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ARTICLE TYPE

The Modern Interpretation of the Wittig Reaction Mechanism

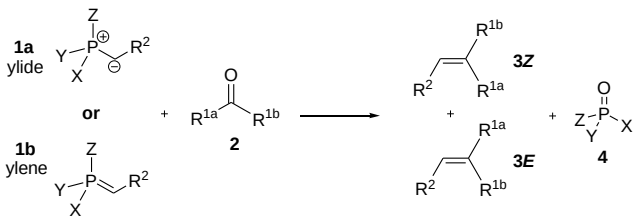
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Abstract: The mechanism of the Wittig reaction has long been a contentious issue in organic chemistry. Even now, more than 50 years after its announcement, its presentation in many modern undergraduate textbooks is either overly simplified or entirely inaccurate. In this review, we gather together the huge body of evidence that has been amassed to show that the Li salt-free Wittig reactions of non-stabilised, semi-stabilised and stabilised ylides all occur under kinetic control by a common mechanism in which oxaphosphetane (OPA) is the first-formed and only intermediate. The numerous recent significant additions to the subject – including computational studies and experimental material pertinent to both steps of the reaction (OPA formation and its decomposition) are discussed in detail, and the currently accepted explanations for the source of the stereoselectivity in Wittig reactions are given. We also present the other mechanistic proposals that have been made during the history of the Wittig reaction, and show how they are unable to account for all of the experimental evidence that is now available. Details of certain experimental facts to do with Wittig reactions in the presence of Li cation are also included, although the precise mechanistic details of such reactions are yet to be established conclusively. We make the case that a clear distinction should henceforth be made between the unknown "Li-present" and the now well-established "Li salt-free" Wittig mechanisms.

1. The Wittig Reaction: Introduction, utility and recent developments

The Wittig reaction[1] is perhaps the most commonly used method for the synthesis of alkenes. Several excellent reviews on the topic have previously been written that contain extensive detail on the Wittig reaction mechanism.[2,3,4,5] More recent reviews do not focus on the details of the mechanism.[6,7,8] The reaction (see Scheme 1) occurs between a carbonyl compound (aldehyde or ketone in general, **2**) and a phosphonium ylide (**1**) to give alkene (**3**) with phosphine oxide (**4**) as the by-product. The ylide can be represented by structures **1a** (fully ionic ylide form) or **1b** (ylene form), which should not be taken as resonance forms.[9] Rather they should be understood as illustrating the ionic character of the P-C bond with a contribution to the stabilisation of the carbanion by phosphonium. There has been much discussion in the literature over the nature of this stabilistion both in ylides,[10,11,] and in similar bonds in phosphorus stabilised carbanions,[12] phosphine oxides,[11,13,14] and iminophosphoranes.[15] There seems to be a developing consensus that the P=O and P=N bonds are composed of a polar covalent σ bond combined with an electrostatic interaction. However for the ylides the evidence suggests that there may be negative hyperconjugation of the lone pair on the ylide α-carbon into the σ^* orbitals of the bonds of phosphorus to its other substituents, albeit that the P-C bond is still heavily polarised towards carbon.[10,11.12] For convenience, ylides will be represented in the ylene form (**1b**) throughout this review.



Scheme 1. The Wittig Reaction. X, Y and Z may each be alkyl, aryl or alkoxy, and need not necessarily be the same. R^2 may be alkyl, aryl, vinyl, or an electron withdrawing group (e.g. an ester). The carbonyl reactant (**2**) may be formaldehyde (R^{1a} = R^{1b} = H), an aldehyde (R^{1a} = alkyl/aryl, R^{1b} = H), or a ketone (R^{1a} = alkyl/aryl, R^{1b} = alkyl/aryl).

There are a number of features of the Wittig reaction that help to make its use so widespread:[16]

- It is regiospecific – the alkene is invariably formed from the ylide α-carbon to the carbonyl carbon.
- Reaction conditions are usually mild, even in comparison to the other extremely useful regiospecific phosphorus based olefination, the Wadsworth-Emmons reaction.[2,17]
- The starting materials are frequently easily obtainable. Ylides are easily accessible by *in situ* deprotonation of the parent phosphonium salt, obtained in turn by alkylation of a phosphine. Certain salts and even some stabilised ylides (see later for definition) are now commercially available.
- Ylides are tolerant of a number of other functional groups, so the reaction is suitable for synthesis of complex molecules.
- The stereoselectivity of the reaction can often be directed towards the desired alkene isomer by expedient choice of the nature of the reactants used (see later).

Despite the fact that Wittig & Geissler first reported on the reaction 60 years ago, it still remains the subject of many modern publications. Amongst the recent developments reported in the literature are:

- New methods for generation of the ylide.[18,19,20]
- Reactions showing atypical stereoselectivity,[21,22,23,24,25,26,27] which can be induced e.g. by the use of phosphonium ylides with modified "spectator substituents" on phosphorus,[21,22,24,26] by the use of trialkylgallium base to generate the ylide,[27] and by the addition of methanol at low temperature to the oxaphosphetane adducts from reactions of non-stabilised ylides.[22]
- New reaction conditions.[25,28,29]
- One-pot reaction from either phosphine[19,20,29,30,31] or alcohol[32]
- Synthetic studies.[31,33]
- Catalytic variants.[34]
- Our new chromatography-free method for the removal of the phosphine oxide by-product, yielding pure alkene product, and with optional conversion of the oxide to phosphine.[35]
- Reaction kinetics and relative nucleophilicity of ylides.[36]
- Mechanistic studies on reactions of ketones.[37]
- Demonstration by us of a unified mechanism for the Li salt-free Wittig reaction of all phosphonium ylide types from reactions of β-heteroatom-substituted aldehydes.[38,39]
- A study of the decomposition of the OPA intermediate (see later), which indicates that its decomposition may occur by a single step.[40]
- Computational studies on the reaction mechanism[41,42,43] and on the stability of heteroatom-stabilised ylides including phosphonium ylides.[44]
- Recent synthetic applications including: photochromic dithienylethenes,[45] enantioselective synthesis of highly substituted cycloalkanes by organocatalysed domino Michael-Wittig reactions,[46] one-step synthesis of *Z*-allylic esters and alcohols by a SCOOPY-modified Wittig reaction,[47,48] and stereoselective total synthesis of (-)-spirofungin A (involving several Wittig reactions).[49]

The scope of the related reaction of phosphonium ylides with *N*-sulfonyl imines has also been very effectively broadened, with the development of reactions of non-stabilised[50] semi-stabilised[51] and stabilised[52] ylides that can be tuned to give complete *E or* Z selectivity by choice of the appropriate *N*-sulfonyl alkyl group.

2. Classification and selectivity trends of phosphonium ylides in the Wittig reaction

Phosphonium ylides are broadly categorised according to the nature of the substituent(s) attached to the α-carbon (R^2 in Fig. 1). If R^2 is an alkyl group, the ylide is referred to as being *non-stabilised* or *reactive*, as ylides of this type readily react with ambient moisture, and as such are not stable in air. If R^2 is a phenyl or alkenyl group, the ylide is somewhat less prone to hydrolysis owing to the conjugative stabilisation by the unsaturated group, and so these ylides are called *semi-stabilised* ylides. Triphenylphosphine-derived ylides (X, Y, Z = Ph in Fig. 1) in which R^2 is a carbonyl, ester, nitrile, sulfone or other such conjugating group are typically stable to hydrolysis in air. As a

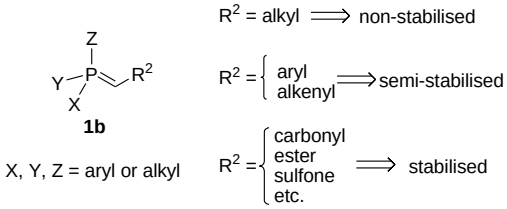


Fig. 1. Classification of ylides.

result, these ylides are referred to as *stabilised* ylides. This name has also come to refer to all ylides in which R^2 is a conjugating group, even though certain ylides derived from phosphines other than triphenylphosphine are somewhat sensitive to hydrolysis in air.[b]

Most ylides undergo Wittig reactions with carbonyl compounds very rapidly,[3] although quantitative rate data on this subject is sparse. Where such data is available,[36,53,54,55,56,57,58] quantitative comparison of ylide reactivities is difficult, since the Wittig reactions in different studies were often carried out under different conditions and, most significantly, with different solvents. However, qualitatively, it is known that non-stabilised ylides react essentially instantaneously (giving stable oxaphosphetane – abbreviated OPA - at low temeprature), while reactions of semi-stabilised ylides are generally complete in a matter of seconds or minutes (especially with aldehydes), even at low temperature. Some triphenylphosphine-derived stabilised ylides do not undergo Wittig reactions or require heating to effect the reaction,[3] but we have observed methyldiphenylphosphine-drived stabilised ylides to react rapidly with aldehydes even at -78 °C.[38,39] This is consistent with the observation of Frøyen that the reaction rates of fluorenylides with *p*-nitrobenzaldehyde increases with successive replacement of the *P*-phenyl groups of the ylide phosphonium moiety with *P*-ethyl groups.[53]

A very significant aspect of the Wittig reaction is that, broadly speaking, the nature of the ylide used in a Wittig reaction dictates the stereoselectivity of the reaction. Certainly, in the case of triphenylphosphine-derived ylides it is true that in general the *E* or *Z* selectivity can be predicted based on the degree of anion stabilisation conferred on the ylide by its α-substituent (R^2). These trends are set out below. For reactions of ylides derived from other phosphines, prediction of the stereochemical outcome is not so straightforward and may be further complicated by the presence or absence of dissolved salts (especially Li salts, *vide infra*).

Alkylidenetriphenylphosphoranes (Chart 1) are the most frequently used non-stabilised ylides. These show very consistently high *Z*-selectivity in Li-salt free reactions with a broad range of aldehydes.[4] The only known exceptions involve reactions of ethylidenetriphenylphosphorane with aromatic aldehydes (and these reactions have been shown not to proceed under kinetic control - see below). Selectivity is generally highest in reactions with tertiary aldehydes, although in most cases even reactions of primary aldehydes still show overwhelming *Z*-selectivity for the alkene. By comparison, (alkylidene)alkyldiphenylphosphoranes (Chart 1 (b)) typically show very significantly reduced *Z*-selectivity; some reactions with primary aldehydes even showing moderate *E*-selectivity.[4] Alkylidene-*t*-butyldiphenylphosphoranes (Chart 1 (c)) show comparable *Z*-selectivity to alkylidenetriphenylphosphoranes.

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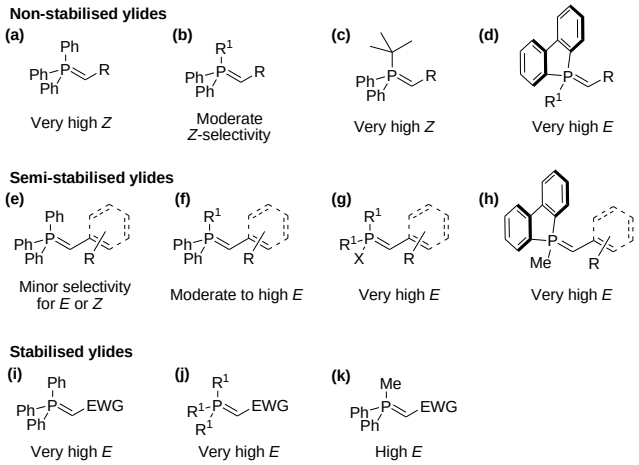


Chart 1. Summary of observed selectivity trends for reactions of representative ylides. EWG = electron-withdrawing group (e.g. C(O)R, SO2R, CN etc.); R, R^1, R^2 = alkyl; X = aryl or aryl.

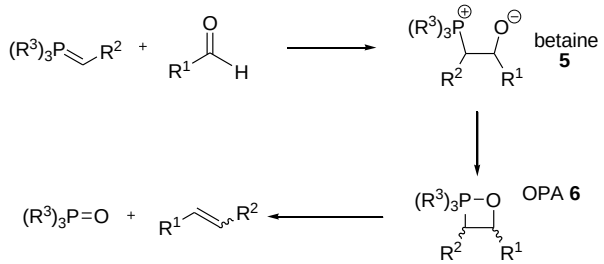
(Alkylidene)alkyl-dibenzophospholanes (Chart 1 (d)) show extremely high *E*-selectivity.[59] A generally applicable observation on the reactions of all of these non-stabilised ylides is that selectivity for *Z*-alkene is highest for a particular ylide in reactions with tertiary aldehydes, while reactions with primary aldehydes show the highest *E*-selectivity.

Wittig reactions of the most commonly encountered semi-stabilised stabilised ylides, derived from triphenylphosphine, are generally not very selective for one isomer or another. Thus allylidene or benzylidene triphenylphosphoranes (Chart 1 (e)) generally react to give approximately equal proportions of *E* and *Z* alkene, while semi-stabilised alkyldiphenylphosphine-derived ylides (Chart 1 (f)) show moderate and in some cases very high *E*-selectivity.[4] Semi-stabilised ylides with two or more of the *P*-phenyl groups replaced by alkyl groups (Chart 1 (g))[4] and also those derived from methyldibenzophosphole (Chart 1 (h))[60] show exceptionally high *E*-selectivity. As with non-stabilised ylides, the general observation applies that for a given semi-stabilised ylide *Z*-selectivity is highest for reactions with tertiary aldehydes, and *E*-selectivity is highest for reactions with primary aldehydes.

Many stabilised ylides are air stable and can be isolated and purified, so reactions of such ylides are often carried out using the pre-formed ylide, without the need for *in situ* generation. Wittig reactions of stabilised ylides derived from both triphenylphosphine (Chart 1 (i)) and trialkylphosphine (Chart 1 (j)) generally show very high selectivity for *E*-alkene in polar aprotic solvents.[4] Methyldiphenylphosphine-derived ester stabilised ylides (Chart 1 (k)) show decreased although still predominant *E*-selectivity. In many cases diminished *E*-selectivity and even predominant *Z*-selectivity is observed in reactions of stabilised ylides in alcohol solvents.

3. Proposed mechanisms: Description and evaluation in the light of experimental evidence

A large number of mechanisms have been proposed for this reaction throughout its history. Johnson was able to enumerate a total of eight in his review of the Wittig reaction.[3] Most have been ruled out on the basis of experimental evidence, but for completeness, each of the mechanistic proposals identified by



Scheme 2. The betaine mechanism for the Wittig reaction.

Johnson are summarised here, along with details of work pertinent to the proposed mechanisms that has appeared since Johnson's review. Particular emphasis is placed on the [2 + 2] cycloaddition mechanism of Vedejs and co-workers (case 8), since it forms the basis of the modern understanding of the Wittig reaction mechanism, and on the betaine mechanism (case 1), since it still appears so widely in literature publications and organic chemistry textbooks despite the overwhelming evidence indicating that it is not in operation.

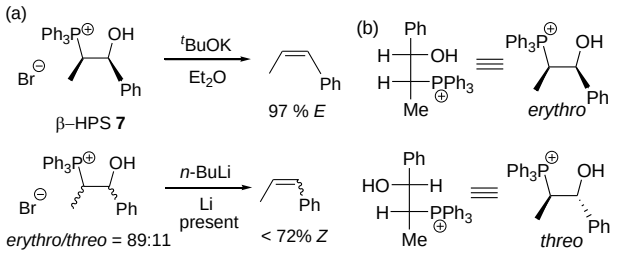
3.1. The Betaine mechanism

Essential features: Nucleophilic addition of ylide to carbonyl to form betaine (dipolar species **5** in Scheme 2; similar to an aldol reaction), followed by ring closure to OPA (species **6**) and decomposition of OPA to alkene and phosphine oxide (see Scheme 2).[61]

At the time of the development[c,62,63] of this mechanism[61] by Wittig and co-workers, there was a significant amount of experimental evidence strongly suggesting the involvement of betaine intermediates in the Wittig reaction. There was also an absence of evidence to the contrary and the alternative explanations for the observed phenomena that have since been amassed had not yet been recognised. The experimental observations informing the betaine rationale, the alternative explanations for these observations, and the evidence that indicates the non-involvement of betaines is summarised below.

(i) *Observation indicating the involvement of betaine*: The most significant evidence came from the Wittig reactions of several ylides (generated using phenyllithium from the parent phosphonium bromide salt) with carbonyl compounds at low temperature, which gave a precipitate that on warming yielded alkene and phosphine oxide but if treated with HBr gave β-hydroxyphosphonium salt (β-HPS, an example of which is species **7** in Scheme 3). Subsequently the precipitate was isolated and shown to be a betaine-LiBr complex[64] (which has since been detected spectroscopically[65]).

Alternative explanation of observation: Since the above experiments were carried out, it has been conclusively shown that solutions containing only OPA (as confirmed by NMR monitoring of the solution) undergo acid quenching reactions to give β-HPS[70] and react with LiBr to give a betaine-LiBr complex.[65] So, the formation of β-HPSs by acid quenching of Wittig reaction mixtures, or the formation of betaine-LiBr complexes do not require an uncomplexed betaine as the precursor.



Scheme 3. (a) Experiments of Schlosser and Christmann on deprotonation of β-HPSs derived from non-stabilised ylide.[64] (b) Fischer projections of Schlosser's β-HPSs, showing that the β-HPS derived from *cis*-OPA is *erythro*, and that derived from *trans*-OPA is *threo*.

(ii) *Observation indicating the involvement of betaine*: Betaines (and hence OPAs) were generated by means independent of the Wittig reaction, either by nucleophilic cleavage of epoxide (of defined stereochemistry) with phosphine,[66] or by deprotonation of β-HPS (of defined stereochemistry),[54,62,64,67] and were shown to decompose to alkene and phosphine oxide (Scheme 3(a)).

Rebuttal / alternative explanation of observation: The epoxide cleavage and β-HPS deprotonation experiments necessarily produce betaine and, plainly, betaine gives OPA. However, while a betaine-LiBr complex has been observed by NMR,[65] *uncomplexed* betaines have never been detected spectroscopically in a Wittig reaction mixture, or in an independent betaine generation experiment. OPAs are also necessarily produced in each of the independent generations of betaine, and they can be detected by NMR in solution in such experiments, and in Wittig reactions.[59,60,68,69,70] Therefore experiments that necessarily involve betaine and that ultimately give alkene and phosphine oxide do not mean that they must be involved *en route* from ylide and aldehyde to alkene and phosphine oxide in the Wittig reaction. To be excluded as a Wittig intermediate, it is sufficient if betaine lies at a relatively higher energy than OPA and that there be a plausible alternative mechanistic route to OPA (which there is – mechanism 8).

(iii) *Explanation of stereoselectivity of reactions of non-stabilised ylides within the context of the Wittig betaine mechanism*:[54,71,72,73] The universally high *Z*-selectivity in Li salt-free Wittig reactions of aldehydes with alkylidenetriphenylphosphoranes was rationalised as being a consequence of addition of the ylide to the carbonyl in such a way as to give *anti*-betaine (with a P-C-C-O dihedral angle of 180°, as shown in Fig. 2). The minimisation of steric repulsion in the transition state (TS) leading to an *anti*-betaine would dictate that there should also be a 180° dihedral angle between the vicinal R^1 and R^2 groups, thus giving an *anti-erythro*-betaine, which could undergo bond rotation to the *syn*-conformation and ring-close to *cis*-OPA, which ultimately leads to *Z*-alkene. So the high *Z*-selectivity was proposed to be due to kinetically favoured formation of *erythro*-betaine. Consistent with this interpretation was that deprotonation of *erythro*-(1-hydroxy-1-phenylprop-2-yl)triphenylphosphonium bromide[d] with ^{t}BuOK in diethyl ether gave the *Z*-alkene product almost exclusively, indicating high stereospecificity (and thus irreversibility) of conversion of the *erythro*-betaine, and *cis*-OPA necessarily produced, to *Z*-alkene under Li-salt free conditions (see Scheme 3).[64] Similar experiments in the presence of Li showed considerable conversion to the *E*-alkene (Scheme 3),[64]

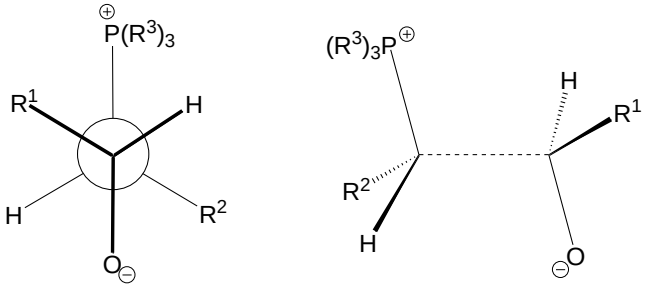


Fig. 2. Two diagrams of the transition state leading to the *anti*-conformer of *erythro*-betaine, which has been proposed as the kinetically favoured path for the Wittig reaction.

in keeping with the observation of lower Z-selectivity in Wittig reactions conducted in the presence of Li.

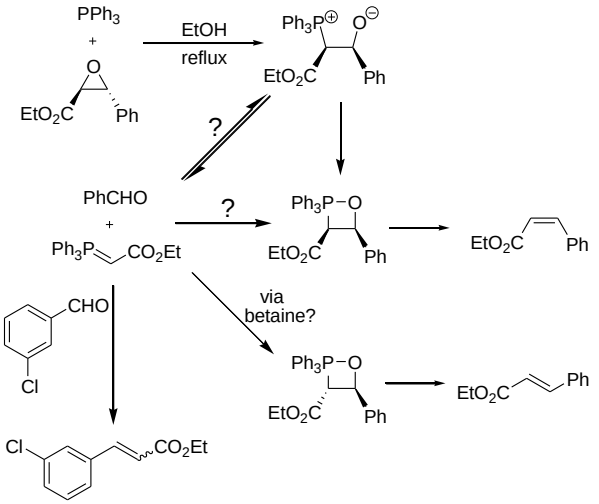
Rebuttal and alternative explanation: Another explanation ([2 + 2] cycloaddition) exists that is consistent with all of the observations that support the betaine mechanism, but which also accounts for several other facts that the betaine mechanism cannot explain. This is discussed in sections 3.8 and 4. However, it is appropriate to briefly state at this point that according to the betaine rationale, all Wittig reactions of non-stabilised ylides – even those that are not derived from triphenylphosphine – should be irreversible and highly *Z*-selective. In fact, Wittig reactions of non-stabilised ylides derived from other phosphines frequently show little stereoselectivity, and in some cases very high *E*-selectivity has even been observed.[35] Irreversibility of OPA formation has been demonstrated for selected examples of these reactions (ones showing low selectivity).[38] Thus, the betaine mechanism is unable to account for moderate to low *Z*-selectivity under kinetic control in Wittig reactions of non-stabilised ylides. Furthermore, the reactions of certain non-stabilised ylides (primarily ethylides – see later) are the only ones that are know not to be irreverisble under Li salt-free conditions. It is also pertinent that OPA is the only observable intermediate in reactions of non-stabilised ylides, and that betaines have been shown conclusively not to be involved in the Wittig reactions of dibenzophosphole-derived non-stabilised ylides.[74]

(iv) *Explanation of stereoselectivity of reactions of stabilised ylides within the context of the Wittig betaine mechanism*: Wittig reactions of stabilised ylides derived from triphenylphosphine are usually highly *E*-selective. The reaction of triphenylphosphine with ethyl-*trans*-2-phenylglycidate in refluxing ethanol in the presence of *m*-chlorobenzaldehyde gave a large amount of *m*-chlorocinnamate (crossover product)[e] as well as the expected ethyl *Z*-cinnamate. This was interpreted to be occurring by the mechanism shown in Scheme 4.[54] Subjecting the *cis*-epoxide to the same reaction conditions gave *E*-cinnamate and a smaller proportion of crossover product.

These observations were rationalised by postulating an increased propensity for equilibration of the kinetically favoured *erythro*-betaine and/or *cis*-OPA in reactions of these ylides, so that there would be equilibration of the intermediates by reversion to Wittig reactants. The increased reversion was supposed to be as a result of the greater stability, and thus longer lifetime, of the intermediates in reactions of stabilised ylides. If this scenario were true, greater *E*-selectivity should be observed if

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the irreversible decomposition to alkene and phosphine oxide

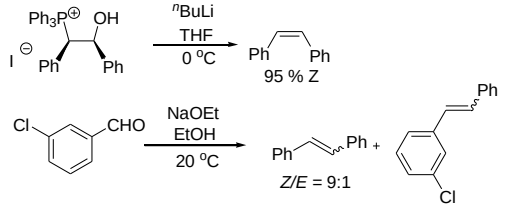


Scheme 4. Independent betaine generation by nucleophilic cleavage of epoxide with phosphine.[54] Reversal of OPAs derived from stabilised ylides to Wittig starting materials had not been unequivocally ruled out[60] at the time of the formulation of the betaine mechanism, so would have been considered in principle to be a possibility, as indicated in this scheme.

were faster for *trans*-OPA than for *cis*-OPA, or if OPA formation were irreversible and ring-closure was faster for the *threo*-betaine than for the *erythro* isomer.

Rebuttal and counter-evidence: The betaine mechanism requires reversible formation of betaine and/or OPA in reactions of stabilised ylides in order to explain the observed selectivity – it is unable to account for *E*-selectivity under kinetic control. It has been shown that deprotonation of *erythro*-β-HPSs derived from ester-stabilised ylides decompose stereospecifically to *Z*-alkene (presumably this necessarily occurs through *erythro*-betaine and then *cis*-OPA).[59,60] Since neither the betaine nor the OPA precursor of *Z*-alkene underwent reversion, it follows that the highly *E*-selective reactions of these ester-stabilised ylides are under kinetic control. Thus the betaine mechanism cannot be in operation in these reactions. See section 4 for full details. The positive crossover results in the epoxide-cleavage experiments of Scheme 4 were obtained under conditions in which betaine was *necessarily* generated (and at a temperature much higher than is typically used for Wittig reactions), and do not mean that betaine is an essential intermediate in Wittig reactions of stabilised ylides, especially since it has been demonstrated that both high *E*[60] and high *Z*-selectivity[38] are possible under kinetic control in reactions of these ylides.

(v) *Explanation of stereoselectivity of reactions of semi-stabilised ylides within context of the betaine mechanism*: Reactions of triphenylphosphine-derived semi-stabilised ylides show little or no selectivity (i.e. significantly decreased *Z*-selectivity relative to reactions of non-stabilised ylides). Deprotonation of *erythro*-(2-hydroxy-1,2-diphenyleth-1-yl)methyldiphenylphosphonium by ^{n}BuLi (Li present) in THF showed almost completely stereospecific conversion to *Z*-alkene, indicating that the corresponding Wittig reaction is likely to be under kinetic control (see Scheme 5).[67] However, deprotonation experiments using the same β-HPS in ethanol with sodium ethoxide base in the presence of reactive aldehyde *m*-chlorobenzaldehyde gave a large amount of crossover product,



Scheme. 5. Deprotonation experiments on β-HPSs derived from semi-stabilised ylides.

while the stilbene that did form showed a *Z*/*E* ratio of around 90:10, indicating significant reversal of either *erythro*-betaine or *cis*-OPA to ylide and aldehyde under the reaction conditions (see Scheme 5).[67]

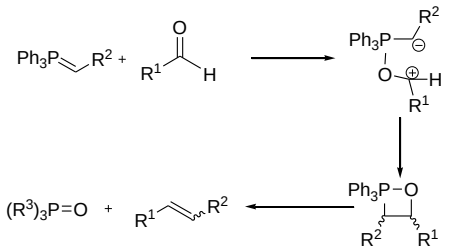
These results were rationalised in a similar fashion to reactions of stabilised ylides; the increased stability of the ylide (vs. non-stabilised) was supposed to translate to the betaine and/or OPA intermediate, which was thought to lead to increased reversion of one of the intermediates to ylide and aldehyde. The reversion to starting materials was thought to be less prevalent than in stabilised ylides since the intermediates derived from the latter should be more stable and thus longer-lived. As with stabilised ylides, reversion of the intermediate(s) would lead to greater *E*-selectivity if the decomposition to products were faster for *trans*-OPA than for *cis*-OPA, or if ring-closure of the betaine were irreversible, and faster for the *threo*-betaine than for the *erythro* isomer.

Rebuttal and counter evidence: The same arguments that were presented in point (iv) above (stabilised ylides) apply here. Stereospecific decomposition of both *erythro* and *threo*-β-HPSs (via betaine and OPA – the latter of which was observed by NMR) indicates that reactions of semi-stabilised ylides are irreversible.[60] Relevant to the positive crossover experiment of Scheme 4 is a report that, at least in certain circumstances, the addition of methanol *at low temperature* (i.e. before OPA decomposition occurs) to the Wittig reactions of non-stabilised ylides causes very high *E*-selectivity in the reactions, which in the absence of methanol (or if it is added after warming to room temperature) would show high *Z*-selectivity.[22]

3.2. Bergelson's "C-P-O-C" betaine mechanism

Essential features: Nucleophilic attack of carbonyl oxygen at phosphorus of ylide to give a "C-P-O-C" betaine (with charges on the carbon atoms) followed by ring closure to OPA and decomposition of OPA to alkene, as shown in Scheme 6.[75] A similar proposal was made by Schneider, which took account of the trigonal bipyramidal geometry at phosphorus in the proposed transition state (TS), who postulated that the observed *Z*-selectivity in reactions of non-stabilised ylides was a consequence of the steric effects that would result in such a TS.[76]

Evidence against this mechanism: Rate-determining attack of the carbonyl at phosphorus should show a negative ρ value for carbonyl reactants since a positive charge is developed at the carbonyl carbon. However, carbonyl compounds have been experimentally found to show positive ρ for the Wittig reaction in reactions of all ylide types.[77] Furthermore, no dipolar intermediate can be observed by NMR in Wittig reactions.



Scheme 6. Alternative betaine mechanism.

3.3. Schweizer mechanism

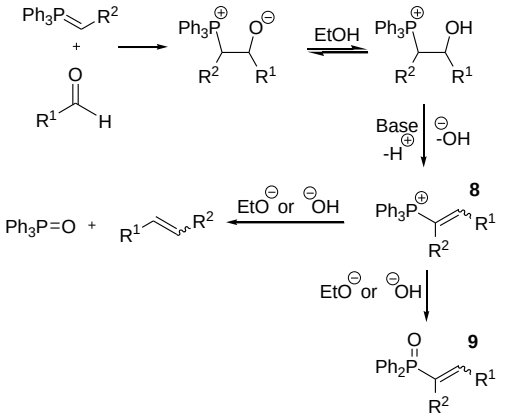
Essential features: On the basis of the observation that certain semi-stabilised and stabilised phosphonium ylides and conjugated carbonyl compounds reacted in alcohol solvents to give vinylphosphine oxides in addition to the expected alkene and phosphine oxide products, Schweizer *et al.* proposed that in this medium, these reactants initially form a betaine, which becomes protonated by the alcohol, and then undergo net elimination of water to give a vinylphosphonium salt **8**. This could undergo nucleophilic attack at phosphorus by either alkoxide or hydroxide. The resultant alkoxy or hydroxy phosphonium salt could expel either the vinyl group as alkene, giving triphenylphosphine oxide (the expected Wittig product), or benzene, giving vinyl phosphine oxide **9**. See Scheme 7.[78]

Evidence against this mechanism: Nucleophilic attack at phosphorus should result in at least partial inversion of the configuration at phosphorus. It has been shown that Wittig reactions of (benzylidene)ethylmethylphenylphosphorane with benzaldehyde give phosphine oxide with retention of configuration at phosphorus in ether solvent,[79] while the same reaction (in which the ylide was generated from the parent phosphonium salt using ethoxide base) in ethanol was shown subsequent to the publication of Schweizer's paper to proceed with retention of configuration at phosphorus.[80] It was thus proposed that formation of Wittig products by OPA formation (from betaine) and the formation of vinylphosphine oxide occur by separate pathways.

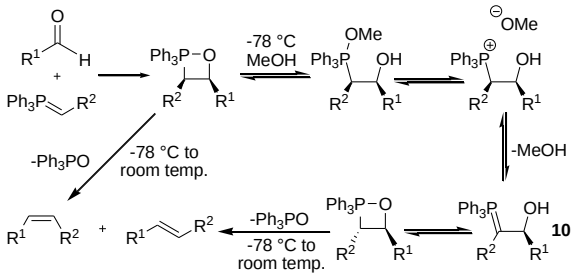
It has since been shown that, at least in certain circumstances, the addition of methanol *at low temperature* (i.e. before OPA decomposition occurs) to the Wittig reactions of non-stabilised ylides causes very high *E*-selectivity in the reactions, which in the absence of methanol (or if it is added after warming to room temperature) show high *Z*-selectivity.[22] This was proposed to be as a result of β-HPS formation from OPA and methanol, and deprotonation of the β-HPS by methoxide to give β-hydroxy ylide (**10** in Scheme 8), which can re-form OPA (non-stereospecifically) by proton transfer from the hydroxyl group to the ylidic carbon (see Scheme 8). It is likely that the vinylphosphonium salts produced in the study of Schweizer *et al.* were produced from reaction of OPA, not betaine, with ethanol.

3.4. Olah's single electron transfer mechanism

Essential features: Attempted Wittig reactions in refluxing solvents of non-stabilised ylides with adamantanone, 4-hydroxyadamantan-2-one, bicyclo[3,3,1]nonan-9-one or benzophenone gave the carbonyl reduction product (alcohol) and phosphonium salt as the only products after work-up, or in addition to the Wittig products. Based on these observations, the



Scheme 7. Proposed mechanism for Wittig reactions and vinylphosphine oxide formation in alcohol solvent.



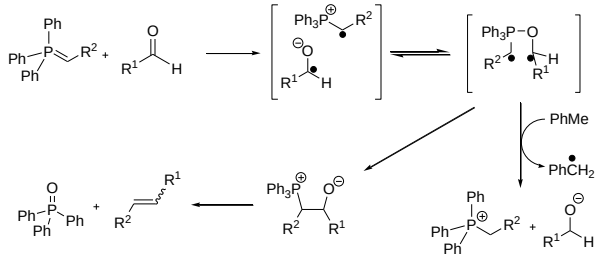
Scheme 8. Proposed mechanism for OPA isomerisation via β-hydroxy ylide in the presence of alcohol.

Wittig reaction was proposed to proceed by a one electron transfer mechanism,[81] i.e. the transfer of an electron from the ylide to the carbonyl compound to initially give a tight radical ion pair, supposed to be in equilibrium with a P-O bonded diradical species (see Scheme 9), which would subsequently form betaine and then alkene. The alcohol formation was particularly favoured in the reactions of sterically bulky ylides *iso*-propylidenetriphenylphosphorane and diphenylmethylidenetriphenylphosporane. The hydrogen source was the reaction solvent, as reactions in toluene gave benzylated toluenes. The one electron transfer mechanism was also advocated by Yamataka and co-workers on the basis of their observation that there is no significant kinetic isotope effect for the reaction of *iso*-propylidenetriphenylphosphorane with benzaldehyde having a ^{14}C-labelled carbonyl group.[82]

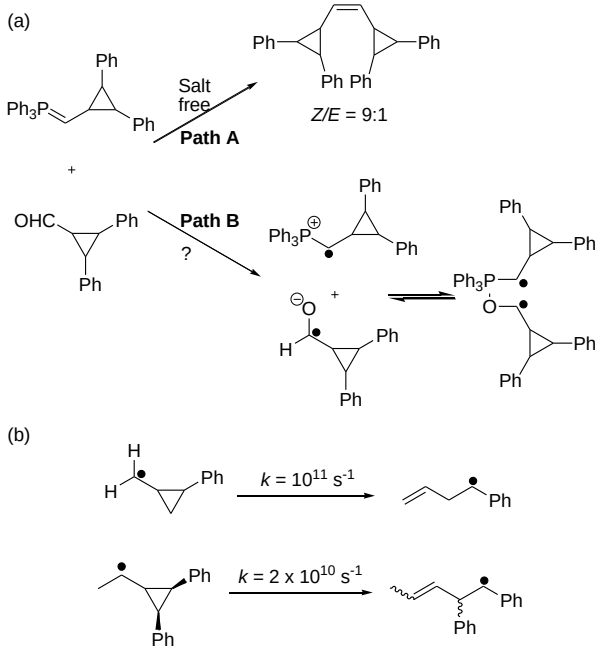
Evidence against this mechanism: A number of tests for radical involvement in Wittig reactions are described in the review of Vedejs and Peterson.[4] One of these is reproduced here. The unimolecular rate constants for ring opening of cyclopropylcarbinyl radicals are extremely large (Scheme 10(b)).[83] By analogy, if the formation of radical ions from the Wittig reactants shown in Scheme 10(a) was occurring (see path B) then exceptionally fast ring cleavage would occur. Instead, the reaction gives the expected Wittig product in high yield with the expected high *Z*-selectivity (see Scheme 10(a), path A).[83] This strongly implies that electron transfer is not an intrinsic part of the Wittig reaction mechanism, although electron transfer may be possible between suitable Wittig reactants under the right experimental conditions. In cases where it is possible, this probably leads to the formation of side-products. In one of their

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publications, Vedejs and Marth list a series of examples of



Scheme 9. Proposed mechanism for the Wittig mechanism involving single electron transfer from ylide to carbonyl species.



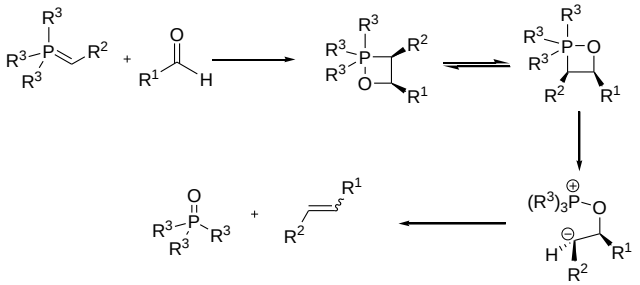
Scheme 10. (a) Test for involvement of radical species in the Wittig reaction, (b) Rates of ring opening for cyclopropylcarbinyl radicals.

reactions which, if radical species were involved in the manner that is proposed in this mechanism, should give products derived from radical-type reactions, but instead react to give normal Wittig products.[74]

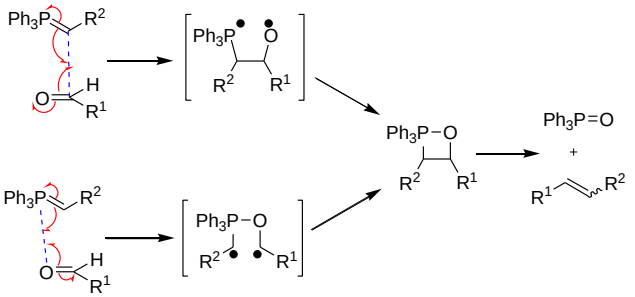
3.5. Bestmann's "P-O-C-C" betaine mechanism

Essential features: Direct *cis*-selective cycloaddition of ylide and carbonyl to give OPA with oxygen in an axial position in the phosphorus-centred trigonal bipyramid (although no rationale for the *cis*-selectivity was presented), followed by pseudorotation about phosphorus to place oxygen in an equatorial site, subsequent cleavage of the P-C bond to give a "P-O-C-C" betaine and finally scission of the C-O bond to give alkene and phosphine oxide, as shown in Scheme 11.[84] Betaines derived from non-stabilised ylides were supposed to be very short-lived and thus to quickly decompose to Wittig products, whereas betaines with a stabilising group on the carbanion carbon (i.e. derived from a stabilised ylide) were thought to be longer lived due to the greater stabilisation of the negative charge, so that rotation could occur about the C-C bond before C-O bond breakage occurred, thus giving rise to *E*-alkene.

Evidence against this mechanism: OPA formation has been shown to be irreversible and stereospecific for Wittig reactions of



Scheme 11. Bestmann mechanism for the Wittig reaction.



Scheme 12. Mechanisms involving spin-paired diradical intermediates prior to OPA formation.

all ylide types in all but a small and well-defined set of reactions (of non-stabilised ylides; see section 4.1 part (i)) by stereospecific decomposition of β-HPS to alkene.[60,68] Thus there can be no equilibration of intermediates after OPA has been formed (except in the cases detailed in section 4.1 part (i)), and intermediates such as the betaine shown in Scheme 12 can play no part in the Wittig reaction.

3.6. McEwen's spin-paired diradical mechanisms

McEwen and co-workers have proposed two mechanisms involving the initial formation of spin-paired diradical intermediates that subsequently ring-closed to OPA (see Scheme 12).

Essential features: The first mechanism involved an entity with a C-C bond and an unpaired electron on each of phosphorus and oxygen, presumably formed by transfer of one electron from each of the C=O and P=C bonds into the new C-C bond, and movement of the remaining electron from each bond on to oxygen and phosphorus, respectively.[85] The second involved a P-O bond with two carbon-centred radicaloids formed by an analogous process[86] (this differs from the mechanism of Olah, in which electron transfer from ylide to carbonyl was suggested to occur before the occurrence of P-O bonding). The kinetically favoured pathway was postulated to favour *cis*-OPA formation due to orthogonal approach of the ylide and aldehyde in the diradical *intermediate*, which was proposed for non-stabilised ylides to be short lived, while it would be longer lived for stabilised ylides and could thus undergo bond rotation to give *trans*-OPA and *E*-alkene.

Evidence against this mechanism: The first case, involving the C-C bonded diradical, can be ruled out by the same experiment that quashed the involvement of betaines in reactions of non-stabilised ylides (mentioned in section 3.1 part (iii), and discussed fully in section 4.2 below).[74] The second, involving the

P-O bonded diradical, can be ruled out for the same reasons as

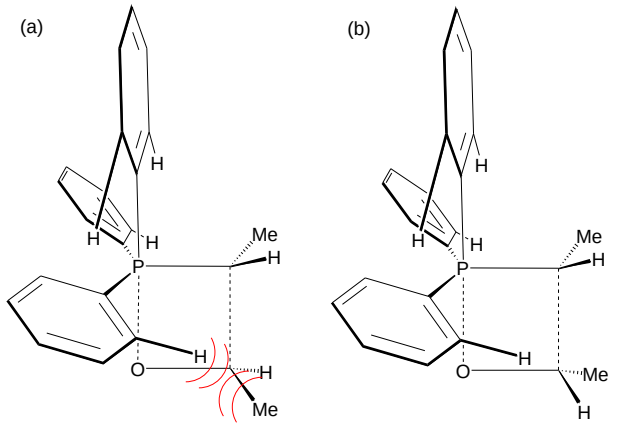


Fig. 3. Transition states for formation of (a) *trans*-OPA and (b) *cis*-OPA according to the Schlosser model for the Wittig reaction.

were invoked for the Bergelson-Schneider mechanism (see section 3.2 above), and in particular by the fact that this mechanism would predict a negative ρ value for carbonyl compounds in the Wittig reaction where a positive value is observed. Furthermore, no evidence has been reported in support of the existence of either of the proposed diradical intermediates.

3.7. Schlosser "leeward approach" mechanism

Schlosser and Schaub proposed the formation of OPA by [2 + 2] cycloaddition of ylide and aldehyde,[87] with the mechanistic details differing somewhat from its original proposal by Vedejs and Snoble,[88] and from later variants by Vedejs & co-workers (see section 3.8).

Essential features: The kinetically favoured OPA-forming TS was postulated to be planar, with trigonal bipyramidal geometry about phosphorus (i.e. complete reorganisation had occurred of the substituents about phosphorus to the new geometry). The ylide α-substituent was supposed to influence the arrangement of the *P*-phenyl groups (1-2 interactions) in such a way as to make steric interactions of the carbonyl substituent with the phosphorus substituents (1-3 interactions) much greater in the TS leading to *trans*-OPA (see Fig.3 (a)) than in the *cis*-selective TS (Fig. 3(b)). This would mean that the *cis*-OPA would be favoured kinetically - hence its preferential formation in Wittig reaction of non-stabilised ylides.

Evidence against this mechanism: Based on the above rationale for the cycloaddition TS, it follows that *cis*-OPA should be the most thermodynamically stable OPA isomer. However, there exists no known example of isomerisation of *trans*-OPA to *cis*-OPA (whether by reversal to Wittig reactants or otherwise). On this basis it can be concluded that *trans*-OPA is thermodynamically favoured over *cis*-OPA, which is intuitively sensible, as the former should have similar 1-3 steric interactions but significantly decreased 1-2 interactions compared to the latter. Therefore the cycloaddition TS cannot be product-like (i.e. it must be *early*), as otherwise it would be *trans*-selective, and so could not have a trigonal bipyramidal arrangement of the substituents about phosphorus - an arrangement that is intrinsic to the explanation of selectivity in the Schlosser mechanism. Also, it is difficult to rationalise *E*-selectivity in reactions of stabilised ylides in the context of this mechanism, involving as it does direct OPA formation, given that OPA formation has been shown to be irreversible for reactions of all ylide types.[60,68] Although the rationale put forth to explain the observed selectivity in the context of this mechanism is not consistent with all experimental observations, it is close to the currently accepted mechanism in that it involves OPA formation by direct [2+2] cycloaddition of ylide and aldehyde.

3.8. Vedejs cycloaddition mechanism

Vedejs and Snoble were the first to advance the proposal of direct irreversible cycloaddition of the ylide and aldehyde to give OPA, followed by irreversible and stereospecific cycloreversion of the OPA to give phosphine oxide and alkene (see Scheme 13). Later, having adduced the evidence that established that all Li salt-free Wittig reactions are irreversible (see section 4.1), this [2 + 2] cycloaddition mechanism was elaborated by Vedejs and co-workers to include details of how the stereochemistry of the product alkene is decided at the TS of the cycloaddition step (see Fig. 4).[60,89] The intimate details of the cycloreversion mechanism were not specified, although the necessity for the formation of a C-apical OPA (from the more stable O-apical pseudorotamer(s)), or indeed of any particular OPA pseudorotamer, before cycloreversion could occur was called into question.[90] Indeed, it is only recently that definitive computational and experimental results have appeared that shed light on the elusive details of this part of the mechanism (see the section on the modern mechanstic interpretation for the Wittig reaction).[40,91] In any case, it is the origin of the stereoselectivity induced in the OPA intermediate that is of greatest interest since this stereochemistry is retained exactly in the alkene product after decomposition, and this was the primary focus in the work of Vedejs and co-workers.

Reactions of aldehydes with non-stabilised alkylidenetriphenylphosphoranes were suggested to proceed through an early puckered TS (meaning that the carbonyl C=O bond and ylide P-C bond approach each other at a relatively large angle) in which both bond formation and rehybridisation about the atoms in the forming ring are at an early stage (see Fig. 4(a)). The fact that the four substituents bound to phosphorus in the ylide remain in a nearly tetrahedral arrangement about phosphorus in the TS has particular consequences for the shape of the TS. This disposition of the phosphorus substituents means that planar approach of the ylide and aldehyde is disfavoured for two reasons – firstly one of the *P*-phenyl groups must necessarily project in the direction of the forming P-O bond, and secondly there exists the possibility of large 1-3 steric interactions between the phosphorus substituents and the aldehyde substituent. Puckering relieves both of these unfavourable interactions, and minimises 1-2 steric interactions (between aldehyde and ylide substituents) if the large substituent on the carbonyl is placed in a pseudo-equatorial position and the ylide α-substituent is pseudo-axial in the forming ring. This energetically favoured TS leads to *cis*-OPA. The lowest energy *trans*-selective TS would necessarily be significantly higher in energy whether puckered[f] or planar.[g] Thus, *cis*-OPA is thought to be formed selectively under conditions of kinetic control, and to decompose irreversibly and stereospecifically to *Z*-alkene and phosphine oxide by *syn*-cycloreversion.

Reactions of stabilised ylides were proposed by Vedejs and

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co-workers to proceed through a later transition state in which

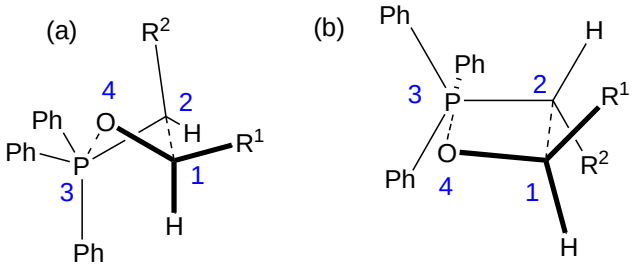
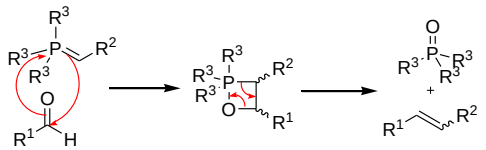


Fig. 4. (a) Proposed *cis*-selective cycloaddition transition state in reactions of alkylidenetriphenylphosphoranes (b) Proposed *trans*-selective cycloaddition transition state in reactions of stabilised ylides in Vedejs mechanism.[60,89]



Scheme 13. The irreversible [2+2] cycloaddition mechanism of Vedejs.

bond formation and rehybridisation about the reactive centres are advanced (see Fig. 4(b)). That the geometry of the substituents about phosphorus (including the carbonyl oxygen) is close to trigonal bipyramidal in such a TS was postulated to mean that 1-3 interactions would be much less significant, so the driver for TS puckering is removed. Planar approach was thus thought to be eminently possible and probably favourable over puckering given the more advanced nature of bond formation. 1-2 steric interactions would naturally be lower in a planar *trans*-selective TS than in a planar *cis*-selective TS, which would suffer significantly from torsional strain between R^1 and R^2. *trans*-OPA is formed selectively and irreversibly, and hence high selectivity for *E*-alkene is seen after cycloreversion of the OPA.

The cycloaddition mechanisms proposed by Vedejs for different ylides could also be used to account for the selectivity observed in reactions of ylides with different substitution patterns at phosphorus. Computational results by Aggarwal, Harvey and co-workers show that the details of this mechanism are consistent with experimental observations, with one exception. They propose that the *trans*-selective cycloaddition TS in reactions of stabilised ylides is puckered to take into account the effect of the interaction of the dipoles along the ylide C-R^2 and aldehyde C-O bonds.[41,42]

The finer details of the mechanism, including unresolved issues related to the second step of the mechanism and especially the experimental and computational evidence that has been amassed in its favour, are described fully in the next section.

4. Modern mechanistic interpretation of the Wittig reaction

There are many questions to be answered in considering how the reaction of a phosphonium ylide and aldehyde progresses to give an alkene and phosphine oxide progresses. These include:

(i) Is the reaction under kinetic or thermodynamic control?

(ii) What is the nature of the first-formed intermediate? Many have been proposed, but OPAs and betaines are the only ones for which sufficient experimental evidence has been presented to enable them to gain widespread acceptance.

(iii) What is the origin of the observed pattern of *Z/E*-selectivity? This is intrinsically linked to the first two points.

(iv) Much more recently, the process by which the OPA intermediate decomposes to alkene & phosphine oxide has come into question. Does this process involve two steps – pseudorotation to a "C-apical" intermediate followed by cycloreversion – or just one step (cycloreversion), without formation of intermediate(s)?

4.1. The operation of kinetic control in the Wittig reaction

The substantial evidence available on this issue strongly suggests that, in all but a few exceptional cases, the Li-salt free Wittig reaction proceeds irreversibly. Below is presented the evidence that has been put forth implying the operation of kinetic control in the reactions of each of the three major classes of ylide. The exceptional cases in which thermodynamic control has been shown to operate in Li-salt free reactions will also be described.

(i) Non-stabilised ylides

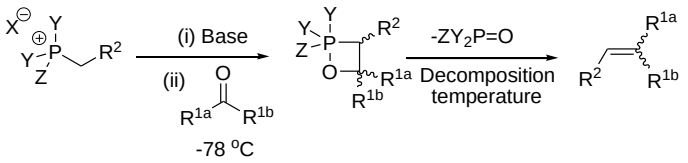
It is generally accepted that OPA must occur at some point along the reaction coordinate from phosphonium ylide and aldehyde to alkene and phosphine oxide – either as an intermediate or TS. OPAs have been shown to be the only observable intermediates many times in reactions of non-stabilised ylides.[38,65,68,69,88] It has also been demonstrated in such reactions that the final step of the Wittig reaction is decomposition of OPA to alkene and phosphine oxide, since the rate of OPA decomposition equals the rate of alkene formation (i.e. this is a first order process),[69,70] and since the diastereomeric ratio of the OPA generally matches that of the derived alkene.[60,69,70]

The operation of kinetic control in a Wittig reaction is established if the kinetic OPA *cis/trans* ratio (usually determined by low temperature ^{31}P NMR) is identical to the *Z/E* ratio of the alkene produced by warming of the OPA. There are surprisingly few examples in which kinetic control has been absolutely proven in this way. Many of the examples of the application of low temperature ^{31}P NMR monitoring of the OPA intermediate of a Wittig reaction have been used to demonstrate the operation of OPA equilibration in reactions involving aromatic or tertiary aldehydes and/or trialkylphosphonium alkylides (see discussion later). However, stereospecific conversion of the OPA diastereomers produced in the Wittig reactions shown in Table 1 to alkene has been demonstrated by low temperature ^{31}P NMR, implying the operation of kinetic control in these reactions.[24,38,59,69,70,92,93]

As shown in Table 1 entry 1, stereospecific conversion of the OPA (*cis/trans* ratio of 5.8:1) produced in the reaction of hexanal with *n*-butylidenetriphenylphosphorane (generated using LiHMDS) to a 5.8:1 mixture of *Z* and *E* dec-4-ene has been reported.[69,70] This is consistent with the fact that LiBr has been shown to exert an effect on the stereoselectivity of OPA formation in the reaction of $Ph_3P{=}CHCH_3$ and $PhCH_2CH_2CHO$, but not to affect the stereochemical ratio of the OPA formed from these reactants if added to a pre-formed solution of the OPA to give betaine-LiBr complex.[65] These observations suggest that OPA formation is irreversible in reactions of aliphatic aldehydes, even in the presence of Li^+, and that the diminished *Z*-selectivity in these reactions arises from the effect of Li^+ on the initial

formation of OPA.

Table 1. Wittig reactions for which kinetic control (and stereospecific decomposition of OPA) have been demonstrated by direct comparison of the OPA *cis/trans* and alkene *Z/E* ratios.[a] X = halide counter-ion.



Entry	Y	Z	R^2	R^{1a}	R^{1b}	Base	OPA *cis/trans* ratio	Alkene *Z/E* ratio	Ref
1	Ph	Ph	*n*-Pr	*n*-C_5H_{11}	H	LiHMDS	5.8:1	5.8:1	69
2	Ph	Ph	*n*-Pr	Ph	H	NaHMDS	100:0[b]	96:4	70
3	Ph	Ph	*n*-Pr	Ph	H	NaHMDS	*ca.*95:5	95:5[c]	92
4	Ph	Ph	*n*-Pr	Ph	H	NaHMDS	≥98:2	96:4	69
5[d]	DBP	Ph	Me	$(CH_2)_2Ph$	H	$NaNH_2$	6:94	5:95	59
6	Ph	Ph	Me	*c*-C_6H_{11}	Me	KHMDS	95:5	-[e]	93
7[f]	Et	Ph	Me	Me	*c*-C_6H_{11}	KHMDS	4:96	10:90	93
8[g,h]	Ph	2-fur	Me	Ph	H	NaHMDS	94:6	94:6	24
9 [g,h]	2-fur	Ph	Me	Ph	H	NaHMDS	96:4	96:4	24
10[g,h]	2-fur	2-fur	Me	Ph	H	NaHMDS	98:2	98:2	24
11[i]	DBP	Ph	*i*-Pr	Ph	H	NaHMDS	89:11	89:11	38
12[i]	DBP	Ph	*i*-Pr	2-BrC_6H_4	H	NaHMDS	94:6	91:9	38
13[i]	DBP	Ph	*i*-Pr	*c*-C_5H_9	H	NaHMDS	45:55	43:57	38
14[i]	DBP	Ph	*i*-Pr		H	NaHMDS	94:6	91:9	38

[a] Phosphonium salt counter-ion is bromide in all cases except entries 5-7, for which it is iodide. The decomposition temperature is the temperature at which OPA decomposition to alkene was effected experimentally. Unless otherwise specified, decomposition was carried out at "room temperature" (15-20 °C).

[b] Only one OPA signal observed in ^{31}P NMR spectrum obtained at -20 °C.

[c] The paper in question states that the reaction "did not exhibit stereochemical drift", but does not quote the alkene *Z/E* ratio.

[d] The specific ylide used in this reaction, incorporating the dibenzophosphole (DBP) system, is shown in Fig. 5(a). The experimental OPA decomposition temperature for this reaction was 110 °C. See reference 59.

[e] Alkene *Z/E* ratio not reported.

[f] OPA decomposition temperature not specified.

[g] "2-fur" indicates a *P*-fur-2-yl group. OPA decomposition in this reaction carried out in refluxing THF, quoted as 70 °C.

[h] In a separate reaction, *n*-BuLi was used to generate the ylide. Stereospecific OPA decomposition was also noted from the OPA in this case, but with the exception of entry 8 the yield of alkene was much lower than when NaHMDS was employed.

[i] OPA decomposition in this reaction carried out in refluxing THF (heating bath temperature 80 °C).

OPAs are generally air and temperature sensitive. The decomposition products from exposure to (relatively) high temperatures are alkene and phosphine oxide, so at low temperature the OPAs derived from non-stabilised ylides are kinetically stable. If the phosphorus of the OPA is constrained by being in a five-membered ring, as in dibenzophosphole (DBP) derived OPAs, then the OPA is kinetically stable at room temperature, and requires heating to induce alkene formation.[59] Such OPAs can conveniently be monitored spectroscopically at room temperature, and as a consequence they have been used in a number of studies to elucidate details of the Wittig reaction mechanism.[59,68] DBP-derived OPAs have been generated from Wittig reactions (e.g. from the ylide shown in Fig. 5(a)) and by β-HPS deprotonation (e.g. of the β-HPS shown in Fig. 5(b)). They have also been used in similar investigations on reactions of semi-stabilised ylides (see section 4.1 part (ii)).

As shown in Table 2, individual OPA isomers generated by a process independent of the Wittig reaction (by deprotonation of β-HPS using sodium or potassium base, which transiently gives betaine and then OPA) have been demonstrated by low temperature ^1H and ^{31}P NMR to undergo stereospecific decomposition to alkene. That is, *erythro* β-HPS gave only *cis*-OPA and hence only *Z*-alkene, and likewise *threo* β-HPS gave *trans*-OPA and hence *E*-alkene.[68,69,93] Other examples exist in which the β-HPS deprotonation technique has been used to demonstrate the operation of kinetic control in Wittig reactions of non-stabilised ylides.[94]

Another method for OPA generation independent of a Wittig reaction involves S_N2 epoxide ring-opening by lithium diphenylphosphide to give β-oxidophosphine, which is quaternised with methyl iodide to give betaine and hence OPA. *cis*-Epoxide was shown to give *E*-alkene stereospecifically by this method via *trans*-OPA, while *trans*-epoxide stereospecifically gave *Z*-alkene via *cis*-OPA.[95,96] The latter is shown in Scheme 14.

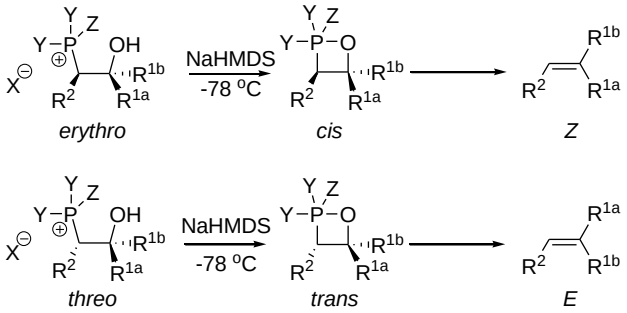
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Table 2. β-Hydroxyphosphonium salts for which stereospecific decomposition to alkene has been demonstrated for either both isomers or the *erythro* isomer only.



Entry	Y	Z	R^2	R^{1a}	R^{1b}	OPA decomposition temperature[a]	Ref
1	Ph	Et	Me	$C(Me)_2CH_2Ph$	H	20 °C	68
2	DBP[b]	Et	Me	$C(Me)_2CH_2Ph$	H	110 °C	68
3	Ph	Ph	Me	$C(Me)_2CH_2Ph$	H	20 °C	68
4	DBP[b]	Et	Me	$C(Me)_2CH_2Ph$	H	110 °C	59[c]
5	Ph	Ph	*n*-Pr	Ph	H	20 °C	69,70
6	Ph	Et	Me	*c*-C_6H_{11}	Me	> -50 °C	93

[a] Temperature at which OPA decomposition was effected experimentally.

[b] The specific β-HPS used in this reaction, incorporating the dibenzophosphole (DBP) system, is shown in Fig. 5(b).

[c] Deprotonation carried out using $NaNH_2$.

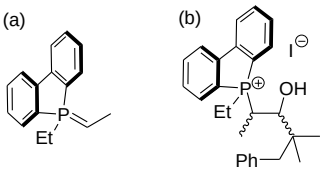
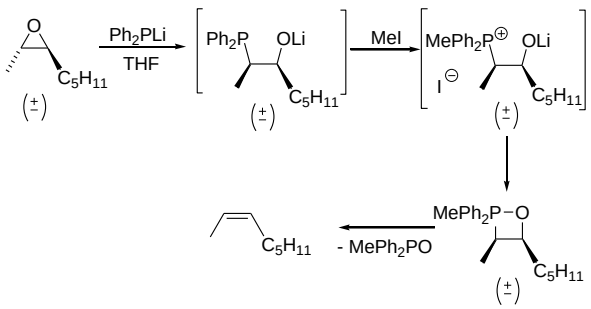


Figure 5. (a) (Ethylidene)ethyldibenzophosphole.[59] (b) *erythro* or *threo* (3-hydroxy-4,4-dimethyl-5-phenylpent-2-yl)ethyldibenzophospholium iodide, incorporating the dibenzophosphole (DBP) system.[68]

It can be concluded from these results that the formation of OPA is irreversible, as *cis* and *trans* isomers do not interconvert under Li-salt free conditions, and that OPA decomposition to alkene and phosphine oxide is stereospecific, irreversible, and occurs through a *syn*-cycloreversion. Therefore the alkene *Z/E* ratio is identical to the kinetic OPA *cis/trans* ratio, and the stereochemistry of the alkene product is decided in a TS in the step(s) leading from starting materials to OPA.

There exist some exceptional cases where a non-correspondence has been observed between the diastereomeric ratios of the OPA and of the alkene – this has been termed "stereochemical drift". In all cases of stereochemical drift so far observed, the *E*-isomer has been favoured to a greater extent in the alkene diastereomeric ratio than the *trans*-isomer had been in the OPA *cis/trans* ratio. The augmentation of the production of *E*-alkene *cannot* be a consequence of its greater stability, since OPA decomposition is irreversible, and so it must be due to



Scheme 14: Reaction system for which OPA is produced by nucleophilic cleavage of an epoxide by diphenylphosphide and quaternisation of the resulting phosphine and shown to decompose stereospecifically to alkene.[95,96]

preferential (and probably irreversible) formation of the more thermodynamically favoured of the OPA isomers, the *trans*-OPA.

Stereochemical drift is in certain circumstances linked to the presence of Li^+. As was mentioned above, the presence of Li^+ affects the stereoselectivity of OPA formation in reactions of alkylidenetriphenylphosphoranes with aliphatic aldehydes (higher $[Li^+]$ results in more *trans*-OPA[69]), but these reactions are nonetheless irreversible.[65,69] Similarly, the OPA diastereomeric ratio in the reaction of butylidenetriphenylphosphorane with benzaldehyde is different in the presence of Li^+ (favouring *trans*-OPA) than it is in Li salt-free conditions, but the initial ratio

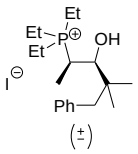
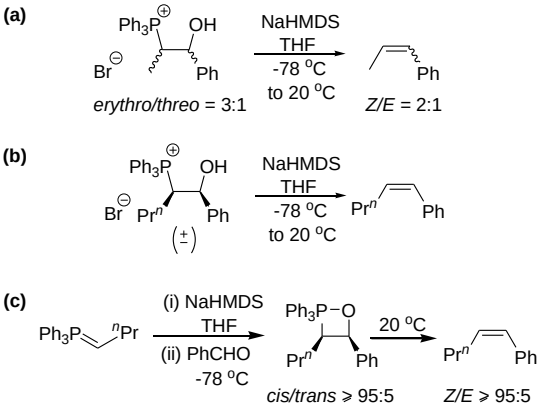


Figure 6. *erythro*-(3-hydroxy-4,4-dimethyl-5-phenylpent-2-yl)triethylphosphonium iodide.

remains constant with time at low temperature in both Li^+-free and Li^+-present conditions.[69,97] It is only when the Li^+-present reaction mixture is warmed up that stereochemical drift occurs, resulting in the observation of a change in the diastereomeric ratio on going from OPA to alkene (favouring *E*-alkene). The Li salt-free case does not exhibit stereochemical drift (as already stated; see Table 1 entry 1).[69] Positive crossover experiments indicate that the conversion of *cis*-OPA into *trans*-OPA in the examples mentioned above of reactions of alkylidenetriphenylphosphoranes with benzaldehyde in the presence of Li^+ involve OPA reversal to ylide and aldehyde.[65,69] Thus, in reactions of non-stabilised ylides with benzaldehyde(s), Li^+ exerts an effect both on the stereoselectivity of the initial formation of OPA *and* plays a role in bringing about stereochemical drift in reactions of longer-chain alkylides that would otherwise be under kinetic control. The role of Li^+ in the process of stereochemical drift may be related to the formation of betaine-lithium halide complexes, which have been isolated from reactions of non-stabilized ylides.[64,65] There exists one report in which betaine-LiBr complexes have been formed in reactions of a *semi-stabilised* ylide and undergo Wittig reversal, as judged by positive crossover experiments.[98]

There is also a small and well-defined set of Wittig reactions – all involving non-stabilised ylides – that exhibit stereochemical drift under Li salt-free conditions ("Li^+-free stereochemical drift"). Li^+-free stereochemical drift and has been observed only for the OPAs produced in the reactions of trialkylphosphonium alkylides with tertiary or aromatic aldehydes,[68,69,92] and in reactions of aromatic aldehydes with the ethylides of triphenylphosphine,[38,65] ethyldiphenylphosphine[38] and *P*-phenyl-5*H*-dibenzophosphole.[38] In the first two cases, the augmentation of *trans*-OPA at the expense of the *cis*-isomer occurred at temperatures below which OPA cycloreversion to alkene and phosphine oxide could not occur, and thus it could be monitored by NMR. These experiments represent the only examples in which stereochemical drift has been observed in action. In the latter three cases, the OPA *cis/trans* ratio was invariant with time below the temperature at or above which alkene formation could occur, and so stereochemical drift could only be detected to have occurred by comparison of the kinetic OPA *cis/trans* and alkene *Z/E* ratios.

An example that illustrates the observation of stereochemical drift is the experiment of Vedejs *et. al.* involving deprotonation of the *erythro*-β-HPS shown in Fig. 6 at –78 ˚C. This reaction would be expected to give only the *cis*-OPA that would be produced in the Wittig reaction of ethylidenetriethylphosphorane and 2,2-dimethyl-3-phenylpropanal. However, the reaction mixture upon warming to –40 °C was observed to consist of a 80:20 mixture of *cis* and *trans* OPA.[68] On warming to –5 °C, the amount of *trans*-OPA was observed to increase at the expense of the *cis*-OPA, while a small amount of alkene formation also



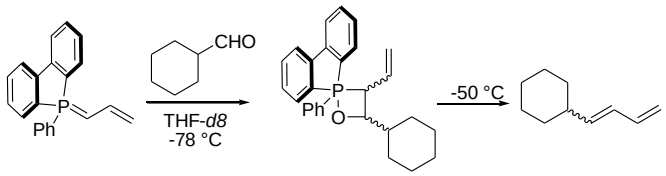
Scheme 15. (a) Deprotonation of a mixture of *erythro* and *threo* (1-hydroxy-1-phenyl-*n*-prop-2-yl)triphenylphosphonium bromide, (b) Deprotonation of *erythro* (1-hydroxy-1-phenyl-*n*-pent-2-yl)triphenylphosphonium bromide, (c) Wittig reaction of *n*-butylidenetriphenylphosphorane with benzaldehyde.

occurred. Decomposition of OPA to alkene and phosphine oxide was effected at >30 °C giving a final *Z/E* ratio of 17:83. Some 2,2-dimethyl-3-phenylpropanal was also isolated, indicating reversal to ylide and aldehyde. Reversal was confirmed by the observation of crossover product in an experiment involving deprotonation of the same β-HPS in the presence of *m*-chlorobenzaldehyde. At least some of this reversal is likely to be due to reversal of the betaine transiently produced upon β-HPS deprotonation, but OPA reversal must be involved in view of the fact that the OPA *cis/trans* ratio was observed to change after the passage of some time with an increase in temperature. The *threo*-diastereomer of this β-HPS decomposed stereospecifically to *E*-alkene.[68]

Stereochemical drift was shown to operate in the reaction of ethylidenetriphenylphosphorane with benzaldehyde by a series of crossover experiments.[65] The isomeric ratio of the OPA produced from these reactants remained constant with time below –30 ˚C. When spectroscopic monitoring of the reactions was carried out below this temperature, no crossover products could be observed. The mechanism of equilibration of the OPA isomers was shown conclusively in this case to involve cycloreversion to Wittig starting materials. Li-salt free OPA equilibration was also demonstrated for these reactants by an experiment in which deprotonation of a 3:1 mixture of *erythro* and *threo* (1-hydroxy-1-phenylprop-2-yl)triphenylphosphonium bromide gave a 2:1 mixture of *Z* and *E*-1-phenylprop-1-ene,[69] as shown in Scheme 15(a).

Related to the previous example and in the same study, β-HPS *erythro*-(1-hydroxy-1-phenyl-*n*-pent-2-yl)triphenylphosphonium bromide (see Scheme 15(b) and Table 2 entry 5) was shown to undergo stereospecific conversion to *Z*-1-phenylpent-1-ene.[69] As mentioned above, the OPA produced in the reaction of Scheme 15(b) was also formed with very high *cis*-selectivity in the Li-salt free Wittig reaction of benzaldehyde + *n*-butylidenetriphenylphosphorane, and its decomposition proceeded stereospecifically,[92] or with negligible stereochemical drift (see Scheme 15(c) and Table 1 entries 2-4).[69] Thus it appears that the reactions of most types of alkylide with benzaldehyde are under kinetic control; only certain ethylides and alkylidenetrialkylphosphoranes show reversibility.

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Scheme 16. Wittig reaction of allylidenephenyldibenzophosphole and cyclohexanecarboxaldehyde.

It is noteworthy that all instances of stereochemical drift observed thus far involve the production of increased amounts of *trans*-OPA at the expense of the *cis*-OPA, or the production of a greater proportion of *E*-alkene than had been present of the *trans*-OPA. In other words, stereochemical drift always results in an increased proportion of *trans*-OPA, since *E*-alkene must be produced from *trans*-OPA, and alkene formation is irreversible. An obvious conclusion is that the *trans*-OPA is thermodynamically favoured; this is corroborated by the observation that *trans*-OPAs typically require higher temperatures to effect their decomposition to alkene and phosphine oxide than do their *cis* counterparts.[68,69,93] Thus the proportion of *Z*-alkene produced in a Wittig reaction always represents a lower bound to the kinetic selectivity for (Reviewer requests a change – we should discuss this one, I don't see a problem!) the *cis*-OPA; in other words high selectivity for *Z*-alkene is directly indicative of kinetic control, and cannot occur "by mistake" (i.e. due to equilibration) as long as the *cis*-OPA is indeed thermodynamically disfavoured.

(ii) Semi-stabilised ylides

It is not possible, in general, to detect OPAs derived from semi-stabilised ylides by low temperature NMR. Consequently, a kinetic diastereomeric OPA ratio cannot be established to compare with the final alkene *Z/E* ratio. However, in one case an OPA produced in a Wittig reaction of a semi-stabilised ylide has been reported. As shown in Scheme 16, the reaction of cyclohexanecarboxaldehyde with the phenyldibenzophosphole-derived semi-stabilised ylide allylidenephenyl-dibenzophosphole in THF-*d8* at –78 °C gave an OPA (^{31}P NMR δ = -72 ppm) that decomposed above –50 °C to 1-cyclohexyl-1,3-butadiene with *Z/E* = 5:95.[60] Such a "constrained" OPA (in which the phosphorus atom is a spiro centre between four and five-membered rings) is kinetically relatively stable (compared to other semi-stabilised ylide-derived OPAs)[90] because increasing bond angle strain is induced in the phosphole ring on going from OPA to phosphine oxide. This effectively raises the barrier to OPA decomposition to alkene and phosphine oxide, and may even lower the barrier to OPA formation.

In addition to the impossibility of spectroscopic observation of OPAs in Wittig reactions of semi-stabilised ylides, with the above singular exception, crossover experiments with such ylides[c] do not give meaningful results because the reaction of the semi-stabilised ylide proceeds so quickly that the reaction is already complete by the time the crossover ylide or aldehyde is added. Thus, proof for the operation of kinetic control in Wittig reactions of semi-stabilised ylides requires OPA generation from a source other than a Wittig reaction, and demonstration of stereospecific conversion either (a) of the precursor of *cis* or *trans*-OPA to *Z* or *E*-alkene, respectively, or (b) of a mixture of the precursors of known diastereomeric ratio to alkene of corresponding *Z/E* ratio. This has been done for reactions of semi-stabilised ylides by forming alkene from either (i) β-HPS by deprotonation or (ii) epoxide by nucleophilic ring cleavage by phosphide followed by protonation of the alkoxide and then quaternisation of phosphorus. Both methods presumably form betaine and OPA transiently *en route* to alkene, and have both been described in connection with reactions of non-stabilised ylides in section 4.1 part(i).

Each of these methods suffers from the fact that betaine generation is inherent in the process of OPA formation. The formation of OPA in Wittig reactions does not necessarily require the intermediacy of a betaine. There may exist processes in experiments involving β-HPS deprotonation or nucleophilic cleavage of epoxide that do not necessarily operate in Wittig reactions which result in the OPA *cis/trans* ratio being different to the diastereomeric ratio of the starting material. For example, dissociation of the transiently formed betaine into ylide & aldehyde ("betaine reversal"), and non-stereospecific recombination of these Wittig starting materials to give OPA may occur in either type of experiment, whereas Wittig reactions do not necessarily form betaines. Also in β-HPS deprotonation experiments, there exists the possibility of the formation of β-hydroxy ylide (by deprotonation of the α-carbon, not the β-hydroxy group), which then undergoes non-stereospecific proton transfer to form betaine and hence OPA. This latter process has been demonstrated to occur in corresponding experiments involving β-HPSs derived from stabilised ylides when strong bases are used (see section 4.1 part (iii)).[60] In each case, stereospecific decomposition of the OPA mixture of changed diastereomeric ratio to alkene product with a *Z/E* ratio that is not identical to the initial β-HPS *erythro/threo* ratio or epoxide diastereomeric ratio could be erroneously interpreted as indicating the operation of some equilibration of OPA diastereomers in the corresponding Wittig reaction. The same problem of the apparent operation of stereochemical drift applies in crossover experiments involving β-HPS deprotonation. Despite such limitations, these methods have been successfully used to demonstrate the irreversibility of OPA formation in reactions of semi-stabilised ylides.

The *cis* and *trans*-OPAs that would be produced in the reaction of allylidenemethyldibenzophosphole with cyclohexanecarboxaldehyde were independently synthesised in separate experiments by deprotonation of *erythro* and *threo* β-HPSs **11** and **12** respectively (see Chart 2).[60] Similarly, the *cis* and *trans*-OPAs from the reaction of benzylidenemethyldibenzophospole with cyclohexanecarboxaldehyde were obtained by deprotonation of β-HPSs **13** and **14** respectively (see Chart 2). Each deprotonation experiment gave a single OPA (as evaluated by low temperature ^{31}P NMR), which decomposed stereospecifically to the expected alkene isomer – i.e. *erythro* β-HPS gave *Z*-alkene, and *threo*-β-HPS gave *E*-alkene. These experiments prove that there is no equilibration of either the betaine or of the OPA which are each necessarily formed in the path from β-HPS to alkene. The corresponding Wittig reaction must occur under kinetic control, since the formation of each of the possible intermediates is irreversible.

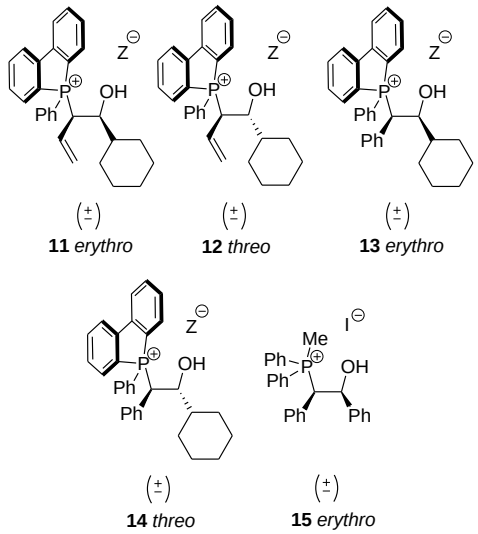


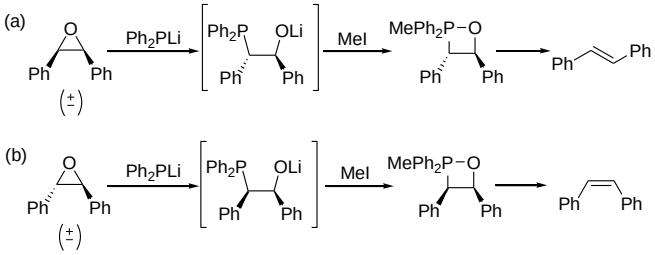
Chart 2. β-hydroxyphosphonium salts used for the independent OPA generation experiments described in references 60 and 86. Counter-ion Z is iodide or triflate (trifluoromethanesulphonate).

Kinetic control has also been shown indirectly to be in operation in the reactions of *unconstrained* semi-stabilised ylides (i.e. where the phosphorus atom of the ylide is not part of a ring system), although as alluded to above, observation of the transient OPA intermediate by NMR is not possible in these cases. Thus, deprotonation of (2-hydroxy-1-phenyl-2-phenyleth-1-yl)methyldiphenylphosphonium iodide **15** with each of *n*-BuLi, NaHMDS and KHMDS gave *Z*-alkene stereospecifically.[86] Treatment of stilbene oxide with lithium diphenylphosphide gave a β-oxidophosphine intermediate, which was quaternised with methyl iodide, resulting in the formation of alkene, presumably by transient formation of a betaine which then underwent ring-closure to OPA as shown in Scheme 17.[96] The process was shown to proceed with inversion – *trans*-stilbene oxide gave *Z*-stilbene, and *cis*-stilbene oxide gave *E*-stilbene.

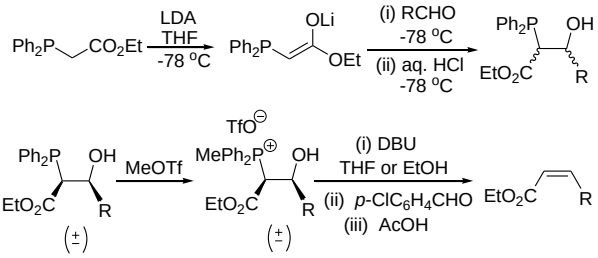
These results show that there is no inter-conversion of OPA intermediates derived from semi-stabilised ylides that have been generated by non-Wittig processes (and also that there is no interconversion of the associated betaines, whether they are involved in the Wittig mechanism or not). This confirms that both OPA formation and OPA decomposition to alkene and phosphine oxide are irreversible, at least in the case of Wittig reactions of *P*-phenyl-5*H*-dibenzophosphole-derived semi-stabilised ylides, and also most significantly in the case of Wittig reactions of unconstrained methyldiphenylphosphine-derived ylides with benzaldehyde.

(iii) Ester-stabilised ylides

No OPAs derived from stabilised ylides have ever been detected by NMR, not even dibenzophosphole derived ones. Consequently, proof for the operation of kinetic control in reactions of these ylides rests on the demonstration of stereospecific conversion of *erythro* or *threo* β-HPS to *Z* or *E* alkene, respectively. *erythro*-β-HPSs (reviewer says to capitalise e, but I'm not sure that's right – could avoid the problem by putting "The" at the start of the sentence?) derived from primary, secondary, tertiary, and aromatic aldehydes and ester stabilised ylide (ethoxycarbonylmethylidene)methyldiphenylphosphorane were obtained by addition of phosphino-enolate [$Ph_2PCHCOOEt$]Li to aldehyde followed by acid quenching to



Scheme 17. Stereospecific conversion of (a) *cis*-stilbene oxide to *E*-stilbene and (b) *trans*-stilbene oxide to *Z*-stilbene by nucleophilic ring cleavage and quaternisation of the resulting β-oxidophosphine.



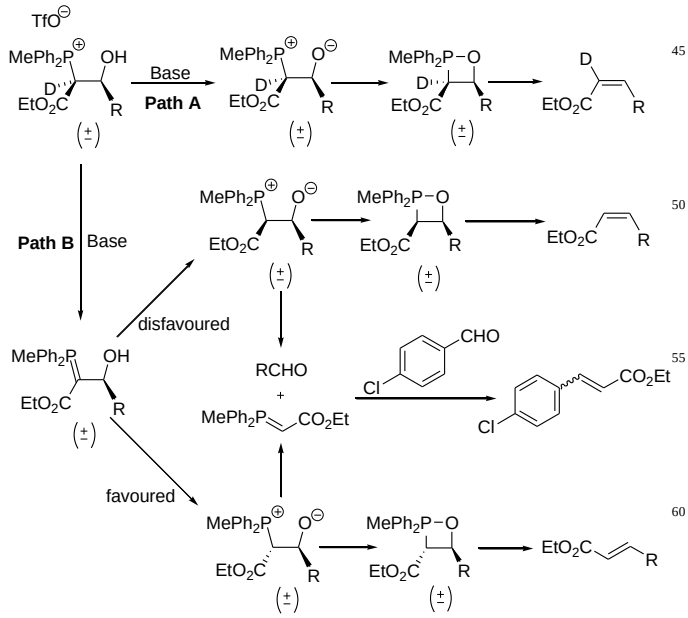
Scheme 18. Synthesis of β-hydroxyphosphine, and hence β-HPS corresponding to the acid quench product of a Wittig reaction of a stabilised ylide, and stereospecific conversion of the *erythro*-β-HPS to *Z*-alkene. R = Ph, CH_2CH_2Ph, *c*-C_6H_{11}, or CMe_2CH_2Ph.[60]

give β-hydroxyphosphine, as shown in Scheme 18. The *erythro*-β-hydroxyphosphine was isolated by column chromatography and then quaternised with methyl triflate to give *erythro*-β-HPS.[60]

Deprotonation experiments using the β-HPSs thus obtained were carried out in THF and ethanol. DBU (1,8-diazabicyclo[5,4,0]undec-7-ene), mesityllithium and KHMDS bases were used in separate experiments. Two equivalents of *p*-chlorobenzaldehyde were added to the reaction mixture 30 seconds after the addition of base. This aldehyde reacts with any ylide produced by potential reversal of OPA or betaine to Wittig starting materials, thus preventing recombination of the reactants derived from reversal. Delayed addition of *p*-chlorobenzaldehyde prevented it from exerting any effect on the betaine that is necessarily transiently produced in β-HPS deprotonation. High yield and stereospecificity and negligible crossover were observed in the conversion of the *erythro*-β-HPSs to *Z*-alkene (*Z*/*E* ≥ 98:2) using DBU as base for the cases with R = CH_2CH_2Ph, *c*-C_6H_{11}, or CMe_2CH_2Ph. Greater production of each of crossover alkene and *E*-cinnamate was observed in the case with R = Ph. In deprotonation experiments at 20 ˚C using KHMDS in THF, the production of crossover product was observed to have increased relative to the experiments with DBU – 8% for the case with R = CH_2CH_2Ph, 5% for R = *c*-C_6H_{11}, 23% for R = CMe_2CH_2Ph and 48% for R = Ph. The production of crossover alkene showed that ylide derived from some form of reversal to Wittig starting materials had to have been present. *E*-Cinnamate could not have resulted from any OPA or betaine reversal process since ylide would have been intercepted as crossover product, and it was shown not to result from isomerisation of the *Z*-cinnamate under the reaction conditions.

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The pathway by which crossover product and *E*-alkene were formed was elucidated using α-deuterated *erythro*-β-HPSs (see Scheme 19). Under "strong base conditions", deprotonation of α-



Scheme 19. Experiments on α-deuterated *erythro*-β-HPSs. R = Ph, CH_2CH_2Ph, *c*-C_6H_{11}, or CMe_2CH_2Ph.[60]

deuterated *erythro*-β-HPS at low temperature (-78 ˚C) yielded a very high proportion of *Z*-alkene with high deuterium content, while at higher temperatures a much lower proportion of *Z*-alkene was produced, *and* its deuterium content was also much lower. Most significantly, no deuterium could be detected under any circumstances in the *E*-alkene or crossover alkene. None of these observations are consistent with reversal of the betaine or OPA produced by β-HPS deprotonation, because if this was undergoing reversal then the *E*-alkene or crossover alkene should show some deuterium content.

In explanation of the experimental observations (see Scheme 19), it was proposed that the base can remove either the hydroxyl proton (**path A**) or the α-deuterium (**path B**). In the former case, the betaine formed reacts to give *cis*-OPA and hence *Z*-cinnamate with full deuterium content. In the latter case, a β-hydroxy ylide (that has lost its deuterium) results, which can undergo proton transfer (by an unknown mechanism) to either face of the β-hydroxy ylide yielding *erythro* or *threo* betaine (the latter being favoured). This can either undergo ring closure to give *cis* or *trans*-OPA and hence deuterium-free *Z*- or *E*-alkene, respectively, or can revert to ylide and aldehyde and hence to crossover alkene. Dedeuteration is more likely at higher temperature (due to poorer discrimination of acidic sites by the base), so that more of each of the crossover product and the *E*-alkene are observed. There is also a lower proportion of deuterium in the *Z*-alkene that is produced, as some of it is derived from non-deuterated *erythro*-betaine, which is itself derived from β-hydroxy ylide. The fact that the *Z*-alkene alone retains the deuterium label in these experiments confirms that *cis*-OPA is formed irreversibly and that it undergoes stereospecific decomposition to *Z*-alkene. This means that OPA is necessarily the final intermediate in the Wittig reaction of stabilised ylides, regardless of how it is formed.

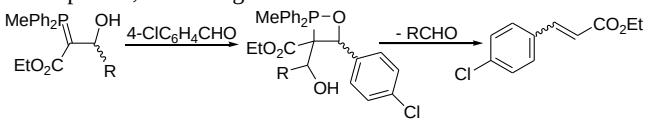
That crossover alkene is produced in these deprotonation experiments (especially the ones involving strong base) indicates that it is highly likely that some ylide is present after deprotonation has occurred. It has been explained above how it was shown that this ylide *cannot* be derived from OPA. If formed, it must thus result from C-C bond scission in either the betaine or the β-hydroxy ylide. There is no definitive evidence to prove which entity undergoes reversal to ylide and aldehyde. Betaine reversal is not an issue for the *erythro*-betaine produced by hydroxyl deprotonation of the initial *erythro*-β-HPS, as proved by the complete absence of deuterium labelled *E*-enoate in all cases, but based on the above results, it is in principle possible. If betaine reversal does occur, a possible explanation given by Vedejs and Fleck[60] is that β-HPS deprotonation by weak base (e.g DBU) produces a *syn*-betaine rotamer that can easily cyclise to OPA, whereas proton transfer involving a β-hydroxy ylide or β-HPS deprotonation by strong base (e.g. KHMDS) may produce rotamers that are more prone to reversal to Wittig starting materials.

It may be assumed that betaine (whether produced as *syn* or *anti* rotamer) is energetically uphill from Wittig starting materials based on its apparent readiness to decompose to ylide and aldehyde or to alkene and phosphine oxide *via* OPA. Certainly OPAs produced in Wittig reactions of non-stabilised and semi-stabilised ylides have been demonstrated to be the only observable intermediates in those reactions, so in these cases, OPA is more stable than betaine. Since *cis*-OPA is shown by the above experiments to be formed irreversibly, and to decompose very quickly to alkene and phosphine oxide, *E*-selectivity in reactions of stabilised ylides cannot be the result of the decomposition of *trans*-OPA being more rapid than that of *cis*-OPA. The remaining possibility for involvement of betaine in reactions of stabilised ylides requires that they equilibrate *via* ylide and aldehyde, and that ring closure for *threo*-betaine is kinetically preferred compared to that for the *erythro* isomer. This would require there to be a large energy barrier between betaine and OPA. In light of the rapidity of alkene formation in β-HPS deprotonation experiments, and of the fact that the first step of Wittig reactions of stabilised ylides (the bimolecular step) is rate-limiting, this seems highly unlikely. All signs indicate the operation of kinetic control in reactions of stabilised ylides. Since the betaine mechanism cannot account for high *E*-selectivity under kinetic control, it can be concluded that it is not in operation in reactions of stabilised ylides.

Another (perhaps less likely) possibility for the formation of crossover product is that the β-hydroxy ylide itself perhaps might undergo a Wittig reaction with the *p*-chlorobenzaldehyde, giving the OPA shown in Scheme 20. This OPA can give crossover alkene either directly by elimination of the non-crossover aldehyde, or by forming β'-hydroxy enoate, which could itself eliminate aldehyde. This suggestion might be outlandish enough – elimination of aldehyde RCHO from the β'-hydroxy enoate derived from the OPA of Scheme 20 - i.e. transient formation of an allenolate – folllowed by protonation of the allenolate to give the crossover enoate.

Since the β-hydroxy ylide pathway can not be involved in a normal Wittig reaction, and since it plays at most a minor role in stabilised ylide-derived β-HPS deprotonation experiments in the

absence of strong base, it may be concluded that *erythro*-β-HPSs derived from stabilised ylides decompose stereospecifically to *Z*-alkenes upon deprotonation. Thus, the typically observed high *E*-selectivity in Wittig reactions of ester-stabilised ylides results from a kinetic preference for the formation of *trans*-OPA (i.e. the pathway leading to *E*-alkene), since OPA decomposition to alkene & phosphine oxide is shown by these results to be stereospecific, and is in general irreversible. Irreversible



Scheme 20. Postulated mechanism for the formation of crossover alkene by a Wittig reaction of β'-hydroxy ylide.

formation of *trans*-OPA in reactions of stabilised ylides can be inferred from the fact that *cis*-OPA is formed irreversibly, since *trans*-OPAs are generally thermodynamically favoured over *cis*-OPA and decompose more slowly than *cis*-OPAs (with few exceptions),[87] indicating a greater barrier to cycloreversion for *trans*-OPAs.

(iv) Further evidence for kinetic control in Wittig reactions of all ylide types

Based on the material presented in sections (i) to (iii) above, it can be concluded that *any* Wittig reaction that forms predominantly *Z*-alkene is under kinetic control, regardless of whether irreversibility of OPA formation has been explicitly demonstrated. There are many examples in the review of Vedejs and Peterson[4] of highly *Z*-selective Wittig reactions which are thus irreversible.

Very recently, we have shown that reactions of both aromatic and aliphatic aldehydes bearing a β-heteroatom substituent systematically show very high selectivity for *Z*-alkene (or its precursor, *cis*-OPA) in their reactions with non-stabilised, semi-stabilised and ester-stabilised ylides.[38] Control reactions of analogous aldehydes lacking the suitably-placed heteroatom with the same ylides show much lower selectivity for *Z*-alkene, and in fact in many cases these reactions are *E*-selective. The existence of this counter-intuitive effect that is common to all three ylide types indicates that not only are the reactions of these ylides irreversible, but, more significantly, that they have a common mechanism.

That the results involving the β-heteroatom-substituted aldehydes mentioned above is indicative of general irreversibility of OPA formation in the Wittig reaction of all ylide types may be demonstrated by the following argument: Let us assume that any *E*-selective Wittig reaction is so as a consequence of reversible formation of *cis*-OPA. The activation barrier for cycloreversion of *cis*-OPA to ylide + aldehyde ($\Delta G^{\ddagger}_1$ in Fig. 7) must therefore be surmountable. In the reactions of the β-heteroatom substituted aldehydes, the free energy of the reactants and OPA intermediates is similar to that of the analogous species in reactions where the aldehyde lacks a heteroatom substituent. If it is correct, as seems likely, to assume that the *cis*-OPA is thermodynamically disfavoured relative to the *trans*-isomer in these reactions, then the energy of the *cis*-selective TS on the path from reactants to OPA must be lower than in the *E*-selective reactions. Therefore the activation barrier for cycloreversion of *cis*-OPA to ylide + aldehyde in reactions of β-heteroatom substituted aldehydes ($\Delta G^{\ddagger}_2$ in Fig. 7) is *lower* than in the *E*-selective reactions. If OPA reversal was a significant factor in the stereoselectivity of the *E*-selective reactions, then reactions of β-heteroatom substituted aldehydes should also be *E*-selective, but to an even greater extent.

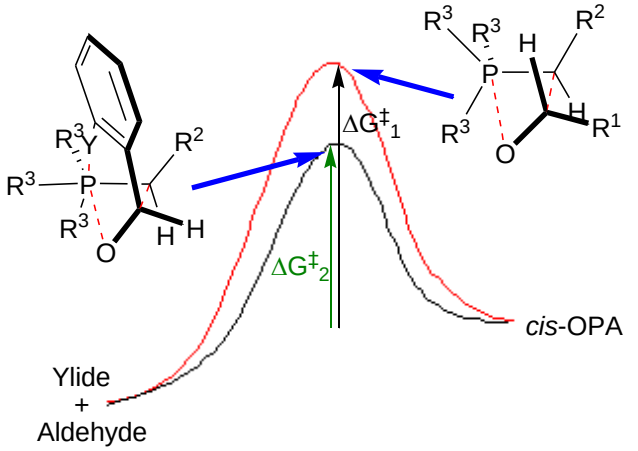


Fig. 7. Reaction coordinate diagrams for formation of *cis*-OPA in Wittig reactions of stabilised ylides, with diagrams of TS geometries.

4.2. The nature of the first formed intermediate in the Wittig reaction

The non-involvement of betaine intermediates (or spin-paired diradical C-C bonded species proposed by McEwen and co-workers)[86] in Wittig reactions of non-stabilised ylides has been conclusively demonstrated using a phenyldibenzophosphole-derived ylide, *iso*-propylidenephenyldibenzophospholane (see Schemes 21 & 22).[74] The OPA derived from this ylide can be detected by NMR. It is pseudorotationally restricted because of the high ring strain that would be induced if the five-membered ring were forced to span two equatorial sites. The two possible OPA pseudorotamers that have the five-membered ring spanning axial and equatorial sites interconvert sufficiently slowly at low temperature that they can be distinguished by ^{31}P NMR. Their equilibrium pseudorotameric ratio was established by observation of the ^{31}P NMR of the Wittig reaction of *iso*-propylidenephenyldibenzophospholane and 3-phenylpropanal at –78 ˚C in Et_2O (see Scheme 21) to be 1.8:1. The kinetic OPA pseudorotameric ratio (initial ratio) for this Wittig reaction in Et_2O was observed to be 6.5:1 by the addition of the aldehyde to the ylide at –109 ˚C, and subsequent ^{31}P NMR observation of the reaction mixture at –78 ˚C.

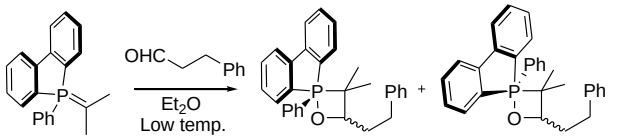
The kinetic OPA pseudorotameric ratio produced in the deprotonation of the corresponding β-HPS in Et_2O at –109 ˚C (see Scheme 22), which must necessarily proceed through a betaine, was also observed by ^{31}P NMR at –78 ˚C, and was found to be 1:4.2 - different from the kinetic pseudorotameric ratio produced in the Wittig reaction, and also from the equilibrium ratio of the pseudorotamers at this temperature.

The kinetic OPA pseudorotameric ratios were also determined in a similar manner for this reaction at low temperature in THF and CH_2Cl_2. In each case, the ratio was found to be different for the OPA formed by Wittig reaction compared to that formed by β-HPS deprotonation. That a different kinetic pseudorotameric ratio is produced in each instance shows that the formation of

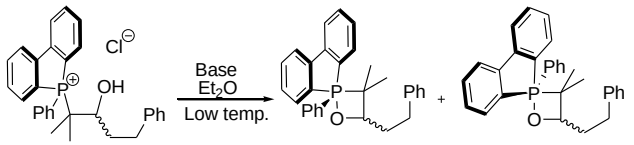
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OPA by Wittig reaction does not occur through a betaine intermediate, at least in the case of these non-stabilised ylides.

In addition to this very conclusive direct evidence that OPAs are the first-formed and only intermediates in Wittig reactions, the very substantial evidence presented above for the operation of kinetic control in Wittig reactions can itself be interpreted as



Scheme 21. Wittig reaction of *iso*-propylidenephenyldibenzophospholane with 3-phenylpropanal to give OPA pseudorotamers that are distinguishable by NMR.



Scheme 22. β-HPS deprotonation to give OPA pseudorotamers that are distinguishable by NMR.

evidence for this same thing. Experiments that necessarily produce betaines and hence OPAs by processes independent of the Wittig reaction have been shown to result in stereospecific conversion to alkene. Since high *E*-selectivity (or high selectivity for *trans*-OPA) in a kinetically controlled process cannot be accounted for within the context of the betaine mechanism, it must be discounted as a possible mechanism for the Wittig reaction.

As a final point, it should also be noted that in the betaine mechanism, there is no easy way to account for the influence of the substituents at phosphorus on the selectivity in reactions of each ylide type.

4.3. Oxaphosphetane structure and cycloreversion mechanism

Westheimer's rules on apical entry and departure requires that any bond made to phosphorus to form a trigonal bipyramidal species must initially place the new substituent in an apical site, and that upon departure of a substituent from a trigonal bipyramidal species the bond broken must be to a substituent in an apical site.[99] Trigonal bipyramidal species are stabilised to the greatest extent possible if the most electronegative atom(s) occupy the apical sites. This arrangement of the substituents results in the HOMO being as low in energy as is possible.[100] Based on these concepts, the most stable OPA pseudorotamers should have oxygen in an apical site, and formation of OPA in the Wittig reaction should (at least initially) give a pseudorotamer of OPA with apical oxygen. Furthermore, decomposition of OPA to alkene and phosphine oxide by breakage of the P-C and C-O bonds must involve an entity in which ring carbon-3 (formerly the ylide α-carbon) is in an apical site and therefore, necessarily, oxygen is in an equatorial site. It has long been thought that this set of constraints necessitated the formation of a *second* OPA intermediate (with apical C) from the initially formed O-apical OPA by a pseudorotation process.[3] The available computational evidence indeed suggests that the formation of a C-apical OPA is necessary.[42] A C-apical OPA should be less stable than one with apical oxygen, for the reason stated above, and certainly no C-apical OPA has ever been observed spectroscopically in the course of a Wittig reaction. Vedejs & Marth have questioned whether the formation of any particular pseudorotamer (or set of pseudorotamers) is essential to the mechanism of decomposition of the initially formed O-apical OPA.[90]

Recently, Lamertsma & co-workers have shown that permutation of ligands in trigonal bipyramidal species may occur *in a single step* by processes that are comprised of multiple consecutive Berry pseudorotations.[91,101,102] González, López-Ortiz & co-workers have shown that one or more of these single step mechanisms is highly likely to operate in the interconversion (stereomutation) of OPAs very similar to those produced in typical Wittig reactions.[40] Although there exists at least one example of a Wittig reaction of a chiral ylide in which the chirality of the phosphorus centre is retained in the phosphine oxide product,[79] the implication of the results of González, López-Ortiz & co-workers is that retention of configuration at phosphorus is unlikely in any Wittig reaction in which OPA stereomutation is faster than OPA decomposition.[40] Of even greater significance is that the same group have shown computationally that OPA cycloreversion may occur in a single step without the need for the formation of a C-apical OPA *intermediate*. If this is the case, then the C-apical OPA would not be a local minimum on the reaction coordinate, but would still occur on the pathway from O-apical OPA to the cycloreversion TS. In either case, the TS for the cycloreversion process would be a *pseudo*-trigonal-bipyramidal entity with the (elongated) P-C bond in an apical position. The computational and experimental activation parameters for the decomposition of the OPA were found to agree closely with each other, lending support to the single step mechanism.[40]

Below is presented the experimental data that has been amassed pertaining to the structure of OPAs produced in Wittig reactions and to OPA pseudorotation.

Vedejs and Marth were able to resolve signals due to two different pseudorotamers of a dibenzophosphole-derived OPA (see Chart 3 structures **16** and **17**) by low temperature ^{1}H NMR, and to prove that these pseudorotamers had oxygen in the apical position.[90] This was established by an evaluation of the one bond coupling ^{13}C-^{31}P constants $^{1}J_{PC}$ in the ^{13}C NMR for the phosphorus-bound carbons in the dibenzophosphole unit. In such a system there must necessarily be one carbon apical and one equatorial. Indeed, by low temperature ^{13}C NMR, there appear three signals for quaternary aromatic carbons with small coupling constants to phosphorus (less than 20 Hz) – diagnostic of aromatic carbons in an apical position[103] or not directly joined to phosphorus and thus not in the trigonal bipyramid – and a fourth quaternary aromatic carbon showing coupling to phosphorus of 132 Hz. The latter is characteristic of an sp^2-hybridised equatorial carbon in a phosphorus-centred trigonal bipyramid.[103] The OPA ring carbon (δ 54.5) decisively shows $^{1}J_{PC}$ = 82 Hz, which is indicative of an equatorial aliphatic (sp^3) carbon in a phosphorus-centred trigonal bipyramid. This means that the most stable OPA in solution has either the structure **16** or **17** in Chart 3, but not structure **18**. In a separate publication, Vedejs and Marth disclosed the resolution by low temperature ^{1}H and ^{31}P

NMR of signals due to two different pseudorotamers of another DBP-derived OPA (shown above in Scheme 21),[74] for which the presence of an apical oxygen was established. This data was used by Vedejs & Marth,[74] and by ourselves,[38] to establish that other dibenzophosphole-derived OPAs (**19**-**23** in Chart 3) as well as some examples of unconstrained OPAs are also likely to have

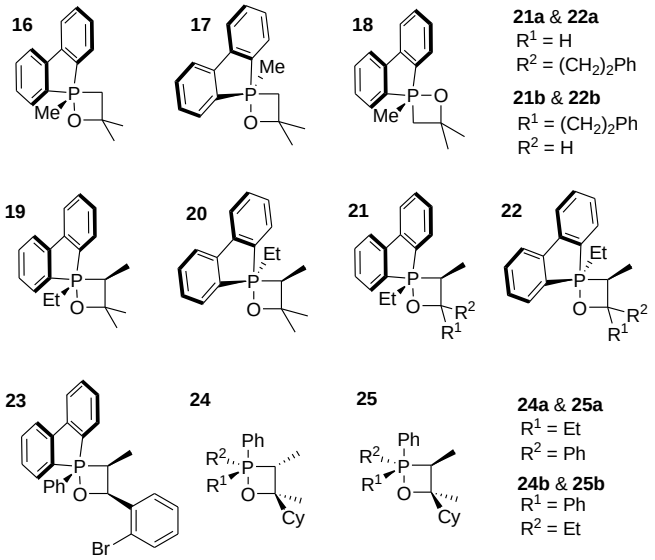


Chart 3. Dibenzophosphole-derived OPAs **16**-**23**,[38,90] and ethyldiphenylphosphine-derived OPAs **24** and **25**.[93]

oxygen in the apical position in their favoured solution pseudorotamer(s). Other spectra collected on unconstrained OPAs with the ylide α-carbon ^{13}C labelled show $^{1}J_{PC}$ values of very similar magnitude for carbon-3 in the OPA ring.[70]

Bangerter *et. al.* resolved signals due to pseudorotameric OPAs **24a** and **24b** (see Chart 3), and in a separate experiment those of the same for OPA pseudorotamers **25a** and **25b** by low temperature ^{31}P NMR.[93] They established a $^{1}J_{PC}$ value of 86.7 Hz for ring carbon-3 in OPAs **25a** and **25b**, thus showing that the dominant solution structure for these OPAs has oxygen in an apical site.[103] The $^{1}J_{PC}$ values for the *P*-ethyl group of **25a** and **25b** labelled with ^{13}C at the methylene group were determined to be 92.4 and 106.8 Hz respectively. These values are characteristic of an equatorial sp^3-hybridised group,[103] which leads to the conclusion that the alkyl group is preferentially placed in an equatorial position in both pseudorotamers.[93]

In the studies of Vedejs and Marth[74,90] and Bangerter *et. al.*,[93] the rate of pseudorotation of each OPA was established by line shape analysis of variable temperature NMR spectra of the resolved OPA pseudorotamers. It was concluded that in each case the rate of OPA pseudorotation is too fast relative to the rate of OPA decomposition to have any effect on the decomposition rate.

The pseudorotameric forms of dibenzophosphole-derived OPAs that have the P-O bond and one of the 5-membered ring P-C bonds in the apical positions of the phosphorus-centred trigonal bipyramid are very strongly favoured thermodynamically over other possible pseudorotamers.[*h*] There are only two pseudorotamers of any dibenzophosphole-derived OPA that satisfy these constraints on the positioning of the phosphorus-substituents, and hence a maximum of two major signals only should be expected (and are observed) in the ^{31}P NMR spectra of these OPAs. For example, pseudorotamers **19** and **20** are the two possibilities for the OPA produced in the reaction of (ethylidene)ethyldibenzophosphole with acetone (see Chart 3). The ^{13}C NMR spectrum of this OPA (**19**/**20**) contains only one set of signals.[90] This can mean either that **19** and **20** are undergoing rapid interconversion in solution or that one of these two OPA pseudorotamers is heavily favoured in solution. Other OPAs (**21a**/**22a** and **21b**/**22b**, see Chart 3) also only show a single set of signals by ^{13}C NMR. Since the pseudorotamers of OPAs very similar to these can be resolved by low temperature NMR, Bangerter *et. al.*[93] concluded that in the case of each of the OPAs **19**/**20**, **21a**/**22a** and **21b**/**22b**, one of the two possible pseudorotamers is predominant in solution, and that the pseudorotamers do not interconvert rapidly at low temperature.

4.4. How does the observed selectivity for *Z* or *E* alkene in the Wittig reaction arise? An explanation of how the currently accepted mechanism explains the stereoselectivity.

(i) Summary of experimental evidence:

(a) OPAs are the only observable intermediates in reactions of non-stabilised ylides.

(b) Betaines and diradical species have been proven not to play a part in the reactions of these ylides.

(c) Stereospecific conversions of *erythro* and *threo* betaines that would be derived from semi-stabilised ylides (generated either from β-HPSs or epoxides) to *Z* and *E* alkene respectively have been demonstrated.

(d) Stereospecific conversion of dibenzophosphole-derived *erythro*-β-HPS to *cis*-OPA (which would be formed from semi-stabilised ylide) by deprotonation (presumably via *erythro*-betaine) and hence *Z*-alkene has been observed by low temperature NMR. This has also been done for the conversion of *threo*-β-HPS to *E*-alkene. A DBP-derived OPA has also been observed in the case of one Wittig reaction of a semi-stabilised ylide, and was demonstrated to undergo stereospecific decomposition to alkene and phosphine oxide.

(e) Stereospecific conversion of *erythro*-betaines derived from stabilised ylides (and generated from *erythro*-β-HPSs) to *Z*-alkenes has also been observed.

(f) It seems safe to assume that conversion of *trans*-OPA derived from stabilised ylides to *E*-alkene is irreversible and stereospecific, since *E*-alkene formation is generally very favoured in such reactions, and also *trans*-OPAs are typically more stable than their *cis* counterparts.

(g) OPAs are obligatory at some point along the Wittig reaction coordinate (either as intermediates or TSs). Decomposition of OPA derived from non-stabilised ylides has been shown to occur at the same rate as alkene formation. OPAs derived from all three types of ylide has been shown to decompose irreversibly and stereospecifically. Thus it has been shown that OPA is the final intermediate in the Wittig reaction (regardless of how it is formed).

(h) The betaine mechanism cannot account for kinetic *E*-selectivity.

(i) These facts, all together, strongly suggest that OPAs are the

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first-formed and only intermediates formed in Li-salt free Wittig reactions.

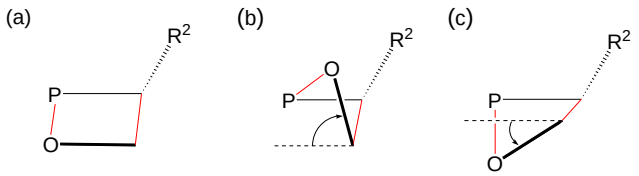


Fig. 8. (a) Planar TS with puckering angle of 0°, (b) TS with positive puckering angle, (c) TS with negative puckering angle.

(ii) Selectivity in reactions of non-stabilised ylides

By the convention employed in the paper of Aggarwal, Harvey and coworkers,[42] when the ylide P=C bond and the aldehyde C=O bond are parallel (i.e. a planar TS), the puckering angle of the TS is defined as 0° (see Fig. 8(a)). If the dihedral angle between the carbonyl C=O bond and the ylide C-R^2 bond is smaller than the corresponding angle in the planar TS (see Fig. 8(b)), then the TS puckering angle is positive. If the dihedral angle is greater than in the planar TS, then the TS puckering angle is negative (see Fig. 8(c)).

The following is Vedejs's rationale for the mechanism of the Wittig reaction of non-stabilised ylides.[89] Alkylidenetriphenylphosphoranes (non-stabilised ylides) react preferentially through an early, puckered, transition state in which the carbonyl substituent occupies a *pseudo*-equatorial position (see Fig. 9(a)). The forming P-O and C-C bonds are long, and rehybridisation about the ring atoms is not particularly advanced. In this lowest energy TS, the puckering angle is *positive*. This arrangement minimises steric interactions between the carbonyl substituent and the *P*-phenyl groups (referred to as "1-3 interactions", with the numbering of the ring positions as shown in Fig. 9), which are still in a pseudo-tetrahedral arrangement about phosphorus. It also results in the minimisation of steric interactions between the carbonyl substituent and the ylide substituent ("1-2 interactions"), and allows the forming P-O bond to avoid the *P*-phenyl group that is necessarily projecting in the direction of carbonyl approach to the ylide. The steric interactions of the ylidic substituent R^2 with the carbonyl substituent ("1-2 interactions") and with the *P*-phenyl groups ("2-3 interactions") are minimised if it is in a pseudo-axial site, as shown in Fig. 9(a), and hence this TS leads to *cis*-OPA and *Z*-alkene. Calculations on the Wittig reaction of Ph_3P=CHMe and MeCHO at the B3LYP/6-31G*(THF) level of theory (employing a continuum solvent with the dielectric properties of THF) confirm this to be the lowest energy TS, and indicate that there may be a stabilising hydrogen bonding interaction between the aldehyde oxygen and one of the *P*-phenyl C-H bonds in *both* diastereomeric TSs.[42]

In contrast to the *cis*-selective TS, there is no clear picture of the precise geometry of the lowest energy *trans*-selective TS in reactions of alkylidenetriphenylphosphoranes. A possible puckered *trans*-selective TS with the ylide α-carbon substituent in a pseudo-equatorial site (Fig. 9(a) with R^2 and H swapped at carbon-2) would suffer from large 1-2 interactions and hence would be disfavoured relative to the *cis*-selective TS. A possible planar *trans*-selective TS is shown in Fig. 9(b). Like the *cis*-selective TS described above, bond formation and rehybridisation about the ring atoms are each not particularly advanced – so the TS is early. 1-2 steric interactions between the carbonyl substituent and the ylide α-carbon substituent are avoided in this

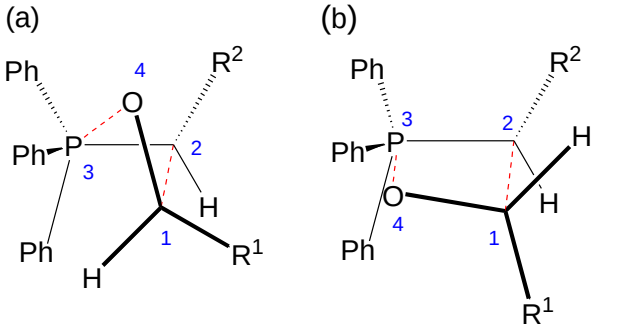


Fig. 9. Cycloaddition TSs leading to OPA in Wittig reactions of alkylidenetriphenylphosphoranes: (a) kinetically favoured *cis*-selective cycloaddition TS showing a *positive* angle of puckering, with R^2 in a pseudo-axial site and R^1 in a pseudo-equatorial site; (b) lowest energy *trans*-selective TS. R^1 is the large carbonyl substituent, and R^2 is the large ylide α- substituent.

TS due to the *trans* arrangement of these substituents. However, it is less stable than the *cis*-selective TS because one of the *P*-phenyl groups encumbers the approach of the carbonyl oxygen to phosphorus, and because of large 1-3 steric interactions between the carbonyl substituent R^1 and one of the *P*-phenyl groups. As with the *cis*-selective TS there may exist hydrogen bonding between the carbonyl oxygen and a *P*-phenyl C-H in this TS.[42]

It is postulated that the OPAs form irreversibly (as has been very comprehensively shown experimentally), and decompose stereospecifically to alkene and phosphine oxide by [2+2] cycloreversion, so stereoselectivity is decided in the cycloaddition step. The computational results of Aggarwal, Harvey & coworkers[42] on the reaction of Ph_3P=CHMe + MeCHO indicate that *cis*-OPA is less thermodynamically stable than the *trans*-OPA due to increased 1-2 steric interactions in the former, and that OPA formation is exothermic. The barrier to OPA cycloreversion to alkene and phosphine oxide is found to be higher for *cis*-OPA than for *trans*-OPA. Based on this, it can be surmised that in some circumstances the barrier to cycloreversion to alkene and phosphine oxide for *cis*-OPA is similar to the barrier to reversal to ylide and aldehyde. This may provide an explanation for the observation of stereochemical drift in certain reactions of alkylidenetriphenylphosphoranes – in particular those with aromatic aldehydes.[65,92]

Non-stabilised ylides for which one or more of the *P*-phenyl groups are replaced by alkyl group(s) show much lower *Z*-selectivity than alkylidenetriphenylphosphoranes;[4] in the context of the cycloaddition mechanism this is explained by decreased 1-3 interactions and thus a to lower propensity to cycloaddition TS puckering. Computational results on the reaction of Me_3P=CHMe + MeCHO (B3LYP/6-31G* (THF)) indicate that both the *cis* and *trans*-selective cycloaddition TSs are planar, and very similar in energy – the role of 1-2 steric interactions does not particularly militate against the *cis*-selective TS in this case due to the very long forming bonds in an early TS.[42] In reactions of alkylidenetrialkylphosphoranes with tertiary or aromatic aldehydes, an extra factor (stereochemical drift – see section 4.1

part (i)) is known to be at play in the experimentally observed *E*-selectivity. The *cis*-OPA is believed to undergo reversal to ylide and aldehydes, while the *trans*-OPA does not. [68,92]and thus *trans*-OPA accumulates and gives rise to *E*-alkene. The computational study, referred to earlier, found that the kinetic barriers to *cis*-OPA cycloaddition and reversal to ylide and aldehyde were similar, which is consistent with the experimentally observed depletion of this intermediate. The lower *Z*-selectivity in reactions of alkyldiphenylphosphine-derived ylides compared to alkylidenetriphenylphosphoranes is, however, truly dependent on the energetic discrimination of the TSs in the OPA forming cycloaddition step, as irreversible OPA formation has been proven for such ylides.[68] Thus in those reactions, the higher *E*-selectivity reflects an increased kinetic advantage (or decreased kinetic disadvantage) for *trans*-OPA formation.

A further aspect of the currently accepted mechanism for Wittig reaction of non-stabilised ylides has to do with pseudorotation of the OPA intermediate. The OPA formed by the cycloaddition step is postulated to have the oxygen in the apical position, in accordance with Westheimer's rule on apical entry and departure for a phosphorus-centred trigonal bipyramid.[99] This OPA, (which could be any one of a number of pseudorotamers with apical oxygen) is proposed to undergo rapid pseudorotation to a less stable pseudorotamer with ring carbon-3 in an apical position, and the ring oxygen in an equatorial site. This pseudorotamer undergoes [2+2] cycloreversion to alkene and phosphine oxide. The computational work of Aggarwal, Harvey & co-workers is consistent with the operation of this process. [42]

Calculations on the reactions of MeCHO with Ph_3P=CHMe and Me_3P=CHMe respectively show that betaines are significantly higher in energy than OPAs and likewise TSs involving *anti* addition of the reactants (in the style of an aldol reaction to form an *anti*-betaine) are higher in energy than cycloaddition TSs.[42]

The cycloaddition mechanism of Vedejs for the Li-salt free Wittig reaction of non-stabilised ylides – that being direct, irreversible cycloaddition of ylide and aldehyde to give OPA, followed by facile pseudorotation of the OPA and then by irreversible, stereospecific [2+2] cycloreversion of OPA to alkene and phosphine oxide – is consistent with the following facts:

- OPA formation has been shown to be irreversible, [68,69,93] and the OPA *cis/trans* ratio corresponds to the *Z/E* ratio of the alkene ultimately obtained from the reaction. [68,69,93] This implies that the stereoselectivity is determined in the OPA forming step. OPA decomposition has been shown to occur at the same rate as alkene formation for reactions of alkylidenetriphenylphosphoranes. [68,69,70,93] Thus OPA is the final intermediate formed in the Wittig reaction, and phosphine oxide is formed by *syn*-elimination.
- Tests for the involvement of radicaloids or ionic species (betaines) indicate that neither type of species play a part in the Wittig reaction.
- OPA accumulates during the reaction, and OPA decomposition is the final step of the reaction. Therefore this step is rate-determining. It has been observed that reactions of non-stabilised ylides with benzaldehydes have ρ values for the carbonyl component of 0.2 to 0.59.[57,104,105] A kinetic isotope effect of 1.053 has also been observed in the Wittig reaction of *iso*-propylidenetriphenylphosphorane with benzophenone with a ^{14}C-labelled carbonyl group.[57] Thus in the rate-determining step the bonding is changing at the carbonyl carbon. The decomposition of each of the *cis* and *trans* OPAs (independently generated form β-HPSs) derived from (ethylidene)ethyldiphenylphosphorane and cyclohexyl methyl ketone has been shown to be first order, and to have a positive entropy of activation.[93] The results from investigations on the kinetics of reactions of non-stabilised ylides thus support the operation of a rate-determining cycloreversion as the final step of the reaction.
- *Z*-selectivity increases in line with the increasing steric bulk of the aldehyde in reactions with a common ylide; so tertiary aldehydes show higher *Z*-selectivity than secondary aldehydes, which show higher selectivity than primary aldehydes. Likewise, increasing the steric bulk on the *P*-phenyl groups of triphenylphosphine-derived ylides (e.g. using tri(*ortho*-tolyl)phosphine derived ylides) results in increased *Z*-selectivity. Thus, the factors that should exacerbate the need to relieve 1-3 steric interactions in a puckered cycloaddition TS show increased *Z*-selectivity, as this mechanism would predict.
- The rate of OPA pseudorotation is much greater than the rate of OPA decomposition to alkene and phosphine oxide both for dibenzophosphole-derived OPAs[74,90]and for unconstrained OPAs.[93,90] The rate of OPA decomposition is thus independent of the rate of OPA pseudorotation.
- The mechanism is in agreement with the computational results of Aggarwal, Harvey and co-workers.[41,42,43]

(iii) Selectivity in reactions of semi-stabilised ylides

The Wittig reactions of semi-stabilised ylides are proposed to proceed by an irreversible [2 + 2] cycloaddition to give OPA, with C-C bonding being more advanced at the TS than P-O bonding. The initially formed OPA with oxygen in an axial position undergoes pseudorotation to place the ylidic carbon in an apical position in the phosphorus-centred trigonal bipyramid. This OPA then undergoes stereospecific and irreversible cycloreversion to alkene & phosphine oxide.[89] The TS is thought to occur later along the reaction coordinate than in reactions of non-stabilised ylides. A consequence of this is that the phosphorus substituents (spectator ligands, ylidic carbon and aldehyde oxygen) are in a tighter, more nearly trigonal bipyramidal arrangement about phosphorus than is the case in TSs of reactions of non-stabilised ylides (see Fig. 10). Also the shape of the sp^2 hybridised phenyl or vinyl substituent at carbon-2 of the forming ring is postulated to result in less severe steric interactions between all of the substituents in the TS compared to the alkyl group in the same position in the TSs derived from non-stabilised ylides.[89] It can be envisaged that the unsaturated group could orient itself to avoid steric interactions in a way that an alkyl group could not in such TSs. This may in turn have an effect on how the substituents on phosphorus are disposed. The upshot is that there is less of an energetic advantage to TS puckering, which in reactions of non-stabilised ylides neatly minimises both 1-3 and 1-2 steric interactions. The somewhat decreased importance of 1-3 (and presumably also of 2-3) interactions means that parallel (or nearly parallel) approach of the ylide and aldehyde can be competitive energetically with a TS

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involving the puckered approach of the reagents. In such a scenario the minimisation of 1-2 interactions dictates that a planar TS should be selective for *trans*-OPA (Fig. 10(b)). The *cis*-selective TS is likely to be puckered, and thus to be similar in appearance to the *cis*-selective TS in reactions of non-stabilised

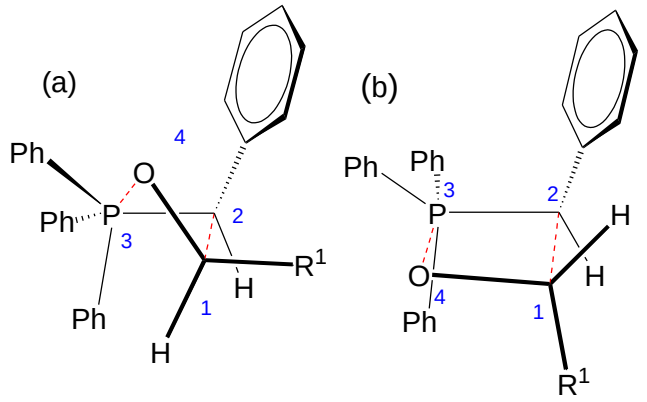


Fig. 10. Cycloaddition TSs leading to OPA in Wittig reactions of benzylidenetriphenylphosphoranes: (a) *cis*-selective cycloaddition TS showing a *positive* angle of puckering; (b) *trans*-selective TS.

ylides (ccompare Fig. 8(a) and Fig. 10(a)), albeit with the phosphorus spectator ligands being in a more compact arrangement.

The computational findings of Aggarwal, Harvey and coworkers[42] are consistent with the operation of the above mechanism in the reaction of benzylidenetriphenylphosphorane with benzaldehyde at the B3LYP/6-31G*(THF) level of theory. The *cis*-OPA selective cycloaddition pathway is marginally favoured over the *trans*-selective pathway. The barrier to OPA decomposition is lower than the barrier to OPA formation. The activation barriers for *both* steps are lower than that for reversal of OPA to starting materials. Thus OPA formation is rate-determining (cf. reaction of ethylidenetriphenylphosphorane with benzaldehyde in which OPA decomposition is rate-dtermining step) and likely to be irreversible. This is in keeping with the experimental observation for semi-stabilised ylides that OPAs cannot be observed spectroscopically except in exceptional circumstances.[60] The barrier to OPA reversal to Wittig starting materials is also higher than in the case of the non-stabilised ylide, and coupled with the lower activation energy for OPA decomposition to alkene and phosphine oxide, this indicates that OPA formation is irreversible. The *cis*-selective TS is found to be puckered (although somewhat less so than the *cis*-selective TS for the non-stabilised ylide) and the trans-selective TS to show slight puckering (with a negative angle). As with non-stabilised ylides, hydrogen bonding between the carbonyl oxygen and a *P*-phenyl C-H is found to play a role in the structure of the TSs. The calculations indicate that the postulated pseudorotation of the initially formed OPA occurs to give a higher energy pseudorotamer with the P-C bond apical, which then undergoes [2 + 2] cycloreversion to give alkene and phosphine oxide.

The cycloaddition mechanism proposed by Vedejs, and verified computationally by Aggarwal, Harvey and co-workers for Wittig reactions of triphenylphosphine-derived semi-stabilised ylides accounts well for the observed alkene diastereoselectivity. Decreased steric interactions in the planar *trans*-selective cycloaddition TS mean that it becomes competitive with the puckered *cis*-selective TS and thus poor selectivity is observed.

In reactions of semi-stabilised ylides for which one or more of the *P*-phenyl groups are replaced by alkyl group(s), 1-3 interactions become less important, as the *P*-alkyl groups effectively free up space around phosphorus in the cycloaddition TS in a way that is not possible with three *P*-phenyl groups. This is thought to be more to do with the shape of the *P*-alkyl group and its effect on how the other substituents on phosphorus are oriented (so its effect on the shape of the "phosphonium" moiety as a whole) than its relative steric bulk *per se*. As a consequence of the above, the main steric interaction that destabilises the nearly planar *trans*-selective TS for triphenylphosphine-derived ylides is dramatically reduced for reactions of these ylides, and so it is energetically favoured over the *cis*-selective TS due to its much smaller 1-2 interactions. This results in much higher kinetic selectivity for the *trans*-OPA in the cycloaddition step, which is why high *E*-selectivity is observed for such semi-stabilised ylides. Computational results on the reaction of benzylidenetrimethylphosphorane with benzaldehyde indicate OPA formation is rate-determining and irreversible, and that the cycloaddition TS is indeed later (i.e. bond formation and rearrangement of substituent geometries about the reactive centres are more advanced) than for the corresponding reaction of a non-stabilised ylide.[42] OPA formation was found to be exothermic, albeit not to the same extent as the in reaction of ethylidenetriphenylphosphorane. The *cis*-selective TS shows only slight puckering, with a positive angle, while the energetically favoured *trans*-selective TS is also slightly puckered but in a negative sense. There is a possibility that the decrease in the puckering in the *cis*-selective TS is as a result of a reduction of the unfavourable electrostatic interaction in the "flatter" conformation between the C-O and ylide C-Ph bond dipoles see later).

The importance of 1-3 interactions is emphasised by the different selectivities observed in reactions of a given semi-stabilised ylide with primary and tertiary aldehydes respectively. The latter generally show much greater *Z*-selectivity than the former as a result of more pronounced 1-3 interactions.

The mechanism described above for the Li-salt free Wittig reaction of semi-stabilised ylides is consistent with the following facts:

- Where OPAs can be observed spectroscopically (i.e. dibenzophosphole-derived OPAs, where the rate of decomposition is retarded sufficiently to make OPA decomposition rate determining), their formation has been shown to be under kinetic control, and stereospecific conversion to alkene has been proven.[60]
- Stereospecific conversion of β-HPS (by deprotonation)[60,86] or epoxide (by nucleophilic cleavage with phosphide, and methylation of the resulting β-oxidophosphine)[96] to alkene via (presumed) betaine and OPA intermediates has been demonstrated.
- Attempted crossover experiments on Wittig reactions of semi-stabilised ylides gave no crossover product,[86,106] although as previously mentioned, this may not be

meaningful if the Wittig reaction is already complete by the time the crossover reactant is added.

- No intermediate is observed in Wittig reactions of semi-stabilised ylides (except for DBP ylides). Kinetic studies show the reaction to be overall second order, and to have a positive ρ value for the carbonyl reagent.[55,56,107] Negative activation volumes[56] and entropies[55] were also reported, which would be in line with a cycloaddition mechanism. Reactions with substituted benzaldehydes showed a kinetic isotope effect at the carbonyl carbon (^{14}C labelled in the study concerned), indicating that the bonding is changing at the carbonyl centre in the rate determining step.[107]
- No betaines derived from semi-stabilised ylides have been detected in the course of spectroscopic monitoring of Wittig reactions,[69,86] β-HPS deprotonation reactions or reactions involving epoxide ring opening and phosphorus quaternisation.[60,86]
- The reaction of *P*-chiral semi-stabilised ylide benzylidene-ethylmethylphenylphosphorane with benzaldehyde gave phosphine oxide in which there is retention of configuration at phosphorus. This indicates the operation of a *syn*-elimination of the phosphine oxide from a cyclic intermediate or TS with trigonal bipyramidal phosphorus.[79]
- The above points are consistent with an irreversible, rate-determining cycloaddition of ylide and aldehyde to give OPA where the aldehyde carbonyl is acting as an electrophilic centre, followed by an irreversible, stereospecific *syn*-cycloreversion of OPA to alkene and phosphine oxide.
- The experimentally observed selectivities are well accounted for by the proposed mechanism. It is consistent with the facts that the most *Z*-selective reactions of semi-stabilised ylides involve tertiary aldehydes or bulky triarylphosphine-derived ylides, and that the most *E*-selective reactions of these ylides involve non-bulky aldehydes or dialkylphenylphosphine, trialkylphosphine or methyldibenzophosphole-derived ylides.

(iv) Selectivity in reactions of stabilised ylides

Stabilised ylides react through a relatively late TS, in which rehybridisation about phosphorus to trigonal bipyramidal and about the ylidic carbon and aldehyde carbonyl centres to tetrahedral is near completion. Vedejs's original proposal contended that this meant the cycloaddition TS was constrained to being planar, and hence 1-2 interactions would generally be the dominating steric interactions, which would be consistent with the generally observed high *E*-selectivity in Wittig reactions of stabilised ylides.[60,89] However, some small inconsistencies did exist with this proposed mechanism; for example it could not adequately explain the high *E*-selectivity observed in reactions of α-alkyl-α-carbonyl disubstituted stabilised ylides. These inconsistencies were resolved by Aggarwal, Harvey and co-workers based on computational studies.[41,42] Notably, they modified the cycloaddition mechanism for stabilised ylides proposed by Vedejs and co-workers to take into account dipole-dipole interactions in the cycloaddition TS.

Calculations on the reaction of (methoxycarbonylmethylidene)-triphenylphosphorane with benzaldehyde at the B3LYP/6-31G*(THF) level of theory indicate rate-determining *endothermic* cycloaddition of ylide and aldehyde to give OPA, which undergoes facile pseudorotation to place the ylidic carbon in an axial position in the phosphorus-centred trigonal bipyramid, and then cycloreverts to alkene and phosphine oxide, as predicted by the Vedejs mechanism. The cycloaddition TS is indeed found in their calculations to be relatively late (i.e. bond formation is quite advanced), and the

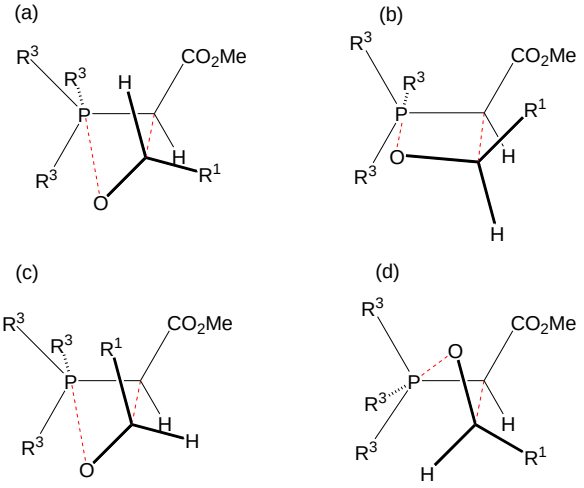


Fig. 11. (a) Favoured *trans*-selective TS showing negative puckering angle, (b) Lowest energy *cis*-selective TS, (c) & (d) Higher energy *cis*-selective TSs.

barrier to OPA decomposition is very low in comparison with the barrier to reversal to ylide and aldehyde, and with the OPA cycloreversion barrier in reactions of non-stabilised and semi-stabilised ylides. Thus OPA formation is irreversible, and the OPA intermediate does not accumulate, which is consistent with experimental observations. Interestingly, the *trans*-OPA with the carbon in the apical position is determined in these calculations to be more stable than the pseudorotamer with oxygen in the apical position.

Where the calculated mechanism differs from the mechanism proposed by Vedejs is in the shape of the cycloaddition TSs. The *trans*-selective TS (shown in Fig. 11(a)) is found to be puckered, but importantly this puckering is in the opposite sense (-40.1°) to that proposed for the *cis*-OPA selective TS in reactions of non-stabilised ylides (Fig. 11(a)).[41,42] This results in a TS that has an electrostatically favourable antiparallel orientation of the carbonyl C-O and ylide C-C(O) bond dipoles. Minimisation of both 1-2 and in particular 1-3 steric interactions then dictates that the large aldehyde substituent (R^1) should be pseudo-equatorial, and so this TS is selective for *trans*-OPA. Puckered *cis*-TSs were found to be disfavoured for this reaction – a TS with a negative puckering angle and thus favourable relative orientation of reactant dipoles (Fig. 11(c)) suffers from strong 1-3 (as well as significant 1-2) interactions, while one with the opposite sense of puckering (Fig. 11(d)) has an electrostatically disfavoured disposition of reactant dipoles. The lowest energy *cis*-selective TS was found to be planar (Fig. 11(b)) – it is not particularly disfavoured electrostatically, but is much higher in energy than the *trans*-selective TS as it suffers from large 1-2 interactions and lacks the electrostatically favoured antiparallel orientation of reactant dipoles that is present in the latter TS. Thus high *E*-selectivity is observed in general in Wittig reactions of stabilised ylides in non-polar or polar-aprotic media, with selectivity being

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extremely high for ylides in which phosphorus bears bulky substituents (e.g. triphenylphosphine-derived ylides), as the possibility of large 1-3 interactions dictates that these discriminate particularly well against puckering of the *cis*-selective TS.

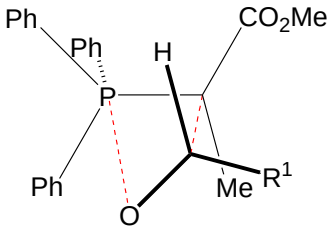


Fig. 12. Proposed *trans*-selective TS in Wittig reactions of α,α-disubstituted stabilised ylides, with electrostatically favourable relative orientation of carbonyl C-O and ylide C-C(O) bond dipoles

The computational results on the reaction of (methoxycarbonylmethylidene)trimethylphosphorane with benzaldehyde (B3LYP/6-31G*(THF) level of theory) indicates a similar shape for the cycloaddition TSs to the above reactions, and indeed a similar energetic advantage for the *trans*-selective TS over the *cis*, which is in keeping with the observed high *E*-selectivity in reactions of trialkylphosphine-derived ylides. However, it may be that in certain circumstances, if the phosphorus substituents are not as bulky as triphenylphosphine-derived ylides (e.g. for methyldiphenylphosphine-derived ylides), then a different *cis*-selective TS with an antiparallel orientation of reactant dipoles is possible (Fig. 11(c)) since placement of the large substituent in the pseudo-axial position is not discriminated against to the same extent by 1-3 interactions, and so somewhat lower *E*-selectivity observed.[4]

Diminished *E*-selectivity, and even predominant *Z*-selectivity, has been observed in reactions of stabilised ylides in methanol. A reasonable explanation is that this results from solvent-induced decrease in the importance of the interaction of reactant dipoles in the cycloaddition TSs. In this scenario, the factors governing TS geometry may be quite similar to those in reactions of semi-stabilised ylides.

This mechanism, in taking account of reactant dipole-dipole interactions in the cycloaddition TS, allows a rationalisation of the consistently high *E*-selectivity observed in Wittig reactions of α-alkyl-α-carbonyl disubstituted stabilised ylides. In reactions of such ylides, 1-2 steric interactions alone cannot account for the observed bias in selectivity towards *trans*-OPA and *E*-alkene. The presence of the additional ylide α-substituent, however, does not alter the operation of the dipole-dipole interaction, so the *trans*-selective TS adopts a similar conformation to that in reactions of the mono-substituted ylide (see Fig. 12), and is similarly favoured energetically over the *cis*-selective TS for the same reasons as are present in reactions of the mono-substituted ylide.

Further experimental evidence for the operation of the cycloaddition mechanism in Wittig reactions of stabilised ylides has been presented recently in a publication quantifying the relative nucleophilicity of phosphonate carbanions (Wadsworth-Emmons reagents), phosphinoxy carbanions and stabilised phosphonium ylides towards substituted quinone methides (Michael acceptors), benzhydrilium ions (carbocations) and benzaldehydes.[36] These nucleophiles are obliged to react by a straightforward nucleophilic substitution with the former two electrophiles. The relative reactivity of all three types of phosphorus ylide towards the benzaldehydes was found to be systematically lower than towards the carbocations and Michael acceptors. Based on this, the authors concluded that the ylides all react with carbonyl compounds through an asynchronous concerted [2+2] cycloaddition. The ρ values determined in this study for the benzaldehydes in their reactions with each phosphorus nucleophile (2.9 for the phosphonium ylide, 3.4-3.6 for the phosphonate carbanions, and 2.7-2.8 for the phosphinoxy carbanions) are consistent with the operation of a cycloaddition mechanism with C-C bonding being more advanced than P-O bonding in the reactions of all three nucleophiles with carbonyl species. The value found for the reactions of the phosphonium ylide is consistent with literature precedent.[54]

The mechanism described above for the Li-salt free Wittig reaction of stabilised ylides is consistent with the following facts:

- Stereospecific conversion of β-HPS (by deprotonation) to alkene via (presumed) betaine and OPA intermediates has been demonstrated. Thus OPAs are formed under kinetic control, and the stereoselectivity is decided in the C-C bond forming step.[60]
- Reactions are second order (first order in each of ylide and carbonyl species), and alkene appears at the same rate as ylide is consumed. [53,54]
- ρ values for the carbonyl reactants have been found to be positive (so it is acting as an electrophile in the rate determining step)[36,54] and for ylides have been shown to be negative (so it is acting as a nucleophile),[54] and their magnitudes are consistent with the operation of an asynchronous cycloaddition mechanism.
- The nucleophilicity of the stabilised ylide (methoxycarbonylmethylidene)-trimethylphosphorane towards benzaldehydes has been found to be quantifiably different from its nucleophilicity towards carbocations and Michael acceptors, with which it must react by nucleophilic addition.[36]
- The entropy of activation for reactions of stabilised ylides is large and negative.[53,54] There are no strong solvent effects in the reaction,[108] and indeed it has been observed that the rate of the reaction of (fluorenylidene)ethyldiphenylphosphorane with *p*-nitrobenzaldehyde is *slower* in acetone or DMF than in benzene. [53] Thus, the TS of the rate determining step is not polar and is highly ordered, characteristic of a cycloaddition TS.
- No OPA or betaine derived from a stabilised ylide has been detected during spectroscopic monitoring of Wittig reactions[69] or β-HPS deprotonations.[60]

5. Conclusions

It is our hope that this review will lead to the widespread recognition of the true course of the Li salt-free Wittig reaction, and that this will be reflected in the content of undergraduate textbooks. The fact that there is a clear distinction between the mechanisms that operate in the presence and absence of Li salts should be delineated, and in particular the fact that the Li-salt free mechanism is now definitively known while the Li-present mechanism is still effectively unknown should be clearly stated.

In summary: the first step of the Li-salt free Wittig reaction is an irreversible [2 + 2] cycloaddition to give OPA. The stereochemistry of the product alkene is set during the formaiton of OPA. The varying shapes of the [2 + 2] cycloaddition TSs lead to different diastereoselectivities in reactions of different ylides. High selectivity for *E*-alkene is not necessarily indicative of the operation of thermodynamic control in any Li-salt free Wittig reaction; with only a small set of well-defined exceptions all such reactions are irreversible. High *E*-selectivity results from a kinetic preference for the formation of *trans*-OPA. The role of OPA pseudorotation in the Wittig reaction has yet to be settled, but it seems likely that OPA decomposition occurs in a single step that is comprised of both a Berry pseudorotation process and P-C and C-O bond breakage. What is certain about the OPA decomposition step is that it is stereospecific with respect to the carbon atoms of the newly-formed alkene.

The simplicity of this modern two-step interpretation of the Li-salt free Wittig reaction mechanism belies great complexity, in particular in the source of diastereoselectivity. It is nonetheless ironic in light of the many proposals made, words written, diagrams drawn and experiments done that it is, at its most basic level, perhaps the simplest possible means of turning ylide + carbonyl into alkene + phosphine oxide that has turned out to be the true mechanism.

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Notes and references

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[b] We have observed this in the course of our own studies (references 38 and 39) using methyldiphenylphosphine-derived stabilised ylides.

[c] This mechanism was originally proposed by Wittig and Schöllkopf, who initially suggested that a betaine was the sole intermediate in the reaction.

[d] See Scheme 3(b) for definition of *erythro* and *threo* β-HPSs.

[e] In crossover experiments for Wittig reactions, a more reactive ylide or aldehyde is added to the reaction mixture after the intermediate has formed but not completely decomposed in order to react with any starting material that re-forms by Wittig reversal.

[f] A puckered *trans*-selective TS would suffer from either increased 1-2 interactions by placing R^2 pseudo-equatorial in Fig. 4(a) or from increased 1-3 interactions by placing R^1 pseudo-axial.

[g] A planar trans-selective TS would suffer from increased 1-3 interactions, and "blocked approach" of the carbonyl oxygen to phosphorus.

[h] In fact, according to reference 91, pseudorotamers in which either oxygen or a 5-membered ring carbon (or both) occupy equatorial positions are likely to be TSs or on the path to a TS rather than being intermediates, as would traditionally have been thought, since it is now established that single-step processes consisting of multiple Berry pseudorotations are possible.

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