

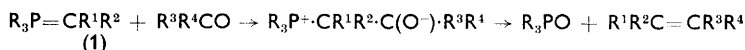
# THE WITTIG REACTION

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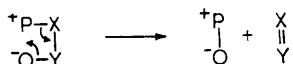
## 1. Introduction

THE Wittig olefin synthesis<sup>1</sup> involves the addition of an alkylidenephosphorane (1; R = alkyl, aryl) to a carbonyl compound, followed by elimination of phosphine oxide from the intermediate betaine to give the olefin:

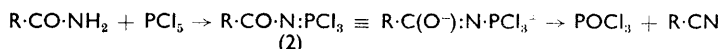


The reaction proceeds under mild conditions and the position of the resulting double bond is not in doubt. The synthesis has been applied with outstanding success in many fields, *e.g.*, carotenoids, polyenes, Vitamins D.<sup>2</sup> Recently, more attention has been paid to the mechanistic aspects of the synthesis, to the development of analogous olefin syntheses, and to the reactions of alkylidenephosphoranes with functional groups other than carbonyls. This review is concerned largely with these topics.

The original Wittig synthesis is one example of the general elimination:



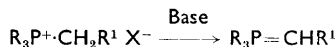
The range of radicals which can be attached to the phosphorus is constantly being widened and includes alkyl, aryl, alkoxy, halogen, dialkylamino, and oxyanion (O<sup>-</sup>); the atoms X and Y may be carbon and/or nitrogen, and they may already be joined by a double bond, while the oxygen may sometimes be replaced by chlorine<sup>3</sup> or by the group NHR (R = H, Ph, ArSO<sub>2</sub>, etc.).<sup>4</sup> A familiar example of this type of elimination occurs in the dehydration of amides with phosphorus pentachloride by way of the betaine (2):<sup>5</sup>



Other examples will be found throughout the review.

## 2. Preparation of Alkylidenephosphoranes

(a) **From Phosphonium Salts.**—Alkylidenephosphoranes are obtained from alkylphosphonium salts by the action of a suitable base:



<sup>1</sup> Wittig and Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.

<sup>2</sup> (a) Schöllkopf, *Angew. Chem.*, 1958, **71**, 260; (b) Trippett in "Advances in Organic Chemistry. Methods and Results," Vol. I, Interscience, New York, 1960.

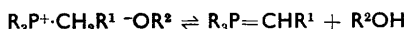
<sup>3</sup> Kirsanov and Derkach, *Zhur. obshchei Khim.*, 1958, **28**, 1887.

<sup>4</sup> Derkach and Kirsanov, *Zhur. obshchei Khim.*, 1959, **29**, 3424; Derkach, Dregval, and Kirsanov, *Zhur. obshchei Khim.*, 1961, **31**, 2385.

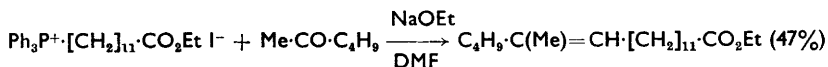
<sup>5</sup> Kirsanov and Derkach, *Zhur. obshchei Khim.*, 1956, **26**, 2009.

The strength of base necessary depends on the acidity of the  $\alpha$ -hydrogen and varies from aqueous sodium carbonate for the diposphonium salt  $(\text{Ph}_3\text{P}^+)_2\text{CH}_2 \cdot 2\text{Br}^-$ ,<sup>6</sup> to alkyl-metals in non-polar solvents for unsubstituted alkylphosphonium salts. Bases and solvents commonly employed include butyl- and phenyl-lithium in ether, benzene, or tetrahydrofuran, and sodium or lithium alkoxides in the corresponding alcohol or in dimethylformamide. Recently,<sup>7</sup> the use of dimethyl sulphoxide metallated by sodium hydride, *i.e.*,  $\text{MeSO}\cdot\text{CH}_2\text{-Na}^+$ , with dimethyl sulphoxide as solvent, has been described. High yields of olefins are claimed from rapid reactions.

Alkoxides lead to an equilibrium between phosphonium alkoxide and phosphorane and are finding increasing use, not only because of their

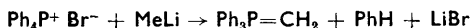
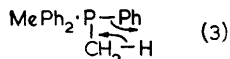


greater convenience but also because they allow the presence in  $\text{R}^1$  of groups which react with alkyl-metals, *e.g.* (DMF = dimethylformamide),<sup>8</sup>



Difficulty sometimes arises through alkoxide-catalysed self-condensation of the carbonyl component, forming water which can lead to hydrolysis of the phosphonium salt.<sup>9</sup>

When alkyl-lithiums are used in the preparation of phosphoranes, addition of the reagent anion to the phosphorus cation to give a derivative of quinquivalent phosphorus may compete with direct phosphorane formation by proton-abstraction. Seyferth *et al.*<sup>10</sup> showed that benzene (26%) is produced when methyltriphenylphosphonium bromide is treated with methyl-lithium in ether, and suggested the intermediate (3). Similarly, tetraphenylphosphonium bromide gives methylenetriphenylphosphorane and benzene when refluxed in tetrahydrofuran with methyl-lithium:



This competing reaction does not occur when the  $\alpha$ -hydrogen atom of the alkyl group is more acidic, *e.g.*, in  $\text{Ph}_3\text{P}^+\cdot\text{CH}_2\text{Ph} \text{Br}^-$ .

Substituents on the  $\alpha$ - and  $\beta$ -carbon atoms of alkyltriphenylphosphonium salts can lead to complications in phosphorane formation.

(i)  *$\alpha$ -Substituted Phosphonium Salts.*—Chloromethyltriphenylphosphonium chloride with phenyl- or butyl-lithium gives the chloromethylene-

<sup>6</sup> Ramirez, Desai, Hansen, and McKelvie, *J. Amer. Chem. Soc.*, 1961, **83**, 3539.

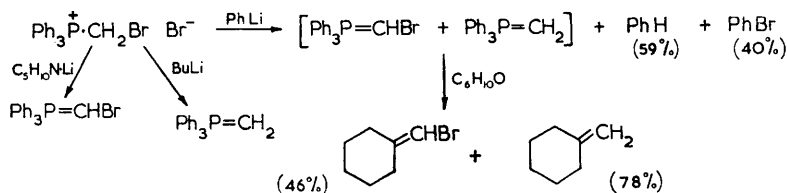
<sup>7</sup> Greenwood, Chaykovsky, and Corey, *J. Org. Chem.*, 1963, **28**, 1128.

<sup>8</sup> Bergelson, Vaver, and Shemyakin, *Izvest. Akad. Nauk. S.S.S.R., Otdel. khim. Nauk.*, 1960, 1900.

<sup>9</sup> Wittig, Böll, and Kruck, *Chem. Ber.*, 1962, **95**, 2514.

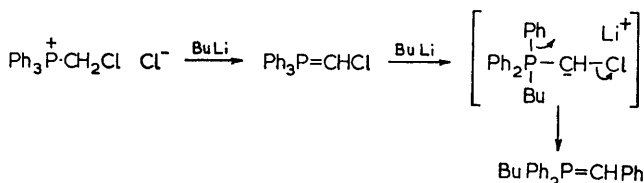
<sup>10</sup> Seyferth, Heeren, and Hughes, *J. Amer. Chem. Soc.*, 1962, **84**, 1764.

phosphorane,<sup>11</sup> but, with the same reagents, the corresponding bromo- and iodo-methyl salts also undergo nucleophilic removal of halogen to give methylenetriphenylphosphorane.<sup>12,13</sup>

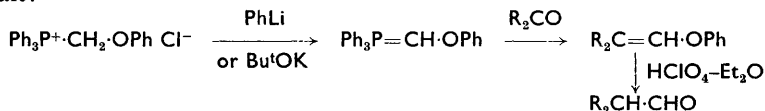


This competing reaction does not occur when the less nucleophilic lithium piperidine is used.<sup>13</sup>

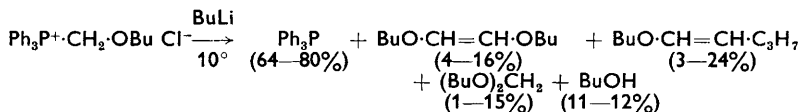
A further complicating reaction, reported so far only with chloromethylenetriphenylphosphorane,<sup>14</sup> is the addition of excess of alkyl- or aryl-lithium to the phosphorane, followed by migration of a phenyl group with simultaneous expulsion of chloride ion:



Alkoxy- and aryloxy-methylphosphonium salts in general take part in normal Wittig reactions to give vinyl ethers, readily hydrolysed by acid to aldehydes.<sup>9,11,15</sup> The best yields are obtained using the phenoxymethyl salt:<sup>9</sup>



However, the higher alkoxy-methylenephosphoranes are rather unstable and decompose exothermically at  $\sim 10^\circ$ . Wittig and Böll<sup>16</sup> studied the decomposition of n-butoxymethylenetriphenylphosphorane with the following results, the proportions of the products varying with the solvent:



<sup>11</sup> Wittig and Schlosser, *Chem. Ber.*, 1961, **94**, 1373.

<sup>12</sup> Seyferth, Heeren, and Grim, *J. Org. Chem.*, 1961, **26**, 4783.

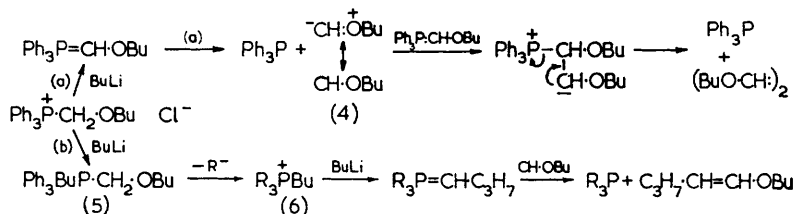
<sup>13</sup> Köbrich, *Angew. Chem.*, 1962, **74**, 33.

<sup>14</sup> Schlosser, *Angew. Chem.*, 1962, **74**, 291.

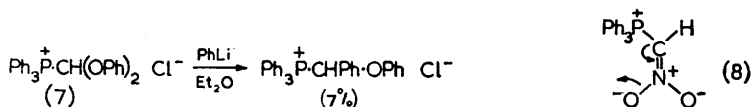
<sup>15</sup> Levine, *J. Amer. Chem. Soc.*, 1958, **80**, 6150.

<sup>16</sup> Wittig and Böll, *Chem. Ber.*, 1962, **95**, 2526.

Two primary reactions were suggested: (a) decomposition of the phosphorane to triphenylphosphine and the resonance-stabilised carbene (4); (b) addition of butyl-lithium to the phosphonium salt to give an intermediate (5) which then loses either a phenyl or a butoxymethyl anion to give a butylphosphonium ion (6). Subsequent reactions are then as formulated:

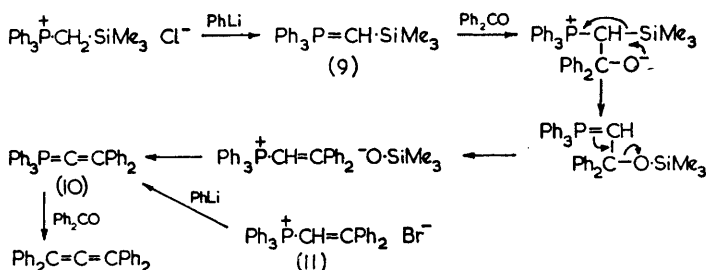


The butanol may be formed by  $S_N2$  attack of butyl anion on the  $\alpha$ -carbon atom of the phosphonium salt. This process certainly occurs when diphenoxymethyltriphenylphosphonium chloride (7) is treated with phenyl-lithium:



Nitromethyltriphenylphosphonium bromide on treatment with aqueous sodium hydroxide at  $0^\circ$  rapidly gives triphenylphosphine oxide and fulminate anion,<sup>17</sup> presumably by way of the phosphorane (8).

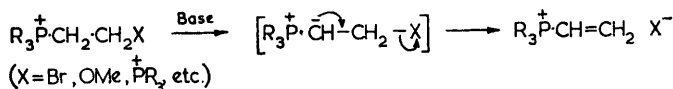
Gilman and Tomasi<sup>18</sup> prepared the trimethylsilylmethylenephosphorane (9). With benzophenone it gives tetraphenylallene, probably through the vinylidenephosphorane (10) formed by elimination of trimethylsilanol from the initially formed betaine. The phosphorane (10) can be obtained directly from the vinylphosphonium salt (11); with benzophenone it gives a 54% yield of tetraphenylallene.



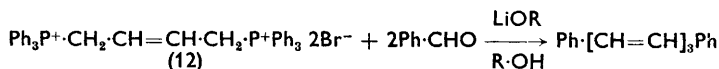
<sup>17</sup> Trippett and Walker, *J.*, 1959, 3874.

<sup>18</sup> Gilman and Tomasi, *J. Org. Chem.*, 1962, 27, 3647.

(ii)  $\beta$ -Substituted Phosphonium Salts.—Phosphonium salts having, on the  $\beta$ -carbon, a substituent capable of forming a stable anion or neutral molecule usually eliminate this substituent when treated with base:<sup>1,19</sup>

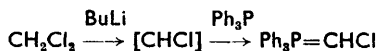


The vinylogous bisphosphonium salt (12) was reported to undergo a similar elimination on treatment with phenyl-lithium, but it can be used successfully in olefin synthesis if a lithium alkoxide is used as base:<sup>20</sup>

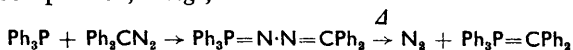


$\beta$ -Substituents (CN, COR, CO<sub>2</sub>R, etc.) capable of stabilising a negative charge on the  $\alpha$ -carbon atom lead to the stable phosphoranes often known as the phosphobetaines.<sup>21,22</sup> These are relatively stable to hydrolysis and are obtained from the salts by using aqueous sodium hydroxide.

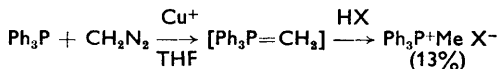
(b) Other Methods.—Alkylidenephosphoranes have also been obtained by the addition of carbenes to triphenylphosphine,<sup>23</sup> e.g.,



and by the thermal decomposition of the adducts of triphenylphosphine and diazo-compounds,<sup>24</sup> e.g.,



This decomposition normally occurs only at temperatures at which the resulting phosphoranes are unstable. Wittig and Schlosser<sup>25</sup> have obtained phosphoranes from triphenylphosphine and diazo-compounds at room temperature in the presence of cuprous halides, the reactions presumably involving intermediate carbenes (THF = tetrahydrofuran):



The yields are low, probably because of reaction between the phosphoranes and unchanged diazo-compounds (see p. 430). Better overall yields are

<sup>19</sup> Wittig, Eggers, and Duffner, *Annalen*, 1958, **619**, 10.

<sup>20</sup> Heitman, Wieland, and Huisman, *Proc., k. ned. Akad. Wetenschap.*, [B], 1961, **64**, 165.

<sup>21</sup> Ramirez and Dershowitz, *J. Org. Chem.*, 1957, **22**, 41.

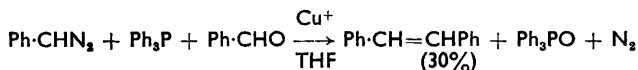
<sup>22</sup> Trippett and Walker, *J.*, 1961, 1266.

<sup>23</sup> Seyferth, Grim, and Read, *J. Amer. Chem. Soc.*, 1960, **82**, 1510; 1961, **83**, 1617; Speziale, Marco, and Ratts, *ibid.*, 1960, **82**, 1260; Wittig and Schlosser, *Angew. Chem.*, 1960, **72**, 324.

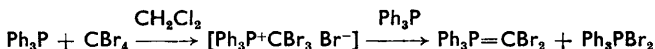
<sup>24</sup> Staudinger and Meyer, *Helv. Chim. Acta*, 1919, **2**, 635.

<sup>25</sup> Wittig and Schlosser, *Tetrahedron*, 1962, **18**, 1023.

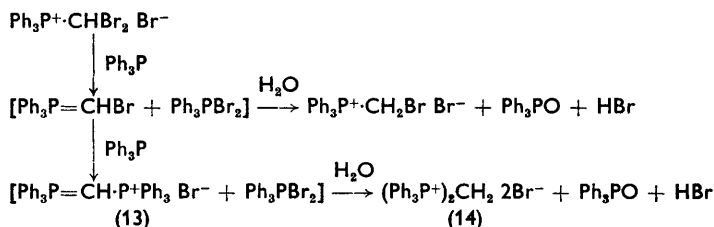
obtained by carrying out the reactions in the presence of a carbonyl compound to trap the phosphorane as formed, *e.g.*,



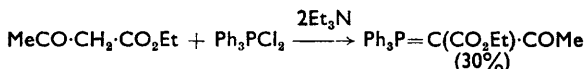
Triphenylphosphine reacts with carbon tetrahalides at room temperature to give dihalogenomethylene- and dihalogeno-phosphoranes.<sup>26,27</sup> This involves the nucleophilic removal of halogen from the initially formed trihalogenomethylphosphonium salts, *e.g.*,



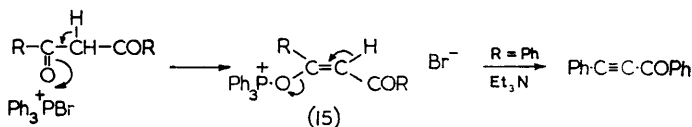
A similar removal of halogen is involved in the reaction of triphenylphosphine with dibromomethyltriphenylphosphonium bromide.<sup>27</sup> In wet methylene chloride this gives triphenylphosphine oxide and the bromomethyl phosphonium salt; in dry solvent, reaction of the intermediate phosphorane with a second molecule of phosphine gives the phosphorane (13), isolated, after hydrolysis, as the bisphosphonium salt (14):



Stable phosphoranes of the formula  $\text{Ph}_3\text{P}:\text{CXY}$  ( $\text{X}, \text{Y} = \text{CN}, \text{CO}_2\text{R}, \text{COR}$ ) can be obtained by the action of dichlorotriphenylphosphorane and triethylamine on compounds containing a reactive methylene group,<sup>28</sup> *e.g.*,



This reaction fails when applied to  $\beta$ -diketones, the initial attack here being on oxygen to give enol phosphonium salts (15).<sup>29</sup> In favourable cases, *e.g.*, when  $\text{R} = \text{Ph}$ , these give acetylenic ketones on treatment with triethylamine.<sup>30</sup>



<sup>26</sup> Rabinowitz and Marcus, *J. Amer. Chem. Soc.*, 1962, **84**, 1312.

<sup>27</sup> Ramirez, Desai, and McKelvie, *J. Amer. Chem. Soc.*, 1962, **84**, 1745.

<sup>28</sup> Horner and Oediger, *Chem. Ber.*, 1958, **91**, 437.

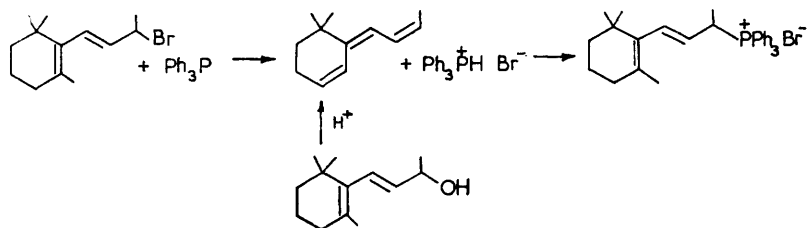
<sup>29</sup> Gough and Trippett, *J.*, 1962, 2333.

<sup>30</sup> Hoffman and Diehr, *Tetrahedron Letters*, 1962, 583.

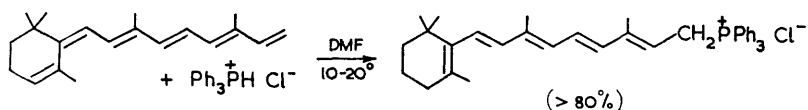
### 3. Preparation of Phosphonium Salts

Alkyl and aryl tertiary phosphines quaternise readily with primary alkyl halides,  $RCH_2Hal$ , the speed of reaction being according to the series  $I > Br > Cl$ , and  $Me > Et > Pr$ , etc. With simple alkyl bromides above  $C_2$  the reactions are best carried out without solvent. Polar solvents, *e.g.*, nitromethane, acetonitrile, and formic acid, are often usefully employed.

Olefin formation may occur with secondary and tertiary alkyl halides. Isopropyl iodide reacts normally, but *s*-butyl iodide when refluxed in excess with triphenylphosphine gives but-2-ene and triphenylphosphonium iodide.<sup>31</sup> Similarly, *t*-butyl chloride rapidly gives 2-methylpropene when a solution in formic acid is refluxed with triphenylphosphine.<sup>31</sup> As the same mixture, when heated under pressure to  $150^\circ$ , is reported to give triphenyl-*t*-butylphosphonium chloride,<sup>32</sup> the olefin may be an intermediate in the reaction. Pommer<sup>33</sup> has shown that polyenes are intermediates in the quaternisation of triphenylphosphine with allylic halides in the carotenoid field, *e.g.*,

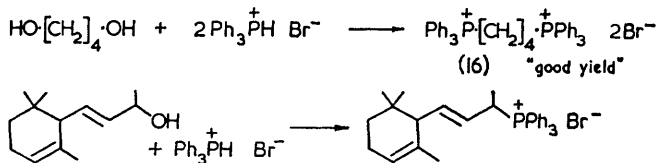


and from this has developed a general synthesis of phosphonium salts, involving the addition of a triphenylphosphonium halide to a polyene in a suitable polar solvent, *e.g.*,



Anhydrovitamin A

Pommer<sup>33</sup> has also obtained phosphonium salts by the action of triphenylphosphonium halides on alcohols, *e.g.*,



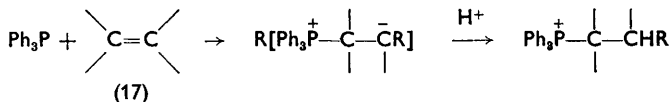
<sup>31</sup> Trippett, unpublished results.

<sup>32</sup> Horner and Mentrup, *Annalen*, 1961, **646**, 65.

<sup>33</sup> Pommer, *Angew. Chem.*, 1960, **72**, 811.

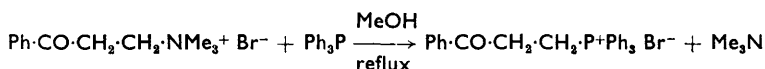
These reactions are thought not to involve dehydration to intermediate olefins; butadiene is reported to give only traces of the salt (16). Unfortunately this important and interesting method appears so far only in the patent literature.

Phosphonium salts have also been prepared by the addition of triphenylphosphine to activated olefins (17; R = CN, NO<sub>2</sub>, CO<sub>2</sub>R, etc.) under acidic conditions:<sup>34</sup>



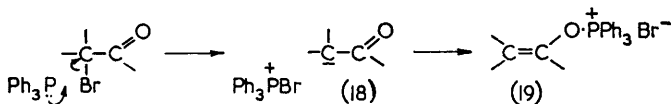
Dihalogenomethanes react normally with triphenylphosphine. Bromoform gives the expected dibromomethylphosphonium bromide in a reaction markedly accelerated by ultraviolet light and dibenzoyl peroxide and thought to involve a free-radical chain process.<sup>35</sup> For the reaction of tetrahalogenomethanes with triphenylphosphine (see p. 411).

Alkylphosphonium salts may also be prepared by the action of triphenylphosphine on the quaternary salts of Mannich bases,<sup>36</sup> *e.g.*,



and by the addition of alkyl halides to alkylidenephosphoranes (see p. 423).

**(a) Abnormal Reactions of Phosphines with Alkyl Halides.**—Compounds containing “active” halogen, *e.g.*,  $\alpha$ -halogeno-ketones, aldehydes, nitro-compounds, etc., react abnormally with phosphines,<sup>30,37</sup> although in most cases the simple methylene compounds, Hal-CH<sub>2</sub>X, give the expected phosphonium salt. The abnormal reactions are analogous to the Perkow reaction of phosphites.<sup>38</sup> They probably involve nucleophilic attack of phosphorus on *halogen* to form ion-pairs [*e.g.*, (18) from  $\alpha$ -bromocarbonyl compounds] which then give the enol phosphonium salts (19):



These on hydrolysis give debrominated carbonyl compounds and triphenylphosphine oxide. The intermediates (20) in the reactions between  $\alpha$ -halogenonitroalkanes and triphenylphosphine eliminate a proton and

<sup>34</sup> Hoffmann, *Chem. Ber.*, 1961, **94**, 1331.

<sup>35</sup> Ramirez and McKelvie, *J. Amer. Chem. Soc.*, 1957, **79**, 5829.

<sup>36</sup> Hellmann and Schumacher, *Annalen*, 1961, **640**, 79.

<sup>37</sup> Trippett, *J.*, 1962, 2337; Borowitz and Grossman, *Tetrahedron Letters*, 1962, 471.

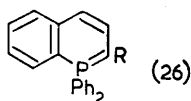
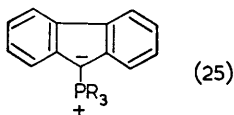
<sup>38</sup> Lichtenthaler, *Chem. Rev.*, 1961, **61**, 607.





(a) **Betaine Formation.**—If we assume that this step involves nucleophilic attack of the  $\alpha$ -carbon of the phosphorane on the carbonyl group, the rate will depend on the nucleophilicity of the  $\alpha$ -carbon and on the susceptibility to nucleophilic attack of the carbonyl group.

Substituents on phosphorus which tend to decrease the positive character of that atom will increase the reactivity of the phosphorane by stabilising the contributing dipolar form, while delocalisation of the negative charge on the  $\alpha$ -carbon, *e.g.*, by substituents  $R^2$  and  $R^3$  having  $-M$  effects, will considerably reduce the reactivity. Thus, while fluorenylidetriphenylphosphorane (25;  $R = \text{Ph}$ ), in which the negative charge is delocalised throughout the fluorene nucleus, reacts with neither aldehydes nor ketones, the trialkylphosphoranes (25;  $R = \text{Me, Bu}$ ) react with aldehydes

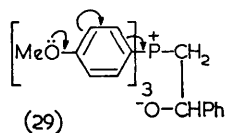
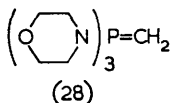
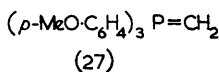


and with the more reactive ketones, *e.g.*, 4-nitroacetophenone.<sup>42</sup> Again, the stable phosphoranes  $\text{Ph}_3\text{P}:\text{CH}\cdot\text{COR}$  react readily with aldehydes but slowly or not at all with ketones.<sup>21,22</sup>

Particularly interesting examples of stable phosphoranes are the cyclic compounds (26),<sup>43</sup> which do not react with carbonyl compounds. They are relatively stable to hydrolysis and seem to have definite aromatic character.

(b) **Betaine Decomposition.**—Although there is no direct evidence on the point, betaine decomposition is usually assumed to proceed through a four-membered cyclic transition state. This step will be retarded by substituents  $R^1$  [as in (24)] which decrease the positive character, and hence the oxygen-affinity, of the phosphorus (by means of  $+I$ ,  $+M$ , or hyperconjugative effects), and accelerated by substituents  $R^2$ — $R^5$  which can conjugate with the incipient double bond in the transition state.

Clearly, factors which help betaine formation hinder betaine decomposition, and *vice versa*. At the one extreme, the reactive phosphoranes (27) and (28) give, with benzaldehyde stable betaines (*e.g.*, 29) in which the positive character of the phosphorus is so reduced that phosphine oxide



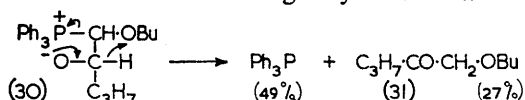
<sup>42</sup> Johnson and LaCount, *Tetrahedron*, 1960, 9, 130.

<sup>43</sup> Märkl, *Angew. Chem., Int. edn.*, 1963, 2, 153.

elimination does not take place;<sup>44</sup> at the other extreme, intermediate betaines have never been isolated in olefin syntheses in which the unreactive phosphoranes  $\text{Ph}_3\text{P}^+\text{C}^-\text{H}\cdot\text{COR}$  were used. Here the slow first stage is followed by a rapid elimination in which the double bond being formed is stabilised by conjugation with a carbonyl group.

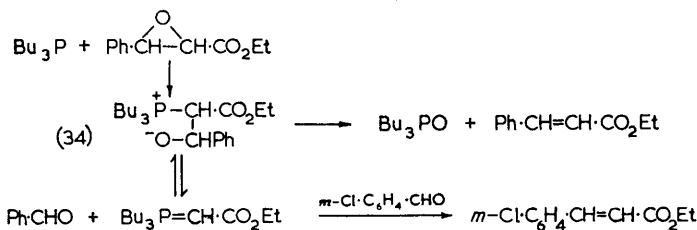
In the "normal" Wittig reaction ( $\text{R}^1 = \text{Ph}$ ;  $\text{R}^2, \text{R}^3 = \text{H}$  or alkyl) the formation of isolated double bonds requires a temperature of  $\sim 60^\circ$ , but this is reduced to room temperature, or below, if the new double bond is highly conjugated.

Wittig and Böll<sup>16</sup> reported an anomalous decomposition of the betaine (30) from butoxymethylenetriphenylphosphorane and butyraldehyde. Besides the expected olefin (12%), the ketone (31) and triphenylphosphine are also formed in a reaction involving a hydride shift.



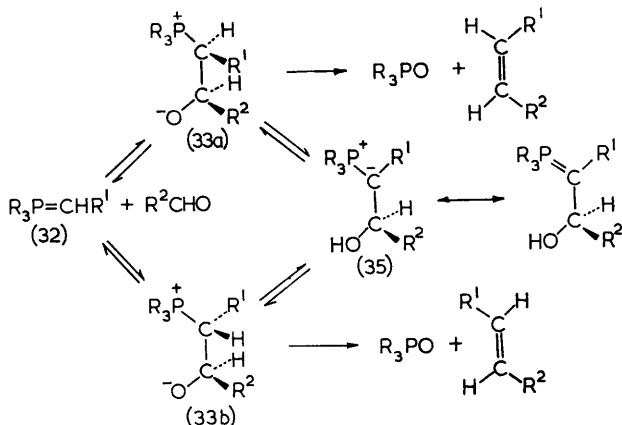
(c) **Stereochemistry of the Resulting Olefin.**—The phosphorane (32) and an aldehyde can give two diastereoisomeric betaines (33a) and (33b) which lead, respectively, to *cis*- and *trans*-olefins. Considering first reactions carried out in non-polar solvents without additives, the results have hitherto usually been rationalised on the assumption that betaine formation can be a reversible process. Until recently there was no direct evidence in favour of this assumption; indeed Wittig<sup>44a</sup> has recorded that when the fairly stable betaine formed from benzaldehyde and methylenetriphenylphosphorane is heated with benzophenone "only a trace" of 1,1-diphenylethylene is formed.

Speziale and Bissing<sup>44b</sup> have now reported evidence for reversible betaine formation at least from the more stable phosphoranes. They treated ethyl *trans*-phenylglycidate with tributylphosphine in the presence of *m*-chlorobenzaldehyde and obtained both ethyl cinnamate and ethyl *m*-chlorocinnamate. The betaine (34) is the presumed intermediate; it can eliminate phosphine oxide to form cinnamate, or dissociate to benzaldehyde and phosphorane ester which is then free to react with the *m*-chlorobenzaldehyde:



<sup>44</sup> (a) Wittig, Weigmann, and Schlosser, *Chem. Ber.*, 1961, **94**, 676; (b) Speziale and Bissing, *J. Amer. Chem. Soc.*, 1963, **85**, 1888; (c) Boskin and Denney, *Chem. and Ind.*, 1959, 330.

The corresponding reactions of *cis*- and *trans*-but-2-ene epoxides with tributylphosphine proceed with a high degree of stereospecificity to give *trans*- and *cis*-but-2-ene, respectively:<sup>44c</sup> reversible betaine formation, which would involve a highly reactive ethylenephosphorane, cannot here be important.



There is, however, a further pathway for betaine *interconversion*, and that is by way of the phosphorane (35) formed by loss of the  $\alpha$ -hydrogen as a proton. This proton will be particularly easy to remove when R<sup>1</sup> is an activating group, in which case the starting phosphorane (32) will be a stable, unreactive phosphorane.

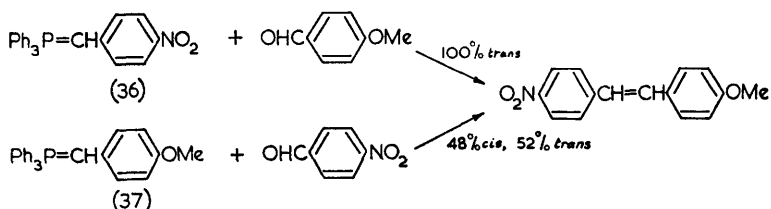
Both reversible betaine formation, and betaine *interconversion* through a common phosphorane, may operate in any given case; on present evidence it is not usually possible to distinguish between them. They would be expected to become important in determining the olefin isomer ratio when (a) the starting phosphoranes are relatively stable (this factor will promote both betaine dissociation and mobility of the  $\alpha$ -hydrogen), (b) the rate of olefin formation is slow relative to the rate of betaine equilibration, and (c) the rates of formation of olefins from the isomeric betaines are markedly different. Operation of these factors will lead to the preferential formation of the olefin isomer which is formed the more rapidly; this is usually the *trans*-isomer when R<sup>1</sup> or R<sup>2</sup> is able to conjugate with the new double bond, for this conjugation can best stabilise the transition state when R<sup>1</sup> or R<sup>2</sup> is coplanar with the new double bond, and this is more readily achieved in the state which leads to the *trans*-olefin.

In the absence of solvating effects, the conformation of the betaines (33a) and (33b) will be determined largely by the electrostatic attraction between the phosphorus and oxygen atoms, and it is reasonable to suppose that formation of the betaine (33b) will be favoured for obvious steric reasons. If betaine equilibration is not important this will lead to a mixture of olefins in which the *trans*-isomer will predominate.

A few specific examples will illustrate the application of these general ideas.

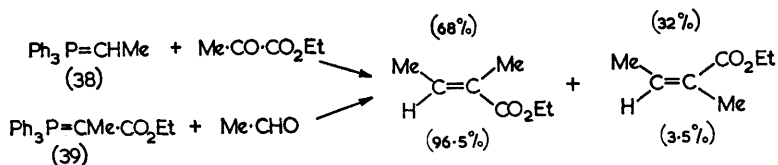
(i) Bestmann and Kratzer<sup>45</sup> have shown that, while the phosphoranes  $\text{Ph}_3\text{P}:\text{CHR}$  ( $\text{R} = \text{Ph}, \text{Ph}\cdot\text{CH}:\text{CH}$ ) give with aldehydes mixtures of *cis*- and *trans*-olefins, the corresponding phosphoranes derived from tricyclohexylphosphine give only *trans*-isomers. The authors suggested that the inductive effect of the cyclohexyl groups reduces the oxygen-affinity of the phosphorus in the intermediate betaines, so slowing up the olefin-forming eliminations and allowing time for equilibration of the betaines to become important.

(ii) The stilbene obtained from the relatively stable phosphorane (36) and anisaldehyde is entirely *trans*, while that from the reactive phosphorane (37) and *p*-nitrobenzaldehyde contains 48% of the *cis*-isomer.<sup>46</sup> The authors suggested that reversible betaine formation is important in the first case but, equally, that betaine equilibration through a phosphorane is more likely when the  $\alpha$ -hydrogen is activated by a *p*-nitrophenyl group than when it is activated by a *p*-methoxyphenyl group.



(iii) House and Rasmusson<sup>47</sup> have shown that the ester obtained from the highly reactive phosphorane (38) and ethyl pyruvate is a mixture of tiglate and angelate in the ratio 68:32, while that from the stable phosphorane ester (39) and acetaldehyde contains only 3.5% of ethyl angelate. In the first case betaine equilibration is not important, either because the  $\alpha$ -hydrogen of the betaines is not sufficiently acidic or because a highly reactive phosphorane is used. Direct equilibration of the betaines from the phosphorane (39) is not possible: here reversible betaine formation must be operating.

In general it is found that use of very stable phosphoranes, *e.g.*,  $\text{Ph}_3\text{P}:\text{CH}\cdot\text{COR}$  ( $\text{R} = \text{OEt}, \text{Me}, \text{Ph}, \text{etc.}$ ), leads almost entirely to the

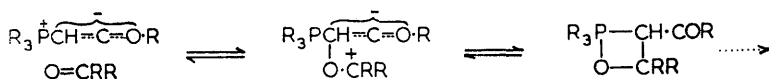


<sup>45</sup> Bestmann and Kratzer, *Chem. Ber.*, 1962, **95**, 1894.

<sup>46</sup> Ketcham, Jambotkar, and Martinelli, *J. Org. Chem.*, 1962, **27**, 4666.

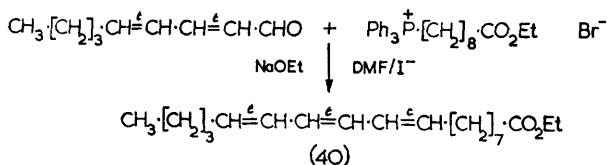
<sup>47</sup> House and Rasmusson, *J. Org. Chem.*, 1961, **26**, 4278.

*trans*-isomer. Russian workers<sup>48</sup> have suggested that in these cases the nucleophilicity of the phosphorane is so reduced that reaction with a carbonyl group now proceeds by attack of the negative oxygen of the carbonyl on the positive phosphorus of the phosphorane, *i.e.*,



this attack being reversible and, for reasons analogous to those outlined above for the normal mechanism, leading predominantly to the *trans*-olefin. This hypothesis does not seem to take into account the fact that stable phosphoranes react only with carbonyls which are highly susceptible to nucleophilic addition, *i.e.*, aldehydes and ketones such as hexafluoroacetone<sup>49</sup> and 4-nitroacetophenone. The hypothesis is unnecessary if it is assumed that betaines can equilibrate by one or both of the pathways discussed above.

The same Russian workers<sup>48</sup> have reported pioneering work on the effect of solvent and of additives on the *cis:trans* ratio of isomers. They studied in particular the formation of  $\beta$ -ethylstyrene from benzylidene-triphenylphosphorane and propionaldehyde, and from propylidene-triphenylphosphorane and benzaldehyde. In both cases, the proportion of *cis*-olefin produced increases with increasing polarity of the solvent (benzene < ether < tetrahydrofuran < ethanol < dimethylformamide), and increases markedly on addition to the reaction mixture of nucleophilic Lewis bases (amines, Br<sup>-</sup>, I<sup>-</sup>, but not Cl<sup>-</sup>). Reactions carried out in dimethylformamide containing lithium iodide give almost pure *cis*-olefins. These conditions have been applied to the synthesis of a number of naturally occurring *cis*-unsaturated acids, *e.g.*,  $\alpha$ -eleostearic acid (40):<sup>50</sup>



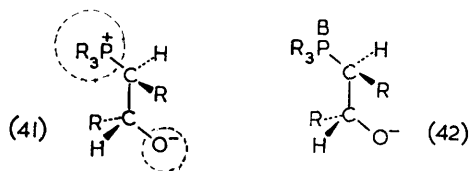
In polar solvents or in the presence of nucleophilic Lewis bases it is apparent that the electrostatic attraction between phosphorus and oxygen is no longer the major factor determining the conformation of the intermediate betaines. This attraction can be diminished either by the screening effect of solvent sheaths round the phosphorus and oxygen atoms, or by co-ordination of the phosphorus with a Lewis base. In the first case the preferred configuration of the betaine will be (41), while co-ordination of

<sup>48</sup> Bergelson and Shemyakin, *Tetrahedron*, 1963, **19**, 149.

<sup>49</sup> Plakhova and Gambaryan, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1962, 681.

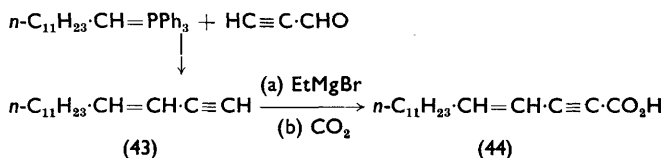
<sup>50</sup> Bergelson, Solodovnik, and Shemyakin, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1962, 1315.

the phosphorus with halide ion will give the preferred configuration (42) because of electrostatic repulsion between the halide and oxygen electronic shells. Both of these preferred configurations lead to a *cis*-olefin. The effect of amines may be a combination of the two effects. The yield of olefin



under these conditions is decreased because of the relative difficulty in forming the four-membered cyclic transition states necessary for phosphine oxide elimination.

By a suitable choice of phosphorane and reaction conditions it is now possible to exercise considerable control over the stereochemistry of the resulting olefin. The striking effect of bromide and iodide ions is the probable cause of several unexpected formations of *cis*-olefins previously reported. Wailes<sup>51</sup> showed that the enyne (43) obtained from *n*-dodecylidene triphenylphosphorane and prop-2-ynal leads to an acid (44) containing 80% of the *cis*-isomer. The phosphorane was prepared by the action of butyl-lithium on the phosphonium bromide. Similarly, much of the earlier work on the formation of isomeric olefins needs to be reassessed in the light of the Russian results, particularly when one remembers that solutions



of butyl- and phenyl-lithium are usually prepared from the organic bromides and therefore already contain one mole of lithium bromide.

**(d) Optically Active Wittig Reagents.**—The use of an optically active phosphonium salt in Wittig reactions leads to an optically active phosphine oxide.<sup>52</sup> If one assumes that the reactions proceed by way of a four-membered cyclic transition state, then the starting salt and resulting oxide have the same configuration. As the enantiomeric oxide is obtained on alkaline hydrolysis of the phosphonium salt, this process must be accompanied by inversion of configuration. The rate of hydrolysis is proportional to  $[\text{OH}^-]^2$ , and the reaction is therefore pictured as shown.

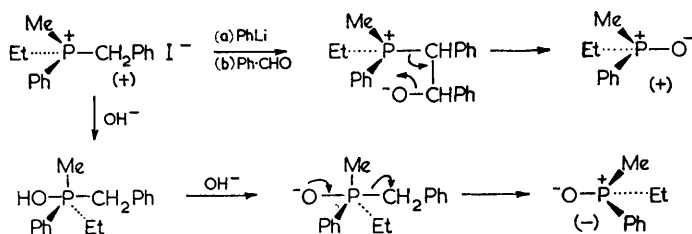
With the preparation by Horner and his co-workers<sup>53</sup> of optically

<sup>51</sup> Wailes, *Chem. and Ind.*, 1958, 1086.

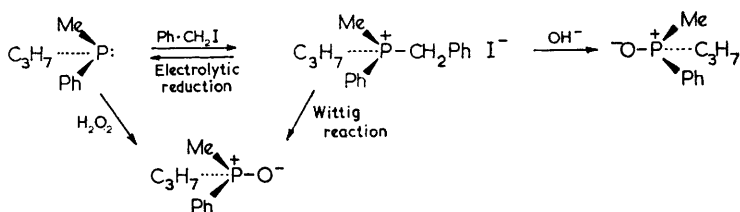
<sup>52</sup> Bladé-Font, VanderWerf, and McEwen, *J. Amer. Chem. Soc.*, 1960, **82**, 2396.

<sup>53</sup> Horner, Winkler, Rapp, Mentrup, Hoffmann, and Beck, *Tetrahedron Letters*, 1961, 161.

active phosphines, direct correlation of the configurations of phosphonium salts and phosphine oxides is possible, since both are presumably formed from the phosphine without change of configuration. This evidence can



now be used to prove that the configuration round the phosphorus atom is unchanged in the Wittig reaction.



Optically active phosphonium salts have also been used in investigations of the mechanisms of the reactions of Wittig reagents with nitriles (p. 429) and epoxides (p. 426).

## 5. The Reactions of Alkylidenephosphoranes with Various Functional Groups

Alkylidenephosphoranes are powerful nucleophilic agents and react with a range of functional groups comparable to those reacting with Grignard reagents.

(a) **Aldehydes and Ketones.**—One of the outstanding features of the Wittig olefin synthesis is its relative freedom from complicating factors. The carbonyl component may contain a wide range of other functional groups, among them hydroxyl, ether, acetal, ester, halogen (including benzylic),<sup>54</sup> dimethylamino, and terminal acetylene. Aromatic nitro-groups may interfere.<sup>55</sup> In contrast with Grignard reagents and with some sulphur ylids (see p. 435), alkylidenephosphoranes normally attack at the  $\beta$ -position of  $\alpha,\beta$ -unsaturated ketones only when the carbonyl group is highly hindered, e.g., in the ketone (45).<sup>56</sup>

<sup>54</sup> Drefahl and Plötner, *Chem. Ber.*, 1961, **94**, 907.

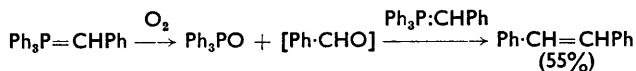
<sup>55</sup> Trippett and Walker, *J.*, 1961, 2130.

<sup>56</sup> Freeman, *Chem. and Ind.*, 1959, 1254. For other abnormal reactions see ref. 2(b).

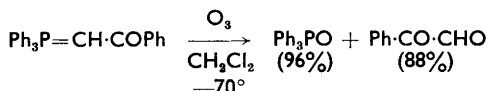




oxides and carbonyl compounds which can then react with unchanged reagent to form olefins,<sup>59a</sup> *e.g.*,

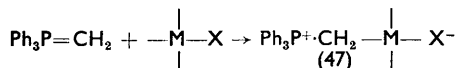


A similar reaction occurs when the more stable phosphoranes are treated with peracetic acid.<sup>59b</sup> Ozonisation of the stable  $\beta$ -ketoalkylidenephosphoranes gives mainly phosphine oxides and  $\beta$ -dicarbonyl compounds,<sup>60</sup> *e.g.*,

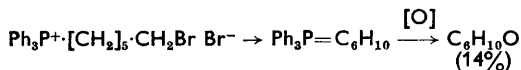


Reduction of alkylidetriphenylphosphoranes with lithium aluminium hydride leads to the corresponding alkylidiphosphine, irrespective of the nature of the alkyl group.<sup>61</sup> Thus, while reduction of benzyltriphenylphosphonium bromide gives entirely triphenylphosphine, benzylidetriphenylphosphorane under the same conditions gives benzylidiphosphine.

Alkylidene phosphoranes form adducts with boron compounds (alkyls, halides, and hydrides),<sup>62</sup> and react with metal and non-metal halides to give the expected phosphonium salts (47; M = Si, Ge, Sn, Hg, Zn, P, Sb).<sup>18, 63</sup>



(c) **Alkyl Halides.**—These react with alkylidene phosphoranes to give C-alkylated phosphonium halides, *e.g.*, isopropylidetriphenylphosphorane with methyl iodide gives triphenyl-*t*-butylphosphonium iodide.<sup>31</sup> Intramolecular alkylation is successful,<sup>64</sup> *e.g.*,



Bestmann and Schulz<sup>65</sup> treated the stable phosphorane ester (48) with alkyl halides and obtained the phosphonium salts (49) when R had a +*I* effect and the phosphoranes (50), formed by ylid exchange, when R had a -*I* effect.

<sup>59</sup> (a) Bestmann, *Angew. Chem.*, 1960, **72**, 34; (b) Denney, Smith, Song, Rossi, and Hall, *J. Org. Chem.*, 1963, **28**, 778.

<sup>60</sup> Ramirez, Mitra, and Desai, *J. Amer. Chem. Soc.*, 1960, **82**, 5763.

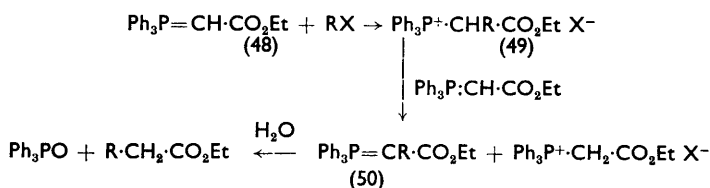
<sup>61</sup> Saunders and Burchman, *Tetrahedron Letters*, 1959, No. 1, 8; Gough and Trippett, *J.*, 1961, 4263.

<sup>62</sup> Hawthorne, *J. Amer. Chem. Soc.*, 1958, **80**, 3480; *ibid.*, 1961, **83**, 367; Seyferth and Grim, *ibid.*, 1961, **83**, 1613.

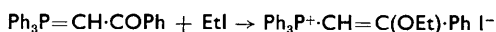
<sup>63</sup> Seyferth and Grim, *J. Amer. Chem. Soc.*, 1961, **83**, 1610; Seyferth and Brändle, *ibid.*, 1961, **83**, 2055; Wittig and Schwarzenbach, *Annalen*, 1961, **650**, 1.

<sup>64</sup> Bestmann and Halberlein, *Z. Naturforsch.*, 1962, **17b**, 787.

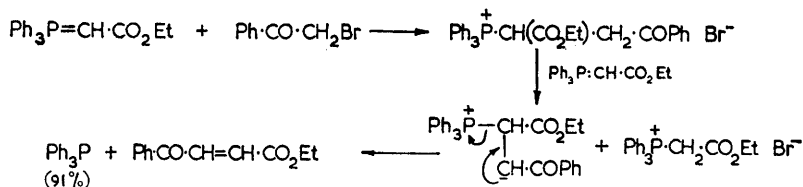
<sup>65</sup> Bestmann and Schulz, *Chem. Ber.*, 1962, **95**, 2921.



Hydrolysis of the phosphoranes (50) with boiling water gives the esters  $\text{RCH}_2\cdot\text{CO}_2\text{Et}$ , making the whole sequence an attractive ester synthesis. Unfortunately, the other  $\beta$ -ketoalkyldienephosphoranes are *O*-alkylated by ordinary alkyl halides,<sup>21</sup> *e.g.*,

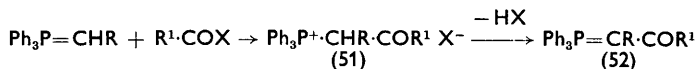


When stable alkyldienephosphoranes react with  $\alpha$ -halogenocarbonyl compounds, the initially formed  $\gamma$ -ketophosphonium salts eliminate halogen acid and triphenylphosphine under the influence of a second molecule of phosphorane to form  $\alpha,\beta$ -unsaturated ketones,<sup>66</sup> *e.g.*,



In the analogous reaction between phenacyl bromide and the phenacyldienephosphorane, tribenzoylcyclopropane (7%) was formed along with dibenzoylethylene (50%).<sup>67</sup>

(d) **Esters, Acid Halides, etc.**—Esters,<sup>1,22</sup> thioesters,<sup>68</sup> acid halides,<sup>22,68</sup> and *N*-acylimidazoles<sup>69,70</sup> react with alkyldienephosphoranes to give initially the  $\beta$ -ketoalkylphosphonium salts (51). When  $\text{X} = \text{OR}$  or  $\text{SR}$ , these eliminate  $\text{XH}$ ; when  $\text{X} =$  halogen or imidazole, ylid exchange occurs with a second molecule of phosphorane. In any case the product is the stable  $\beta$ -ketoalkyldienephosphorane (52):



The corresponding ketones,  $\text{RCH}_2\cdot\text{COR}^1$ , can be obtained from these either by hydrolysis, by reduction with zinc and acetic acid, or by electrolytic reduction at a mercury cathode.

The use of ethyl chloroformate in this sequence of reactions constitutes

<sup>66</sup> Bestmann and Schulz, *Angew. Chem.*, 1961, 73, 620.

<sup>67</sup> Siemiatycki and Strzelecka, *Compt. rend.*, 1960, 250, 3489.

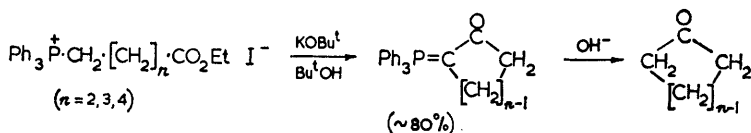
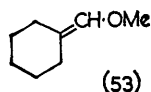
<sup>68</sup> Bestmann and Arnason, *Chem. Ber.*, 1962, 95, 1513.

<sup>69</sup> Bestmann, Sommer, and Staab, *Angew. Chem.*, 1962, 74, 293.

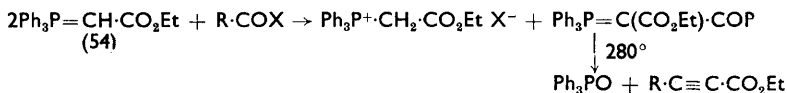
<sup>70</sup> Staab and Sommer, *Angew. Chem.*, 1962, 74, 294.

a convenient synthesis of carboxylic esters.<sup>71a</sup> Ethyl formate gives with alkylidenephosphoranes the expected formylmethylenephosphoranes (52;  $R^1 = H$ ),<sup>22</sup> but the vinyl ether (53) is the reported product from the reaction of methyl formate with cyclohexylidetriphenylphosphorane.<sup>71b</sup>

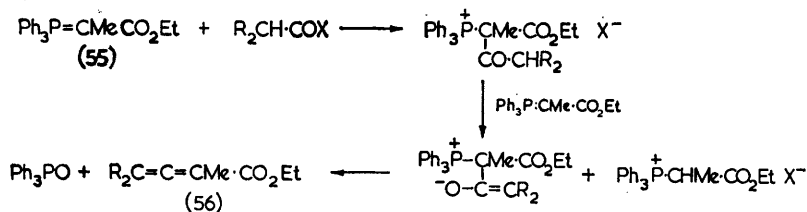
A number of intramolecular phosphorane ester reactions have recently been described.<sup>71c</sup> Hydrolysis of the resulting phosphoranes gives cyclic ketones:



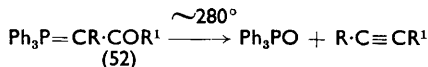
While  $\beta$ -ketoalkylidenephosphoranes in general are *O*-acylated by aromatic acid halides and dehydrohalogenate aliphatic acid halides in a reaction which is still not understood,<sup>68,72</sup> the phosphorane ester (54) is *C*-acylated by all acid halides.<sup>72,73</sup> The resulting phosphoranes are stable to hydrolysis; at 280° they give  $\alpha,\beta$ -acetylenic esters:



The phosphorane ester (55) is also *C*-acylated by acid halides but, in the absence of  $\alpha$ -hydrogen, subsequent reactions now lead to allenic esters (56).<sup>74</sup>



This is a convenient place to mention that  $\beta$ -ketoalkylidenephosphoranes (52) in general give acetylenes when heated to  $\sim 280^\circ$ , provided that neither R nor  $R^1$  is hydrogen and that the acetylenic link being formed is stabilised by conjugation, e.g., with an aromatic nucleus, an ester, or a nitrile group:<sup>72</sup>



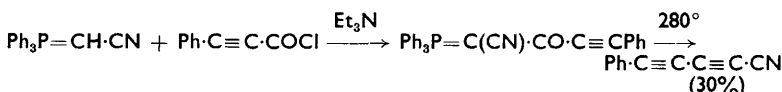
<sup>71</sup> (a) Bestmann and Schulz, *Angew. Chem.*, 1961, 73, 27; (b) G. P. 1,047,763; cited in Ref. 9; (c) House and Babab, *J. Org. Chem.*, 1963, 28, 90.

<sup>72</sup> Gough and Trippett, *J.*, 1962, 2333.

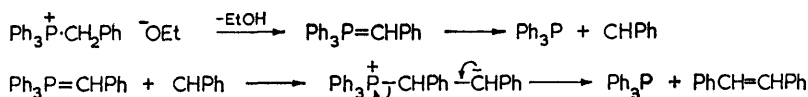
<sup>73</sup> Märkl, *Chem. Ber.*, 1961, 93, 3005.

<sup>74</sup> Bestmann and Hartung, *Angew. Chem., Int. edn.*, 1963, 2, 214.

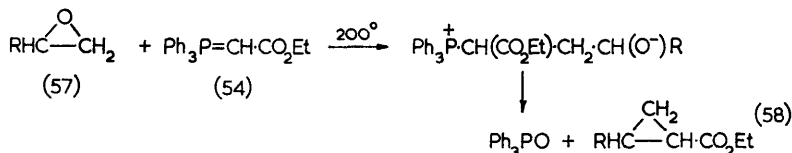
The yields of acetylenes are good, *e.g.*, 91% when  $R = \text{CO}_2\text{Et}$  and  $R^1 = \text{Ph}$ , and the synthesis has been extended to diacetylenes,<sup>75</sup> *e.g.*,



When  $R$  and  $R^1$  are both alkyl groups no acetylene is obtained and the product shows strong allenic absorption. When  $R$  is hydrogen, the only volatile product, obtained in almost quantitative yield, is triphenylphosphine.<sup>75</sup> This decomposition is probably the reverse of the formation of phosphoranes from carbenes and phosphines. A related reaction is the thermal decomposition of benzyltriphenylphosphonium ethoxide to triphenylphosphine and stilbene, presumably by way of a carbene:<sup>76</sup>

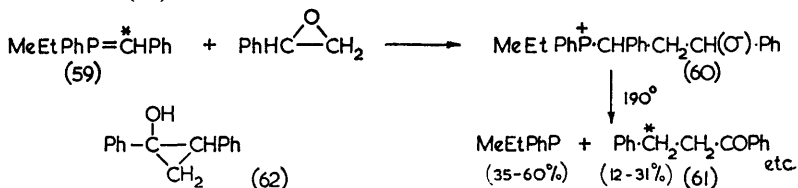


(e) **Epoxides.**—Denney and Boskin<sup>77</sup> treated the epoxides (57;  $R = \text{Ph}$ ,  $\text{C}_6\text{H}_{13}$ ) with the phosphorane ester (54) under vigorous conditions and obtained cyclopropanes in moderate yields:



Cyclohexene epoxide gives ethyl norcaranecarboxylate (56%) and *l*-styrene oxide the *l*-cyclopropane (58;  $R = \text{Ph}$ ). A footnote records that the corresponding tributylphosphorane gives similar results in refluxing benzene.

McEwen *et al.*<sup>78</sup> investigated the reaction of styrene oxide with the phosphorane (59) generated from the phosphonium iodide and phenyllithium. The betaine (60) is precipitated as an adduct with lithium iodide. At 190° in decalin this gives a complex mixture of products, among them the ketone (61):



<sup>75</sup> Gough and Trippett, *J.*, in the press.

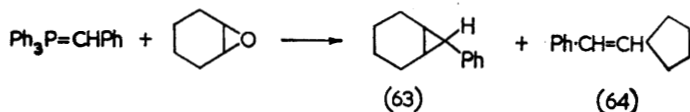
<sup>76</sup> Trippett, *Proc. Chem. Soc.*, 1963, 19.

<sup>77</sup> Denney and Boskin, *J. Amer. Chem. Soc.*, 1959, **81**, 6330; Denney, Vill, and Boskin, *ibid.*, 1962, **84**, 3944.

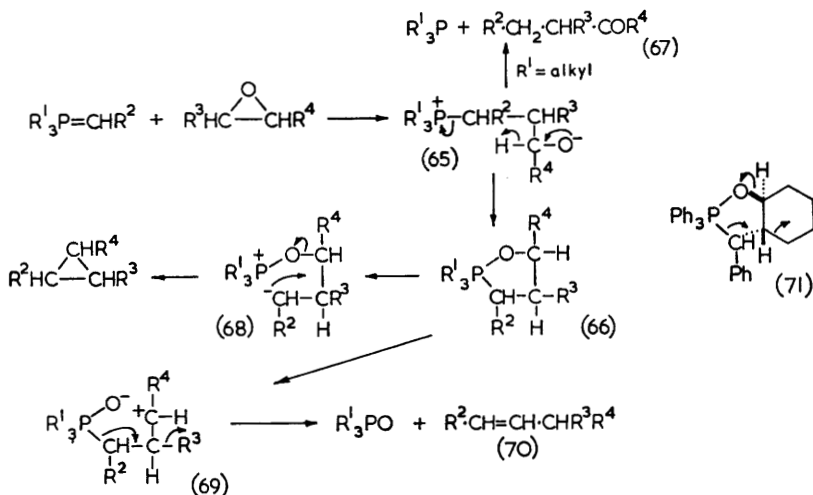
<sup>78</sup> McEwen, Bladé-Font, and VanderWerf, *J. Amer. Chem. Soc.*, 1962, **84**, 677.

Isotopic labelling of the phosphorane at the starred position<sup>79</sup> shows that the ketone is not formed by way of a symmetrical intermediate. Cyclopropanols isomerise to ketones under the influence of base, and the cyclopropanol (62) was suggested as a possible intermediate. A simpler explanation for the formation of the ketone involves a 1,3-hydride shift as in (65).

The reaction of benzylidenetriphenylphosphorane with styrene oxide gives only 0.3% of the ketone (61), the major product being a mixture of *cis*- and *trans*-1,3-diphenylpropene. The same phosphorane with cyclohexene oxide gives the cyclopropane (63) and the olefin (64) in the ratio 2:1.<sup>80</sup> The formation of this olefin obviously involves a rearrangement and is a valuable clue to the mechanism of these reactions.



The above results may be rationalised as follows. Nucleophilic attack of the phosphorane on the epoxide gives the intermediate (65). This may then cyclise to a quinquovalent phosphorus derivative (66), but alkyl groups attached to the phosphorus will reduce the electrophilic character of that atom and make the cyclisation more difficult. The preferred pathway is then elimination of phosphine, with accompanying hydride shift, to give the ketone (67). If the cyclic phosphorane (66) is formed, and R<sup>2</sup> is capable of stabilising a carbanion, the betaine (68) is then the intermediate in cyclopropane formation. Otherwise production of the betaine (69) is followed by, or is simultaneous with, migration of R<sup>3</sup> and elimination of phosphine

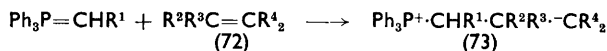


<sup>79</sup> McEwen and Wolf, *J. Amer. Chem. Soc.*, 1962, 84, 676.

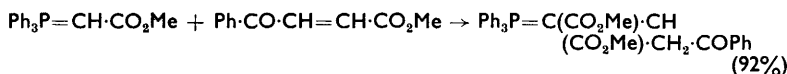
<sup>80</sup> Zbiral, *Monatsh.*, 1963, 94, 78.

oxide to give the olefin (70). The group  $R^3$  which migrates will normally be hydrogen; the rearrangement which occurs with cyclohexene oxide is a necessary consequence of the *trans*-opening of the epoxide which leads to the intermediate (71) in which the grouping *trans* to the leaving oxygen, *i.e.*, the  $CH_2$  of the cyclohexane ring, migrates.

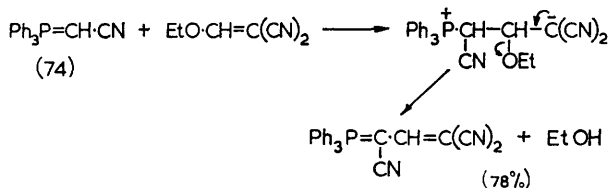
(f) **Carbon-Carbon Double and Triple Bonds.**—Alkylidenephosporanes add to activated carbon-carbon double bonds, as in (72;  $R^4$  having  $-M$  effect) to give intermediates (73) which may then react in one of three ways depending on the nature of the substituents.



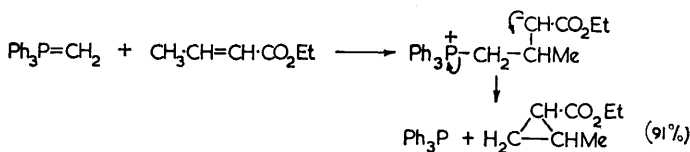
When  $R^1$  has a  $-M$  effect, transfer of a proton from the  $\alpha$ - to the  $\gamma$ -carbon leads to a new stable phosphorane,<sup>81</sup> *e.g.*,



When  $R^2$  is capable of forming a stable anion, the intermediate eliminates  $R^2^-$  which then abstracts the  $\alpha$ -proton to give a new stable phosphorane,<sup>82</sup> *e.g.*,



Finally, if neither of the above features is present, the intermediate may eliminate triphenylphosphine to form a cyclopropane,<sup>81,83</sup> *e.g.*,



The cyanomethylenephosporane (74) adds to dimethyl acetylenedicarboxylate to give the phosphorane (75).<sup>82</sup> The same acetylene with phenacylidetriphenylphosphorane gives a compound for which the alternative structures (76)<sup>84</sup> and (77)<sup>85</sup> have been suggested.

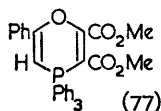
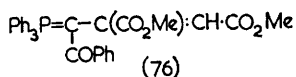
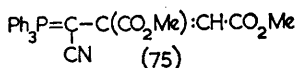
<sup>81</sup> Bestmann and Seng, *Angew. Chem.*, 1962, **74**, 154.

<sup>82</sup> Trippett, *J.*, 1962, 4733.

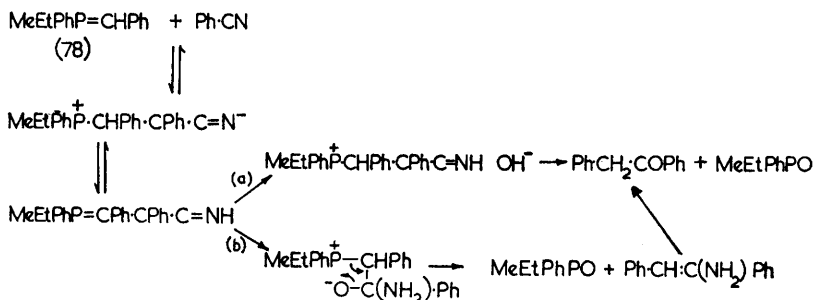
<sup>83</sup> Mechoulam and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 4386.

<sup>84</sup> Gough and Trippett, *Proc. Chem. Soc.*, 1961, 302.

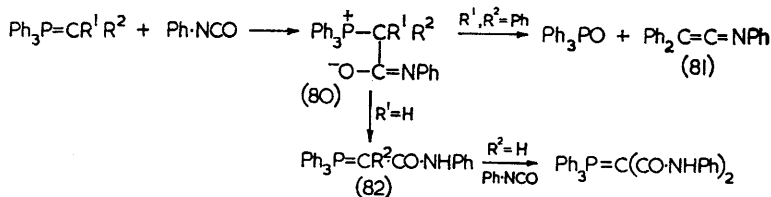
<sup>85</sup> Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**, 2018.



(g) **Cyanides.**—When the optically active benzylidenephosphorane (78) is treated in ether with benzonitrile<sup>86</sup> the characteristic orange colour of the reagent is not discharged, but hydrolysis of the reaction mixture with methanolic potassium hydroxide gives deoxybenzoin (78%) and the phosphine oxide (71%) with activity indicating that inversion of configuration has occurred to the extent of 68%. Two competing reactions are envisaged for the hydrolysis of the betaine (79), (a) involving inversion and (b) involving retention of configuration around the phosphorus.



(h) **Isocyanates.**—Alkylidenephosphoranes add to phenyl isocyanate<sup>17</sup> to give the betaines (80). When R<sup>1</sup> and R<sup>2</sup> are both phenyl, a normal Wittig reaction then gives the imidoethylene (81), but, if either R<sup>1</sup> or R<sup>2</sup> is hydrogen, migration of that hydrogen to nitrogen occurs to give a more stable phosphorane (82). With the methylenephosphorane (when R<sup>1</sup> = R<sup>2</sup> = H) this process is then repeated with a second molecule of isocyanate.



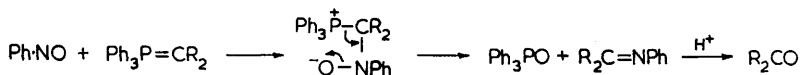
(i) **Nitroso-compounds.**—Alkylidetriphenylphosphoranes react with nitrosobenzene as in a normal olefin synthesis to give phosphine oxide and anils.<sup>87</sup> As these are readily hydrolysed to carbonyl compounds this gives

<sup>86</sup> Bladé-Font, McEwen, and VanderWerf, *J. Amer. Chem. Soc.*, 1960, **82**, 2646.

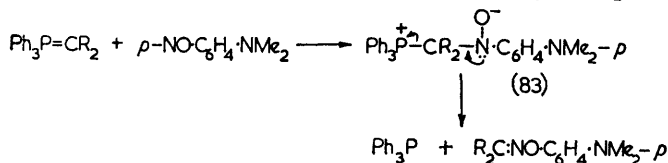
<sup>87</sup> Schöllkopf, Dissertation, Tübingen, 1955. Cited in ref. 2(a); Schönberg and Brosowski, *Chem. Ber.*, 1959, **92**, 2602.



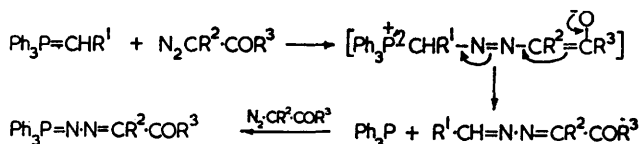
a convenient method of converting RRCHBr into RRCO, *e.g.*, geranyl bromide into citral (74% from the phosphonium salt).



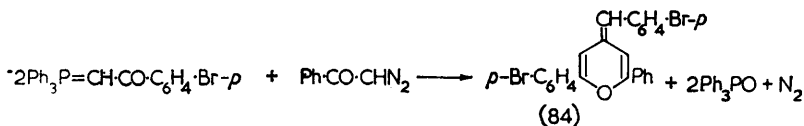
The reactions with *p*-dimethylaminonitrosobenzene take an alternative course,<sup>31</sup> analogous to the Kröhnke aldehyde synthesis using pyridinium betaines. Elimination of triphenylphosphine from the betaines (83) leads to nitrones which again can be hydrolysed to carbonyl compounds.



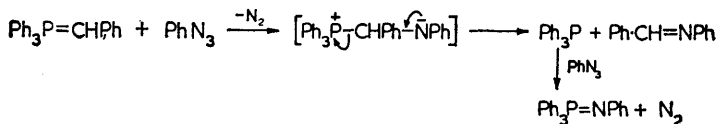
(j) **Diazo-compounds, Diazonium Salts, and Azides.**—Compounds containing electrophilic nitrogen react with alkylidenephosphoranes in the expected way. Diazo-ketones and the more reactive phosphoranes give intermediates which eliminate triphenylphosphine, as shown, to form mixed azines.<sup>88</sup> The phosphine then reacts with a second molecule of diazo-ketone:



The more stable phenacylidene phosphoranes with diazoacetophenone give benzylidenepyranes,<sup>89</sup> *e.g.*, (84)



The intermediates from azides and alkylidenephosphoranes eliminate triphenylphosphine to form Schiff's bases.<sup>90</sup> The phosphine then reacts with a second molecule of azide, if available:

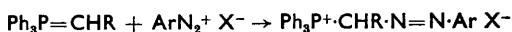


<sup>88</sup> Märkl, *Tetrahedron Letters*, 1961, 811.

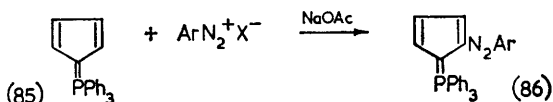
<sup>89</sup> Strzelecka, Simalty-Siematycki, and Prevost, *Compt. rend.*, 1962, **254**, 696; Strzelecka, *ibid.*, 1962, **255**, 731.

<sup>90</sup> Hoffmann, *Chem. Ber.*, 1962, **95**, 2563.

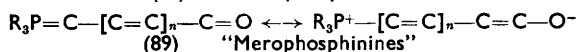
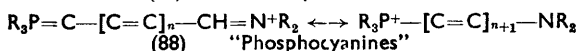
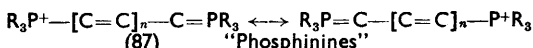
Diazonium salts<sup>91</sup> couple with alkylidenephosphoranes by the reaction:



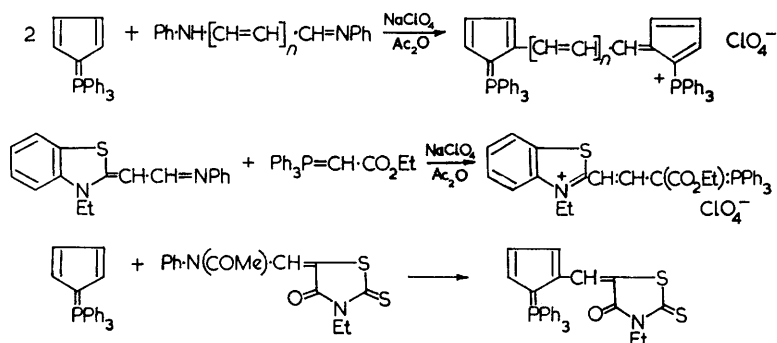
The very stable cyclopentadienylidetriphenylphosphorane (85) couples at the 2-position to give the azo-compound (86).<sup>92</sup> This is the only phosphorane so far reported which reacts at a position other than that adjacent to the phosphorus, that is, at a formally allylic position.



(k) **The Preparation of Phosphorus-containing Dyes.**—The Gevaert group of workers<sup>93</sup> have prepared, from stable alkylidenephosphoranes, dyes containing the chromophores (87)—(89).



Examples of the reaction employed are as follows:



## 6. Related Olefin Syntheses

(a) **Phosphine Oxides and Phosphonates.**—Horner and his co-workers<sup>94</sup> were the first to show that phosphine oxide (90; R = Alk, Ph) and phosphonate (90; R = OEt) anions add to carbonyl groups to give inter-

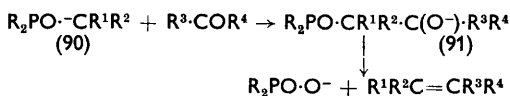
<sup>91</sup> Märkl, *Tetrahedron Letters*, 1961, 807.

<sup>92</sup> Ramirez and Levy, *J. Amer. Chem. Soc.*, 1957, **79**, 6167.

<sup>93</sup> Depoorter, Nys, and Van Dormael, *Tetrahedron Letters*, 1961, 199.

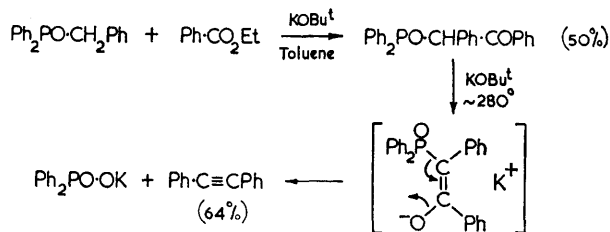
<sup>94</sup> Horner, Hoffmann, and Wippel, *Chem. Ber.*, 1958, **91**, 61; Horner, Hoffmann, Wippel, and Klahre, *ibid.*, 1959, **92**, 2499.

mediates which eliminate phosphinate or phosphate anions to form olefins:

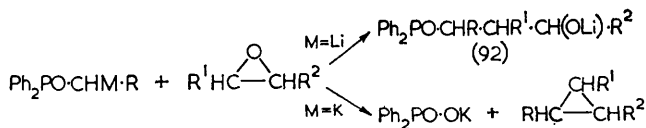


The anions were generated using sodamide or potassium *t*-butoxide in refluxing benzene. When phenyl-lithium in ether was employed, the lithium salt of the anion (91; R = Ph) did not eliminate phosphinate anion and the  $\beta$ -hydroxyphosphine oxides were isolated. While ordinary alkylphosphine oxides may be used for olefin synthesis, only those phosphonates in which R<sup>1</sup> or R<sup>2</sup> is able further to stabilise the anion (*i.e.*, R<sup>1</sup>, R<sup>2</sup> = CO, CN, Ph, etc.) can be successfully employed.

The phosphine oxide anions with esters give  $\beta$ -ketoalkylphosphine oxides.<sup>94</sup> These, when heated with a suitable base, eliminate phosphinate ion to form acetylenes, <sup>72</sup> *e.g.*,



Lithium-metallated phosphine oxides give with epoxides the lithium alkoxides (92), but the potassium-metallated oxides lead to cyclopropanes and potassium diphenylphosphinate.<sup>95</sup> In view of these findings it would be interesting to repeat the work of McEwan *et al.*, on the reaction of alkylidenephosphoranes with epoxides, in the absence of lithium salts (see p. 426).



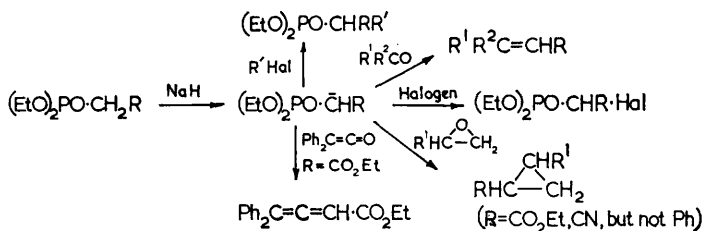
Wadsworth and Emmons<sup>96</sup> extended the use of phosphonate anions in olefin syntheses, using sodium hydride for their generation, either at room temperature [*e.g.*, (EtO)<sub>2</sub>PO<sup>-</sup>CH<sup>-</sup>CO<sub>2</sub>Et] or at 60° [*e.g.*, (EtO)<sub>2</sub>PO<sup>-</sup>CHPh]. When warming to 60° is necessary, the anions, because of their thermal instability, are generated in the presence of the compound with which they are to react. Sodium alkoxides in, for example, dimethylformamide may also be used as base with the more reactive phosphonates.<sup>97</sup>

<sup>95</sup> Horner, Hoffmann, and Toscano, *Chem. Ber.*, 1962, **95**, 536.

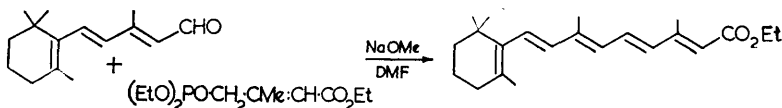
<sup>96</sup> Wadsworth and Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.

<sup>97</sup> Trippett and Walker, *Chem. and Ind.*, 1961, 990.

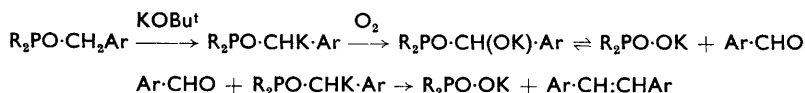
Phosphonate anions have also been treated with halogens,<sup>96</sup> alkyl<sup>98</sup> and acyl halides,<sup>99</sup> ketens,<sup>96</sup> and epoxides,<sup>96</sup> with the results shown:



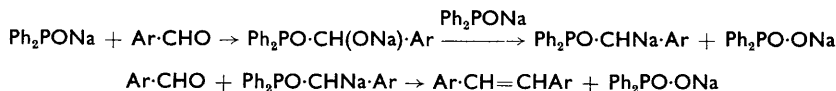
Following unpublished work by Wittig, the use of phosphonate anions in olefin synthesis was also developed by Pommer,<sup>33,100</sup> and applied extensively in the Vitamin A and carotenoid fields. Typical of many beautiful syntheses is the following of Vitamin A acid ethyl ester:



Phosphine oxide and phosphonate olefin syntheses presumably occur in the formation of stilbenes by the autoxidation of metallated phosphine oxides and phosphonates;<sup>101</sup>



and in the formation of stilbenes by the action of sodium diphenylphosphinate on aromatic aldehydes:<sup>102</sup>



The phosphonate olefin synthesis has the following advantages over the conventional Wittig reaction.

(a) Phosphonate anions are much more reactive, *i.e.*, nucleophilic, than the corresponding alkylidenephosphoranes. Phenacylidetriphenylphosphorane reacts with aldehydes only on prolonged refluxing in benzene solution; the phenacylphosphonate anions react exothermically. Again, the phosphorane ester,  $\text{Ph}_3\text{P}=\text{CH}\cdot\text{CO}_2\text{Et}$ , takes part in olefin syntheses

<sup>98</sup> Arbuzov and Razumov, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 623.

<sup>99</sup> Kreutzkamp, *Chem. Ber.*, 1955, **88**, 195.

<sup>100</sup> Pommer, *Angew. Chem.*, 1960, **72**, 911.

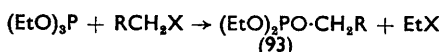
<sup>101</sup> Horner, Hoffmann, Klahre, Toscano, and Ertel, *Chem. Ber.*, 1961, **94**, 1987.

<sup>102</sup> Horner, Beck, and Toscano, *Chem. Ber.*, 1961, **94**, 1323.

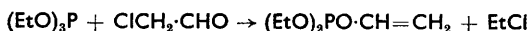
with unhindered ketones only during a period of days<sup>103</sup> and with hindered ketones vigorous conditions (boiling xylene or 150° without solvent) are required.<sup>104</sup> The corresponding phosphonate ester, (EtO)<sub>2</sub>PO·CH<sub>2</sub>·CO<sub>2</sub>Et, in dimethylformamide in the presence of sodium methoxide, gives high yields of α,β-unsaturated esters with most ketones at room temperature.<sup>97</sup>

(b) Separation of the required olefin from the water-soluble phosphate ion is much easier than separation from phosphine oxide. Phosphonium salts containing a basic group (leading to acid-soluble phosphine oxides) have been used in Wittig olefin syntheses to overcome this difficulty.<sup>55</sup>

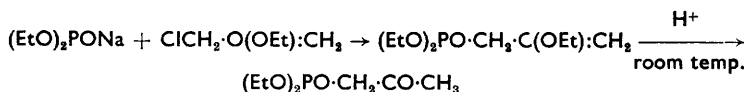
(c) Alkylphosphonates are readily prepared using the Arbuzov reaction and are cheaper than alkylphosphonium salts.



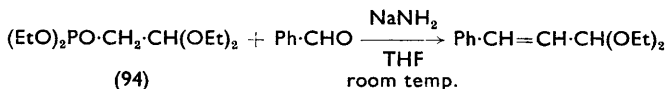
However many beta-ketoalkylphosphonates cannot be obtained in this way, the general reaction between triethyl phosphite and α-halogenocarbonyl compounds giving vinyl phosphates,<sup>38</sup> e.g.,



Normant and Sturtz<sup>105a</sup> have overcome this difficulty by protecting the carbonyl group of α-halogenocarbonyl compounds either as an acetal or by conversion into the corresponding vinyl ether. The resulting β-ketoalkylphosphonates have been used in olefin synthesis:<sup>105b</sup>



In general, only those phosphonates (93) having a substituent R able further to stabilise the phosphonate anion have been successfully used in olefin synthesis. An exception is the phosphonate (94) which is reported<sup>106</sup> to give, with benzaldehyde in the presence of sodamide, a 61% yield of cinnamaldehyde diethyl acetal.



## 7. The Reactions of "Ylids" other than those of Phosphorus

(a) **Nitrogen Ylids.**—These, e.g., (95), are obtained by the action of a powerful base on quaternary ammonium salts having replaceable hydrogen

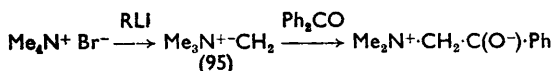
<sup>103</sup> Sugasawa and Matsuo, *Chem. and Pharm. Bull. (Japan)*, 1960, **8**, 819.

<sup>104</sup> Openshaw and Whittaker, *Proc. Chem. Soc.*, 1961, 454; Fodor and Tömösközi, *Tetrahedron Letters*, 1961, 579.

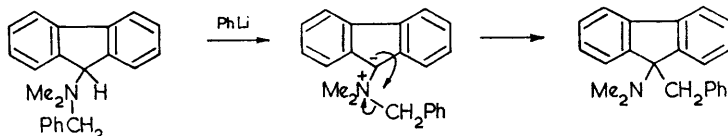
<sup>105</sup> (a) Normant and Sturtz, *Compt. rend.*, 1961, **253**, 2366; (b) Normant and Sturtz, *ibid.*, 1963, **256**, 1800.

<sup>106</sup> Takahashi, Fujiwaha, and Ohta, *Bull. Chem. Soc. Japan*, 1962, **35**, 1498.

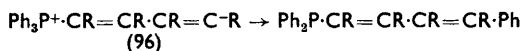
on an  $\alpha$ -carbon atom. Nitrogen ylids are not stabilised by  $d$ -orbital conjugation as in phosphorus ylids, and are powerful nucleophiles, adding to carbonyl groups to give betaines.<sup>107</sup> These do not eliminate amine oxide to form olefins.



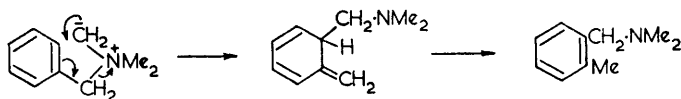
Nitrogen ylids may undergo electrophilic (Stevens) rearrangement, *e.g.*,<sup>108</sup>



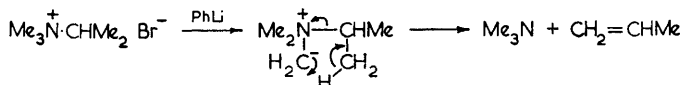
a reaction which so far has no direct analogy in phosphorus chemistry, although electrophilic migration of phenyl from phosphorus to the  $\delta$ -carbon occurs in the adduct (96; R = CO<sub>2</sub>Me) of triphenylphosphine and two molecules of acetylenedicarboxylic ester:<sup>109</sup>



Nitrogen ylids derived from quaternary benzylamines rearrange in a different way to give tertiary amines,<sup>110</sup> *e.g.*,



Internal abstraction of the  $\beta$ -hydrogen in a nitrogen ylid can lead to tertiary amine and olefin,<sup>111</sup> *e.g.*,



(b) **Sulphur.**—Johnson and LaCount<sup>112</sup> investigated the reactions of the relatively stable ylid (97), from dimethylfluorenylsulphonium bromide, with aldehydes. In general, three products were isolated, in proportions which varied markedly with the solvent, the olefin (98) formed in a typical Wittig reaction, the epoxide (99) formed by extrusion of dimethylsulphide, and the alcohol (100) formed by rearrangement of the intermediate betaine.

<sup>107</sup> Wittig and Wetterling, *Annalen*, 1947, **557**, 193.

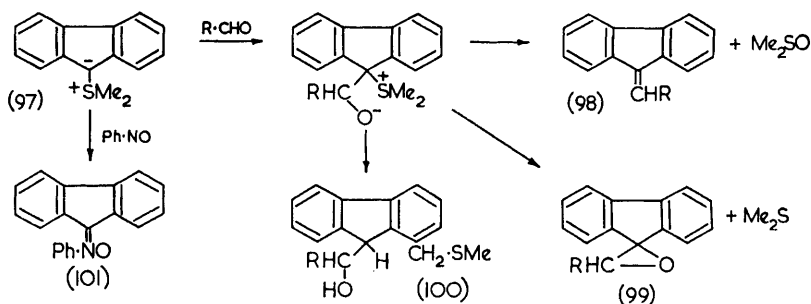
<sup>108</sup> Wittig and Felletschin, *Annalen*, 1944, **555**, 133.

<sup>109</sup> Johnson and Tebby, *J.*, 1961, 2126.

<sup>110</sup> Kantor and Hauser, *J. Amer. Chem. Soc.*, 1951, **73**, 4122.

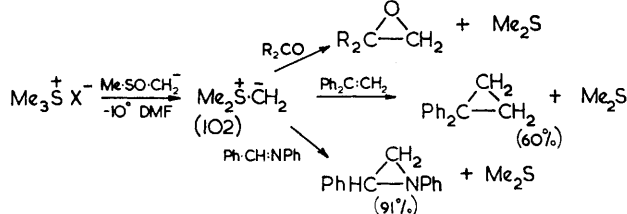
<sup>111</sup> Wittig and Polster, *Annalen*, 1956, **599**, 13.

<sup>112</sup> Johnson and LaCount, *J. Amer. Chem. Soc.*, 1961, **83**, 417.

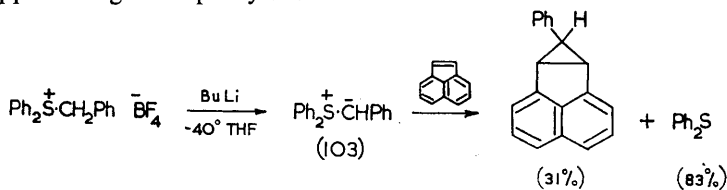


The same ylid with nitrosobenzene<sup>113</sup> gave the nitrone (101) in high yield.

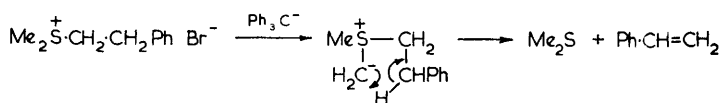
A systematic investigation of sulphur ylids and of metallated sulfoxides and sulphones has been made by Corey and Chaykovsky. The simplest ylid (102)<sup>114</sup> from a trimethylsulphonium salt has a half-life of only a few minutes at room temperature, decomposing to ethylene probably by way of carbene. With carbonyl compounds, including  $\alpha,\beta$ -unsaturated ketones, it gives high yields of epoxides.<sup>115</sup> Activated double bonds lead to cyclopropanes, and Schiff's bases to azirines, e.g.,



The carbene formed in the decomposition of the related ylid (103) has been trapped using acenaphthylene.<sup>116</sup>



As with their nitrogen analogues, sulphur ylids can also form olefins by  $\alpha',\beta$ -elimination,<sup>117</sup>



<sup>113</sup> Johnson, *J. Org. Chem.*, 1963, **28**, 252.

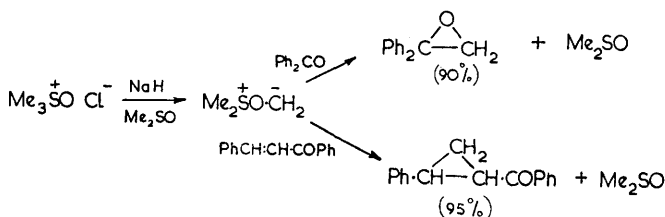
<sup>114</sup> Corey and Chaykovsky, *J. Amer. Chem. Soc.*, 1962, **84**, 3782.

<sup>115</sup> Corey and Chaykovsky, *Tetrahedron Letters*, 1963, 169.

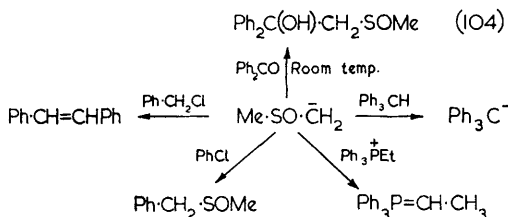
<sup>116</sup> Hruby and Johnson, *J. Amer. Chem. Soc.*, 1962, **84**, 3586.

<sup>117</sup> Franzen and Schmidt, *Chem. Ber.*, 1961, **94**, 2937.

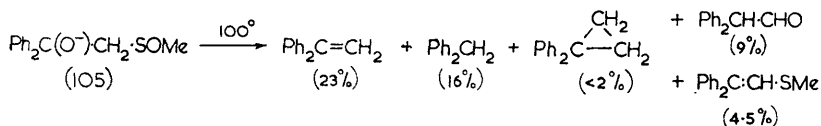
The ylid from trimethylsulphoxonium chloride<sup>118</sup> also gives high yields of epoxides with carbonyl compounds. With  $\alpha,\beta$ -unsaturated ketones this ylid gives the corresponding cyclopropanes, e.g.,



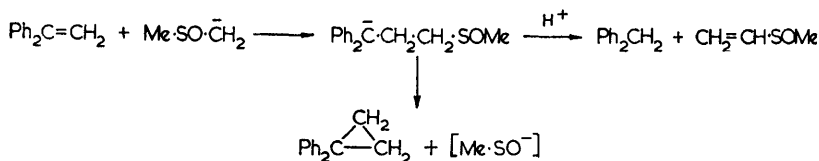
Dimethyl sulphoxide is metallated by sodium hydride at 65–70°. Some of the reactions of the resulting anion are as follows:<sup>119</sup>



The general reaction with ketones is proton transfer to give enolate anions. With benzophenone, nucleophilic addition leads at room temperature to the  $\beta$ -hydroxysulphoxide (104), but at 75–100° the intermediate anion (105) gives a complex mixture of products.<sup>120</sup>



The cyclopropane and diphenylmethane are formed by the addition of sulphoxide anion to diphenylethylene, itself formed in a normal Wittig reaction.



<sup>118</sup> Corey and Chaykovsky, *J. Amer. Chem. Soc.*, 1962, **84**, 867.

<sup>119</sup> Corey and Chaykovsky, *J. Amer. Chem. Soc.*, 1962, **84**, 866.

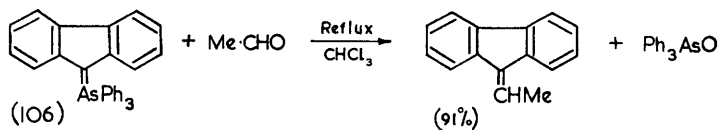
<sup>120</sup> Chaykovsky and Corey, *J. Org. Chem.*, 1963, **28**, 254; Walling and Bollyky, *ibid.*, 1963, **28**, 256; see also Johnson, *Chem. and Ind.*, 1963, 1119.



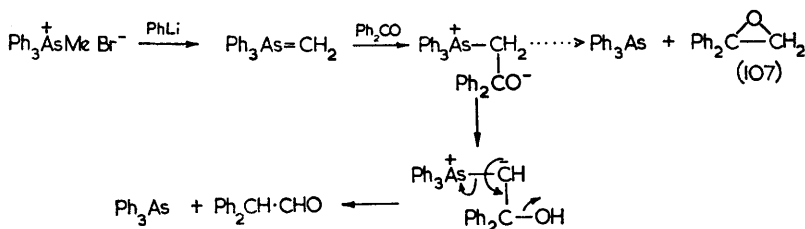
The anion from dimethyl sulphone is reported<sup>120</sup> to react in a similar way with benzophenone.

The solution of metallated dimethyl sulphoxide shows great promise in the titration of all forms of active hydrogen, using as indicator triphenylmethane (the blood-red colour of the triphenylmethyl anion is formed instantaneously in the presence of excess of the reagent).<sup>121</sup>

(c) **Arsenic and Antimony.**—The stable fluorenylidetriphenylarsorane (106) takes part in typical Wittig olefin syntheses with aldehydes,<sup>122</sup> e.g.,



but methylenetriphenylarsorane gives with benzophenone only 2% of olefin, the major product being diphenylacetaldehyde (68%), which is also formed in 92% yield in the reaction of the corresponding antimony compound with benzophenone.<sup>123</sup> It was originally suggested that this is formed by isomerisation of an intermediate epoxide (107), but, as Johnson points out,<sup>112</sup> this epoxide is not isomerised either by base or triphenylarsine, and the aldehyde is probably a primary product. It may be formed as indicated:



## 8. The Iminophosphoranes

Historically, the iminophosphoranes,  $R_3P:NR$ , have precedence over the alkylidene phosphoranes,  $R_3P:CR_2$ , which they closely resemble in their reactions.<sup>123</sup> Iminophosphoranes may be prepared by the action of azides on phosphines:<sup>124</sup>



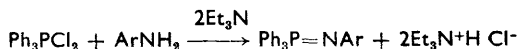
<sup>121</sup> Price and Whiting, *Chem. and Ind.*, 1963, 775.

<sup>122</sup> Johnson, *J. Org. Chem.*, 1960, **25**, 183.

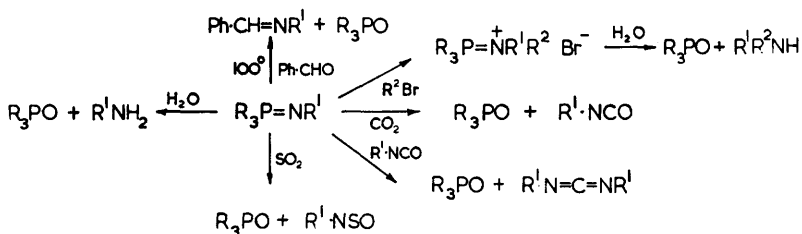
<sup>123</sup> Henry and Wittig, *J. Amer. Chem. Soc.*, 1960, **82**, 563.

<sup>124</sup> Staudinger and Hauser, *Helv. Chim. Acta*, 1921, **4**, 861.

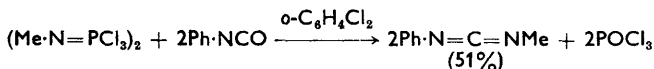
and from aromatic amines by reaction with dichlorotriphenylphosphorane in the presence of triethylamine:<sup>125</sup>



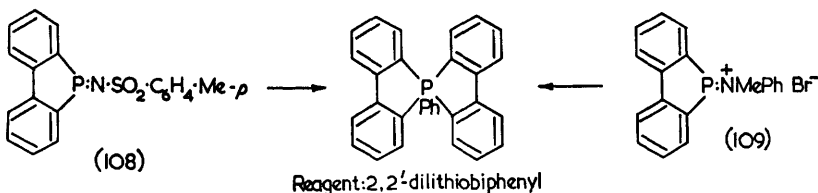
The following chart illustrates the remarkable similarities in the reactions of iminophosphoranes and Wittig reagents:



More recently the dimeric phosphoranes  $(\text{R}\cdot\text{N}:\text{PCl}_2)_2$  have been used in typical syntheses of C—N bonds,<sup>126</sup> e.g.,

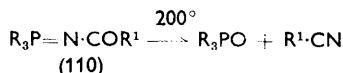


An important use of iminophosphoranes is in the preparation of penta-arylphosphoranes by the action of aryl-lithiums on either toluene-*p*-sulphonyliminophosphoranes (e.g., 108),<sup>127</sup> or on the salts (e.g., 109) formed by the addition of methyl bromide to iminophosphoranes:<sup>128</sup>



Penta-aryl derivatives of arsenic, antimony, and bismuth have been obtained using similar reactions.<sup>127</sup>

Acyliminophosphoranes (110) decompose at 200° to phosphine oxides and nitriles,<sup>124</sup> a reaction analogous to the formation of acetylenes on pyrolysis of  $\beta$ -ketoalkylidenephosphoranes (see p. 425).



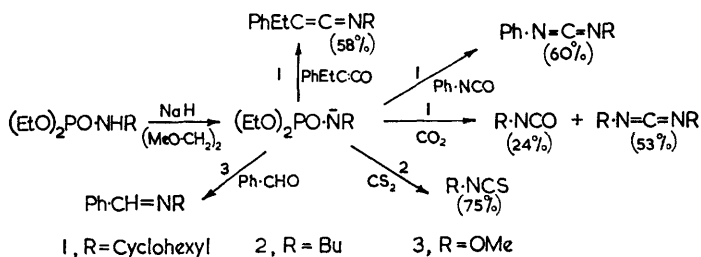
<sup>125</sup> Horner and Oediger, *Annalen*, 1959, **627**, 142.

<sup>126</sup> Ulrich and Sayigh, *Angew. Chem.*, 1962, **74**, 900.

<sup>127</sup> Wittig and Hellwinkel, *Angew. Chem.*, 1962, **74**, 76.

<sup>128</sup> Wittig and Kochendörfer, *Angew. Chem.*, 1958, **70**, 506.

Wadsworth and Emmons<sup>129</sup> have recently investigated the reactions of the nitrogen analogues of the phosphonate anions, *i.e.*, the phosphoramidate anions  $(\text{EtO})_2\text{PO}\cdot\bar{\text{N}}\text{R}$ . Their reaction with a wide variety of carbonyl compounds constitutes a general synthesis of the C:N bond.



<sup>129</sup> Wadsworth and Emmons, *J. Amer. Chem. Soc.*, 1962, **84**, 1316.