# Chapter 2
# Wittig Reactions of Aldehydes Bearing a β-Heteroatom Substituent

## 2.1 Fragility of Alkene Stereochemistry: The True *Z/E* Ratio

In this work, the kinetic selectivity of the OPA forming step in Wittig reactions of semi-stabilised and stabilised 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 both during and after the Wittig reaction. The latter problem is prosaic but pernicious. It is not sufficiently recognised 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 (especially benzoic acid) [1], strong bases [2], the chromatographic stationary phase used in purification, the solvent, heat and sunlight [3]. Previous literature reports have been identified in a publication by the Gilheany group [4], and also in the review of Vedejs and Peterson where there was undoubtedly isomerisation in favour of the *E*-alkene subsequent to the actual Wittig reaction. This can be synthetically convenient, for example, it may contribute to the results of recently reported microwave accelerated reactions, e.g. [5]. Indeed, in the course of this project, isomerisation of certain *Z*-alkenes has been observed simply by allowing the sample to stand for a period—this isomerisation is most likely to have been caused by light. *Z*-4-arylbut-3-en-2-ones were found to be particularly susceptible, to the point where they could not be purified from a reaction mixture due to almost complete conversion to the *E*-isomer. Others—notably 2-iodostilbene,

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2,2′-diiodostilbene, and 2,2′-difluorostilbene[1]—were also found to undergo partial, if not complete isomerisation when allowed to stand in the light. Extensive precautions have been taken in this study to ensure that the observed *Z/E* ratio is truly reflective of that rendered by the Wittig reaction in question. Thus all aldehydes used were checked by NMR prior to use for the presence of the carboxylic acid, the alkene *Z/E* ratio in each reaction was measured immediately after a minimal work-up before chromatography and great care was taken to ensure that the reactions were carried out under conditions for which the operation of kinetic control has been demonstrated. Dry solvents were used for reactions and NMR studies, dry phosphonium salts and non-nucleophilic bases NaHMDS and KHMDS were employed to form the ylides, and both were stored under argon in a glove box. Reaction flasks were flame dried and cooled under vacuum to ensure the exclusion of moisture. The rubber tubing used to conduct nitrogen to the reaction flask from the Schlenk manifold was kept dry by fitting a syringe barrel and needle to the open end of the tubing when it was not in use and inserting the needle through a septum into a flask of solid dry KOH pellets. The hygroscopic KOH gradually dries the rubber tubing of water if the procedure described is continued for a period of time. 2,2′-difluorostilbene is excluded from Table 2.1 since it has been shown to be prone to isomerisation after completion of the Wittig reaction [4].

Several of the above factors are also relevant to the issue of *stereochemical drift*, which is another, more mechanistically significant, source of erosion of the stereochemistry. It describes the well-established phenomenon that, under certain circumstances, the first-formed OPAs from cycloaddition may equilibrate [3, 6, 7], leading to a different (thermodynamic) ratio of *cis/trans* OPAs and therefore a different *Z/E* alkene ratio. Reactions conducted in the presence of additives such as salts that are soluble in the reaction solvent—in particular lithium cation [3, 8] and iodide anion [9, 10] salts—have been shown to give *Z/E* ratios that are altered with respect to reactions conducted in the absence of such additives. Lithium halide with small amounts of alcohol [3], and benzoic acid [1] have also exhibited this effect when present in Wittig reaction mixtures. The addition of methanol to reactions of non-stabilised ylides at low temperature has also been shown to result in increased formation of *E*-alkene compared to reactions conducted by the same procedure without alcohol addition; no such increase is observed if the methanol is added after the reaction mixture has been warmed to room temperature [11]. The role of lithium ion is solvent dependent, with a profound effect being observed for reactions in non-polar solvents, and essentially no effect in solvents that readily complex $Li^+$ [8, 12]. Hydroxylic solvents and high temperature have also been implicated as possible initiators of OPA equilibration in reactions of aromatic aldehydes [3]. In some cases, it is even possible for stereochemical drift to occur *in the absence of dissolved salts* (Li-containing or otherwise). This has been described in detail in Sect. 1.4.1.1, but briefly, it has been observed for OPAs derived from trialkylphosphonium alkylides and tertiary or aromatic aldehydes [6, 7, 13], and also for

[1] 2,2′-difluorostilbene is extremely prone to isomerisation—see Ref. [4].

OPAs derived from ethylidenetriphenylphosphoranes and aromatic aldehydes (although in the latter of these OPA equilibration only occurs at or above the temperature at which OPA can decompose to alkene) [14]. In all cases, equilibration results in transformation of the *cis*-OPA into the *trans*-OPA, since the observed proportion of *E*-alkene is greater than that of the *trans*-OPA [6, 7].

This is why, in order to discuss the relevance of the results obtained in this project to the Wittig mechanism it must be ensured that the reactions occur under conditions of kinetic control—i.e. conditions for which irreversibility of OPA and alkene formation has been explicitly demonstrated. The "true *Z/E* ratio" is defined as that obtained from a kinetically controlled reaction and preserved subsequently during isolation and measurement.

For reactions of non-stabilised ylides with benzaldehyde, it is not sufficient to rely on *Z/E* ratios to indicate the kinetic selectivity of the OPA forming step, since stereochemical drift has been shown to be in operation by our low temperature NMR and acid quenching experiments with these ylides. Instead, the OPA *cis/trans* ratios have in some cases been obtained directly by low temperature $^{1}$H and $^{31}$P NMR observation of Wittig reaction mixtures. In others, low temperature acid quenching of the Wittig reaction has been carried out and the *erythro/threo* ratio of the *β*-hydroxyphosphonium salt (*β*-HPS) determined to establish the kinetic *cis/trans* ratio of OPA. These two methods of obtaining the kinetic OPA *cis/trans* ratio have been found to be in excellent agreement in the experiments conducted in this project, and in reports from other groups [15].

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. 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 [6]. 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) on the results of reactions of semi-stabilised and stabilised ylides are dependent on high *Z/E* ratios, which have a strong probability of being the "true" values, given the conditions under which they were carried out, and the fact that they generally show very high *Z*-selectivity. For reactions of non-stabilised ylides the kinetic OPA *cis/trans* ratio has been explicitly determined. The operation of kinetic control (or lack thereof) in these reactions, although not required for the determination of the kinetic selectivity of OPA formation, has been explicitly demonstrated by comparison of kinetic OPA *cis/trans* ratios and alkene *Z/E* ratios.

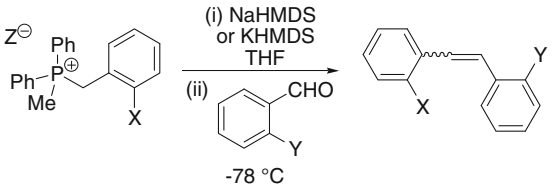
## 2.2 *Z/E* Ratios of Alkenes Produced in the Reactions of Benzylides with Benzaldehydes

Kinetic control has been shown to operate in the reactions of methyldiphenylphosphine-derived semi-stabilised ylides by demonstration of stereospecific decomposition of the betaines and OPAs transiently produced in β-HPS deprotonation experiments [16, 17], as described fully in Sect. 1.4.1.2. Thus to prove that the high *Z*-selectivity observed in reactions of benzylides with *ortho*-heteroatom substituted benzaldehydes [4] was due to the selectivity inherent in a kinetically controlled process, reactions of several benzylidenemethyldiphenylphosphoranes with various benzaldehydes were carried out under the experimental conditions for which this operation of kinetic control had been established, i.e. using a non-nucleophilic base to generate the ylide (NaHMDS or KHMDS), in THF (polar aprotic) solvent, in the absence of dissolved salts (especially Li-salts), and at −78 °C. Reactions of similar benzylidenetriphenylphosphoranes were also carried out to allow comparison of the *Z/E* ratios obtained. A minimal work-up was carried out, involving removal of dissolved salts (and *some* phosphine oxide) by a water wash of the crude reaction product dissolved in pentane or cyclohexane. *Z/E* ratios were usually assigned based on integration of signals characteristic of the *Z* and *E* isomers in the $^{1}$H NMR spectrum of the material produced after this work-up. In instances where the signals of the alkene isomers could not be unambiguously assigned or identified, the material was purified by elution through a neutral alumina plug using pentane or cyclohexane as solvent. This resulted in the removal of aldehyde and phosphine oxide, which allowed many or all of the signals belonging to each alkene isomer to be assigned and integrated. The stilbenes for which alumina plug purification was necessary were shown not to isomerise in contact with the stationary phase by subjecting samples of known *Z/E* ratio to the purification procedure; the *Z/E* ratio was shown to be the same before and after this procedure. Subsequent to much of this work, a new technique for the removal of phosphine oxide and aldehyde from the Wittig reaction mixture was discovered. Treatment of the crude product with oxalyl chloride caused the phosphine oxide to form chloro phosphonium salt. Addition of cyclohexane to this mixture and cannula filtration resulted in the complete isolation of the alkene after solvent removal. The *Z/E* ratio of the alkene was unaffected by this process. See Chap. 3, and Sect. 4.9 of Chap. 4 for full details.

### *2.2.1 Reactions of Benzylidenemethyldiphenylphosphoranes with Benzaldehydes*

Shown in Table 2.1 are the stilbene *Z/E* ratios (determined by comparison of the integrations of signals assigned to the *Z* and *E* isomers in the $^{1}$H NMR of the crude product) found for reactions of benzylidenemethyldiphenylphosphoranes with

**Table 2.1** *Z/E* ratio[a] for stilbenes produced in the reactions of benzylidenemethyldiphenylphosphoranes, derived from the parent phosphonium salts[b] (with *ortho*-substituent X) with benzaldehydes (with *ortho*-substituent Y)




| Entry | Ylide X | Ald Y | *Z:E* ratio |
|---|---|---|---|
| 1 | H | Cl | 93:7 |
| 2 | H | Br | 94:6 |
| 3 | H | I | 97:3 |
| 4 | H | F | 84:16 |
| 5 | H | OMe | 88:12 |
| 6 | H | H | 15:85 |
| 7 | Cl | H | 34:66 |
| 8 | Br | H | 33:67 |
| 9 | I | H | 28:72 |
| 10 | F | H | 41:59 |
| 11[c] | Me | H | 7:93 |
| 12[c] | OMe | H | 12:88 |
| 13 | Cl | Cl | 97:3 |
| 14 | Br | Br | 99:1 |
| 15 | I | I | >99:1 |
| 16 | F | F | 94:6 |
| 17 | F | Br | 94:6 |
| 18 | Br | F | 84:16 |
| 19[c] | Me | Cl | 94:6 |
| 20[c] | OMe | OMe | 48:52 |
| 21 | Br | OMe | 95:5 |
| 22[c] | Me | Me | 31:69 |
| 23 | Br | Me | 75:25 |
| 24 | Cl | Me | 73:27 |
| 25 | F | Me | 51:49 |
| 26 | H | Me | 33:67 |
| 27[c] | OMe | Me | 66:34 |

[a] *Z/E* ratio determined by $^1$H NMR analysis of the crude product obtained after aqueous work-up. See Sects. 4.3 and 4.4 for full details of the reaction, the base used to generate the ylide, work-up and analyses

[b] Counterion Z = $Br^-$ in all cases except where otherwise noted

[c] Counterion Z = $Cl^-$

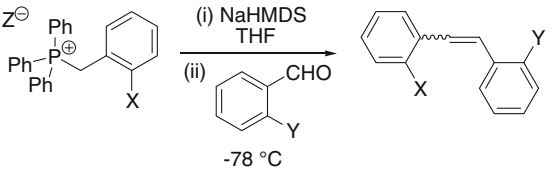
benzaldehydes under the conditions described above. The ylide in each reaction was generated in situ from the parent phosphonium salt using NaHMDS or KHMDS as base.

From the results in Table 2.1 the following observations can be made:

1. The reaction of benzylidenemethyldiphenylphosphorane and benzaldehyde (the unsubstituted reaction partners) gives stilbene with a *Z/E* ratio of 15:85 (see entry 6), in good agreement with literature precedent for this reaction under the same reaction conditions.[2]
2. Reactions of benzylidenemethyldiphenylphosphorane with *ortho*-heteroatom substituted benzaldehydes show very high *Z*-selectivity (entries 1–5). This *Z*-selectivity is observed for benzaldehydes more reactive at the carbonyl than benzaldehyde (entries 1, 2, 4), for 2-methoxybenzaldehyde, which is less reactive than benzaldehyde (entry 5), and for 2-iodobenzaldehyde (entry 3), which is similar in reactivity to benzaldehyde.
3. Reactions of ylides bearing an *ortho*-substituent on the benzylidene group with benzaldehyde show moderate to very high *E*-selectivity (see entries 7–12). *E*–selectivity increases approximately in parallel with the increasing activating ability of the *ortho*-substituent i.e. in the order F, Cl, Br, I, H, OMe, Me—so that more reactive ylides give greater *E*-selectivity.
4. Reactions of *ortho*-substituted benzylides with *ortho*-heteroatom substituted benzaldehydes show equivalent or *even greater* *Z*-selectivity than the reactions mentioned in point 2 (see entries 13–19, 21). This is the case for aldehydes that bear an electron withdrawing substituent and are thus more reactive than benzaldehyde (entries 13, 14, 16–19), for those bearing an electron donating substituent that are therefore less reactive than benzaldehyde (entry 21), and for 2-iodobenzaldehyde (entry 15), which is of similar reactivity to benzaldehyde. In the context of these results, 2-methoxybenzylidenemethyldiphenylphosphorane shows unusually low *Z*-selectivity in its reaction with 2-methoxybenzaldehyde (entry 20), although the same aldehyde was shown to react with 2-bromobenzylidenemethyldiphenylphosphorane with very high *Z*-selectivity (entry 21). That the reaction of 2-methylbenzylidenemethyldiphenylphosphorane with 2-chlorobenzaldehyde shows comparably high *Z*-selectivity to the other reactions shows that the contribution of the ylide benzylidene substituent to the selectivity is of steric origin i.e. it is *not* an electronic effect.
5. The reaction of 2-methylbenzaldehyde with benzylidenemethyldiphenylphosphorane shows moderate *E*-selectivity (entry 26), as does the reaction of this aldehyde with 2-methylbenzylidenemethyldiphenylphosphorane (entry 22). Its reaction with *ortho*-heteroatom substituted benzylides shows poor to moderate *Z*-selectivity (entries 23–25 and 27). That high *Z*-selectivity is not observed in these reactions shows that the effect observed in the reactions of *ortho*-heteroatom substituted benzaldehydes is dependent on the *ortho* substituent being lone-pair bearing—i.e. *the effect is not of steric origin*.

[2] See Ref. [3] pp. 61–70.

**Table 2.2** *Z/E* ratio[a] for stilbenes produced in the reactions of benzylidenetriphenylphosphoranes derived from the parent phosphonium salts[b] (with *ortho*-substituent X) with benzaldehydes (with *ortho*-substituent Y)




| Entry | Ylide X | Ald Y | *Z*:*E* ratio |
|---|---|---|---|
| 1 | H | Br | 87:13 |
| 2 | H | I | 88:12 |
| 3[d] | H | H | 59:41 |
| 4 | H | OMe | 90:10 |
| 5 | Br | H | 42:58 |
| 6[e] | OMe | H | 42:58 |
| 7[c] | Br | Br | 94:6 |
| 8 | I | I | 94:6 |
| 9 | Me | Cl | 95:5 |
| 10[e] | OMe | OMe | 90:10 |

[a] *Z/E* ratio determined by $^1$H NMR analysis of the crude product obtained after aqueous work-up. See Sects. 4.3 and 4.4 for full details
[b] Counterion Z = $Br^-$ in all cases except where otherwise noted
[c] Result cross-checked by normal phase HPLC
[d] From Ref. [3]
[e] Counterion Z = $Cl^-$

## 2.2.2 *Reactions of Benzylidenetriphenylphosphoranes with Benzaldehydes*

A similar (but smaller) set of reactions involving various benzaldehydes were also carried out using benzylidenetriphenylphosphoranes under the same experimental conditions. The *Z/E* ratios of the stilbenes produced in these reactions are shown in Table 2.2. The ylide in each reaction was generated in situ from the parent phosphonium salt using NaHMDS as base.

Examination of the results in Table 2.2 reveals the following:

1. The reaction of benzylidenetriphenylphosphorane and benzaldehyde has previously been found to give stilbene with a *Z/E* ratio of 59:41 (see entry 3) [3].
2. Reactions of benzylidenetriphenylphosphorane with *ortho*-heteroatom substituted benzaldehydes show high *Z*-selectivity (entries 1, 2, 4). This is observed for 2-bromobenzaldehyde (entry 1), which is more reactive than benzaldehyde, for 2-iodobenzaldehyde, which is of similar reactivity to benzaldehyde, and for 2-methoxybenzaldehyde (entry 4), which is less reactive than benzaldehyde.

3. Reactions of *ortho*-heteroatom substituted ylides with benzaldehyde show low *E*-selectivity (entries 5 and 6).
4. Reactions of ylides bearing an *ortho*-substituent on the benzylidene group with *ortho*-heteroatom substituted benzaldehydes show even higher *Z*-selectivity than the reactions mentioned in point 2. This is observed for benzaldehydes that are more reactive than benzaldehyde (entries 7 and 9), for 2-methoxybenzaldehyde (entry 10), which is less reactive than benzaldehyde, and for 2-iodobenzaldehyde, whose reactivity is similar to that of benzaldehyde. The result shown in entry 9 (reaction of 2-methylbenzylidenetriphenylphosphorane with 2-chlorobenzaldehyde) shows that it is the increased steric bulk of the *ortho*-substituted ylides of entries 7–10 that causes increased *Z*-selectivity compared to reactions of point 2 (entries 1, 2, 4).

### 2.2.3 Discussion

The result in Tables 2.1 and 2.2 are entirely consistent with each other, with the exception of Table 2.1 entry 20. Reactions of unsubstituted benzylides with *ortho*-heteroatom substituted benzaldehydes show very high *Z*-selectivity—far higher than that observed in the reaction of the same ylide with benzaldehyde itself. Benzylides with an *ortho*-substituent react with *ortho*-heteroatom substituted benzaldehydes with even higher *Z*-selectivity than the corresponding reactions of the unsubstituted ylides. The average proportion of *Z*-alkene produced in reactions of benzaldehydes lacking a heteroatom substituent, calculated from entries 6–12 and 22–27 of Table 2.1, and entries 3, 5 and 6 of Table 2.2, is 49 %. The same quantity calculated for reactions of *ortho*-heteroatom substituted benzaldehydes using Table 2.1 entries 1–5 and 13–21, and Table 2.2 entries 1, 2, 4, and 7–10 is 90 %, so there is an average jump of 41 % in *Z*-selectivity induced in reactions of semi-stabilised ylides by there being an *ortho*-heteroatom on the benzaldehyde.

The increase in *Z*-selectivity from reactions of unsubstituted benzylides to *ortho*-substituted benzylides appears to be as a result of a steric effect, since it operates whether the ylide *ortho*-substituent is lone-pair bearing or otherwise. The same *ortho*-substituted benzylides react with benzaldehyde with moderate to high *E*-selectivity; this indicates that the geometry of the TSs in this latter set of reactions is completely different to that of the TSs in reactions involving *ortho*-heteroatom substituted benzaldehydes. It is also obvious by examination of the results that methyldiphenylphosphine-derived benzylides consistently show higher *Z*-selectivity than their triphenylphosphine-derived analogues; we believe this to be of mechanistic significance, and it will be discussed more fully later in this section and following sections of this chapter.

Two very important observations on the set of results presented in Tables 2.1 and 2.2 indicate firstly that the high *Z*-selectivity induced by the presence of an *ortho*-heteroatom on the benzaldehyde arises from an electronic effect and not a

steric one, and secondly that the electronic effect operates through space and not by electron withdrawal or donation through the aromatic system of the benzaldehyde. The reactions detailed in Table 2.1 entries 22–27 (involving 2-methylbenzaldehyde) show no great *Z*-selectivity, and thus it can be concluded that the presence of an *ortho*-substituent *per se* on the benzaldehyde partner, although necessary, is not sufficient to induce high *Z*-selectivity in Wittig reactions—the *ortho* substituent should bear a lone pair of electrons. 2-Methoxybenzaldehyde, which is *less* reactive than benzaldehyde itself, shows comparably high *Z*-selectivity to reactions of 2-halobenzaldehydes. In the previous work in the laboratory, it had been thought that the explanation for the high *Z*-selectivity laid in the earlier cycloaddition TS, induced by the higher inherent reactivity of the electron-deficient 2-halobenzaldehydes. The cycloaddition TS in a Wittig reaction of 2-methoxybenzaldehyde cannot be earlier than the TS in the reaction of benzaldehyde with the same ylide due to the fundamentally lower reactivity of the former. The same comments apply to the reactions of 2-iodobenzaldehyde, whose reactivity towards nucleophiles is similar to that of benzaldehyde. Thus, *Z*-selectivity cannot be simply due to the *cis*-selective TS being early and hence puckered, given that none of the control reactions with benzaldehyde are *Z*-selective. The observation of *Z*-selectivity in reactions of *ortho*-heteroatom substituted benzaldehydes is therefore the consequence of the existence of a fundamentally different cycloaddition TS in these reactions. Since the *Z*-selective effect is not of steric origin and not an electronic effect conducted through the aromatic system, it must operate through space—that is, there must be a bond formed (transiently or otherwise) in the TS leading to OPA, which causes the *cis*-selective TS to be favoured over the *trans*-selective TS.

It is proposed, in light of the results of Tables 2.1 and 2.2, that in these reactions there exists a bonding interaction between the *ortho*-heteroatom and phosphorus in the TS leading to *cis*-OPA, as shown in Fig. 2.1. The phosphorus atom has low-lying acceptor orbitals ($P-R^3$ $\sigma^*$ orbitals) in the TS structure that could facilitate the existence of such a bond.

The very existence of the putative phosphorus-heteroatom bond requires the heteroatom-bearing aryl group of the benzaldehyde to be close to phosphorus. As a result, this TS has an entirely different set of steric interactions than would be expected for a TS of an analogous reaction involving an aldehyde that lacks an *ortho*-heteroatom substituent. This is so not least because the other substituents joined to phosphorus presumably rearrange (perhaps to pseudo-octahedral geometry) to allow room for the bond to form. Thus 1–3 steric interactions are not an issue in this TS to the same extent that they would be in "normal" Wittig cycloaddition TSs—both because of the rearrangement of the phosphorus-substituents, and because of the existence of the phosphorus-heteroatom bond. In proposing such a TS it is initially impossible to say with certainty whether the TS should be puckered or planar. However, $^{31}$P NMR studies of the OPAs produced in reactions of non-stabilised ylides with aldehydes bearing heteroatom in the $\beta$-position relative to the carbonyl (which will be described in detail later, in Sect. 2.4) shed some light on the issue. OPAs are constrained to being essentially planar (puckering angle $< 30°$). The chemical shifts of the OPAs in the $^{31}$P NMR ($\delta_P$ in the range of

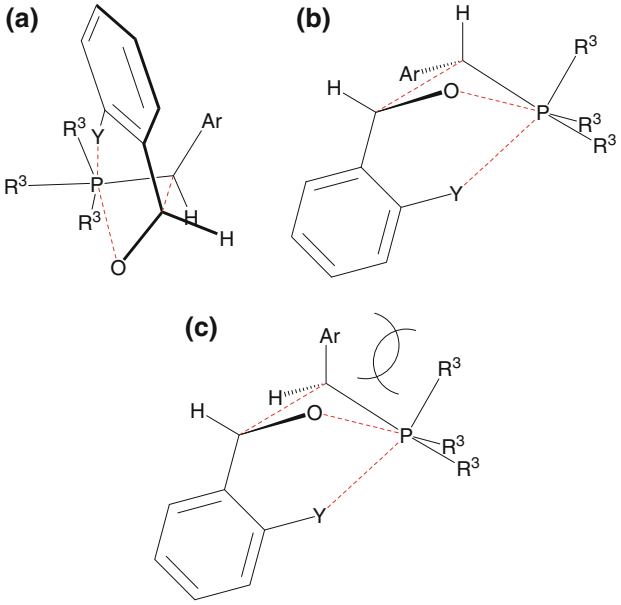



**Fig. 2.1** **a** and **b** show different perspectives of the puckered *cis*-selective TS with phosphorus-heteroatom bonding. The ylide α-substituent (Ar) is oriented as shown to minimise 2–3 steric interactions by avoiding the phosphorus $R^3$ substituents. **c** A *trans*-selective TS with phosphorus-heteroatom bonding suffers from large 2–3 steric interactions

−60 to −75 relative to $H_3PO_4$) are entirely characteristic of pentacoordinate phosphorus, and so it is clear that no phosphorus-heteroatom bond exists in the planar OPA. We conclude that the geometry of a planar ring is such that the formation of the phosphorus-heteroatom bond is not possible. Based on this observation, it is postulated that the *cis*-selective TSs in reactions of heteroatom substituted aldehydes that show high *Z*-selectivity are puckered in order to facilitate the phosphorus-heteroatom binding interaction.

In a puckered TS involving phosphorus-heteroatom bonding, it seems likely that there should be large steric interactions between the rearranged phosphorus ligands ($R^3$) and the ylide α-substituent (2–3 interactions), since there are six substituents around phosphorus in this species. Minimisation of 2–3 interactions dictates that the ylide α-substituent points to the same side of the forming ring as the aldehyde substituent. The relatively small 1–2 interactions (*gauche* interaction between ylide and aldehyde substituent) inherent in this conformation are much less significant than the 2–3 interactions present in a TS in which the ylide α-substituent and the aldehyde aryl group point to opposite sides of the forming ring (*trans*-selective TS, see Fig. 2.1c). Thus, the most energetically favourable cycloaddition TS (with 2–3 interactions minimised) is selective for *cis*-OPA (see two schematic representations of this TS from different perspectives in Fig. 2.1a and b), which gives rise ultimately to *Z*-alkene.

Further evidence for the existence of a bonding interaction between phosphorus and the heteroatom can be seen by examination of results from Tables 2.1 and 2.2:

1. The effect increases as the heteroatom polarizability increases and electronegativity decreases (Table 2.1, entries 1–5: i.e. in the order F, O, Cl, Br, I), which correlates with the ability of the heteroatom to bond to phosphorus.
2. The effect increases in line with the increasing length of the carbon-heteroatom bond. The relatively long C–I and C–Br bonds may place these heteroatoms more easily in bonding range of phosphorus.
3. The reaction of 2-fluorobenzylidenemethyldiphenylphosphorane with 2-bromobenzaldehyde is more *Z*-selective than the reaction of 2-bromobenzylidenemethyldiphenylphosphorane with 2-fluorobenzaldehyde (Table 2.1 entries 17 and 18), which again is in line with a greater TS bonding interaction in the former case.
4. There must be some significant effect resulting in the dramatic reversal of selectivity from *E* to *Z* when going from the reaction of 2-methylbenzylidene methyldiphenylphosphorane with benzaldehyde (Table 2.1 entry 11, *Z/E* = 7:93) to its reaction with 2-chlorobenzaldehyde (Table 2.1 entry 19, *Z/E* = 94:6), and indeed to result in such extraordinarily high *Z*-selectivity in the reaction giving 2,2′-diiodostilbene, shown in Table 2.1 entry 15.
5. The latter reaction is overwhelmingly selective for the thermodynamically disfavoured isomer, strongly indicating the operation of kinetic control. Since phosphorus-heteroatom bonding has been shown by NMR experiments to be absent in OPAs produced in the reactions of non-stabilised ylides with 2-bromobenzaldehyde (see Sect. 2.4), and since the operation of stereochemical drift observed in these reactions furnishes an increased proportion of *E*-alkene via *trans*-OPA, the *cis*-OPA must be thermodynamically disfavoured relative to the *trans*-isomer in these reactions of non-stabilised ylides. It can reasonably be assumed that the same is true for OPAs in reactions of semi-stabilised and stabilised ylides.

As alluded to earlier, *Z*-selectivity in reactions of benzylides with *ortho*-heteroatom substituted benzaldehydes is consistently higher when the benzylide bears an *ortho*-substituent compared to the corresponding reaction of the unsubstituted benzylide (see Tables 2.1 and 2.2). A possible explanation for this phenomenon is that the *cis*-selective TS is 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 2.1 entry 19, Table 2.2 entry 9) shows that this is indeed a steric effect.

If this subtle augmentation of the remote heteroatom effect in reactions of benzylides with benzaldehydes is genuine, as is suggested by the consistency of the results in Tables 2.1 and 2.2, then it is not consistently reproduced in the corresponding reactions of other types of ylides, as described below. Acetonylides with increased steric bulk on the ylide $\gamma$-carbon (relative to phosphorus) do show

significantly increased *Z*-selectivity compared to the unsubstituted acetonylide.[3] However, there is no significant effect of ylide steric bulk on selectivity in reactions of non-stabilised[4] and ester-stabilised[5] ylides respectively with *ortho*-heteroatom substituted benzaldehydes. The operation of this effect may be very dependent on the shape of the cycloaddition TSs in these particular reactions.

## 2.3 *Z/E* Ratios of Alkenes Produced in the Reactions of Stabilised Ylides with Benzaldehydes

Following the above work on the selectivity in reactions of semi-stabilised ylides, the possibility of the operation of similar *ortho*-heteroatom induced *Z*-selectivity in Wittig reactions of stabilised ylides was investigated. The reactions were carried out under identical conditions to those employed in the investigation of reactions of semi-stabilised ylides, with the exception that in many cases the reaction was quenched at −78 °C in order to prove that the Wittig reaction had actually occurred at that temperature (and not in the course of warming up to room temperature). Kinetic control had been shown to operate in the reactions of methyldiphenylphosphine-derived ester-stabilised ylides at 20 °C in both THF and methanol solvents by stereospecific decomposition to *Z*-alkenes of the betaines and OPAs necessarily produced in the deprotonation of *erythro*-*β*-HPSs derived from stabilised ylides [16]. Kinetic control for reactions in THF at −78 °C could thus be assumed. The ylides employed in the investigation were methyldiphenylphosphine and triphenylphosphine-derived ester and keto-stabilised ylides.

### *2.3.1 Reactions of (Alkoxycarbonylmethylidene) methyldiphenylphosphoranes (Ester-Stabilised Ylides)*

The *Z/E* ratios of the alkyl cinnamates produced in the reactions of selected (alkoxycarbonylmethylidene)methyldiphenylphosphoranes with benzaldehydes in THF at −78 °C are shown in Table 2.3. The ylide in each reaction was generated in situ from the parent phosphonium salt using NaHMDS or KHMDS as base. The reactions were quenched at low temperature by the addition of saturated aqueous ammonium chloride solution.

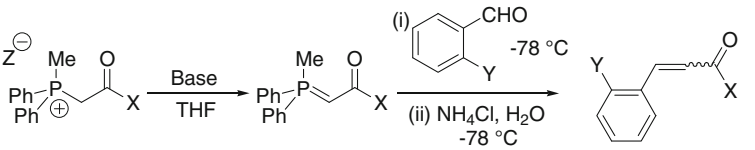
Reactions of the three ester-stabilised ylides investigated with benzaldehyde showed moderate *E*-selectivity (see Table 2.3 entries 1–3). The reactions of the

[3] See Sect. 2.3.2.

[4] See Sect. 2.4.

[5] See Sect. 2.3.1.

**Table 2.3** *Z/E* ratio for reactions of selected (alkoxycarbonylmethylidene)methyldiphenylphosphoranes (generated in situ from the parent phosphonium salts) with selected benzaldehydes[a] Counter-ion Z = Br unless otherwise indicated




| Entry | Base | Ylide X | Aldehyde Y | Enoate *Z/E* ratio |
|---|---|---|---|---|
| 1[b] | NaHMDS | OMe | H | 36:64 |
| 2 | KHMDS | OEt | H | 36:64 |
| 3 | NaHMDS | O(*t*-Bu) | H | 40:60 |
| 4 | KHMDS | OEt | OMe | 66:34 |
| 5 | KHMDS | O(*t*-Bu) | OMe | 77:23 |
| 6 | KHMDS | OMe | Cl | 79:21 |
| 7 | KHMDS | OEt | Cl | 77:23 |
| 8[b] | NaHMDS | OMe | Br | 83:17 |
| 9 | KHMDS | OEt | Br | 83:17 |
| 10 | NaHMDS | O(*t*-Bu) | Br | 85:15 |

[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 work-up of the reaction mixture. See Sects. 4.3 and 4.5 for full details

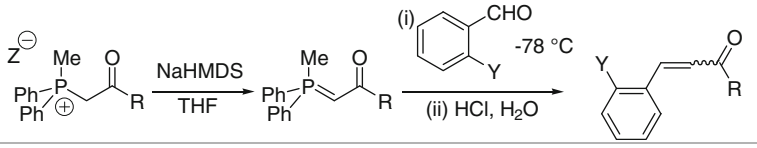
[b] Phosphonium salt counter-ion Z = $Cl^-$

same ylides with *ortho*-heteroatom substituted benzaldehydes exhibit very high *Z*-selectivity, both in reactions in which the aldehyde is more reactive than benzaldehyde itself (Table 2.3 entries 6–10) and in reactions of 2-methoxybenzaldehyde, which is less reactive than benzaldehyde (Table 2.3 entries 4 and 5). Such high *Z*-selectivity for reactions of stabilised ylides in aprotic solvents is unprecedented; its like has only ever previously been reported for reactions of stabilised ylides in methanol[6] [18–22]. *Z*-selectivity is highest for reactions of 2-bromobenzalehyde (Table 2.3 entries 8–10), while reactions of 2-chlorobenzaldehyde (Table 2.3 entries 6 and 7) give similar or slightly enhanced *Z*-selectivity compared to 2-methoxybenzaldehyde (Table 2.3 entries 4 and 5). Thus there is an apparent trend, similar to that observed in the reactions of semi-stabilised ylides, that *Z*-selectivity increases in line with the polarizability of the aldehyde *ortho*-heteroatom.

The steric bulk of the ester alkyl group appears to have no significant effect on the stereo selectivity of the reactions since all three ester stabilised ylides gave very similar results. The very high *Z*-selectivity observed in the reactions of the *ortho*-heteroatom substituted benzaldehydes lends credence to the previously reported evidence that Wittig reactions of ester-stabilised ylides occur under kinetic control [16].

[6] See Ref. [3], pp. 61–70.

**Table 2.4** *Z/E* ratio[a] for reactions of selected 2-oxoalkylidenemethyldiphenylphosphoranes (generated in situ from the corresponding phosphonium salts)[b] with selected benzaldehydes




| Entry | Ylide R | Aldehyde Y | Temp °C | Enone *Z/E* ratio |
|---|---|---|---|---|
| 1[c] | $CH_3$ | H | −45 | 19:81 |
| 2[d] | $CH_3$ | H | 20 | 20:80 |
| 3[c] | $CH_3$ | Cl | −45 | 33:67 |
| 4[d] | $CH_3$ | Br | 20 | 40:60 |
| 5[e] | $CH_2Cl$ | H | −78 | 12:88 |
| 6[c,f] | *t*-Bu | H | −78 | 17:83 |
| 7[c] | $CH_2Cl$ | Cl | −78 | 50:50 |
| 8[e] | $CH_2Cl$ | Br | −78 | 50:50 |
| 9[c,f] | *t*-Bu | Br | −78 | 48:52 |

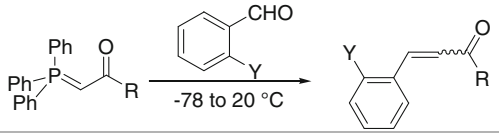
[a] *Z/E* ratio determined by $^1$H NMR analysis of the crude product obtained after aqueous work-up of the reaction mixture. See Sect. 4.6.2 for full details
[b] Phosphonium salt counter-ion Z = $Cl^-$ in all cases except where otherwise noted
[c] Quenched with 5 % aqueous HCl after 20 min at the reaction temperature indicated
[d] Reactions at 20 °C stirred for 4 h, then quenched with 5 % aqueous HCl
[e] Removed from cooling bath after 20 min, and stirred for 12 h at room temperature before being quenched with 5 % aqueous HCl
[f] Counter-ion Z = $Br^-$

### 2.3.2 *Reactions of (2-oxoalkylidene)methyldiphenylphosphoranes (Keto-Stabilised Ylides)*

Reactions of a number of keto-stabilised ylides with benzaldehydes were investigated to see if enhanced *Z*-selectivity could be observed in reactions of *ortho*-heteroatom substituted benzaldehydes compared to the reaction of the same ylide with benzaldehyde. The results for ylides derived from methyldiphenylphosphine are shown in Table 2.4. The ylides were generated in situ from the parent phosphonium salt using NaHMDS as base. The reactions were quenched by the addition of acid to ensure that the reaction had occurred at the desired temperature. Some reactions were quenched at low temperature, while others were allowed to warm to room temperature before being quenched.

Acetonylidenemethyldiphenylphosphorane (or (2-oxopropylidene)-methyldiphenylphosphorane, R = $CH_3$ in the diagram accompanying Table 2.4) was found to be insoluble in THF below −50 °C. Any attempts to carry out Wittig reactions with this ylide below −50 °C (with low temperature quenching) yielded no alkene product. Its reactions were thus carried out at −45 or 20 °C. The reactions of this ylide with benzaldehyde showed high *E*-selectivity (Table 2.4 entries 1 and 2), while its reactions with *ortho*-heteroatom substituted benzaldehydes showed a moderate increase in *Z*-selectivity (up to 30 or 40 % *Z*-isomer produced, see Table 2.4 entries 3 and 4).

**Table 2.5** *Z/E* ratio[a] for enones produced in the reactions of selected acetonylidenetriphenylphosphoranes with selected benzaldehydes (all reactions at −78 °C)




| Entry | Ylide R | Aldehyde Y | Enone *Z/E* ratio |
|---|---|---|---|
| 1 | $CH_3$ | H | 3:97 |
| 2 | $CH_3$ | Br | 11:89 |
| 3 | $CH_3$ | OMe | 10:90 |
| 4 | $CH_2OMe$ | Br | 17:83 |

[a] *Z/E* ratio determined by $^1$H NMR analysis of the crude product obtained after aqueous work-up of the reaction mixture. See Sect. 4.6.1 for full details

Ylides with one or more substituents on carbon-3 of the 2-oxoalkylidene group gave rise to increased *E*-selectivity in their reactions with benzaldehyde (Table 2.4 entries 5 and 6) relative to the reaction of acetonylidenemethyldiphenylphosphorane with this aldehyde. Reactions of these ylides with *ortho*-heteroatom substituted benzaldehydes (Table 2.4 entries 7–9) resulted in considerably increased *Z*-selectivity by comparison. The trends observed in the series of reactions shown in Table 2.4 thus replicate those observed in reactions of semi-stabilised ylides (see Tables 2.1 and 2.2, Sect. 2.2). That is, the unsubstituted acetonylide reacts with *ortho*-heteroatom substituted benzaldehydes with moderate *Z*-selectivity, 2-oxoalkylidenemethyldiphenylphosphoranes with greater steric bulk at carbon-3 of the oxoalkylidene moiety exhibit significantly increased *Z*-selectivity in their reactions with the same aldehydes, despite the fact that these ylides are more *E*-selective than the unsubstituted acetonylide in their reactions with benzaldehyde itself.

### 2.3.3 *Reactions of (2-oxoalkylidene)triphenylphosphoranes (Keto-Stabilised Ylides)*

The *Z/E* ratios for alkenes produced in reactions of ylides derived from triphenylphosphine are shown in Table 2.5. The ylides used were pre-formed, and all reactions were carried out at −78 °C but not quenched until they had been allowed to warm to room temperature. Thus the actual reaction temperature is not certain for these reactions.

The reaction of acetonylidenetriphenylphosphorane (or (2-oxopropylidene)-triphenylphosphorane) with benzaldehyde yields the expected very high *E*-selectivity in its reaction with benzaldehyde (Table 2.5 entry 1), while its reactions with *ortho*-heteroatom substituted benzaldehydes are somewhat more *Z*-selective (Table 2.5 entries 2 and 3). The reaction of 3-methoxy-2-oxopropylidenetriphenylphosphorane with 2-bromobenzaldehyde shows a further increase in

*Z*-selectivity (Table 2.5 entry 4). Thus the trends observed for the reactions of 2-oxoalkylidenemethyldiphenylphosphoranes detailed in Table 2.4 are reproduced here, albeit with far less dramatic shifts in *Z*-selectivity.

### 2.3.4 Discussion

Kinetic control has been proven in reactions of ester-stabilised ylides [16], and the high *Z*-selectivity observed for the reactions in Table 2.3 strongly implies its operation here. Kinetic control in the reactions of keto-stabilised ylides has not been explicitly proven, but is assumed by analogy. The average proportion of *Z*-alkene produced in the reactions of stabilised ylides with benzaldehydes, calculated from Table 2.3 entries 1–3, Table 2.4 entries 1, 2, 5 and 6 and Table 2.5 entry 1, is 23 %. The average proportion of *Z*-alkene produced in the reaction of these aldehydes with *ortho*-heteroatom substituted benzaldehydes, calculated from Table 2.3 entries 4–10, Table 2.4 entries 3, 4, 7–9 and Table 2.5 entries 2–4, is 54 %, so the *Z*-selectivity is caused to jump 31 % on average by the presence of the *ortho*-heteroatom.

That the electronic effect of the *ortho*-heteroatom on the reactivity of the carbonyl group of the benzaldehyde does not affect the occurrence of high *Z*-selectivity in reactions of stabilised ylides indicates that this selectivity is not a consequence of the cycloaddition TS occurring early on the reaction coordinate. Indeed, the comparatively low reactivity of stabilised ylides means that the TS for the initial reaction between ylide and aldehyde is more or less certain to be relatively late. The highly atypical selectivity observed in these reactions implies the existence of *cis*-selective TS in the step where selectivity is decided that is fundamentally different to the corresponding TS in reactions of aldehydes lacking a suitably placed heteroatom. It is proposed that the reaction proceeds by irreversible cycloaddition, and that in the *cis*-selective cycloaddition TS (shown in Fig. 2.2) there exists a phosphorus-heteroatom bond, similar to that proposed for semi-stabilised ylides (see Fig. 2.1). This TS is favoured over the *trans*-selective TS in reactions of ester-stabilised ylides, and is competitive with the *trans*-selective TS in reactions of keto-stabilised ylides due to the existence of the phosphorus-heteroatom bond and also due to minimisation of 2–3 steric interactions in the *cis*-selective TS. *Z*-selectivity thus arises from a kinetic preference for the formation of *cis*-OPA. This rationale is consistent with *Z*-selectivity being higher with increased polarizability of the *ortho*-heteroatom, as one would expect that the more polarizable a heteroatom is, the greater its capacity to form a bond to phosphorus. The aldehyde carbon-heteroatom bond length may also be important—there is an apparent parallel between the increase in bond length across the series of aldehydes employed and the increase in observed *Z*-selectivity. It may be that the relatively long C–Br bond of 2-bromobenzaldehyde puts the bromine atom in a disposition relative to phosphorus that is more conducive to the establishment of a phosphorus-heteroatom bond than is the case for other aldehydes with shorter

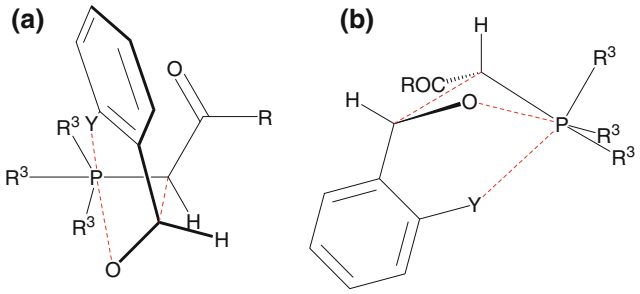



**Fig. 2.2** Two views of the proposed *cis*-selective transition state for reactions of stabilised ylides, with phosphorus-heteroatom bond. The *trans*-selective variant of this TS is much higher in energy due to strong 2–3 steric interactions

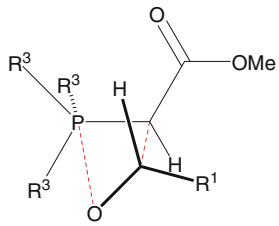



**Fig. 2.3** The *trans*-selective transition state found to occur in Wittig reactions of stabilised ylides in the computational findings of Aggarwal, Harvey and co-workers [23–25]. This TS shows a *negative* puckering angle, which is proposed to be as a consequence of the aldehyde C–O and ylide C–C(O) bond dipoles aligning in an electrostatically favourable antiparallel orientation

carbon-heteroatom bonds. The existence of the proposed TS is consistent with selectivity being essentially independent of aldehyde reactivity. The observed selectivity is nigh-on impossible to rationalise outside of the context of the cycloaddition mechanism.

The currently accepted mechanism for Wittig reactions of stabilised ylides is described in Sect. 1.4.3. Vedejs and co-workers were the first to suggest that reactions of stabilised ylides could proceed by irreversible cycloaddition, which implies that the high *E*-selectivity observed in most reactions of stabilised ylides is as a result of a kinetic preference for the formation of *trans*-OPA in the initial cycloaddition step [16]. They were able to prove that the OPAs that are thought to be produced in Wittig reactions of ester-stabilised ylides do not equilibrate. In their computational investigations into the Wittig reaction, Aggarwal, Harvey and co-workers [23–25] found that the kinetically favoured *trans*-selective cycloaddition TS in reactions of stabilised ylides is puckered, with the puckering angle being *negative,* as shown in Fig. 2.3. They proposed that this TS geometry arises as a result of there being an electrostatically favourable antiparallel orientation of the dipoles along the aldehyde C–O bond and the ylide C–C(O) bond in this TS. With the four atoms of the incipient OPA ring disposed as dictated by this

electrostatic interaction, the most sterically favourable arrangement of the ylide and aldehyde substituents is to place them, respectively, in pseudo-axial and pseudo-equatorial sites in the forming ring. Hence, this TS gives rise to the formation of *trans*-OPA. See Sect. 1.4.3 for a full discussion of this topic, and in particular of why the *trans*-selective TS is energetically favoured over the *cis*-selective TS.

It is clear, then, that interactions between dipoles of the ylide and aldehyde reactants are very important in dictating transition state geometry, especially in reactions of stabilised ylides. The model shown in Fig. 2.2 for the *cis*-selective TS that is proposed to explain the high *Z*-selectivity observed in reactions of stabilised ylides and *ortho*-heteroatom substituted benzaldehydes also has a negative puckering angle (as indeed does the corresponding model for semi-stabilised ylide shown in Fig. 2.1). Such a TS can thus benefit from the favourable antiparallel orientation of reactant dipoles that normally is available only to *trans*-selective TSs, and *not* to *cis*-selective TSs (see Sect. 1.4.3). This may help to explain why the *Z*-selective route in reactions of stabilised ylides with *ortho*-heteroatom substituted benzaldehydes is competitive with the *E*-selective route, and why it can in some cases be favoured over the *E*-selective route (i.e. in reactions of ester-stabilised ylides). The difference between the *cis*-selective TS in reactions of stabilised ylides with *ortho*-heteroatom substituted benzaldehydes and that in reactions of aldehydes lacking a suitably placed heteroatom is that in the former case it is energetically favourable for the *ortho*-heteroatom substituted aryl group of the aldehyde to be close to phosphorus. There is a bonding interaction between the heteroatom and phosphorus, and also presumably some significant reorganisation of the substituents about phosphorus occurs to facilitate such bonding in the TS of the former case. A *cis*-selective TS in a reaction of an aldehyde lacking a suitably placed heteroatom which had similar geometry, and in particular the same proximity between phosphorus and the large carbonyl substituent of the aldehyde, would suffer greatly from 1–3 steric interactions due to the lack of a bonding interaction and little or no phosphorus-substituent reorganisation (see Fig. 1.10c and the associated discussion in Sect. 1.4.3).

The results for the highly *Z*-selective reactions presented in Tables 2.3 and to a lesser extent those in Table 2.4 strongly imply the operation of kinetic control in these reactions. The energies and structures of the OPA diastereomers formed in these reactions are likely to be very similar to those of the OPA diastereomers from Wittig reactions of benzaldehydes lacking *ortho*-heteroatom substituents (i.e. no phosphorus-heteroatom bonding in the OPAs; see the details on NMR studies of OPAs produced in reactions of non-stabilised ylides in Sect. 2.4). The energy of the *cis*-selective TS is clearly very much lower in reactions of *ortho*-heteroatom substituted benzaldehydes than in reactions of other aldehydes given the high *Z*-selectivity observed in these reactions. Thus, if reversal of OPA to ylide and aldehyde were an issue in Wittig reactions of stabilised ylides in general, it would be *more likely to be in operation in these reactions* than in any others due to the lower activation energy for OPA reversal. Since any equilibrating process would naturally lead to the thermodynamically favoured *trans*-OPA, OPA equilibration is

ruled out for these *Z*-selective reactions, and therefore for all other Li-salt free Wittig reactions of stabilised ylides, which are likely to have a higher barrier to OPA reversal than is the case for the *Z*-selective reactions. This, of course, is predicated on the assumption that the *trans*-OPA in reactions of stabilised ylides is thermodynamically favoured.

The results also provide convincing evidence against the involvement of betaines in the Wittig reactions done in the course of the present study, and also against their involvement in Li-salt free Wittig reactions in general. This is significant in particular for reactions of stabilised ylides where, despite the substantial evidence available to support the cycloaddition mechanism, the assumption of the involvement of betaines persists. Many recent reviews concerning Wittig chemistry sit on the fence on the issue, cautiously stating that betaines were initially thought to be the first-formed intermediates but that much evidence has been presented in favour of direct OPA formation.

*E*-selectivity in reactions of stabilised ylides is explained in the context of the betaine mechanism by the postulation of the existence of an equilibrium between the betaine or OPA intermediates, with one of the *trans*-selective intermediates decomposing faster to produce *E*-alkene as the major product [3]. The non-equilibration of OPAs has been proven beyond doubt for all ylide types, and is confirmed by the results obtained in the course of this project [6, 16]. Thus, the only possibility that remains through which a reaction proceeding by the betaine mechanism could selectively furnish *E*-alkene is if there were an equilibrium between the betaines (by reversal to ylide and aldehyde) and if the *threo*-betaine ring-closes (irreversibly) to OPA faster than does the *erythro*-betaine.

So, in the context of the betaine mechanism, the set of results presented in Table 2.3 would be explained as follows: The reaction of an ester-stabilised ylide with either benzaldehyde or an *ortho*-heteroatom substituted benzaldehyde initially gives *anti-erythro*-betaine for the usual reason of minimisation of steric repulsion in the formation of such a betaine. In order for the reaction of benzaldehyde to be *E*-selective, the *erythro*-betaine would necessarily equilibrate with *threo*-betaine, resulting in proportional enrichment of the latter, which ring-closes faster than *erythro*-betaine to give *trans*-OPA and hence *E*-alkene predominantly. The reactions of the *ortho*-heteroatom substituted benzaldehydes would necessarily involve less betaine equilibration or have kinetically favoured ring-closure to *cis*-OPA in order to explain the high *Z*-selectivity. There is no reason why betaines formed from *ortho*-heteroatom substituted benzaldehydes should be less susceptible to equilibration than benzaldehyde itself, especially as the set of aldehydes involved contains some that are more reactive than benzaldehyde and another that is less reactive. There is also no reason why ring closure should be faster for *erythro*-betaine specifically in the case of *ortho*-heteroatom substituted benzaldehydes. Any contribution that might be available from phosphorus-heteroatom bonding would be equally available to the *threo*-betaine. Also, it seems highly likely that the TS in the ring-closing process of the *threo*-betaine would benefit from the same advantages that the *trans*-OPA does with regard to minimisation of steric interactions, regardless of the nature of the species involved. The

two phenomena cannot simultaneously be explained by the betaine mechanism, and thus it is concluded that betaines are not involved at all in Li-salt free Wittig reactions of stabilised ylides, whether they are *Z*-selective or otherwise.

## 2.4 Oxaphosphetane *cis/trans* Ratios in Reactions of Non-stabilised Ylides with Benzaldehydes

### *2.4.1 The Determination of OPA* cis/trans *Ratios in Reactions of Non-stabilised Ylides*

An investigation was also carried out to determine whether there was a similar *ortho*-heteroatom-induced effect in operation in reactions of non-stabilised ylides with benzaldehydes. Since it is generally possible to observe spectroscopically the mixture of OPAs produced in Wittig reactions of non-stabilised ylides, an opportunity was available in studying these reactions to measure the kinetic OPA *cis/trans* ratio directly rather than inferring it from alkene *Z/E* ratios, as was (necessarily) done for reactions of semi-stabilised and stabilised ylides. Since the heteroatom effect is proposed to operate in the putative irreversible cycloaddition step of the Wittig reaction, it was therefore appropriate to ascertain the kinetic selectivity of the OPA-forming process directly. Furthermore, Wittig reactions of ethylidenetriphenylphosphorane have previously been shown *not* to be under kinetic control i.e. the OPAs formed in the Wittig reaction equilibrate by reversal to ylide and aldehyde [14]. The investigations undertaken in this project have shown that OPAs produced in Wittig reactions of ethylides in general (i.e. not just those derived from triphenylphosphine) are prone to equilibration at or above the temperature at which alkene formation begins to occur. Consequently, the activation energy for Wittig reversal is comparable to that for cycloreversion to alkene and phosphine oxide, at least for the *cis*-OPA. At the time that this project started, it was generally believed (based mainly on evidence from reactions of ethylidenetriphenylphosphorane and alkylidenetrialkylphosphoranes) [6, 7, 14] that reactions of all alkylides with aromatic aldehydes might in principle be susceptible to equilibration in a similar way. The experiments carried out in the present project, coupled with some previously reported results for Wittig reactions of *n*-butylidenetriphenylphosphorane with benzaldehyde [7, 13, 15], show that Wittig reversal may not generally be an issue in Wittig reactions of longer chain alkylides. The details of these findings will be discussed more fully later in this section, but for now it will suffice to say that at the outset of this project we thought that OPA *cis/trans* ratios could not be reliably inferred from alkene *Z/E* ratios for reactions of *any* alkylide with an aromatic aldehyde, and so it was deemed particularly appropriate to directly observe OPA *cis/trans* ratios for the reactions of interest.

A further complication that is present in reactions of non-stabilised ylides is that the most widely used of these ylides, alkylidenetriphenylphosphoranes, generally

react with very high *Z*-selectivity. Hence in certain cases it would be quite difficult even to demonstrate improved *Z*-selectivity since the reaction with benzaldehyde would be likely to be highly *Z*-selective itself. For this reason, reactions of non-stabilised ylides derived from other phosphines were also investigated.

In contrast to reactions of semi-stabilised and stabilised ylides, in reactions of non-stabilised ylides OPA cycloreversion to alkene and phosphine oxide is the rate determining step. Consequently, the OPAs produced in Wittig reactions of non-stabilised ylides have a finite lifetime. The ratio of OPA diastereomers produced at temperatures well below the temperature at which decomposition occurs is generally invariant for OPAs derived from triphenylphosphine, alkyldiphenylphosphines and *P*-phenyl-5*H*-dibenzophosphole. Furthermore, all known instances of OPA equilibration result in an increase in the proportion of *trans*-OPA at the expense of *cis*-OPA (which may sometimes be judged by there being a greater proportion of *E*-isomer in the alkene product than there was of the *trans*-isomer in the OPA intermediate), so for any reaction that gives a high proportion of *cis*-OPA or *Z*-alkene, the low temperature OPA *cis/trans* ratio corresponds to the kinetic OPA *cis/trans* ratio.

Experimentally, the kinetic OPA *cis/trans* ratio may conveniently be determined by either of two means, which have been found by us and others [15, 18] to give identical results. One is low temperature NMR observation of the OPA mixture, which involves either carrying the reaction out in an NMR tube or transferring the reaction mixture at low temperature to an NMR tube under an inert atmosphere and then obtaining NMR spectra of the intermediate. $^{31}$P NMR is particularly useful for this method, since the OPAs appear in a region of the spectrum that is highly diagnostic of pentacoordinate phosphorus species (−60 to −80 ppm). The second is low temperature acid quenching of the reaction mixture to give $\beta$-hydroxyphosphonium salt ($\beta$-HPS), whose *erythro/threo* ratio exactly matches the OPA *cis/trans* ratio. This method requires transfer of the reaction mixture at low temperature into an acid solution also at low temperature, and is experimentally quite complex, but the analysis of the product is often more straightforward since $\beta$-hydroxyphosphonium salts are not air sensitive.

### 2.4.2 Determination of the Kinetic OPA cis/trans Ratio in Wittig Reactions of Non-stabilised Ylides by Low Temperature Acid Quenching

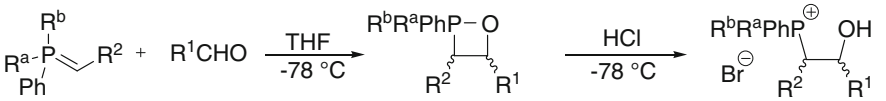
Low temperature acid quenching was carried out for Wittig reactions of several non-stabilised ylides with benzaldehydes. In most of these reactions, the ylide was generated at room temperature from the precursor phosphonium bromide salt. However, *P*-(ethylidene)-*P*-phenyldibenzophospholane proved to be considerably more demanding to handle than other ylides. The optimised procedure for reactions with this ylide involved adding dry phosphonium salt and solid KHMDS together in the right proportions (an “instant ylide mix”) in a Schlenk flask inside

a glove box under argon, and then transferring the Schlenk flask to a Schlenk manifold, where it was charged with nitrogen by the pump and fill technique (see Chap. 4 for full details) [26]. The mixture of white solids was cooled to −25 °C and dry THF was added slowly to give a maroon solution of ylide, which was not stirred until the septum on the Schlenk flask was replaced with a stopper, and the tap was closed. The solution was then cooled to −45 °C, at which temperature it was stirred for 15–20 min. It was then further cooled to −78 °C, the reaction temperature. Attempting to generate this ylide at too low a temperature resulted in very slow deprotonation, while at too high a temperature it was observed to decompose (perhaps by hydrolysis) quite readily.

The Wittig reactions were all carried out at −78 °C, followed 15 min later by cannula transfer of the reaction mixture into a solution of HCl in THF/methanol cooled to −78 °C to quench the OPA. It has previously been reported that the β-HPS counter-ion is the counter-ion from the starting phosphonium salt (and not that from the acid) [6], and it has been confirmed from a crystal structure of the *erythro*-β-HPS of entry 2 in Table 2.6 (obtained by crystallisation of the crude product from acetonitrile) that bromide is the counter-ion, not chloride. The crude β-HPS product was analysed by a series of NMR techniques ($^{1}$H, $^{31}$P, $^{13}$C, COSY, TOCSY, $^{1}$H-$^{31}$P HMBC, HSQC, HMBC) in order to assist assignment of signals in the $^{1}$H and $^{31}$P NMR spectra. Of particular aid in the assignment of diastereomeric ratios for β-HPSs or OPAs generated from β-HPSs was a two-dimensional $^{1}$H-$^{31}$P HMBC NMR technique. This allows all of the hydrogen nuclei in a molecule that undergo long-range coupling to phosphorus to be identified as being in the same molecule as that phosphorus and each other. Another NMR technique that gives the same result is selectively decoupled $^{1}$H{$^{31}$P} NMR, in which a $^{1}$H spectrum is obtained while selectively decoupling from a single signal in the $^{31}$P spectrum. The signals in the $^{1}$H{$^{31}$P} spectrum whose coupling to phosphorus had been removed could then be identified by their decreased multiplicity, and so all of the phosphorus-coupled proton signals belonging to each diastereomer could be determined. This is essentially the one-dimensional NMR equivalent of the $^{1}$H-$^{31}$P HMBC technique. In this way, multiple signals can be assigned to belong to one diastereomer or another, and a diastereomeric ratio can be determined by integration of all of the signals in the $^{1}$H spectrum and the single peak in the $^{31}$P spectrum that can be unambiguously assigned to each diastereomer. The diastereomeric ratios determined in this way are shown in Table 2.6.

Establishing which set of signals belongs to which diastereomer was done in a number of ways. Most of the Wittig reactions under consideration are predominantly *Z*-selective, and therefore the major β-HPS produced in that reaction can be taken to be the *erythro*-isomer. The OPA generated by deprotonation of the (1-(2-bromophenyl)-1-hydroxy-3-methylbut-2-yl)phenyldibenzophospholium bromide produced in the low temperature acid quenching of the reaction shown in Table 2.6 entry 8 was proven to be *cis* by 1D-NOESY NMR (see Sect. 2.4.5 for further details), and therefore must have been derived from *erythro*-β-HPS. The major diastereomer of (1-(2-bromophenyl)-1-hydroxyprop-2-yl)triphenylphosphonium bromide produced in the reaction of ethylidenetriphenylphosphorane and

**Table 2.6** Wittig reactions of non-stabilised ylides (generated from phosphonium bromide salt using NaHMDS) with benzaldehydes to give OPA (initially), and subsequently *β*-HPS after low temperature acid quenching of OPA




| Entry | Ylide $R^a$ | Ylide $R^b$ | Ylide $R^2$ | Aldehyde | *β*-HPS *erythro/threo* ratio[a] | Alkene *Z/E* ratio[b] |
|---|---|---|---|---|---|---|
| 1 | Ph | Ph | Me | PhCHO | 90:10 | 85:15 |
| 2 | Ph | Ph | Me | 2-$BrC_6H_4CHO$ | 95:5 | 75:25 |
| 3 | Ph | Et | Me | PhCHO | 54:46 | 32:68 |
| 4 | Ph | Et | Me | 2-$BrC_6H_4CHO$ | 64:36 | 55:45 |
| 5 | DBP system | | Me | PhCHO | 72:28 | 53:47[d] |
| 6 | DBP system | | Me | 2-$BrC_6H_4CHO$ | 94:6[c] | 81:19[d] |
| 7 | DBP system | | *i*-Pr | PhCHO | 89:11 | 90:10[e] |
| 8 | DBP system | | *i*-Pr | 2-$BrC_6H_4CHO$ | 94:6 | 91:9[e] |
| 9 | Ph | Ph | *i*-Pr | PhCHO | 100:0 | – |
| 10 | Ph | Ph | *i*-Pr | 2-$BrC_6H_4CHO$ | 100:0 | 82:18 |

[a] All reactions were carried out at −78 °C, and subsequently quenched by cannulation of the reaction mixture into HCl solution in THF/methanol. The *erythro/threo* ratio was determined by $^1H$ and $^{31}P$ NMR of the crude product after minimal aqueous work-up

[b] Unless otherwise specified, this is the *Z/E* ratio of 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 $^1H$ NMR of the crude product after aqueous work-up

[c] The *threo-β*-HPS could not be unambiguously assigned, as it is present to only a small degree. A large amount of ylide hydrolysis appears to have occurred based on the quantity of phosphine oxide (non-Wittig product) and unreacted 2-bromobenzaldehyde present in the crude spectrum. A peak of matching chemical shift to the *threo-β*-HPS of entry 5 ($\delta_P = 33.8$) is present in the crude spectrum ($\delta_P = 34.0$) that integrates to give the *erythro/trheo* ratio shown. Also, direct monitoring at −20 °C of the OPA produced in the Wittig reaction (carried out at −78 °C) reveals a kinetic OPA *cis/trans* ratio of 94:6

[d] *Z/E* ratio of the corresponding unquenched Wittig reaction heated to 80 °C for 2 h after stirring for 15 min at −78 °C, as determined by integration of characteristic signals in the $^1H$ NMR of the crude product

[e] *Z/E* ratio of alkene produced in *β*-HPS deprotonation experiment in toluene-*d8*

2-bromobenzaldehyde (see Table 2.6 entry 2) was also recrystallised, and was shown to be of the *erythro*-configuration by obtaining a crystal structure of the solid.[7] NMR characterisation of the isomers of (1-hydroxy-1-phenylprop-2-yl) triphenylphosphonium bromide has been reported [7]. The major diastereomer of *β*-HPS (assigned to be *erythro* in each case) produced in each reaction of

[7] CCDC-883627 contain the X-ray crystallographic data for this compound. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. An image of the crystal structure can be found in Sect. 4.7.2.

(ethylidene)ethyldiphenylphosphorane (see Table 2.6 entries 3 and 4) was isolated by careful recrystallisation of the crude product. The spectral characteristics of the β-HPSs derived from the reactions of (ethylidene)ethyldiphenylphosphorane with benzaldehydes are sufficiently similar to those of the definitively characterised β-HPSs that it is possible to assign each set of diastereomeric signals to one isomer or another of the former β-HPSs by analogy with the spectra of the known β-HPSs. In particular, the coupling constant $^{3}J_{PH}$ between phosphorus and the OC*H* signal is typically larger for the *threo* isomer (9 Hz up to 14.5 Hz) than for the *erythro* (6–8 Hz), the *erythro* OC*H* signal invariably has a higher chemical shift than the corresponding signal of the *threo*-isomer, and the double doublet arising from resonance of the PCHC$H_3$ protons typically has a higher chemical shift for the *erythro*-isomer than for the *threo*-isomer. Assignment of the configuration of the *erythro*-β-HPSs produced in low temperature acid quenching reactions of (*iso*-butylidene)triphenylphosphorane (see Table 2.6 entries 9 and 10) were done by analogy with (1-hydroxy-1-phenylpent-2-yl)triphenylphosphonium bromide [7]. Assignments made in this manner invariably agreed with assignments made on the basis of the selectivity of the corresponding unquenched Wittig reaction.

The *erythro/threo* ratios obtained from the $^{1}$H and $^{31}$P spectra of the crude β-HPS product invariably agreed very closely with each other. Other products present included some phosphine oxide (from ylide hydrolysis) and phosphonium salt (from unreacted ylide).

Ethylidenetriphenylphosphorane reacted with benzaldehyde to give the expected high *erythro*-selectivity in the β-HPS quench product (Table 2.6 entry 1). The same ylide reacted with 2-bromobenzaldehyde showing increased selectivity for *erythro*-β-HPS (Table 2.6 entry 2). (Ethylidene)ethyldiphenylphosphorane reacted with benzaldehyde with marginal selectivity for the *erythro* isomer (Table 2.6 entry 3), and its reaction with 2-bromobenzaldehyde showed moderate *erythro*-selectivity (Table 2.6 entry 4).

*P*-(ethylidene)phenyldibenzophospholane reacted with benzaldehyde to give β-HPS with an *erythro/threo* ratio of 72:28 (Table 2.6 entry 5), while the diastereomeric ratio of β-HPS produced in the reaction of this ylide with 2-bromobenzaldehyde showed very high *erythro*-selectivity (Table 2.6 entry 6). The reactions of *P*-(*iso*-butylidene)-*P*-phenyldibenzophospholane also showed increased *erythro*- selectivity with 2-bromobenzaldehyde (Table 2.6 entry 8) compared with benzaldehyde (Table 2.6 entry 7). These *erythro/threo* ratios shown in Table 2.6 entries 4–8 agree exactly with the kinetic OPA *cis/trans* ratios determined for the same reactions by $^{31}$P NMR analysis of the Wittig reaction mixtures (see Table 2.7 below). These results confirm the occurrence of increased kinetic selectivity for *cis*-OPA in Wittig reactions of *ortho*-heteroatom substituted benzaldehydes.

No *threo*-β-HPS could be detected in the crude products obtained after low temperature acid quenching of the Wittig reactions of (*iso*-butylidene)triphenylphosphorane with either benzaldehyde or 2-bromobenzaldehdye, and so it can be inferred that OPA formation in these reactions is completely selective for *cis*-OPA.

Discussion of the *Z/E* ratios of the alkenes produced in these reactions is deferred until Sect. 2.4.4.

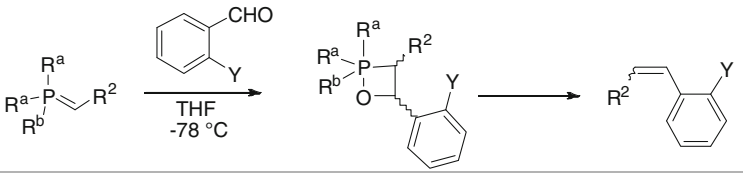
The Wittig reaction of (ethylidene)ethyldiphenylphosphorane with benzaldehyde (unquenched) is predominantly *E*-selective (see Table 2.6 entry 3), and so it is not possible to infer the stereochemistry of the (1-hydroxy-1-phenylprop-2-yl)ethyldiphenylphosphonium bromide Wittig reaction quench product from the observed selectivity of the unquenched Wittig reaction. Crystals of the major diastereomer of this *β*-HPS (isolated from the crude product by crystallisation) were deprotonated at −78 °C under an inert atmosphere to form OPA, which was then allowed to warm to 20 °C to decompose to alkene and phosphine oxide. $^{1}$H NMR analysis of the crude product showed it to be *Z*-1-phenylprop-1-ene, thus confirming the configuration of the precursor *β*-HPS to be *erythro*, in agreement with the assignment made based on comparison of its spectral characteristics with those of characterised *β*-HPSs.[8]

### 2.4.3 Determination of the Kinetic OPA cis/trans Ratio in Wittig Reactions of Non-stabilised Ylides by $^{31}$P NMR

OPA adducts from Wittig reactions of *P*-(alkylidene)-*P*-phenyldibenzophospholanes are generally stable at room temperature and above; indeed they must be heated to effect alkene formation. This confers significant practical advantages to the NMR observation of these OPAs compared to unconstrained analogues. The relative stability of dibenzophosphole-derived OPAs is kinetic. OPA decomposition must necessarily go through TS in which the DBP ring C–P–C bond angle is in the process of being stretched from 94° in the trigonal bipyramidal OPA (the five-membered ring spans axial and equatorial sites) to the 104–107° angle present in the phosphine oxide product [27], which induces considerable angle strain in the five-membered ring. This results in a dramatically increased activation energy for the cycloreversion process compared to unconstrained OPAs. The convenience of being able in principle to determine kinetic OPA selectivity in Wittig reactions at room temperature by using DBP-derived ylides was, however, somewhat offset by the difficulty of handing the ylides themselves. They are exceptionally sensitive to the presence of any water, and many of our initial experiments were marred by the presence of large amounts of phosphine oxide derived from ylide hydrolysis. No alkene product was observed, and the same phosphine oxides as had been observed in the OPA generation experiments were produced even without the addition of aldehyde, indicating that the phosphine oxide was not derived from a Wittig reaction or hydrolysis of a Wittig intermediate.

[8] This assignment has been confirmed by X-ray crystallographic analysis, which is yet to be published. See CCDC-883627 for the full crystallographic data.

**Table 2.7** Wittig reactions of non-stabilised ylides (generated from phosphonium bromide salt using NaHMDS or KHMDS) with benzaldehydes to give OPA (initially), and subsequently alkene[a]




| Entry | Base | Ylide | | | Aldehyde Y | OPA *cis/trans* ratio | Alkene *Z/E* ratio[b] |
|---|---|---|---|---|---|---|---|
| | | $R^a$ | $R^b$ | $R^2$ | | | |
| 1[c] | KHMDS | DBP | Ph | Me | H | 71:29 | 53:47 |
| 2[c] | KHMDS | DBP | Ph | Me | Br | 94:6 | 82:18 |
| 3 | NaHMDS | DBP | Ph | *i*-Pr | H | 89:11 | 89:11[d] |
| 4 | NaHMDS | DBP | Ph | *i*-Pr | Br | 94:6 | 91:9[d] |
| 5 | KHMDS | Ph | Et | Me | Br | 64:36[e] | 56:44 |
| 6 | KHMDS | Ph | Et | Me | Br | –[f] | 32:68 |

[a] All reactions were carried out at −78 °C. OPA *cis/trans* ratios were determined by $^{31}$P NMR (obtained at 30 °C unless otherwise indicated) after cannula filtration of the reaction mixture into an NMR under an inert atmosphere and addition of toluene-*d8*. The $^{31}$P NMR spectra all indicated the presence of relatively small amounts of phosphine oxide by-product, which were shown to be derived directly 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] This alkene was obtained from experiments involving deprotonation of β-HPS of *erythro/threo* ratio matching the indicated OPA *cis/trans* ratio, as described in Sect. 2.4.2

[e] OPA *cis/trans* ratio determined at −40 °C

[f] OPA signals have same $^{31}$P chemical shifts both at −40 and at −20 °C [7], so no diastereomeric ratio could be determined

In general for reactions of non-stabilised ylides it has been found that conducting the experiments in long, thin Schlenk tubes with minimal nitrogen flow is optimal in order to reduce the flux through the reaction flask. Tubing connecting the flask to the nitrogen source (which is distributed to various flasks using a Schlenk manifold) must be dried. This was done by fitting a syringe barrel with an attached needle to the tubing when not in use, and keeping the needle inserted into a sealed flask of dried solid potassium hydroxide, with the needle tips embedded in the KOH. The ylide *P*-(*iso*-butylidene)-*P*-phenyldibenzophospholane proved to be relatively robust—it could be generated at room temperature, and its OPA adducts could be monitored by NMR at room temperature. (Ethylidene)ethyldiphenylphosphorane was also generated at room temperature. The exceptionally moisture sensitive *P*-(ethylidene)-*P*-phenyldibenzophospholane was generated by the more

cautious procedure referred to in Sect. 2.4.2. Full details of the experimental procedures employed are given in Chap. 4.

OPA formation was carried out at −78 °C in all cases. All manipulations were carried out under an inert atmosphere. After OPA formation was complete (as judged by the fading of the colour of the ylide as the aldehyde was added), the solution was usually stirred for approximately 10 min at −78 °C. OPAs derived form *P*-(ethylidene)-*P*-phenyldibenzophospholane were transferred by cannula filtration into an NMR tube pre-cooled to ca. −50 °C. NMR observation was then carried out at −20 °C. OPAs derived from (ethylidene)ethyldiphenylphosphorane were transferred in the same manner to an NMR tube pre-cooled to −78 °C, and were monitored by NMR initially at −40 °C or lower (and thereafter by variable temperature NMR in one case). In this way minimal non-Wittig production of phosphine oxide was observed. Solutions of OPAs derived from *P*-(*iso*-butylidene)-*P*-phenyldibenzophospholane were allowed to warm to room temperature before being passed though a cannula filter into an NMR tube under nitrogen, and NMR observation was performed at 30 °C. Initial OPA generation experiments involved removal of the THF reaction solvent and addition of anhydrous toluene-*d8* to allow analysis of the OPA by $^{1}$H and $^{13}$C NMR and various 2D NMR techniques. However, significant amounts of phosphine oxide were produced during these experiments. Much of this was likely to have come from ylide hydrolysis, but there still remains the possibility that OPA may form phosphine oxide by a hydrolytic (non-Wittig) process. In order to minimise this, and thereby maximise the yield of OPA, a sample of the reaction mixture was simply transferred (via cannula filter to remove inorganic salts) into an NMR tube. Enough toluene-*d8* was then added to allow the NMR spectrometer to find a deuterium lock, thus obviating the need for solvent removal. Although meaning that the kinetic OPA *cis/trans* ratios were determined based on $^{31}$P NMR only, this precaution along with the others employed—drying the Schlenk manifold tubing with KOH, closing the Schlenk flask taps to nitrogen flow whenever possible, and generating *P*-(ethylidene)phenyldibenzophospholane by the rather exacting procedure described above—resulted in OPA being successfully transferred to the NMR in very high yield. The only other major species appearing in the $^{31}$P NMR was the ylide at ca. −10 ppm. This method allowed definitive determination of the kinetic OPA *cis/trans* ratio.

The OPA signals appeared around −60 to −70 ppm in the $^{31}$P NMR. Assignment of the signals to one diastereomer or the other was done based on the *Z/E* ratio of the alkene product after OPA cycloreversion. Since all of the reactions in which assignments were done in this manner were predominantly *Z*-selective, it can be concluded that the major diastereomer of OPA produced as intermediate in the Wittig reaction is the *cis*-isomer. The kinetic OPA *cis/trans* ratios determined by $^{31}$P NMR for the reactions of non-stabilised ylides derived from *P*-phenyldibenzophosphole are shown in Table 2.7.

*P*-(ethylidene)-*P*-phenyldibenzophospholane reacted with benzaldehyde to give an OPA *cis/trans* ratio of 71:29 (Table 2.7 entry 1). This ylide reacted with 2-bromobenzaldehyde with very high selectivity for the *cis*-OPA (entry 2). *P*-(*iso*-

butylidene)-*P*-phenyldibenzophospholane reacted with benzaldehyde with high selectivity for the *cis*-OPA (entry 3) but the *cis*-selectivity in its reaction with 2-bromobenzaldehyde was even higher (entry 4). These results were also reproduced by low temperature acid quenching experiments (see Sect. 2.4.2 and particularly Table 2.6 above). The reaction of (ethylidene)ethyldiphenylphosphorane and 2-bromobenzaldehyde was observed to form OPA with a *cis/trans* ratio of 64:36 (entry 5). This is identical to the β-HPS *erythro/threo* ratio obtained by low temperature acid quenching of this Wittig reaction (see Table 2.6 entry 4 above). The OPA signals in the reaction of (ethylidene)ethyldiphenylphosphorane with benzaldehyde could not be resolved (a single, relatively broad peak was observed at −61.6 ppm in the $^{31}$P NMR), which is consistent with a similar report for the OPA produced in the reaction of ethylidenetriphenylphosphorane with benzaldehyde [7]. The *erythro/threo* ratio of the β-HPS produced by low temperature acid quenching of the reaction of (ethylidene)ethyldiphenylphosphorane with benzaldehyde was 54:46 (see Table 2.6 entry 3 above).

It can be seen from these results that selectivity for *cis*-OPA is increased for the reaction of each ylide with 2-bromobenzaldehyde relative to its reaction with benzaldehyde. This demonstrates the operation of the *ortho*-heteroatom effect in Wittig reactions of non-stabilised ylides. Discussion of the *Z/E* ratios of the alkenes produced in these reactions is deferred until Sect. 2.4.4.

### 2.4.4 Investigation of the Operation of Stereochemical Drift in Reactions of Non-Stabilised Ylides

The kinetic OPA *cis/trans* ratios of reactions of a number of non-stabilised ylides have been determined by the methods described in Sects. 2.4.2 and 2.4.3. In order to aid assignment of the diastereomeric OPA signals, and in order to test for the possible operation of stereochemical drift in these reactions, the *Z/E* ratios of the alkene products of the relevant Wittig reactions were determined. The *Z/E* ratios for the Wittig reactions of benzaldehyde and 2-bromobenzaldehyde respectively with of each of ethylidenetriphenylphosphorane, (ethylidene)ethyldiphenylphosphorane and *P*-ethylidene-*P*-phenyldibenzophospholane are shown in both Tables 2.6 and 2.7. Comparison of the *Z/E* ratio of the alkene produced in each reaction with the relevant kinetic OPA *cis/trans* ratio (compare the alkene *Z/E* and β-HPS *erythro-threo* ratios of Table 2.6 entries 1–6; also compare the alkene *Z/E* and OPA *cis/trans* ratios of Table 2.7 entries 1, 2, 5 and 6) clearly shows that stereochemical drift is in operation in these reactions, since there is a non-correspondence between the alkene *Z/E* ratio and the β-HPS *erythro-threo* ratio or OPA *cis/trans* ratio in favour of the *E*-alkene, as would be expected. Despite this, the *Z*-alkene is still the predominant product in all cases but one, and so for each of these the major OPA isomer can be assigned to be the *cis*-isomer.

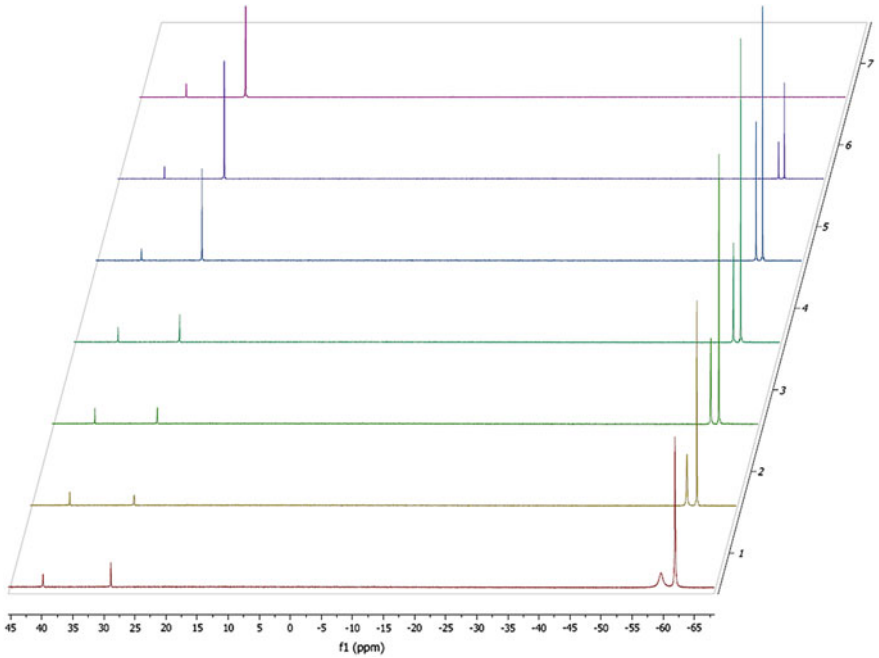



**Fig. 2.4** Set of stacked $^{31}$P spectra at −70 (*bottom spectrum*), −40, −20, −10, 0, 10 and 20 °C (*top spectrum*) for the reaction of (ethylidene)ethyldiphenylphosphorane with 2-bromobenzaldehyde in THF (NMR sample spiked with a small quantity of toluene-*d8*)

The OPAs produced in the reaction of (ethylidene)ethyldiphenylphosphorane with 2-bromobenzaldehyde (Table 2.7 entry 5) were monitored by variable temperature $^{31}$P NMR. The spectra obtained at −70, 40, −20, −10, 0, 10 and 20 °C are shown in the stacked array of Fig. 2.4. A small amount of phosphine oxide is present (ethyltriphenylphosphine oxide at $\delta = 29$, diethylphenylphosphine oxide at $\delta = 40$) even at low temperature (ca. 10 % of total amount of phosphorus present), resulting from a small amount of ylide hydrolysis. It can be seen that the relative proportion of ethyltriphenylphosphine oxide begins to increase between −10 and 0 °C, and then grows further at higher temperatures, until the OPAs have vanished completely at 20 °C. Although the relative amount of OPA decreases as the temperature goes up, the *cis/trans* ratio remains invariant at 64:36 in all recorded spectra. However, the final alkene *Z/E* ratio (determined from the same sample dissolved in $CDCl_3$) was unsurprisingly found to be 56:44, as had previously been observed. This demonstrates that no interconversion of OPA occurs until at least 10 °C in this reaction, in keeping with an earlier observation by Vedejs et al. that OPA interconversion did not take place below the temperature at which alkene formation had also begun to occur in the reaction of ethylidenetriphenylphosphorane and benzaldehyde [14].

The β-HPS crude product from the acid quenching of each of the reactions of *P*-(*iso*-butylidene)-*P*-phenyldibenzophospholane (Table 2.6 entries 7 and 8) was precipitated (along with *P*-(*iso*-butyl)-*P*-phenyldibenzophospholium salt and some phosphine oxide) from chloroform/ethyl acetate to remove residual aldehyde, and was then deprotonated at low temperature in toluene-*d8*. This OPA produced was characterised by a series of NMR techniques. The *cis/trans* ratio of the OPA matched that of the precursor β-HPS. Heating of this OPA to 80 °C for two hours gave alkene (whose *Z/E* ratio is also indicated in Table 2.6 entries 7 and 8). The close correspondence between the OPA *cis/trans* ratio and the alkene *Z/E* ratio indicates minimal, if any, stereochemical drift in these reactions. More details on the NMR studies of the OPAs produced in these reactions are given in Sect. 2.4.5.

The β-HPS (1-(2-bromophenyl)-1-hydroxy-3-methylbut-1-yl)triphenylphosphonium bromide produced by low temperature acid quenching of the reaction of (isobutylidene)triphenylphosphorane and 2-bromobenzaldehyde was found to be made up exclusively of the *erythro*-isomer, but the corresponding unquenched Wittig reaction gave alkene with a *Z/E* ratio of 82:18 (see Table 2.6 entry 10), clearly indicating the operation of stereochemical drift in this reaction.

The operation of stereochemical drift observed here in reactions of ethylides with aromatic aldehydes is in keeping with literature precedents [7, 14]. Stereochemical drift in reaction of longer chain alkylides appears to depend on the exact nature of the ylide; OPAs derived from *P*-(isobutylidene)-*P*-phenyldibenzophospholane with benzaldehydes decompose with negligible stereochemical drift, while those derived from (isobutylidene)triphenylphosphorane appear not to decompose stereospecifically. Kinetic control has also been demonstrated for reactions of longer chain alkylides with these aldehydes (Table 2.1 entries 7–9) [7, 13, 15].

### 2.4.5 NMR Observation of Oxaphosphetanes and β-Hydroxyphosphonium Salts Derived from Non-stabilised Ylides: Experimental Techniques and Further Information Acquired

The primary goal of the NMR observations of OPAs produced in Wittig reactions of *ortho*-heteroatom benzaldehydes (which have already been described in Sect. 2.4.1 above) was to establish the kinetic OPA *cis/trans* ratio and thus the kinetic selectivity of the Wittig reaction in question. A subsidiary goal was to determine whether there was any evidence suggesting that the OPAs produced in these reactions contained a phosphorus-heteroatom bond like the one that is proposed to exist in the transition state leading to OPA. The $^{31}$P NMR chemical shifts found for OPAs generated in Wittig reactions of *P*-(alkylidene)-*P*-phenyldibenzophospholanes are in the range −60 to −75 ppm, which is the same range previously reported for OPAs with pentacoordinate phosphorus [6, 16, 28, 29, 30]. 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 [31, 32]. Hence it can be surmised that the phosphorus in the OPAs produced in these reactions is pentacoordinate, i.e. not bearing a phosphorus-heteroatom bond. We must conclude therefore that the proposed bonding interaction, for which there is a very substantial body of evidence presented here, exists only in the *transition state* leading to OPA. Furthermore, we may postulate that due to geometrical constraints, a planar structure (such as an OPA or a planar TS) does not allow a phosphorus-heteroatom bond. The logical extension of this proposal is that the cycloaddition TS in these reactions must be puckered, as has already been suggested above for the TS model for reactions of semi-stabilised and stabilised ylides.

As was briefly mentioned in Sect. 2.4.4, the $\beta$-HPSs of Table 2.7 entries 7 and 8, produced by the method described in Sect. 2.4.2, were subsequently precipitated (along with any remaining starting phosphonium salt and some phosphine oxide) from chloroform/ethyl acetate to remove aldehyde. The sample thus obtained was treated with NaHMDS in toluene-*d8* at −78 °C under a nitrogen atmosphere to generate OPA (as a mixture of diastereomers), which was observed by NMR after cannula filtration into an NMR tube under a nitrogen atmosphere. The OPA was typically characterised by $^{1}$H, $^{31}$P, COSY, TOCSY, 1D and 2D NOESY, $^{13}$C, HSQC and HMBC NMR techniques. The *cis/trans* ratio of OPA produced by $\beta$-HPS deprotonation does not necessarily correspond to the *erythro/threo* ratio of the $\beta$-HPS (which itself *does* correspond to the kinetic ratio of OPA diastereomers produced in the Wittig reaction), but in all cases investigated here the ratios were found to be identical.

The OPA produced from (1-(2-bromophenyl)-1-hydroxy-3-methylbut-2-yl)-*P*-phenyldibenzophospholium bromide (Table 2.7 entry 8) was characterised by $^{1}$H-$^{31}$P HMBC NMR (as well as several other techniques) at −20 °C, which in tandem with the COSY spectrum of the reaction mixture facilitated the assignment of signals in the $^{1}$H NMR to *trans*-OPA (the minor diastereomer in this case). Each of the OPA isomers was shown to be in its most stable pseudorotameric form(s) by $^{13}$C NMR. Since the dibenzophosphole system in these OPAs must span axial and equatorial sites, there is only one possible axial site that remains. The OPA ring must also span axial and equatorial sites, and therefore the remaining axial site may only be occupied by the ring oxygen or the carbon at ring position 3. The large one bond coupling constant $^{1}J_{PC}$ for ring carbon 3 signal (82.0 Hz for the *trans*-OPA ring C−3 at $\delta = 76.1$, 85.9 Hz for the *cis*-OPA ring C−3 at $\delta = 73.3$) is indicative of an aliphatic carbon in an equatorial position in a phosphorus-centred trigonal bipyramid [29, 33], and so oxygen must be in the axial position, as would be expected for an electronegative element. The major diastereomer was also shown to be the *cis*-OPA by 1D NOESY spectroscopy. Irradiation of the sample at the resonant frequency of the OC*H* proton ($\delta = 5.50$) resulted in an NOE response from the PC*H* proton ($\delta = 5.19$), as shown in Fig. 2.5. There is also NOE contact with some of the hydrogens of the dibenzophosphole group, and at longer mixing times with the *iso*-propyl C$H_3$ hydrogens.

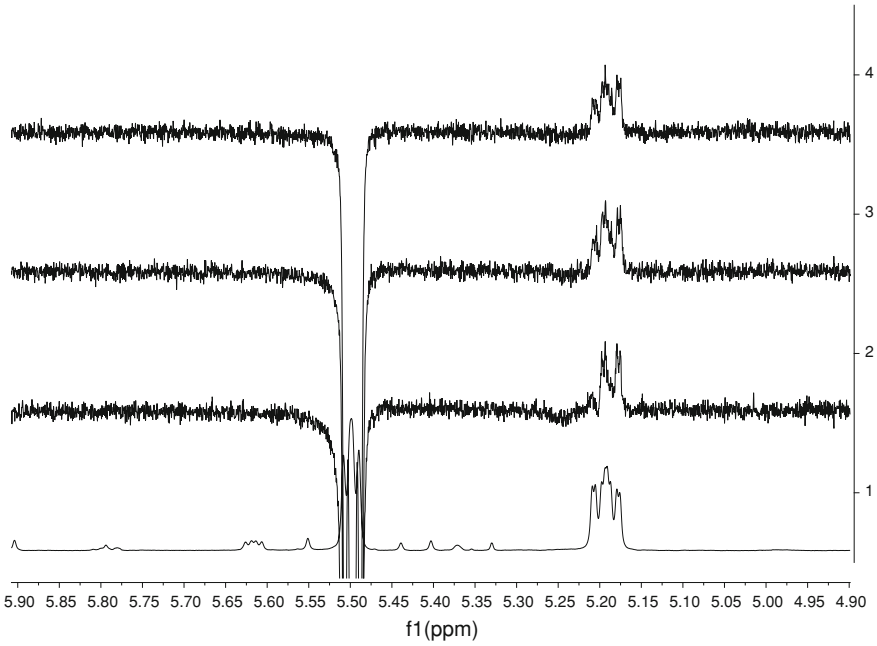



**Fig. 2.5** 1D NOESY experiment on the OPA generated from (1-(2-bromophenyl)-1-hydroxy-3-methylbut-2-yl)phenyldibenzophospholium bromide, irradiated at the resonant frequency of the OC*H* proton. The original $^{1}$H spectrum is shown at the bottom, and also the spectra obtained with three different NOE mixing times (0.5, 1.0 and 1.5 s)

### 2.4.5.1 Description of the $^{1}$H- $^{31}$P HMBC NMR Technique

The use of $^{1}$H-$^{31}$P HMBC to assign signals in each of the crude $^{1}$H and $^{31}$P spectra in the β-HPS produced in the low temperature acid quenching of the Wittig reaction of *iso*-butylidenephenyldibenzophospholane with benzaldehyde will now be described as an example of the technique. In Fig. 2.6 is shown the $^{1}$H-$^{31}$P HMBC spectrum of the crude product optimised for a $^{1}$H-$^{31}$P coupling constant $J_{PH} = 6$ Hz.

In Fig. 2.7 is shown a close-up from the $^{1}$H-$^{31}$P HMBC spectrum optimised for 6 Hz coupling. The two large signals in the $^{1}$H spectrum (which are the highest field of the three signals shown) are shown by COSY and TOCSY spectra to be coupled; the signal at $\delta = 5.39$ is assigned to the OC*H* of the major diastereomer (shows heavily roofed double doublet due to splitting by phosphorus and PC*H*), and the signal at $\delta = 5.15$ is assigned to the PC*H* of the major diastereomer. As can be seen from the spectrum in Fig. 2.7, both couple to the phosphorus signal at $\delta_P = 31.7$, confirming that these three signals belong to one compound. The double doublet at $\delta = 5.49$ is assigned to the C*H*OH of the minor diastereomer (it couples with PC*H* at $\delta = 4.03$). This is shown by the $^{1}$H-$^{31}$P HMBC spectrum in Fig. 2.7 to be coupled to the phosphorus signal at $\delta_P = 30.6$, confirming it to be the phosphorus

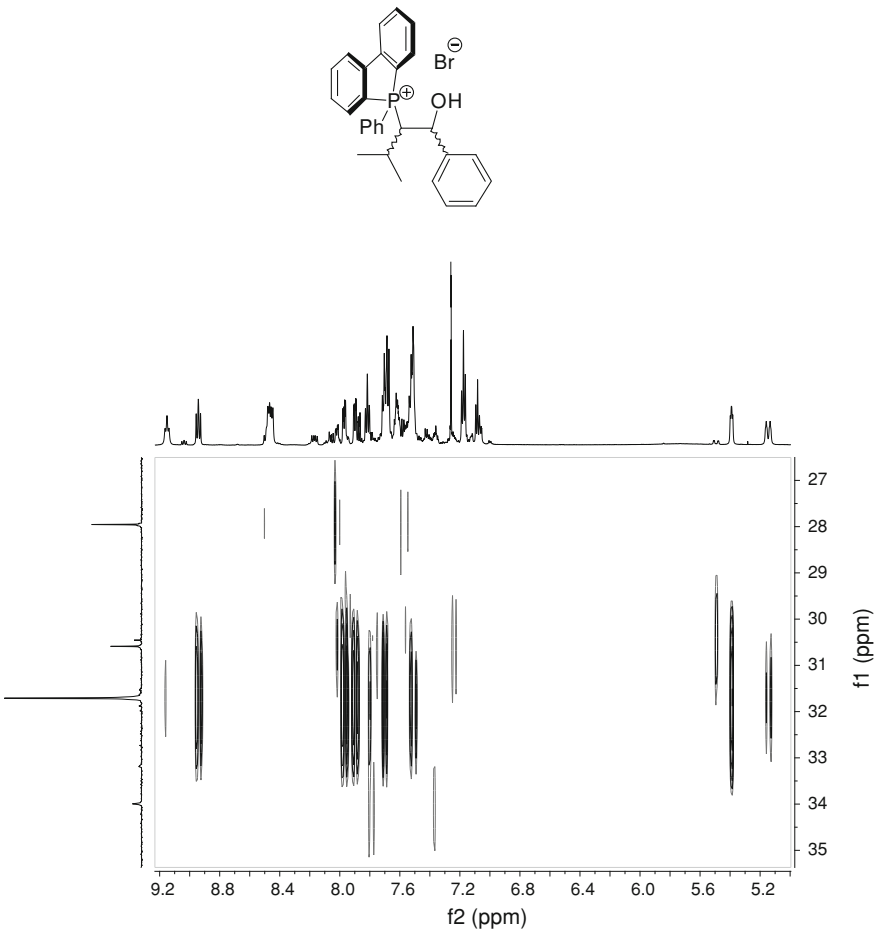



**Fig. 2.6** $^{1}$H-$^{31}$P HMBC spectrum of the crude *P*-(1-hydroxy-1-phenyl-3-methylbut-2-yl)-*P*-phenyldibenzophospholium bromide from low temperature acid quenching of the reaction of *P*-(isobutylidene)-*P*-phenyldibenzophospholane and benzaldehyde optimised for a coupling constant $J_{PH} = 6$ Hz. On the abscissa is the $^{1}$H spectrum, and on the ordinate is the $^{31}$P spectrum

signal of the minor diastereomer. The diastereomeric ratio obtained by comparison of the integrals of all the baseline-separated signals belonging to the major and minor diastereomers respectively in the $^{1}$H NMR spectrum is 89:11, which is agreed upon by comparison of the integrals of the major and minor diastereomer signals in the $^{31}$P spectrum. Since deprotonation of this $\beta$-HPS sample gave alkene with a *Z/E* ratio of 90:10, it can be surmised that the major $\beta$-HPS diastereomer is *erythro*, and hence the *erythro/threo* ratio is 89:11.

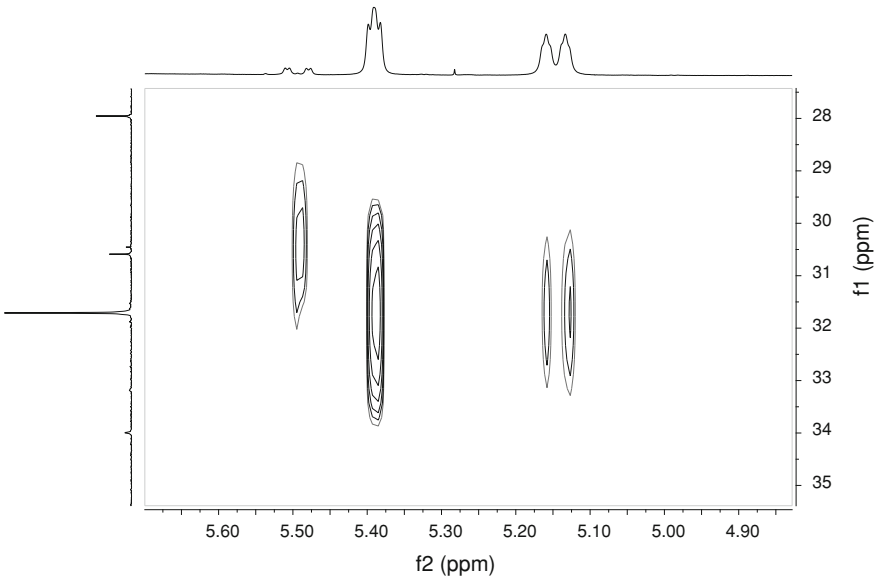



**Fig. 2.7** Close-up on a region of the $^{1}$H-$^{31}$P HMBC spectrum of the crude product from low temperature acid quenching of reaction of *P*-(isobutylidene)-*P*-phenyldibenzophospholane and benzaldehyde optimised for a coupling constant $J_{PH} = 6$ Hz. On the abscissa is the $^{1}$H spectrum, and on the ordinate is the $^{31}$P spectrum

### 2.4.5.2 Description of the $^{1}$H{$^{31}$P} Selective Decoupling Technique

The second technique that can be used to establish connectivity between the atoms giving rise to signals in the $^{1}$H and $^{31}$P NMR spectra is selectively decoupled $^{1}$H{$^{31}$P} NMR. This technique involves the selective irradiation the NMR sample with a pulse equal to the resonant frequency of a particular $^{31}$P signal while acquiring $^{1}$H NMR spectrum. Any signals in the $^{1}$H spectrum that are coupled to the specific $^{31}$P peak are decoupled and can be identified by their reduced multiplicity compared to the non-decoupled $^{1}$H spectrum. As an example of this technique, it will now be described how it was used to determine connectivity between the atoms giving rise to signals in the $^{1}$H and $^{31}$P spectra of the crude (1-(2-bromophenyl)-1-hydroxyprop-2-yl)ethyldiphenylphosphonium bromide product obtained from the low temperature acid quenching of the Wittig reaction of *P*-(ethylidene)ethyldiphenylphosphorane and 2-bromobenzaldehyde.

Shown in Fig. 2.8 is a section of the $^{31}$P spectrum of the crude product of acid quenching of the reaction of *P*-(ethylidene)ethyldiphenylphosphorane and 2-bromobenzaldehyde. There are no other signals in the spectrum. The peaks at $\delta = 32.5$ and $\delta = 34.2$ are indicated by the selective decoupling experiments to be diethyldiphenylphosphonium bromide (starting phosphonium salt) and phosphine oxide (likely to be ethyldiphenylphosphine oxide, whose $^{31}$P NMR chemical shift has previously been reported as $\delta = 34$ ppm) [24].

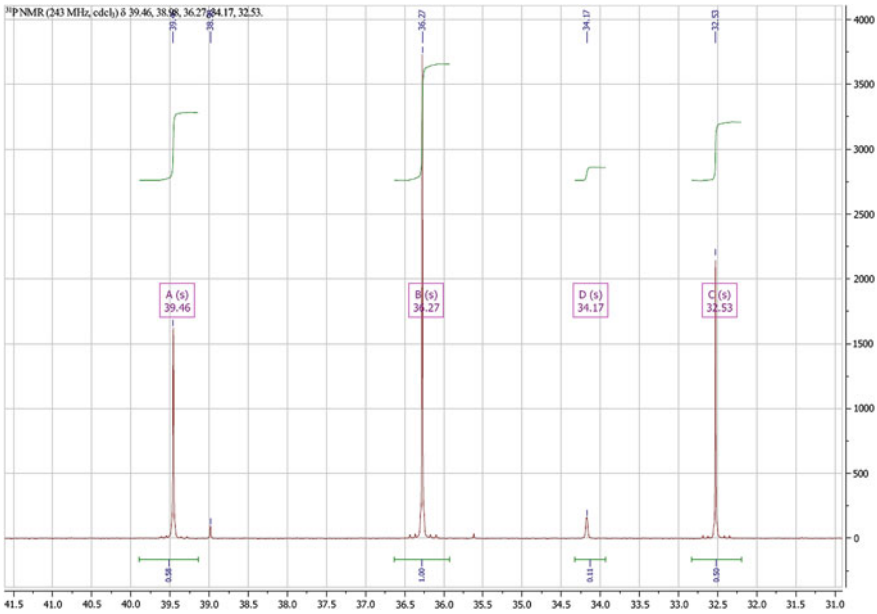



**Fig. 2.8** $^{31}$P NMR spectrum of the crude product of acid quenching of the reaction of (ethylidene)ethyldiphenylphosphorane and 2-bromobenzaldehyde

Two stacked spectra are shown in Fig. 2.9. The lower of these is the non-decoupled $^{1}$H spectrum, which is very useful for comparison with the selectively decoupled spectrum. Running a $^{1}$H spectrum while selectively irradiating the sample at the frequency of the peak at $\delta = 36.3$ gives the upper spectrum. These spectra show that the phosphorus coupling to the signals at $\delta = 5.81$ (double doublet collapses to doublet, OC*H* of major diastereomer), $\delta = 1.31$ (double triplet collapses to triplet, $PCH_2CH_3$ of major diastereomer), and the partially obscured signal at $\delta = 1.05$ (double doublet collapses to doublet, $PCHCH_3$ of major diastereomer) is removed, indicating that these signals are all in the same molecule as the phosphorus that gives the signal at $\delta = 36.3$ in the $^{31}$P NMR. The connectivity of the molecule giving rise to this network of signals is confirmed by COSY and TOCSY spectra. The $PCHCH_3$ signal of this diastereomer at $\delta = 3.67$ (not shown in Fig. 2.9) is also observed to collapse from a double quartet of doublets to a quartet of doublets. The diastereotopic $PCH_2CH_3$ hydrogens of the major diastereomer appear at approximately $\delta = 3.48$ and $\delta = 3.82$, overlapping with the corresponding signals for the minor diastereomer at $\delta = 3.54$ and $\delta = 3.89$. The integrations of the various signals (where baseline separated) are equal to those of the other signals assigned to this compound, while the integrations of the combined signals of each of the overlapping $PCH_2CH_3$ signals add up to the sum of the integrations of two major protons and two minor protons.

In Fig. 2.10 is shown the $^{1}$H spectrum of the same sample selectively decoupled from the peak at $\delta = 39.5$ (upper of the two spectra), again compared with the

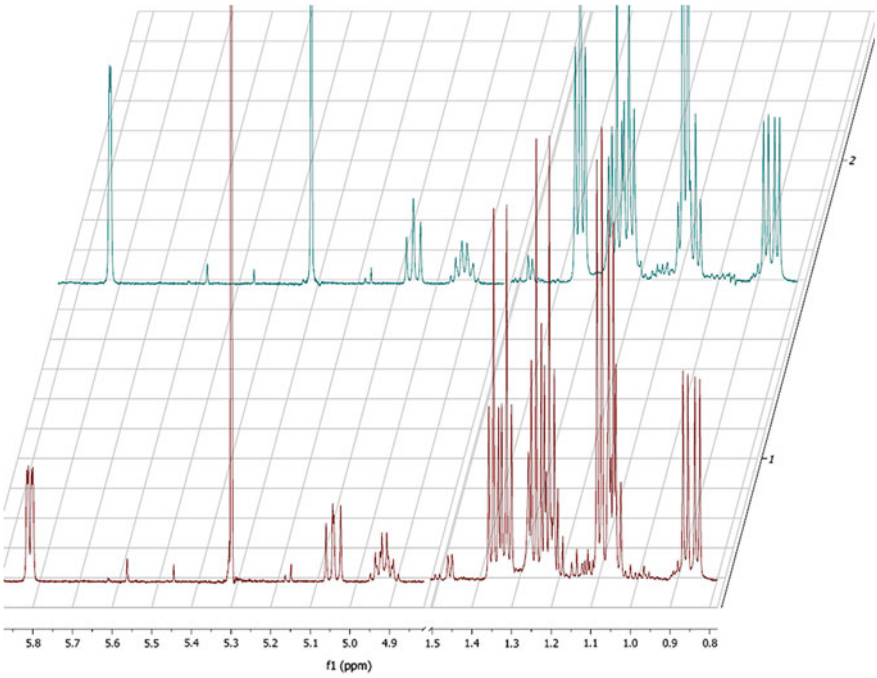



**Fig. 2.9** $^{1}$H spectra on the crude product of acid quenching of the reaction of (ethylidene)ethyldiphenylphosphorane and 2-bromobenzaldehyde. The bottom spectrum is the non-decoupled $^{1}$H spectrum. The top spectrum is selectively decoupled from the peak at $\delta = 36.3$ in the $^{31}$P spectrum. The region $\delta = 1.5$–$4.9$ is not shown

non-decoupled spectrum (lower spectrum). These spectra demonstrate that the phosphorus coupling to the signals at $\delta = 5.02$ (double doublet collapses to doublet, minor diastereomer C*H*OH), $\delta = 4.89$ (multiplet shows simplified coupling, minor diastereomer PC*H*) and $\delta = 0.83$ (double doublet collapses to doublet, minor diastereomer PCHC$H_3$) is eliminated by decoupling from the peak at $\delta = 39.5$ in the $^{31}$P spectrum. This indicates that all of the hydrogens and the phosphorus involved are part of the same molecule. The assignments of these signals are confirmed by the relative magnitudes of their integrations, and by the coupling patterns indicated in the COSY and TOCSY spectra of the crude $\beta$-HPS.

In the experiment giving entry 2 in Table 2.7, (1-(2-bromophenyl)-1-hydroxyprop-2-yl)triphenylphosphonium bromide was synthesised by low temperature acid quenching of the Wittig reaction of ethylidenetriphenylphosphorane and 2-bromobenzaldehyde. The diastereomeric ratio was obtained using selective phosphorus decoupling of $^{1}$H NMR spectra of the crude product, as described above. The major $\beta$-HPS isomer was then isolated by recrystallisation of the crude product from chloroform/ethyl acetate, and confirmed to be the *erythro* isomer by X-ray diffraction. Based on the NMR spectral data of *erythro*-(1-(2-bromophenyl)-1-hydroxyprop-2-yl)triphenylphosphonium bromide, and previous

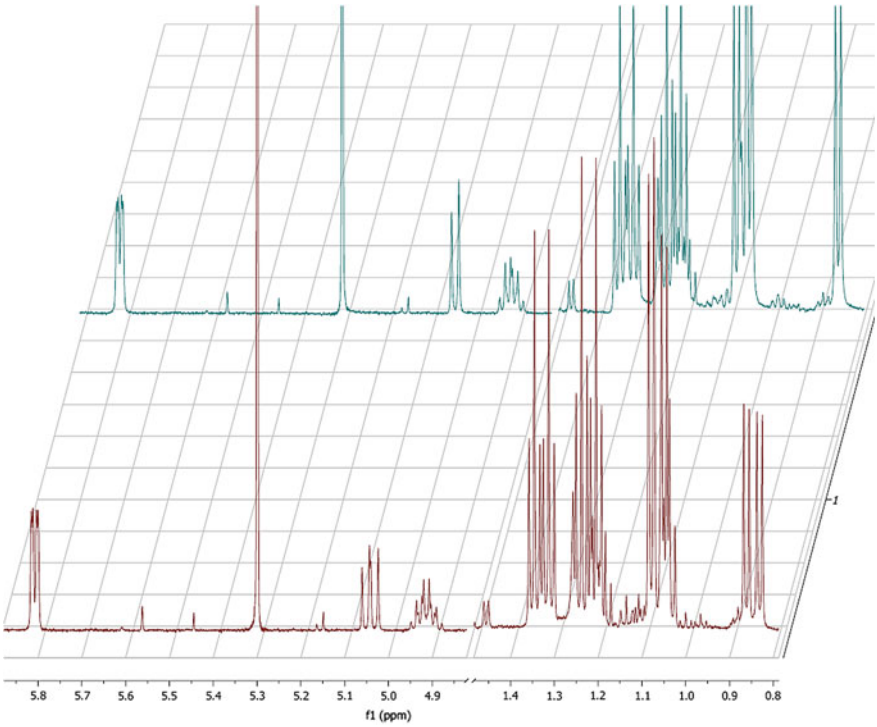



**Fig. 2.10** $^{1}$H spectra on the crude product of acid quenching of the reaction of (ethylidene)ethyldiphenylphosphorane and 2-bromobenzaldehyde. The bottom spectrum is the non-decoupled $^{1}$H spectrum. The top spectrum is selectively decoupled from the peak at $\delta = 39.5$ in the $^{31}$P spectrum. The region $\delta = 1.5$–$4.9$ is not shown

characterisations in the literature of the *erythro* and *threo* isomers of the closely related *β*-HPS (1-hydroxy-1-phenylpent-2-yl)triphenylphosphonium bromide [7], the major diastereomer in the experiment described above was assigned to be *erythro*-(1-(2-bromophenyl)-1-hydroxyprop-2-yl)ethyldiphenylphosphonium bromide, and the minor diastereomer was assigned to be the *threo* isomer. Integration of the signals belonging to these species in the $^{1}$H and $^{31}$P spectra of the crude product allows the *erythro/threo* ratio to be determined to be 65:35. This corresponds to the kinetic OPA *cis/trans* selectivity in the Wittig reaction.

Care must be taken in establishing connectivity by the selectively decoupled $^{1}$H{$^{31}$P} NMR technique, as if there is another signal close to the one for which narrowband decoupling is intended then $^{1}$H signals coupled to this second $^{31}$P signal may also show reduced multiplicity and could thus be erroneously assigned to the wrong compound. This problem can usually be anticipated based on the signal dispersion in the $^{31}$P NMR spectrum, and can often be detected by the $^{1}$H signals being only *partially* decoupled—so for example a double doublet might collapse to a pseudo-triplet or a heavily roofed AB-type double doublet.

#### 2.4.5.3 Variable Temperature $^{31}$P NMR Monitoring of OPAs Produced in Reactions of P-(ethylidene)-P-phenyldibenzophospholane

The OPAs produced in the Wittig reactions of dibenzophosphole-derived ylide *P*-(ethylidene)-*P*-phenyldibenzophospholane with benzaldehyde and 2-bromobenzaldehyde respectively (the same reactions as were quenched at low temperature for entries 5 and 6 of Table 2.7) were monitored by variable temperature $^{31}$P NMR. All manipulations were carried out under an inert atmosphere. The ylide was generated in situ from the precursor phosphonium salt (by the procedure described in Sect. 2.4.2) and reacted with aldehyde at −78 °C. The solution of OPA produced was stirred for 10 min. Approximately 0.6 ml of the OPA solution was then cannula filtered into an NMR tube (in a long Schlenk flask) at −40 °C and toluene-*d8* was added. The NMR tube was kept at −40 °C until such time as it could be placed in the NMR spectrometer at −20 °C. $^{31}$P spectra were taken at every 10 °C between −20 and 40 °C, allowing sufficient time at each temperature for the solution to equilibrate before acquisition. The *cis*-OPA was determined to be the major OPA diastereomer in each reaction by subsequent decomposition of the mixture of OPAs to predominantly *Z*-alkene at higher temperature, and by comparison with the low temperature acid quenching experiments of Table 2.6 (entries 5 and 6). In each reaction, four major species were observed in the $^{31}$P NMR—OPA (*cis* and *trans*, $\delta = -60$ to $-70$), ylide (integrates for ca. 15 % vs. *cis*-OPA, $\delta = -10.0$), and phosphine oxides (two signals, each integrate for ca. 5 % vs. *cis*-OPA). There were also up to two minor signals in the OPA region, each integrating for ca. 1 % vs. the *cis*-OPA. It is proposed that the small signals in the OPA region observed here indicate that OPA pseudorotamers have been resolved in these spectra. The resolution of OPA pseudorotamers by low temperature NMR has been reported previously for OPAs derived from unconstrained phosphines and also from *P*-methyl-5*H*-dibenzophosphole [29, 30, 35]. Bangerter et al. concluded in their publication that dibenzophosphole-derived OPAs which show only one set of signals by low temperature $^{13}$C NMR have one pseudorotamer (with an apical oxygen) that is the predominant solution structure, rather than the single set of signals being the average of two rapidly converting pseudorotamers (see Sect. 1.4.3 for further details) [35]. The major pseudorotamer for each of the *cis* and *trans*-OPAs in each case is very likely to be one of the O-apical pseudorotamers. The presence of more than one pseudorotamer for each of the *cis* and *trans*-OPAs may in principle affect the assigned *cis/trans* ratios, but because the minor pseudorotamers are present to such a small extent this effect is negligible. In any case, the accuracy of the OPA *cis/trans* ratios determined by $^{31}$P NMR (Table 2.7) has been confirmed by the determination of the *erythro/threo* ratios of the β-HPSs produced by low temperature acid quenching of the same reactions (Table 2.6).

It can be seen from the set of stacked spectra shown in Fig. 2.11 for the reaction of *P*-(ethylidene)-*P*-phenyldibenzophospholane with 2-bromobenzaldehyde that very significant broadening of the OPA peaks occurs as the temperature is raised, with the *trans*-OPA spreading into the baseline to such an extent that above 10 °C

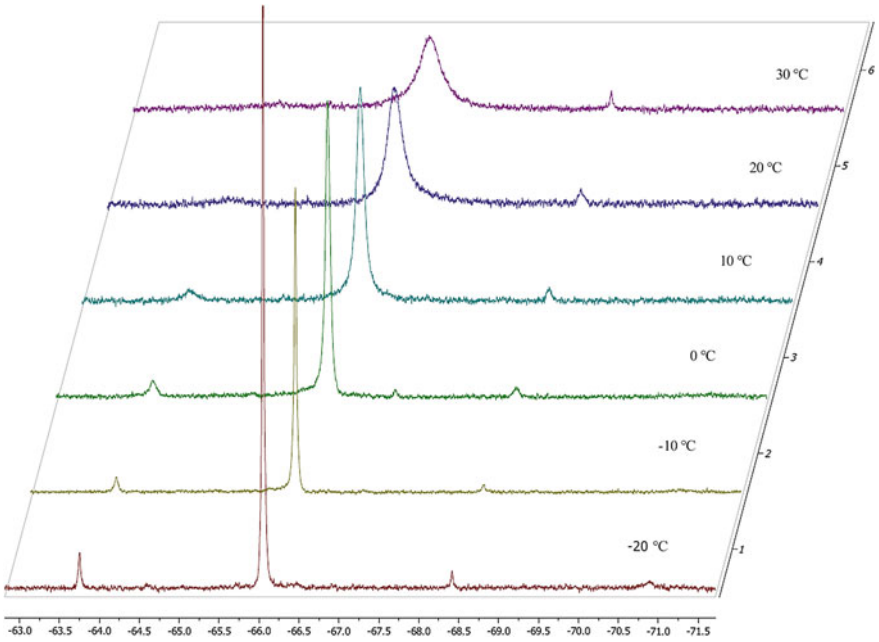



**Fig. 2.11** OPA region of Variable Temperature $^{31}$P NMR of the reaction of ethylidene phenyldibenzophospholane with 2-bromobenzaldehyde

its presence can barely be detected. The peaks of the phosphine oxide and ylide (not shown) remain the same shape at each temperature for which a $^{31}$P spectrum was obtained. The relative proportions of OPA, ylide, and phosphine oxide are also invariant over the whole range of temperatures, indicating at least that no decomposition to alkene and phosphine oxide (which is irreversible) is occurring. The relative proportions of the *cis* and *trans*-OPA can only be ascertained up to 10 °C due to signal broadening, which results in the two signals overlapping to some degree. Up to 10 °C the OPA *cis/trans* ratio is invariant at 94:6.

A very similar set of observations can also be made about the corresponding experiment involving *P*-(ethylidene)-*P*-phenyldibenzophospholane and benzaldehyde, with the exception that significantly more *trans*-OPA is produced in that reaction, and it appears that the *cis*-OPA signal does not broaden to the same extent as the *trans*-OPA, nor indeed to the same extent as the *cis*-OPA in Fig. 2.11.

### *2.4.6 Discussion*

The results presented in Tables 2.6 and 2.7 show that the reactions of non-stabilised ylides with *ortho*-heteroatom substituted benzaldehydes are more selective for *cis*-OPA than are reactions of the same ylides with benzaldehyde. Thus the

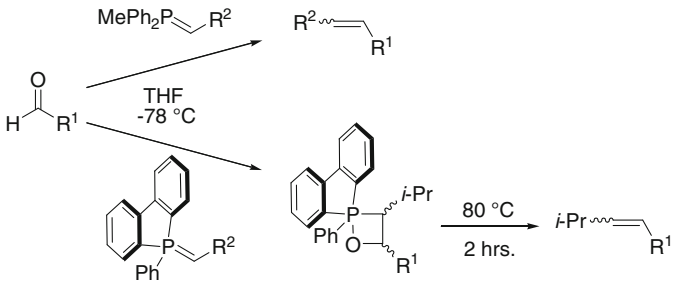
*ortho*-heteroatom effect is demonstrated for non-stabilised ylides. The absence of phosphorus-heteroatom bonding in the OPAs intermediates of these reactions has been demonstrated by NMR. This implies that a planar structure cannot engage in phosphorus-heteroatom bonding. Consequently, the *cis*-selective TS with this bonding interaction is likely to be puckered. It is thus postulated that the TS for the cycloaddition step in these reactions is entirely analogous to those shown in Figs. 2.1 and 2.2.

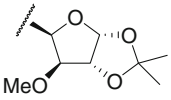
The average selectivity of the Wittig cycloaddition step for *cis*-OPA in reactions of non-stabilised ylides with benzaldehyde is 76 % (calculated from Table 2.6 entries 1, 3, 5, and 7), while in reactions of the same ylides with 2-bromobenzaldeyde it is 87 % (calculated from Table 2.6 entries 2, 4, 6, and 8). Thus, even though reactions of non-stabilised ylides with benzaldehdyes show a relatively high inherent selectivity for *cis*-OPA, the reactions of *ortho*-heteroatom substituted benzaldehyde are on average 11 % more *cis*-selective.

## 2.5 Reactions of an Aliphatic Aldehyde Showing Increased Z-Selectivity Due to a "β-Heteroatom Effect"

The results described above are common to all three ylide classes. They are self-consistent and can all be explained by the same transition state arguments. Therefore they argue strongly for a common mechanism for Wittig reactions of all ylide types. However, it could be argued that the effect is solely confined to *ortho*-heteroatom benzaldehydes and might not extend to other aldehydes. Many Wittig reactions of aliphatic aldehydes bearing heteroatoms on the carbon β to the carbonyl have been shown to give alkene with anomalously high *Z*-selectivity. A number of examples are given in Sect. 1.5.2. Consequently, it was necessary to investigate whether high *Z* or *cis*-selectivity would be observed in Wittig reactions under our conditions of strict kinetic control with an aldehyde that had previously been shown to induce high *Z*-selectivity in its reactions with semi-stabilised and stabilised ylides, 1,2-O-isopropylidene-3-O-methyl-α-D-xylopentodialdofuranose-(1,4) [18, 19]. 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, so the relative disposition of the carbonyl and the heteroatom is almost identical to that in *ortho*-heteroatom substituted benzaldehydes. The *Z/E* ratios for the alkenes produced in the reactions of this aldehyde with representative non-stabilised, semi-stabilised and stabilised ylides at −78 °C in THF under Li-salt free conditions are shown in Table 2.8. *P*-(isobutylidene)-*P*-phenyldibenzophospholane was also reacted with cyclopentanecarboxaldehyde under the same conditions in order to ascertain its selectivity with a non-heteroatom-bearing aliphatic aldehyde. In addition, the kinetic OPA *cis/trans* ratio for the reactions of the non-stabilised dibenzophosphole-derived ylide with these aldehydes was determined by $^{31}$P NMR.

**Table 2.8** *Z/E* ratios for Wittig reactions of non-stabilised, semi-stabilised and stabilised ylides (generated in situ from phosphonium salt using NaHMDS) with aliphatic aldehydes. OPA *cis/trans* ratios were also determined for reactions of non-stabilised ylides




| Entry | Aldehyde $R^1$ | Ylide $R^2$ | Ylide $R_3P$ group | Alkene Z/E ratio |
|---|---|---|---|---|
| 1 | | Ph | $MePh_2P$ | 95:5 |
| 2 | | 2-BrC6H4 | $MePh_2P$ | 95:5 |
| 3 |  | COOMe | $MePh_2P$ | 79:21[a] |
| 4 | | COO(t-Bu) | $MePh_2P$ | 79:21[a] |
| 5 | | COOEt | $MePh_2P$ | 79:21[a] |
| 6 | | i-Pr | PhDBP | 90:10[b] |
| 7 | cyclopentyl | i-Pr | PhDBP | 43:57[c] |

[a] Reactions of stabilised ylides were quenched at −78 °C by addition of aqueous $NH_4Cl$ in order to ensure the reaction had occurred at this temperature

[b] The kinetic OPA *cis/trans* ratio was observed by $^{31}P$ NMR at −20 °C and found to be 94:6

[c] The kinetic OPA *cis/trans* ratio was observed by $^{31}P$ NMR at 30 °C and found to be 45:55

1,2-O-isopropylidene-3-O-methyl-α-D-xylopentodialdofuranose-(1,4) was found to react with semi-stabilised ylides with very high *Z*-selectivity (Table 2.8 entries 1 and 2). This aldehyde also reacted with ester-stabilised ylides (Table 2.8 entries 3–5) with remarkably high *Z*-selectivity, particularly for reactions of stabilised ylides in an aprotic solvent. The kinetic OPA *cis/trans* ratio for the reaction of *P*-(isobutylidene)-*P*-phenyldibenzophospholane and 1,2-O-isopropylidene-3-O-methyl-α-D-xylopentodialdofuranose-(1,4) was determined by $^{31}P$ NMR at −20 °C and found to strongly favour the *cis*-OPA.

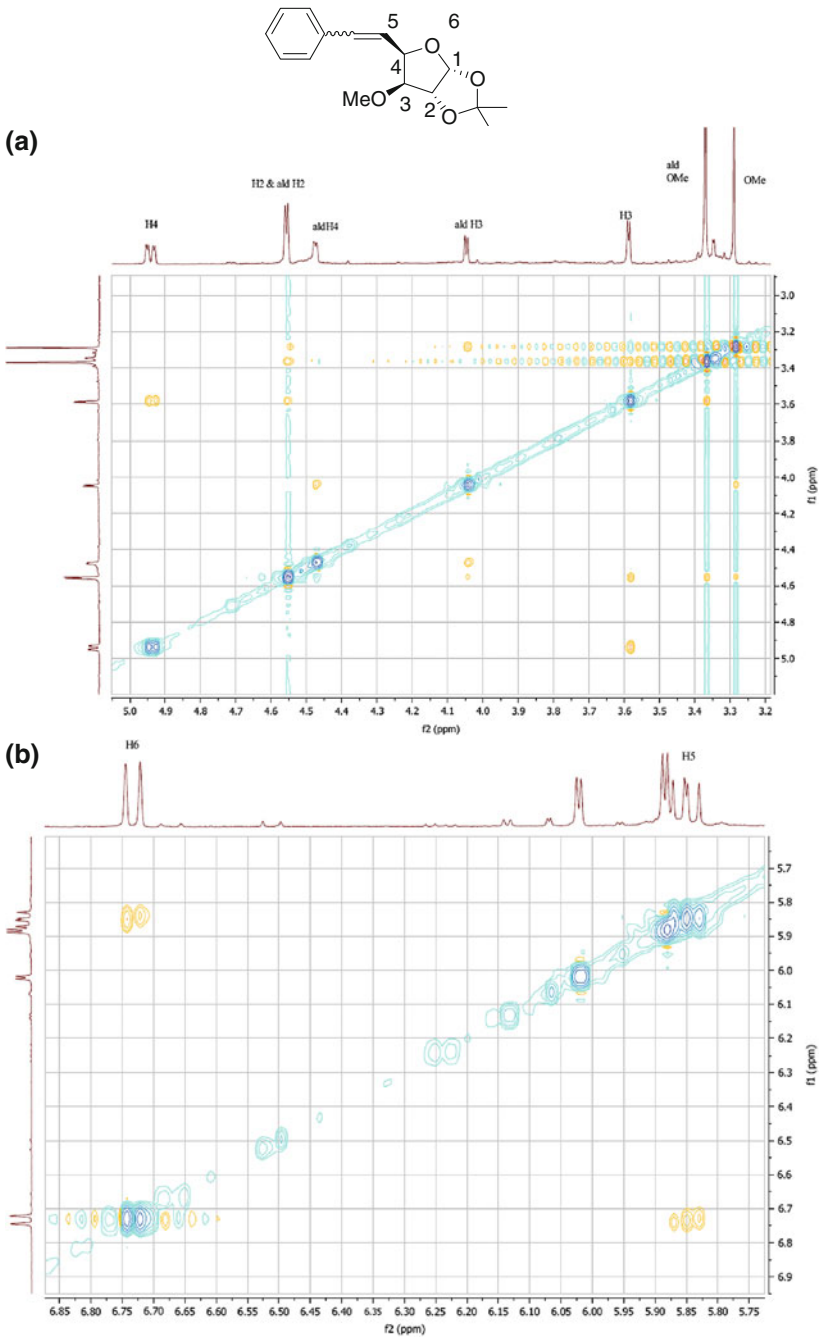
A sample of *β*-HPS heavily enriched in the *erythro*-isomer was obtained by low temperature acid quenching of the same reaction. Deprotonation of this *β*-HPS at low temperature and subsequent heating of the OPA to 80 °C for 2 h gave alkene with a *Z/E* ratio of 90:10 (as indicated in Table 2.8 entry 6). The high stereospecificity of OPA decomposition to alkene indicates that OPA formation is under dominant kinetic control. *P*-(isobutylidene)-*P*-phenyldibenzophospholane was also reacted with cyclopentanecarboxaldehyde, and the kinetic OPA *cis/trans* ratio was determined by $^{31}P$ NMR at 30 °C. This ratio was found to be almost the same as the *Z/E* ratio of the alkene produced after heating of the OPA to effect its

decomposition to alkene and phosphine oxide (Table 2.8 entry 7). Kinetic control is thus in operation in this reaction, and stereospecific OPA decomposition is also proven. The results of Table 2.8 entries 6 and 7 show that there is a very dramatic jump in selectivity for *cis*-OPA, and hence *Z*-alkene, in reactions of *P*-(isobutylidene)-*P*-phenyldibenzophospholane in its reactions with aldehydes bearing a suitably disposed β-heteroatom substituent.

The *Z*-selectivity observed in the reactions of 1,2-O-isopropylidene-3-O-methyl-α-D-xylopentodialdofuranose-(1,4) with representative stabilised, semi-stabilised and non-stabilised ylides is of comparable magnitude to that observed in the corresponding reactions of *ortho*-heteroatom substituted benzaldehydes with the same ylides. This selectivity is far greater than what would be expected for reactions of these ylides involving an aldehyde that lacks a suitably disposed β-heteroatom. The magnitude of the enhancement of *Z*-selectivity in these reactions is emphasised by the moderate *E*-selectivity observed in the kinetically controlled reaction of *P*-(isobutylidene)-*P*-phenyldibenzophospholane with cyclopentanecarboxaldehyde, which lacks a β-heteroatom substituent. There is no apparent influence on the magnitude of the *Z*-selectivity in reactions of 1,2-O-isopropylidene-3-O-methyl-α-D-xylopentodialdofuranose-(1,4) with representatives of a certain class of ylide from the steric bulk of the substituent on the ylide α-carbon. The high *Z*-selectivity observed in these reactions strongly implies that reactions all occur under kinetic control, especially given that they were carried out under conditions for which the operation of kinetic control in Wittig reactions has been verified. Indeed, the operation of dominant kinetic control was directly demonstrated for the reactions of the non-stabilised ylide.

In all of the alkenes in Table 2.8 derived from 1,2-O-isopropylidene-3-O-methyl-α-D-xylopentodialdofuranose-(1,4), no coupling is observed between H-2 and H-3 (as confirmed by multiplicity of these signals by $^1$H NMR, and the lack of cross-signals in gCOSY and TOCSY spectra), exactly as in the precursor aldehyde. This implies that the conformation of the ring is such that H-2 and H-3 are oriented at approximately 90° with respect to each other. Examination of the NOESY spectrum of the crude product from the reaction of the aldehyde with benzylidenemethyldiphenylphosphorane (shown in Fig. 2.12 for a sample containing a significant amount of the aldehyde starting material, blue = phase down, yellow = phase up) shows that H-2 experiences NOE contact with *both* H-3 and OMe, which are geminal substituents. This is consistent with it having a dihedral angle close to 90° with each of H-3 and OMe. The NOESY spectrum shows NOE contact between H-3 and H-4, indicating that they remain *cis* to each other, as in

**Fig. 2.12** NOESY spectra of the alkene derived from the reaction of benzylidenemethyldiphenylphosphorane and 1,2-O-isopropylidene-3-O-methyl-α-D-xylopentodialdofuranose-(1,4). **a** Close-up on 3–5 ppm region of the 2D NOESY spectrum, showing NOE contact for alkene H-3 with H-4, thus showing relative *cis* geometry of these hydrogens, and for H-2 (whose signal overlaps with aldehyde H-2 in $^1$H spectrum) with both H-3 and OC$H_3$, which are geminal substituents. Note that an identical set of interactions are shown in this spectrum to be present in the aldehyde starting material. **b** Close-up on the alkene region of the 2D NOESY spectrum, showing NOE contact between the *Z*-alkene hydrogens ▶


(a)
H4
H2 & ald H2
ald H4
ald H3
H3
ald OMe
OMe
f2 (ppm)
f1 (ppm)
(b)
H6
H5
f2 (ppm)
f1 (ppm)

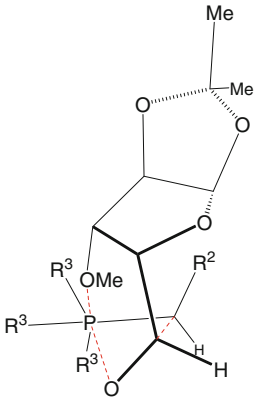



**Fig. 2.13** Diagram of the proposed *cis*-selective transition state in reactions of 1,2-O-isopropylidene-3-O-methyl-α-D-xylopentodialdofuranose-(1,4)

the aldehyde, and thus that there was no epimerisation at the aldehyde α-carbon under the reaction conditions. The NOESY spectrum also confirms that the alkene is of *Z*-configuration, since there is NOE contact between H-5 and H-6.

The conservation of the relative stereochemistry of the aldehyde in the alkene product (and therefore the non-epimerisation at the aldehyde α-carbon) and was confirmed in a similar manner using 1D or 2D NOESY for the *Z*-isomer of the alkene of Table 2.8 entry 2, for the *E*-isomer of alkene of entry 4, and for both the *E* and *Z* isomers of the alkene of entry 3 (see Sect. 4.8 for full details).

Given that the same trends are observed in the reactions of this aliphatic aldehyde that bears a *β*-heteroatom substituent as are observed in reactions of *ortho*-heteroatom substituted benzaldehydes, it is reasonable to conclude that the same effect is in operation in both types of reaction. The kinetic preference for *cis*-OPA formation in these reactions is thus postulated to be as a consequence of the existence of a phosphorus-heteroatom bond in the *cis*-selective cycloaddition TS. As with the TS model proposed for reactions of *ortho*-heteroatom substituted benzaldehydes, this TS is thought to be *cis*-selective due to the bonding interactions and the minimisation of 2–3 steric interactions that comes about if the reactants are arranged in the cycloaddition TS as shown in Fig. 2.13. This TS would also benefit from a favourable antiparallel orientation of the ylide C–C($R^2$) and aldehyde C = O bond dipoles, especially for reactions of stabilised ylides (with $R^2$ = COOR and R = alkyl).

## 2.6 Conclusions

All of the reactions described in this chapter were carried out under conditions for which the operation of kinetic control in Wittig reactions has been proven. In the reactions involving non-stabilised ylides the irreversibility of OPA formation at

the temperature at which the *cis/trans* ratio was measured was directly demonstrated by NMR. Thus it can be concluded that each of the results is truly indicative of the kinetic selectivity for *cis* or *trans* OPA in that reaction. A phenomenon that has its origins in the existence of a bonding interaction in the TS leading to OPA and results in the formation of *cis*-OPA and hence *Z*-alkene has been discovered in Wittig reactions of aldehydes bearing a suitably oriented *β*-heteroatom. This effect has been shown to be in operation in reactions of representatives of all three major types of ylide, and for both aromatic and aliphatic aldehydes.

That an effect that is undoubtedly common to Li-salt free Wittig reactions of all types of ylide has been uncovered indicates at the very least that a common mechanism is in operation in all such reactions. The reactions described are all under kinetic control, and thus there is no contribution to the selectivity from equilibration of intermediates. In particular, the high *Z*-selectivity observed in the reactions of stabilised ylides indicates that these are under kinetic control. It is unlikely that there is any difference in the OPA intermediates produced in the reactions of *β*-heteroatom substituted aldehydes and those produced in reactions of aldehydes lacking such a substituent based on the NMR studies of the OPAs produced in reactions of non-stabilised ylides. Furthermore, the *cis*-selective TS is clearly lower in energy in reactions of *β*-heteroatom substituted aldehydes than in reactions of analogous unsubstituted aldehydes, and thus if OPA equilibration by Wittig reversal was of significant mechanistic significance, it would be *more likely* to exert an effect in these reactions than otherwise since the barrier to OPA reversal is lower than it would otherwise be.

The results presented here also provide convincing evidence that there is no role played by betaines *in any Li-salt free Wittig reaction*. An increased tendency towards betaine equilibration has previously been suggested as a possible reason why reactions of stabilised ylides are so consistently *E*-selective. This possibility would also require ring closure to OPA to be faster for *threo*-betaine than for the *erythro*-isomer, given that OPA equilibration has been ruled out for reactions of all ylide types [6, 16]. Betaine equilibration is highly unlikely to be in operation in the reaction of one aldehyde and not in another that only differs in having a *β*-heteroatom substituent. The operation of kinetic control in the reactions of stabilised ylides reported here implies that all Li-salt free Wittig reactions of stabilised ylides are irreversible processes.

Since the involvement of betaine intermediates or equilibration of OPAs have been demonstrated not to play a part in the Wittig reactions of *β*-heteroatom substituted aldehydes,[9] it can be concluded that these reactions occur by kinetically controlled cycloaddition of ylide and aldehyde to give OPA, which decomposes stereospecifically to alkene and phosphine oxide. The TS model for the cycloaddition step of these reactions was initially proposed in order to

[9] OPA equilibration does occur in reactions of benzaldehydes with non-stabilised ethylides, but only at or above the temperature at which alkene formation occurs. Below this temperature, OPAs are formed under kinetic control.

rationalise the observed selectivity in reactions of semi-stabilised ylides with *ortho*-heteroatom substituted benzaldehydes. Based on this, high *Z*-selectivity was predicted in the reactions of non-stabilised, semi-stabilised and stabilised ylides with any aldehyde bearing a suitably oriented β-heteroatom. This prediction was tested and proved to be correct in the reactions that have been described above. The observed results are all entirely consistent with the operation of the cycloaddition mechanism under Li-salt free conditions, and with the existence of a phosphorus-heteroatom bond in the cycloaddition TS leading to *cis*-OPA. Since a cycloaddition mechanism operates in this subset of Wittig reactions that includes examples using all three different types of ylide, it is concluded that all Li-salt free Wittig reactions proceed by the cycloaddition mechanism proposed by Vedejs [6, 16], and modified by Aggarwal, Harvey and co-workers for reactions of stabilised ylides [23–25].

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