Synthetic Applications of Dialkyl (Chloromethyl)phosphonates and *N,N,N′,N′*-Tetraalkyl(chloromethyl)phosphonic Diamides

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I. Introduction

A number of reviews dealing with phosphonate chemistry have appeared over the years.[1] Most concern the use of phosphonate-stabilized carbanions as olefination reagents in Horner−Wadsworth−Emmons (HWE) reactions. A few deal with specific classes of compounds such as difluoromethyl- or vinylphosphonates. This review will emphasize the peculiar properties of α-chloro-substituted phosphonates.

Horner−Wadsworth−Emmons reactions were not commonly observed from the (chloromethyl)phosphonate carbanion since the chlorine atom is not a strong enough withdrawing group to induce the cleavage of the P−C bond (see reactions with carbonyl compounds, section III.4). Indeed, most of the chemistry of chloromethylphosphonate **1** deals with the cleavage of the carbon−chlorine bond by either a halogen−metal exchange reaction or the action of nucleophiles. On the other hand, introduction of functional groups on the carbon bearing both the phosphorus group and chlorine make the P−C bond more labile and Horner−Wadsworth−Emmons reactions can thus occur. In this way, (chloromethyl)phosphonate **1** can be used as a reagent for the preparation of a number of functionalized organic substrates such as alkenes or alkynes. To date, the finding of new methods based on these reactions is still of growing interest.

Both the preparation of α-substituted phosphonates from chloroalkyl derivatives and their applications to the synthesis of nonphosphorylated organic compounds will be highlighted here. We will cover the literature from 1950 to the present. At first, we shall give a detailed account of the properties of diethyl (chloromethyl)phosphonate (**1**), as the parent compound. Literature reports on the higher analogues will be discussed in the final part of this review.

II. Synthesis of Diethyl (Chloromethyl)phosphonate

Diethyl (chloromethyl)phosphonate (**1**) is a stable, easy to handle liquid (bp 109−110 °C/10 mmHg; ^{31}P NMR ($CDCl_3$) δ = +16.0 ppm, d^{20} 1.1992, n_D^{20} 1.4415). It is a commercially available (Aldrich, Fluka) but expensive compound. Nevertheless, it is conveniently prepared, on a laboratory scale, by ethanolysis of (chloromethyl)phosphonic dichloride (**2**) (bp 77−78 °C/10 mmHg; ^{31}P NMR ($CDCl_3$) δ = +38.0 ppm, d^{20} 1.6361, n_D^{20} 1.4978), which is itself commercially available (Aldrich, Fluka). The Kinnear−Perren reaction between phosphorus trichlo-

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Angela Marinetti was born in San Damiano d'Asti, Italy, in 1956. In 1979 she completed graduate studies at the University of Torino and she received her Ph.D. degree in 1984 at the University of Paris VI under the supervision of Professor F. Mathey. She worked as postdoctoral fellow at the University of Rennes, France, in 1980 (Prof. G. Jaouen) and at the University of Wisconsin in Madison in 1986 (Prof. R. West). Since 1981 she has been a member of the CNRS research group directed by Professor F. Mathey at the Ecole Polytechnique, France, where she is currently Directeur de Recherche (CNRS). Her research interests include the organic and organometallic chemistry of phosphorus and its implications concerning asymmetric catalysis.

Philippe Savignac was born in Versailles, France, 1939. 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 around F. Mathey. 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.

ride and dichloromethane in the presence of $AlCl_3$ is currently used on laboratory scale for the synthesis of **2** in 85% yield.[2] On an industrial scale, **2** is synthesised via the (hydroxymethyl)phosphonic acid (obtained by heating phosphorous acid and paraformaldehyde at 100 °C).[4a] The so-formed (1-hydroxymethyl)phosphonic acid is converted into **2** under drastic conditions with phosgene ($COCl_2$) at 150 °C in the presence of Ph_3P as catalyst; yields are almost quantitative.[3] Thionyl chloride ($SOCl_2$) at 55−65 °C in the presence of pyridine has also been introduced as chlorinating agent but the yield of **2** is lower (57%).[4a,b] An alternative two step method whereby the phosphorus acid is substituted with phosphorus trichloride can also be used. The mixture of phosphorus trichloride and anhydrous paraformaldehyde is heated at 250 °C for 10 h in an autoclave to give **2** with a maximum yield of 60−65% (Scheme 1).[5] Treatment of phosphorus trichloride with excess

Scheme 1

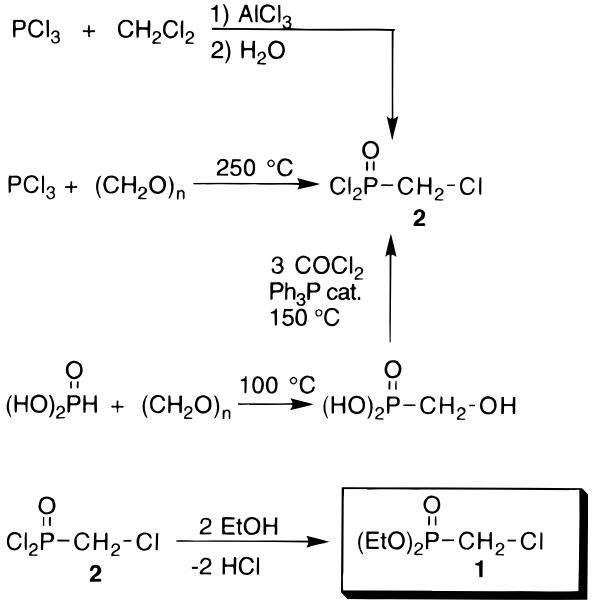


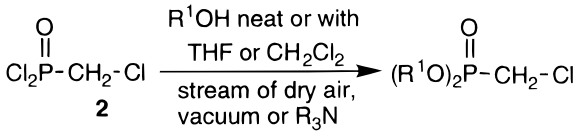
Table 1. Reactions of 2 with Alcohols

R^1OH	yield, %	ref
methanol	66 or 90	7 or 8, 9
ethanol	72−95	5c, 7, 8, 10−14
1-chloro-2-ethanol	66 or 72	5f or 15
2-ethylsulfanyl-ethanol	32	16
2−2′-(5′-vinylpyridyl)-ethanol		17
1,1,1-trichloro-2-ethanol	59 or 90	5f or 11
1,1,1-trifluoro-2-ethanol	92	11
2-morpholino-ethanol	76	18
n-propanol	82	19
isopropanol	74−79 or 85	8, 14, 20, or 11
butanol	55−94	8, 20, 21
isopentanol	79	20
4-hydroxy-2,2,6,6-tetramethyl-piperidinoxide	97	22
n-pentanol, hexanol, nonanol, decanol, 6-methylheptanol		19
2-ethylhexanol	94−99	19, 9
octanol	51	23
ethanediol	63	24
1,2-propanediol	81	24
1,3-propanediol	47 or 94	25
2,2-dimethyl-1,3-propanediol	42 or 93	26 or 27, 11, 28
pentaerythritol	77	29
1,4-butanediol	42	30
vinyl alcohol	35	31
allyl alcohol	60 or 78 or 92	20, 32, or 13 or 11
3-hydroxy-1-propyne	73	33
phenol	77−96	9, 34, 7, 35, 5f
4-chlorophenol	80	36, 5f
2-chlorophenol	87	37
4-methylphenol (cresol)	74−77	7, 9, 38
4-tertiobutylphenol		37
pyrocatechol	90	39

paraformaldehyde yields **2** and other products such as the bis(chloromethyl) (chloromethyl)phosphonate.[5d] Standard alcoholysis of **2** with ethanol under anhydrous conditions yields diethyl (chloromethyl)phosphonate (**1**).

Diester homologues of **1** are obtained from (chloromethyl)phosphonic dichloride (**2**) by alcoholysis in THF or CH_2Cl_2. The quenching alcohol can be simply added pure and the resulting hydrogen chloride removed with a stream of dry air or under vacuum; however, the addition of a tertiary amine remains the most widely used method. The direct addition of sodium alcoholates is also a useful synthetic method (Scheme 2 and Table 1). Formation of

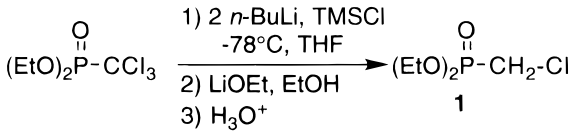
Scheme 2



organosilicon esters from **2** is not usual, it occurs via the reaction of trialkylsilanol acetates and **2** with continuous removal of the acetyl chloride formed by distillation.[6]

Compound **1** is also prepared by selective and successive chemical or electrochemical reduction of two chlorine atoms of the readily available diethyl (trichloromethyl)phosphonate. The chemical procedure involves the double exchange of chlorine with *n*-butyllithium in the presence of chlorotrimethylsilane as protecting group (Scheme 3). After treat-

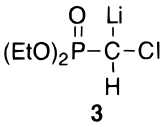
Scheme 3



ment, **1** is obtained in almost quantitative yield.[40] The electrochemical reduction of diethyl (trichloromethyl)phosphonate was successfully applied to the synthesis of diethyl (chloromethyl)phosphonate (**1**) on preparative scale.[41] It was formed with a small amount of diethyl (dichloromethyl)phosphonate (less than 10%) and was obtained in pure form and good yield (80%) after distillation. This electrochemical method can compete with chemical reduction and is currently of increasing use.[42,43]

III. Diethyl (1-Lithiochloromethyl)phosphonate: Preparation and Uses

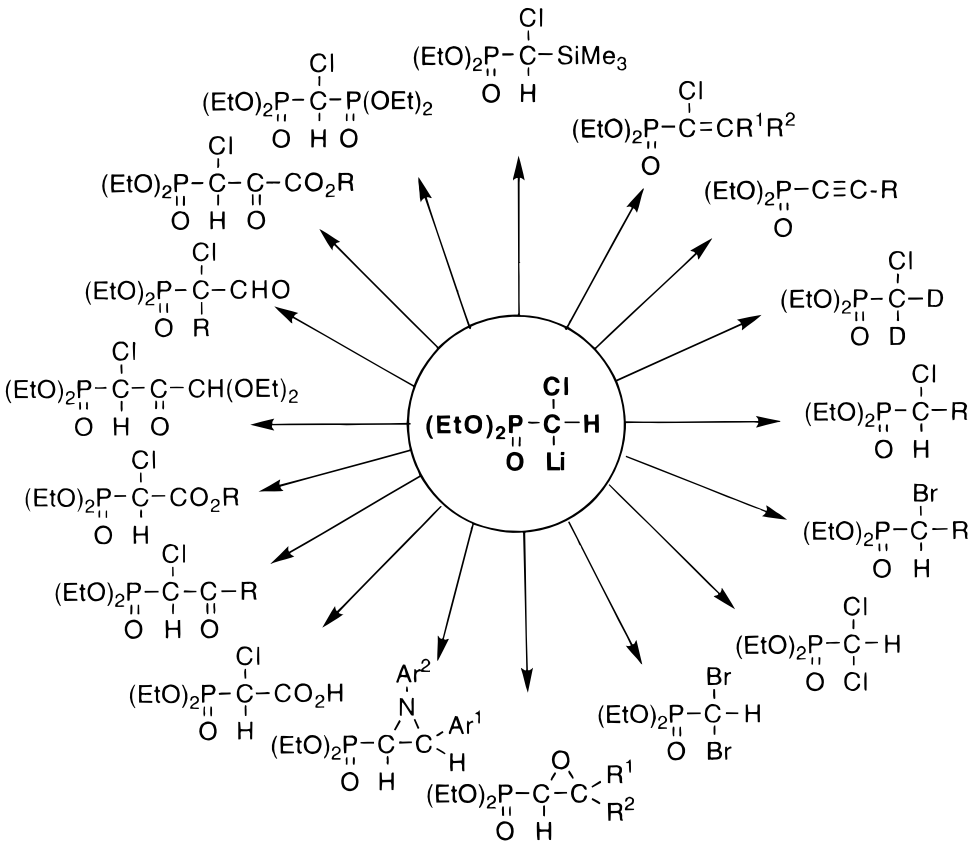
Several phosphonate derivatives owe their use to the ease of formation of a carbanion α to phosphorus. Similarly, by abstraction of a proton of the methylene group with a lithiated base, **1** forms the (1-lithiochloromethyl)phosphonate **3** which has wide applications. It has been shown, by application of known carbanionic reactions to **3** (Scheme 4), that it is a good nucleophile useful in providing several functionalized phosphonates with or without a chlorine atom on the α-carbon.



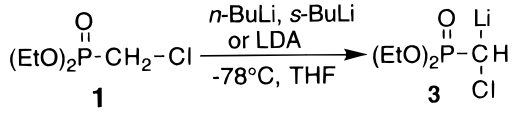
1. Preparation and Stability

In THF at low temperature, *n*-butyllithium, *sec*-butyllithium and lithium diisopropylamide (LDA) cleanly abstract a proton from the methylene group of **1** to give a quantitative yield of (1-lithiochloromethyl)phosphonate **3** (Scheme 5). Compound **1** is not very sensitive to the structure of these lithiated reagents and no significant effect on the nature of the reaction products has been observed. By contrast *tert*-butyllithium gives in part H/Li and Cl/Li exchanges resulting in a mixture of **3** (90%) and diethyl (1-lithiomethyl)phosphonate (10%). Generated under these conditions, **3** is stable exclusively at low temperature. An α-elimination is probably accomplished thermally producing chlorocarbene or diethyl phosphonocarbene in which the leaving group would be the diethyl phosphite or the chloride anion, respectively. Complete reaction of **3** is often handicapped by its instability but this disadvantage can be overcome on generation of **3** from **1** and two equiv of LDA. The first equivalent of LDA deprotonates the methylene group to give **3**, while the second equivalent participates in the stabilization of the carbanionic species by steric interaction between the phosphoryl group and the hindered amide. Under these conditions **3**

Scheme 4



Scheme 5

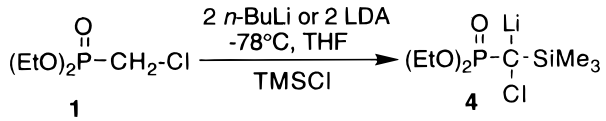


can be kept at 0 °C (^{31}P NMR (THF) $\delta = +45.3$ ppm) for 30 min without apparent degradation.[44] The effect of hindered amides on the thermal stability of α-phosphorylated carbanions has also been observed with other (lithiochloromethyl)- and (lithioalkyl)-phosphonate carbanions.

2. Reaction with Chlorotrimethylsilane

At low temperature, **3** reacts readily and quantitatively with TMSCl to give the monosilylated compound only. When the reaction between **1** and TMSCl was accomplished at low temperature in the presence of 2 equiv of lithiated reagent (*n*-BuLi or LDA), the [1-lithiochloro(trimethylsilyl)methyl]phosphonate **4** was obtained directly (Scheme 6).[40] The

Scheme 6

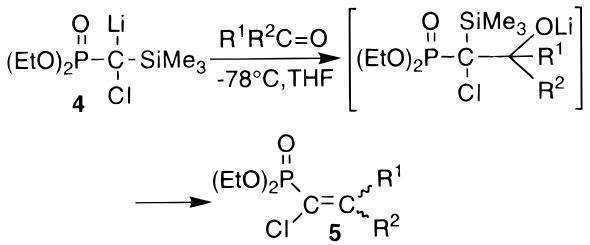


trimethylsilyl group has been shown to be useful as a directing group (Peterson reaction) as well as a protecting group for further reactions.

A. Peterson Reaction

When [1-lithiochloro(trimethylsilyl)methyl]phosphonate **4** reacted with carbonyl compounds, an unambiguous preference of a Peterson over a Horner−Wadsworth−Emmons reaction was observed. In this case the trimethylsilyl group acts as a directing group. Thus, vinylphosphonates **5** are formed from **4** and aldehydes or ketones by elimination of trimethylsilanolate. Usually mixtures of the *E* and *Z* isomers are obtained (Scheme 7).[45] This method of

Scheme 7

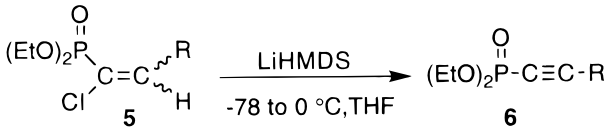


converting carbonyl to vinyl groups is an efficient approach for preparing both isomers of vinylphosphonates **5**. The alternative approach to **5**, the Horner−Wadsworth−Emmons reaction using 1-lithiochloromethylenebisphosphonates **50** (see section III.9), affords selectively the *Z* isomer.[46]

When the carbonyl compound is an aromatic or heteroaromatic aldehyde, 1-alkynylphosphonates **6** are obtained in high yield (87−96%) from (1-chlorovinyl)phosphonates (*E* + *Z*) **5** in a one pot process by treatment at low temperature with LiHMDS or LDA and subsequent elimination (syn and anti) of LiCl (Scheme 8).[47] Compounds **6** are difficult to obtain by other methods.[48]

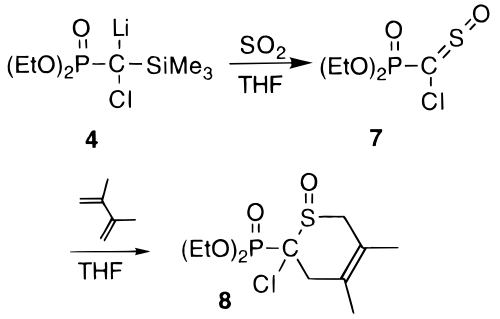
The Peterson reaction also provides a route to phosphorylated sulfines by reaction of **4** with SO_2.

Scheme 8



Compound **7** is rather unstable and was converted into a [4 + 2] cycloadduct **8** by Diels−Alder reaction with 2,3-dimethylbutadiene (Scheme 9).[49]

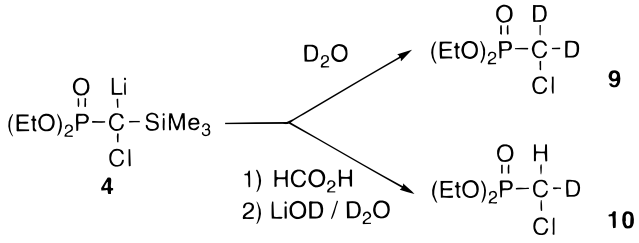
Scheme 9



B. Deuteriation

Conditions have been devised to produce 1,1-dideuteriated diethyl (chloromethyl)phosphonate (**9**). These involve the deuteriation and desilylation under basic conditions of the thermally stable [1-lithiochloro(trimethylsilyl)methyl]phosphonate **4**. Trapping this carbanion at low temperature with D_2O generates LiOD in the reaction medium, which promotes the elimination of the protecting trimethylsilyl group by nucleophilic attack on the silicon atom. This process provides access to 1,1-dideuteriated (chloromethyl)phosphonate **9** in nearly quantitative yield and with high incorporation of deuterium (D % > 95).[50] Trapping of the carbanion **4** with formic acid followed by removal of the trimethylsilyl group with $LiOD/D_2O$ provides access to monodeuteriated diethyl (chloromethyl)phosphonate (**10**) (Scheme 10).[40]

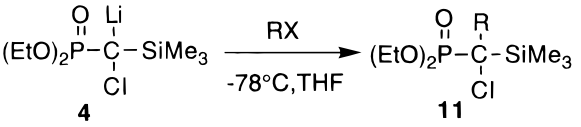
Scheme 10

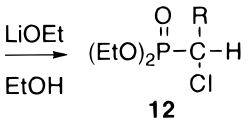


C. Alkylation

Formation of diethyl (chloroalkyl)phosphonates (**12**) by direct alkylation of the lithiated reagent **3** with alkyl halides is not recommended. The acid−base equilibrium between **3** and **12** induces competing side formation of dialkylated products which renders this route not applicable on a preparative scale. By contrast the [1-lithiochloro(trimethylsilyl)-methyl]phosphonate **4** in THF at low temperature is particularly well-suited to the alkylation reaction. The trimethylsilyl group acts as a protecting group and desilylation of the adducts can be easily conducted under basic conditions with $LiOH/H_2O$ in THF or with LiOEt or NaOEt in ethanol to give pure diethyl (chloroalkyl)phosphonates (**12**) in high yield (Scheme 11).[40]

Scheme 11

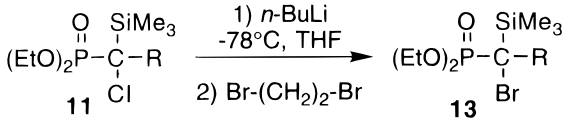


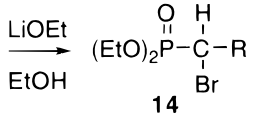


R	X	Yield (%)
Me	I	91
Et	I	88
n-Bu	I	81
$CH_2CH{=}CH_2$	Br	87
$CH_2CH{=}CH\text{-}Me$	Br	88
$CH_2C_6H_5$	Cl	80

Prior to elimination of the trimethylsilyl group the intermediates **11** can undergo at low temperature a halogen−metal exchange reaction to give the [1-lithio-(trimethylsilyl)alkyl]phosphonates. These react with dibromoethane at a temperature lower than −80 °C to produce pure diethyl [bromo(trimethylsilyl)alkyl]-phosphonates (**13**) by a new halogen−metal exchange reaction. The trimethylsilyl group is eliminated under the same conditions as for chlorinated compounds **11** to give pure diethyl (bromoalkyl)phosphonates (**14**) in good yield (Scheme 12).[40]

Scheme 12





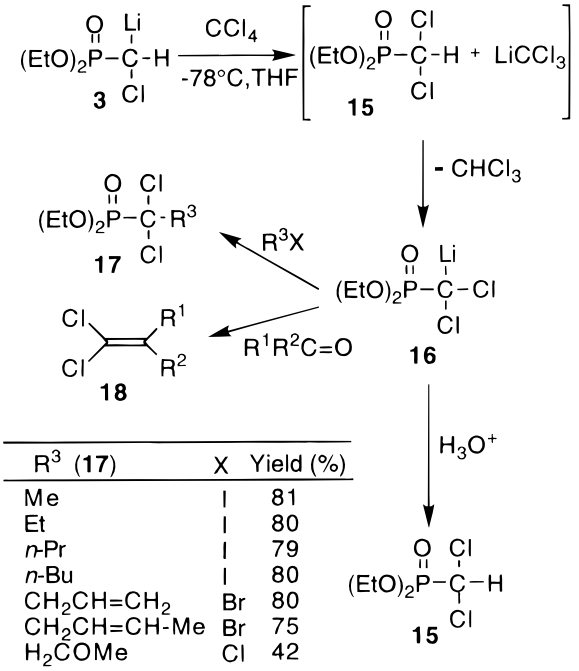
R	X	Yield (%)
Me	I	88
Et	I	78
n-Pr	I	80
$CH_2CH{=}CH_2$	Br	76

3. Reaction with Carbon Tetrachloride/ Tetrabromide and Further Transformations

A. Reaction with Carbon Tetrachloride

The lithiated reagent **3** abstracts a chlorine atom from carbon tetrachloride to produce, in a clean reaction, the transient diethyl (1,1-dichloromethyl)-phosphonate **15** which is sufficiently acidic to undergo a hydrogen-lithium exchange with trichloromethyllithium generated in the reaction medium. The thus obtained (1-lithiodichloromethyl)phosphonate **16** is a carbenoid species capable of undergoing ambiphilic reactions depending on the temperature. At low temperature (−100 °C) where the carbon−lithium bond has mainly covalent character, **16** behaves as an ordinary nucleophile and reacts with various electrophiles to give the expected products of alkylation (**17**) or olefination (**18**, Scheme 13). At higher temperature (−70 °C), due to metal-assisted ionization, **16** behaves as an electrophile and as such

Scheme 13



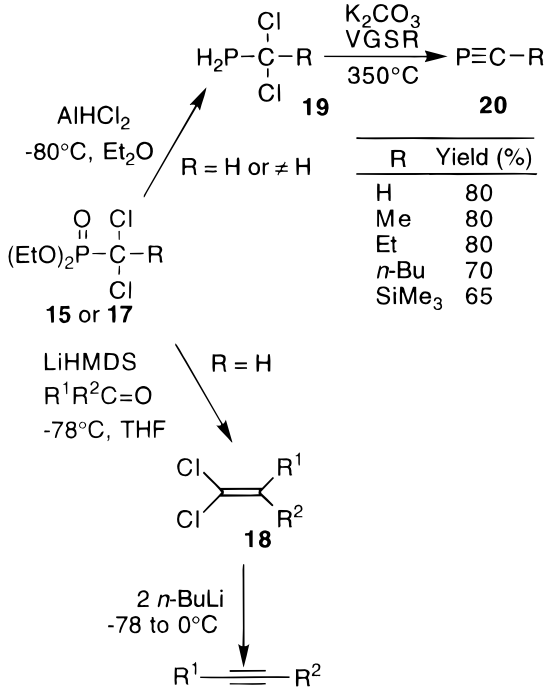
R^3 (**17**)	X	Yield (%)
Me	I	81
Et	I	80
n-Pr	I	79
n-Bu	I	80
$CH_2CH{=}CH_2$	Br	80
$CH_2CH{=}CH{-}Me$	Br	75
H_2COMe	Cl	42

it can react, for example, with lithium salts (LiBr) added to the reaction medium to give (1-lithiobromochloromethyl)- **22** and (1-lithiodibromomethyl)-phosphonate **23**. At higher temperatures, **16** undergoes α-elimination and is converted to a carbene.

Thus as nucleophile **16** reacts at low temperature with alkyl iodides and activated alkyl bromide to give in high yields diethyl (1,1-dichloroalkyl)phosphonates (**17**),[51] it also reacts smoothly with aldehydes and ketones to give *gem*-dichloroolefins **18** through a Horner−Wadsworth−Emmons reaction (Scheme 13).[52] A large variety of carbonyl compounds can participate in the reaction, such as aliphatic and aromatic aldehydes, cyclic ketones, sterically hindered ketones, enolizable ketones, conjugated ketones, etc. Examples of this are shown in Table 2.

The chlorination reaction described in Scheme 13 has been applied to the large-scale synthesis of diethyl (dichloromethyl)phosphonate (**15**) (the use of lithium salts, LiCl and LiBr, increases stability of the lithium intermediate **16** and increases yields of **15** up to 60−90%).[56,57] On a preparative scale chlorination of carbanion **3** can also be effected with diethyl (trichloromethyl)phosphonate to give **15** in an efficient reaction and respectable yield (80−86%).[56] However, a recently reported procedure offers a safer, more efficient route to **15** via the Grignard reagent obtained from diethyl (trichloromethyl)phosphonate and magnesium isopropyl chloride.[58,59] In addition to their use in *gem*-dichloroolefin formation, **15** and **17** have further synthetic applications. Conversion to dichlorophosphines **19** followed by vacuum gas−solid HCl elimination (VGSR) provides a route to nonstabilized phosphaalkynes **20** which have been illustrated by the synthesis of series of derivatives.[60] Compound **15** on reaction with diaromatic ketones is also an efficient precursor of symmetrical or unsymmetrical diarylacetylenes through the Fritsch−Buttenberg−Wiechell rearrangement (Scheme 14).[61]

Scheme 14



R	Yield (%)
H	80
Me	80
Et	80
n-Bu	70
$SiMe_3$	65

R^1	R^2	Yield (%)
C_6H_5	C_6H_5	95
p-MeC_6H_4	C_6H_5	93
p-$MeOC_6H_4$	C_6H_5	88
p-FC_6H_4	*p*-FC_6H_4	89
p-$MeOC_6H_4$	*p*-$MeOC_6H_4$	86

B. Reaction with Carbon Tetrabromide

The lithium reagent **3** abstracts one bromine atom in tetrabromomethane to produce the transient diethyl (1-bromo-1-chloromethyl)phosphonate (**21**) which in turn is deprotonated by the tribromomethyllithium generated in the reaction medium to give the (1-lithio-1-bromo-1-chloromethyl)phosphonate **22**. In the presence of lithium bromide in large excess, **22** formally undergoes a chlorine−bromine exchange to produce the (1-lithio-1,1-dibromomethyl)phosphonate **23**. This lithium reagent is an excellent precursor

Scheme 15

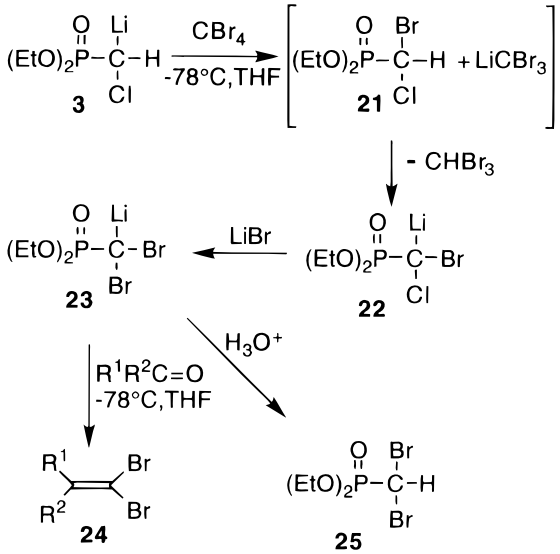
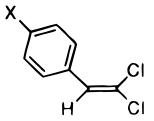
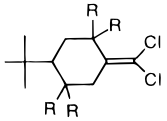
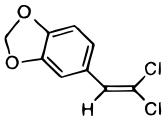
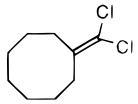
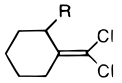
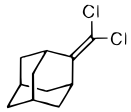
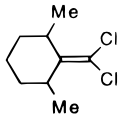
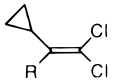
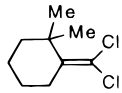
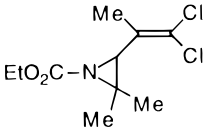
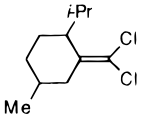
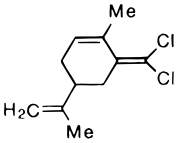
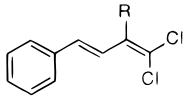
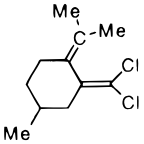
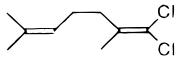
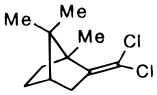
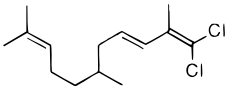
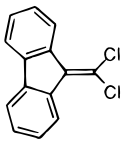
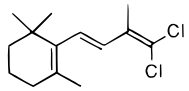
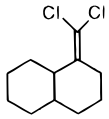
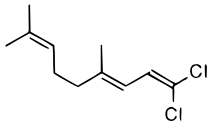
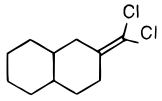
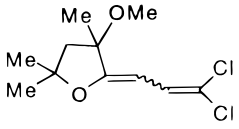
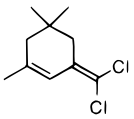


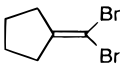
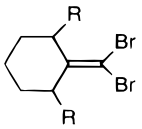
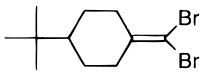
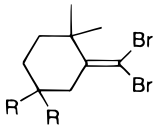
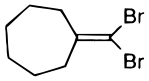
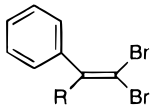
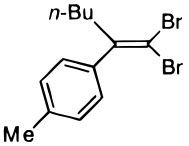
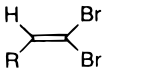
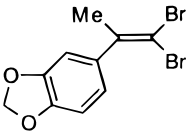
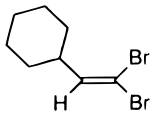
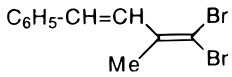
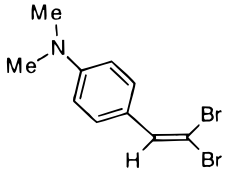
Table 2. *gem*-Dichloroolefins from Horner−Wadsworth−Emmons Reactions of 16

dichloroolefin **18**		yield, %	ref	dichloroolefin **18**		yield, %	ref
	X = F X = Cl	80 67	52 52		R = H R = Me	82[a] 90	53 53
		62[a]	52			79	53
	R = H R = Me	77 78	52 52			77[a]	53
		71	52		R = C_6H_5 R = Me	80 65	53 53
		84	52			10	54
		70	52			70	53
		88	52		R = H R = Me	80[a] 82[a]	53 53
		90	52			75	53
		80[a]	52			73	53
		70	52			84	53
		78	53			84[a]	53
		80	53		*Z* + *E*	58	55
		64	53				

[a] Purified on alumina, not distilled.

to *gem*-dibromoolefins **24** via the Horner−Wadsworth−Emmons reaction (Scheme 15, Table 3).[62] *gem*-Dibromoolefins are used as source of alkynes (Fritsch−Buttenberg−Wiechell reaction).[63] On acidic hydrolysis, **23** gives the diethyl (dibromomethyl)-phosphonate **25** in 80−90% yield.

Table 3. *gem*-Dibromoolefins from Horner−Wadsworth−Emmons Reactions

dibromoolefin **24**		yield, %	ref
			64
	R = H		64
	R = Me	53	62
		70	62
	R = H	45	62
	R = Me	61	62
		67	62
	R = $(CH_2)_5OPv$		63d
	R = C_8H_{17}		63c,d
	R = C_6H_5	50	62
			63d
	R = $(CH_2)_3OBz$		63d
	R = C_8H_{17}		63c
	R = C_6H_{13}		63c
	R = C_6H_5	40	62
			63c
			63c
		50	62
		61	62

4. Reaction with Carbonyl Compounds

A solution of **3** in THF at low temperature reacts with carbonyl compounds to give an intermediate chlorohydrin **26**, stable under the reaction conditions. On heating, elimination of lithium chloride occurs to form the epoxyphosphorus derivatives **27** without side reactions (Darzens procedure). Formation of the chloroalkene via a Horner−Wadsworth−Emmons type rearrangement is never observed. The reaction is well-suited to either aliphatic and aromatic aldehydes or ketones. Even sterically hindered or readily enolizable ketones react generally in good yield (Scheme 16, Table 4).[65] Several other metallic de-

Scheme 16

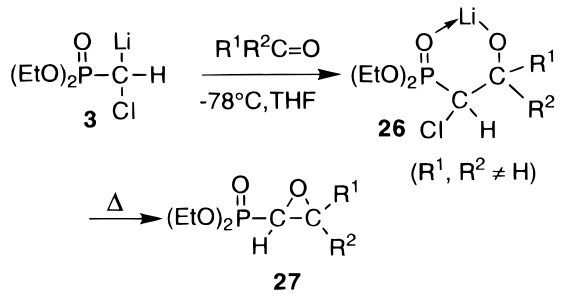


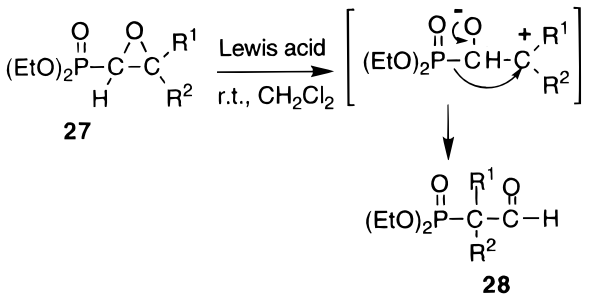
Table 4. (1,2-Epoxyalkyl)phosphonates 27[65]

R^1	R^2	yield, %
Me	Me	80
Et	Et	89
i-Pr	*i*-Pr	88
Me	Et	85
Me	*i*-Pr	86
Me	*t*-Bu	75
Me	*i*-Bu	81
Me	$CH{=}CH_2$	36
Me	$C(Me){=}CH_2$	75
Me	$CH(OMe)_2$	76
Me	*cyclo*-Pr	90
Me	C_6H_5	51
H	Me	65
H	*i*-Pr	66
H	*i*-Bu	56
	$(CH_2)_4$	76

rivatives of diethyl (chloromethyl)phosphonate (**1**), including sodium or potassium, have been reported to provide access to epoxy phosphonates; however, they are not particularly effective for this method and the reaction remains synthetically limited.[66] A useful supplement to the Darzens condensation, applicable to aliphatic aldehydes, has been used to convert **1** into phosphonomycin.[67]

This method of converting carbonyl compounds to epoxy phosphonates **27** has been extended to a large variety of acyclic and cyclic ketones, which lead to 2,2-disubstituted derivatives. Epoxy phosphonates **27** are well-suited starting materials for the preparation of 1,1-disubstituted (1-formylmethyl)phosphonates **28**.[68] Lewis acids, especially $BF_3{\cdot}Et_2O$, are effective catalysts in the rearrangement of epoxyphosphonates **27** into 1,1-disubstituted (1-formylmethyl)phosphonates **28**. The [1,2] transfer of the phosphorus moiety is conducted in dichloromethane with high selectivity and in good yield (Scheme 17, Table 5).[69]

Scheme 17



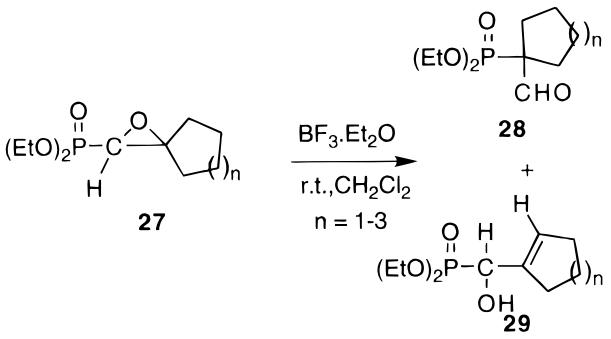
Side reactions do not usually occur except with cyclic ketones which undergo a competing proton

Table 5. 1-Formylphosphonates 28[69]

R^1	R^2	yield, %
Me	Me	76
Me	Et	78
i-Pr	Me	75
Me	*n*-Pr	75
cyclo-Pr	Me	72
t-Bu	Me	62
Me	*n*-pent	68
C_6H_5	Me	68[68a, 69]
Et	Et	78
n-Pr	*n*-Pr	75
i-Pr	*i*-Pr	76
i-Bu	*i*-Bu	76
$(CH_2)_4$		25
$(CH_2)_5$		61
$C(Me)_2(CH_2)_4$		71
$(CH_2)_6$		60

migration and consequently give a mixture of 1,1-disubstituted formylphosphonates **28** and (1-hydroxyallyl)phosphonates **29** (Scheme 18).[69]

Scheme 18



A further application of the reaction between **3** and carbonyl compounds is the synthesis of β-keto phosphonates **32** when the intermediate chlorohydrin **30** issued from **3** and an aldehyde (R = aliphatic, aromatic, or heteroaromatic) is treated at low temperature with excess LDA (2.2 equiv). Under these conditions **30** undergoes deprotonation and subsequent elimination of lithium chloride to provide selectively the lithio phosphonoenolate **31** in its stable chelate form. Under acidic conditions **31** gives the synthetically useful β-keto phosphonates **32**. The overall result is that diethyl (1-lithio-1-chloromethyl)-phosphonate (**3**) allows the direct phosphonomethylation of a large variety of alkyl and aryl aldehydes under advantageous experimental conditions and in good overall yield (Scheme 19, Table 6).[70]

Scheme 19

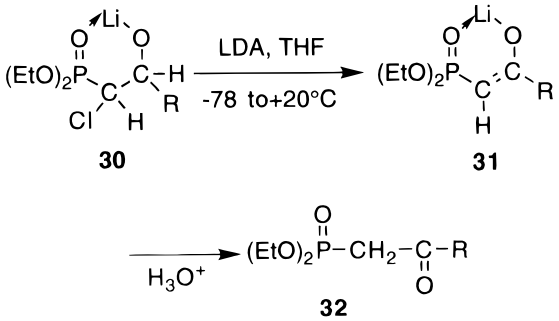
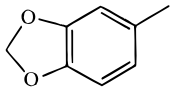
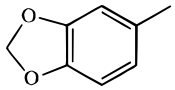


Table 6. (2-Oxoalkyl)phosphonates 32[70]

R	yield, %
i-Pr	89
i-Bu	90
n-Bu	92
n-Hept	88
MeCH=CH	85[a]
C_6H_5	41[c]
C_6H_5	68
4-ClC_6H_4	40[c]
4-$MeOC_6H_4$	70
	65
4-$(Me)_2NC_6H_4$	76[b]
2-thienyl	72

[a] Polymerizes on distillation. [b] Product partially polymerized. [c] Base used = *n*-BuLi.

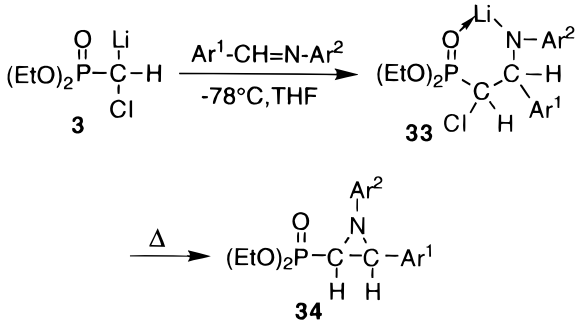
Table 7. (1,2-Aziridinylalkyl)phosphonates 34[71]

Ar^1	Ar^2	yield, %
C_6H_5	C_6H_5	85
3-ClC_6H_4	C_6H_5	30
4-ClC_6H_4	C_6H_5	95
3-$NO_2C_6H_4$	C_6H_5	67
4-$NO_2C_6H_4$	C_6H_5	51
3-MeC_6H_4	C_6H_5	70
	C_6H_5	94
4-$MeOC_6H_4$	C_6H_5	53
C_6H_5	4-BrC_6H_4	80

5. Reaction with Imines

Reaction of **3** with arylimines leads to the lithiated intermediate **33**, which on elimination of LiCl cyclizes to give the aziridines **34** in moderate to good yield. Elimination of the chlorine atom is preferred with respect to Horner−Wadsworth−Emmons reaction, presumably due to entropic considerations. Significant stereochemical control of the reaction is observed; the syn isomer of the aziridine **34** is mainly formed and represents 80−100% of the final product (Scheme 20, Table 7).[71]

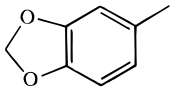
Scheme 20



6. Reaction with Carbon Dioxide and Further Transformation

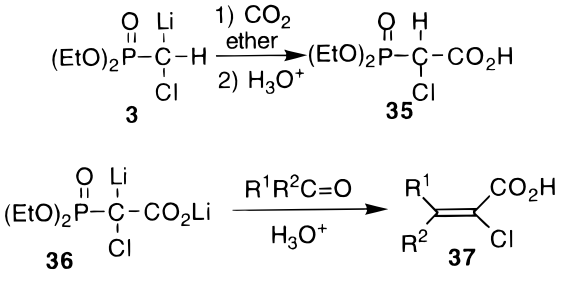
(Chlorocarboxymethyl)phosphonate **35** was first obtained as a crystalline compound from the reaction of **3** with carbon dioxide. In order to prevent any acid−base equilibrum on the formation of **35** it is important to quench a THF solution of **3** with dry

Table 8. α-Chloroacrylic Acids 37[72]

R^1	R^2	isomer	yield, %
C_6H_5	H	Z	67
2-$MeOC_6H_4$	H	Z	83
4-$MeOC_6H_4$	H	Z	83
4-$(Me)_2NC_6H_4$	H	Z	86
4-ClC_6H_4	H	Z	86
	H	Z	91
3-pyridyl	H	Z	41
2-thiophenyl	H	E + Z	85
$C_6H_5CH{=}CH$	H	E + Z	96
C_6H_5	Me	E + Z	65
$Me(CH_2)_3$	H	E + Z	88
$(Me)_2CH$	H	E + Z	91
$(Me)_2CHCH_2$	H	E + Z	85
Et	Me	E + Z	80
$(Me)_2CH$	Me	E + Z	45
$(Me)_2C{=}CH(CH_2)_2$	Me	E + Z	84

ice in large excess in diethyl ether followed by treatment under acidic conditions. The dilithiated reagent **36** is a useful precursor for the conversion of carbonyl compounds into α-chloroacrylic acids **37** via a Horner−Wadsworth−Emmons-type reaction (Scheme 21).[72] There is a stereochemical preference

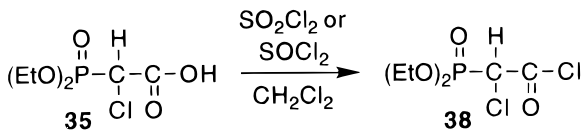
Scheme 21



for production of the *Z* isomer with aromatic and heteroaromatic aldehydes whereas both *Z* and *E* isomers are produced with aliphatic aldehydes and ketones (Table 8).

In addition to its use in the formation of α-chloroacrylic acids, **35** is a valuable synthetic intermediate for several other purposes, for example, direct conversion of **35** into the carboxylic acid chloride **38** is achieved in quantitative yield by treatment with sulfuryl or thionyl chloride in dichloromethane at room temperature (Scheme 22).[73,74] However, sulfu-

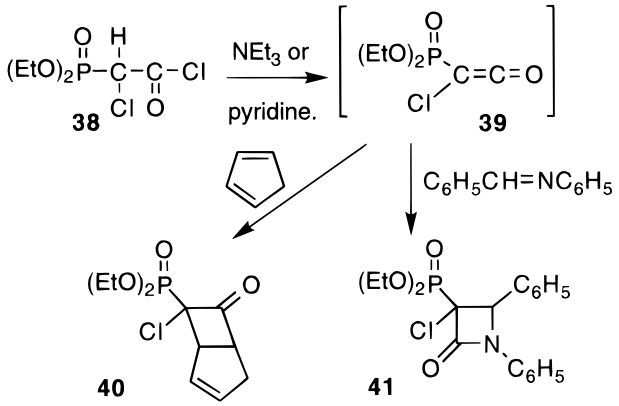
Scheme 22



ryl chloride is much less selective than thionyl choride for the conversion of the carboxylic acid into its acid chloride, and it can also chlorinate the carbon α to the phosphorus atom.[75] The crude carboxylic acid chloride **38** is used for further transformations, because it decomposes on distillation.

Diethyl (chloroketyl)phosphonate (**39**) is the product formed when the carboxylic acid chloride **38** is treated with triethylamine or pyridine in ether at −40 °C (Scheme 23).[76] At room temperature the

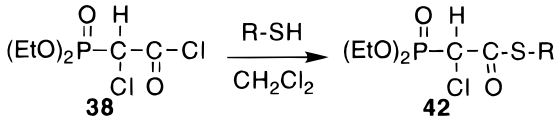
Scheme 23



ketene solution gradually darkens indicating its instability. However, **39** has been trapped *in situ* and converted to series of cycloadducts such as cyclobutanone **40** or β-lactam **41**.

Thioesters **42** were obtained by reaction of **38** with thiols in dichloromethane at room temperature in the presence of triethylamine (Scheme 24). In this way

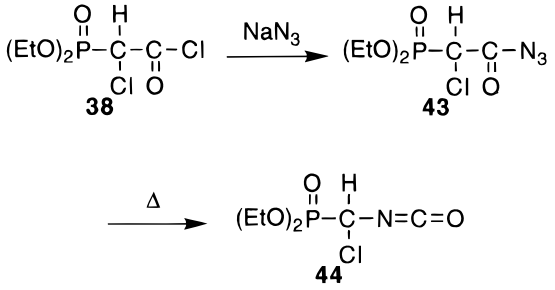
Scheme 24



the thioates **42** were isolated in 95% crude yield (32% after column chromatography).[77] These derivatives are valuable synthetic intermediates, sufficiently pure for subsequent use without purification.

An almost quantitative yield of **43** results from reaction of **38** with sodium azide in biphasic medium (Et_2O/H_2O). This offers the advantages of mild conditions and thus provides a convenient preparation of acyl azide **43** in 89% yield. On heating in refluxing benzene, **43** undergoes a Curtius rearrangement into isocyanate **44** in 88% yield (Scheme 25).[74] An early reported preparation of **44** used a

Scheme 25



Michaelis−Arbuzov reaction between triethyl phosphite and dichloromethyl isocyanate, but the yield of pure diethyl 1-chloromethyl isocyanate **44** did not exceed 10−15%.[78]

7. Reaction with Esters

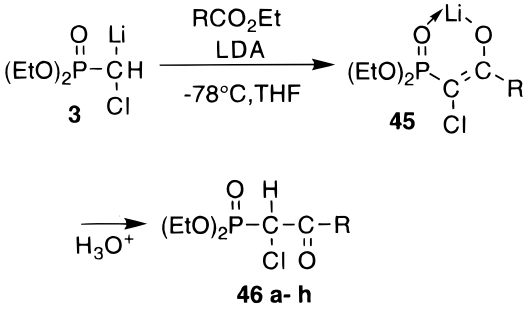
The lithium reagent **3** in the presence of 1 equiv of LDA selectively attacks the carbonyl group of carboxylic esters and analogues to produce the lithio chloroenolates **45**. In most cases, chelates **45** which

Table 9. (1-Chloro-2-oxoalkyl)phosphonates 46

46	R	yield, %	ref
a	Me	82	79
b	Et	81	79
c	$(CH_2)_4Me$	75	79
d	C_6H_5	72	79
e	CO_2Et	76	79, 80
f	CO_2-*i*-Pr	40	79, 80
g	$CH(OEt)_2$	81	79
h	H	85	79, 82

are highly stabilized do not undergo Horner−Wadsworth−Emmons reactions with carbonyl compounds. Acidic hydrolysis of these enolates gives the (1-chloro-2-oxoalkyl)phosphonates **46a**−**h** which are isolated in high yields (Scheme 26 and Table 9).[79,80] This

Scheme 26



reaction can easily be used to provide a large scale conversion of various carboxylic esters into (1-chloro-2 oxoalkyl)phosphonates **46a**−**d**.

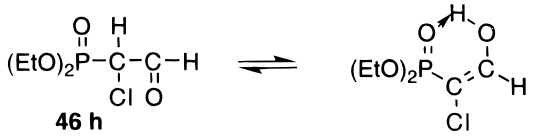
These compounds (**46a**−**d**) can also be obtained from the lithiated derivative of diethyl (trichloromethyl)phosphonate in reaction with acid chlorides. This occurs via a halogen−metal exchange reaction at −125 °C in a THF/diethyl ether mixture in moderate to good yield.[81] This route is analogous to that reported for the synthesis of diethyl [1-(ethoxycarbonyl)-1-chloromethyl]phosphonate (**49**, Scheme 29).

Reaction of **3** with ethyl or isopropyl oxalate provides a convenient preparation of α-chlorinated phosphonopyruvates **46e**,**f**. The reaction proceeds in the presence of LDA via the formation of a transient lithio enolate **45** (R = CO_2Et, R = CO_2-*i*-Pr) and without any byproducts (Scheme 26).[79,82] After acidic hydrolysis the 1-chlorophosphonopyruvates **46e**,**f** are isolated in moderate to good yield (Table 9). With the same process the reaction between **3** and ethyloxalate monoamide gives 1-chlorophosphonopyruvamide (38%).[80]

In a similar manner, reaction of **3** with ethyl diethoxyacetate affords (1-chloro-3,3-diethoxy-2-oxopropyl)phosphonate **46g** in 81% yield after acidic hydrolysis of the corresponding lithio chelate (Scheme 26). The product is obtained in the keto form only.[79]

Reaction of **3** at low temperature with ethyl formate, or DMF, produces in high yield the synthetically useful (1-chloro-2-oxoethyl)phosphonate **46h** (Scheme 26), an excellent precursor to imino- or enaminophosphonates. This water soluble compound exists in keto−enol tautomeric forms (Scheme 27).[79,80] By a similar procedure the carbanion derived from (chloroalkyl)phosphonates **12** (Scheme 11) reacts

Scheme 27



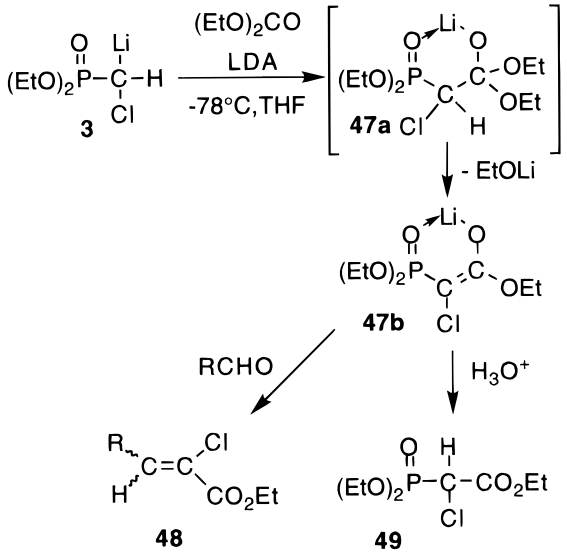
with ethyl formate, the most practical formylating agent, to give 1-(formylchloroalkyl)phosphonates.[79]

An alternative procedure for the preparation of the (1-chloro-2-oxoethyl)phosphonate **46h** is the mild selective chlorination of the readily accessible diethyl (2-oxoethyl)phosphonate with gaseous chlorine in CCl_4 in 79% yield.[83] This procedure was also used for the preparation of a series of (1-alkyl-1-chloro-1-formylmethyl)phosphonates.[84] A more recent approach consists of the chlorination of phosphorylated enol ethers in CCl_4 at room temperature, followed by hydrolysis of the phosphorylated α,β-dichloro ethers. The resulting hemiacetal decomposes to form **46h**.[85]

8. Reaction with Diethyl Carbonate

Reaction of **3** with diethyl carbonate affords the lithio chelated phosphonoenolate **47b** by elimination of EtOH from the unstable intermediate **47a**. When the reaction of carbanion **3** is performed in the presence of 1 equiv of LDA, the yield of phosphonoenolate **47b** is quantitative, while a maximum yield of 50% is achieved when no additional LDA is used. Generated *in situ*, **47b** has been used as a source of diethyl [1-(ethoxycarbonyl)-1-chloromethyl] phosphonate (**49**) prepared in 87% yield or as a precursor to α-chloroacrylic ethyl esters **48** in a Horner−Wadsworth−Emmons-type reaction with carbonyl compounds. These α,β-unsaturated esters usually have *Z* geometry when prepared from aromatic aldehydes or a mixture of *Z* and *E* geometries when prepared from aliphatic aldehydes (Scheme 28 and Table 10).[86]

Scheme 28



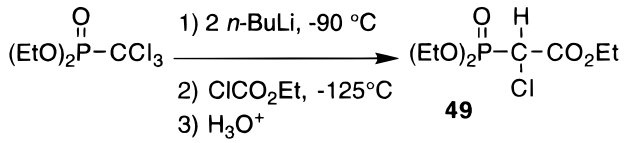
Of significant synthetic importance is the application of the halogen−metal exchange reaction to the generation of (lithiodichloromethyl)phosphonate from *n*-butyllithium and diethyl (trichloromethyl)phospho-

Table 10. α-Chloroacrylic Esters 48[86]

R	Z/E ratio	yield, %
i-Pr	60/40	33
C_6H_5	100/0	75
2-ClC_6H_4	100/0	81
4-MeC_6H_4	100/0	44
4-FC_6H_4	100/0	62
2-thiophenyl	100/0	88

nate at −90 °C in the mixture THF/diethyl ether. Trapping with ethyl chloroformate provides a convenient and advantageous route to **49** in 80% yield (Scheme 29).[87] An alternative procedure for the

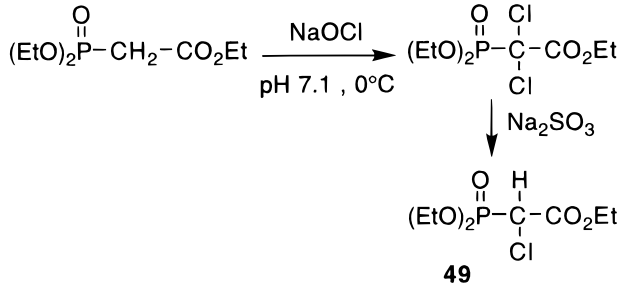
Scheme 29



preparation of **49** via a carbanionic pathway is the reaction of ethyl trichloroacetate in THF at room temperature with the sodium carbanion of diethyl [1-(ethoxycarbonyl)-1-chloromethyl]phosphonate. Despite mild experimental conditions the yield of **49** remains modest (52%).[88]

The other available synthetic procedures for the preparation of diethyl [1-(ethoxycarbonyl)-1-chloromethyl]phosphonate (**49**) are multistep procedures. A nearly quantitative yield of diethyl [1-(ethoxycarbonyl)-1,1-dichloromethyl]phosphonate was obtained from diethyl [1-(ethoxycarbonyl)methyl]phosphonate and sodium hypochlorite at pH 7.1 by moderating the reaction temperature. The subsequent selective reduction of the dichlorophosphonocarboxylate to the corresponding monochloro ester **49** was efficiently accomplished with sodium sulfite (Scheme 30).[89]

Scheme 30



9. Reaction with Phosphoryl Chlorides

Condensation of **3** with phosphoryl chlorides, in the presence of LDA, results in the lithiochloromethylenebisphosphonate **50**.[46] The intermediate **50** acts as a phosphonomethylenation reagent in reaction with carbonyl compounds providing an efficient route to vinylphosphonates **53** of controlled geometry via a Horner−Wadsworth−Emmons reaction (Scheme 31, Table 11).[90,91] This olefination reaction using **50** has been found to be the method of choice for preparing (*Z*)-vinylphosphonates.

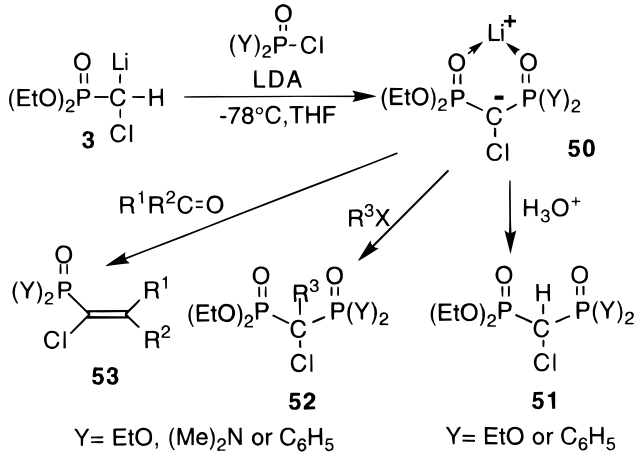
The intermediate bisphosphonate **50** can be a symmetrical or an unsymmetrical reagent obtained by condensation of **3** with a variety of phosphoryl chlorides including acyclic or cyclic chlorophosphates,

Table 11. (1-Chloro-1-vinyl)phosphonates 53

Y	R^1	R^2	Z/E	yield, %	ref
EtO	H	Me	89/11	89	90
EtO	H	Et	90/10	90	90
EtO	H	*i*-Pr	80/20	91	90
EtO	H	*n*-Pr	*a*	61	91
EtO	H	*i*-Bu	85/15	91	90
EtO	H	C_6H_5	90/10	80	90
EtO	H	4-$MeOC_6H_4$	*a*	92	91
EtO	H	3-BrC_6H_4	*a*	78	91
EtO	Me	Me		84	90
EtO	Me	C_6H_5		28	91
EtO		$(CH_2)_5$		59	91
EtO		$(CH_2)_4$		60	90
C_6H_5	H	Me	83/17	60	90
C_6H_5	H	C_6H_5	85/15	50	90
$(Me)_2N$	H	Me	72/28	65	90

[a] Unknown ratio.

Scheme 31



chlorophosphoramides, chlorodiphenylphosphine oxide,[92] chlorothiophosphates, etc. In the case of unsymmetrical bisphosphonates, condensation of **50** with carbonyl compounds is accompanied by the elimination of the more electrophilic phosphorus moiety.

The chemistry of **50** also provides novel routes to chloromethylenebisphosphonates **51** and **52** after either acidic hydrolysis (HCl 6 M) (except where Y = NMe_2) or reaction with an alkyl halide, respectively. This chemistry is well-suited to the preparation of bisphosphonates bearing various substituents on carbon (R^3) and phosphorus (Y) atoms.[90,93,94a] When considering this reaction, it should be noted that formation of methylenebisphosphonates is work-up dependent. On treatment in acidic medium (HCl 6 M) **51** is obtained in moderate to good yield (Table 12). On treatment in basic medium only formation of diethyl (chloromethyl)phosphonate (**1**) and diethyl phosphate is observed resulting from total cleavage of a P−C bond by attack of the LiOH on one of the phosphoryl groups.[90]

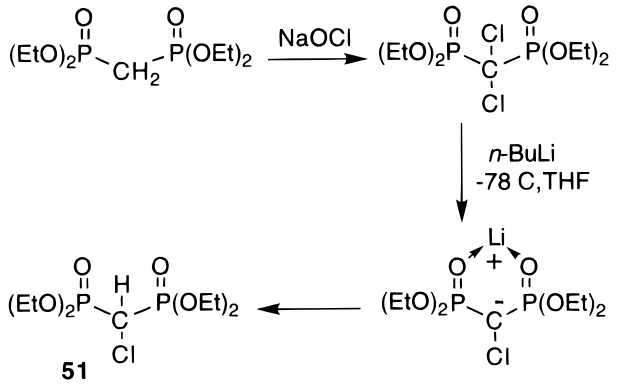
The chloromethylenebisphosphonates **51** can also be obtained by monodehalogenation of the corresponding dichloromethylenebisphosphonates which are readily prepared by the direct chlorination[94] of tetraalkyl methylenebisphosphonates with sodium hypochlorite (as in Scheme 30). Positive chlorine abstraction has been observed during the reaction between potassium fluoride and tetraisopropyl dichlo-

Table 12. 1-Chloromethylenebisphosphonates 51[90]

Y	yield, %
EtO	81
	51
$(Me)_2N$	53
C_6H_5	69

romethylenebisphosphonate in the presence of 18-crown-6 ether. This reaction requires 7 days for completion and is followed by workup and chromatography (55%).[95] A more effective reaction involving chlorine abstraction occurs between tetraethyl dichloromethylenebisphosphonate and *n*-BuLi at −80 °C followed by hydrolysis with a saturated $NaHCO_3$ solution to yield the monochloromethylphosphonate derivative **51** in 79% yield (Scheme 32).[96]

Scheme 32

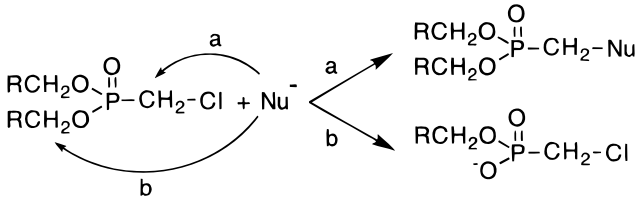


The same result can be achieved by reduction with NaSH at approximately 0 °C, although reductions are particularly sensitive to the nature of the phosphonate esters. Yields are also closely dependent on the reaction temperature used, for example, lower temperatures are required for ethyl esters (0 °C, 91% yield; 25 °C, 49% yield) than for isopropyl (0 °C, 84% yield; 25 °C, 94% yield).[97] This dehalogenation reaction was also performed by using Na_2SO_3 as the reducing agent.[94c,d] A recently introduced procedure is the selective electrochemical reduction of one chlorine atom of tetraethyl dichloromethylenebisphosphonate, which has been accomplished in 70% yield using a buffered medium.[98]

IV. Diethyl (Chloromethyl)phosphonate: Chlorine Substitution

Nucleophilic substitution of the chlorine atom in **1** with other groups (amines, thiols, phenols, thiophenols) produces several useful derivatives. It is particularly important to note that nucleophilic substitution of the chlorine atom (route a) competes with the direct attack of the nucleophile on the carbon atom of the ester groups, resulting in the cleavage of a C−O bond (route b) (Scheme 33). However, the undesirable alkylation reaction (route b) can be avoided by using phosphonate esters bearing electron-withdrawing groups (R = CCl_3 or CF_3).[102] The attack of the nucleophilic reagent on the ester carbon atom is thus slowed down. Alkylation can also be avoided

Scheme 33

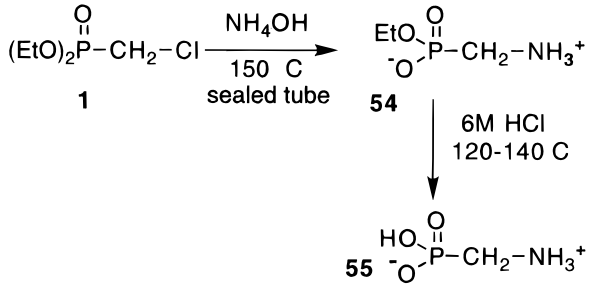


by using phosphonamides instead of phosphonate esters.[99]

1. Amino Derivatives

It has been increasingly recognized that a number of amino phosphonic acids structurally related to natural aminocarboxylic acids are able to inhibit or perturb a given metabolic reaction. So it is common to find the introduction of a phosphonic acid group in place of the normal carboxylic acid group. This analogy has induced a lot of work devoted to the nucleophilic amination of **1**, the aminating agents being NH_4OH,[100] R^1R^2NH,[101] or NaN_3.[102] The first method for the preparation of diethyl (aminomethyl)-phosphonate involved the amination of **1** with a 25% aqueous solution of NH_3 in a sealed tube at 150 °C.[100] It has been demonstrated that the replacement of Cl by NH_2 is more rapid in H_2O than in absolute ethanol. The only product obtained was **54** (45% yield); **54** treated with aqueous solution of HCl at 120−140 °C for 3 h gives **55** in 94% yield (Scheme 34).[100] Other methods for the preparation of **55**

Scheme 34

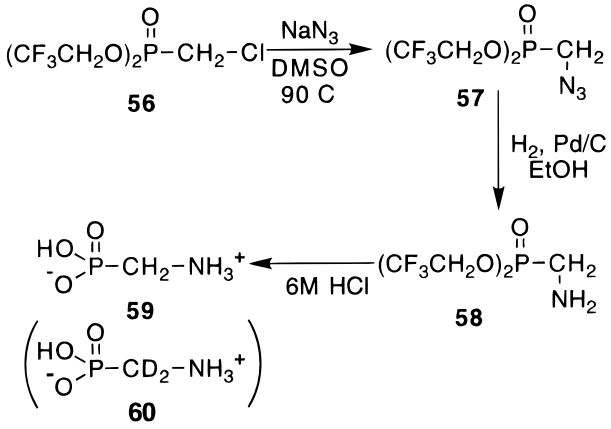


involve the interaction of (chloromethyl)phosphonic acid with NH_4OH (25 h at 100 °C),[100] an aqueous solution of methylamine (7 h at 150 °C and 25 bar),[101a] aniline in excess (20 h at 160−170 °C),[101b] hydrazine hydrate,[101c] or polymethylenediamines (20 h at reflux in water).[101d] By the reaction of tertiary amines with **1** (120−130 °C for 12 h in a sealed tube) a series of (diethoxyoxophosphoranyl)methyl trialkylammonium salts were obtained in low yield (15−19%).[101e]

An almost quantitative yield of azidophosphonate results from reaction of bis(trifluoroethyl) (chloromethyl)phosphonate (**56**) with sodium azide in DMSO at 90 °C. This reaction offers the advantages of mild conditions and higher yields than those obtained from other dialkyl esters issued from **2**. (Chloromethyl)-phosphonates bearing less attracting groups than the trifluoromethyl lead to increasing C−O bond cleavage instead of C−Cl cleavage. Reduction of the intermediate azido phosphonate with H_2 over Pd/C followed by acidic hydrolysis delivers the (aminomethyl)-

phosphonic acid (**59**) in 66% overall yield (Scheme 35).[102] The process has been applied to the synthesis

Scheme 35

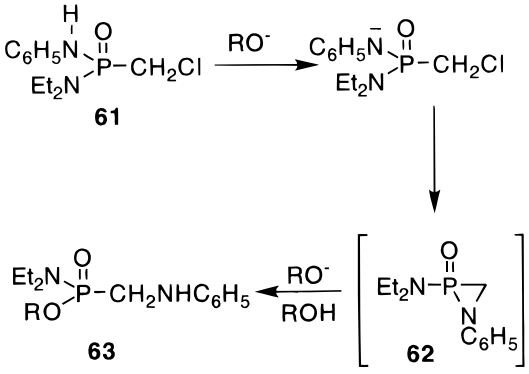


of (1,1-dideuteriomethyl)phosphonic acid **60** (55% overall yield from dideuteriated **56** (% D > 95).[102] Azidophosphonic diamides have been also prepared from reaction of (chloromethyl)phosphonic diamide with sodium azide in DMF at 140 °C.[103]

An unsuccessful attempt to prepare the triazole derivatives of **1** was by reaction of diethyl (chloromethyl)phosphonate (**1**) with potassium 1*H*-1,2,4-triazole in DMSO as solvent. Rather 1-ethyl-1*H*-1,2,4-triazole was isolated in this experiment.[104]

A novel rearrangement involving an intramolecular substitution of the chlorine atom by an aromatic amine has recently been described. When the unsymmetrical phosphonic diamide **61** is treated with alkoxide, loss of a proton from the anilino group leads to the synthesis of **63** via a highly reactive three membered ring intermediate **62** (Scheme 36).[105a]

Scheme 36

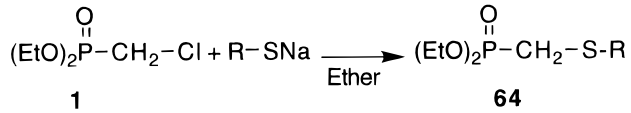


This reaction has been extended to chloro phosphonamidates in which the *N*-phenyl group has been replaced by *N*-alkyl. In this case the reaction can give two products: by P−N cleavage of the three membered ring to give an α-amino phosphonate or by P−C cleavage to give a phosphoramidate.[105b,c]

2. Sulfur-Containing Derivatives

Nucleophilic displacements of chlorine in **1** by sulfur-containing reagents has been well developed. This reaction is of synthetic importance because it gives access to synthetically useful α-phosphoryl sulfide derivatives **64**. However, full utilization of this reaction is often handicapped by the formation of alkyl sulfide through the dealkylation process.[106] Reaction of **1** with sodium alkyl or aryl mercaptides in boiling ether produces the α-phosphoryl sulfides **64** in low to reasonable yield (15−58%) (Scheme 37).[107] Recently the reaction has been extended to

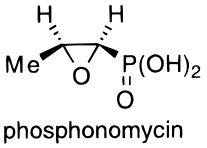
Scheme 37



R	Yield (%)
Me	56
Et	58
C_6H_5	15

sodium mercaptoethanol which reacts with **1** in boiling THF to give the substitution product in only 40% yield.[108] Sodium sulfide (Na_2S) on reaction with compound **1** undergoes a double substitution to provide the corresponding sulfide in low yield (6%).[107]

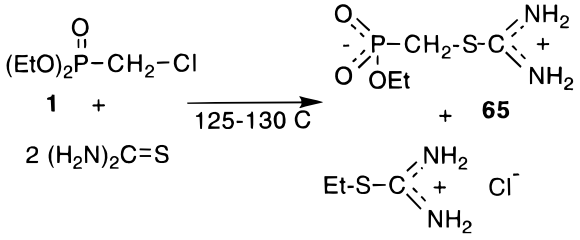
A variation of this reaction with sulfur-containing reagents is exemplified by the reaction of **1** with dimethyl sulfide. This gives a sulfonium salt which via its ylide is converted into an epoxy phosphonate by reaction with acetaldehyde and then to phosphonomycin.[67]



phosphonomycin

The reaction between **1** and thiourea was also reported. It was found that thiourea in excess at 125−130 °C without solvent effects both a substitution reaction of the chlorine and a dealkylation reaction of the phosphonate **1**, leading to the formation of the salt **65** as the main product (20%, Scheme 38).[109]

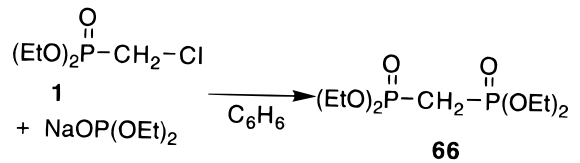
Scheme 38



3. Phosphorus Derivatives

The methylenebisphosphonate **66** is obtained from **1** and sodium diethyl phosphite (Scheme 39). Apart

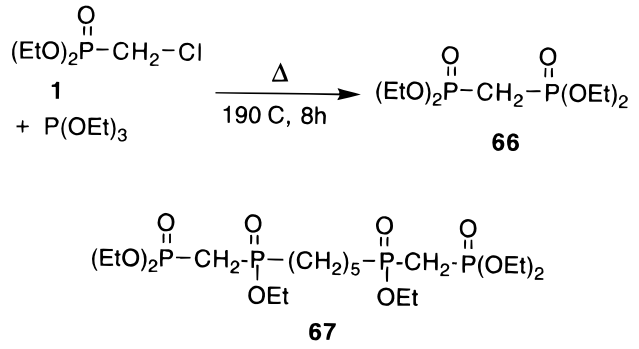
Scheme 39



from diphosphonate **66**, a large quantity of solid products is formed as the result of dealkylation of phosphonate esters **1** by sodium dialkyl phosphite, thus the yield of **66** (47%)[110] is significantly lower than that obtained by other methods.

Reaction of **1** with triethyl phosphite under drastic conditions (190 °C for 8 h) affords **66** in 27% yield, according to a Michaelis–Arbuzov process.[111] Under analogous conditions, tetraethyl pentamethylene-1,5-diphosphonite reacts with **1** to afford the pentamethylene-1,5-bis[[(diethoxyphosphonyl)methyl]phosphinates] (**67**) in high yield (88%, Scheme 40).[112] The

Scheme 40

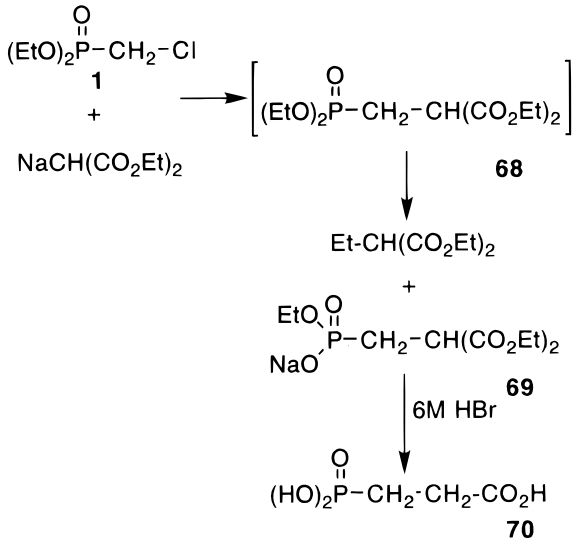


Michaelis–Arbuzov reaction between **1** and the tris-(trimethylsilyl) phosphite is also described.[113]

4. Malonate Derivatives

By a similar procedure, compounds containing an activated methylene group react in their anionic form with **1** to give substituted derivatives; e.g., sodiomalonate reacts with **1** leading to a mixture of ethyl phosphonomalonate **69** and ethyl malonate resulting from a dealkylation of **68**. After acidic hydrolysis and decarboxylation, **69** is converted into *β*-phosphonopropionic acid **70** (Scheme 41).[101b]

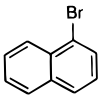
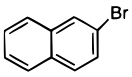
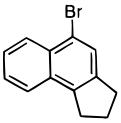
Scheme 41



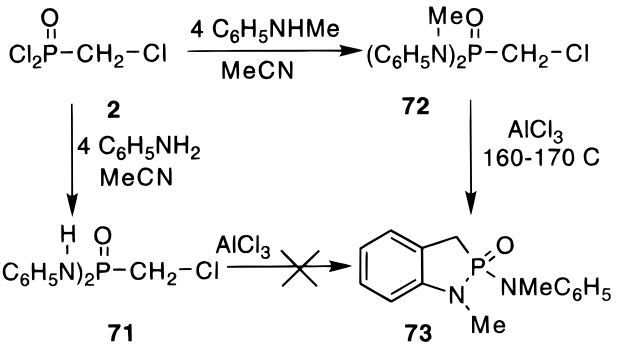
5. Friedel–Crafts Reactions

Reaction of **2** with 4 equiv of aniline in acetonitrile gives 70% yield of (chloromethyl)phosphonic dianilide **71**. Attemps to cyclize **71** by treatment with $AlCl_3$ at 160–170 °C give unidentified polymeric materials probably because of the presence of the secondary nitrogen atom. By contrast, the corresponding *N*,*N*′-dimethylphosphonic dianilide **72**, prepared either by bismethylation of **71** or by reaction of **2** with *N*-methyl aniline, undergoes an intramolecular Friedel–Crafts cyclization on heating with $AlCl_3$ at 160–170 °C to give **73** in 63% yield (Scheme 42). Extension

Table 13. (1-Arylmethyl)phosphonates 74[115]

Ar–Br	yield, %
	65
	64
	56
	69

Scheme 42

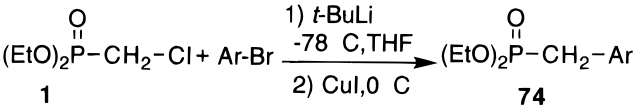


of the cyclization reaction to monoamide derivatives by treatment of **2** with 2 equiv of *N*-methyl aniline and $AlCl_3$ was unsuccessful and the starting material recovered. It seems that the propensity for cyclization is reserved for phosphonic diamides bearing tertiary nitrogen atoms.[114]

6. Aromatic Derivatives

A variety of compounds **74** containing a phosphonomethyl group bonded to an aryl group have been prepared in one step from **1** and aryl bromides when combined in THF at first with *tert*-butyllithium at −78 °C and then with cuprous iodide at 0 °C (Scheme 43, Table 13). The carbon–carbon coupling takes

Scheme 43

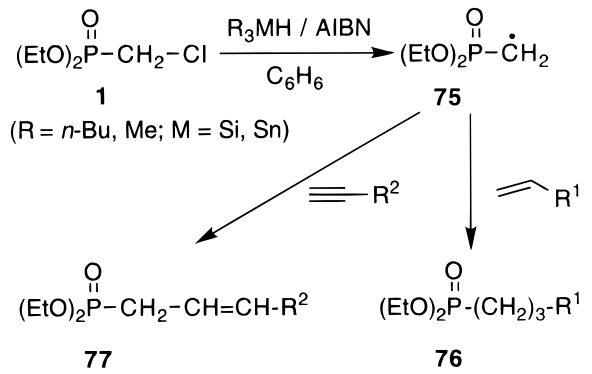


place slowly at room temperature. A series of compounds can be obtained in 56–69% overall yield by using this process.[115]

7. Radical Reaction

This new approach to the synthesis of γ-functionalized phosphonates **76** and **77** (R^1 or R^2 = alkyl, ethoxy, butoxy, acetoxy, acetyl, and cyanide groups) is based on the addition reaction of α-phosphorylmethyl radicals to terminal alkenes and alkynes.[116] The radical species are formed in benzene or toluene from (1-halogenomethyl)phosphonates, using tin or silicon hydrides as radical sources (Scheme 44). The

Scheme 44



reaction has been applied to both electron-rich and electron-deficient alkenes and alkynes. Under these conditions the direct generation of the (diethoxyoxophosphoranylmethyl radical (**75**) from diethyl (chloromethyl)phosphonate (**1**) allows moderate yields of functionalized phosphonates **76** and **77** (10−62%). The only byproduct is diethyl methylphosphonate, which is formed via recombination of the intermediate radical with a hydrogen atom. Thus, this methodology is an alternative to the Michaelis−Abuzov and Michaelis−Becker methods for the synthesis of phosphonates, which suffer from a lack of generality.

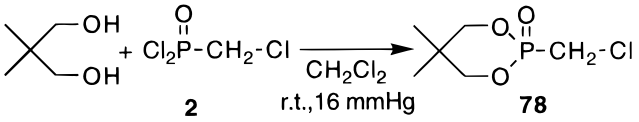
V. Other (Chloromethyl)phosphonic Acid Derivatives

Several (chloromethyl)phosphonic acid derivatives, other than **1**, have been utilized as synthetic intermediates. The literature concerning their preparation and properties also reports their utility in organic synthesis. The structure of these (chloromethyl)phosphonic acid derivatives plays an important role in determining the outcome of their reactions. The presence on the phosphorus atom of suitable alkoxy or aminoalkoxy groups promotes specific transformations and allows better stereochemical control of the reactions.

1. 2-(Chloromethyl)-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane

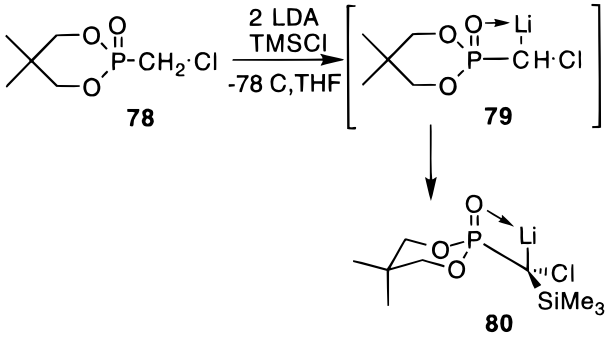
2-(Chloromethyl)-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (**78**) is a stable, easy to handle solid (mp 116−118 °C; ^{31}P NMR ($CDCl_3$) δ = +11.4 ppm). An early reported preparation of **78** includes condensation of **2** with 2,2-dimethylpropane-1,3-diol in dioxane in the presence of pyridine with a modest yield (42%).[26] On a laboratory scale, a recently reported synthesis offers an easy and efficient route to **78** (93% yield) from the same starting materials. The reaction takes place in dichloromethane without base using a vacuum procedure.[27] The product is soluble in THF, benzene, acetone, ethanol, and water (Scheme 45).

Scheme 45



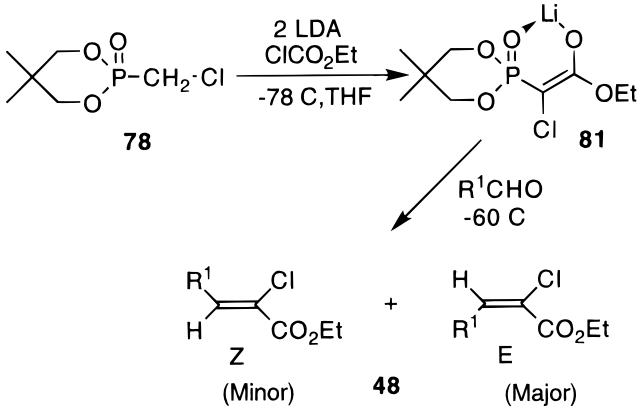
Generation of the lithio derivative of **78** is accomplished with LDA at low temperature. The carbanion **79** is very unstable and has to be kept at low temperature; however, it is stabilized when generated from 2 equiv of LDA. This method of generating **79** was found to be preferable to the use of *n*-BuLi, as **79** is formed in high yield with LDA with only a trace of byproducts.[44] Metallation of **78** in the presence of TMSCl gives **80** as the equatorial conformer (^{31}P NMR ($CDCl_3$) δ = +42.6 ppm) which is stable at 0 °C (Scheme 46). Other silyl chlorides,

Scheme 46



TESCl, TIPSCl, and TBDMSCl, condense to give their respective organosilylated derivatives.[53] Compound **78** has been used in reaction with ethyl chloroformate in the presence of 2 equiv of LDA for the preparation of **81**, which, on reaction with aldehydes, undergoes a typical Horner−Wadsworth−Emmons reaction.[118] The selectivity observed is never high and the thus obtained α-chlorinated acrylic esters **48** show a *Z*/*E* ratio of 25/75 (Scheme 47).

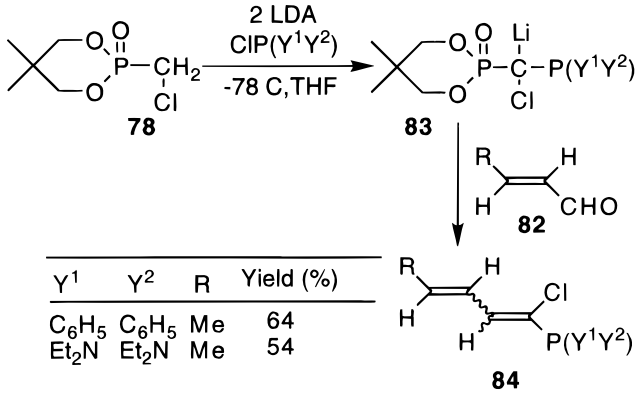
Scheme 47



Other applications of **78** include condensation with diphenylchlorophosphine and α,β-unsaturated aldehydes **82** to give 1,3-butadienylphosphine **84** (Scheme

48).[119] The newly formed double bond shows a *Z*/*E* ratio of 70/30.

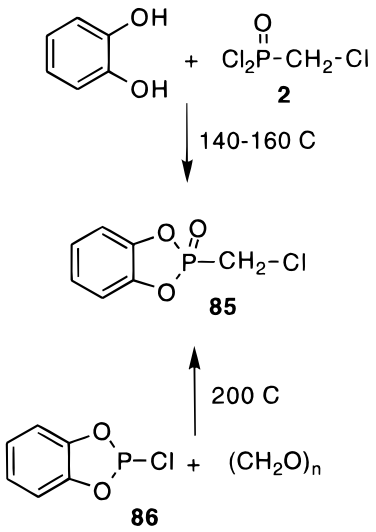
Scheme 48



2. 2-(Chloromethyl)-2-oxo-4,5-benzo-1,3,2-dioxaphospholane

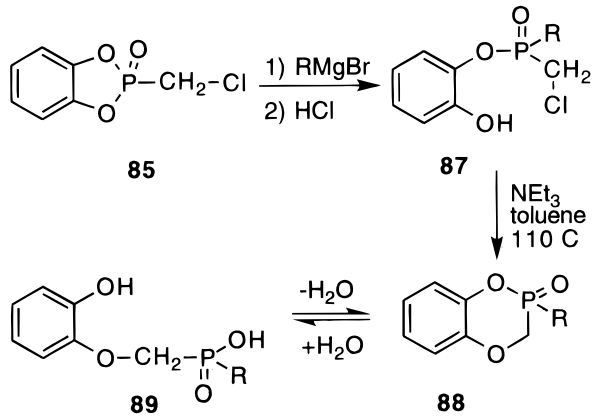
2-(Chloromethyl)-2-oxo-4,5-benzo-1,3,2-dioxaphospholane (**85**) is obtained via two methods. In the more recent approach **2** reacts with pyrocatechol at 140−160 °C for 1.5 h to give **85** with a good yield (90%) (bp 158−160 °C/3 mmHg, mp 63−64 °C; ^{31}P NMR ($CDCl_3$) $\delta = +19.1$ppm).[120] This method gives better results than that described earlier from 2-chloro-4,5-benzo-1,3,2-dioxaphosphole (**86**) and paraformaldehyde at high temperature (200 °C) for 3 h for which the yield did not exceed 50% (Scheme 49).[5a]

Scheme 49



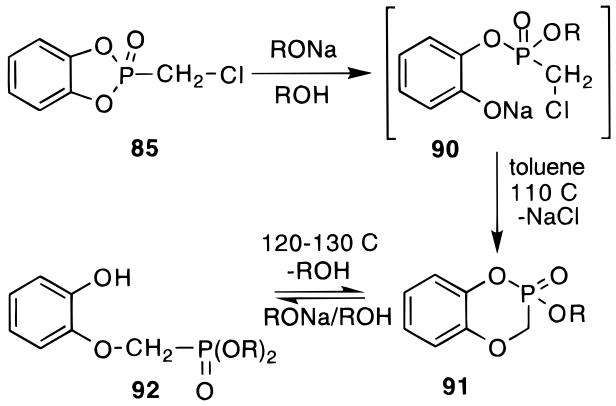
Compound **85** can be used in the synthesis of alkyl and aryl [(*o*-oxyphenoxy)methyl]phosphinic acids (**89**). Attack at the phosphorus atom of **85** by a Grignard reagent leads to ring opening.[121] The magnesium atom appears to be bonded to the phosphoryl group rather than the phenolic oxygen and thus the intermediate magnesium ion does not undergo intramolecular chloride displacement. After neutralization with HCl, it gives the *o*-phenyl esters **87**, which upon reflux in toluene in the presence of triethylamine cyclize to give the phosphorines **88** (Scheme 50). The cyclic esters **88** are very easily hydrolyzed to the phosphinic acids **89**. Cleavage of the phosphorine ring is observed on contact with atmospheric moisture. Compounds **89** are able to eliminate water on reflux in xylene, thereby quantitatively reverting to the cyclic esters **88**.

Scheme 50



A similar reaction using various alkoxides in absolute alcohol instead of the Grignard reagents is equally described.[120] This leads to the ring-opened compound **90**, which recyclizes, when heated under reflux in an inert solvent, to give mixtures of the dioxaphosphorin 2-oxides **91** and phosphonates **92** in ratio a depending on the amount of residual alcohol in the reaction mixture (Scheme 51).

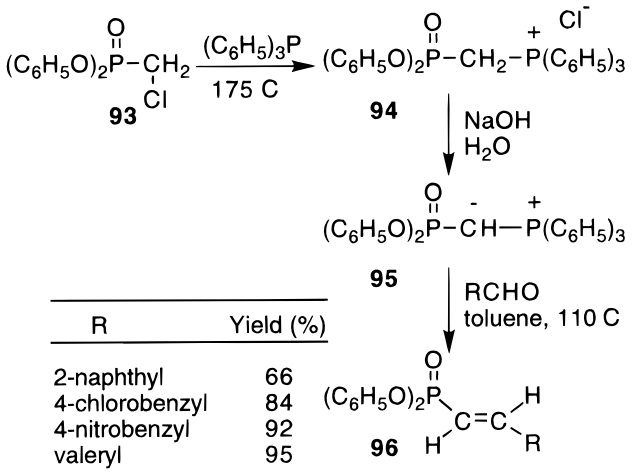
Scheme 51



3. Ylide Chemistry of Diphenyl (Chloromethyl)-phosphonate

Diphenyl (chloromethyl)phosphonate has been utilized as an ylide precursor (bis(*o*-chlorophenyl) (chloromethyl)phosphonate is also described). The triphenyl(diphenoxyoxophosphoranyl)methylene phosphorane (**95**) is obtained on a large scale by quaternarization of triphenylphosphine with diphenyl (chloromethyl)phosphonate (**93**) at 175 °C for 4 h followed by treatment with an aqueous solution of sodium hydroxide. The desired ylide **95** was recrystallized from ethyl acetate (mp 149−150 °C) in an overall yield of 77%. It proved to be very stable toward storage at room temperature but reacted smoothly with a variety of aromatic and aliphatic aldehydes at 100−110 °C in DMSO to produce only the trans isomers of the appropriate diphenyl vinylphosphonates **96** (Scheme 52).[122] The use of stabilized ylides such as **95** offers the advantage of not requiring strongly basic reagents for carbanion formation.

Scheme 52

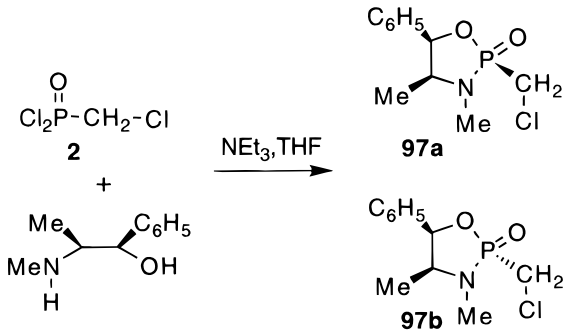


R	Yield (%)
2-naphthyl	66
4-chlorobenzyl	84
4-nitrobenzyl	92
valeryl	95

4. 2-(Chloromethyl)-3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholane

A mixture of diastereomeric (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-2-(chloromethyl)-3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholanes (**97a** and **97b**) is obtained in 60% yield from the reaction of (−)-ephedrine with **2** in THF in the presence of triethylamine at room temperature. The 3/1 mixture of the two diastereomers is separated by silica gel column chromatography to afford enantiomerically pure samples of **97a** (mp 85 °C; ^{31}P NMR ($CDCl_3$) δ = +35.84 ppm) and **97b** (mp 80 °C; ^{31}P NMR ($CDCl_3$) δ = +34.47 ppm), respectively (Scheme 53).[123]

Scheme 53

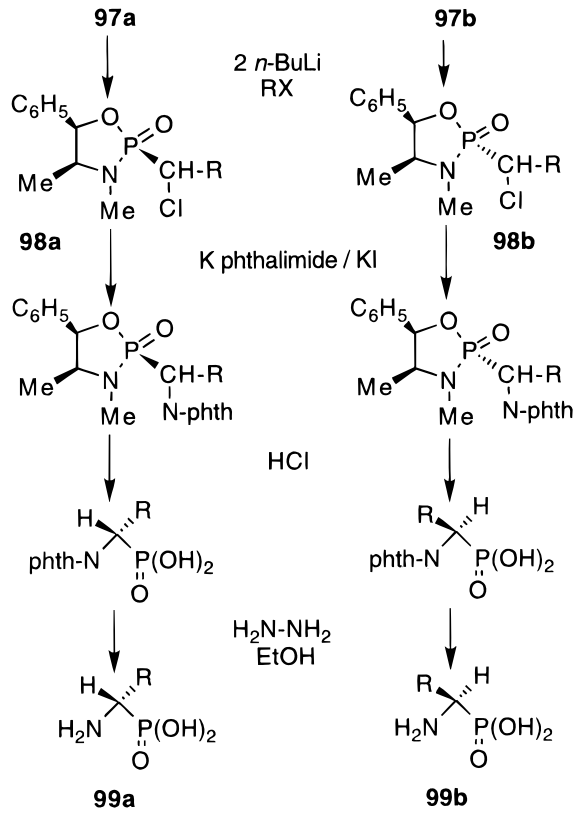


Deprotonation of each diastereomer with *n*-BuLi in THF at low temperature followed by alkylation at the same temperature results in formation of the corresponding α-substituted oxazaphospholanes **98a** and **98b** in moderate yield (40−65%). Reaction of each isomer with potassium phthalimide in toluene at 50 °C under sonication conditions gives the corresponding *N*-phthalimido oxazaphospholanes which are converted into (*R*)- and (*S*)-(aminoalkyl)phosphonic acids **99a** and **99b** after acidic hydrolysis followed by treatment with ethanolic hydrazine (Scheme 54).[123]

5. 3-*tert*-Butyl-2-(chloromethyl)-6,6-dimethyl-2-oxo-1,3,2-oxazaphosphorinane

The readily available *N*-*tert*-butyl-3,3-dimethyl-1-aminopropyl 3-alcohol is coupled with **2** in dichloromethane in the presence of triethylamine to afford racemic 2-(chloromethyl)-1,3,2-oxazaphosphorinane

Scheme 54



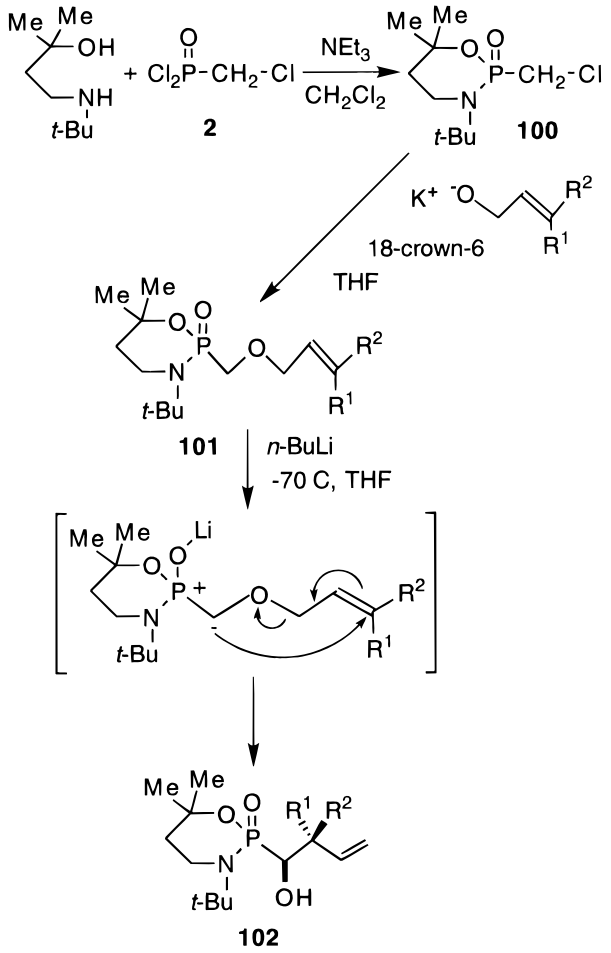
100 in 72% yield. Displacement of the chloride is accomplished by treatment with an allylic potassium alkoxide in the presence of a stoichiometric amount of 18-crown-6 ether to give the corresponding racemic 1,3,2-oxazaphosphorinane **101**. Deprotonation of **101** at −70 °C with *n*-BuLi in THF generated the phosphorus-stabilized anion which underwent a [2,3]-Wittig rearrangement to afford the 2-(1′-hydroxybut-3′-enyl)-1,3,2-oxazaphosphorinanes **102** in good yield (Scheme 55).[124] In the rearrangement, a single product is observed when $R^1 = R^2 = H$ or $R^1 = Me$, $R^2 = H$; a mixture of two diastereomeric products is observed when $R^1 = H$ and $R^2 = Me$.

The same reaction sequence has been performed starting from optically pure 4-(*N*-*tert*-butylamino)-2-butanol. The corresponding rearrangement products were obtained in enantiomerically pure form.

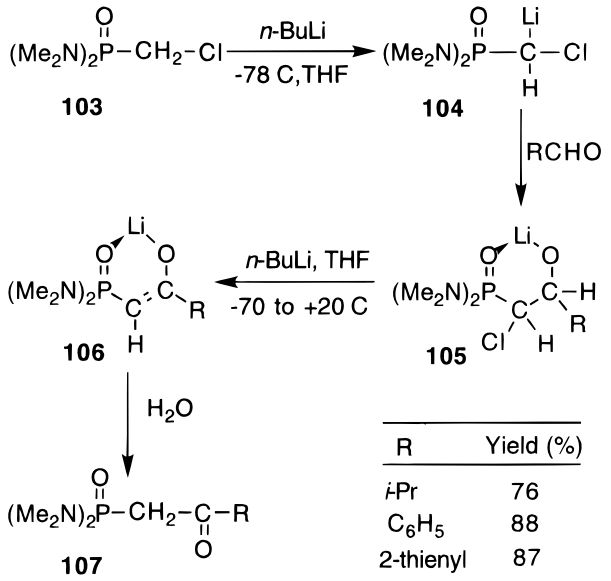
6. *N*,*N*,*N*′,*N*′-Tetramethyl(chloromethyl)phosphonic Diamide

N,*N*,*N*′,*N*′-Tetramethyl(chloromethyl)phosphonic diamide (**103**) is a highly hygroscopic white crystalline solid (bp 117−118 °C/4 mmHg; mp 48.5−49.5 °C; ^{31}P NMR ($CDCl_3$) δ = +30.4 ppm). The compound is prepared by the reaction of **2** with excess dimethylamine in THF. The reaction proceeds in nearly quantitative crude yield. The lithium reagent **104**, prepared at low temperature from **103** and *n*-butyllithium, reacts with aldehydes to give an intermediate chlorohydrin **105**. In the presence of a second equivalent of metalating agent, **105** undergoes dehydrochlorination to produce, after hydrolysis, the synthetically useful (2-oxoalkyl)phosphonic diamides **107** in high yield (Scheme 56).[70,125]

Scheme 55



Scheme 56



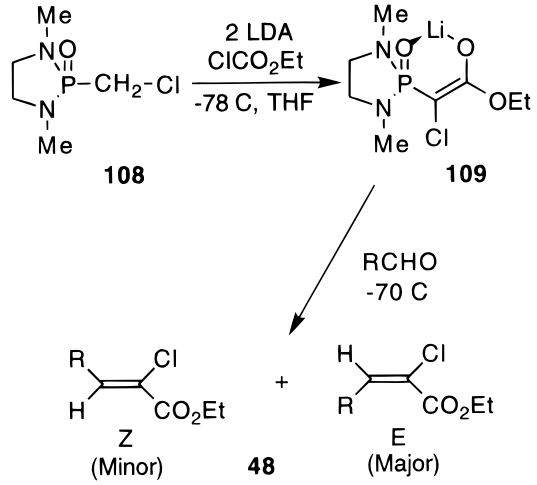
7. 2-(Chloromethyl)-1,3-dimethyl-2-oxo-1,3,2-diazaphospholane

2-(Chloromethyl)-1,3-dimethyl-2-oxo-1,3,2-diazaphospholane (**108**) is a stable but moisture-sensitive solid (mp 75−77 °C, ^{31}P NMR ($CDCl_3$) δ = +29.8 ppm).[117] The compound is prepared in THF by reaction of (chloromethyl)phosphonic dichloride **2** with *N*,*N*′-dimethylethylenediamine in the presence of triethylamine. The reaction proceeds in nearly quantitative crude yield. When reacted simultaneously with 2 equiv of LDA and a chloroformate, **108** yields the lithium enolate **109**. On reaction with an aldehyde, the α-chlorinated acrylic esters **48** are formed. The cyclic diazaphospholane moiety appears to exert a major influence on the stereoselectivity of the reaction and **48** show predominantly *E* stereochemistry (Scheme 57 and Table 14).[118] By contrast,

Table 14. α-Chloroacrylic Esters 48[118]

R	yield, %	Z/E
n-Pr	94	2/98
i-Bu	99	3/97
Et_2CH	99	3/97
n-C_6H_{12}	96	2/98
cyclo-C_6H_{12}	98	2/98
n-C_9H_{19}	99	2/98
C_6H_5	99	9/91

Scheme 57



48 are obtained from the diethyl [1-(ethoxycarbonyl)-1-chloromethyl]phosphonate **49** as either isomeric mixtures or pure *Z* isomers (Scheme 28 and Table 10).

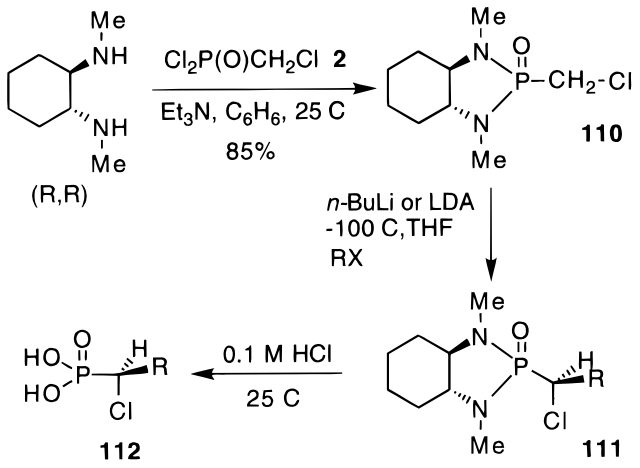
8. *N*,*N*′-Dimethyl-*N*,*N*′-(1,2-cyclohexanediyl)-chloromethylphosphonic Diamide

Compound **110** is synthesized in benzene from the reaction between (chloromethyl)phosphonic dichloride (**2**) and 1,2-bis(*N*-methylamino)cyclohexane in the presence of triethylamine. When the (*R*,*R*)-1,2-bis(*N*-methylamino)cyclohexane (a readily available C_2 symmetrical template) is used, the resulting phosphonic diamide **110** is obtained. In the presence of a base such as *n*-BuLi or LDA in THF at −100 °C, **110** can be alkylated at the prochiral α-position to give essentially a single diastereoisomer of the alkylated phosphonic diamides **111** in high yields and excellent optical purity (Scheme 58 and Table 15).[126] Attack takes place from the "pro *R*" side of the planar anion, through a Li-coordinated intermediate. Furthermore these phosphonic diamides can easily be hydrolyzed under mild conditions to give optically pure (*R*)-α-chloroalkylphosphonic acids again in excellent yields. The opposite enantiomer (*S*) of the phosphonic acids **112** can be obtained starting from the phosphonic diamide **110** prepared from the (*S*,*S*)-diamine.

Table 15. Optically Active (1-Chloroalkyl)phosphonic Acids 112[126]

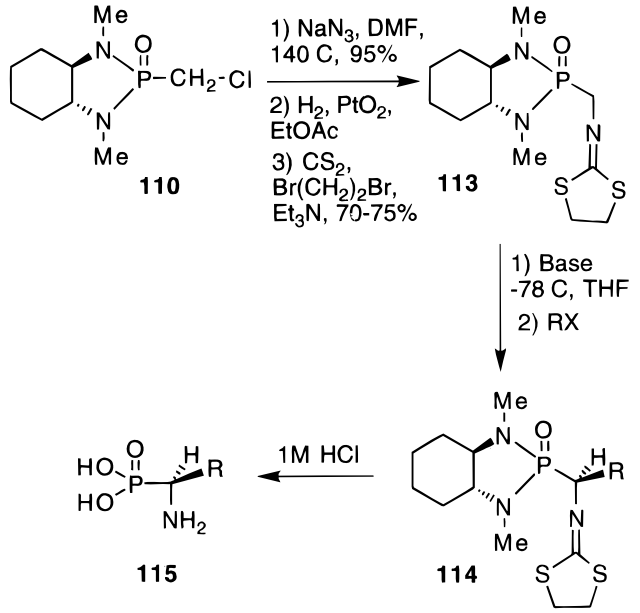
	ratio R:S of **111**	yield of **112**, %
R,R series RX		
MeI	90:10	95 (*R*)
EtI	>99:1	98
n-PrI	>99:1	97
CH_2=$CHCH_2Br$	>99:1	quant
$C_6H_5CH_2Br$	91:9	quant
S,S series RX		
$C_6H_5CH_2Br$	7:93	98 (*S*)
EtI	>1:99	97

Scheme 58



(α-Aminoalkyl)phosphonic acids **115**, which are probably the most important analogues of α-amino acids in biological systems,[127] can be synthesized in enantiomerically pure or enriched form via a similar methodology by using the (chloromethyl)phosphonic diamide **110** and sodium azide as precursor of the amino group (Scheme 59 and Table 16).[103]

Scheme 59

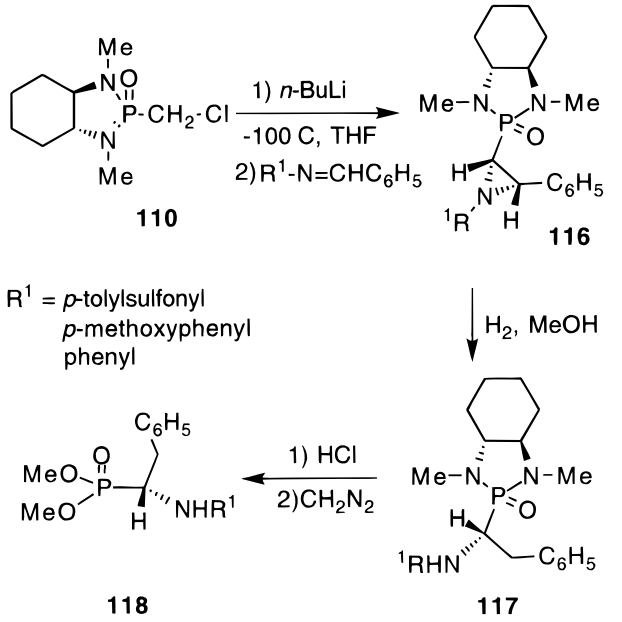


An alternative approach for the asymmetric synthesis of (α-aminoalkyl)phosphonic acids from **110** is based on the stereoselective addition of the corresponding lithiated carbanion to imines. The thus obtained aziridines **116** are then ring opened by hydrogenolytic cleavage to give the (α-aminoalkyl)-phosphonic diamides **117** which are in turn hydrolyzed to the corresponding phosphonic acids, isolated as the dimethyl phosphonate **118** (Scheme 60).[128]

Table 16. Optically Active (1-Aminoalkyl)phosphonic Acids 115[103]

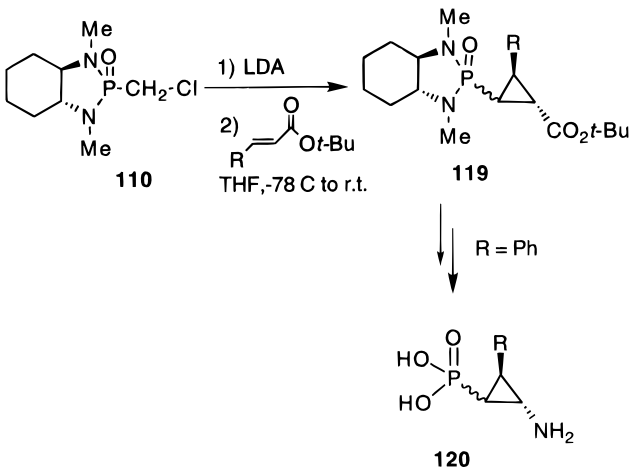
	ratio *R*:*S* of **114**	yield of **115**, %
R,R series RX		
MeI	90:10	82 (*R*)
EtI	>95:5	84
n-PrI	>99:1	86
CH_2=$CHCH_2Br$	>99:1	88
$C_6H_5CH_2Br$	>99:1	87
S,S series RX		
MeI	8:92	84 (*S*)
$C_6H_5CH_2Br$	>1:99	86

Scheme 60



The (chloromethyl)phosphonic diamide **110** is also used as chiral starting material for the synthesis of the enantiomerically pure cyclopropylphosphonic diamides **119**. The stereocontrolled conjugate addition of anion derived from **110** to α,β-unsaturated esters leads to the corresponding (1-chloro-3-carboxypropyl)-phosphonate adduct which undergoes intramolecular

Scheme 61



expulsion of the chlorine atom to give the corresponding cyclopropanes **119** (Scheme 61). Further transformations of **119** allowed the synthesis of (2-aminocyclopropyl)phosphonic acid **120** in optically pure form.[129]

VI. Conclusion

This review demonstrates the versatility of (chloromethyl)phosphonyl compounds as starting materials for preparing a vast array of useful functionalized phosphonates and nonphosphorylated organic materials. These can be realized either by the use of (1-lithiochloromethyl)phosphonate or by nucleophilic substitution of the chlorine atom. The rich and various chemistry of (chloromethyl)phosphonic acid derivatives, esters and amides, covers a large area from the formation of synthetically useful derivatives to the preparation of phosphorus compounds possessing biological activity. In addition, many of the methods described in this aricle can be accomplished with complete stereochemical control thanks to the suitable choice of substituents of the phosphorus atom. We hope that this review will help the exploration of this valuable area of phosphorus chemistry.

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