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Fluorine-containing Halogenomethylenephosphoranes

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The methods of synthesis of fluorine-containing halogenomethylenephosphoranes, their stability, and their applications in the Wittig reaction in order to obtain fluorine-substituted olefins are examined.
The bibliography includes 80 references.

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I. INTRODUCTION

Phosphorus ylids are widely used in organic synthesis[1-7], mainly in order to obtain various unsaturated compounds by the Wittig reaction. In recent years phosphorus ylids containing fluorine or fluorinated residues in the methylene group have been used on an increasing scale. The properties of fluorine-containing phosphorus ylids and the methods of their generation depend on the relative positions of the fluorine atoms and the carbanionic centre of the methylene group.

Fluorine-containing halogenomethylenephosphoranes, which are the subject of the present review†, constitute a special group of such phosphorus ylids.

Fluorine-containing mono- and di-halogenomethylenephosphoranes (I, a–h) are apparently insufficiently stable for their isolation in a pure form.

$R_3P{=}CFX$ (I)

R	Ph	Ph	Ph	Ph	n-Bu	n-Bu	Me_2N	Me_2N
X	H	F	Cl	Br	F	Cl	F	Cl
	(Ia)	(Ib)	(Ic)	(Id)	(Ie)	(If)	(Ig)	(Ih)

These compounds are obtained by different methods and are used without isolation in the "carbonyl olefinating" Wittig reaction. Two cases are then possible.

(1) The phosphorus ylid is generated in the presence of the reagent (carbonyl compound) involved in the subsequent reaction (reaction *in situ*).

(2) The phosphorus ylid is generated and then, without its isolation, the carbonyl compound is added to the reaction mixture ("the olefinating solution").

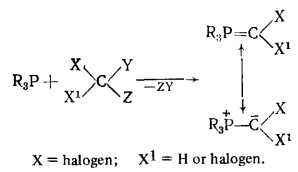
The superiority of a particular method depends not only on the method of generation and stability of the ylid but also on the nature of the reagent, mainly on its reactivity in reactions with the ylids and with the initial compounds from which the ylid is obtained.

Usually, even when the ylids are generated in a preliminary step, there is no certainty that the reaction mixture actually contains the ylid. Although, on subsequent interaction with the reagent, the final products which should have been obtained from the phosphorus ylid are indeed formed, nevertheless in certain cases the ylid is absent from the mixture or is present in very insignificant amounts. This is sometimes confirmed by spectroscopic data (see below), but, even if such evidence is lacking, in their subsequent exposition it will be arbitrarily assumed that the "olefinating solution" does contain the phosphorus ylid.

† In writing this review, the authors used the automated information searching system for the chemistry of organofluorine compounds—AIPS "FTOR" [All-Union Institute of Scientific and Technical Information (VINITI),

II. SYNTHESIS

Regardless of the reaction mechanism, the methods of synthesis of mono- and di-halogenomethylenephosphoranes are based as a rule on the interaction of a tertiary phosphine with some source of a mono- or di-halogenomethylene fragment:

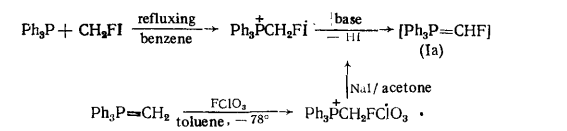


X = halogen; X^1 = H or halogen.

Such sources of halogenomethylenes can be methylene halides, haloforms, carbon tetrahalides, derivatives of halogenoacetic acids, and certain other compounds.

1. Interaction of Tertiary Phosphines with Methylene Halides

Fluoroiodomethane readily alkylates triphenylphosphine to form a stable phosphonium salt[8]. A particularly pure iodide can be obtained by the fluorination of methylenetriphenylphosphorane with subsequent replacement of the anion on treatment with sodium iodide[9]. The dehydroiodination of this salt by BuLi,[8,10] iso-PrNLi,[8] t-BuOK,[11] or the adduct PhLi.LiBr [9] leads to fluoromethylenetriphenylphosphorane (Ia):



(1)

The deuterated ylid $Ph_3P{=}CDF$ has been obtained similarly[12].

2. Interaction of Tertiary Phosphines with Haloforms

The stable fluoroiodomethyltriphenylphosphonium iodide# is formed from triphenylphosphine and fluorodi-iodomethane and is then converted under the influence of the zinc–copper couple into fluoromethylenetriphenylphosphorane (Ia)§ :[8,10]

It may be that in this process the "positively charged" iodine atom is initially attacked by the phosphine with subsequent "anionic exchange" in the phosphonium salt (see below).

§ The phosphorus ylid (Ia) is probably formed as a complex with zinc iodine[8].

$$Ph_3P + CHFI_2 \xrightarrow[CH_2Cl_2]{60^\circ} Ph_3\overset{+}{P}CHFI\ \bar{I} \xrightarrow[DMF]{Zn/Cu,\ 0^\circ} \underset{(Ia)}{[Ph_3P{=}CHF]}\ . \qquad (2)$$

In the presence of strong bases haloforms give rise to dihalogenocarbenes, which can add to a tertiary phosphine to form the corresponding phosphorus ylid. Thus chlorofluoromethylenetriphenylphosphorane (Ic) has been obtained from dichlorofluoromethane and triphenylphosphine in the presence of t-BuOK:[13–16]

$$CHFCl_2 \xrightarrow[-KCl,\ -Me_3COH]{+Me_3COK} [:CFCl] \xrightarrow{+Ph_3P} \underset{(Ic)}{[Ph_3P{=}CFCl]}\ . \qquad (3)$$

It was not possible to obtain by a similar procedure difluoromethylenetriphenylphosphorane (Ib) from chlorodifluoromethane (the initial triphenylphosphine was recovered unchanged)[13]. It has been suggested that the diflurocarbene formed reacts preferentially with t-BuOH and not with Ph_3P. Nor was it possible to obtain analogously difluromethylenetributylphosphorane (Ie) [13] and chlorofluoromethylene-tributylphosphorane (If).[13,14]

3. Interaction of Tertiary Phosphines with Carbon Tetrahalides

The accumulation of electron-accepting halogen atoms in the carbon tetrahalide molecules makes possible the attack by the tertiary phosphine on the "positively charged" halogen. This results in the formation of a halogenophosphonium salt, which can be converted into a trihalogenomethylphosphonium salt by "anion exchange":[17,18]

$$R_3P + CX_4 \rightarrow R_3\overset{+}{P}X\ \bar{C}X_3 \xrightarrow{O} R_3\overset{+}{P}CX_3\ \bar{X}\ .$$

In the reaction with mixed fluorine-containing carbon tetrahalides the less electronegative atom of the other halogen is attacked rather than the fluorine atom, which results in the formation of fluorine-containing quaternary phosphonium salts.

Thus the reaction of triphenylphosphine with dibromodifluoromethane yielded the stable bromodifluoromethyltriphenylphosphonium bromide[19,20]. Trichlorofluoromethane does not react with triphenylphosphine under mild conditions, while under more severe conditions a complex mixture of substances is formed[21]. However, the reaction with tris(dimethylamino)phosphine yields readily the stable dichlorofluoromethyltris(dimethylamino)phosphonium chloride[18,22]:

$$Ph_3P + CF_2Br_2 \longrightarrow Ph_3\overset{+}{P}CF_2Br\ \bar{Br}\ ;$$
$$(Me_2N)_3P + CFCl_3 \longrightarrow (Me_2N)_3\overset{+}{P}CFCl_2\bar{Cl}\ .$$

Dehalogenation of phosphonium salts leads to fluorine-containing halogenomethylenephosphoranes. The reaction frequently takes place without the isolation of the phophonium salts, the tertiary phosphine taken in excess serving as the dehalogenating agent. The corresponding ylids (I, b and d) have been obtained in this way from triphenylphosphine and dichlorodifluoromethane[23,24], dibromodifluoromethane[23–29], and tribromofluoromethane[30]:

$$2Ph_3P + CFXY_2 \xrightarrow[\text{diglyme or triglyme};\ -Ph_3PY_2]{70^\circ} \underset{(I,\ b\ and\ d)}{[Ph_3P{=}CFX]}\ . \qquad (4)$$

X	F	F	Br
Y	Cl	Br	Br

The ylid (Ig) is formed similarly from tris(dimethylamino)phosphine and CF_2Br_2:[26,29]

$$2(Me_2N)_3P + CF_2Br_2 \xrightarrow[\text{triglyme},\ -(Me_2N)_3PBr_2]{20^\circ} \underset{(Ig)}{[(Me_2N)_3P{=}CF_2]}\ . \qquad (5)$$

However, in many instances a multistage synthesis is more convenient: the interaction of equimolar amounts of the phosphine and carbon tetrahalide yields a phosphonium salt, which is then dehalogenated by treatment with a second mole of the phosphine (another tertiary phosphine can be used at this stage). "Olefinating solutions"—sources of difluoromethylenetriphenylphosphorane[20,31], difluoromethylenetris(dimethylamino)phosphorane (Ig),[20,31] and chlorofluoromethylenetris(dimethylamino)phosphorane (Ih) [18,32,33]—have been obtained in this way:

$$R_3\overset{+}{P}CF_2Br\ \bar{Br} + R_3P \xrightarrow[-R_3PBr_2]{} \underset{(I,\ b\ and\ g)}{[R_3P{=}CF_2]}\ ; \qquad (6)$$

$$(Me_2N)_3\overset{+}{P}CFCl_2\ \bar{Cl} + R_3P \xrightarrow[-R_3PCl_2]{} \underset{(Ih)}{[(Me_2N)_3P{=}CFCl]}\ ; \qquad (7)$$

R = Ph or Me_2N.

It must be emphasised that in reality these solutions may not contain phosphorus ylids, although their interaction with carbonyl compounds does yield the products of the Wittig reaction. Thus, after refluxing an acetonitrile solution of equimolar amounts of Ph_3P and bromodifluoromethyltriphenylphosphonium bromide for 6 h, only the initial phosphonium salt was detected by ^{19}F NMR, while difluoromethylenetriphenylphosphorane was not found; nevertheless, on treatment with a carbonyl compound, the Wittig reaction takes place successfully[20]. Evidently the dehalogenation of the phosphonium salt by triphenylphosphine is reversible, the equilibrium being strongly displaced towards the initial compounds. In the presence of a carbonyl compound the phosphorus ylid (Ib) is removed from the reaction, which shifts the equilibrium towards the final products:

$$Ph_3\overset{+}{P}CF_2Br\ \bar{Br} + Ph_3P \rightleftharpoons \underset{(Ib)}{[Ph_3P{=}CF_2]} + Ph_3PBr_2$$
$$\Big| \diagdown C{=}O \qquad (8)$$
$$\downarrow$$
$$\diagup C{=}CF_2 + Ph_3PO\ .$$

The $(Me_2N)_3\overset{+}{P}CF_2Br\ \bar{Br}$ + $(Me_2N)_3P$ [20] and $(Me_2N)_3\overset{+}{P}CFCl_2\ \bar{Cl}$ + Ph_3P [18] systems behave similarly. On the other hand, when dichlorofluoromethyltris(dimethylamino)phosphonium chloride is acted upon by $(Me_2N)_3P$, an exothermic reaction is observed even in the absence of the third component and the resulting solution does not exhibit an "olefinating" activity¶.[18] Evidently in this case the equilibrium is displaced to the right; in the absence of a carbonyl compound, the resulting ylid (Ih) is removed from the reaction as a result of decomposition[18,33]:

$$(Me_2N)_3\overset{+}{P}CFCl_2\ \bar{Cl} + (Me_2N)_3P \rightarrow \underset{(Ih)}{[(Me_2N)_3P{=}CFCl]} + (Me_2N)_3PCl_2\ .$$
(decomposition products)

Trihalogenomethylphosphonium salts can be dehalogenated successfully even by metals. Thus the interaction of $CFCl_3$ with triphenylphosphine and zinc in the presence of carbonyl compounds leads to the formation of the products of the Wittig reaction[21,33]. This probably involves the formation of a quasi-complex organometallic compound+, which dissociates into $ZnCl_2$ and the phosphorus ylid (Ic):

$$Ph_3P + CFCl_3 + Zn \xrightarrow[DMF]{60^\circ} \left[Ph_3\overset{+}{P}(ZnCl)-CFCl\ \bar{Cl} \right]$$
$$\Big\| \qquad (9)$$
$$\diagup C{=}CFCl \xleftarrow[-Ph_3PO]{+\diagdown C{=}O} \underset{(Ic)}{[Ph_3P{=}CFCl]} + ZnCl_2\ .$$

¶ When the reaction is carried out *in situ* (in the presence of a carbonyl compound), the same system gives rise to the products of the Wittig reaction with high yields[18].

+ Similar quasi-complexes of non-fluorinated ylids with mercury(II) chloride are known[34–37].

The formation of the ylid (Ib) is postulated when metals act on a mixture of triphenylphosphine and CF_2Br_2 [29] or on bromodifluoromethyltriphenylphosphonium bromide[28,38]:

$$Ph_3P + CF_2Br_2 + Zn \xrightarrow[AcNMe_2]{100-110^\circ} \underset{(Ib)}{[Ph_3P{=}CF_2]} + ZnBr_2 \quad ; \qquad (10)$$

$$Ph_3\overset{+}{P}CF_2Br\ \bar{B}r \xrightarrow[-HgBr_2]{+Hg} \underset{(Ib)}{[Ph_3P{=}CF_2]} \quad . \qquad (11)$$

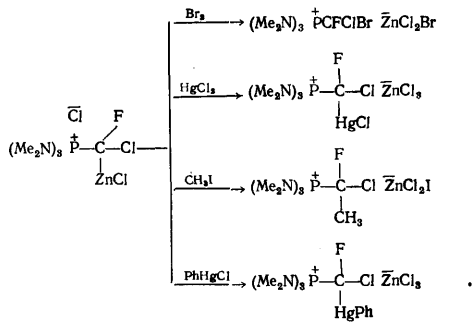
The ylid (Ig) has been obtained similarly[29]:

$$(Me_2N)_3P + CF_2Br_2 + Zn \xrightarrow{AcNMe_2} \underset{(Ig)}{[(Me_2N)_3P{=}CF_2]} + ZnBr_2 \quad . \qquad (12)$$

The action of Group IIB metals (zinc, cadmium, and mercury) on dichlorofluoromethyltris(dimethylamino)phosphonium chloride has been studied in particular detail. This entails the formation of an exceptionally stable "olefinating solution" containing a quasi-complex organometallic phosphonium salt#, [32,33] for example:

$$(Me_2N)_3\overset{+}{P}CFCl_2\ \bar{C}l + Zn \xrightarrow[THF]{60^\circ} (Me_2N)_3\overset{+}{P}{-}\underset{ZnCl}{\overset{F}{C}}{-}Cl\ \bar{C}l \quad . \qquad (13)$$

The structure of the quasi-complex salts obtained was confirmed by ^{19}F and ^{31}P NMR and also by chemical reactions[32]:



On treatment with carbonyl compounds, the quasi-complex salts undergo the Wittig reaction, probably as a result of the reversible dissociation into the ylid and a metal salt[32,33]:

$$(Me_2N)_3\overset{+}{P}{-}\underset{ZnCl}{\overset{F}{C}}{-}Cl\ \bar{C}l \rightleftarrows \underset{(I3)}{[(Me_2N)_3P{=}CFCl]} + ZnCl_2$$

$$[(Me_2N)_3P{=}CFCl] \xrightarrow[-(Me_2N)_3PO]{+C=O} \rangle C{=}CFCl \quad .$$

In the synthesis of a phosphorus ylid from a trihalogenomethylphosphonium salt the trihalogenomethyl anion can evidently also act as a dehalogenating agent. It has been shown[19,39,40] that trihalogenomethylphosphonium salts serve as convenient sources of trihalogenomethyl anions and dihalogenocarbenes in the presence of alkali metal fluorides, for example:

$$Ph_3\overset{+}{P}CF_2Br\ \bar{B}r \xrightarrow{+\bar{F}} Ph_3PFBr + [\bar{C}F_2Br] \xrightarrow[-Br^-]{} [:CF_2] \quad .$$

In the presence of benzoyl fluoride the product of the Wittig reaction, namely 3-bromotetrafluoro-2-phenylpropene (yield 57%), was obtained in addition to ω-bromo-ω,ω-difluoroacetophenone (yield 9%). [39] It is suggested that this involves the intermediate formation of the ylid (Ib) as a result of the dehalogenation of the phosphonium salt by the anion $\bar{C}F_2Br$:

$$Ph_3\overset{+}{P}CF_2Br\ \bar{B}r \xrightarrow[-Ph_3PFBr]{+KF} [\overset{+}{K}\bar{C}F_2Br] \xrightarrow[-KBr,\ -CF_2Br_2]{+Ph_3\overset{+}{P}CF_2Br\ \bar{B}r} \underset{(Ib)}{[Ph_3P{=}CF_2]} \quad ;$$

$$[\overset{+}{K}\bar{C}F_2Br] + PhCOF \xrightarrow{-K\bar{F}} PhCOCF_2Br \quad ;$$

$$PhCOCF_2Br + \underset{(Ib)}{[Ph_3P{=}CF_2]} \xrightarrow[-Ph_3PO]{} \begin{matrix} Ph \\ \diagdown \\ BrCF_2 \end{matrix}\!\!>C{=}CF_2 \quad .$$

The "conserving" influence of mercury(II) chloride on non-fluorinated phosphorus ylids is also known[36].

The presence of the phosphorus ylid (Ib) was confirmed by the reaction with trifluoroacetophenone[39]:

$$\underset{(Ib)}{[Ph_3P{=}CF_2]} + PhCOCF_3 \rightarrow \begin{matrix} Ph \\ \diagdown \\ CF_3 \end{matrix}\!\!>C{=}CF_2\ (33\%) \quad .$$

The ylid (Ib) has also been obtained from CF_2Cl_2 under the influence of triphenylphosphine and KF.[15]

The formation of the ylid (Ib) from equimolar amounts of dibromodifluoromethane, triphenylphosphine, and butyllithium was described in 1960 (without experimental details) (the intermediate formation of difluorocarbene was postulated):[41]

$$CF_2Br_2 \xrightarrow[-LiBr]{+BuLi} [:CF_2] \xrightarrow{+Ph_3P} \underset{(Ib)}{[Ph_3P{=}CF_2]} \quad .$$

However, in a later study[13] this result could not be reproduced.

4. The Interaction of Tertiary Phosphines with Derivatives of Trihalogenoacetic Acids

The decarboxylation of trihalogenoacetate salts is frequently used to generate dihalogenocarbenes[40,42]. Decarboxylation in the presence of tertiary phosphines leads to the formation of the corresponding phosphorus ylids. Thus difluoromethylenetriphenylphosphorane has been obtained from lithium[43-46], sodium[43-54], or potassium[44] chlorodifluoroacetate and triphenylphosphine:

$$Ph_3P + ClCF_2COOM \xrightarrow[\text{diglyme, DMF, } N\text{-methylpyrrolidone, etc.}]{80-180^\circ} \underset{(Ib)}{[Ph_3P{=}CF_2]} + MCl + CO_2 \quad ; \qquad (14)$$
$$M = Li, Na \text{ or } K.$$

The analogous reaction with tributylphosphine led to difluoromethylenetributylphosphorane:[51,55]

$$Bu_3P + ClCF_2COONa \xrightarrow[\text{DMF or } N\text{-methylpyrrolidinone}]{180^\circ} \underset{(Ie)}{[Bu_3P{=}CF_2]} + NaCl + CO_2, \qquad (15)$$

Chlorofluoromethylenetriphenylphosphorane§,[14,16,46,54] bromofluoromethylenetriphenylphosphorane,[30] and chlorofluoromethylenetributylphosphorane[14] have been obtained similarly:

$$Ph_3P + X_2CFCOOM \xrightarrow[\text{triglyme}]{80-90^\circ} \underset{(I,\ c \text{ and } d)}{[Ph_3P{=}CFX]} + NaX + CO_2 \quad ; \qquad (16)$$
$$X{=}Cl, Br;\ M{=}Li, Na$$

$$Bu_3P + Cl_2CFCOONa \xrightarrow[\text{triglyme}]{85^\circ} \underset{(If)}{[Bu_3P{=}CFCl]} + NaCl + CO_2 \qquad (17)$$

It is sometimes suggested[40,47] that these reactions proceed via the intermediate formation of a dihalogenocarbene:

$$Y{-}\underset{F}{\overset{X}{C}}{-}C\overset{O}{\diagup\!\!\diagdown}OM \xrightarrow[-MY,\ -CO_2]{\Delta} \left[\begin{matrix} X \\ \diagdown \\ F \end{matrix}\!\!>C:\right] \xrightarrow{+R_3P} \left[R_3P{=}C\begin{matrix} X \\ \diagup \\ F \end{matrix}\right] \quad .$$

However, there is important evidence against the "carbene" mechanism. Thus the reaction of chlorofluorocarbene generated from dichlorofluoromethane and t-BuOK with an equimolar mixture of triphenylphosphine and tetramethylethylene leads to almost identical yields of a substituted cyclopropane (II) and the phosphorus ylid (Ic) (the yield of the latter was determined from the results of the Wittig reaction with trifluoroacetophenone):[14,16]

$$CHFCl_2 \xrightarrow[-Me_2COH,\ -KCl]{+Me_3COK} [:CFCl] \xrightarrow{Me_2C{=}CMe_2+Ph_3P} \underset{F\quad Cl}{\overset{C}{Me_2C{-}\!\!-\!\!CMe_2}} + \underset{(Ic),\ (19\%)}{[Ph_3P{=}CFCl]}$$
(II), (14%)

Consequently tetramethylethylene and triphenylphosphine have comparable reactivities in reactions with dichlorofluorocarbene. However, the decarboxylation of sodium dichlorofluoroacetate in the presence of tetramethylethylene and triphenylphosphine results in the formation of only the phosphorus ylid (Ic) and the cyclopropane (II) is not detected§. The authors[14,16] therefore concluded that the phosphorus ylid is not formed via the halogenocarbene in the present instance. Evidently the trihalogenoacetate behaves in this reaction like carbon tetrahalides (see above), giving rise to the betaine (III) on interaction with phosphine and the betaine is then decarboxylated to give the phosphorus ylid:

$$Ph_3P + Cl_2CFCOONa \xrightarrow{-NaCl} \underset{(III)}{[Ph_3\overset{+}{P}CFClC\overline{O}O]} \xrightarrow{-CO_2} \underset{(Ic)}{[Ph_3P{=}CFCl]} .$$

Analogous evidence in support of the formation of the betaine $Ph_3\overset{+}{P}CF_2C\overline{O}O$ when difluoromethylenetriphenylphosphorane (Ib) is generated has been adduced by other workers[43]. It has also been shown that the presence of triphenylphosphine accelerated the decarboxylation of sodium chlorodifluoroacetate[43].

Naturally, the mode of reaction should depend on the nucleophilic activity of the tertiary phosphine and on the nature of the halogen atoms in the trihalogenoacetate. The latter affects both the ease of the nucleophilic attack by the phosphine on the halogen atom and the ease of decarboxylation. Nor can one rule out the possibility that in various specific instances the reaction mechanism is different (the "carbene" or "phosphobetaine" mechanism).

In the synthesis of difluoromethylenetriphenylphosphorane (Ib) it is also possible to use trimethyltin trifluoroacetate as the initial trihalogenoacetate[56]:

$$Ph_3P + CF_3COOSnMe_3 \xrightarrow[-Me_3SnF,\ -CO_2]{150^\circ,\ NaI} \underset{(Ib)}{[Ph_3P{=}CF_2]} .$$

The interaction of methyl trihalogenoacetates with a tertiary phosphine in the presence of nucleophiles capable of demethylating esters is a variety of the method of synthesis of fluoromethylenephosphoranes described. Thus difluoromethylenetriphenylphosphorane is formed when methyl chlorodifluoroacetate is acted upon by triphenylphosphine and the complex of LiCl with hexamethylphosphoramide (HMP):[57]

$$Ph_3P + ClCF_2COOMe \xrightarrow[\sim 80^\circ,\ \text{triglyme}]{LiCl\cdot 2(Me_2N)_3PO} \underset{(Ib)}{[Ph_3P{=}CF_2]} . \qquad (18)$$

The ylid (Ib) could be formed via two pathways: via the difluorocarbene (a) or via the phosphonium salt (IV)¶ and the phosphobetaine (V)† (b):

a) $ClCF_2COOMe \xrightarrow[-MeCl]{+LiCl} ClCF_2COOLi \xrightarrow[-LiCl,\ -CO_2]{} [:CF_2] \xrightarrow{+Ph_3P} \underset{(Ib)}{[Ph_3P{=}CF_2]}$

b) $Ph_3P + ClCF_2COOMe \rightarrow \underset{(IV)}{[Ph_3\overset{+}{P}CF_2COOMe\overline{Cl}]} \xrightarrow[-MeCl]{(LiCl)}$

$\rightarrow \underset{(V)}{[Ph_3\overset{+}{P}CF_2C\overline{O}O]} \xrightarrow{-CO_2} \underset{(Ib)}{[Ph_3P{=}CF_2]}$

§ In the absence of triphenylphosphine the cyclopropane (II) was obtained in 37% yield[14,16].

¶ It has been shown[58,59] that, on heating (90–120 °C in DMF), the salt $Ph_3\overset{+}{P}CH_2COOMe\overline{Br}$ decomposes into MeBr, CO_2, and the ylid $Ph_3P{=}CH_2$.

† From the point of view of stoichiometry, the reaction should take place, in principle, in the presence of catalytic amounts of LiCl regardless of its mechanism. However, an excess of the complex of LiCl with HMP was used[57], evidently in order to increase the rate of reaction [the resulting ylid (Ib) was used in the Wittig reaction *in situ*].

Since the presence of triphenylphosphine does not accelerate the decomposition of methyl chlorodifluoroacetate, the "carbene" mechanism (a) is more probable[57].

The chlorofluoro-substituted phosphorus ylid (Ic) has been obtained from methyl dichlorofluoroacetate and triphenylphosphine in the presence of NaH and methanol under mild conditions, possibly via chlorofluorocarbene[60]:

$$Ph_3P + Cl_2CFCOOMe \xrightarrow[\substack{25-30^\circ;\\ \text{heptane or}\\ \text{benzene}}]{NaH/MeOH} \underset{(Ic)}{[Ph_3P{=}CFCl]} . \qquad (19)$$

5. Other Methods of Synthesising Fluorine-Containing Halogenomethylenephosphoranes

On interaction with triphenylphosphine, the usual source of chlorofluorocarbene—dichlorofluoromethylphenylmercury—gives rise to chlorofluoromethylenetriphenylphosphorane:[15]

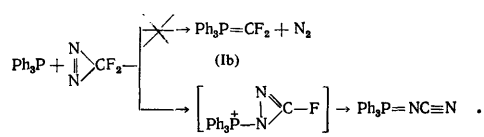
$$Ph_3P + PhHgCFCl_2 \xrightarrow[\text{xylene}]{80^\circ} \underset{(Ic)}{[Ph_3P{=}CFCl]} + PhHgCl . \qquad (20)$$

It has been claimed[61] that difluoromethylenetriphenylphosphorane is formed when trifluoronitrosomethane interacts with ammonia and triphenylphosphine. Difluorodiazomethane is then postulated as an intermediate:

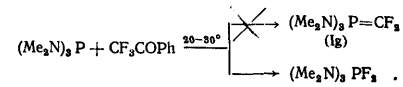
$$CF_3NO \xrightarrow[-H_2O]{+NH_3} [CF_3N{=}NH] \xrightarrow[-NH_4F]{+NH_3} [\overline{C}F_2{-}\overset{+}{N}{\equiv}N] \xrightarrow[-N_2]{+Ph_3P} \underset{(Ib)}{[Ph_3P{=}CF_2]} .$$

However, no evidence has been produced in support of the formation of the ylid (Ib).[61]

The ylid (Ib) cannot be obtained from difluorodiazirine (difluorocyclodiazomethane) and triphenylphosphine[62]:

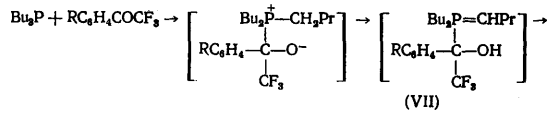


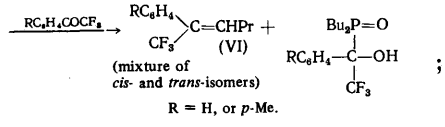
Mark[63] reported the synthesis of difluoromethylenetris(dimethylamino)phosphorane and its ethyl analogue $(Et_2N)_3P{=}CF_2$ by the reaction of the corresponding phosphorus acid triamides [tris(dialkylamino)phosphines] with trifluoroacetophenone. These phosphorus ylids have been described[63] as stable distillable liquids. However, it was shown later[64] that in fact the reaction products are not phosphorus ylids but tris(dialkylamino)difluorophosphoranes, whose structure was demonstrated rigorously by spectroscopic data and by specific synthesis[62,64,65]. The properties of tris(dimethylamino)difluorophosphorane agree fully with those of the compound described by Mark[63], who incorrectly attributed to it the structure (Ig):



Only traces of the ylid (Ig) were detected in the reaction medium by mass spectrometry[64].

Tributylphosphine reacts differently with difluoroacetophenone (and *p*-methyltrifluoroacetophenone); the reaction yields the olefins (VI) probably via the phosphorus ylids (VII):[66]





Other trialkylphosphines react similarly[66].

III. PROPERTIES

As already mentioned, fluorine-containing mono- and di-halogenomethylenephosphoranes (I, a–h) have not been isolated in a pure state#. When different methods of synthesis are used, the reaction mixtures frequently contain different compounds, which are in principle capable of interacting both with the phosphorus ylid (reversibly or irreversibly) and with other reagents. All this causes extreme difficulties in the determination of reliable data on the comparative stabilities and reactivities of fluorine-containing halogenomethylenephosphoranes, despite the extensive experimental results which have been accumulated. However, since these compounds have already assumed a fairly considerable importance and are widely used in the synthesis of fluorine-containing olefins by the Wittig reaction, it is necessary to describe the available data concerning their stabilities. In the first place we shall consider the use of fluorine-containing halogenomethylenephosphoranes in the Wittig reaction.

1. Stability of Fluorine-Containing Halogenomethylenephosphoranes

When the stabilities of compounds (I) are considered, one must not overlook the fact that in practice one is not dealing with a phosphorane as such but with a reaction mixture containing different components. In each case attention must therefore be directed not only to the nature of the ylid but also to the method of its synthesis.

(*a*) *Fluoromethylenetriphenylphosphorane* $Ph_3P=CHF$ (*Ia*). The phosphorus ylid (Ia), obtained in the form of a lemon-yellow solution in tetrahydrofuran (THF) on dehydroiodination of a phosphonium salt by PhLi [(Eqn.(1)], is readily attacked by nucleophiles and decomposes. In its synthesis it is necessary to add slowly, with very thorough stirring, a solution of PhLi to fluoromethyltriphenylphosphonium iodide and to maintain a fairly low temperature (<–50 °C) to avoid self-condensation§ [9] (see also Vanderhaar et al.[30]). Nevertheless this ylid can be generated in solution in the absence of a carbonyl compound and then used in the Wittig reaction[9]. The use of BuLi in a mixture of THF and hexane also leads to a relatively stable solution of the ylid (Ia) (it does not decompose at 0 °C for 40 min but does decompose at 28 °C).[8]

The "olefinating solution", obtained by the dehalogenation of fluoroiodomethyltriphenylphosphonium iodide with the zinc–copper couple in dimethylformamide (DMF) [Eqn.(2)], apparently contains the complex $Ph_3\overset{+}{P}CHFZnI\ \overset{-}{I}$ and not the free ylid (Ia). The solution is relatively unstable—after 90 min at 0 °C it loses almost completely its "olefinating" capacity and is therefore used in the Wittig reaction *in situ*[8].

(*b*) *Difluoromethylenetriphenylphosphorane* $Ph_3P=CF_2$ (*Ib*). Under the conditions of its synthesis by the "halogenoacetate" method [Eqn.(14)], the ylid (Ib) is unstable and can be used in the Wittig reaction only *in situ* in solvents such as diglyme, DMF, and *N*-methylpyrrolidinone. The attempts to use dimethyl sulphoxide as the solvent were unsuccessful, evidently as a result of the interaction of the ylid (Ib) with Me_2SO (dimethyl sulphide was isolated from the reaction product in 84% yield)[43].

When triphenylphosphine reacts with dibromodifluoromethane or bromodifluoromethyltriphenylphosphonium bromide in diglyme, triglyme, or acetonitrile [Eqns.(4) and (6)], stable "olefinating solutions" are formed (they do not decompose in 60 h at 70 °C).[20,26] Their stability can be explained by the reversibility of the formation of the ylid (Ib) and the appreciable shift of the equilibrium [Eqn.(8)] to the left. However, in DMF it is impossible to obtain a stable solution—probably as a consequence of the interaction of the solvent with dibromotriphenylphosphorane Ph_3PBr_2, which shifts the equilibrium to the right[20].

(*c*) *Chlorofluoromethylenetriphenylphosphorane* $Ph_3P=CFCl$ (*Ic*). In contrast to the difluoroylid (Ib), the chlorofluoroylid (Ic) is comparatively stable under the conditions of its synthesis from triphenylphosphine and sodium dichlorofluoroacetate [Eqn.(16)]. After the evolution of CO_2 (after heating for several hours at 80–90 °C in triglyme), a solution with "olefinating" activity was obtained; however, the yields in the Wittig reaction were nevertheless higher when the ylid was employed *in situ*.[14,16]

When chlorofluoromethylenetriphenylphosphorane was generated under mild conditions from methyl dichlorofluoroacetate, Ph_3P, and NaH [Eqn.(19)][60] or from $CHFCl_2$, Ph_3P, and t-BuOK [Eqn.(3)],[13,14,16] relatively stable "olefinating" solutions are also formed.

(*d*) *Bromofluoromethylenetriphenylphosphorane* $Ph_3P=CFBr$ (*Id*). The solution obtained by the reaction of triphenylphosphine with tribromofluoromethane in diglyme or triglyme at 70 °C [Eqn.(4)] does not lose its "olefinating" capacity after 21 h at 37 °C.[30]

(*e*) *Tributyldifluoromethylenephosphorane* $Bu_3P=CF_2$ (*Ie*) *and tributylchlorofluoromethylenephosphorane* $Bu_3P=CFCl$ (*If*). The tributyl-substituted ylids (Ie) and (If) are apparently less stable than the corresponding triphenyl ylids (Ib) and (Ic).[13,14,16] Tributyldifluoromethylenephosphorane[51] and tributylchlorofluoromethylenephosphorane[14] can be generated by the "halogenoacetate" method [Eqns.(15) and (17)] and used in the Wittig reaction *in situ*; however, the attempts to obtain them from a haloform, a phosphine, and t-BuOK [as in Eqn.(3)] proved unsuccessful[13,14,16]. It has been suggested[13] that the ylid (If) reacts with t-BuOH under the reaction conditions.

(*f*) *Difluoromethylenetris(dimethylamino)phosphorane* $(Me_2N)_3=CF_2$ (*Ig*). The "olefinating" solutions which behave as sources of the ylid (Ig) are prepared by treating dibromodifluoromethane [Eqn.(5)][26] or bromodifluoromethyltris(dimethylamino)phosphonium bromide [Eqn.(6)] with tris(dimethylamino)phosphine in triglyme[20,31]¶. These solutions are stable at room temperature (they hardly decompose after 300 h),[26] probably as a consequence of the establishment of a dynamic equilibrium, which ensures the virtual absence of the ylid from the mixture[20] (see above).

Dichloromethylenetriphenylphosphorane $Ph_3P=CCl_2$ has been isolated in the form of a yellow powder; its structure was demonstrated spectroscopically[67].

§ Schlosser and Zimmermann[9] do not give any details.

¶ The report of the isolation of the ylid (Ig) in a pure form[63] was erroneous (see above).

(*g*) *Chlorofluoromethylenetris(dimethylamino)phosphorane* $(Me_2N)_3P=CFCl$ (*Ih*). When Ph_3P reacts with dichlorofluoromethyltris(dimethylamino)phosphonium chloride in benzonitrile [Eqn.(7)], a very stable "olefinating" solution is formed (it does not decompose after 500 h at room temperature or after 24 h at 60 °C). On the other hand, if tris(dimethylamino)phosphine is used instead of triphenylphosphine, the above system can be used in the Wittig reaction only *in situ*[18]. These results can be explained by the different equilibrium positions[18,33] (see above).

The quasi-complex salts obtained when dichlorofluoromethyltris(dimethylamino)phosphonium chloride is acted upon by metals [Eqn.(13)] are usually very stable[32,33]. The organozinc phosphonium salt does not decompose in THF after 10 h at 60 °C or after 30 days at room temperature; the solution in PhCN is less stable (2 h at 60 °C). The analogous cadmium derivative decomposes after 2 h at 60 °C in THF and after 1 h in PhCN. The mercury derivative is particularly stable (it does not decompose after 83 h at 60 °C in PhCN).

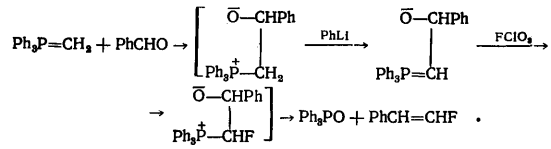
2. Fluorine-Containing Halogenomethylenephosphoranes in the Wittig Reaction. The Synthesis of Fluoro-olefins

The synthesis of olefins by the Wittig reaction is the principal application of phosphorus ylids[1,2,4,6]. Fluorine-containing halogenomethylenephosphoranes are also widely used to synthesise fluoro-olefins from carbonyl compounds†.

The important role of fluoro-olefins as "key" compounds in organofluorine chemistry is known. Despite the abundance of methods for the synthesis of fluoro-olefins, the expansion of this field with the aid of the Wittig reaction is important.

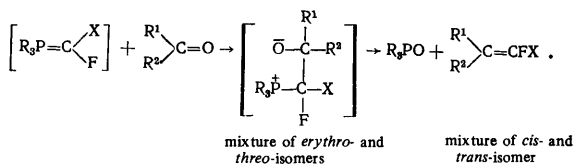
The ease of the Wittig reaction depends on the nucleophilic properties of the ylid and the electrophilic properties of the carbonyl compound[1,2]. The introduction of a halogen into methylenephosphorane apparently reduces somewhat its nucleophilic reactivity[4], but it is nevertheless sufficient for interaction with aldehydes and also with ketones having electron-accepting fluoroalkyl groups. The conversion of inactive ketones into olefins is achieved with much more difficulty. The method of enhancing the nucleophilic properties of the ylid based on the introduction of electron-donating groups at the phosphorus atom has been used recently on an increasing scale. The employment of tris(dimethylamino)-phosphoranes $(Me_2N)_3P=CFX$ instead of triphenyl derivatives $Ph_3P=CFX$ makes it possible in a number of instances to convert into olefins also inactivated ketones. Equilibrium mixtures containing the phosphorus ylid in very low amounts are frequently used in the Wittig reaction instead of the "pure" halogenomethylenephosphoranes; only under the influence of a carbonyl compound does the ylid react with the latter and the equilibrium is displaced to the right. Such "olefinating" systems include mixtures of trihalogenomethylphosphonium salts with tertiary phosphines (see above) and quasi-complex organometallic phosphonium salts (see above). This form of the ylid usually ensures the stability of the "olefinating" agent, but reduces its reactivity.

Apart from using fluorine-containing phosphorus ylids in order to obtain fluoro-olefins, it is possible to apply also another procedure, which likewise involves the Wittig reaction. This is the SCOOPY method (α-substitution plus carbonyl olefination via β-oxido-phosphorus ylids)[4,71-73]. The method is based on the conversion with the aid of a strong base of the phosphobetaine formed from the phosphorus ylid and the carbonyl compound into a "β-oxido-phosphorus ylid", which reacts with an electrophile to form a new α-substituted phosphobetaine; the decomposition of the latter leads to a substituted olefin. For example, when "β-oxido-phosphorus ylid" is fluorinated with subsequent decomposition of the α-fluorophosphobetaine, an α-fluoro-olefin is formed[71]:

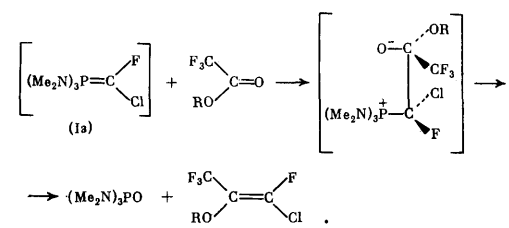


Thus, in terms of its results, this reaction is equivalent to the Wittig reaction with fluoromethylenephosphorane.

In reactions of monofluoro-, chlorofluoro-, and bromofluoro-methylenephosphoranes with aldehydes and asymmetric ketones there is a possibility of the *cis-trans* isomerism of the final products#. In contrast to the reactions with non-fluorinated active phosphorus ylids, which are frequently stereoselective[2,3,11,73,74], the reactions with halogenomethylenephosphoranes as a rule yield *cis*- and *trans*-olefins in approximately equal amounts[8,9,11,12,14-16,18,21,30,32,60]:



Only the interaction of chlorofluoromethylenetris(dimethylamino)phosphorane with fluorocarboxylate esters proved to be stereoselective—mainly the *Z*-isomers of alkylpolyfluoroalkenyl esters are then formed[18,32] (see below). Evidently only one of the diastereoisomeric intermediate phosphobetaines is formed under these conditions:

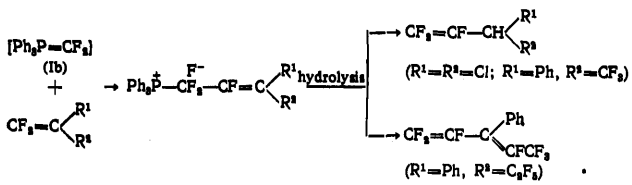


The synthetic applications of fluorine-containing halogenomethylenephosphoranes are virtually limited to the Wittig reaction. However, there are data (without experimental details)[38] showing that difluoromethylenetriphenylphosphorane, generated by treating bromodifluoromethyltriphenylphosphonium bromide with mercury [Eqn.(11)], reacts with fluoro-olefins to form allylphosphonium salts—the products of the "vinyl" substitution of the fluorine atom in the olefin.

† Fluoro-olefins are also obtained from phosphorus ylids without fluorine and from fluorocarbonyl compounds[68,69]. An interesting pathway leading to fluoro-olefins arises from the reaction of phosphorus ylids with halogenocarbenes[70]: $Ph_3P=CR^1R^2 + :CF_2 \rightarrow Ph_3P + R^1R^2C=CF_2$.

For the mechanism and stereochemistry of the Wittig reaction, see Refs.2–4 and 73–77.

Hydrolysis of these salts leads to the cleavage of the C–P bond and the formation of olefins or dienes:



Methods for the introduction of the =CHF, $=CF_2$, =CFCl, and =CFBr groups with the aid of the Wittig reaction are examined below:

(*a*) *The introduction of the =CHF group.* α-Fluoro-α-hydro-olefins are obtained from fluoromethylenetriphenylphosphorane, generated either by the dehydrohalogenation of a fluoromethyltriphenylphosphonium salt [Eqn.(1)][8,9,11] or by the dehalogenation of a fluoroiodomethyltriphenylphosphonium salt [Eqn.(2)].[8,10] The reaction involves aldehydes (aliphatic and aromatic)[8–11] and ketones (activated and non-activated)[8,10]:

$$[Ph_3P{=}CHF] + RCHO \rightarrow RCH{=}CHF + Ph_3PO$$
(Ia) — mixture of *cis*- and *trans*-isomers (~ 1 : 1)

R = n-C_5H_{11}, n-C_6H_{13}, Ph, *m*-ClC_6H_4, or *m*-$CF_3C_6H_4$ (~ 20 °C, THF or CH_2Cl_2, yield 25–65%);
R = n-C_6H_{13}, Ph, or C_6F_5 (0 °C, DMF, yield 52–65%);

$$[Ph_3P{=}CHF] + \underset{R^1}{\overset{R}{>}}C{=}O \rightarrow \underset{R^1}{\overset{R}{>}}C{=}CHF + Ph_3PO$$
(Ia)

$RR^1 = -(CH_2)_5-$; Ph, PhMe
(~20 °C, THF/hexane, yield 48–69%); RR^1 = $PhCF_3$ (0 °C, DMF, yield 80%).

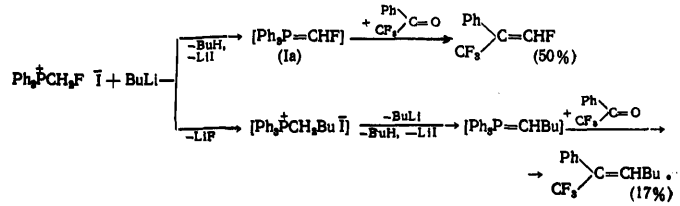
A deuterated olefin was obtained similarly (yield 48%):[12]

$$[Ph_3P{=}CDF] + PhCHO \xrightarrow[THF]{20^\circ} PhCH{=}CDF .$$

A 17-fluoromethylene-substituted steroid has been formed from the 2-tetrahydropyranyl ether of 3β-hydroxo-17-oxo-5-androstene (yield 16%).[9] The attempts to obtain by this method fluoromethylene-substituted sugars from the corresponding ketones were unsuccessful[15].

In the case of non-activated ketones best results are obtained by generating the ylid (Ia) from a fluoromethylphosphonium salt [Eqn.(1)] and, in the case of aldehydes and trifluoroacetophenone, from a fluoroiodomethylphosphonium salt [Eqn.(2)] using the ylid *in situ* in a DMF solution[8].

When BuLi is used to dehydrohalogenate a phosphonium salt in accordance with Eqn.(1), the resulting "olefinating" solution is made to react with a carbonyl compound and the mixture is then treated with potassium t-butoxide; without such treatment, the yields of olefins are reduced[8]. It has been suggested that the betaines produced as intermediates in the Wittig reaction form stable complexes with lithium salts, which hinders their cyclisation to oxaphosphetans preceding the cleavage to the final product—an olefin and a phosphine oxide (cf. Schlosser and Christmann[78]). However, in certain cases the yield of the product of the Wittig reaction is reduced as a consequence of its interaction with t-BuOK. Another cause of the reduced yield of the fluoro-olefin is the formation of a butylolefin as a side product[8]:



Since it has been shown that the entire butyl-lithium is consumed before the ketone is added, the source of the butyl group in the side reaction is apparently a butyl-substituted phosphorus ylid.

It must be emphasised that in many cases it is more convenient to synthesise α-hydrofluoro-olefins by the selective reduction of the corresponding α,α-difluoro-olefins[29] or α-chloro-α-fluoro-olefins[15] and not by the Wittig reaction.

(*b*) *The introduction of the* $=CF_2$ *group.* α,α-Difluoro-olefins are usually obtained from difluoromethylenetriphenylphosphorane, but tributyldifluoromethylenephosphorane and difluoromethylenetris(dimethylamino)phosphorane are also used.

Difluoromethylenetriphenylphosphorane is usually generated from $ClCF_2COONa$ and Ph_3P [Eqn.(14)][43–54] and is used *in situ* in the Wittig reaction§. This ylid gives rise to satisfactory yields of α,α-difluoro-olefins on reaction with aldehydes[45,47,50] and activated ketones[43,52]:

$$[Ph_3P{=}CF_2] + RCHO \xrightarrow[\text{N-methylpyrrolidinone, etc}]{80-180^\circ} RCH{=}CF_2 + Ph_3PO \quad (50-75\%);$$
(Ib)

R = n-C_6H_{13}, Ph, *p*-$MeOC_6H_4$, or *p*-FC_6H_4 ;

$$[Ph_3P{=}CF_2] + \underset{CF_3}{\overset{R}{>}}C{=}O \xrightarrow[\text{diglyme, DMF; etc.}]{75-145^\circ} \underset{CF_3}{\overset{R}{>}}C{=}CF_2 + Ph_3PO \quad (60-85\%);$$
(Ib)

R = n-Bu, C_6H_{11}, $PhCH_2$, Ph¶, *p*-FC_6H_4, *p*-MeC_6H_4 or *p*-$MeOC_6H_4$.

In the reaction with *p*-dimethylamino-ω,ω,ω-trifluoroacetophenone the yield of the olefin *p*-$Me_2NC_6H_4C(CF_3){=}CF_2$ is only 16%.[43]

In many instances the products include, apart from α,α-difluoro-olefins, the products of their reactions in the presence of the F^- anion†. The use of lithium chlorodifluoroacetate instead of the sodium salt usually suppresses these reactions, since LiF is less reactive with respect to fluoro-olefins than NaF.[43,44] Thus the olefin *p*-$ClC_6H_4C(CF_3){=}CF_2$ (yield 32%) and the product of the addition of hydrogen fluoride *p*-$ClC_6H_4CH(CF_3)_2$ (yield 37%) have been obtained from *p*-chlorotrifluoroacetophenone, $ClCF_2COONa$, and Ph_3P in diglyme; in the reaction with the lithium salt in DMF the yield of the olefin increases to 64%.[43]

In the reaction with ketones containing perfluoroalkyl groups the isomerisation of the terminal fluoro-olefin to an internal fluoro-olefin is frequently observed[44], for example:

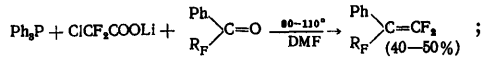
$$[Ph_3P{=}CF_2] + \underset{CF_3CF_2}{\overset{Ph}{>}}C{=}O \xrightarrow{-Ph_3PO} \underset{CF_3CF_2}{\overset{Ph}{>}}C{=}CF_2 \xrightarrow{400^\circ F} \underset{CF_3CF}{\overset{Ph}{>}}C{-}CF_3 .$$
(Ib)

§ A mixture of a phosphine, an acid salt, and a carbonyl compound is heated in the solvent until the evolution of CO_2 ceases. When large amounts of the reactants are used, it is more convenient to add the salt solution dropwise to a heated solution of Ph_3P and the carbon compound[43,50]. When a lithium salt is used, the yield of the α,α-difluoro-olefin is increased[45].

¶ The best yield of 2-phenylpentafluoropropene (80%) was obtained when the ylid (Ib) was generated from methyl chlorodifluoroacetate [Eqn.(18)].[57]

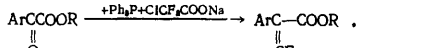
† It has been suggested[43,44] that the F^- anion is generated on decomposition of the ylid (Ib) or directly by the decarboxylation of $ClCF_2COOM$. The yield of the olefin *p*-$O_2NC_6H_4CH{=}CF_2$, formed from *p*-nitrobenzaldehyde, in only 2%, while the yield of the addition product HF–*p*-$O_2NC_6H_4CH_2CF_3$ is ~20%.[50]

However, the use of a lithium salt suppresses the isomerisation[43,44]:

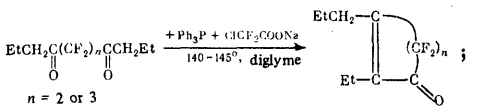


$R_F = C_2F_5$ or C_3F_7 .

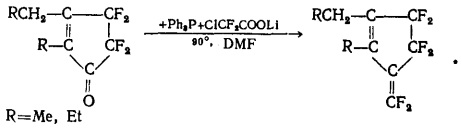
In contrast to aldehydes and activated ketones, cyclohexanone[51] and acetophenone[52] do not react with difluoromethylenetriphenylphosphorane, evidently owing to the insufficiently pronounced electrophilic properties of the carbonyl carbon[43]. The esters of aromatic α-ketoacids enter into the Wittig reaction, forming the esters of α-aryl-β,β-difluoroacrylic acids[54,79,80]:



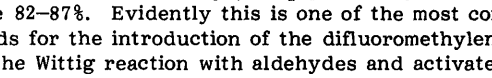
When the ylid (Ib) was generated by the "halogenoacetate" method, it was not possible to achieve the Wittig reaction with the diketones $PhCO(CF_2)_nCOPh$ (n = 2 or 3).[46] In the reaction with the analogous dipropyl-substituted diketones the ylid (Ib) induces their cyclisation to unsaturated ketones[46]:



Fluorocyclopentorones undergon the Wittig reaction (in contrast to the corresponding cyclohexanones) and give low yields of difluoromethylenecyclopentenes[46]:



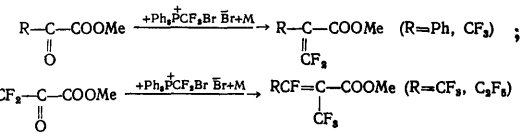
When another method of synthesis of the ylid (Ib) is used, namely from Ph_3P and CF_2Br_2 [Eqn.(4)], it is possible to involve also diketones in the Wittig reaction[28]:



This method of generation of the ylid (Ib) has been used successfully in the reactions with PhCHO,[23,24,29] PhCH=CHCHO,[29] $PhCOCF_3$,[20,25] p-$ClC_6H_4COCF_3$,[25] $PhCOC_2F_5$,[25] m-$BrC_6H_4COCF_3$,[25] and m-$BrC_6H_4COC_2F_5$;[25] the yields of olefins are 82–87%. Evidently this is one of the most convenient methods for the introduction of the difluoromethylene group in the Wittig reaction with aldehydes and activated ketones. However, particularly severe requirements are then imposed on the dryness of solvents[29].

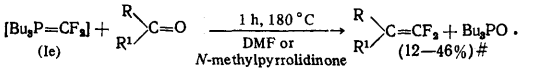
In the reaction with aldehydes the method of generation of difluoromethylenetriphenylphosphorane from Ph_3P, CF_2Br_2, and zinc [Eqn.(10)] is even more convenient. α,α-Difluoro-olefins are readily obtained by this procedure from n-C_6H_{13}.CHO, n-$C_{10}H_{21}CHO$, and PhCHO (yields ~80%), as well as PhCH=CHCHO (yield 33%);[29] there is then no need for especially thorough drying of solvents. In the reaction with PhCOMe the yield of difluoro-olefin does not exceed 5%.

The esters of α-substituted perfluoroacrylic acids and their isomerisation products have been obtained by the interaction of the esters of α-ketoacids with bromodifluoromethyltriphenylphosphonium bromide and a metal[28]:



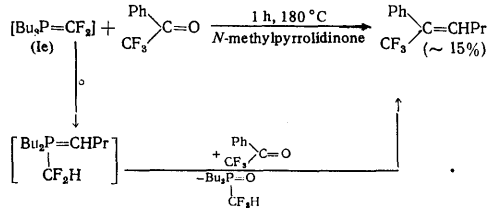
Difluoromethylene-substituted sugars have been prepared by treating the corresponding oxo-derivatives with triphenylphosphine, dichlorofluoromethane, and KF.[15] The intermediate formation of the ylid (Ib) in the reaction of bromodifluoromethyltriphenylphosphonium bromide with KF and PhCOF was described above.

Since difluoromethylenetriphenylphosphorane does not as a rule enter into the Wittig reaction with non-activated ketones, the corresponding difluoro-olefins must be synthesised using other more active difluoromethylenephosphoranes. The use of tributyldifluoromethylenephosphorane, generated by the "halogenoacetate" method [Eqn.(15)], for this purpose has been described[51,55]:



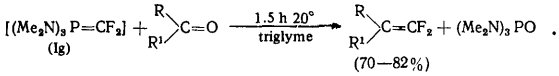
The reaction is carried out *in situ* with cyclohexanone, benzophenone, and methylketones MeCOR (R = C_5H_{11}, Ph, 2-furyl, or 2-thienyl). In the reaction with heptanal the yield of the olefin n-$C_6H_{13}CH=CF_2$ is only 7%.[51]

In the interaction with trifluoroacetophenone the carbonyl oxygen is replaced by the butylidene group and not the difluoromethylene group, probably as a consequence of the isomerisation of the ylid (Ie):[43,51]



α,α-Difluoro-olefins could not be obtained either by treating phenyl α-pyridyl ketone, p-benzoquinone, hexachloroacetone, and camphor with tributyldifluoromethylenephosphorane[51].

The most convenient source of the difluoromethylene group in the Wittig reaction with non-activated ketones is evidently difluoromethylenetris(dimethylamino)phosphorane generated from dibromodifluoromethane [Eqns.(5) and (6)].[20,26,29,31]§ The enhanced nucleophilic activity of the ylid (Ig), induced by the electron-donating influence of the dimethylamino-groups, ensures high yields of difluoro-olefins from cyclohexanone, diethyl ketone, acetophenone, and propiophenone[20,26]:



The reaction can be carried out *in situ* or with preliminary generation of the "olefinating solution"[20,26]. However, one should use very thoroughly dried solvents[29].

This method is evidently unsuitable for the Wittig reaction with activated fluorine-containing ketones, because fluoroketones react with tris(dimethylamino)phosphine[64].

The ylid (Ig), generated from $(Me_2N)_3P$, CF_2Br_2 and zinc [Eqn.(12)] has been used successfully in reactions with aldehydes. The yield of 1,1-difluoro-oct-1-ene from n-$C_6H_{13}CHO$ is 77%. β,β-Difluoro-α-methylstyrene is formed in ~40% yield from acetophenone[29]. Careful drying of the solvent is not required.

#In a later communication it is stated[26] that the yields do not exceed 10%.

§For a description of the equilibrium in the $(Me_2N)_3\overset{+}{P}CF_2Br\ \overline{Br} + (Me_2N)_3P \rightleftharpoons (Me_2N)_3P=CF_2 + (Me_2N)_3PBr_2$ system, see above.

(c) *The introduction of the group =CFCl.* Chlorofluoromethylenetriphenylphosphorane and chlorofluoromethylenetris(dimethylamino)phosphorane are widely used in the synthesis of α-chloro-α-fluoro-olefins by the Wittig reaction.

When the ylid (Ic) is generated by the "halogenoacetate" method [Eqn.(16)][14,16] or its modification Eqn.(19)], aldehydes and activated ketones are successfully "olefinated" with formation of a mixture of *cis*- and *trans*-isomers of chlorofluoro-olefins (in proportions of ~1 : 1):

$$[Ph_3P{=}CFCl] + RCHO \xrightarrow[\text{ether}]{80\text{–}90^\circ,\ \text{triglyme or petroleum}} RCH{=}CFCl + Ph_3PO \quad (25\text{–}63\%)$$
(Ic)

R = n-Bu, Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, or *o*-$MeOC_6H_4$;

$$[Ph_3P{=}CFCl] + \underset{CF_3}{\overset{R}{\diagdown}}C{=}O \xrightarrow[\text{triglyme}]{90^\circ} \underset{CF_3}{\overset{R}{\diagdown}}C{=}CFCl + Ph_3PO \quad (30\text{–}70\%)$$
(Ic)

R=n-Bu, C_6H_{11}, $PhCH_2$, Ph, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$;

$$[Ph_3P{=}CFCl] + \underset{R_F}{\overset{Ph}{\diagdown}}C{=}O \xrightarrow[\text{triglyme}]{90^\circ} \underset{R_F}{\overset{Ph}{\diagdown}}C{=}CFCl + Ph_3PO \quad (41\text{–}42\%)$$
(Ic)

R_F=C_2F_5, n-C_3F_7.

Non-activated ketones enter into this reaction with difficulty, so that there is sufficient time for the decomposition of the ylid (Ic).[14,16] It has been shown[60] that the reactivity of carbonyl compounds in relation to chlorofluoromethylenetriphenylphosphorane decreases in the sequence *p*-ClC_6H_4. .CHO > PhCHO > $PhCOCF_3$ > PhCOMe. Benzophenone could not be "olefinated" and the reactions with acetophenone, cyclopentanone, and cyclohexanone gave only small yields of the corresponding olefins[14,16,60]. Nor was it possible to make 1,2-dialkylhexafluorocyclohex-3-enones to undergo the reaction[46].

The esters of α-aryl-β-chloro-β-fluoroacrylic acids were obtained from the esters of aromatic α-ketoacids[54]:

$$Ar{-}\underset{\underset{O}{\|}}{C}{-}COOR \xrightarrow{+Ph_3P+Cl_2CFCOONa} Ar{-}\underset{\underset{CFCl}{\|}}{C}{-}COOR .$$

When the ylid (Ic) is generated from Ph_3P, $CHFCl_2$, and t-BuOK [Eqn.(3)], which requires milder conditions than the synthesis by the "halogenoacetate" method, chlorofluoromethylenecyclopentane is formed from cyclopentanone in 27% yield[14,16]. The report that benzophenone was made to undergo the reaction[13] was not confirmed[14,16]. Olefins have also been obtained by this method from benzaldehyde and from activated ketones[14,16]:

$$[Ph_3P{=}CFCl] + \underset{XCF_2}{\overset{Ph}{\diagdown}}C{=}O \xrightarrow[\text{heptane}]{20^\circ} \underset{XCF_2}{\overset{Ph}{\diagdown}}C{=}CFCl + Ph_3PO\ ; \quad (30\text{–}50\%)$$
(Ic)

X = F or Cl .

Yet another method of synthesising chlorofluoromethylenetriphenylphosphorane, namely from Ph_3P, $CFCl_3$, and zinc (60 °C in DMF) [Eqn.(9)], also makes it possible to introduce into the Wittig reaction only aldehydes (heptanal and benzaldehyde) and an activated ketone (trifluoroacetophenone)[21,33]; the yield of the product from cyclopentanone is only 4%.[21]

Ketosugars were converted into chlorofluoromethylene derivatives on treatment with the ylid (Ic), generated from dichlorofluoromethylenephenylmercury in accordance with Eqn.(20).[15]

Chlorofluoromethylenetris(dimethylamino)phosphorane is apparently very convenient for the synthesis of α-chloro-α-fluoro-olefins by the Wittig reaction[18,32,33]. This ylid is generated by the dehalogenation of dichlorofluoromethyltris-(dimethylamino)phosphonium chloride on treatment with a tertiary phosphine [Ph_3P or $(Me_2N)_3P$—Eqn.(7)][18,32,33] or a metal [Eqn.(13)].[32,33]

The phosphorus ylid (Ih) is much more reactive than its triphenyl-substituted analogue (Ic), which makes it possible to carry out the Wittig reaction for non-activated ketones. At the same time the methods for the generation of this ylid ensure the formation of very stable "olefinating solutions" (see above). All this, together with the availability of the initial compounds, makes the use of chlorofluoromethylenetris(dimethylamino)phosphorane in the Wittig reaction particularly promising.

The reaction with aldehydes (heptanal and benzaldehyde) under mild conditions (60 °C, DMF) afforded chlorofluoro-olefins in quantitative yields[32].

The ylid (Ih), generated by the dehalogenation of the phosphonium salt by Ph_3P or Zn/Cu, successfully "olefinates" activated ketones[18,32,33]:

$$(Me_2N)_3P{=}CFCl] + \underset{CF_3}{\overset{R}{\diagdown}}C{=}O \xrightarrow[\text{THF, triglyme, or PhCN}]{0\text{–}40^\circ} \underset{CF_3}{\overset{R}{\diagdown}}C{=}CFCl + (Me_2N)_3PO; \quad (75\text{–}100\%)$$

R = Ph or CF_3.

In dehalogenation by tris(dimethylamino)phosphine, fluoroketones cannot be introduced into the reaction, since they are cleaved[18,64]. However, this method (together with dehalogenation by a metal) is most convenient for reactions with non-activated ketones. The yield of the olefin from acetophenone is 56–70%;[18,32] the reaction does not take place with benzophenone and that with cyclopentanone gives an 18% yield of the olefin[32].

The reactions of the ylid (Ih) with the esters of fluoroacids, leading to alkyl fluoroalkenyl ethers, are of particular interest[18,32]¶:

$$\underset{(Ih)}{[(Me_2N)_3P{=}CFCl]} + \underset{RO}{\overset{R_F}{\diagdown}}C{=}O \xrightarrow[\text{or PhCN}]{80^\circ,\ \text{triglyme}} \underset{RO}{\overset{R_F}{\diagdown}}C{=}C\overset{F}{\underset{Cl}{\diagup}} + (Me_2N)_3PO\ ; \quad (21\text{–}90\%)$$

R_F=CF_3, HCF_2, $ClCF_2$, C_2F_5 or C_3H_7; R=Me, Et or iso-Pr.

The best results were obtained with methyl trifluoroacetate; methyl dichlorofluoroacetate and *N*,*N*-dimethyldifluoroacetamide do not enter into the reaction[32].

In contrast to the interaction with aldehyde and ketones, the reaction with esters is stereoselective—the Z-isomers are mainly formed[18,32].

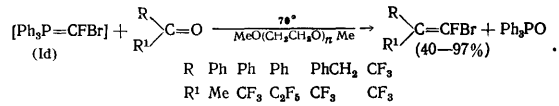
The use of tributylchlorofluoromethylenephosphorane in the Wittig reaction is much less convenient than that of the ylids (Ic) and (Ih). The tributyl-substituted phosphorus ylid is more reactive in reactions with carbonyl compounds than the triphenyl-substituted ylid, but the instability of the ylid (If) precludes its wide-scale employment[14,16]. Nevertheless, when the ylid (If) was generated by the "halogenoacetate" method [Eqn.(17)], chlorofluoromethylenecyclopentane was obtained in 25% yield by the reaction with cyclopentanone (85 °C, triglyme, *in situ*); when the triphenylylid (Ic) is used under the same conditions, the yield of the olefin is only 9%.[14,16]

(d) *The introduction of the group =CFBr.* α-Bromo-α-fluoro-olefins are obtained by the Wittig reaction with the aid of bromofluoromethylenetriphenylphosphorane generated from triphenylphosphine and tribromofluoromethane [Eqn.(4)].[30]† The reaction can be carried out either *in situ* or

¶These unsaturated ethers polymerise when an attempt is made to isolate them, but their formation has been rigorously demonstrated with the aid of NMR.[18,32]

†The use of the "halogenoacetate" method [Eqn.(16)] is less convenient[30].

with preliminary preparation of a stable "olefinating" solution. The ylid (Id) reacts fairly readily even with non-activated ketones. The Wittig reaction results in the formation of bromofluoro-olefins in the form of mixtures of *cis*- and *trans*-isomers (in proportions of ~1 : 1):



(Id)

R	Ph	Ph	Ph	$PhCH_2$	CF_3
R^1	Me	CF_3	C_2F_5	CF_3	CF_3

It is clear from the data presented that fluorine-containing halogenomethylenephosphoranes are highly reactive intermediates, which can be used successfully in the synthesis of fluoro-olefins and related compounds by the Wittig reaction. The use of a wide variety of methods for their generation and the introduction of different kinds of groups at the phosphorus atom permit a specific regulation of the stability and nucleophilic activity of these intermediates.

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