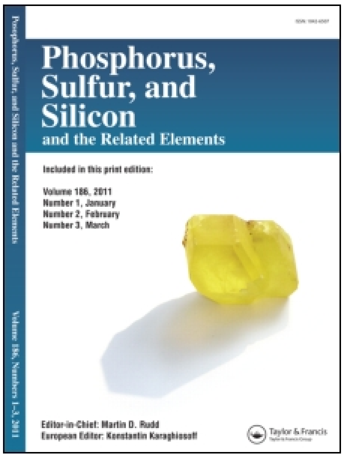

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MECHANISMS OF WITTIG REACTIONS; A NEW POSSIBILITY FOR SALT-FREE REACTIONS

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MECHANISMS OF WITTIG REACTIONS; A NEW POSSIBILITY FOR SALT-FREE REACTIONS

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Spin paired diradicals have been implicated as unstable intermediates in a wide variety of reaction mechanisms. A critical evaluation of the available sterochemical, kinetic and spectroscopic data is found to be consistent, for some Wittig reactions, with a mechanism that involves the intermediacy of a spin paired diradical.

The proposed mechanism not only addresses the major stereochemical considerations around the phosphorus atom during the course of the Wittig reaction, but also provides a rational accounting of the observed cis olefin stereospecificity.

INTRODUCTION

The reaction of phosphorus ylides with aldehydes and ketones has, in the past thirty years, been developed into one of the most potent tools available for the preparation of alkenes. The discovery of Wittig and Geissler that 1,1-diphenylethylene was produced by reaction of methylenetriphenylphosphorane with benzophenone led to the development of the synthetic procedure which is now known as the Wittig reaction.[1]

The scope of the Wittig reaction is wide. The carbonyl compound may be an aliphatic, alicyclic, or aromatic aldehyde or ketone. Esters, amides and carbonates have also been caused to react with phosphorus ylides in an analogous fashion. Additionally, a variety of phosphorus ylides have been prepared and used successfully in Wittig reactions.

Advantages of the Wittig reaction over other olefination procedures include its regioselectivity (e.g., cyclohexanone gives only methylenecyclohexane in reaction with methylenetriphenylphosphorane and no 1-methylcyclohexene), mildness, and the ready availability of the starting materials. A principal drawback of the Wittig reaction is that it is often sensitive to steric factors, so that the preparation of

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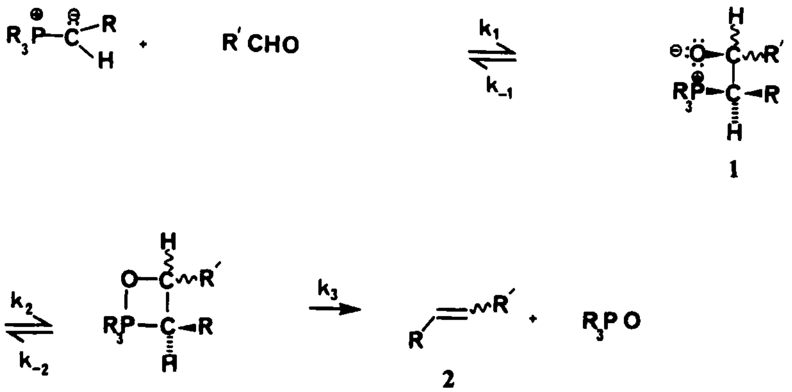
tetra-substituted olefins by this route is often not feasible. Also, the removal of the phosphine oxide is sometimes troublesome. A number of excellent review articles on the synthetic utility of the Wittig reaction are available.[2-8]

FUNDAMENTAL INVESTIGATIONS OF THE STEREOCHEMISTRY OF THE WITTIG REACTION

The standard textbook mechanism for the Wittig reaction is outlined in Scheme 1. In this mechanism, which is probably not entirely correct, the carbonyl compound and the phosphorus ylide first react to form an intermediate "betaine" (**1**), which can then form an oxaphosphetane, which subsequently decomposes, with elimination of phosphine oxide, to form the desired alkene. At this point, the question of stereochemistry becomes immediately apparent, since (**2**) may be formed as either the *Z* or *E* geometrical isomer, depending on the structures of the reagents and reaction conditions.



SCHEME 1

It is our intention to discuss several of the more pertinent investigations that have been concerned with stereoselectivity of alkene formation in Wittig reactions other than those catalyzed by lithium ion, the latter having been covered in our most recent publication.[9] There are a number of excellent review articles covering the pertinent literature prior to 1970,[10] while Schlosser has recently summarized the work of his group in this area.[11]

Where applicable, control of the configuration of the alkenes produced by the Wittig reaction must be an attainable objective if this olefination scheme is to be used to the greatest effect. Since the nature of the phosphorus ylides often dictates the stereoselectivity of the olefination, this variable will be examined first.

With respect to the Wittig reaction, phosphorus ylides can be classified as "unstable", "stable", and of "intermediate" stability.

STEREOSELECTIVITY OF OLEFINATION WITH UNSTABLE YLIDES

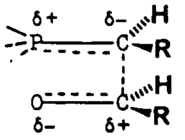
Phosphorus ylides which contain no carbanionic stabilizing moieties bonded to the ylide carbon are the most reactive of the phosphoranes used in the Wittig reaction. Simple phosphorus ylides derived from phosphonium salts obtained by reaction of triphenylphosphine with alkyl halides are in this category. Some examples of unstable ylides are:

$$Ph_3\overset{+}{P}-\overset{-}{C}HCH_3 \qquad Ph_3\overset{+}{P}-\overset{-}{C}H_2$$

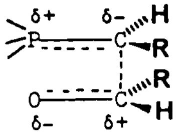
$$Ph_3\overset{+}{P}-\overset{-}{C}HOMe \qquad Ph_3\overset{+}{P}-\overset{-}{C}=CR_2$$

Unstable ylides react with oxygen and moisture and must be prepared by use of a strong base in an anhydrous solvent, and under an inert atmosphere. With these ylides, the Wittig reaction is observed to occur with most aldehydes and ketones. In appropriate instances, the alkene is generally formed with a preponderance of the thermodynamically less stable *Z* configuration over the more stable *E*. Credit must be given to Bohlmann *et al.*[12] and Bergelson *et al.*[13] who first recognized the preparative value of this unexpected *cis* selectivity. Schlosser originally suggested that formation of the intermediate betaine (Scheme 1, step 1) occurs rapidly and irreversibly to give mostly the "erythro" betaine, which rapidly decomposes to products (step 3) before it can return to reactants.[7] The reason why the free energy of activation should be lower for the generation of the erythro betaine than for the threo betaine is unknown. Schlosser considered this question, and his comments indicate his frustration at being unable to account for the observed stereochemical preference.[7]

> "Moreover, at least in nonpolar solution, the *syn* arrangement of the heteroatoms would seem to be the preferred one, since attractive interactions should be strong enough to more than outweigh opposed eclipsing effects. Without any doubt steric strain in the *erythro-syn* array must be considerably higher than in the *threo-sun* array. However, it appears to be a fundamental (though rather obscure) principle in organic chemistry that carbon-carbon linking usually occurs in such a manner as to yield the thermodynamically less stable isomer preferentially."



erythro-syn



threo-syn

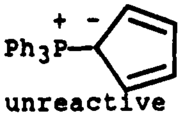
Later evidence, obtained by trapping experiments, indicates that formation of the intermediate betaine (and/or oxaphosphetane) can be reversible for α,β-unsaturated and aromatic aldehydes.[14] Furthermore, the very high *cis* stereoselectivity is retained in these instances. This fact has led Vedejs to state: "If high *cis* selectivity is maintained in a reversible Wittig condensation, it follows that high *trans* selectivity should no longer be accepted as sufficient evidence for reversibility in moderated or stable ylide condensations."[14] The significance of this statement will soon be made apparent.

STEREOSELECTIVITY OF OLEFINATION WITH STABLE YLIDES

Phosphorus ylides containing effective carbanion stabilizing moieties on the ylide carbon are the least reactive of phosphoranes in the Wittig reaction. These "stable ylides" generally react with aldehydes but not with ketones, and they tend to give more *E* olefin than *Z* (in marked contrast to the stereoselectivity of unstable ylides). Stable ylides can often be generated in the presence of oxygen and protic species, and it is occasionally even possible to recrystallize them. Some examples of stable ylides are:

$$Ph_3\overset{+}{P}-\overset{-}{C}H-COPh \qquad Ph_3\overset{+}{P}-\overset{-}{C}H-COOR$$

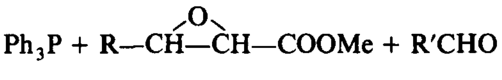
$$Ph_3\overset{+}{P}-\overset{-}{C}HCN$$



The first example of a Wittig reaction giving almost exclusive production of an *E* alkene was provided by House and Rasmusson in 1961. Upon treating triphenylphosphonium carbomethoxyethylide with acetaldehyde, they observed the formation of *E* $CH_3CH{=}C(CH_3)COOCH_3$ in 24-fold excess over the less stable *Z* isomer.[15] The rationalization by House and Rasmussen of the observed *E* stereoselectivity with stable ylides was based on the following concepts:

1. Stable ylides form intermediate betaines in a slow and reversible fashion (step 1 in Scheme 1).
2. Steps 2 and 3, decomposition of the betaines into products, are rate-determining.
3. The transition state of the path leading to *E* product is of lower energy than that leading to *Z* product.

However, Vedejs has more recently stated that although "... reversible adduct formation with stabilized ylides is generally accepted, ... the only direct evidence on this point comes from the assumed generation of Wittig intermediates... under distinctly atypical conditions."[14] He was referring to an earlier study by Speziale and Bissing,[16] in which a trapping experiment suggested reversible betaine dissociation for a stabilized ylide:



$$Ph_3P + R-\overset{\;O\;}{CH-CH}-COOMe + R'CHO$$

$$\rightarrow RCH{=}CHCOOMe + R'CH{=}CHCOOMe$$

$$(R = Ph, R' = m\text{-}Cl{-}Ph)$$

Although stable ylides usually form the more thermodynamically stable *E* alkenes preferentially, this is not always the case. If the carbonyl compound is highly reactive, and if the stable ylide is not too unreactive, then it becomes possible for the *Z* product to become the major one.

STEREOSELECTIVITY OF OLEFINATION WITH YLIDES OF INTERMEDIATE STABILITY

Phosphorus ylides which contain groups capable of limited stabilization of the ylide carbon's negative charge usually display moderate reactivity in the Wittig reaction. Such ylides react with most aldehydes readily, but they often fail to react with ketones. Strong bases, anhydrous solvents, and inert atmospheres are routinely employed in the generation of these ylides from the appropriate phosphonium salts. Examples of "intermediate" ylides are:

$$Ph_3\overset{+}{P}-\overset{-}{C}H-Ph \qquad Ph_3\overset{+}{P}-\overset{-}{C}H-C\equiv CH \qquad Ph_3\overset{+}{P}-\overset{-}{C}H-CH=CH_2$$

The stereoselectivity of the Wittig reaction of intermediate ylides is frequently poor, with comparable yields of both *Z* and *E* olefins resulting in appropriate reactions. By altering reaction conditions (e.g., solvent, temperature, base used to generate the ylide), it is often possible to favor production of one isomer to a considerable extent, thereby increasing the synthetic utility of these ylides.

EFFECT OF REACTION CONDITIONS ON OLEFIN STEREOSELECTIVITY

As previously stated, many factors affect the observed olefin stereoselectivity in Wittig condensations with aldehydes. Some of the more important factors are the structure of the phosphorane, the nature of the solvent, and the presence or absence of dissolved salts in the reaction medium. Bergelson[17,18] has shown that the presence of excess ylide or aldehyde can affect the observed olefin ratio. There also seems to be some confusion as to whether the observed salt effects on the olefin ratio are of cationic or anionic origin.[19-22] In order to note briefly the generally accepted trends in olefin stereoselectivity with change in ylide structure, solvent, and presence of salts, the reader is referred to Chart 1. Also, Maryanoff has recently shown that the presence of oxido ylide intermediates can influence the *E*-*Z* ratio of products.[23]

Generally, by altering the solvent used in a Wittig reaction, it is often possible to influence the stereoselectivity in a desired manner. Thus, it has been found that upon changing from a non-polar aprotic solvent to a highly polar aprotic solvent, it is possible to maximize the proportion of *Z* olefin formed by use of unstable and intermediate ylides. Similarly, a change from a non-polar to polar solvent (protic or aprotic) will increase the amount of *Z* alkene produced from a stable ylide (although the *E* isomer remains the principal product). The reason for these observed solvent effects remains unclear. Trippett has suggested that, in the event of better solvation (in a more polar medium), the relative stability of the intermediate betaines changes so as to make the erythro betaine (which goes on to form *Z* olefin) more stable than it would be in a less polar medium.[10]

CHART 1

Salt Effect on the Stereochemistry of Olefin Formation[24,25]

Ylide Stability	RCHO R=	Solvent	Olefin Stereospecificity	Salt Effect	Ref.
non	alkyl or aryl	nonpolar	predominately *cis* when salt free	depend.	14 19 26
non	alkyl or aryl	nonpolar	when LiX present, *trans* olefin increases in the order: $X = Cl > Br > I > BPh_4$	depend.	19 21
non	alkyl or aryl	polar aprotic	predominately *cis*	independ.	26
semi	alkyl or aryl	nonpolar	salt free predominately *trans* (poor stereoselectivity)	depend.	26
semi	Et	nonpolar	*cis* olefin increases with LiX in the order $I > Br > Cl$	depend.	26
semi	Ph	nonpolar	*cis* olefin increases with LiX in the order $I > Br > Cl$	depend.	26
semi	propyl	nonpolar	predominately *trans*	independ.	7
semi	alkyl or aryl	polar aprotic	non stereospecific	independ.	26 19
semi	Ph	polar protic	non stereospecific	independ.	27
semi	Ph	polar protic	non stereospecific NaI or LiI increases *trans*, LiCl no effect)	depend.	10, 27
stable	alkyl or aryl	nonpolar	predominately *trans*	independ.	28
stable	alkyl or aryl	polar aprotic	predominately *trans*	independ.	28
stable	Ph	polar aprotic	predominately *trans*	independ.	29

The addition of lithium salts (e.g. LiBr) to the reaction medium, or the use of an organolithium compound as the base for ylide generation, has been found to influence the stereoselectivity of the Wittig reaction. This influence is most strongly felt in reactions involving unstable ylides, which can be induced to form a significant amount of *E* alkene under these conditions. The mechanism of action of the lithium ion is not well understood. Vedejs and co-workers have shown, however, that for reaction of $Ph_3P{=}CHCH_3$ with $PhCH_2CH_2CHO$ (in the presence of LiBr), the decrease in *Z* selectivity is not due to equilibration of the betaine intermediates (to reactants).[14] They conclude, that for this system, the effect of LiBr is manifested during the initial condensation of the ylide with the aldehyde. The presence of lithium ion in Wittig reactions involving stable and intermediate ylides has much less effect upon the stereoselectivity of the reaction; in fact, a slight increase in the amount of Z olefin produced has been observed with stable ylides.[30]

A rather interesting means for increasing the stereoselectivity of the Wittig reaction towards the E olefinic product involves replacing the phenyl groups on the phosphorus ylide with alkyl substituents.[31] These electron-donating groups increase the nucleophilicity of the phosphorus ylide, rendering it more reactive in the initial condensation step of the Wittig reaction. However, they also cause a decrease in the rate at which betaine decomposition to products occurs, to the point where phosphine oxide elimination is difficult (or does not even occur).[32–34] As a consequence, the erythro-threo betaine intermediate equilibration implicated by Schlosser is claimed to be more effective, and an enhancement of E product is observed.[7] This is also consistent with the concept of "stereochemical drift" observed in the reaction of the ylide derived from tetrabutylphosphonium bromide with either benzaldehyde or pivaldehyde.[23(c)]

KINETICS STUDIES

In the earliest kinetics studies of the Wittig reaction,[16,35] the condensation of an acylmethylenetriphenylphosphorane with an aromatic aldehyde was shown to exhibit second order kinetics, first order in the ylide and first order in the aldehyde. The first step was believed to be reversible and, based on the observation that the reaction rate parallels the nucleophilicity of the ylide, it was hypothesized to be the rate controlling step. The observed large negative entropy of activation (40 eu) and a ρ value of $+2.8$ were interpreted as being consistent with Wittig's initial proposal of a stepwise formation of a betaine and an oxaphosphetane,[1] with subsequent decomposition of the oxaphosphetane into olefin and phosphine oxide (Scheme 1). This interpretation was also invoked by Kuchar *et al.*[36] to rationalize the kinetics results of the reaction of α-ethoxycarbonylalkylidenephosphoranes with aromatic aldehydes.

Trippett[37] utilized the ratios of *cis*- and *trans*-stilbene produced from the erythro form of the phosphonium salt,

$$CH_3Ph_2PCHPhCHPh(OH)I,$$

and a base, under varying reaction conditions, to investigate the reaction of semistabilized phosphoranes with benzaldehyde. Trippett suggests a similar mechanism for the condensation of both reactive and semistabilized phosphoranes with an aromatic aldehyde which involves: (a) reversible betaine formation; (b) betaine dissociation at a rate comparable to that of betaine elimination; (c) little double bond character in the transition state leading to olefin; and (d) a transition state leading to betaine dissociation which involves considerable desolvation.

Froyen[38] examined the condensation of fluorenylidenephosphoranes with p-nitrobenzaldehyde and suggested a mechanism involving a reversible, rate determining first step to form an oxaphosphetane without the intermediacy of a betaine (*vide infra*). Froyen points out the contention raised by Ruchardt[39] that the second step (oxaphosphetane decomposition) could be rate controlling[40] if the rate of oxaphosphetane reversion to the reactants is high. This situation is kinetically indistinguishable from a reversible, rate controlling first step followed by rapid oxaphosphetane decomposition into products. In any event, Froyen points out that, with current kinetic data, it is not possible to label definitely the rate determining step.

As stated previously, Froyen hypothesized that the first step is the rate limiting step. Based upon the observed rate decrease with increasing solvent polarity (polar aprotic solvents) and variation of the entropy of activation with change in solvent, Froyen suggests a mechanism that invokes a "more or less" concerted formation of an oxaphosphetane in a reversible first step.

Aksnes[41] has thoroughly examined kinetically the solvent effect in the Wittig condensation of benzoylmethylenetriphenylphosphorane with *p*-nitrobenzaldehyde. Based on the observed solvent effects on the rate constants, Arrhenius parameters, and thermodynamic functions of the activated complex, Aksnes has concluded that the rate controlling step involves the formation of a cyclic transition state of relatively low polarity.

Essentially the same conclusion concerning the nature of the transition state in the condensation of methylenetriphenylphosphorane with substituted benzaldehydes was reported by Schlosser.[42] The ρ value of 1.1 reported for this reaction is also consistent with a transition state of relatively low polarity.

RECENT MECHANISTIC INTERPRETATIONS

In 1981, Vedejs, Meier and Snoble[14] reported direct ^{31}P-NMR observation of formation of oxaphosphetanes (to the exclusion of any tetravalent phosphorus species) in salt free Wittig reactions, which led them to suggest that salt free betaines are neither observable nor stable. Citing evidence for the trapping of betaines with electrophiles, Schlosser[43] has postulated the existence of an equilibrium between the betaine and oxaphosphetane with the oxaphosphetane generally being more stable. Bestmann[44] has calculated that an oxaphosphetane is approximately 20 kcal per mole more stable than the corresponding betaine.

Theoretical calculations[45,46] suggest that the Wittig reaction is essentially a concerted process. However, Trindles' calculations indicate that, in oxaphosphetane decomposition, C—P cleavage is more advanced than C—O cleavage.[46] This conclusion can be supported by an interpretation of experimental results.[47,48]

It should now be evident that any proposed mechanism for the Wittig reaction must address not less than two distinct stereochemical problems. First, the stereochemistry of the oxaphosphetane formation in the first step (or sequence of rapid steps) must be evaluated. Secondly, the correspondence between oxaphosphetane stereochemistry and the observed olefin stereochemistry must be evaluated.[49]

There have been many recent attempts to provide a Wittig reaction mechanism that accounts for the observed olefin stereochemistry. Schlosser[51] has suggested that the cis selectivity observed with salt free reactive phosphoranes having three phenyl groups bonded to phosphorus might be rationalized by invoking a transition state in which the aldehydic R group preferentially fits into a "leeward pocket" created by

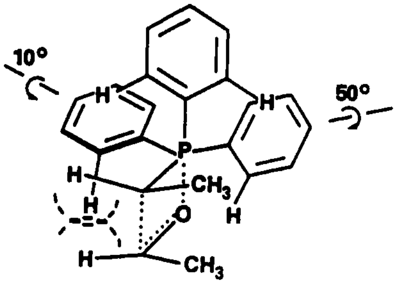


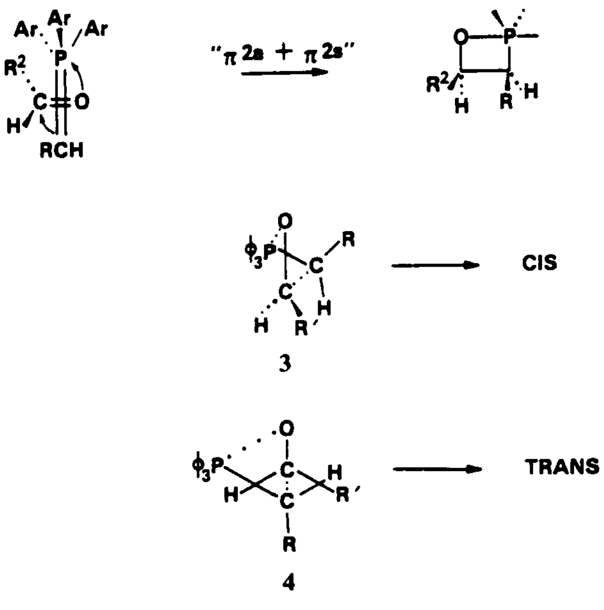
FIGURE 1

steric interactions between the "stationary" phenyl groups around phosphorus and the alkyl group on the ylide carbon atom (Figure 1).

This reaction pathway indicates that, in the transition state for oxaphosphetane formation, the trans orientation would be sterically less favorable than the cis orientation. However, the recent observations of "stereochemical drift" in certain Wittig reactions[23] devalues this particular model offered by Schlosser.

Vedejs[14] has suggested that the observed cis stereoselectivity in salt free Wittig condensations can be accounted for by invoking "...a crisscrossed cycloaddition rationale, in which the aldehyde and ylide planes are tilted toward an orthogonal arrangement to minimize steric interactions." (See 3 in Scheme 2).

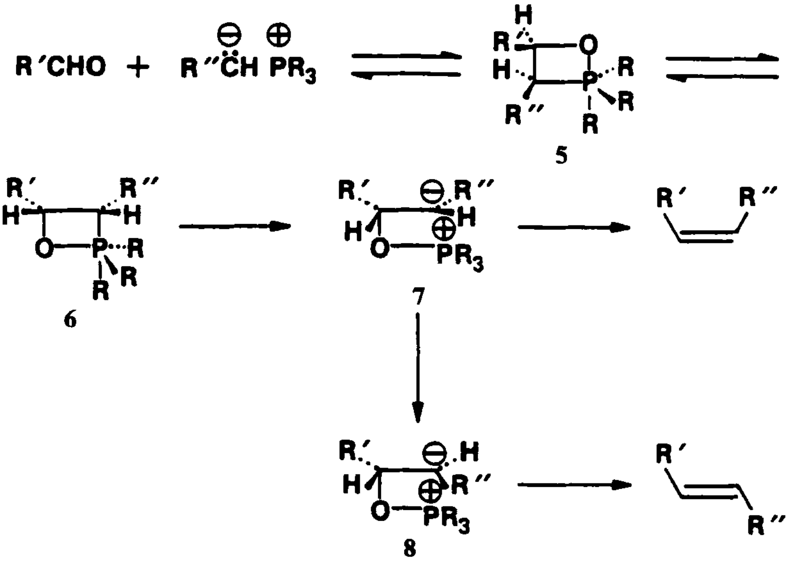
However, he does not maintain that the mechanism is necessarily of the "$\pi 2a$ + $\pi 2s$" variety.



SCHEME 2

Vedejs claimed transition state geometries that require carbonyl and ylide planes to be nearly parallel for trans olefin formation and for Wittig reactions of ketones (see Figure 7 in Reference 14). In Scheme 2, this would involve only a slight tilting of the carbonyl plane from the plane of the paper in **4**, with a more pronounced tilting present in **3**. Bestmann[44] has proposed a cycloaddition with a "quasi-betaine" transition state, in which carbon-carbon bond formation is more complete than phosphorus-oxygen bond formation, to yield a cis substituted oxaphosphetane. He stated that "the stereochemistry of this first step is defined along the Dunitz trajectory for nucleophilic addition to the aldehyde." Vedejs[14] criticized Bestmann's use of the Dunitz trajectory on the basis that it does not adequately explain why the transition state leading to the cis oxaphosphetane should be favored over the transition state leading to the trans oxaphosphetane.

Bestmann[44] has provided a plausible basis for the relationship between the phosphorane structure and the observed olefin stereochemistry. In the Bestmann mechanism (Scheme 3) the first step involves formation of the oxaphosphetane (**5**) in which R′ and R″ are erythro with the oxygen atom occupying an apical position. Pseudorotation about phosphorus in accord with the rules[52,53] for exit and entry of nucleophiles at pentavalent phosphorus yield (**6**), in which the departing carbanionic center is apical. According to this mechanism, the stereospecificity of the Wittig reaction is determined by the lifetime of betaine (**7**), which is determined by the nature of R″ and R. For example, when R″ is a carbanion stabilizing group (R = phenyl), the lifetime of (**7**) is sufficient to allow rotation about the carbon-carbon bond, yielding threo betaine (**8**) in which R′ and R″ are trans. The syn elimination of phosphine oxide from (**8**) yields the predominately trans substituted olefin. In the case where R″ is not a carbanion stabilizing group (R = phenyl), the rate of phosphine oxide elimination from (**7**) is greater than carbon-carbon bond rotation and the cis substituted olefin is produced as the major product.



SCHEME 3

In this manner, the Bestmann mechanism can provide a rational accounting for many of the observed stereochemical preferences in the reactions of unstable, intermediate, and stable phosphoranes. The principal weakness of the Bestmann mechanism is its inability to account for the high cis selectivity invoked in the first step. Also, the mechanism does not address the issue of the existence of an initial oxaphosphetane-betaine equilibrium, nor are the effects of type of aldehyde or of solvent polarity explained.

The Bestmann mechanism has received some experimental support from Allen,[54] who reported that the Wittig condensation of the ylide derived from benzyldiphenylferrocenylphosphonium bromide with benzaldehyde in ethanol afforded a modest enhancement of the *trans*-stilbene produced as compared with the same reaction in which benzyltriphenylphosphonium bromide was used. Allen suggested that the enhanced *trans*-stilbene production is consistent with the expected stabilization of betaine intermediate (**7**) (Scheme 3) by specific electronic donation from the ferrocenyl group to the phosphonium center.

In the condensation of the ylide derived from benzyldiphenyl(*o*-methoxyphenyl)phosphonium bromide with benzaldehyde in ethanol, Allen[54] reported only a very slight degree of *trans*-stilbene enhancement. This *trans*-stilbene enhancement was attributed to a through-space $2p$-$3d$ overlap effect which affords some stabilization of the betaine intermediate (**7**) (Scheme 3), allowing some degree of isomerization to betaine intermediate (**8**). The fact that only a small amount of *trans*-stilbene enhancement is observed is thought by Allen to be attributable to a steric effect by the *o*-methoxy group which competes with the expected electronic effect.[29]

McEwen and Cooney[48] have recently shown that the Wittig condensation of (2,6-dimethoxyphenyl)diphenyl(3-phthalimidopropyl)phosphonium bromide with aromatic aldehydes in THF/t-BuOK gave substantial *trans* olefin enhancement in each case. This observation is consistent with the expected stabilization effect of through-space $2p$-$3d$ overlap on the betaine intermediate (**7**) of the Bestmann mechanism.

A NEW MECHANISM FOR SALT FREE WITTIG REACTIONS

A large part of the literature on the Wittig reaction relates to the use of salt free Wittig reagents.[24] Generally, maximal *cis*-olefin stereoselectivity is achieved in Wittig condensations that employ reactive phosphoranes under salt free conditions.[14] If these reactions are monitored with ^{31}P-NMR spectroscopy, only a signal that corresponds to the oxaphosphetane is observed.[14,50] Also, the available kinetic data[42] suggest a transition state of low polarity. It has been reported that, with aliphatic aldehydes, *cis* selectivity increases from ca. 95% to ca. 99% as the R group is varied from *n*-alkyl to *t*-alkyl.[55-57]

As discussed above, several different mechanisms have been proposed for such salt free Wittig reactions,[8,14,44,51] but there is little general agreement with regard to these interpretations. In fact, the most meaningful statement currently extant may be that of Vedejs and Fang:[58]

> "There is at present no concensus regarding the detailed mechanism of the Wittig reaction. However, the most recent rationales postulate a transition state with phosphorus having trigonal-bipyramidal geometry. This area of general agreement should serve as a starting point for future refinements."

In spite of the plethora of mechanisms already extant for salt free Wittig reactions, we wish to add yet another for general consideration.

The major impetus for the suggestion of a new mechanism arises from recent publications of M. J. S. Dewar.[59,60] He contends that almost all multi-bond processes, including cycloaddition reactions, are not in general synchronous.[61] He presents arguments that approximately twice as much activation energy is required for a two bond process as for a single bond process. Dewar believes that there are only three conditions which favor a synchronous multi-bond process:

1. When the "allowed" synchronous reaction has a transition state which is aromatic;
2. When the synchronous transition state is assisted by relief of massive steric strain;
3. When the synchronous mechanism is favored by large exothermicity and the activation energy is small.

Since none of these conditions appear to apply to Wittig reactions in general, there may be a need for another mechanism.

An examination of the recent chemical literature reveals an ever increasing utilization of unstable, spin paired diradical intermediates in a wide variety of reaction mechanisms. Such spin paired diradical intermediates have been postulated to be formed as unstable intermediates in the Diels-Alder reaction[60] and in 1,3-dipolar cycloadditions,[62] including the cycloaddition of Reissert salts with alkenes and alkynes.[63]

We believe that the following arguments (in addition to the general one already provided by Dewar that approximately twice the activation energy is required for a synchronous two bond process as for a single bond process) support the concept of formation of a spin paired diradical intermediate in at least some Wittig reactions of a salt-free ylide with an aldehyde or ketone:

(1) Phosphoranyl radicals are readily formed, and the odd electron is usually considered to be located in an equatorial orbital of a trigonal bipyramidal molecule.[64]

(2) The selection rules for substitution at phosphorus by way of a phosphorane intermediate do not prohibit equatorial attack and apical departure, although apical attack, pseudorotation, and apical departure represent a more common sequence of steps.[52]

(3) Equatorial attack and apical departure represents a retention pathway with respect to phosphorus,[65] and retention of configuration at phosphorus has been observed in reactions of chiral ylides with aldehydes.[66]

(4) No formation of betaines is observed by ^{31}P-NMR studies of salt-free Wittig reactions.[14] This suggests that the intermediate oxaphosphetanes, which are observed by NMR, may be formed either directly from the ylide and carbonyl compound or else by way of an intermediate other than a betaine; e.g., a spin-paired diradical.

(5) Spin paired diradical intermediates are considered by some workers[59,60,67,68] to be formed as unstable intermediates in (4 + 2) cycloaddition reactions, and there is no apparent reason why the same would not hold true for Wittig reactions.

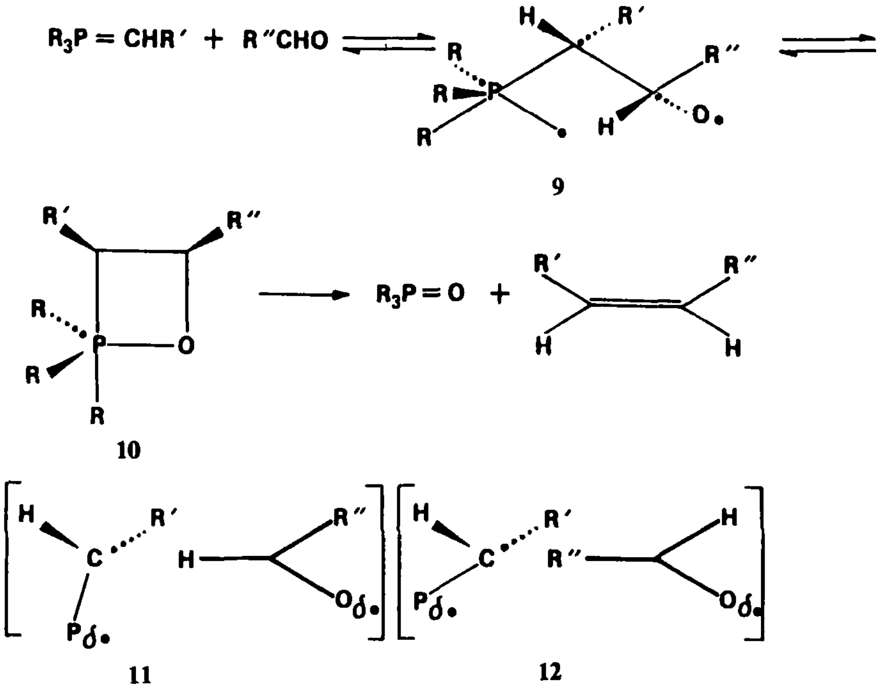
(6) Significant desolvation would be expected in the transition state for formation of an oxaphosphetane from relatively polar molecules (ylide plus carbonyl compound) if the transition state resembles a relatively nonpolar spin-paired diradical. As mentioned previously, Trippett[37] has concluded on the basis of his experimental observations that there is significant desolvation in the formation of the transition state for the Wittig reaction.

(7) Froyen[38] has reported that increasing solvent polarity causes a decrease in the rate of Wittig reactions. This could be consistent with the formation of a relatively non-polar transition state (resembling a spin paired diradical) from polar reagents (ylide and carbonyl compound).

(8) It is known for other chemical systems (e.g. reactions of diaryliodonium salts with bases[69]), that there can be a delicate balance between ionic and radical processes. By the same token, in the Wittig reaction, the presence of a Lewis acid, Li^+, could bring about a change from a spin paired diradical mechanism to an ionic mechanism. On the other hand, Na^+ and K^+ do not behave as Lewis acids, and therefore Wittig reactions carried out in the presence of these ions would behave like salt-free reactions.

(9) With regard to the stereoselectivity of alkene formation in Wittig reactions proceeding by way of spin paired diradical intermediates, we could manage to finesse the matter by adapting the view of Harcourt and Little[68] to the present situation; *viz.*, the formation of oxaphosphetanes proceeds by a concerted (but not synchronous) diradical mechanism. In that case, the geometry of the transition state is essentially indistinguishable from that of a $\pi 2s + \pi 2a$ cycloaddition,[29] and the rationalizations of stereoselectivity in alkene formation previously advanced by Vedejs, Meyer and Snoble[14] and by Schlosser[51] could still be considered. However, we wish to present a somewhat different suggestion as to the geometry of the transition state for oxaphosphetane formation, one that places a greater emphasis on the steric requirements of the trigonal bipyramidal phosphorus moiety in relation to the other groups involved in the reaction.

Our proposal for the mechanism leading to the Z-oxaphosphetane (**10**) is depicted in Scheme 4. It is assumed that the transition state leading to the spin paired diradical **9**, when viewed down the developing C—C bond, would place the largest groups, the phosphorus moiety and R″ in a pseudo antiperiplanar conformation (**11**). Also, based on arguments similar to those of Vedejs[14] and those of Schneider,[70] the most favorable approach of the aldehyde toward the ylide is achieved by tilting the aldehyde plane defined by R″CH in a nearly perpendicular manner to the ylide carbon plane defined by R′CH, with the oxygen directed away from the ylide plane. In (**11**) and (**12**) the ylide carbon is in the plane of the paper while the aldehyde is above and parallel to the plane of the paper. Concomitant with the formation of the new C—C bond, to yield (**9**), the aldehydic H pivots out of the plane of the paper. While this mode of rotation brings both R groups on the newly forming bond into a gauche conformation, the alternative mode of rotation (aldehydic H into the plane of the paper) results in a more serious initial steric interaction between the oxygen and the groups about the phosphorus. Therefore, the Z-oxaphosphetane **10** is formed preferentially.



SCHEME 4

It can be argued that the formation of the transition state (**12**), which would ultimately result in formation of the diastereomeric E-oxaphosphetane based on the above arguments, is sterically more congested than (**11**), since in (**12**) the R″ group is in the position adjacent to the phosphorus, defined by HCP. Thus, transition state **12** would have a higher E_a and the rate of formation of the *E*-oxaphosphetane would be slower than that of the Z-oxaphosphetane (**10**).

In this manner, the observed olefin stereoselectivity is determined by the balance of steric interactions between R′, R″ and the phosphorus moiety in the formation of spin paired diradical intermediates such as (**9**).[71]

It should be mentioned that (**9**) represents a limiting case in the spectrum of possibilities for oxaphosphetane formation. At the other end of the spectrum for formation of (**9**) we have the classical betaine intermediate with full formal changes located on both the phosphorus and oxygen atoms. It is conceivable that, for oxaphosphetane formation, a range of charge separation in various transition states could be a function of structural features in both the ylides and carbonyl compound and reaction conditions (solvents, temperatures, salts).[73] For example, this state of affairs is suggested by the observation of a ρ value of +2.8 for the Wittig condensation of salt-free acylmethylenetriphenyl phosphoranes with aldehydes[16,35] as against a ρ value of +1.1, which was reported for similar reactions of methylenetriphenylphosphorane.[42]

One additional feature of the Wittig reaction mechanism needs to be considered; *viz.*, that of formation of products (alkene(s) plus phosphine oxide) from the oxaphosphetane(s). It is our belief that the syn elimination of alkene(s) and phosphine oxide can also occur by way of a spin paired diradical intermediate. This would be in accord with Trippett's suggestion[37] that the transition state leading to alkene has little double bond character. Also, since substituents which stabilize an adjacent carbanionic center also stabilize an adjacent radical center, Bestmann's concept[44] of the formation of an unstable intermediate which has a sufficient half life to permit isomerization to occur still retains merit.

CONCLUSIONS

In summary, it is almost certain that more than one mechanism for Wittig reactions is possible. The choice of mechanism probably depends on many factors, but mainly on the structure of the ylide and carbonyl compound and the presence or absence of lithium ions (or other Lewis acids).[73] For at least some Wittig reactions occurring under salt free conditions, a new mechanism employing the concept of spin paired diradical intermediates has been presented here which is consistent with current experimental data and theoretical treatments.

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free ylides, i) The reaction of a phosphonium salt with NaH is carried out in benzene, followed by filtration of insoluble NaBr. Vedejs[14] and House[15] have found that "salt free" ylide solutions prepared as above actually contain a small amount of dissolved NaBr. ii) The most widely used method for preparing salt free ylides involve generation of the ylide with sodium amide in liquid ammonia. The liquid ammonia is then removed, and to the resulting residue is added the desired reaction solvent. Any insoluble salts are then removed by filtration.

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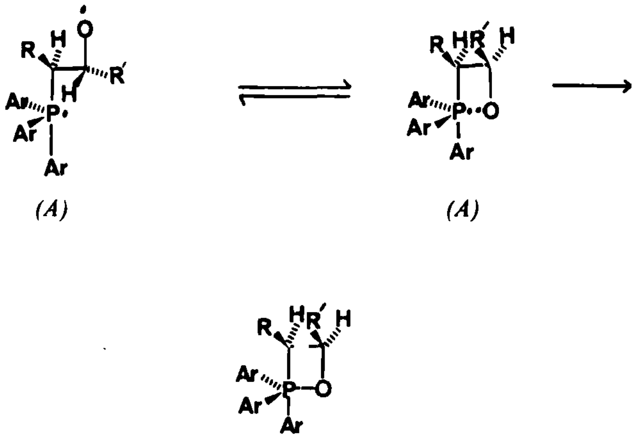

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