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Unequivocal Experimental Evidence for a Unified Lithium Salt-Free Wittig Reaction Mechanism for All Phosphonium Ylide Types: Reactions with β-Heteroatom-Substituted Aldehydes Are Consistently Selective for *cis*-Oxaphosphetane-Derived Products

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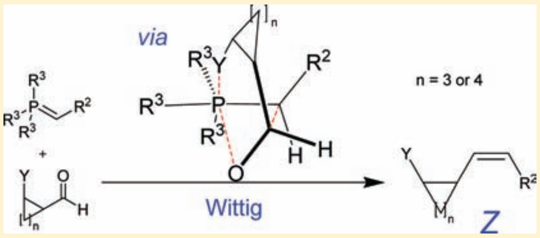
Ⓢ *Supporting Information*



ABSTRACT: The true course of the lithium salt-free Wittig reaction has long been a contentious issue in organic chemistry. Herein we report an experimental effect that is common to the Wittig reactions of all of the three major phosphonium ylide classes (non-stabilized, semi-stabilized, and stabilized): there is consistently increased selectivity for *cis*-oxaphosphetane and its derived products (*Z*-alkene and *erythro*-β-hydroxyphosphonium salt) in reactions involving aldehydes bearing heteroatom substituents in the β-position. The effect operates with both benzaldehydes and aliphatic aldehydes and is shown not to operate in the absence of the heteroatom substituent on the aldehyde. The discovery of an effect that is common to reactions of all ylide types strongly argues for the operation of a common mechanism in all Li salt-free Wittig reactions. In addition, the results are shown to be most easily explained by the [2+2] cycloaddition mechanism proposed by Vedejs and co-workers as supplemented by Aggarwal, Harvey, and co-workers, thus providing strong confirmatory evidence in support of that mechanism. Notably, a cooperative effect of *ortho*-substituents in the case of semi-stabilized ylides is confirmed and is accommodated by the cycloaddition mechanism. The effect is also shown to operate in reactions of triphenylphosphine-derived ylides and has previously been observed for reactions under aqueous conditions, thus for the first time providing evidence that kinetic control is in operation in both of these cases.

■ INTRODUCTION

The Wittig reaction[1−3] of carbonyls with phosphorus ylides is one of the most important and widely used methods for the synthesis of alkenes[4] and, even now—almost 60 years after its discovery—is still being intensively studied.[5−13] Concurrently, its mechanism has been the focus of intense and vigorous debate[2,3,14,15] and could be described as one of the great long-running investigations of organic chemistry. Johnson[3] enumerated eight different mechanistic proposals that had been advanced at various times, reflecting the tortuous path to the currently emerging consensus on the mechanism. This was the result of a discontinuous uncovering of the operation of several different factors that can have a bearing on the mechanism and, especially, on the stereoselectivity of the reaction. Only in hindsight can we see that the results of valid and well-constructed studies concerned with the involvement of betaines (salt-free or otherwise),[16−18] and the related issues of the effect of lithium cation[19−22] and reversible formation of intermediate(s),[23−28] led incorrectly to the twin hypotheses of the involvement of betaines and the operation of thermodynamic control in Wittig reactions.[29] That these ideas persist in the modern literature[30−34] perhaps may be attributed to their simplicity. For example, it is easy to assume (but ill-founded on experimental evidence)[35] that reactions of stabilized ylides are under thermodynamic control because they are *E*-selective. Similarly, the apparent involvement of betaines as intermediates was alluring because non-Wittig reactions deliberately designed to produce betaines gave the same products as the analogous Wittig reactions. We know now that both processes produce oxaphosphetane (OPA, Scheme 1). Subsequent work has conclusively shown that solutions containing only OPA (as confirmed by NMR monitoring of the solution) give β-hydroxyphosphonium salt (β-HPS) upon quenching with acid[36] and react with LiBr to give a betaine−LiBr complex.[19] Thus, there is no need to invoke the involvement of betaines in Wittig reactions. Furthermore, the non-involvement of betaines has been unequivocally demonstrated in the reaction of a particular dibenzophosphole (DBP)-derived non-stabilized ylide.[37] Irreversible formation of OPAs has been established for representatives of all three types of ylide, which means also that reversibility of Wittig reactions—whether they involve betaines or not—cannot be invoked to explain the high *E*-selectivity.[26,35] It is significant (and ironic) that the very limited number of cases in which genuine reversibility of OPA formation occurs involve non-stabilized ylides.[23−26]

The present emerging consensus on the mechanism centers on [2+2] cycloaddition of the ylide and carbonyl to give OPA directly (Scheme 1). As developed by Vedejs and co-workers,[35,38]

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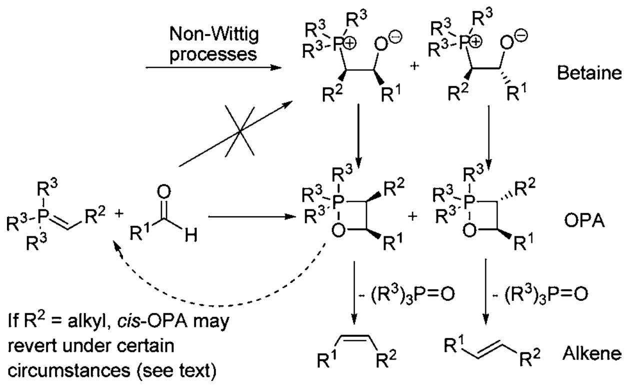
Scheme 1. Present Understanding of the Mechanism of the Lithium Salt-Free Wittig Reaction[a]



[a] Oxaphosphetane formation is generally irreversible, with well-defined exceptions (all from non-stabilized ylides, see text). Betaines are not formed in the process of the salt-free Wittig reaction but, if independently generated (e.g., from *β*-HPS), rapidly form OPAs. Each OPA diastereomer undergoes stereospecific decomposition to alkene and phosphine oxide, perhaps after undergoing pseudo-rotation.

and modified for reactions of stabilized ylides by Aggarwal, Harvey, and co-workers,[13] it is the mechanism that best accounts for experimental observations.[39,40] Consideration of this mechanism grew from the initial observation by Vedejs and Snoble[41] that OPA was the only intermediate observable by low-temperature NMR and that the high *Z*-selectivity from non-stabilized alkylidenetriphenylphosphoranes could be explained by a kinetically controlled [2+2] cycloaddition of ylide and aldehyde. Subsequently the Vedejs group[14,15,19,26,35,38,42−46] did extensive work to establish the operation of the cycloaddition mechanism in the reactions of non-stabilized,[26,38] semi-stabilized, and stabilized ylides.[35] Maryanoff, Reitz, and co-workers[2,20,23−25,47] and Schlosser and co-workers[48] also contributed significantly to its development; the former group of workers also identified and did extensive studies on the issue of stereochemical drift (*vide infra*). More recently, extensive kinetic studies by Mayr and co-workers confirmed that the reactivities of stabilized ylides were consistent with the cycloaddition mechanism.[49]

■ CONTEXT OF THE PRESENT EXPERIMENTS

The [2+2] Cycloaddition Mechanism. We may summarize the emerging consensus as follows: It has been categorically established that salt-free non-stabilized ylides react with aldehydes by rapid and irreversible formation of *cis*- and *trans*-OPA intermediates,[23−26,46,50,51] with no involvement of betaine intermediates (Scheme 1 and Figure 1a) prior to OPA formation.[37] In a limited number of cases (discussed below), "Wittig reversal" of the *cis*-OPA to ylide and aldehyde has been observed (Scheme 1), resulting in enhanced production of *trans*-OPA and hence *E*-alkene.[23−26,47] It is also established that the OPAs (generated by non-Wittig processes) that are thought to be necessary intermediates in the analogous Wittig reactions of semi-stabilized[35,42,52] and stabilized[35,43] ylides do not equilibrate under the typical experimental conditions for a Wittig reaction. The presence of OPAs as intermediates has been demonstrated in the reaction of a particular DBP-derived semi-stabilized ylide[35] but not, as yet, for any stabilized ylide. Reactions of stabilized ylides have been observed to be slower in acetone or dimethylformamide (DMF) than in benzene[53] and to have large negative activation entropy,[53] which is consistent with a cycloaddition mechanism. In the reactions of all three types of ylide, the initially formed OPA (with apical carbon) undergoes facile pseudo-rotation to place the ring oxygen in an apical position in the OPA trigonal bypyramid.[13,37,45,51] Finally, alkene and phosphine oxide are formed by irreversible, stereospecific *syn*-cycloreversion of the OPA.[54,55] For reactions of non-stabilized ylides, the straightforward formation of OPA and substantial barrier to OPA decomposition mean that the latter is the rate-determining step (see Figure 1a). For reactions of semi-stabilized and stabilized ylides, the barrier to [2+2] cycloaddition is increased and that to OPA cycloreversion is significantly decreased (especially for OPAs derived from stabilized ylides), and so OPA formation is rate-determining (Figure 1b). Consequently, the OPA intermediates are reasonably long-lived (at low temperature) and thus spectroscopically observable in reactions of non-stabilized ylides, but not in those of semi-stabilized or stabilized ylides, with the exception of OPAs formed from DBP-derived semi-stabilized ylides.

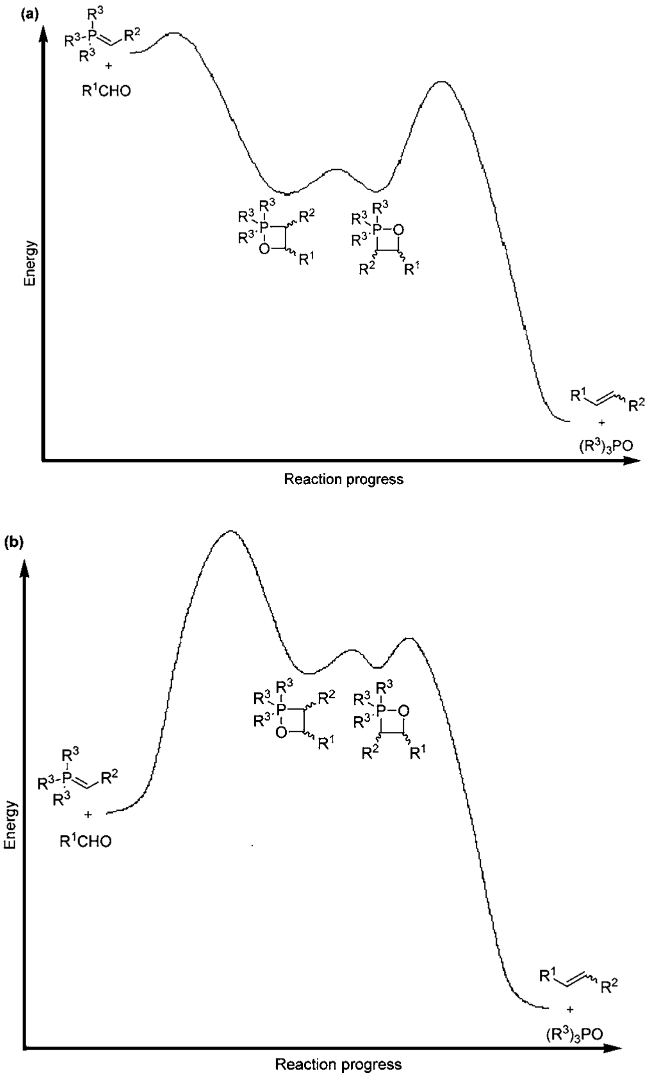


Figure 1. Reaction coordinate diagrams for Wittig reactions. (a) Reaction of a non-stabilized ylide (R^3 = Ph, R^2 = alkyl), indicating rate-determining OPA decomposition. (b) Reaction of a stabilized ylide (e.g., $R^2 = CO_2Me$), indicating rate-determining OPA formation.

Powerful indirect evidence supporting the [2+2] cycloaddition as a unified Wittig mechanism is related to its use in a consistent explanation of the variation of the *Z*/*E* ratios in the product alkenes.[3,14] It is postulated that alkylidenetriphenylphosphoranes (non-stabilized ylides) react preferentially through an early, puckered transition state (TS) in which the carbonyl substituent occupies a pseudo-equatorial position. This minimizes steric interactions between it and the *P*-phenyl groups, which are still in a pseudo-tetrahedral arrangement about phosphorus (see Figure 2a). In such a TS, the steric interactions of the ylide α-substituent (with the *P*-phenyl groups in particular) are minimized if it is in a pseudo-axial site, and hence this TS leads to *cis*-OPA and *Z*-alkene. This TS simultaneously minimizes 1−2 and 1−3 interactions (see Figure 2a for numbering of ring positions) for the particular arrangement of substituents about phosphorus involved, as well as allowing the forming P−O bond to avoid the *P*-phenyl group that is necessarily projecting in the direction of the carbonyl approach to the ylide, and is thus highly favored for alkylidenetriphenylphosphoranes.[56]

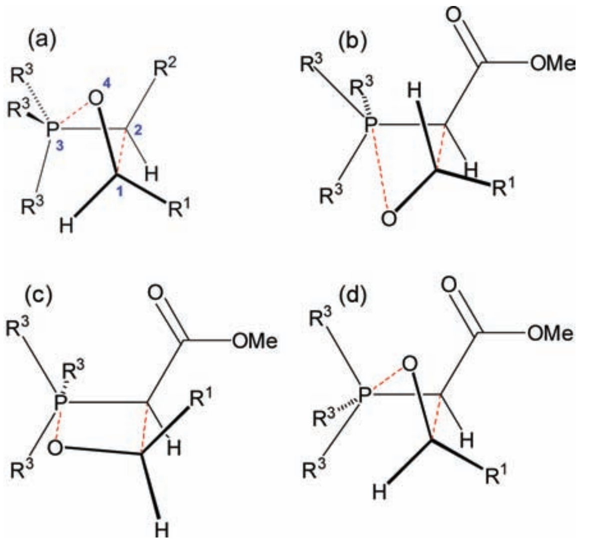


Figure 2. Proposed [2+2] cycloaddition transition states for various Wittig reactions. (a) Early puckered TS with pseudo-tetrahedral arrangement of phosphorus substituents and pseudo-trigonal planar geometry of the ylidic and carbonyl carbon substituents (for non-stabilized ylides). (b) *trans*-selective TS for the reaction of a stabilized ylide, with favorable anti-parallel orientation of carbonyl and C−CO_2Me dipoles. (c) Planar *cis*-selective TS for the reaction of a triphenylphosphine-derived stabilized ylide. (d) Disfavored *cis*-selective TS for the reaction of a stabilized ylide, with approximately parallel orientation of carbonyl and C−CO_2Me dipoles.

In reactions of triphenylphosphine (TPP)-derived semi-stabilized ylides, the somewhat more advanced nature of the TS and the shape of the sp^2-hybridized substituent on the ylide result in decreased 1−3 and 2−3 steric interactions. As a consequence, a planar *trans*-selective TS can become competitive with a *cis*-selective puckered TS, and poor selectivity results. In reactions of semi-stabilized ylides for which one or more of the *P*-phenyl groups are replaced by alkyl group(s), the shape of the phosphonium moiety is such that 1−3 and 2−3 interactions are further reduced, resulting in a greater preference for the planar *trans*-selective TS (which ensures minimal 1−2 interactions), and hence the *trans*-OPA and *E*-alkene.

Stabilized ylides react through a relatively late TS.[57] Recent calculations by Aggarwal, Harvey, and co-workers indicate that the *trans*-selective TS (shown in Figure 2b) in reactions of stabilized ylides is puckered, but importantly that this puckering is of the *opposite sense* to that proposed for the *cis*-OPA-selective TS in reactions of non-stabilized ylides (Figure 2a).[13] This results in a TS that has an electrostatically favorable anti-parallel orientation of the carbonyl C−O and ylide C−C(O) bond dipoles. Minimization 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. The possible (late) *cis*-selective TSs (planar and puckered) in these reactions of stabilized ylides (see Figure 2c,d) were found to be significantly higher in energy than the *trans*-selective TS.[58,59]

Confusion in the Secondary/Tertiary Literature about the Mechanism. The evidence and arguments summarized above are the basis for the consensus among mechanistic organophosphorus chemists on the underlying simplicity and unity of the mechanism of the salt-free Wittig reaction and how it manifests itself in practice. It can be seen however that the explanation of the source of stereoselectivity in the [2+2] cycloaddition mechanism relies on fairly complex technical arguments, with a number of caveats and exceptions to be explained. This has not helped to dispel (previously accepted) older descriptions of the mechanism involving reversible steps and/or betaine intermediates.[30−33,60−62] The persistence of both of these issues may also be related to the fact that the mechanism of the Li salt-containing Wittig reactions is still uncertain.[33] Modern textbooks tend not to distinguish between Wittig reactions conducted in the presence of Li^+, for which the mechanism is essentially unknown, and those that occur under Li salt-free conditions, for which the mechanism is now well established.

In the present study, for the first time, we demonstrate an effect that is common to Li salt-free Wittig reactions of all three classes of phosphonium ylide. This is powerful confirmatory evidence that there is a unitary mechanism in operation in all kinetically controlled Wittig reactions. In addition we shall demonstrate that our results are entirely consistent with the [2+2] cycloaddition mechanism. We hope that the unmasking of an unexpected effect that is common to all ylide types and which is easily explicable by the cycloaddition mechanism will enable clarity on the mechanism of the Li salt-free Wittig reaction for non-experts in organophosphorus mechanism.

■ PRELIMINARY REMARKS ON THE EVALUATION OF KINETIC DIASTEROSELECTIVITY IN WITTIG REACTIONS

There are many variables that may affect the mechanism of the Wittig reaction and thus the observed diastereomeric ratio of the alkene product. An understanding of these variables has come about through the substantial body of work carried out by Vedejs and co-workers, Maryanoff, Reitz, and co-workers, Aggarwal, Harvey, and co-workers, Schlosser and co-workers, and others. The importance of the foundations laid by these workers is such that it is only recently, in the aftermath of their work, that it has become possible to conduct meaningful experiments on the mechanism of the Wittig reaction with sufficient confidence that the numerous variables at play are under control. We now briefly discuss these variables, the effect that they exert in the reaction, and how to prevent these effects giving rise to misleading results in the context of the reaction mechanism.

Operation of Kinetic Control. Conditions have been established in which reactions of all three different ylide types occur under kinetic control—meaning that the OPA intermediates are formed irreversibly and undergo stereospecific decomposition to alkene and phosphine oxide. These conditions are now described.

In reactions of non-stabilized ylides it is possible to observe the OPA intermediates by low-temperature NMR, and also to quench the OPA at low temperature with acid to give β-HPS (whose *erythro*/*threo* ratio corresponds directly to the *cis*/*trans* ratio of the OPA precursor). Both of these techniques have been used to determine kinetic OPA *cis*/*trans* ratios, and in cases where both techniques have been used, the ratios have been in excellent agreement.[2,36] Comparison of the diastereomeric ratio of the intermediate determined by either method with the Z/E ratio of the alkene product in all but a small number of exceptional circumstances (see the Stereochemical Drift section below) shows the ratios to be identical.[23−26,46,50,51] Thus it can be inferred that these reactions occur under kinetic control.

For Li salt-free reactions of semi-stabilized and stabilized ylides, OPA intermediates are generally not sufficiently long-lived to permit spectroscopic detection.[63] Kinetic control has been established in these challenging cases by generating the OPA intermediates through processes independent of a Wittig reaction and proving that these OPAs do not interconvert, but instead undergo stereospecific decomposition to alkene and phosphine oxide.[35] TPP-derived OPAs are not amenable to these routes (all of which require quaternization at phosphorus), and so methyldiphenylphosphine-derived OPAs, which are accessible by non-Wittig processes, have been employed in these experiments.

Based on the above experiments, if one carries out a Wittig reaction under conditions mimicking those for which the operation of kinetic control has been verified, a direct correspondence between the kinetic OPA *cis*/*trans* ratio and the observed alkene Z/E ratio can be assumed (as long as steps have been taken to ensure that no isomerization of the alkene occurs after the reaction is complete; see the Dependability of Z/E Ratios section below). The exceptional circumstances under which the kinetic OPA *cis*/*trans* ratio changes from its original value are well defined (see the Stereochemical Drift section below), and steps can be taken to evaluate the relevant ratio before it changes.

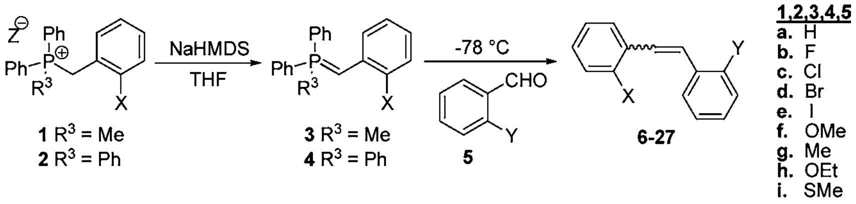
Dependability of *Z*/*E* Ratios. In the present work, the kinetic selectivity of the OPA-forming step in Wittig reactions of semi-stabilized and stabilized ylides is inferred from the observed Z/E ratio of the alkene product. It is thus very important to be sure that the alkene Z/E ratio is truly reflective of the kinetic OPA *cis*/*trans* ratio, and to be aware of possible means by which there may arise a non-correspondence between the two ratios. Changes may occur to the Z/E ratio after completion of the reaction and/or during workup or chromatographic purification of the alkene product. It is not sufficiently recognized that *Z*-1,2-disubstituted alkenes are quite easily converted, under a variety of conditions, to a Z/E mixture and sometimes completely to the *E*-isomer. Therefore the Z/E ratio resulting from the reaction is fragile and can be affected by the presence of acids[64] or strong bases,[65] the chromatographic stationary phase used, the solvent, heat, and sunlight. Both ourselves[66] and Vedejs and Peterson[14] have identified multiple previous literature reports where there was undoubtedly isomerization in favor of the *E*-alkene subsequent to the actual Wittig reaction.[67] It may even occur simply if the reaction mixture is allowed to stand for a period.[68] We have taken extensive precautions[69,70] and performed a substantial number of control experiments[71] to ensure that our observed Z/E ratio is truly reflective of that rendered by the Wittig reaction in question.

Stereochemical Drift. This is a more mechanistically significant source of variation in stereochemistry. Under certain circumstances, the proportion of *trans*-OPA present in the initially formed mixture of OPA isomers (which reflects the extent to which the *trans*-OPA is preferred kinetically) may be augmented at the expense of the *cis*-OPA,[14,25,26,47] leading to a different ratio of *cis*- and *trans*-OPAs and therefore a Z/E alkene ratio which is not reflective of the intrinsic kinetic selectivity of the [2+2] cycloaddition step. This phenomenon has been termed "stereochemical drift".[25] Reactions conducted in the presence of additives such as salts that are soluble in the reaction solvent—in particular Li cation,[14,20] but also iodide anion,[52] lithium halide with small amounts of alcohol,[72] and benzoic acid[64]—have been shown to give Z/E ratios that are altered with respect to reactions conducted in the absence of such additives. The effect of Li ion is solvent dependent, with a profound effect being observed for reactions in non-polar solvents, and essentially no effect in solvents that effectively complex Li^+.[3,20] Hydroxylic solvents and high temperature have also been implicated as possible initiators of OPA equilibration in reactions of aromatic aldehydes.[14]

More challenging is that, in certain reactions of non-stabilized ylides, stereochemical drift can occur in the absence of dissolved salts (Li or otherwise). This has been observed to occur for OPAs derived from trialkylphosphonium alkylides with tertiary or aromatic aldehydes,[23−26,47] and for OPAs derived from ethylidenetriphenylphosphorane with benzaldehyde (although in the latter of these, stereochemical drift only occurs at or above the temperature at which OPA can decompose to alkene, while below this temperature the OPA diastereomeric ratio remains identical to the low-temperature kinetic ratio).[19] By the use of crossover experiments, the enhanced production of *trans*-OPA in these examples was shown to arise from reversal of the *cis*-OPA exclusively to ylide and aldehyde and subsequent recombination of these reactants. In each of the above examples, the OPAs were generated by deprotonation of β-HPS. In the course of the present study the occurrence of this phenomenon has been confirmed by comparison of the kinetic *cis*/*trans* ratio of the OPA and the Z/E ratio of the alkene produced in the reactions of non-stabilized ylides ethylidenetriphenylphosphorane,[73] *P*-(ethylidene)ethyldiphenylphosphorane,[73] and *P*-(ethylidene)-*P*-phenyldibenzophospholane[74] with each of benzaldehyde and 2-bromobenzaldehyde. In each case, a greater proportion of the *E*-isomer was observed to be present in the alkene product than would have arisen from the *trans*-OPA initially generated.

Our Interest in This Area. This arose some years ago,[66] when we reported on a curious phenomenon in the Wittig reactions of triphenylphosphonium benzylides with *ortho*-substituted benzaldehydes. Strong *ortho*-effects from substituents on phosphorus were already well known through the work of McEwen and co-workers,[75,76] and these had been extended to the Wittig reaction, although with conflicting results.[77,78] It was also known that *Z*-selectivity in stilbene synthesis could be induced by *ortho*-substituents with heteroatom lone pairs on the aldehyde.[79,80] However, remarkably, we found that this latter *Z*-selectivity could be substantially augmented by an additional *ortho*-substituent on the benzylide, despite the fact that such a substituent would ordinarily lead to *E*-selectivity. This counter-intuitive cooperative effect was strong enough to be preparatively useful (Z/E up to 95:5), and the resulting *Z*-2,2′-disubstituted stilbenes have been used to good effect in synthesis by others.[81,82] At the time, we rationalized the results within the cycloaddition mechanism by proposing that the increased

Table 1. Z/E Ratio[a] for Stilbenes 6−27 Produced in the Reactions of Benzylidenemethyldiphenylphosphoranes 3a−g, Derived from Phosphonium Salts[b] 1a−g (with *ortho*-Substituent X) with Benzaldehydes 5a−i (with *ortho*-Substituent Y)



entry	ylide X	ald Y	Z/E ratio	entry	ylide X	ald Y	Z/E ratio	entry	ylide X	ald Y	Z/E ratio	entry	ylide X	ald Y	Z/E ratio
1	H	Cl	92:8	9	Cl	H	34:66	16	Cl	Cl	97:3	24[c]	Me	Cl	94:6
2	H	Br	94:6	10	Br	H	33:67	17	Br	Br	98:2	25	Br	Me	70:30
3	H	I	96:4	11	I	H	28:72	18	I	I	99:1	26	Cl	Me	73:27
4	H	F	84:16	12	F	H	41:59	19[d]	F	Br	94:6	27	F	Me	52:48
5	H	Me	35:65	13[c]	Me	H	7:93	20[c]	Me	Me	31:69	28[c]	OMe	Me	66:34
6	H	OMe	86:14	14[c]	OMe	H	12:88	21[e]	OMe	OMe	44:56	29	Br	OMe	95:5
7	H	OEt	77:23	15	H	H	15:85	22	Br	OEt	92:8	30	OMe	Br	72:28
8	H	SMe	42:58					23	Br	SMe	61:39				

[a] Z/E ratio determined by ^{1}H NMR analysis of the crude product obtained after minimal aqueous workup. See Supporting Information for full details of the reaction, workup, Z/E analyses, and characterization of the starting materials and product alkenes. [b] Counterion Z = Br^- unless otherwise noted. [c] Counterion Z = Cl^-. [d] The corresponding result for X = Br, Y = F: Z/E = 84:16. The case X = Y = F is excluded because the alkene is especially prone to isomerization. [e] This reaction was also carried out using the phosphonium chloride salt, and the Z/E ratio was found to be 46:54.

Z-selectivity arose from the induction by the *ortho*-heteroatom of a lower energy TS in the kinetically controlled cycloaddition step leading to a lower energy *cis*-OPA. However, the experimental conditions employed (aqueous, room temperature, presence of sodium salts in solution, use of TPP-derived ylides), while very convenient, were not such that kinetic control in the Wittig reaction could be assumed and rendered the analysis provisional at best. We have now re-investigated comprehensively the original *ortho*-heteroatom phenomenon under conditions ensuring kinetic control; much more significantly, we have extended it to non-stabilized and stabilized ylides, and also to aliphatic aldehydes.

Standard Wittig Reaction Conditions Used in This work. For Wittig reactions of semi-stabilized and stabilized ylides, we adopted a standard set of conditions designed to (i) ensure kinetic control, (ii) avoid possible initiators of stereochemical drift, and (iii) ensure that the Z/E ratio of the alkene product rendered by the reaction remains unchanged after completion of the reaction. For each reaction, the (Li salt-free) ylide was pre-generated from the parent phosphonium bromide or chloride salt using non-nucleophilic bases NaHMDS or KHMDS in dry aprotic solvent (tetrahydrofuran (THF)) under an atmosphere of dry nitrogen. The ylide solution was cooled to −78 °C, and aldehyde (verified free of carboxylic acid by ^{1}H NMR) was then added dropwise. The operation of kinetic control in reactions of methyldiphenylphosphine-derived semi-stabilized and stabilized ylides has been unequivocally verified for just these reaction conditions,[35] and so the bulk of our reactions involve such ylides. We have also carried out some reactions of TPP-derived ylides for comparison. The inorganic salts produced in these reactions (NaCl, NaBr, KCl, KBr) are insoluble in THF and thus are out of solution and exert no effect on the reaction of ylide with aldehyde.[83] For reactions of semi-stabilized ylides, the reaction mixture was allowed to warm to room temperature, while reactions of stabilized ylides were quenched at −78 °C by addition of NH_4Cl solution to ensure that the reaction had occurred at low temperature. The Z/E ratio was established on the basis of integrations of characteristic signals in the ^{1}H NMR of the crude alkene obtained after minimal aqueous workup and before chromatographic purification (unless otherwise indicated). Thus, every effort has been made to ensure that the Z/E ratios we have observed in these reactions correspond directly to the kinetic OPA *cis*/*trans* ratio produced in the Wittig reaction. For reactions of non-stabilized ylides with benzaldehydes, alkene Z/E ratios are not used to infer the kinetic selectivity of OPA formation, since in principle it may be possible for stereochemical drift to occur at or above the temperature at which OPA decomposition to alkene and phosphine oxide commences. We instead rely on OPA *cis*/*trans* ratios (obtained by low-temperature ^{1}H and ^{31}P NMR of the Wittig reaction mixture) and β-HPS *erythro*/*threo* ratios (from low-temperature acid quenching of Wittig reactions) to establish the kinetic *cis*/*trans* ratio of OPA. In all cases, as expected,[36] these two methods were in agreement.

Finally we note that, in general, the OPA *cis*/*trans* ratio for a Wittig reaction must be at least as high as the observed alkene Z/E ratio since OPA decomposition is stereospecific and irreversible, reflecting the fact that *cis*-OPAs are normally higher in energy than *trans*-OPAs. Therefore, as long as the *cis*-OPA is indeed higher in energy than the *trans* isomer, it can be assumed that the reactions that are highly selective for the Z-alkene are under dominant or total kinetic control.[26] The consequence is that it is not ordinarily possible to obtain Z-selectivity by accident or by intervention of equilibration. Therefore, it is apposite that our conclusions (vide infra) are dependent on high Z/E ratios, which have a high likelihood of being the "true" values.

■ REACTIONS OF BENZALDEHYDES

Results for Semi-stabilized Ylides. Salts **1a**−**g** (and selected triphenyl analogues **2**) were converted to the corresponding ylides **3a**−**g** (and analogues **4**) and reacted with benzaldehydes **5a**−**i**. The Z/E ratios of the stilbene products (**6**−**27**) obtained in these reactions are shown in Tables 1 and 2. At the outset, we note that in reactions with benzaldehyde, the unsubstituted benzylide of methyldiphenylphosphine shows high E-selectivity (Table 1, entry 15), in good agreement with

Table 2. *Z*/*E* Ratio[a] for Stilbenes Produced in the Reactions of Selected Benzylidenetriphenylphosphoranes 4a,d−g, Derived from Phosphonium Salts[b] 2a,d−g (with *ortho*-Substituent X) with Selected Benzaldehydes 5a,c−f (with *ortho*-Substituent Y)

entry	ylide X	ald Y	*Z*/*E* ratio	entry	ylide X	ald Y	*Z*/*E* ratio	entry	ylide X	ald Y	*Z*/*E* ratio
1[c]	H	Cl	90:10	5[c]	Cl	H	51:49	9[c]	Cl	Cl	94:6
2	H	Br	87:13	6	Br	H	42:58	10	Br	Br	94:6
3	H	OMe	90:10	7[d]	OMe	H	42:58	11	OMe	OMe	90:10
4	H	I	88:12	8[e]	H	H	59:41	12	I	I	94:6
								13	Me	Cl	95:5

[a] *Z*/*E* ratio determined by ^{1}H NMR analysis of the crude product obtained after minimal aqueous workup. See Supporting Information for full details of the reaction, workup, *Z*/*E* analyses, and characterization of the starting materials and product alkenes. [b] Counterion Z = Br$^-$ unless otherwise noted. [c] Phosphonium salt used for this reaction was not dried in the standard manner and was not stored under argon; as a consequence, the yield of alkene from the Wittig reaction was lower and the amount of phosphine oxide produced by ylide hydrolysis higher. [d] Counterion Z = Cl$^-$. [e] From ref 14; KHMDS used to generate the ylide.

literature precedent,[84] whereas that from TPP is known to show slight *Z*-selectivity (Table 2, entry 8).[84] Tables 1 and 2 show the following trends:

(1) Reactions of unsubstituted benzylides with benzaldehydes bearing an *ortho*-heteroatom (lone-pair-bearing) substituent show markedly increased *Z*-selectivity (see Table 1, entries 1−4, 6, and 7, and Table 2, entries 1−4). This effect is observed both for benzaldehydes that are more electrophilic at the carbonyl ("reactive") than benzaldehyde itself and for *ortho*-alkoxy-substituted benzaldehdyes, which are less electrophilic than benzaldehyde. The effect is less pronounced with an *ortho*-methylthio substituent (Table 1, entry 8). Considering their very different starting points (Table 1, entry 15, vs Table 2, entry 8), the magnitude of the shift toward *Z*-selectivity on *ortho*-substitution is very much greater in the methyldiphenyl series than in the triphenyl series (Table 1, entries 1−3 and 6, vs Table 2, entries 1−4).[85] There appears to be a trend in the observed *Z*-selectivity depending on the identity of the aldehyde *ortho*-heteroatom substituent, increasing in the order F < O < Cl < Br < I.

(2) Reactions of *ortho*-substituted benzylides with benzaldehyde are moderately *E*-selective. This is less pronounced in the TPP series (Table 2, entries 5−7) than in the methyldiphenylphosphine series (Table 1, entries 9−14), and in the latter series ylides with electron-donating groups ("reactive") give the highest *E*-selectivity (Table 1, entries 13 and 14).

(3) Reactions of *ortho*-substituted benzylides with *ortho*-heteroatom-substituted benzaldehydes show *Z*-selectivity equivalent to or even greater than that of the corresponding reactions of the same aldehydes mentioned in point 1. This is almost always the case for either electron-withdrawing or -donating substituents (Table 1, entries 16−19, 22, 24, 29, and footnote *d*; Table 2, entries 9−13 and ref 69). The only notable exceptions are the reactions of *ortho*-heteroatom-substituted benzaldehydes with 2-methoxybenzylidenemethyldiphenylphosphorane **3f** (Table 1, entries 21 and 30). Once again the increase in *Z*-selectivity in these reactions in comparison to the reaction of the same ylide with benzaldehyde is generally much greater[85] in the methyldiphenylphosphine series (Table 1, entries 16−18 and 24, vs Table 2, entries 9, 10, 12, and 13), with the exception of reactions of **3f**. As with the reactions in point 1, the magnitude of the *Z*-selectivity appears to depend on the identity of the heteroatom, increasing in the order F < O < Cl ≤ Br ≤ I, culminating in the particularly striking di-iodo cases (Table 1, entry 18, and Table 2, entry 12). Although the reaction of 2-(methylthio)benzaldehyde (**5i**) with the *ortho*-bromobenzylide **3d** does show increased *Z*-selectivity (Table 1, entry 23 vs entries 8 and 10), the magnitude of the increase is not as great as with other aldehydes.

(4) The reaction of 2-methylbenzaldehyde with the unsubstituted methyldiphenylphosphine-derived benzylide shows moderate *E*-selectivity (Table 1, entry 5), as does its reaction with 2-methyl-substituted ylide (entry 20). Its reaction with *ortho*-heteroatom-substituted benzylides shows poor to moderate *Z*-selectivity (Table 1, entries 25−28). That high *Z*-selectivity is not observed in these reactions shows that the unusual effects observed in the reactions of *ortho*-heteroatom-substituted benzaldehydes are dependent on the *ortho*-substituent being lone-pair-bearing; i.e., the effect is not of steric origin.

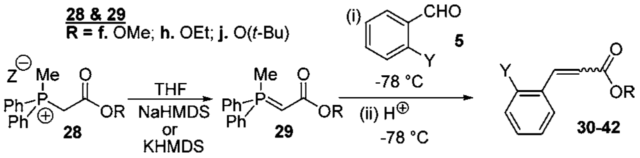
In summary, lone-pair-bearing *ortho*-substituents on benzaldehyde result in significantly enhanced *Z*-selectivity with benzylides. There is also a counter-intuitive secondary effect whereby this *Z*-selectivity is increased by *ortho*-substituents on the benzylide.

The reactions in Table 1 have been carried out under conditions for which irreversible OPA formation has been verified in reactions of semi-stabilized ylides,[35] and many of them show very high *Z*-selectivity. Consequently, we are confident that kinetic control is in operation in these reactions.[26] Table 2 shows that the same magnitudes and trends in *Z*/*E* ratios are obtained in the analogous reactions of benzylidenetriphenylphosphoranes, including the unusual *ortho*-heteroatom effects. This continuity of unexpected effects is strong evidence that the triphenyl cases too are under kinetic control. Furthermore, the trends in the results shown in Table 2, again including the signature *ortho*-effects, are entirely consistent with those obtained in our previous report,[66] except that the observed *Z*-selectivities are in general higher here. This, again, is evidence that kinetic control persists even under the aqueous bi-phasic conditions that we previously used. The effect persists even when non-dry phosphonium salt is used (Table 2, entries 1, 5, and 9), so the THF solvent is wet to some degree due to water of crystallization in the phosphonium salt. In these reactions of non-dry phosphonium salts, a significant amount of phosphine oxide is produced by ylide hydrolysis and, consequently, the yield of alkene is lower. Thus the anhydrous conditions we adopted for the purposes of ensuring kinetic control also improve the preparative utility of the reactions.

The high *Z*-selectivity in these reactions of semi-stabilized ylides points to an energy lowering of the TS leading to the *cis*-OPA (see later discussion).

Stabilized Ylides. We reasoned that, if a low-energy TS that is strongly selective for the *cis*-OPA is available to the Wittig reactions of benzylidenephosphoranes with *ortho*-heteroatom-substituted benzaldehydes, there might be a similar low-energy TS available to the reactions of stabilized ylides such as (alkoxycarbonylmethylidene)methyldiphenylphosphoranes **29**. Reactions of such ylides have previously been shown to be under kinetic control by stereospecific formation of *Z*-alkene from the *erythro*-*β*-HPSs derived from (ethoxycarbonylmethylidene)methyldiphenylphosphorane and each of several aldehydes (including benzaldehyde).[35] Therefore we examined several Wittig reactions of heteroatom-substituted aldehydes with such ylides, generated in situ from the corresponding phosphonium salt **28**, under the same conditions as were employed for the reactions of semi-stabilized ylides. The *Z*/*E* ratios determined for these reactions are shown in Table 3.

Table 3. *Z*/*E* Ratios for Reactions of Selected (Alkoxycarbonylmethylidene)methyldiphenylphosphoranes 29f,h,j (Generated *in Situ* from the Corresponding Phosphonium Salts 28) with Selected Benzaldehydes 5 To Give Enoates 30−42[a]



entry	ylide OR	aldehyde Y	enoate *Z*/*E* ratio
1[b]	OMe	H	36:64
2	OEt	H	36:64
3	O(*t*-Bu)	H	40:60
4	OEt	OMe	66:34
5	O(*t*-Bu)	OMe	77:23
6	O(*t*-Bu)	OEt	77:23
7	O(*t*-Bu)	SMe	70:30
8	OMe	Cl	79:21
9	OEt	Cl	77:23
10[b]	OMe	Br	83:17
11	OEt	Br	83:17
12	O(*t*-Bu)	Br	85:15
13	O(*t*-Bu)	I	84:16

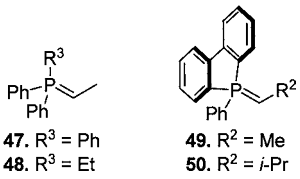
[a] All reactions were carried out at −78 °C and subsequently quenched with aqueous ammonium chloride at this temperature. *Z*/*E* ratio determined by ^{1}H NMR analysis of the crude product obtained after aqueous workup of the reaction mixture—see Supporting Information for full details. Phosphonium salt counterion Z = Br unless otherwise indicated. [b] Phosphonium salt counterion Z = Cl^-.

The *Z*/*E* ratio for the reaction of ester-stabilized ylide (ethoxycarbonylmethylidene)triphenylphosphorane[86] with benzaldehyde in THF at 20 °C has previously been found to be 23:77.[14,35] The reactions of benzaldehyde with the (alkoxycarbonylmethylidene)methyldiphenylphosphoranes investigated here show slightly decreased *E*-selectivity compared to this literature example (see Table 3, entries 1−3). The reactions of the same ylides with *ortho*-heteroatom-substituted benzaldehydes show significantly enhanced *Z*-selectivity, both in reactions in which the aldehyde is more reactive than benzaldehyde itself (Table 3, entries 4−6) and in those where it is less reactive than benzaldehyde (Table 3, entries 8−12), as well as in reactions of benzaldehydes of similar reactivity to benzaldehyde itself (Table 3, entries 7 and 13). Such selectivity is almost unprecedented outside of alcohol solvents.[2,14] As in the reactions of semi-stabilized ylides, 2-(methylthio)benzaldehyde **5i** shows somewhat reduced *Z*-selectivity compared to other *ortho*-heteroatom-substituted benzaldehydes.

These results are entirely consistent with those observed in the reactions of the semi-stabilized ylides, with the aldehydes bearing the larger bromo and iodo substituents showing the highest *Z*-selectivity, again strongly implying that the reactions occur under kinetic control.

Non-stabilized Ylides. The Li salt-free reactions of alkylidenetriphenylphosphoranes with aldehydes normally show exceptionally high *Z*-selectivity.[14] Therefore, it is experimentally almost impossible to demonstrate unequivocally an enhancement in *Z*-selectivity due to the presence of an *ortho*-heteroatom on the benzaldehyde in such Wittig reactions. In our search for suitable candidates we settled on the ylides shown in Chart 1, which do not show intrinsically high selectivity for *cis*-OPA in their reaction with benzaldehyde. This meant that there could be a demonstrable change in the selectivity for reactions of these ylides with an *ortho*-heteroatom-substituted benzaldehyde. Although reactions of ethylidenetriphenylphosphorane (**47**, see Chart 1) are typically highly *Z*-selective, there is still some scope for increased *Z*-selectivity with this particular ylide that would not be available with longer chain alkylidenetriphenylphosphoranes.

Chart 1. Non-stabilized Ylides 47−50 Used in This Study[a,b]



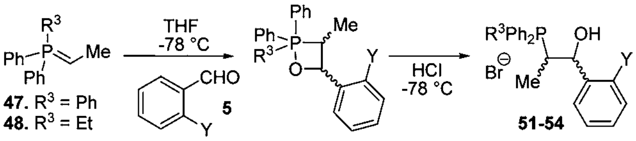
[a] Generated *in situ* by treatment of the parent phosphonium bromide salts **43−46** with NaHMDS or KHMDS. [b] The *P*-ethyl ylide **48** (rather than the *P*-methyl analogue) had to be used to avoid transylidation.

However, a complication in the context of this project was that, in several instances in the reaction of ethylidenetriphenylphosphorane with benzaldehyde, it has been shown that kinetic control does not operate, even under Li salt-free conditions, and so enhanced production of *E*-alkene is observed (see Stereochemical Drift section above).[19,25] Based on this, we felt that we could not infer the kinetic OPA *cis*/*trans* ratio from alkene *Z*/*E* ratio with certainty in Wittig reactions of non-stabilized ylides with benzaldehydes. In order to circumvent these limitations, we decided to deal with the stereochemical drift issue by determining the kinetic selectivity of the reactions through evaluation of low-temperature OPA *cis*/*trans* ratios or *erythro*/*threo* ratios of *β*-HPS obtained by low-temperature acid quenching of the reactions.

The *erythro*/*threo* ratio of the *β*-HPSs produced in the reactions of some non-stabilized ylides with benzaldehydes are shown in Table 4. The proportion of *erythro*-*β*-HPS was found to be larger in each of the reactions of ethylidenetriphenylphosphorane (**47**) and of (ethylidene)ethyldiphenylphosphorane (**48**) with 2-bromobenzaldehyde (see Table 4, entries 2 and 4) than in the reactions of the same ylides with benzaldehyde (see Table 4, entries 1 and 3). However, in the latter case the increase is modest at best. The *Z*/*E* ratios for the alkenes produced in the corresponding unquenched Wittig reactions are also shown in Table 4 (and in Table 5 below). In certain cases, these provide evidence for the occurrence of stereochemical drift in the process of OPA decomposition (see below).

The reactions of phenyldibenzophosphole (PhDBP)-derived ylides (**49**, **50**) with benzaldehydes were also investigated and

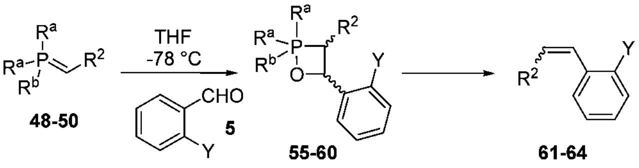
Table 4. Results of Wittig Reactions of Non-stabilized Ylides 47 and 48 with Selected Benzaldehydes 5a and 5d To Give OPA Initially and Subsequently β-HPS (51−54) after Low-Temperature Acid Quenching of OPA[a]



entry	ylide R^3	ald Y	β-HPS *erythro*/*threo* ratio[b]	alkene *Z*/*E* ratio[c]
1	Ph	H	92:8	85:15
2	Ph	Br	97:3[d]	79:21
3	Et	H	54:46[d]	32:68
4	Et	Br	65:35	56:44

[a] Ylides **47** and **48** (see Chart 1) were generated from the parent phosphonium bromide salts **43** and **44**, respectively, using NaHMDS at 20 °C. All Wittig reactions were carried out at −78 °C and subsequently quenched by cannulation of the reaction mixture into HCl solution in THF/methanol. See Supporting Information for full details. [b] The *erythro*/*threo* ratio was determined by ^{1}H and ^{31}P NMR of the crude product after minimal aqueous workup. [c] Alkene *Z*/*E* ratio from the corresponding unquenched Wittig reaction allowed to warm to room temperature after 15 min at −78 °C, as determined by integration of characteristic signals in the ^{1}H NMR of the crude product. [d] Stereochemical assignments verified from crystal structure of the *erythro* isomer.[87]

Table 5. Results of Wittig Reactions of Non-stabilized Ylides 48−50 with Benzaldehydes 5a and 5d To Give OPAs 55−60 Initially and Subsequently Alkenes 61−64[a]



entry	ylide $R^a{}_2R^bP$	ylide R^2	ald Y	OPA *cis*/*trans* ratio	alkene *Z*/*E* ratio[b]
1[c]	PhDBP[d]	Me	H	71:29	53:47
2[c]	PhDBP	Me	Br	94:6	82:18
3[e]	PhDBP	*i*-Pr	H	89:11	89:11
4[e]	PhDBP	*i*-Pr	Br	94:6	91:9
5	$EtPh_2P$	Me	H	–[f]	32:68
6	$EtPh_2P$	Me	Br	64:36[g]	56:44

[a] Ylides **48**−**50** (see Chart 1) were generated from the parent phosphonium bromide salts **44**−**46**, respectively, using KHMDS unless otherwsie indicated. All Wittig reactions were carried out at −78 °C. OPA *cis*/*trans* ratios were determined by ^{31}P NMR after cannula filtration of the reaction mixture into an NMR tube under an inert atmosphere and addition of toluene-d_8. The ^{31}P NMR spectra all indicated the presence of small amounts of phosphine oxide by-product, which were shown to be derived from the ylide by control reactions in which no aldehyde was added, and by the fact that no alkene product could be observed by NMR prior to heating. [b] Alkene *Z*/*E* ratios were determined by integration of characteristic signals in the ^{1}H NMR of the crude product. DBP-derived OPAs were heated to 80 °C for 2 h to effect alkene formation, while the $EtPh_2P$-derived OPA began to decompose to alkene and phosphine oxide at ca. −10 °C. [c] The ylide was generated at −20 °C and then stirred for 0.5 h at −45 °C before cooling to −78 °C for the reaction. The OPA generated in this reaction was monitored by ^{31}P NMR at −20 °C. [d] PhDBP = *P*-phenyldibenzophosphole moiety of ylide. [e] NaHMDS was used to generate the ylide from the parent phosphonium salt. [f] OPA signals have the same ^{31}P chemical shifts at −40 and −20 °C, so no diastereomeric ratio could be determined. [g] OPA *cis*/*trans* ratio determined at −40 °C.

provided more clear-cut evidence of the operation of the *ortho*-heteroatom effect for non-stabilized ylides. These reactions have the advantage of furnishing OPAs that are stable at room temperature (although still air sensitive), and thus it is possible to directly investigate kinetic OPA *cis*/*trans* ratios by NMR at temperatures significantly higher than −78 °C. The OPA *cis*/*trans* ratios for the reactions of benzaldehyde and 2-bromobenzaldehyde respectively with each of the ylides *P*-(ethylidene)phenyldibenzophospholane (**49**), *P*-(isobutylidene)phenyldibenzophospholane (**50**), and (ethylidene)-ethyldiphenylphosphorane (**48**) are shown in Table 5, as are the alkene *Z*/*E* ratios from the same reactions after OPA decomposition at higher temperature. The OPA *cis*/*trans* ratios were assigned by integration of characteristic signals from −60 to −70 ppm in the ^{31}P NMR spectrum of the reaction mixture. All the reactions investigated gave *Z*-alkene as the major product, and thus the largest OPA signal was assigned to the *cis*-OPA in the ^{31}P NMR spectra of the reaction mixtures, with the exception of entry 5, for which OPA diastereomers could not be resolved spectroscopically.

Comparison of Table 5, entries 2 and 4, with entries 1 and 3 again shows a distinct increase in the preference for the formation of *cis*-OPA in the reactions of 2-bromobenzaldehyde relative to the reactions of benzaldehyde. The diastereomeric ratio of the OPA produced in the reaction of benzaldehyde with (ethylidene)ethyldiphenylphosphorane (**48**) could not be determined. However, the *cis*/*trans* ratio of the OPA from the reaction of the same ylide with 2-bromobenzaldehyde closely matches the *erythro*/*threo* ratio of the β-HPS produced in the corresponding low-temperature acid quenching experiment using the same reactants, thus affirming conclusions drawn on the basis of the results in Table 4.

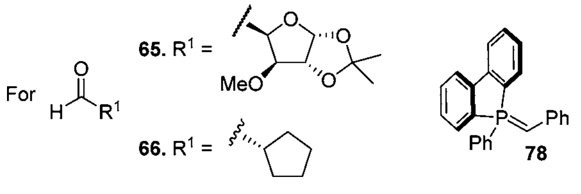
Based on the low-temperature acid quenching experiments detailed in Table 4 and the low-temperature NMR experiments in Table 5, we conclude that the *ortho*-heteroatom-induced effect is indeed in operation in the reactions of non-stabilized ylides.

A non-correspondence was observed between the kinetic OPA *cis*/*trans* ratios (evaluated as the β-HPS *erythro*/*threo* ratio) shown in Table 4 and the alkene *Z*/*E* ratio obtained in the relevant Wittig reactions. Similar non-correspondence was also observed in the decomposition of the OPA adducts of *P*-(ethylidene)phenyldibenzophospholane (Table 5, entries 1 and 2) and of (ethylidene)ethyldiphenylphosphorane (Table 5, entry 5). This demonstrates the operation of stereochemical drift in these reactions, even under Li salt-free conditions, in keeping with earlier observations of this phenomenon in reactions of ethylidenetriphenylphosphorane with aromatic aldehydes.[19] However, no variance of the OPA *cis*/*trans* ratio was observed at temperatures well below that required to effect alkene formation, so the diastereomeric ratios of the β-HPSs and OPAs can reliably be equated to the kinetic ratios of the OPA-forming steps of the reactions. Negligible stereochemical drift was observed in the formation of alkene by heating the OPA adducts of *P*-(isobutylidene)phenyldibenzophospholane (ylide **50**, see Table 5, entries 3 and 4). It appears that the irreversibility or otherwise of OPA formation in reactions of non-stabilized ylides with benzaldehydes is heavily dependent on the structure of the non-stabilized ylide, and especially on the nature of the alkylidene moiety. There may now be sufficient evidence to suggest that the Li salt-free reactions of ethylides generally undergo stereochemical drift. The reactions of longer chain alkylidenetriphenylphosphoranes with benzaldehyde may generally be under kinetic control, although there are an insufficient number of examples to allow definitive conclusions to be made.

Reactions of Non-aromatic Aldehydes. The results described above are common to all three ylide classes. They are also self-consistent and, as will be shown below, can be explained by a common TS argument. Therefore they indicate a common mechanism for the Wittig reaction of all ylide types. However, it could be counter-argued that the effect is solely confined to *ortho*-heteroatom-substituted benzaldehydes and might not extend to other aldehydes. Therefore we were anxious to find other examples.

As it turns out, we did not have far to look. Enhanced *Z*-selectivity is a known effect in Wittig reactions of aldehydes bearing a heteroatom substituent (typically an oxygen) on the *β*-carbon relative to the carbonyl group (i.e., similarly disposed relative to the carbonyl as the *ortho*-heteroatoms in benzaldehydes).[88] The literature examples of this phenomenon for the most part involve stabilized ylides[2,14,89,90] (although in these, the mechanistic origin of the high *Z*-selectivity has not been identified), but there are also some examples involving semi-stabilized ylides.[2,88] In many of these examples, the carbonyl and the *β*-substituent of the aldehyde are substituents on a ring, and high *Z*-selectivity is observed only if the carbonyl and *β*-heteroatom are oriented *cis* with respect to each other, and it is highest in alcohol solvents. High *E*-selectivity is observed for similar aldehydes in which the carbonyl and *β*-heteroatom have *trans* relative orientation[89−93] or if there is no *β*-heteroatom.[89,90]

Chart 2. Structures of Aldehydes 65 and 66 and Ylide 78[a]

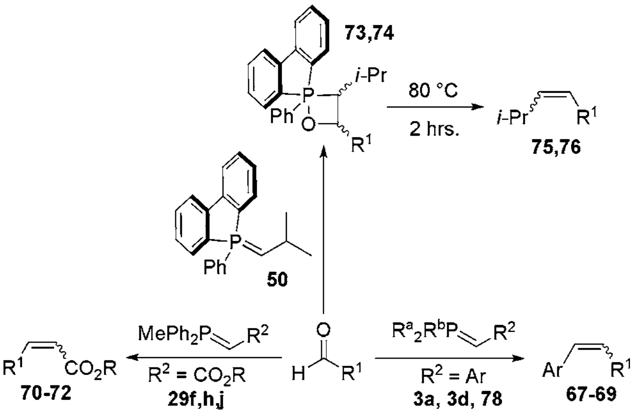


[a]Ylide **78** was generated *in situ* from the parent phosphonium bromide salt.

We chose the aliphatic aldehyde, 1,2-*O*-isopropylidene-3-*O*-methyl-*α*-D-xylopentodialdofuranose-(1,4)[94] (**65**, see Chart 2), as our non-benzaldehyde test, and we reacted it under our standard reaction conditions with some of the same ylides used in the reactions described above. The carbonyl group of this aldehyde is a substituent on a five-membered ring, and there is a *β*-methoxy substituent oriented *cis* with respect to the carbonyl.[88] High *Z*-selectivity is observed in the reactions of this aldehyde with both semi-stabilized ylides **3a,d** and **78** (Table 6, entries 1, 2, and 6) and stabilized ylides **29f,h,j** (Table 6, entries 3−5) to give alkenes **67**−**72**.[95] The reaction of benzylide **78** with a control aldehyde (**66**) lacking a *β*-heteroatom substituent showed complete *E*-selectivity (Table 6, entry 7).

The reaction of aldehyde **65** with non-stabilized ylide *P*-(isobutylidene)-*P*-phenyldibenzophospholane (**50**) was also investigated,[96] and ^{31}P NMR observation of the kinetic *cis*/*trans* ratio of the resulting OPA (**73**) at −20 °C showed it to be 94:6, as corroborated by the *Z*/*E* ratio of 92:8 observed for the alkene product **75** after heating of the OPA solution to effect OPA decomposition (Table 6, entry 8). To show that this selectivity is indeed out of the ordinary, the reaction of the same non-stabilized ylide with cyclopentanecarbaldehyde (**66**) was carried out. Observation of the *cis*/*trans* ratio of OPA **74** (by ^{31}P NMR) for this reaction showed it to be 45:55. Subsequent ^{1}H NMR observation of the *Z*/*E* ratio of the alkene (**76**) produced by heating the OPA solution showed it to be 43:57 (Table 6, entry 9), again indicating a close correspondence between the OPA and alkene diastereomeric ratios.

Table 6. *Z*/*E* Ratios for Wittig Reactions of Aliphatic Aldehydes 65 and 66[a] **with Semi-stabilized Ylides 3a,d and 78, Stabilized Ylides 29f,h,j, and Non-stabilized Ylide 50**[b]



entry	ald	ylide $R^a_2R^bP$	ylide R^2	alkene *Z*/*E* ratio
1	65	$MePh_2P$	Ph	95:5
2	65	$MePh_2P$	$2\text{-}BrC_6H_4$	95:5
3[c]	65	$MePh_2P$	CO_2Me	79:21
4[c]	65	$MePh_2P$	$CO_2(t\text{-}Bu)$	79:21
5[c]	65	$MePh_2P$	COOEt	79:21
6[d]	65	PhDBP	Ph	85:15
7[d]	66	PhDBP	Ph	0:100
8	65	PhDBP	i-Pr	92:8[e]
9	66	PhDBP	i-Pr	43:57[f]

[a]See Chart 2 for definition of R^1 in structure of **65** and **66**. [b]Ylides **3**, **29**, and **50** were generated from the parent phosphonium bromide salts **1**, **28**, and **46**, respectively, using NaHMDS at 20 °C. All Wittig reactions were carried out at −78 °C. Alkene *Z*/*E* ratios were determined by integration of characteristic signals in the ^{1}H NMR of the crude product. [c]Reactions of stabilized ylides were quenched at −78 °C by addition of aqueous NH_4Cl in order to ensure the reaction had occurred at this temperature. [d]Ylide **78** was generated from the correspoding phospholium bromide (**77**) at −20 °C by addition of THF to a mixture of the salt and KHMDS. [e]The kinetic OPA *cis*/*trans* ratio was observed by ^{31}P NMR at −20 °C and found to be 94:6. The OPA solution was heated to 80 °C for 2 h to effect alkene formation. [f]The kinetic OPA *cis*/*trans* ratio was observed by ^{31}P NMR at 30 °C and found to be 45:55. The OPA solution was heated to 80 °C for 2 h to effect alkene formation.

Thus, a very striking shift in selectivity in favor of the *Z*-alkene occurs in reactions of non-stabilized ylides with 1,2-*O*-isopropylidene-3-*O*-methyl-*α*-D-xylopentodialdofuranose-(1,4) (**65**) compared to a similar aliphatic aldehyde lacking a suitably oriented *β*-heteroatom. This non-aromatic aldehyde was shown not to undergo epimerization at the *α*-carbon under our reaction conditions. Using 1D and 2D NOESY NMR, it was shown that the hydrogen that had been at the *α*-carbon of the aldehyde remains *cis* to the *α*-hydrogen in each of the *Z*-alkene products (see Supporting Information for details). This is consistent with earlier reports of non-epimerization of this and other related aliphatic aldehydes in Wittig reactions carried out under similar conditions.[89−93,97]

Comparing phospholium ylides **50** and **78**, it is noticeable that there is a much greater shift from *E* to *Z* selectivity for the semi-stabilized analogue **78** in its respective reactions with **66** and **65**. Thus it shows complete *E*-selectivity in its reaction with **66**,[98] but very high *Z*-selectivity in its reaction with **65** (albeit not quite as high as the $MePh_2P$-derived analogue), demonstrating a very dramatic shift in the energy of the *cis*-selective TS as a consequence of the presence of the heteroatom.

This high selectivity for *cis*-OPA and/or *Z*-alkene in reactions of stabilized, semi-stabilized, and non-stabilized ylides with non-aromatic aldehyde **65** is strikingly similar to the effect seen with benzaldehydes. Therefore we ascribe it to be a consequence of the same remote heteroatom effect.

Rationalization of the Effects within the Cycloaddition Mechanism. The reactions detailed in this paper have been carried out in conditions under which OPAs derived from reagents similar to those used here have been shown not to equilibrate;[26,35] therefore, they can be assumed to be under kinetic control. We rationalize the signature aldehyde *β*-heteroatom effect within the TS model for the [2+2] cycloaddition mechanism[38] with the single additional proposal of the existence of a stabilizing phosphorus−heteroatom bonding interacction[66,79] in the *cis*-selective cycloaddition TS (see Figure 3). This results in a three-center, four-electron (3c4e) bond, with the acceptor orbital being one of the P−C bond *σ** orbitals, analogous to the (orthogonal) interaction forming the P−O bond. The proposal of such a through-space interaction has long-time precedent in organophosphorus chemistry, having been used most notably by McEwen and co-workers in simple rationalizations of the rates of quaternization of *ortho*-substituted arylphosphines[75] and *ω*-*N*,*N*-dimethylaminoalkylphosphines[99] and hydrolysis of *ortho*-substituted arylphosphonium salts.[76,100] More recently, similar through-space interactions have been proposed to explain O−Se *peri*-interactions in 1,8-substituted naphthalenes[101,102] and anthroquinones[103] and large long-range PP coupling constants in 1,8-diphosphanaphthalenes,[104−106] a phosphorus-containing carborane,[107] tetraphosphine ferrocenyl complexes,[108] biaryl bisphosphines,[109] and calix[4]arene bisphosphites.[110]

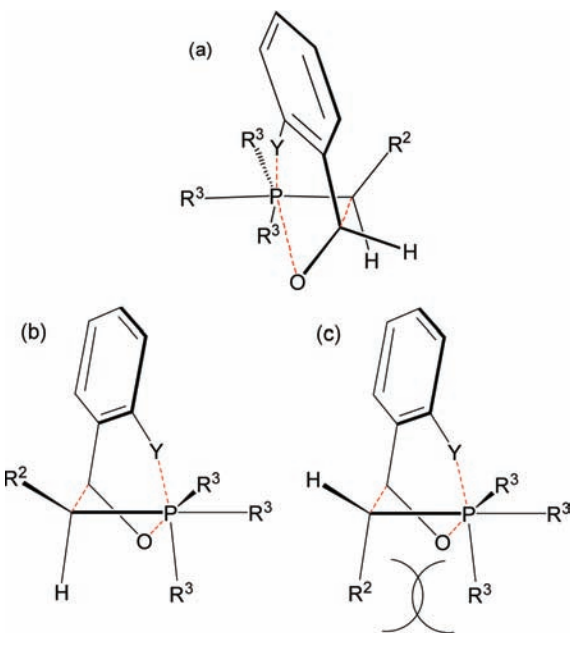


Figure 3. (a,b) Different perspectives of the puckered *cis*-selective TS with phosphorus−heteroatom bonding. The ylidic substituent R^2 is oriented as shown to minimize 2−3 steric interactions by avoiding the phosphorus R^3 substituents. (c) A *trans*-selective TS with phosphorus−heteroatom bonding suffers from large 2−3 steric interactions.

The immediate consequence of the postulated phosphorus−heteroatom bond is that the TS is forced to be puckered in order to facilitate the existence of this bond (i.e., to get the heteroatom within bonding range of phosphorus). The already sterically encumbered environment around phosphorus becomes even more crowded, and the six substituents around phosphorus assume pseudo-octahedral geometry. There now exists the potential for significant increases in the steric interactions between the phosphorus substituents and the ylide *α*-carbon substituent (2−3 interactions), in particular if the *α*-carbon substituent is in a pseudo-axial site on the forming ring. These are minimized when the *α*-carbon substituent R^2 is in a pseudo-equatorial site and thus points to the same side of the forming ring as the aldehyde substituent (see Figure 3a,b). This then is the source of the stabilization of the TS to *cis*-OPA. It is noteworthy that this *cis*-selective TS is very similar to the *trans*-selective TS proposed by Aggarwal, Harvey, and co-workers[13] for reactions of stabilized ylides (see Figure 2b above). The similarity is that the ring-puckering angle is negative—meaning that the dihedral angle between the C−O and C−R^2 bonds is greater than in a planar TS. This is the opposite of a *cis*-selective TS in a reaction of a non-stabilized ylide, so the C−O bond is approximately anti-parallel to the ylide C−R^2 bond (Figure 3a). The important difference in this case is that it is favorable for the aldehyde substituent to be close to phosphorus (i.e., in a pseudo-axial position in the forming ring) due to the phosphorus−heteroatom bond. In the absence of this bond, 1−3 interactions would dictate that the aldehyde substituent would preferentially take up a pseudo-equatorial position. The geometry of the proposed TS is consistent with the fact that high *Z*-selectivity is observed even in reactions of stabilized ylides. Such a TS should benefit from both the phosphorus−heteroatom bond *and* the advantageous anti-parallel orientation of the carbonyl C−O and ylide C−R^2 bond dipoles that is normally only present in a *trans*-selective TS.[13]

Apart from its precedence in organophosphorus chemistry, several factors argue for the existence of phosphorus−heteroatom bonding in the cycloaddition TS: (i) The effect is observed for both aromatic and aliphatic aldehydes bearing a suitably oriented remote heteroatom, whereas aldehydes with no such heteroatom substituent do not show such high *Z*-selectivity.[89,90] (ii) The effect is seen for benzaldehydes with both electron-donating and electron-withdrawing *ortho*-heteroatom substituents but hardly at all with a methyl substituent. (iii) The effect increases as the heteroatom polarizability increases and electronegativity decreases in the order F, OMe, Cl, Br, I (e.g., see Table 1, entries 1−4 and 6, and Table 3, entries 4−13), which would correlate with the ability of the heteroatom to bond to phosphorus—this has precedent in the reported structures of 1,8-selenyl-substituted naphthalenes,[101,102] where the magnitude of the proposed 3c4e selenium−heteroatom bonding interaction also appears to increase in the order F < Cl < Br. (iv) Related to point (iii) is the fact that *cis*-selectivity also increases in line with the bond length of the carbon−heteroatom bond of the aldehyde—the longer this bond and the larger and more polarizable the heteroatom, the closer the heteroatom can approach to phosphorus in the TS, thus facilitating stronger phosphorus–heteroatom bonding. (v) When the heteroatoms are switched (Table 1, entry 19 and footnote *d*), the effect is stroger for the bromoaldehyde than the fluoro. (vi) There must be some significant effect lowering the energy of the *cis*-OPA-selective cycloaddition TS particularly to make *Z*-alkene formation predominant in the reactions of ester-stabilized ylides.

With reference to points (iii) and (iv) above, we emphasize that the strength of the phosphorus–heteroatom bond is expected to depend on the ability of the heteroatom to be in close proximity to phosphorus, and therefore need not correlate with the (much greater) strengths of the corresponding phosphorus–heteroatom single bonds of stable compounds.[111] It is also expected to be subject to the intervention of steric effects, especially in reactions of semi-stabilized ylides where 2-ethoxybenzaldehyde and 2-(methylthio)benzaldehyde show less dramatic shifts toward *Z*-selectivity than other *ortho*-heteroatom-substituted benzaldehydes. In these cases there also exists the possibility of π-symmetry repulsive steric interactions between the heteroatom lone pairs or the S–Me σ-bond and the P–C σ-bonds. Another factor that could militate against phosphorus–heteroatom bonding in certain circumstances is that its existence in the *cis*-selective TS may require the conjugation between the heteroatom and the benzaldehyde ring to be broken, which would also have an associated energy cost.

The magnitude of the heteroatom-induced energy decrease of the *cis*-selective TS also appears to be affected by the degree of steric congestion about phosphorus. For reactions of semi-stabilized ylides the shift is greater for benzylides derived from PhDBP and methyldiphenylphosphine than for those derived from TPP. For non-stabilized ylides, the shift toward *Z*-selectivity decreases in the order PDBP > TPP > ethyldiphenylphosphine. Stabilized ylides derived from methyldiphenylphosphine show markedly increased *Z*-selectivity compared to those derived from TPP.[14,68]

The strongest and most compelling evidence for a phosphorus–heteroatom interaction, however, is its ability to easily accommodate and explain the counter-intuitive co-operative effect found in the semi-stabilized ylide cases. As alluded to above, *Z*-selectivity in reactions of benzylides with *ortho*-heteroatom-substituted benzaldehydes is consistently higher when the benzylide also bears an *ortho*-substituent compared to the corresponding reaction of the unsubstituted benzylide (see Tables 1 and 2 and the associated text). This can be explained as due to the *cis*-selective TS being better able to accommodate the increased steric demands (and especially 2–3 interactions) of the bulkier ylidic substituent than is the *trans*-selective TS, resulting in greater discrimination between the two. The high *Z*-selectivity obtained in the reactions of the *ortho*-heteroatom-substituted benzaldehydes with the *ortho*-methyl-substituted benzylides (Table 1, entry 24, and Table 2, entry 13) shows that this is a steric effect. This subtle augmentation of the remote heteroatom effect in reactions of benzylides with benzaldehydes appears to be specific to these reactions only. It must be very dependent on the shape of the cycloaddition TSs in this particular class of reactions because we found no noticeable change in *cis*- or *Z*-selectivity in the reactions of bulky non-stabilized or ester-stabilized ylides with heteroatom-substituted aldehydes. This observation is consistent with others indicating that the energy of the *cis*-selective TS in reactions of semi-stabilized ylides is more sensitive to steric effects than analogous TSs in reactions of non-stabilized and stabilized ylides leading to a greater influence on selectivity from the nature of the phosphonium moiety, the ylide C-substituent, and the aldehyde heteroatom substituent (if present).

Some further insight into the nature of the proposed cycloaddition TS can be gleaned from the ^{31}P NMR shifts of the OPA reaction intermediate in these reactions. We looked for any evidence of phosphorus–heteroatom bonding in the OPAs derived from the non-stabilized ylides *P*-(ethylidene)-phenyldibenzophospholane (**49**) and *P*-(isobutylidenephenyldibenzophospholane (**50**) with 2-bromobenzaldehyde and also with 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylopentodialdofuranose-(1,4) for the latter ylide. These OPA intermediates have a reasonable lifetime at low temperature. We found that the ^{31}P NMR chemical shifts of all of the OPAs generated in the course of this project were in the range δ −60 to −70 ppm. An OPA with a phosphorus–heteroatom bond (and thus hexacoordinate phosphorus) would be expected to have a significantly more negative chemical shift in the ^{31}P NMR, analogous to oxaphosphetanides, which have previously been reported to have chemical shifts below −100 ppm.[112,113] We conclude that the phosphorus in the OPA intermediates in these reactions is penta-coordinate. We reason that, although the phosphorus–heteroatom bond could in principle be present in either a puckered or a planar TS, it seems likely that if a planar TS was capable of engaging in this stabilizing interaction, then the resulting OPA should also benefit from such stabilization. The lack of any noticeable phosphorus–heteroatom interaction in the planar OPA is then consistent with the proposed puckered *cis*-selective TS.

■ CONCLUSION

The high *Z*-selectivity observed here in the Wittig reactions of heteroatom-substituted aldehydes with all ylide types is easily explicable if all ylides react with aldehyde to form OPA by irreversible direct cycloaddition through a puckered transition state. The results obtained here then, in tandem with the computational results of Aggarwal, Harvey, and co-workers, corroborate the cycloaddition mechanism proposed by Vedejs and strongly support the contention that there is a common mechanism of the Wittig reaction for all ylide types and that, ordinarily, it operates under kinetic control. In particular we believe that the results for the reactions of ester-stabilized ylides with *ortho*-heteroatom-substituted benzaldehydes provide striking evidence that the reactions of stabilized ylides occur by irreversible cycloaddition of the reactants to give OPA. We hope therefore that our results will ensure that the following points become widely known:

(A) There is one mechanism of the salt-free Wittig reaction.
(B) It is an irreversible [2+2] cycloaddition to OPA followed by a stereospecific *syn*-cycloreversion to give alkene and phosphine oxide.
(C) The stereoselectivity of all Wittig reactions is explicable by the single mechanism (especially stabilized ylide cases).

Corollaries of (A)–(C) are:

(D) OPAs are the first-formed and only intermediates in Li salt-free Wittig reactions.
(E) With very limited exceptions, no salt-free Wittig reaction is reversible.

Our view is that the now-established Li salt-free [2+2] cycloaddition mechanism should be presented in textbooks, and that a clear distinction should be made between this mechanism and that of Wittig reactions conducted in the presence of Li salts, for which the mechanism is as yet unknown.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures; details of the assignments of alkene *Z*/*E* ratios, OPA *cis*/*trans* ratios, and β-HPS *erythro*/*threo* ratios; and full characterization of all new phosphonium salts, alkenes, and β-HPSs. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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(31) For example, see ref 4a, pp 99 and 104.

(32) The isolation from Wittig reactions of non-stabilized ylides of betaine−lithium halide complexes[16] or *β*-HPS[17] after addition of acid, along with the fact that alkene could be generated by the reaction of epoxide with phosphine,[18] led, not unreasonably, to the presumption that betaines are necessarily involved as intermediates in the Wittig reaction. *Z*-Selectivity in Wittig reactions of alkylidenetriphenylphosphoranes was proposed to arise from irreversible addition of ylide to aldehyde to form *erythro*-betaine and hence *cis*-OPA and *Z*-alkene. *Anti*-addition of ylide to aldehyde was proposed to be the kinetically preferred route, giving *anti-erythro*-betaine. Bond rotation of the initially formed betaine gives *syn-erythro*-betaine, which cyclizes to *cis*-OPA and hence gives *Z*-alkene. *E*-Selectivity in Wittig reactions of stabilized ylides, and mixed selectivity in reactions of semi-stabilized ylides, was explained by reversible formation of the betaine intermediate or the subsequent OPA intermediate, with kinetically favored cyclization of *threo*-betaine to *trans*-OPA or decomposition of *trans*-OPA to *E*-alkene resulting in the equilibrium between the betaines or OPAs being effectively biased toward the (already *thermodynamically* favored) *threo*-betaine or *trans*-OPA.[29] However, the operation of kinetic control in Li salt-free Wittig reactions of all three ylide types has been demonstrated (most significantly for stabilized ylides),[26,35] and there is no evidence for kinetically preferred decomposition of *threo*-betaine or *trans*-OPA to *E*-alkene, which renders these mechanistic arguments inoperative.

(33) Only a handful of Li salt-free Wittig reactions are known to undergo reversible formation of OPA, and all such examples are reactions of non-stabilized ylides. The proposal that Wittig reactions (especially of semi-stabilized and stabilized ylides) are generally reversible grew out of the betaine mechanism (see footnote 32) and the effects exerted by Li cation on the stereoselectivities of the reaction.[19−21] However, even for reactions conducted in the presence of Li salts, the involvement of betaine in the process of OPA formation from ylide and aldehyde is not certain. Li^+ causes diminished *Z*-selectivity in reactions of alkylidenetriphenylphosphoranes,[3,14] and also results in altered selectivity in reactions of semi-stabilized ylides compared to Li salt-free conditions, while little is known regarding the effect of Li^+ (or other cations) on reactions of stabilized ylides, which are usually formed and purified (and are thus salt-free) prior to the reaction.[3] Betaine−LiBr complexes have been isolated from reactions of non-stabilized ylides,[16,19] and there exists one report in which betaine−LiBr complexes have been formed in reactions of a semi-stabilized ylide and undergo Wittig reversal, as judged by positive crossover experiments.[22] Furthermore, a non-correspondence between the initial low-temperature OPA *cis*/*trans* ratio and ultimate alkene *Z*/*E* ratio after warming of the OPA (favouring production of the *E*-isomer, "stereochemical drift") has been observed in the reaction of $Ph_3P{=}CH(n\text{-}Pr)$ and benzaldehyde in the presence of LiBr.[20] 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^+ involves OPA reversal to ylide and aldehyde.[19,25] 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.[19] Also no stereochemical drift was observed in the reaction of $Ph_3P{=}CH(n\text{-}Pr)$ with hexanal in the presence of LiBr in THF.[20] Thus it appears 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. Although the direct formation of betaine−LiBr complex from ylide and aldehyde in the presence of LiBr is certainly plausible, the presence of such complexes in Wittig reaction mixtures does not prove the involvement of betaines (salt-free or as complexes with lithium halide) in the process of OPA formation from ylide and aldehyde in the presence of Li salt, since it has been shown that betaine−LiBr complex can be formed directly from OPA.[19] Similarly, the fact that reactions of benzaldehyde with non-stabilized ylides in the presence of Li^+ undergo reversal of OPA to ylide and aldehyde[19,25] (and that the betaine−LiBr complex produced in the reaction of the semi-stabilized ylide mentioned above undergoes reversal)[22] does not necessarily mean that betaines are involved on the pathway from OPA to ylide and aldehyde—rather it may occur by direct cycloreversion. It should also be noted that the "Li salt-free" cycloaddition mechanism operates in reactions conducted in the presence of Li salts in solvents that coordinate Li ion strongly (DMSO, DMF),[33] in reactions with *low* Li ion concentration in solvents that coordinate Li ion poorly (THF, toluene),[20] and in reactions of alkylidenetriphenylphosphoranes with tertiary aldehydes, on which Li salts appear to exert no influence.[14]

(34) The observation of crossover product in *β*-HPS deprotonation experiments in alcohol solvent has also led to the suggestion of the operation of reversibility in Wittig reactions in alcohol solvents.[27] However, 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-stabilized 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.[28]

(35) Vedejs, E.; Fleck, T. *J. Am. Chem. Soc.* **1989**, *111*, 5861.

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(37) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1990**, *112*, 3905.

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(39) Although the necessity for the formation of oxaphosphetane was recognized by Wittig at the outset (ref 1), he did not consider how exactly it would be formed, nor did he specify whether it would be a true intermediate or a transition state. Subsequently, in the absence of definitive evidence, he settled on the betaine mechanism as being the most plausible: Wittig, G.; Haag, A. *Chem. Ber.* **1963**, *96*, 1536.

(40) Among the earlier mechanistic workers, the fact that the [2+2] mechanism superficially contravenes the Woodward−Hofmann rules was a factor in slowing its acceptance/development: Trippett, S., personal communication to D.G.G., 1983.

(41) Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778.

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(49) Reference 12a.

(50) See ref 6e.

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(54) Blade-Font, A.; Vanderwerf, C. A.; McEwen, W. E. *J. Am. Chem. Soc.* **1960**, *82*, 2396.

(55) The rate of OPA decomposition equals the rate of alkene formation in reactions of non-stabilized ylides,[24,25,51] and the diastereomeric ratios of the OPA and alkene are identical in these reactions and in those of semi-stabilized ylides in which OPAs can be observed spectroscopically.[23−26,35,46,50,51] In experiments involving generation of OPA by means independent of a Wittig reaction (via transient betaine species) from precursors of defined stereochemistry (e.g., *β*-HPS, epoxide), the stereochemistry of the precursor is retained in the alkene product after OPA decomposition. This has been observed in experiments involving OPAs derived from non-stabilized,[23−26,41,42,46,51] semi-stabilized,[35,42,52] and stabilized ylides.[35] In a particular Wittig reaction of a *P*-stereogenic semi-stabilized phosphonium ylide, the stereochemistry at phosphorus was retained in the phosphine oxide.[54] All of this evidence is consistent with the operation of a *syn*-elimination of phosphine oxide from a cyclic intermediate with trigonal bipyramidal phosphorus.

(56) Non-stabilized ylides of the general structure $R^aR^bR^cP{=}CHR^1$, where R^1 = alkyl and the phosphonium $R^aR^bR^cP$ moiety is not Ar_3P or *t*-$BuAr_2P$, show much lower kinetic selectivity for *cis*-OPA.[14,25,26] This can be rationalized as being a consequence of decreased 1−3 interactions and thus a lower propensity toward TS puckering. The lower *Z*-selectivity generally observed in reactions of alkylidenetrialkylphosphoranes (see ref 14) is not only a consequence of the lower kinetic selectivity for *cis*-OPA mentioned here. The *cis*-OPA reverts to ylide and aldehyde while the *trans*-OPA does not, and thus the *trans*-OPA accumulates. See refs13, 25, and 26.

(57) The *trans*-selective TS was initially proposed to be planar, which would be consistent with the observed high *E*-selectivity.[35]

(58) For example, a negatively puckered *cis*-selective TS with a favorable relative orientation of reactant dipoles (Figure 1b with aldehyde H and R^1 swapped) suffers from strong 1−3 (as well as significant 1−2) interactions, while one with the opposite sense of puckering (Figure 1d) has an electrostatically disfavored disposition of reactant dipoles. A planar *cis*-selective TS (Figure 1c) should not be particularly *disfavored* electrostatically, but suffers from large 1−2 interactions and lacks the electrostatically favored anti-parallel orientation of reactant dipoles that is present in the TS of Figure 1b. Thus high *E*-selectivity is observed in general in Wittig reactions of stabilized ylides in non-polar or polar-aprotic media, with selectivity being extremely high for ylides in which phosphorus bears bulky substituents (e.g., TPP-derived ylides), as the possibility of large 1−3 interactions dictates that these discriminate particularly well against puckering of the *cis*-selective TS. If the phosphorus substituents are not so bulky (e.g., if one phenyl is replaced by methyl), then a different *cis*-selective TS with an anti-parallel orientation of reactant dipoles can be envisaged (Figure 1b with the positions of R^1 and H swapped) since placement of the large substituent in the pseudo-axial position is not discriminated against to the same extent by 1−3 interactions, consistent with the lower *E*-selectivity observed (see ref 14).

(59) Diminished *E*-selectivity, and even predominant *Z*-selectivity, has been observed in reactions of stabilized ylides in methanol (see refs 2, 14, and 35). It seems likely that this results from a 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-stabilized ylides.

(60) It is still common for modern undergraduate texts to state that one or the other of OPA or betaine is the first-formed intermediate, but then to qualify this by saying that some or all Wittig reactions may react by the other intermediate under certain circumstances. For example see: McMurry, J. *Organic Chemistry*, 8th ed.; Brooks/Cole: 2011; p 747. Carey, F. A. *Organic Chemistry*, 7th ed.; McGraw-Hill: New York, 2008; pp 729−730. Wade, L. G., Jr. *Organic Chemistry*, 7th ed.; Prentice-Hall: Englewood Cliffs, NJ, 2010; p 836. See also refs 29 and 30.

(61) Some texts still retain the betaine mechanism as the only explanation of the Wittig reaction mechanism, e.g.: Vollhardt, K. P. C.; Schore, N. E. *Organic Chemistry: Structure & Function*, 6th ed.; Freeman: 2011; pp 806−807.

(62) Some texts do definitively show OPA as the first-formed intermediate in the Wittig reaction: Bruice, P. Y. *Organic Chemistry*, 6th ed.; Prentice-Hall: Englewood Cliffs, NJ, 2011; pp 805−806. Smith, J. G. *Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 2008; pp 794−795. However, even these do not tackle the source of stereoselectivity in the reaction.

(63) OPAs derived from semi-stabilized ylides containing the dibenzophosphole moiety have been observed by low-temperature NMR. For these, stereospecific conversion to alkene has been demonstrated by the same method as was used for reactions of non-stabilized ylides.[35]

(64) Harcken, C.; Martin, S. F. *Org. Lett.* **2001**, *3*, 3591.

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(67) This can be synthetically convenient; for example, it may have contributed to the results of recent microwave-accelerated reactions (see ref 7c).

(68) Byrne, P. A.; Higham, L. J.; McGovern, P.; Gilheany, D. G., manuscript in preparation. In this study *Z*-enones, derived from keto-stabilized ylides, were found to isomerize spontaneously under ambient conditions. Similar isomerization has also been observed in the present study to occur slowly for *Z*-2,2′-diiodostilbene.

(69) Byrne, P. A.; Rajendran, K. V.; Muldoon, J.; Gilheany, D. G. *Org. Biomol. Chem.* **2012**, *10*, 3531.

(70) For example, although 2,2′-difluorostilbene can be obtained with very high *Z*-selectivity (Z/E = 94:6) in the reaction of 2-fluorobenzylidene-triphenylphosphorane and 2-fluorobenzaldehyde (see ref 69), it is excluded from this study due to the propensity of the *Z*-isomer to undergo isomerzation—see ref 66.

(71) For example: (i) The non-isomerization of many of the other stilbenes in contact with alumina was demonstrated by subjecting samples of purified stilbene heavily enriched in the *Z*-isomer (or in some cases containing only the *Z*-isomer) to the typical chromatographic conditions used to purify the stilbenes—i.e., elution through neutral alumina using cyclohexane or pentane as solvent. In all cases the stilbene Z/E ratio was unchanged after being chromatographed. (ii) For reactions of ester-stabilized ylides, experiments were carried out to show that the *Z*-isomer of the enoate product did not isomerise under the reaction conditions. See the Supporting Information for further details of these control experiments.

(72) See ref 28b.

(73) OPA *cis*/*trans* ratio determined from the *erythro*/*threo* ratio of the *β*-HPS produced in the low-temperature acid quenching of the Wittig reaction.

(74) OPA *cis*/*trans* ratio determined by low-temperature ^{31}P NMR of the Wittig reaction mixture.

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(85) The reaction of benzylidenemethyldiphenylphosphorane **3a** with benzaldehyde favors *E*-selectivity to a much greater extent than the corresponding reaction of benzyildenetriphenylphosphorane **4a**, and hence the greater shift toward *Z*-selectivity in reactions of the former with *ortho*-heteroatom-substituted benzaldehydes represents a much larger decrease in the activation energy of the *cis*-selective pathway in these reactions.

(86) KHMDS was used to generate the ylide from the precursor phosphonium salt.

(87) Byrne, P. A.; Müller-Bunz, H.; Gilheany, D. G., manuscript in preparation.

(88) See ref 2, pp 882−887, in which can be found an extensive collection of examples of atypical Wittig reaction stereoselectivity apparently induced by the presence of a suitably placed heteroatom on the aldehyde reactant. Amongst these are included numerous examples of high *Z*-selectivity in reactions of β-alkoxy aldehydes. The vast majority of these examples were carried out in polar protic solvents—most commonly methanol. The same section of ref 2 also includes examples of high *Z*-selectivity in reactions of α-heteroatom-substituted aldehydes. Aldehyde **65**, in addition to being a β-heteroatom-substituted aldehyde, also has a heteroatom α to the carbonyl, which may have some impact on the level of *Z*-selectivity observed with this aldehyde.

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