulfonates containing nucleosides, as well as an improved method for the synthesis of 3-sulfone and sulfonate carbohydrates. Thus, the reaction of sulfonyl-stabilised α-phosphonate anions **92** (R^1=Et) with a protected adenosine aldehyde **95** gave the α,β-unsaturated sulfonate esters **96**. Reduction of the double bond with $NaBH_4$, followed by hydrolysis of the acetonide and ammonolysis of the sulfonate ester and *N*-benzoyl protecting group gave adenosine 5'-sulfonate **97** in 41% overall yield (Scheme 33).[113]



Scheme 33.

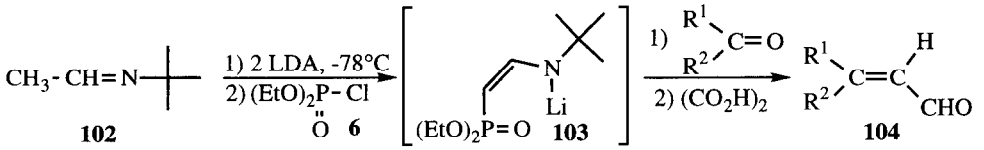
The addition of sulfonyl-stabilised α-phosphonate anions to aldehydes also provides a useful method for the coupling of monosaccharides *via* a sulfonate linkage. For example, the 3-*O*-mesylate of 1,2:5,6-diacetonide allose **98** was converted to the Horner-Wadsworth-Emmons reagent **99** in 60% yield by reaction with diethyl chlorophosphate **6** in the presence of $KN(SiMe_3)_2$. Reaction of the resultant phosphonate **99** with the aldehyde **100**, followed by reduction of the α,β-unsaturated sulfonate with $NaBH_4$ or $[(Ph_3P)CuH]_6$ gave the disaccharide **101** in good yield (Scheme 34).[113]



Scheme 34.

4.6. with α-Lithiated Imines

The direct preparation of α,β-unsaturated aldehydes **104** has been described from metallated imines by a procedure which is a combination of carbanionic displacement of chlorine from phosphorus and Horner-Wadsworth-Emmons olefination. This method avoids the preparation of the phosphonate imine, which generally requires three steps from commercial materials. The procedure involves the *in situ* formation of the lithioenaminophosphonate **103** by reaction between the *N-tert*-butylimine of acetaldehyde and diethyl chlorophosphate **6** in the presence of LDA (2 eq.) (Scheme 35).[114,115] When the resulting lithioenaminophosphonate **103** was allowed to react with a variety of aldehydes and ketones, α,β-unsaturated aldehydes **104** were isolated in fair to good yields (Table 8).[114] The olefination reactions are reported as stereoselective with aldehydes giving the (*E*) isomer as the major product, but with ketones mixtures of (*E*) and (*Z*) isomers are frequently obtained.[114] The reaction has been extended to unsaturated imines. Interestingly, however, instead of the γ-phosphorylated product exclusive attack at the α-position was observed.[116]



102 104

Scheme 35.

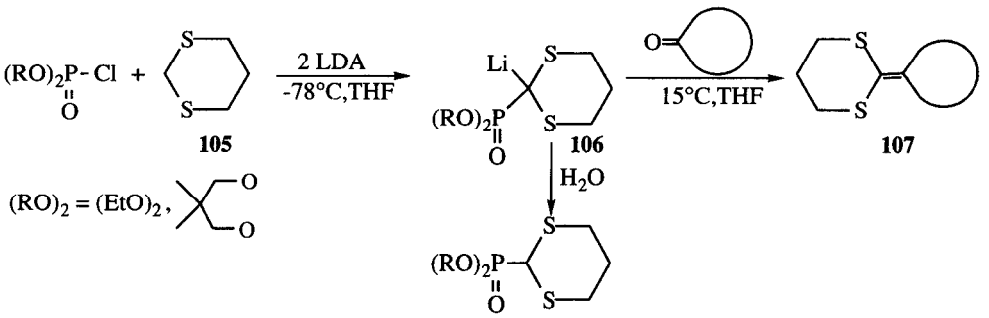
Table 8.[114] Synthesis of α,β-Unsaturared Aldehydes.

104	R^1	R^2	Yield (%)
a	C_6H_5	H	70
b	$C_6H_5(CH_2)_2$	H	73
c	*c*-C_6H_{11}	H	76
d	$C_6H_5CH=CH$	H	67
e	-$(CH_2)_5$-		94
f	*n*-Pr	*n*-Pr	53
g	C_6H_5	C_6H_5	71
h	*i*-Pr	Me	72

4.7. with α-Lithiated Dithiocetals

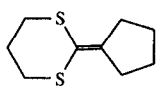
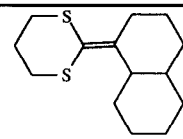
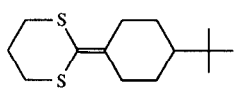
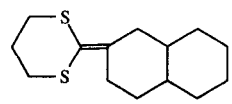
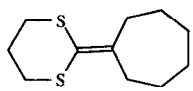
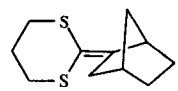
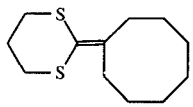
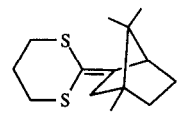
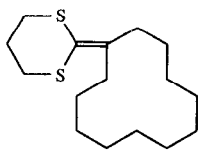
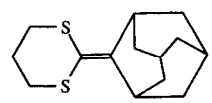
The anions obtained by metallation of dithioacetals **105** are generally used as versatile acyl anion equivalents. The extension to phosphorylated compounds has significantly improved the scope and synthetic utility of the reaction. The metallated 1,3-dithiane, readily obtained in the presence of LDA (2 eq.), reacted with diethyl chlorophosphate **6** (1 eq.) or 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane[53] (1 eq.) under internal quench conditions to give the derived carbanion **106** in quantitative yield (Scheme 36).[117] As shown in Table 9, the experimental results demonstrate clearly that the cyclic phosphorylated anion **106** was reactive towards a large variety of cyclic

ketones (Horner-Wadsworth-Emmons reaction). The yields of ketene dithiocetals **107** were very high, but decrease significantly when the ketone is very hindered.[117]



Scheme 36.

Table 9.[117] Synthesis of Ketenes Dithiocetals.

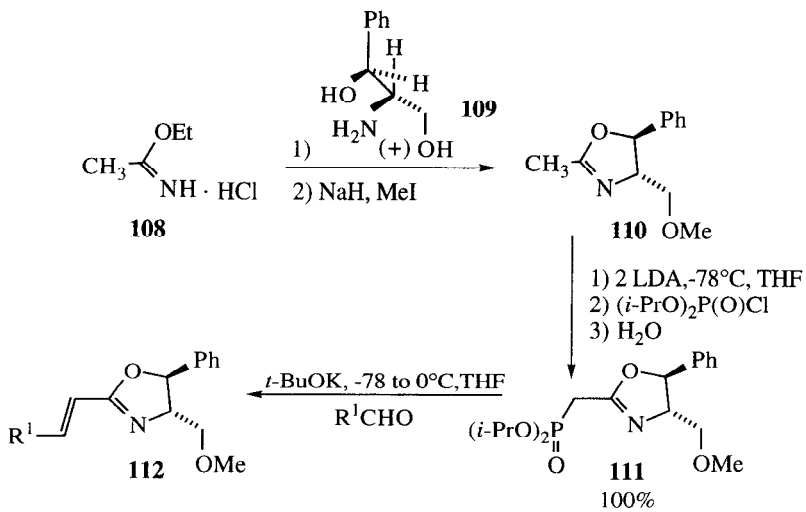
107	Product	Yield (%)	107	Product	Yield (%)
a		93	f		90
b		86	g		94
c		95	h		90
d		92	i		33
e		93	j		15

4.8. with α-Lithiated Oxazolines

The first examples of carbon-carbon bond formation accompanied by high asymmetric induction were performed by nucleophilic addition to electrophilic olefins possessing a chiral auxiliary group. The asymmetric induction observed was attributed to the presence of suitable ligands in the chiral electrophilic olefin which imparted a degree of rigidity to the transition state leading to nucleophilic addition. Thus, for example chiral α,β-unsaturated oxazolines have been effectively employed as electrophiles in conjugate additions with various organolithium reagents to produce in good yield 1,4-addition products in a highly diastereoselective fashion.[118,119] The Horner-Wadsworth-Emmons olefination reaction involving phosphonate-stabilised carbanions was particularly well

suited for elaboration of electrophilic olefins bearing a chiral auxiliary group with a high degree of stereoselectivity (*E* isomer).[120,121]

Deprotonation on large scale of 2-methyloxazoline **110**, prepared from (1*S*,2*S*)-(+)-1-phenyl-2-amino-1,2-propanediol **109** and ethyl iminoacetate hydrochloride **108**, proceeds at -78°C using LDA (2 eq.) in THF to give upon treatment at the same temperature with diisopropyl chlorophosphate (or diethyl chlorophosphate **6**) a gold-colored solution containing the lithiated phosphonate coupling partner which is preferably isolated from the reaction mixture by protic work-up. The crude phosphonomethyloxazoline **111** can be obtained in quantitative yield and was found completely suitable for the subsequent olefination step.[120] A clear illustration of the advantages of this novel synthetic procedure is provided by the conversion of 2-methyloxazoline **110** to α,β-unsaturated oxazolines **112** (Scheme 37).[120] Two independent procedures may be employed for the preparation of α,β-unsaturated oxazolines **112**. The first involves treatment of a mixture of phosphorylated 2-methyloxazoline **111** and aldehyde in THF with *t*-BuOK in the presence of water (2 drops) to give the chiral 2-alkenyloxazolines (*E*) **112** in good to excellent yields (80 to 93%) (Scheme 37).[120] The second variant which is equally useful, requires reaction over several hours at room temperature of **111** with LiCl, DBU and aldehydes in MeCN. The chiral 2-alkenyloxazolines (*E*) **112** are formed in somewhat lower yields (67 to 78%).[122,123] The overall transformation, which has been reexamined recently,[123] appears to offer a fairly general direct route to chiral (*E*)-α,β-unsaturated oxazolines **112** from 2-substituted oxazolines **110** *via* transient phosphorylation.



Scheme 37.

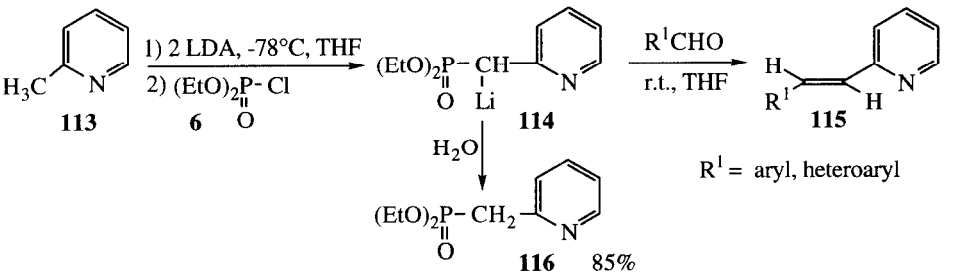
Recently, under the LDA conditions, the 4-isopropyl-2-methyloxazoline has been functionalised with diethyl chlorophosphate **6** then reacted independently with a 4-formyltetrathiafulvalene (LiCl, DBU, MeCN, r.t.) to afford in 50% yield the π-extended *trans*-tetrathiafulvalenyl oxazoline (TTF-oxazoline) containing a donor ligand associated with a chiral auxiliary. The application of this novel TTF-oxazoline as a catalyst for asymmetric palladium-catalysed allylic substitution reactions has been reported.[124]

As part of a programme to discover and develop broad spectrum inhibitors of blood platelet aggregation, a series of 4,5-diphenyloxazole derivatives bearing, among others, a diethoxyphosphoryl group at the carbon atom α to the oxazole ring has been prepared in a similar fashion and evaluated.[125]

4.9. with Lithiated Heterocycles

Phosphonates bearing five- and six-membered heterocycles are valuable synthetic intermediates which are frequently used in the construction of more elaborated cyclic systems by employing Horner-Wadsworth-Emmons reagents. On the other hand, as part of an ongoing interest in exploring the effects of phosphorylation or isosteric replacements in bioactive molecules, the synthesis of heterocycles bearing phosphonate appendages is an area of current interest. In this area, nitrogen heterocycles represent the most important family.

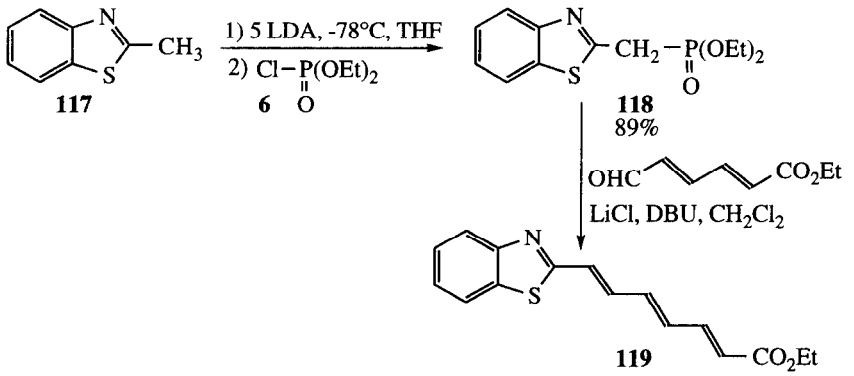
Owing to the limited access and instability of five- and six-membered nitrogen heterocycles possessing a chloromethyl group, it is generally difficult to prepare the corresponding phosphonates by traditional methods (Michaelis-Arbuzov or Michaelis-Becker reactions) using the phosphoryl group as a nucleophile. Consequently these reactions have been employed only to a limited extent, and there was a need for a mild and effective procedure. Within the last ten years, heterocyclic phosphonates have been produced by allowing the appropriately substituted metallated nitrogen heterocycles to react with chlorophosphates. Although the use of anions in carbon-phosphorus bond forming operations is not presently not much developed in heterocyclic chemistry, this technique could supplant traditional approaches in the future. A variety of five- and six-membered heterocycles containing nitrogen atoms have been examined with diethyl chlorophosphate **6**. For example, α-picoline **105**,[126] 1,4-dihydropyridines,[127,128] pyrimidines,[129-131] 2,6-dimethyl-1,2-dehydropiperidine,[132] uridine,[129,130] methyltetrazole,[133] 2,5-dimethylpyrroline,[134,135] 1-methyl-1*H*-1,2,4-triazole,[136] 2-methoxythiazole,[137] 2-methylbenzoxazole,[138] 2-methylbenzothiazole,[139] etc... have been successfully metallated with LDA (2 eq.) at low temperature and phosphorylated to generate the phosphonate coupling partner which was employed for the olefination of carbonyl groups either *in situ* or in a separate step.



Scheme 38.

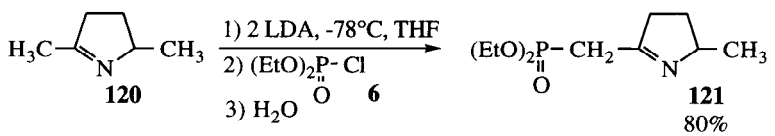
As illustrated by the Scheme 38,[126] α-picoline **113** was converted *in situ* into (*E*)-vinylpyridine derivatives **115** with good overall yields (62 to 85%) through the quantitative formation at low temperature of the stable diethyl 1-lithio-1-(2-pyridyl)methylphosphonate carbanion **114**. Hydrolysis of **114** with aqueous NH_4Cl gave the diethyl 1-(2-pyridyl)methylphosphonate **116** in 85% yield.[126] 2,6-Dimethyl-1,2-dehydropiperidine has been subjected to the same preparative electrophilic phosphorylation conditions.[132]

In marked contrast, a chromophore containing benzothiazole was prepared in two separate steps. 2-Methylbenzothiazole **117** was metallated with LDA (5 eq.) in THF at -78°C, and then reacted with diethyl chlorophosphate **6** to give **118** in 89% yield (Scheme 39).[139] Treatment of **118** with ethyl 6-oxo-2(*E*),4(*E*)-hexadienoate in CH_2Cl_2 for 16 h in the presence of LiCl and DBU produced **119** in 77% yield.[139] 2-[(diethoxyphosphoryl)methyl]benzoxazole was obtained in 81% yield by a similar procedure from 2-methylbenzoxazole.[138]



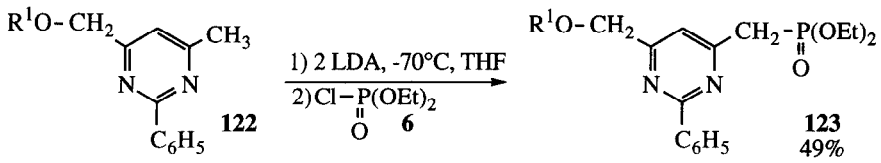
Scheme 39.

In a search for evidence of either an imine or an enamine structure in phosphono intermediates with an appropriate nitrogen substituent, 2,5-dimethylpyrroline **120** was metallated with LDA (2 eq.) at -78°C and phosphorylated with diethyl chlorophosphate **6** to give **121** in good yield (80%) (Scheme 40).[134,135]



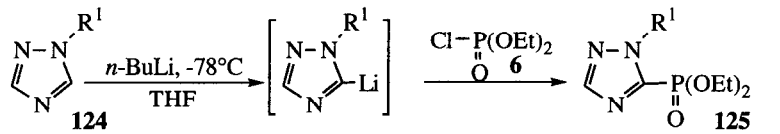
Scheme 40.

Several phosphorus-containing compounds of biological importance have been prepared by electrophilic phosphorylation. For example, the synthesis of phosphorylated derivatives of pyrimidine and purine bases, based upon halogen-metal or proton-metal exchange reaction of bromopyrimidine or purine followed by phosphorylation, has been described.[129,130] The 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic esters were metallated at the NH and the C-2 methyl positions by treatment with *n*-BuLi (2 eq.). The resulting dilithiated species can be phosphorylated to give the C-2 methyl phosphorylated dihydropyridine esters in 87% yield.[127] The reaction has been extended with success to 2-phenyl-4,6-dimethylpyrimidine.[131] After protection of one methyl group **122**, the other was deprotonated with LDA (2 eq.) at -70°C in THF and then treated with diethyl chlorophosphate **6** to give the desired 4-pyrimidine phosphonate **123** (Scheme 41).[131]



Scheme 41.

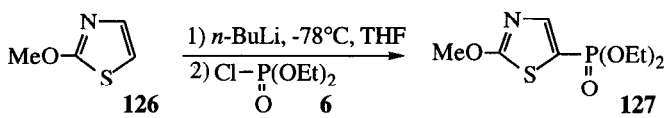
In the family of five-membered rings, the metallation and phosphorylation of several 1-substituted-1*H*-1,2,4-triazoles **124** has been investigated.[136] When various alkyl groups were incorporated in the 1-position, lithiation proceeded exclusively at C-5. The 1-benzyl and 1-methyl derivatives were synthetically more versatile and could be successfully used to prepare several examples of diethyl 1,2,4-triazol-5-ylphosphonates **125** (Scheme 42).[136]



R^1 = Me (72%), $C_6H_5CH_2$ (70%)

Scheme 42.

To provide a series of novel hydroxy substituted heterocyclic phosphonates and phosphonic acids as potential cyclic spatial mimics of glyphosate (*N*-phosphonomethylglycine), a lithiation/phosphorylation procedure has been successfully applied to 2-methoxythiazole **126**. The low temperature metallation can be achieved selectively at the 5-position with *n*-BuLi, and subsequent electrophilic trapping with diethyl chlorophosphate **6** produced the desired diethyl 2-methoxythiazol-5-ylphosphonate **127** in 65% yield (Scheme 43).[137]



Scheme 43.

The viability of this approach has been tested using 1-phenyl-3-methoxy-, 1-phenyl-3-*t*-butyldimethylsilyloxy- and 1-benzyl-3-*t*-butyldimethylsilyloxy-1,2,4-triazole. The lithiation with *n*-BuLi followed by phosphorylation gave very good isolated yields of the corresponding phosphonates.[137] Similarly, reaction of 1-benzyl- and 1-*p*-methoxybenzyltetrazole with *n*-BuLi in the presence of TMEDA at -98°C resulted in complete and regiospecific lithiation at the 5-position. Phosphorylation was successfully performed with diethyl chlorophosphate **6** (68%).[133] Metallation of *N*-*t*-butylthiophene-2-sulfonamide with *n*-BuLi in Et_2O or THF occurs competitively at the 3- and 5-positions according to the temperature (-70 or -10°C). Equilibration of the initial mixture or deprotonation with LDA (2.2 eq.) allows selective formation of the *N*,5-dilithiothiophenesulfonamide. Under conditions where the carbanions were allowed to equilibrate (1.95 eq. of *n*-BuLi), 5-phosphorylated derivatives were almost exclusively obtained.[141]

Thiazole heterocycles have also received attention due to their unique biological activity. For example, treatment of 2-trifluoroacetamido-4-(trifluoromethyl)thiazole with *n*-BuLi (2 eq.) at -78°C in THF produced *in situ* a

thiazole dianion (*N*-acetamido and 5-position), which reacted preferentially at the 5-position with electrophiles and especially with diethyl chlorophosphate **6** to produce the phosphorylated compound in 49% yield.[140]

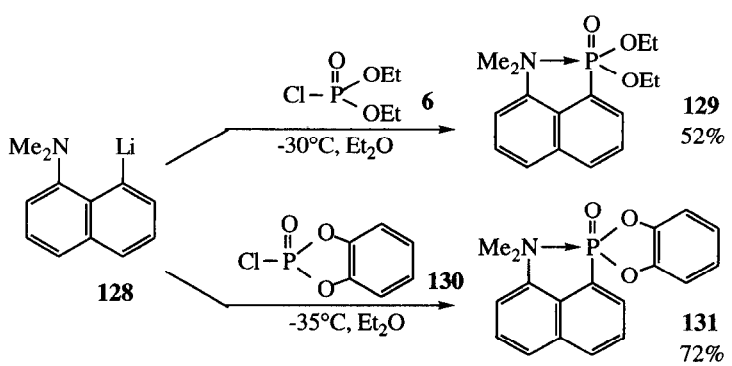
The reaction of 10-methyl-10*H*-pyrido[3,2-*b*]-[1,4]-benzothiazine (1 eq.) with *n*-BuLi (1 eq.) in THF at 0°C affords a mixture of the C-4 deprotonation product and 2-*n*-butyl-4*a*-lithio-10-methyl-2,4*a*-dihydropyridyl-[3,2-*b*]-[1,4]-benzothiazine resulting from nucleophilic addition at the C-2 position. Treatment of the mixture with the diethyl chlorophosphate **6** afforded a mixture of several products isolated in low yields.[142,143]

Diethyl [3,4,6-tri-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-*D*-*arabino*-hex-1-enopyranosyl]phosphonate has also been prepared in moderate yield by vinylic deprotonation of the glucal derivative by *t*-BuLi in THF at -78°C, followed by reaction with diethyl chlorophosphate **6** at the same temperature.[144]

Diethyl 2-furylphosphonate had been prepared by reverse addition of 2-furyllithium, prepared from furan and *n*-BuLi in Et_2O, to diethyl chlorophosphate **6** in refluxing Et_2O solution.[32] The reverse addition of 2-thienyllithium to diphenyl chlorophosphate in Et_2O gave the desired product in low yield (8%) against 75.4% *via* the 2-thienylmagnesium bromide.[26]

4.10. with Aryllithiums

The first recorded investigation in this area was carried out in 1951.[22] It was reported that the reverse addition of an ethereal solution of *p*-tolyllithium to a refluxing solution of diethylchlorophosphate in Et_2O, with a stoichiometric quantity of each reagent, gave, after work-up and distillation, 55% of diethyl *p*-tolylphosphonate. This result was quite encouraging since the yield was better than when the corresponding Grignard reagent was employed.[22] Moreover, in the presence of three equivalents of phenyllithium **28**, one equivalent of diethyl chlorophosphate **6** afforded triphenylphosphine oxide **29**[145] in 80% yield.[42] All of the results have confirmed that organolithium compounds are the reagents of choice to minimize the formation of side products which often result from the incomplete reaction of esters of phosphorus acids with Grignard reagents. Commonly, aryllithium reagents are obtained from the corresponding bromoderivatives by transmetallation (halogen-metal exchange reaction) at low temperature in THF with *n*-BuLi or *t*-BuLi before quenching with diethyl chlorophosphate **6** at the same temperature.[146-150]



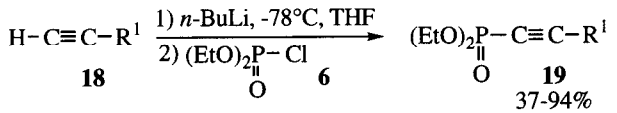
Scheme 44.

This method appears to be general and has been applied with success to aryl derivatives bearing functionality.[151-154] For example, diethyl chlorophosphate **6** underwent condensation with 8-dimethylamino-1-naphthyllithium **128** to give **129** in good yield (52%) while 2-chloro-1,3,2-benzodioxaphosphole-2-oxide **130** reacted with **128**

to give **131** in excellent yield (72 %) with displacement of chloride ion and without ring opening (Scheme 44).[151]

4.11. with Alkynyllithiums

The procedure for the efficient nucleophilic alkynylation of phosphoryl chlorides *via* magnesium derivatives has been discussed previously (*vide supra* 2.3.). A more recently developed procedure employing the same tactic, but using lithium derivatives is, therefore, especially attractive. It has been employed either with simple or with functionalised alkynes. Alkynes **18** were metallated with *n*-BuLi in THF solution at low temperature and the resultant lithium acetylides then reacted with diethyl chlorophosphate **6** at the same temperature. This low temperature procedure minimizes side reactions and provides high and regular yields of diethyl 1-alkynylphosphonates **19** (Scheme 45).[155-163] Some representative examples are collected in Table 10. It should be noted that the use of lithium acetylides in place of the Grignard reagents results in significantly higher yields.



18 **6** **19**

37-94%

R^1 = *n*-Pr, *n*-Bu, *t* -Bu, *n*-Hex, $BnOCH_2$,$Me_2C(OH)$, $THPO(CH_2)_2$, C_6H_5, C_6H_5S ...

Scheme 45.

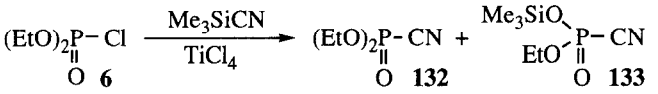
Table 10. Synthesis of Diethyl 1-Alkynylphosphonates.

19	R^1	Yield (%)	Ref.
a	*n*-Pr	80	161
b	*n*-Bu	82	163
c	*t*-Bu	92	163
d	*n*-Hex	91	163
e	C_6H_5	86	163
		80	161
f	$BnOCH_2$	82	163
g	$Me(EtO)CHOCH_2$	94	157
h	$THPO(CH_2)_2$	–	160
i	$Me_2(OH)C$	82	162
j	$MeOCH_2$	80	161
k	$(EtO)_2CH$	75	155
l	C_6H_5S	36	158

There are several other metallated terminal acetylene derivatives, such as those of sodium (R^1-C≡CNa)[40,164] and aluminium [(R^1-C≡C)$_4$AlLi].[165] They have been reported to react under generally mild conditions with dialkyl chlorophosphates producing dialkyl 1-alkynylphosphonates **19** in moderate to good yields (40 to 80%).

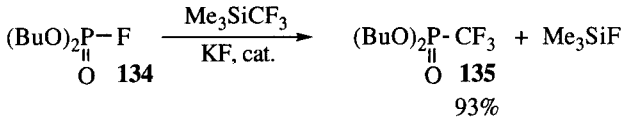
4.12. with Cyanotrimethyl- and Trifluoromethyltrimethylsilanes

The titanium(IV) chloride activation of the diethyl chlorophosphate **6** in the presence of cyanotrimethylsilane has been reported to afford diethyl cyanophosphonate **132** (Scheme 46).[166] Unfortunately, this technique appears to be limited since on heating, the diethyl cyanophosphonate **132** was subjected to partial dealkylation by the chlorotrimethylsilane generated *in situ* to give, with 63% yield, a mixture of diethyl cyanophosphonate **132** and *O*-ethyl-*O*-(trimethylsilyl)cyanophosphonate **133** in an approximately 2/1 ratio.[166]



Scheme 46.

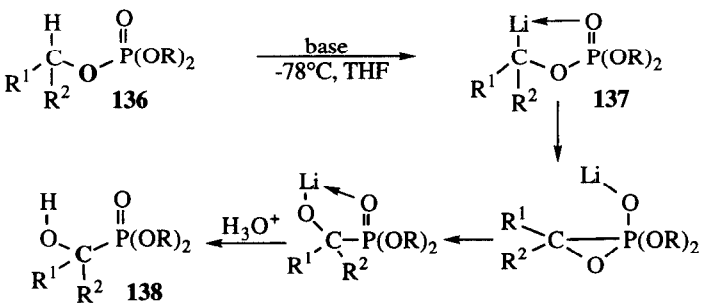
Dibutyl trifluoromethylphosphonate **135** has been conveniently obtained by a remarkably simple and ingenious procedure. In the presence of catalytic amount of KF, the (toxic) dibutyl fluorophosphate **134** reacts with trifluoromethyltrimethylsilane to give the dibutyl trifluoromethylphosphonate **135** in 93% yield (Scheme 47).[167]



Scheme 47.

5. The Phosphate-Phosphonate Rearrangement

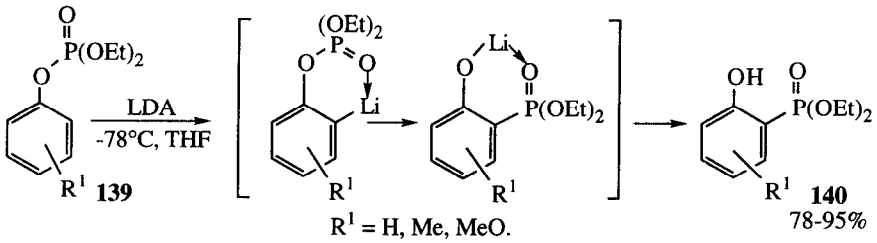
The phosphate-phosphonate rearrangement is an isomerization reaction which is characterised by base-induced migration of a dialkoxyphosphoryl group from oxygen to carbon. A prerequisite for the rearrangement to occur is the deprotonation of phosphate **136** by strong bases such as *n*-BuLi, *s*-BuLi or LDA to generate a dipole-stabilised carbanion **137** in which the lithium counterion is chelated. At least one of the substituents to carbon should be electron withdrawing (phenyl, vinyl or alkynyl groups), to facilitate the removal of the respective benzylic, allylic or propargylic proton, either secondary or tertiary. On work-up, the dialkyl α-hydroxyphosphonate **138** is formed. The driving force for the reaction is that the Li-O bond is stronger than the C-Li bond, which outweighs the loss in energy in going from a P-O to a P-C bond (Scheme 48).[54,171-173]



Scheme 48.

Several rearrangements have been described with dialkyl benzyl-,[54,168-173] allyl-[174,175] and propargylphosphates.[176-178] For example, the α-hydroxyalkynylphosphonate precursors of α-fluoroalkynylphosphonates can be prepared by base-promoted 1,2-migration of phosphorus from oxygen to carbon of propargylic phosphates. The starting alkynols were reacted with diethyl chlorophosphate **6** in toluene at -50°C in the presence of excess LDA (3 eq.), and without isolating the intermediates the resulting diethyl alkynylphosphates rearranged to give the desired diethyl α-hydroxyalkynylphosphonates in yields ranging from 25 to 75% .[177]

In 1981 and 1982 the rearrangement of dialkyl arylphosphates **139** to dialkyl arylphosphonates **140** was reported independently by two laboratories, one using proton-metal exchange with LDA and the other halogen-metal exchange with *n*-BuLi. Phosphate esters of substituted phenols, readily obtained from phenols and dialkylphosphites in CCl_4 in the presence of triethylamine (Atherton-Todd reaction), on treatment at low temperature with a strong base such as LDA, *n*-BuLi in THF or KNH_2 in liquid ammonia-THF, produce excellent overall yields of 2-hydroxyphenylphosphonates **140** (Scheme 49).[179,180]



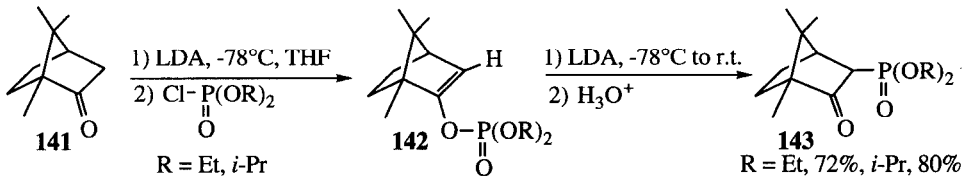
Scheme 49.

This useful and ingenious rearrangement has been studied in depth. It seems generally applicable for the construction of phosphorylated phenols bearing widely varied alkyl appendages. For example, 2-hydroxyphenylphosphonic acid,[181-193] the phosphorus analogue of salicylic acid, was easily obtained in an overall yield of 58%.[185] By a similar procedure, in assessing the importance of the phenolic functionality in cannabinoids for analgesic activity, a series of 9-nor-9β-hydroxyhexahydrocannabinoids was prepared employing the phosphate-phosphonate rearrangement.[189] This rearrangement has been exploited in two directions, preparation of α-hydroxyaryldiphosphonic acid derivatives by double rearrangement on the same phenolic stucture[182,190,191] and preparation of bis(2-hydroxyaryl)phosphinic acids by double rearrangement on two independent phenolic structures.[187] The steric effects of the phosphate appendages, ester or amido, and the influence of the aryl ring substituents on the phosphate-phosphonate rearrangement have been evaluated.[194-197]

In addition, the extension of the rearrangement to mercaptophenol has been reported.[198-200] The diisopropyl *S*-phenylthiophosphate, obtained by phosphorylation of benzenethiolate, on treatment at low temperature with LDA undergoes an S→C migration of the phosphoryl group. The presence of bulky substituents at phosphorus was crucial to the success of the rearrangement in order to exclude nucleophilic attack of LDA on the hard phosphoryl center leading to cleavage of the sulfur-phosphorus bond.[198-200]

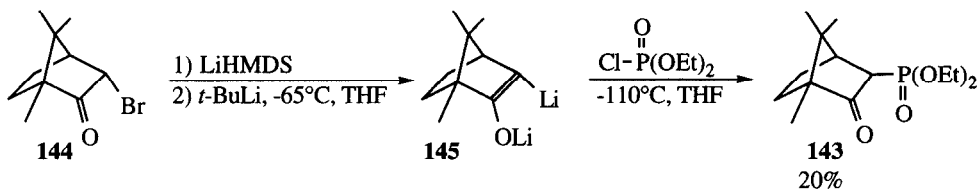
In 1986, a base promoted 1,3-migration of phosphorus from oxygen to carbon was described involving conversion of an enolphosphate into β-ketophosphonate.[201-209] Sequential treatment of camphor **141** with LDA and diethyl chlorophosphate **6** at low temperature in THF resulted in near quantitative formation of the diethyl

vinylphosphate **142**. When treated with LDA from -78°C to room temperature, the camphor-derived vinylphosphate **142** rearranged smoothly to 3-(diethoxyphosphinyl)camphor **143** which was isolated in 72% yield (Scheme 50). The rearrangement is an intramolecular process which was observed with other ring systems thus providing ready access to structures previously available only *via* lengthy routes.[201,202]



Scheme 50.

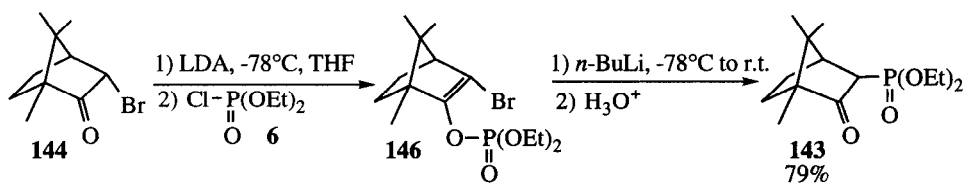
The yield of β-ketophosphonates **143** by phosphate-phosphonate rearrangement is generally high and renders this methodology a better alternative to the previously reported method requiring the phosphorylation of the dilithiated species **145** derived from α-bromocamphor **144** (Scheme 51).[210] Dianion **145**, which may be viewed as both enolates and vinyl reagents,[211] reacts exclusively at carbon with diethyl chlorophosphate to afford 3-(diethoxyphosphinyl)camphor **143** in modest yield.[210]



Scheme 51.

Another attractive feature of this rearrangement lies in its application in the synthesis of α-phosphono lactones. Upon treatment with LDA at low temperature, the diethyl vinylphosphate derivatives of five-, six-, and seven-membered ring lactones undergo rearrangement to α-phosphono lactones in good yields (68 to 78%).[203,207] As previously reported,[201] these reactions were accomplished in one vessel without isolating the intermediates. The reaction has been extended to the preparation of α-phosphono esters in low to fair yields (9 to 73%) and the rearrangement became minimal with esters hindered at the β-position.[203,207]

Recently, a new strategy has been developed for the preparation of β-ketophosphonates **143** *via* a halogen-metal exchange induced 1,3-phosphorus migration of 2-bromovinylphosphates **146** (Scheme 52).[212] Conversion of bromocamphor **144** to the appropriate enolate by reaction with strong base, followed by trapping of the resulting enolate by reaction with diethyl chlorophosphate **6** gave the diethyl 2-bromovinylphosphate **146** in good yield (80%).[212]



Scheme 52.

Subsequent treatment of 2-bromovinylphosphate **146** with *n*-BuLi at -78°C in THF led smoothly to the rearranged 3-(diethoxyphosphinyl)camphor **143**. The rearrangement is a regiospecific process when initiated by halogen-metal exchange, with the phosphoryl group of the product attached to the carbon formerly bearing the bromide.[205,212]

6. Conclusion

The methodology involving nucleophilic substitution at phosphorus constitutes an especially valuable and powerful synthetic tool for the preparation of phosphonates. The process is able to achieve, on a large scale and with high yields, a considerable number of synthetic operations such as the preparation of simple alkyl- and α-substituted alkylphosphonates, arylphosphonates, functionalised phosphonates, α-substituted functionalised phosphonates, and to achieve the one-pot procedure olefination of aldehydes and ketones through *in situ* generation of the phosphonate coupling partner. Historically, although the Michaelis-Becker and Michaelis-Arbuzov reactions remain as the two important methods used for the construction of a C-P bond, nucleophilic substitution at phosphorus appears to be a more versatile method which will in the future be undoubtedly increasingly used and will lead to new synthetic reagents and sequences.

7. Acknowledgments

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Biographical sketch

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Frédéric Eymery was born in 1971 in Chatenay-Malabry, France. Graduating as a technician chemist of the IUT d'Orsay, in 1992, he pursued his studies at the University of Paris XI, where he completed a Master's degree in organic chemistry (DEA) in 1995. After a stay at GlaxoWellcome, he joined the laboratory of Professor F. Mathey in 1996 as a Ph. D. student at the Ecole Polytechnique, France, on the topic of synthesis of new water-soluble phosphines.

Bogdan Iorga was born in 1975 in Ploiesti, Roumania. He received his B. Sc. in chemistry in 1997 at the University of Bucharest working on the synthesis of carbonic anhydrase inhibitors in the research group of Professor C.T. Supuran. In 1997 he joined the European Program at the Ecole Polytechnique, France, where obtained his M. Sc. He is currently pursuing a Ph. D. degree on the electrophilic halogenation of phosphonates under the supervision of Dr. P. Savignac.

Philippe Savignac was born in Versailles, France. He graduated as Ingénieur of the ENSCT in 1963 and obtained his Ph.D from the Sorbonne (Paris) in 1968. He became an Attaché de Recherche (CNRS) in 1970 in the laboratory of Professor Henri Normant in the Sorbonne and Directeur de Recherche (CNRS) in 1976. In 1977 he joined the research group gathered in Thiais working upon phosphorus chemistry. Since 1987 he has been working at the Ecole Polytechnique. His current interests are organic and organometallic chemistry of phosphorus, synthesis of new phosphorylated reagents, phosphoramidates, phosphonates and α-halogenated phosphonates.