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# Investigations on the Operation of Stereochemical Drift in the Wittig Reaction by NMR & VTNMR Spectroscopy of Oxaphosphetane Intermediates & their Quench Products

Peter A. Byrne,<sup>[a]</sup> Jimmy Muldoon,<sup>[a]</sup> Yannick Ortin,<sup>[a]</sup> Helge Müller-Bunz,<sup>[a]</sup> and Declan G. Gilheany\*<sup>[a]</sup>

**Keywords:** Wittig reaction / Stereochemical Drift / Variable Temperature NMR / <sup>1</sup>H-<sup>31</sup>P HMBC / Oxaphosphetane *cis/trans* ratio /  $\beta$ -hydroxyphosphonium salt / Phosphorus NMR / Diastereomeric ratios

Within the currently accepted mechanism of the Li salt-free Wittig reaction, the phenomenon of *stereochemical drift* remains the one remaining “loose end” in an otherwise internally consistent explanation of a huge body of diverse observations. The term describes the non-stereospecific decomposition of the oxaphosphetane (OPA) intermediate in reactions of certain alkylides with certain aldehydes. In this paper, it is shown that the previous examples where drift occurs are not merely isolated aberrations from the observed norm, but rather that there is a general phenomenon in reactions of ethylides with benzaldehydes. Variable Temperature NMR (VTNMR) was used to establish that the amount and diastereomeric ratio of the OPA intermediates do not change below a certain temperature. At and above the temperature at which OPA decomposition to alkene and phosphane oxide begins to occur, the alkene shows a different diastereomeric ratio to the OPA, indicating the occurrence of stereochemical drift.

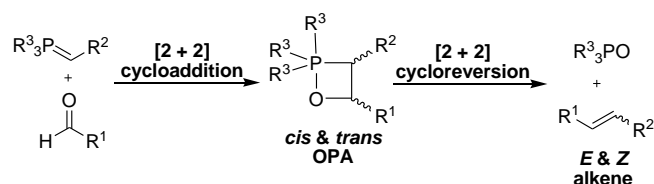
In one example, due to an apparent remarkable coincidence of rates, the diastereomeric ratio of the OPA does not change above the decomposition temperature, even though stereochemical drift is occurring in the formation of the alkene product. An alternative mechanism for drift involving its catalysis by aldehyde was discounted. Drift was also shown not to occur in similar Wittig reactions of structurally related longer chain alkylides by stereospecific decomposition of OPA intermediates generated from  $\beta$ -hydroxyphosphonium salts ( $\beta$ -HPSs). The extremely useful (and generally applicable) NMR techniques, <sup>1</sup>H-<sup>31</sup>P HMBC & selective <sup>1</sup>H{<sup>31</sup>P}, that we have utilised to establish kinetic diastereomeric ratios are described in full for the first time. Details of the determination of the relative stereochemistry of two  $\beta$ -HPSs (derived from acid quenching of OPAs) by X-ray crystallography are also given.

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## Introduction

It has recently been definitively established that Wittig reactions<sup>1,2,3,4</sup> of all phosphonium ylide types conducted in the absence of lithium salts occur by a common mechanism<sup>5</sup> (see Scheme 1) in which the oxaphosphetane (OPA) intermediate is formed by an irreversible [2+2] cycloaddition.<sup>6,7,8,9</sup> The stereoselectivity of the reaction is thus decided in the course of this irreversible first step. The OPA then decomposes<sup>8,10,11,12,13,14</sup> by irreversible [2 + 2] *syn*-cycloreversion to give alkene and phosphane oxide.<sup>6,7</sup> The stereoselectivity of the reaction is thus entirely dependent on the relative energies of the *cis* and *trans*-selective transition states (TSs) in the OPA-forming [2+2] cycloaddition step. The factors that govern the observed stereoselectivity of the cycloaddition step in reactions of non-stabilised ylides,<sup>6</sup> semi-stabilised ylides<sup>7</sup> and stabilised ylides<sup>8</sup> have been elucidated by Vedejs and co-workers and Aggarwal, Harvey and co-workers. The essential features of each proposal have been verified computationally by the latter group.<sup>8,15,16</sup> (albeit that some details to do with the second step of the reaction remain to be confirmed<sup>13,14</sup>). For a full discussion of the mechanism and the source of diastereoselectivity in Wittig reactions of different types of ylide, see our recent review on this topic.<sup>9</sup>

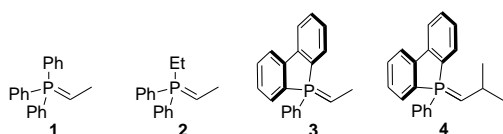
During our investigation of the kinetic diastereoselectivity of the Wittig reactions of  $\beta$ -heteroatom-substituted aldehydes (as part of a wider study on the Li salt-free Wittig reaction mechanism), we had occasion to determine the *cis/trans* ratio of the OPA and *Z/E* ratio of the alkene produced in the Wittig reactions of ylides **1-4** with selected aliphatic and aromatic aldehydes.<sup>5</sup>



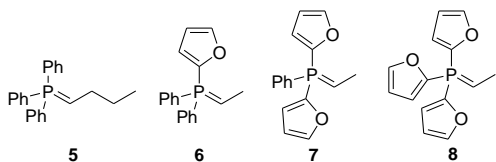
**Scheme 1.** The mechanism of the Li salt-free Wittig reaction.<sup>1-9</sup> In general the diastereomeric ratio of the OPA intermediate exactly matches that of the product alkene, except in (rare) cases where stereochemical drift occurs.<sup>9</sup>

In reactions of **1-3** with benzaldehydes, a non-correspondence was observed between the low temperature OPA *cis/trans* ratio<sup>17,18</sup> and the ultimate *Z/E* ratio of the alkene. This is a known but rare phenomenon termed “stereochemical drift”<sup>19</sup> and its explanation involves a departure from strict kinetic control in the Wittig reaction. Thus, although the formation of OPA has been shown to occur irreversibly<sup>20</sup> (and *without* the intermediacy of any betaine species<sup>21</sup>) in the vast majority of Li salt-free Wittig reactions,<sup>5,19,22,23,24,25,26</sup> there exists this small set of exceptional reactions for which the best explanation is that *cis*-OPA reverts to ylide and aldehyde under Li salt-free conditions.<sup>27</sup> This process

results in augmented production of *trans*-OPA (compared to the initial kinetic diastereomeric ratio) and hence increased *E*-alkene.<sup>5,19,24,28,29</sup>



The operation of stereochemical drift in the reaction of **1** with benzaldehyde has long been known<sup>19,28</sup> and a recent computational study on this reaction does indeed indicate that the *cis*-OPA has a propensity to undergo reversal.<sup>8</sup> Drift has also been shown to occur in some reactions of alkylidetrialkylphosphoranes with aromatic or tertiary aldehydes.<sup>19,24,25</sup> To our knowledge, these few examples constitute the entire list of the Wittig reactions that have been shown not to be under kinetic control in Li salt-free conditions. Stereochemical drift in the reaction of **1** with benzaldehyde only occurs at or above the temperature at which OPA decomposition to alkene and phosphine oxide occurs,<sup>28</sup> while it has been shown that at -20 °C (and below) there is neither interconversion nor decomposition of the OPA diastereomers produced in the reactions of **2** and **3** with benzaldehydes.<sup>5</sup> Stereochemical drift does not occur in Li salt-free Wittig reactions of ylides other than **1-3** and trialkylphosphonium alkylides (demonstrated for (RCH<sub>2</sub>)<sub>3</sub>P=CHR, with R = Me,<sup>24</sup> *n*-Pr<sup>19</sup>), even for reactions of benzaldehyde(s) with structurally similar ylides **4,5** (Li present in reaction)<sup>19,25</sup> or ethylides **6-8**,<sup>26</sup> in which phosphorus bears one or more fur-2-yl substituents; i.e. the reactions of these ylides are under kinetic control. Herein, we report on a series of further experiments that we have undertaken to more fully investigate the phenomenon of stereochemical drift in the reactions of **2** and **3** and the temperature at which its onset occurs, and to confirm the absence of stereochemical drift in reactions of **4**.



The determination of the kinetic diastereomeric ratio of the OPA intermediate in the Wittig reaction is essential to any investigation seeking to establish the operation of kinetic control or stereochemical drift. This can be done by low temperature NMR, or by quenching the OPA at low temperature to give  $\beta$ -hydroxyphosphonium salt ( $\beta$ -HPS),<sup>19,25</sup> the diastereomeric ratio of which directly corresponds to the *cis/trans* ratio of the OPA precursor.<sup>5,25</sup> We also give here full details on the NMR methods used to identify and quantify the  $\beta$ -HPS diastereomers in the crude products of the acid quenching reactions of **1** and **2**, and report on the unequivocal determination by X-ray crystallography of the relative stereochemistry of the major  $\beta$ -HPS diastereomers produced in each of these reactions.

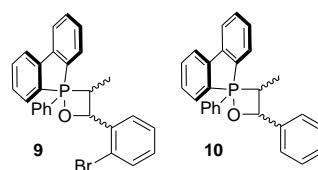
## Variable Temperature NMR Studies of OPA Stereochemical Drift

The Wittig reactions conducted in this study were carried out by the same methods that we have described previously.<sup>5</sup> The ylide was generated by addition of dry THF or THF-*d*<sub>8</sub> to a mixture of dry phosphonium salt and NaHMDS or KHMDS<sup>30</sup> under an atmosphere of dry nitrogen.<sup>31</sup> Ylide generation was typically carried out at 20 °C, but it was found to be optimal to generate ylide **3** at *ca.* -25 °C – a temperature at which ylide hydrolysis to phosphine oxide appears to be suppressed but ylide formation

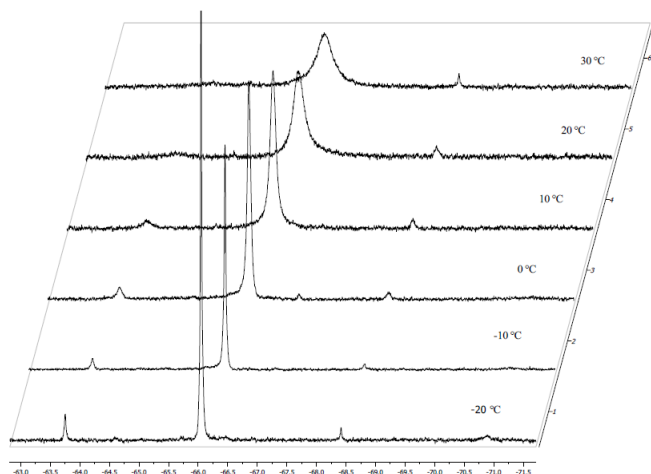
remains rapid – and then to sequentially cool to -45 °C while stirring the ylide solution and finally -78 °C for the reaction. The aldehyde was added to the ylide solution at -78 °C, and after stirring for 5 minutes the resulting OPA solution was transferred by cannula filter to an NMR tube contained in a long Schlenk tube cooled to -78 °C (for reaction of **2**) or -45 °C (for reaction of **3**) under a nitrogen atmosphere (then, if necessary, spiked with *ca.* 0.2 ml toluene-*d*<sub>8</sub>) before being transferred to the NMR spectrometer.

Generally two signals were observed in the <sup>31</sup>P NMR of the reaction mixture.<sup>32</sup> These were assigned to be the *cis* and *trans* isomers of the OPA reaction intermediate,<sup>1,3-5,6,7,10,13,19,21,22,23,24,25,26,28</sup> rather than pseudorotamers of one of the OPA isomers. This assignment is based mainly on the fact that one (major diastereomer, assigned as *cis*) decomposed predominantly to *Z*-alkene and the other (assigned as *trans*) decomposed to *E*-alkene, but furthermore, in certain cases the relative stereochemistry of the OPA intermediate(s) has been proven directly either by obtaining X-ray crystal structures of  $\beta$ -HPSs derived from stereospecific acid quenching of OPA intermediates (see reference 19 and also later in this paper) or by a combination of <sup>1</sup>H-<sup>31</sup>P HMBC NMR (described later in this paper) and 1D NOESY.<sup>5</sup>

At the outset, OPA **9**, produced in the reaction of **3** with 2-bromobenzaldehyde, was considered a particularly suitable candidate for the study of stereochemical drift. It is known to be stable to decomposition at room temperature (heating of OPAs such as **9** is required to effect formation of alkene & phosphane oxide) and is thus convenient to handle, and has been observed to undergo significant stereochemical drift on decomposition in refluxing THF – a sample containing *cis* and *trans*-**9** in a ratio of 94:6 gave alkene of *Z/E* ratio 82:18.5 Stacked VTNMR spectra of OPA **9**, recorded at different temperatures, are shown in Fig. 1. The *cis*-OPA ( $\delta = -66$ ) was determined to be the major OPA diastereomer by subsequent decomposition of the mixture of OPAs to predominantly *Z*-alkene at higher temperature. Four major species were observed in the <sup>31</sup>P NMR – OPA (*cis* and *trans*,  $\delta = -60$  to  $-70$ ), ylide **3** (integrates for *ca.* 15% vs. *cis*-OPA,  $\delta = -10.0$ ), and phosphine oxides (two peaks, each integrate for *ca.* 5% vs. *cis*-OPA). There were also up to two minor peaks in the OPA region, each integrating for *ca.* 1% vs. the *cis*-OPA.



It can be seen from the set of stacked spectra shown in Fig. 1 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 its presence can barely be detected. The peaks of the phosphine oxide and ylide (not shown) retain the same shape at each temperature for which a <sup>31</sup>P spectrum was obtained. The relative proportions of OPA, ylide, and phosphane 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, although it is not possible to rule out interconversion of OPAs above the temperature at which the *trans*-OPA signal can no longer be integrated reliably (30 °C). The OPA *cis/trans* ratio (94:6) is invariant up to this temperature.



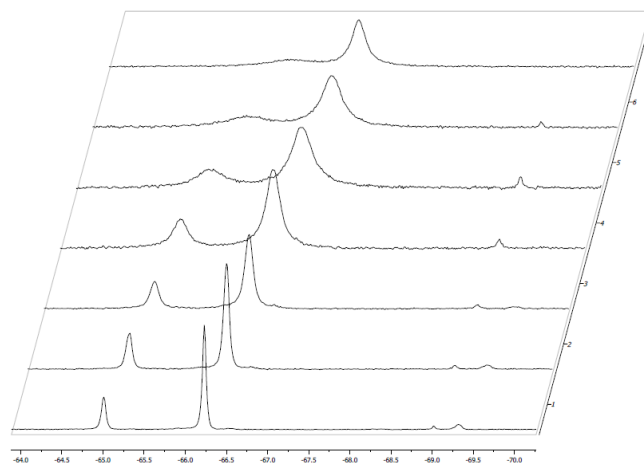
**Figure 1.** OPA region of Variable Temperature  $^{31}\text{P}$  NMR monitoring of the decomposition of OPA **9** (produced by reaction of **3** with 2-bromobenzaldehyde) at  $-20\text{ }^{\circ}\text{C}$ ,  $-10\text{ }^{\circ}\text{C}$ ,  $0\text{ }^{\circ}\text{C}$ ,  $10\text{ }^{\circ}\text{C}$ ,  $20\text{ }^{\circ}\text{C}$ , and  $30\text{ }^{\circ}\text{C}$  (lowest spectrum obtained at  $-20\text{ }^{\circ}\text{C}$ , highest at  $30\text{ }^{\circ}\text{C}$ ). Other signals were also present in the spectrum (not shown) at  $\delta_{\text{p}} -10$  (ylide) and  $\delta_{\text{p}} 30\text{--}42$  (phosphine oxides).

In a separate experiment, the same reaction was carried out in THF-*d*<sub>8</sub> at  $-80\text{ }^{\circ}\text{C}$  to produce OPA **9**. The major OPA diastereomer was assigned to be *cis*, and the *cis/trans* ratio was observed in both the  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of the reaction mixture at  $25\text{ }^{\circ}\text{C}$  to be 94:6. The sample was removed from the spectrometer while the instrument's internal temperature was raised to  $50\text{ }^{\circ}\text{C}$ . The sample was then returned to the spectrometer, and the decomposition of **9** to alkene and phosphane oxide at  $50\text{ }^{\circ}\text{C}$  was observed by  $^1\text{H}$  NMR over 2.5 days. The amounts of each of *cis* and *trans* OPA and *Z* and *E* alkene present at any given time during the experiment could be quantified by the integration of characteristic signals in the  $^1\text{H}$  NMR spectra. OPA decomposition was found to be first-order, as expected, and *cis*-OPA decomposed to give predominantly *Z*-alkene, while *trans*-OPA gave *E*-alkene.<sup>33</sup> The rate constant for decomposition of *cis*-OPA was found to be  $3.9 \pm 0.1 \times 10^{-6}\text{ s}^{-1}$ , while that for *trans*-OPA was found to be almost a factor of 10 larger, at  $3.3 \pm 0.2 \times 10^{-5}\text{ s}^{-1}$  – both reactions, clearly, are quite slow at  $50\text{ }^{\circ}\text{C}$ .<sup>33</sup> To our knowledge, only one example has previously been reported in which decomposition of *trans*-OPA is faster than the *cis*-isomer.<sup>34</sup>

The above reaction was not complete after 6 days, but the maximum possible *Z/E* ratio that could have been achieved in the reaction at this point was 88:12,<sup>35</sup> indicating that some stereochemical drift had occurred. The amount of drift is small, and thus it is difficult to make definitive comment on what stage of the decomposition involves production of *E*-alkene from *cis*-OPA. Stereochemical drift may occur throughout the reaction, or it may occur only at a particular stage e.g. only near the start of the OPA decomposition. Maryanoff, Reitz, and co-workers have suggested that the presence of the *trans*-OPA can influence the manner of the decomposition of the *cis*-OPA in reactions where stereochemical drift occurs<sup>1,36</sup> – thus here, it could be that the *cis*-OPA undergoes stereochemical drift until the *trans*-OPA has completely decomposed, and then stereospecific cycloreversion of the *cis*-OPA occurs thereafter. Certainly in this case, a plot of the sum of the integrations of *cis*-OPA and *Z*-alkene vs. time shows a slight decrease over the course of the experiment, while the corresponding plot for the sum of the integrations of *trans*-OPA and *E*-alkene vs. time shows a slight increase.<sup>33</sup> Thus we tentatively conclude that a small amount of stereochemical drift occurs throughout the reaction. The amount of stereochemical drift in this experiment is smaller than has previously been observed for

this reaction. We believe that this difference reflects the lower temperatures at which the OPA decomposition was carried out in this case ( $50\text{ }^{\circ}\text{C}$  vs. THF reflux in our previous experiment<sup>5</sup>). Since the amount of stereochemical drift appears to be lower at lower temperature, it may be possible to retain the diastereoselectivity of the cycloaddition step (i.e. avoid stereochemical drift) in this reaction by carrying out the decomposition at, say,  $40\text{ }^{\circ}\text{C}$  over a week or more.

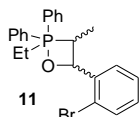
The broadening observed in the higher temperature  $^{31}\text{P}$  spectra shown in Fig. 1 was observed to be even more pronounced in a  $^{31}\text{P}$  NMR of the sample of **9** at  $50\text{ }^{\circ}\text{C}$  in THF-*d*<sub>8</sub>. Certain signals in the  $^1\text{H}$  NMR of **9** are also broadened at  $50\text{ }^{\circ}\text{C}$ , including one of the *cis*-OPA ring hydrogens. Since the signal broadening is observed to occur on an NMR timescale, and stereochemical drift of **9** clearly occurs far slower than this, we are confident that the dynamic process leading to the broadening is independent of the occurrence of stereochemical drift. By analogy with other OPAs, in which one pseudorotamer is thought to be heavily favoured thermodynamically in solution,<sup>9,10,22</sup> we consider that the observed signal broadening at higher temperatures in **9** and related OPAs (*vide infra*) is related to the onset of conversion of the favoured pseudorotamer of **9** to other (less favoured) pseudorotamer(s) in solution – i.e. a stereomutation process at phosphorus.



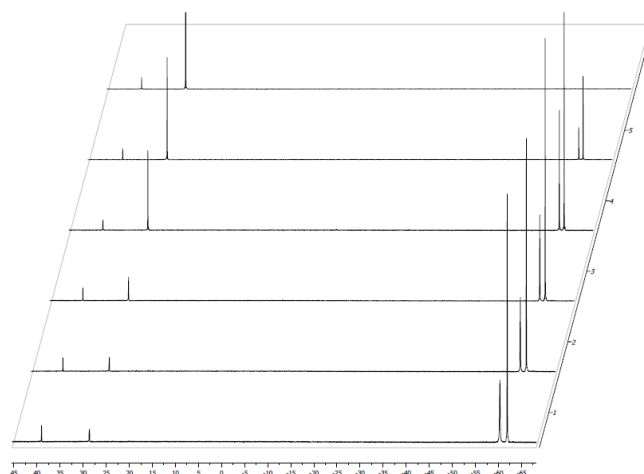
**Figure 2.** OPA region of Variable Temperature  $^{31}\text{P}$  NMR monitoring of the decomposition of OPA **10** (from reaction of **3** and benzaldehyde) at  $-20\text{ }^{\circ}\text{C}$ ,  $-10\text{ }^{\circ}\text{C}$ ,  $0\text{ }^{\circ}\text{C}$ ,  $10\text{ }^{\circ}\text{C}$ ,  $20\text{ }^{\circ}\text{C}$ ,  $30\text{ }^{\circ}\text{C}$  and  $40\text{ }^{\circ}\text{C}$  (lowest spectrum obtained at  $-20\text{ }^{\circ}\text{C}$ , highest at  $40\text{ }^{\circ}\text{C}$ ). Other signals were also present in the spectrum (not shown) at  $\delta_{\text{p}} -10$  (ylide) and  $\delta_{\text{p}} 30\text{--}42$  (phosphine oxides).

A very similar set of observations to those made about **9** can also be made about the corresponding VTNMR experiment on OPA **10**, produced in the reaction of **3** and benzaldehyde (Fig. 2), over the temperature range  $-20\text{ }^{\circ}\text{C}$  to  $+40\text{ }^{\circ}\text{C}$ . Again, the relative proportion of OPA/ylide/phosphine oxide is invariant over the entire temperature range (indicating no OPA decomposition, either in the forward or reverse direction), and each OPA signal broadens considerably as the temperature is increased. Significantly more *trans*-OPA is produced in this reaction (*cis/trans* ratio 71:29), and it appears that the *cis*-OPA signal does not broaden to the same extent as the *trans*-OPA. Accurate integration of the individual diastereomeric OPA signals above  $20\text{ }^{\circ}\text{C}$  was not possible due to poor baseline separation (and thus no definitive comment can be made on whether there is interconversion of the OPAs), but below this temperature the *cis/trans* ratio is constant with time. The *Z/E* ratio of the alkene produced on heating the OPA has previously been found to be 53:47.5

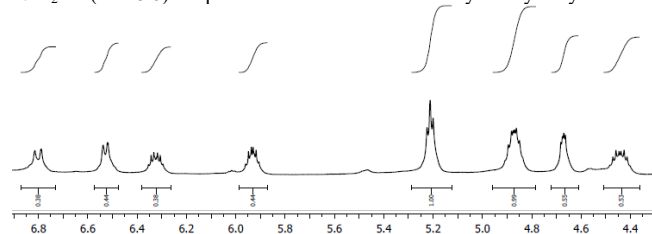
A further comment relating to the  $^{31}\text{P}$  NMR spectra of **9** and **10** is that, in the presence of excess aldehyde, further small signals appear in the pentavalent region ( $\delta$  -50 to -80) in addition to those previously assigned to the OPA diastereomers, which is consistent with the observation of Vedejs *et al.*<sup>28,32</sup> We have attempted to probe the influence that this apparent interaction between OPA and aldehyde may have on the occurrence of stereochemical drift (*vide infra*).



$^1\text{H}$  and  $^{31}\text{P}$  VTNMR spectra of the reaction of **2** with 2-bromobenzaldehyde in THF-*d*<sub>8</sub> over the range -70 to 20 °C are shown in Fig. 3. Significantly, no broadening of the  $^{31}\text{P}$  NMR signals of either isomer of **11** are observed at higher temperatures. This could be a consequence of fast interconversion of two or more pseudorotamers of similar energy of what is an unconstrained OPA (*cf.* **9** & **10**). These spectra indicate that, although the quantity of OPA (**11**; *cis*-isomer  $\delta$  -62; *trans*-isomer  $\delta$  -60) present began to decrease above approximately -20 °C (decomposition to alkene and ethyldiphenylphosphine oxide), the OPA *cis/trans* ratio was invariant at 65:35, at least over the range -70 to 10 °C. The  $^1\text{H}$  NMR spectra obtained indicated that the *Z/E* ratio of the alkene produced was, from the outset of alkene formation at -20 °C, close or equal to 56:44, the *Z/E* ratio of the alkene at the end of the reaction (and equal to that obtained in our previous report<sup>5</sup>). This observation is consistent with the fact that our attempts to arrest stereochemical drift in this particular reaction (i.e. maintain the low temperature diastereoselectivity of the cycloaddition step) by allowing the OPA to decompose at 0 °C were not successful, yielding alkene with a 56:44 *Z/E* ratio. The alkene in question does not isomerise under the reaction conditions. As indicated above, such a difference between the OPA and alkene diastereomeric ratios has previously been ascribed<sup>19,24,25,28</sup> to a process involving reversal of the *cis*-OPA to ylide + aldehyde, followed by recombination to OPA. Astoundingly in this case, this process appears to occur *without any change* in the OPA diastereomeric ratio! In most experiments conducted thus far involving the monitoring of OPA decomposition to alkene and phosphine oxide, it has been observed that *cis*-OPA decomposes more quickly than its *trans* diastereomer.<sup>37</sup> The one previous example that we are aware of in which the *trans*-OPA decomposes more quickly than the *cis*-OPA occurs in the reaction of **1** with benzaldehyde<sup>34</sup> (we have, as already mentioned, now observed another in the reaction of **3** with 2-bromobenzaldehyde). Thus, it is conceivable that there exists an example (perhaps OPA **11**) in which the *cis* and *trans*-OPAs each decompose at a rate that would lead to the observed invariance of the OPA ratio. Since there are no known examples in which *trans*-OPA undergoes reversal to Wittig starting materials,<sup>24</sup> it is reasonable to assume that the *trans*-OPA is formed irreversibly in this case. Therefore, since there is a significant augmentation of the product of decomposition of OPA *trans*-**11** at the expense of the product of *cis*-**11** in the above reaction, we conclude that the net rate of loss of *cis*-**11** (decomposition of *cis*-**11** to alkene + phosphine oxide and conversion of *cis*-**11** to *trans*-**11**) must equal the net rate of decomposition of *trans*-**11** to *E*-alkene (taking into account that some more *trans*-**11** is formed by stereochemical drift of *cis*-**11**).

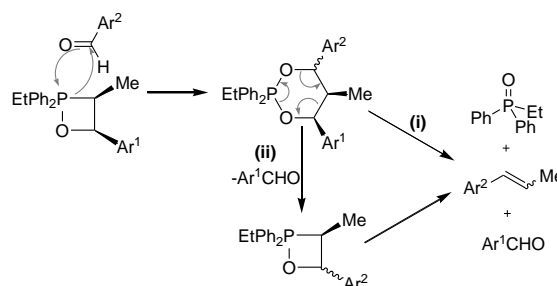


**Figure 3.** Variable Temperature  $^{31}\text{P}$  NMR spectra (from -40 °C at the bottom, through -20 °C, -10 °C, 0 °C, 10 °C to 20 °C at the top) monitoring the decomposition of OPA **11** (produced by the reaction of **2** with 2-bromobenzaldehyde). Small quantities of  $\text{Et}_2\text{PhPO}$  ( $\delta$  +39) and  $\text{EtPh}_2\text{PO}$  ( $\delta$  +28.6) are present from the outset due to ylide hydrolysis.



**Figure 4.** Section of  $^1\text{H}$  NMR at -10 °C monitoring decomposition of OPA **11**, showing  $\text{HC}=\text{CH}$  signals of *E* ( $\delta$  6.79, 6.29) and *Z*-alkene ( $\delta$  6.53, 5.90), and ring  $\text{CH}$  signals of *trans* ( $\delta$  4.67, 4.40) and *cis*-OPA ( $\delta$  5.21, 4.86). The alkene *Z/E* ratio in this  $^1\text{H}$  spectrum is 56:44, while the OPA *cis/trans* ratio is 65:35.

The operation of stereochemical drift is clear in the reactions of **2** with 2-bromobenzaldehyde and **3** with each of benzaldehyde and 2-bromobenzaldehyde, but it is shown by our VTNMR experiments not to occur at temperatures (up to 30 °C) below that at which the decomposition to alkene & phosphane oxide begins, as has previously been observed to be the case in the reaction of **1** with benzaldehyde.<sup>28</sup>



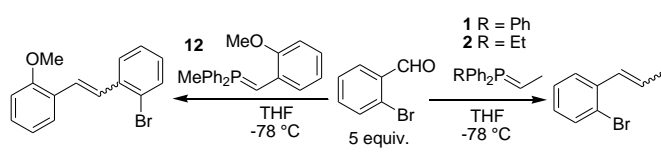
**Scheme 2.** Alternative mechanisms to explain the origin of stereochemical drift in reactions of ethylides with benzaldehydes. In these, unreacted benzaldehyde ( $\text{Ar}^2 = \text{Ar}^1$ ) or crossover aromatic aldehyde ( $\text{Ar}^2 \neq \text{Ar}^1$ ) is postulated to induce stereochemical drift *without* reversal of OPA to ylide & aldehyde.

Prompted by  $^{31}\text{P}$  NMR observations in this study, and by Vedejs *et al.*,<sup>28</sup> indicating the apparent interaction between OPA and aldehyde, we considered one other possibility for the source of stereochemical drift in the reactions where it has been observed: unreacted aldehyde might act as catalyst for OPA decomposition (Scheme 2, route (i),  $\text{Ar}^2 = \text{Ar}^1$ ).<sup>38</sup> Aldehyde intervention could also cause reversal of OPA,<sup>39</sup> and/or facilitate the direct conversion of one diastereomer into another (e.g. Scheme 2, route (ii)).<sup>38</sup> These postulated mechanisms are also all potentially consistent

with the results of previous crossover experiments (Scheme 2, Ar<sup>2</sup> ≠ Ar<sup>1</sup>).<sup>40</sup>

To investigate this possibility, we conducted experiments with each of ylides **1**, **2** and **12**<sup>41</sup> in which either less than one equivalent of 2-bromobenzaldehyde was added, or excess aldehyde (5 equivalents) was added. We then examined the <sup>1</sup>H NMR spectra of the crude alkene products to determine the *Z/E* ratios by integration of characteristic signals. The results are shown in Table 1. In each case, a modest decrease is observed in the amount of *Z*-alkene produced in the reactions carried out in the presence of excess aldehyde. However, based on these results it cannot be said that the presence of excess benzaldehyde exerts a significant effect on stereochemical drift in the decomposition of OPAs derived from ethylides and benzaldehydes. Furthermore, there is still no evidence to suggest that stereochemical drift operates in the reactions of **12**, and we believe that these reactions occur under kinetic control.<sup>42</sup>

**Table 1.** *Z/E* ratios for alkenes produced in Wittig reactions of 2-bromobenzaldehyde with ylides **1**, **2** and **12**.



Ylide	Excess aldehyde <sup>a</sup>	Excess ylide <sup>b</sup>	1:1 ylide/aldehyde <sup>c</sup>
<b>1</b>	77:23	80:20	79:21
<b>2</b>	47:53	56:44	56:44
<b>12</b>	72:28 <sup>d</sup>	76:24 <sup>e</sup>	72:28

<sup>a</sup> Ylide reacted with 5 equivalents of aldehyde.

<sup>b</sup> Ylide reacted with 0.8 equivalents of aldehyde, unless otherwise noted.

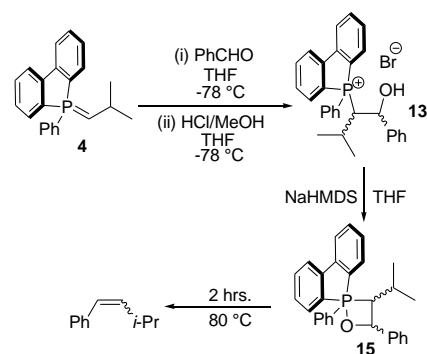
<sup>c</sup> Results from reference 5.

<sup>d</sup> Ylide added by cannula to a dilute solution of 5 equivalents of aldehyde in THF (all at -78 °C).

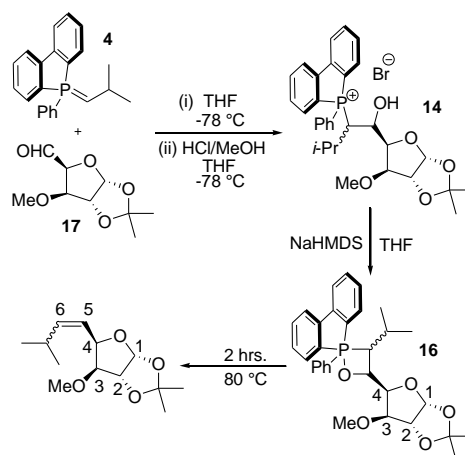
<sup>e</sup> Aldehyde (1 equivalent) was added over 5 hours from syringe using syringe pump.

### Demonstration of kinetic control in longer chain DBP-derived alkylides

In contrast to reactions of ylides **1-3**, Wittig reactions of longer chain branched chain alkylide **4** have been observed to show negligible, if any, stereochemical drift with both aromatic and aliphatic aldehydes.<sup>5</sup> In order to independently verify whether or not stereospecific decomposition occurs of these OPAs to alkene & phosphine oxide, we set about obtaining β-HPSs **13** & **14**, each with known diastereomeric ratio (established using a combination of NMR techniques). Then each of **13** & **14** was deprotonated to re-enter the normal manifold of Wittig processes, giving OPAs **15** & **16**, respectively, and hence the alkene products after cycloreversion of the OPAs. Invariance of the diastereomeric ratio from β-HPS to OPA to alkene would confirm the absence of stereochemical drift, particularly for β-HPSs heavily enriched in the *syn*-isomer.



**Scheme 3.** Low temperature acid quenching of reaction of **4** and PhCHO to give β-HPS **13**, followed by deprotonation to give OPA **15** and hence alkene.



**Scheme 4.** Low temperature acid quenching of reaction of **4** and **17** to give β-HPS **14**, followed by deprotonation to give OPA **16** and hence alkene.

β-HPS **13** was obtained by low temperature acid quenching of the Wittig reaction of **4** with benzaldehyde – a suitable representative aromatic aldehyde (see Scheme 3). The crude β-HPS product was analysed by a series of NMR techniques (<sup>1</sup>H, <sup>31</sup>P, <sup>13</sup>C, gCOSY, TOCSY, <sup>1</sup>H-<sup>31</sup>P HMBC, gHSQC, gHMBC) in order to aid assignment of peaks in the <sup>1</sup>H and <sup>31</sup>P NMR spectra. The diastereomeric ratio was then obtained by comparison integration of all of the peaks belonging to the *syn* and *anti*-diastereomers,<sup>43</sup> respectively. The major diastereomer was assigned to be the *syn*-β-HPS based on the fact that the unquenched Wittig reaction gives *Z*-alkene as the major product.<sup>5</sup> In this manner, the *syn/anti* ratio of **13** was found to be 89:11. β-HPS **14** was obtained in a similar fashion from the reaction of **4** and aldehyde **17**, which is a suitable representative aliphatic aldehyde for our investigation (see Scheme 4), and one that we have used in previous studies.<sup>5</sup> Analysis using the same NMR techniques as were applied to **13** indicated that the *syn/anti* ratio of **14** was 92:8. These *syn/anti* ratios agree closely with the kinetic OPA *cis/trans* ratios determined for the same reactions by <sup>31</sup>P NMR analysis of the Wittig reaction mixtures.<sup>5</sup> Other products are present in the crude product – these are phosphine oxides (very small amounts, from ylide hydrolysis) and phosphonium salt (from unreacted ylide).

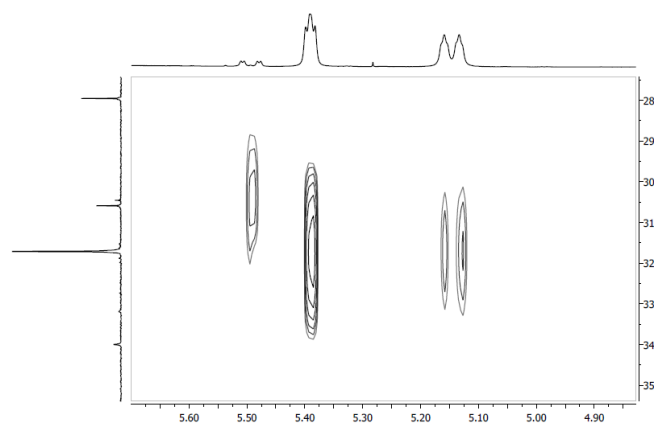
**13** and **14** were each then precipitated (along with any remaining starting phosphonium salt and some phosphine oxide) from dry chloroform/ethyl acetate to remove aldehyde, and were stored under inert atmosphere to prevent the uptake of water by the hygroscopic solids. The sample of β-HPS thus obtained was treated with NaHMDS in toluene-*d*<sub>8</sub> at -78 °C to generate OPA (**15**

or **16**, see Schemes 3 & 4), which was observed by NMR after cannula filtration into an NMR tube (all under a nitrogen atmosphere). The OPAs were each characterised by  $^1\text{H}$ ,  $^{31}\text{P}$ , gCOSY, and TOCSY NMR. To our knowledge, this marks the first time that two-dimensional NMR techniques (COSY, TOCSY, and the  $^1\text{H}$ - $^{31}\text{P}$  HMBC technique that is discussed below) have been applied in the observation of meta-stable Wittig intermediates.<sup>44</sup> In each case only *cis*-OPA could be detected in the reaction mixture at 30 °C – the  $^{31}\text{P}$  NMR signal for the small amount of *trans*-OPA present is likely to be broadened to such an extent that it is indistinguishable from the baseline (see above for similar signal broadening phenomena in related OPAs). Heating of **15** or **16** gave the alkene product. The *Z/E* ratio for each alkene matched the *syn/anti* ratio for the precursor  $\beta$ -HPS, indicating that neither **15** nor **16** undergo stereochemical drift. These results also indicate that the betaines that are necessarily (and transiently) formed on deprotonation of **13** to give **15** and **14** to give **16** do not undergo reversal to ylide and aldehyde.

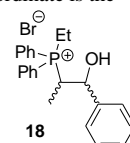
### NMR techniques for the identification of diastereomeric signals

The *syn/anti* ratio of the  $\beta$ -HPS produced by low temperature acid quenching of Wittig reactions of non-stabilised ylides has been shown to correspond to the kinetic OPA *cis/trans* ratio.<sup>5,25</sup> The establishment of the diastereomeric ratio of the crude  $\beta$ -HPS relies heavily on two NMR techniques that allow the connectivity of the constituent molecules of the crude product (and in particular the  $^1\text{H}$ - $^{31}\text{P}$  connectivity) to be determined. These are selectively decoupled one dimensional  $^1\text{H}\{^{31}\text{P}\}$  NMR, and two dimensional  $^1\text{H}$ - $^{31}\text{P}$  HMBC. These techniques are particularly useful for the analysis of reaction mixtures for the purposes of the assignment of diastereomeric ratios, where prior purification of the product is not desirable. They have been utilised in our previous study for this purpose,<sup>5</sup> but are for the first time described fully here.

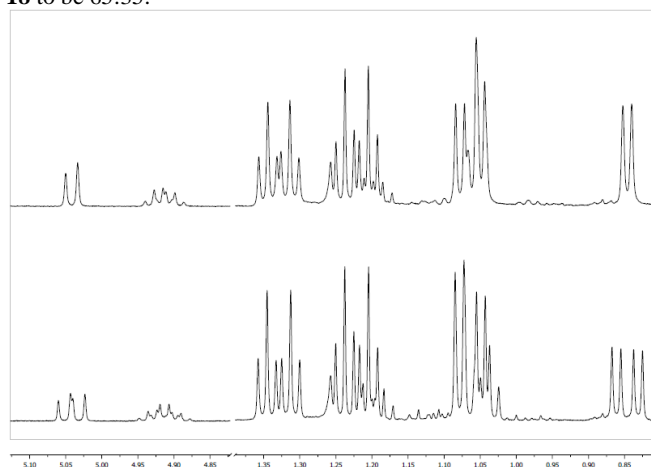
As an example of the  $^1\text{H}$ - $^{31}\text{P}$  HMBC technique, we will now describe its application to the analysis of the crude  $\beta$ -HPS (**13**) produced in the low temperature acid quenching of the Wittig reaction of **4** with benzaldehyde. In Fig. 5 is shown a close-up from the  $^1\text{H}$ - $^{31}\text{P}$  HMBC spectrum of crude  $\beta$ -HPS **13** optimised for a  $^1\text{H}$ - $^{31}\text{P}$  coupling constant  $J_{\text{PH}} = 6$  Hz. The two large signals in the  $^1\text{H}$  NMR 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 OCH of the major diastereomer (shows heavily roofed double doublet due to splitting by phosphorus and PCH), and the signal at  $\delta = 5.15$  is assigned to the PCH of the major diastereomer. As can be seen from the spectrum in Fig. 5, both couple to the phosphorus signal at  $\delta_{\text{P}} = 31.7$ , confirming that these  $^1\text{H}$  and  $^{31}\text{P}$  NMR signals belong to one compound. The double doublet at  $\delta = 5.49$  is assigned to the CHOH of the minor diastereomer (it couples with PCH at  $\delta = 4.03$ ). This is shown by the  $^1\text{H}$ - $^{31}\text{P}$  HMBC spectrum in Fig. 5 to be coupled to the phosphorus signal at  $\delta_{\text{P}} = 30.6$ , confirming it to be the phosphorus 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  $^1\text{H}$  NMR spectrum is 89:11, which is agreed upon by comparison of the integrals of the major and minor diastereomer signals in the  $^{31}\text{P}$  spectrum. Since deprotonation of this  $\beta$ -HPS sample gave alkene with a *Z/E* ratio of 89:11 (see above), it can be surmised that the major  $\beta$ -HPS diastereomer is *syn*, and hence the *syn/anti* ratio is 89:11.



**Figure 5.** Close-up on a region of the  $^1\text{H}$ - $^{31}\text{P}$  HMBC spectrum of crude  $\beta$ -HPS **13** optimised for a coupling constant  $J_{\text{PH}} = 6$  Hz. On the abscissa is the  $^1\text{H}$  spectrum, and on the ordinate is the  $^{31}\text{P}$  spectrum.



As an example of the use of the selectively decoupled  $^1\text{H}\{^{31}\text{P}\}$  NMR technique, we will discuss its application to the analysis of the low temperature quench product ( $\beta$ -HPS **18**) of the reaction of **2** and 2-bromobenzaldehyde. The  $^{31}\text{P}$  NMR spectrum contains four signals –  $\delta_{\text{P}} 39.5$  (minor  $\beta$ -HPS),  $36.3$  (major  $\beta$ -HPS),  $34.2$  (small, likely to be  $\text{EtPh}_2\text{PO}$ )<sup>45</sup> and  $32.5$  ( $[\text{Et}_2\text{Ph}_2\text{P}]\text{Br}$ ).<sup>46</sup> In Fig. 6 is shown the selective  $^1\text{H}\{^{31}\text{P}\}$  NMR spectrum selectively decoupled from the signal at  $\delta_{\text{P}} 39.5$  (upper of the two spectra), and the regular  $^1\text{H}$  NMR spectrum (lower spectrum). These spectra demonstrate that the phosphorus coupling to the signals at  $\delta = 5.02$  (double doublet collapses to doublet, minor diastereomer CHOH),  $\delta = 4.89$  (multiplet shows simplified coupling, minor diastereomer PCH) and  $\delta = 0.83$  (double doublet collapses to doublet, minor diastereomer PCHCH<sub>3</sub>) is eliminated by decoupling from the peak at  $\delta = 39.5$  in the  $^{31}\text{P}$  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. The  $^1\text{H}$  and  $^{31}\text{P}$  NMR signals belonging to the major diastereomer of **18** were identified by a similar NMR experiment, and together these facilitated the assignment of the *syn/anti* ratio of **18** to be 65:35.



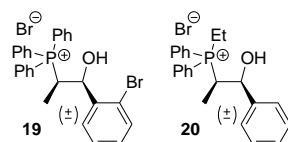
**Figure 6.**  $^1\text{H}$  spectra on the crude product ( $\beta$ -HPS **18**) of acid quenching of the reaction of **2** and 2-bromobenzaldehyde. The bottom spectrum is the non-decoupled  $^1\text{H}$  spectrum. The top spectrum is selectively decoupled from the peak at  $\delta = 39.5$  in the  $^{31}\text{P}$  spectrum.



Care must be taken in establishing connectivity by the selectively decoupled  $^1\text{H}\{^{31}\text{P}\}$  NMR technique, as if there is another signal close to the one for which narrowband decoupling is intended then  $^1\text{H}$  signals coupled to this second  $^{31}\text{P}$  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  $^{31}\text{P}$  NMR spectrum, and can often be detected by the  $^1\text{H}$  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.

### Determination of relative stereochemistry of $\beta$ -HPSs by X-ray crystallography

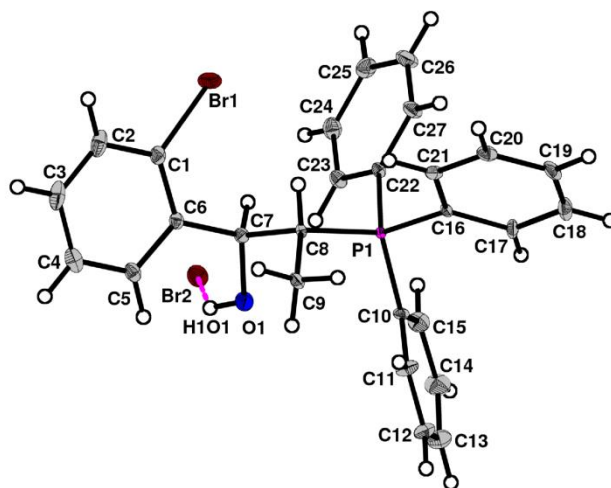
In general in our studies on Wittig reaction intermediates and quench products, we have assigned the major diastereomer to be the precursor of *Z*-alkene (i.e. *cis*-OPA or *syn*- $\beta$ -HPS), since the reactions are generally predominantly *Z*-selective, and since the amount of *Z*-alkene produced represents the lower bound to the kinetic selectivity of the [2+2] cycloaddition step.<sup>6</sup> However, we considered it to be important to establish the relative stereochemistry of the OPA or  $\beta$ -HPS unequivocally in certain cases. Below, we give details on the establishment by X-ray crystallography of the relative stereochemistry of the major diastereomer of two  $\beta$ -HPSs produced in low temperature acid quenches of Wittig reactions of ylides **1** and **2**, respectively.



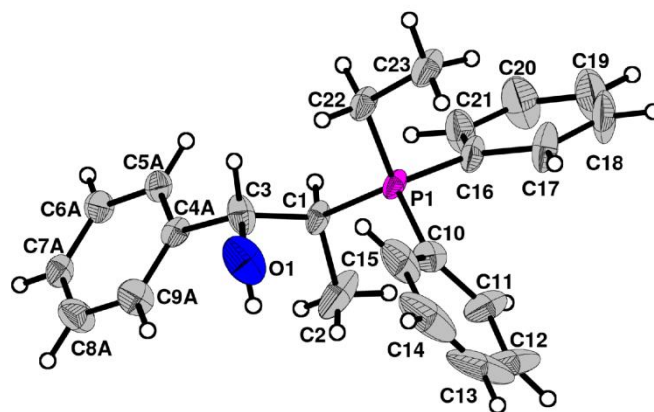
Low temperature acid quenching of the reaction of **1** and 2-bromobenzaldehyde gave crude  $\beta$ -HPS, from which the *syn*-diastereomer **19** (major product) was isolated by crystallisation from acetonitrile. X-ray crystallographic analysis of **19** gave the crystal structure shown in Fig. 7, clearly showing the *syn*-configuration of the compound and proving the *cis* relative stereochemistry of the OPA precursor produced in the Wittig reaction.

*syn*- $\beta$ -HPS **20** was isolated in similar fashion from the crude product of the low temperature acid quenching reaction of **2** and benzaldehyde by crystallisation from ethanol/ethyl acetate. The crystal structure of **20** (Fig. 8) shows the *syn*-configuration of the compound and proves the *cis* relative stereochemistry of the major diastereomer of OPA (*cis*) produced in the Wittig reaction.

Interestingly, the counter-ion of each of **19** and **20** was found to be bromide *i.e.* the counter-ion of the starting phosphonium salt, not chloride from the HCl used to quench the OPA. This is consistent with a previous literature report.<sup>24</sup> The NMR spectral properties of these compounds (chemical shifts, multiplicity and coupling constants of key signals) are consistent with the connectivity observed in the crystal structures, and are similar to those reported for the closely related compound *syn*-(1-hydroxy-1-phenylpent-2-yl)triphenylphosphonium bromide.<sup>19</sup>



**Figure 7.** Crystal structure of *syn*-(1-(2-bromophenyl)-1-hydroxyprop-2-yl)triphenylphosphonium bromide (**19**).



**Figure 8.** Crystal structure of *syn*-(1-(1-hydroxy-1-phenylprop-2-yl)ethyl)diphenylphosphonium bromide (**20**). There is one molecule of water of crystallisation (not shown) per molecule in the lattice.

### Conclusion

The operation of Li salt-free stereochemical drift, previously only demonstrated in isolated examples (the reactions of **1** with benzaldehyde,<sup>28</sup> *n*-butylidetri(*n*-butyl)phosphorane with benzaldehyde & a tertiary aldehyde,<sup>19</sup> and ethylidetriethylphosphorane with a tertiary aldehyde<sup>24</sup>), has been shown here to be quite general in Wittig reactions of ethylides with benzaldehydes,<sup>47</sup> as three further examples of the phenomenon with two further ethylides, **2** and **3**, have been disclosed here. This set of results confirms that ethylides have a particular, and perhaps unique, sensitivity to stereochemical drift.

The Wittig reactions of these ylides with benzaldehydes were investigated by Variable Temperature NMR, and it has been shown that no interconversion of the OPAs occurs below the temperature at which the onset of OPA decomposition to alkene & phosphane oxide occurs, consistent with previous observations on the reactions of **1**, **2** and **3**.<sup>28</sup> In the VTNMR observation of OPA **11**, the OPA kinetic diastereomeric ratio was shown to be 65:35 but, amazingly, this OPA decomposed to alkene with a different diastereomeric ratio (56:44) without any change occurring in the diastereomeric ratio of the OPA at any temperature. This observation is postulated to be a consequence of a remarkable coincidence of rates: the net rate of loss of *cis*-OPA (conversion to

*trans*-OPA, perhaps via ylide and aldehyde, and conversion to alkene and phosphine oxide) and the net rate of loss of *trans*-OPA (conversion to alkene and phosphine oxide, off-set by the formation of *trans*-OPA by stereochemical drift of *cis*-OPA) are equal.

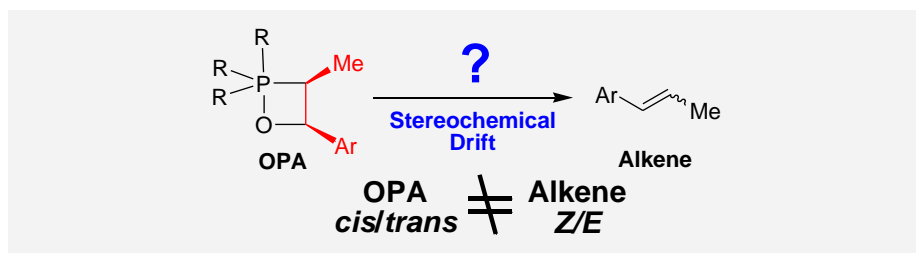
Stereochemical drift in reactions of longer chain alkylides has now been confirmed *not to occur*, even in reactions of benzaldehydes – the reactions of alkylide **4** (a close structural analogue of **3**) with representative aromatic and aliphatic aldehydes have been shown here to be under kinetic control, which again is consistent with literature precedent.<sup>19,25</sup>

In order to determine the kinetic diastereoselectivity of the OPA-forming step of these Wittig reactions that undergo stereochemical drift, it was necessary to observe the OPA intermediate spectroscopically or quench the OPA with acid to give  $\beta$ -HPS at a temperature well below that at which stereochemical drift occurs.<sup>5</sup> The methods used to unambiguously identify the diastereomers of OPA or  $\beta$ -HPS produced in these reactions (<sup>1</sup>H-<sup>31</sup>P HMBC, selective <sup>1</sup>H{<sup>31</sup>P} NMR, X-ray crystallography) have been described here for the first time. The true selectivity of

diastereoselective reactions must often necessarily be evaluated by spectroscopic examination of the crude product, before any work-up or purification step is undertaken. It is anticipated that these techniques, especially the two-dimensional NMR method and analogues with different nuclei, will be of general utility in the determination of kinetic diastereomeric ratios of compounds in such scenarios.

**Supporting Information** (see footnote on the first page of this article): Contains full details of the experimental procedures employed, plots and error analysis from the kinetic study of OPA decomposition, and spectroscopic data for the compounds prepared.

CCDC-883627 (for *syn*-**19**) and 883628 (for *syn*-**20**) contain the supplementary X-ray crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



Stereochemical drift, previously only identified in a handful of isolated examples, is confirmed as a general phenomenon in Wittig reactions of phosphonium ethylides with aromatic aldehydes by VTNMR.

Reactions of structurally related longer chain alkylides are demonstrated to be irreversible. The NMR methods used are described in full.

**Peter A. Byrne, Jimmy Muldoon, Yannick Ortin, Helge Müller-Bunz, and Declan G. Gilheany\***... Page No. – Page No.

Investigations on the Operation of  
Stereochemical Drift in the Wittig Reaction  
by NMR & VTNMR Spectroscopy of  
Oxaphosphetane Intermediates & their  
Quench Products

**Keywords:** Wittig reaction / Stereochemical Drift / Variable Temperature NMR /  $^1\text{H}$ - $^{31}\text{P}$  HMBC / Oxaphosphetane *cis/trans* ratio /  $\beta$ -hydroxyphosphonium salt / Phosphorus NMR / Diastereomeric ratios



- [1] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, 89, 863.
- [2] A. W. Johnson, *Ylides and Imines of Phosphorus*, 1993, Wiley; New York, chapters 8 and 9; pp. 221-305.
- [3] E. Vedejs, M. J. Peterson in *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, New York, 1994; Vol. 21.
- [4] E. Vedejs, M. J. Peterson in *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI: Greenwich, CN, 1996; Vol. 2.
- [5] P. A. Byrne, D. G. Gilheany, *J. Am. Chem. Soc.* **2012**, 134, 9225.
- [6] E. Vedejs C. F. Marth, *J. Am. Chem. Soc.*, **1988**, 110, 3948.
- [7] E. Vedejs, T. Fleck, *J. Am. Chem. Soc.*, **1989**, 111, 5861.
- [8] R. Robiette, J. Richardson, V. K. Aggarwal, J. N. Harvey, *J. Am. Chem. Soc.* **2006**, 128, 2394.
- [9] P. A. Byrne, D. G. Gilheany, *Chem. Soc. Rev.* **2013**, 42, 6670.
- [10] E. Vedejs, C. F. Marth, *J. Am. Chem. Soc.* **1989**, 111, 1519.
- [11] F. H. Westheimer, *Acc. Chem. Res.* **1968**, 1, 70.
- [12] The exact mechanism of the process of OPA decomposition has recently come into question.<sup>9-13</sup> Although this step has no bearing on the stereoselectivity of alkene formation, stereomutation may occur at the phosphorus centre by Berry pseudorotation process(es); thus the deduction of whether the configuration of the phosphorus atom is retained or otherwise would be informative and of considerable consequence in the broader context of phosphorus chemistry. It is widely accepted that nucleophilic attack on a tetrahedral phosphorus-containing entity to give a trigonal bipyramidal phosphorane requires that the nucleophile should be in an apical position; similarly departure of a leaving group from a phosphorane must occur from an apical position in the trigonal bipyramid.<sup>11</sup> Certainly, there are many examples of OPAs produced in Wittig reactions in which oxygen has been shown to be in an apical position by NMR,<sup>5-10,21,22,24</sup> which is in accordance with the work of Westheimer. It had been thought until recently<sup>5-6,15</sup> that the initially formed O-apical OPA must undergo non-rate limiting Berry pseudorotation to give a second OPA intermediate with the ylide  $\alpha$ -carbon in an apical position, and that it is this intermediate that undergoes cycloreversion to alkene and phosphine oxide. Indeed, there is computational evidence in support of this mechanism.<sup>8</sup> However, evidence has come to light recently<sup>14</sup> from related chemistry of trigonal bipyramidal phosphorus-containing species that suggests that the O-apical OPA may be able to directly undergo cycloreversion *by a single step process* that is comprised of two or more Berry pseudorotations.<sup>13</sup> Importantly, this single step would still involve the production along its reaction coordinate of a trigonal bipyramidal entity in which the ylide  $\alpha$ -carbon occupies an apical position, but this entity *is not an intermediate* and may even be a transition state. This mechanistic proposal thus remains consistent with the chemistry of Westheimer despite the absence of the C-apical OPA intermediate.
- [13] J. García López, A. Morán Ramallal, J. González, L. Rocés, S. García-Granda, M. J. Iglesias, P. Oña-Burgos, F. López Ortiz, *J. Am. Chem. Soc.* **2012**, 134, 19504.
- [14] E. P. A. Couzijn, J. C. Slootweg, A. W. Ehlers, K. Lammertsma, *J. Am. Chem. Soc.* **2010**, 132, 18127.
- [15] R. Robiette, J. Richardson, V. K. Aggarwal, J. N. Harvey, *J. Am. Chem. Soc.* **2005**, 127, 13468.
- [16] J. N. Harvey, *Faraday Discuss.* **2010**, 145, 487.
- [17] The reactions in question were carried out at -78 °C. OPAs derived from **2** were maintained at this temperature and observed by <sup>31</sup>P NMR at -40 °C. The OPA solution was then allowed to warm to 20 °C to effect alkene formation. OPAs derived from **3** were maintained at -45 °C and observed by <sup>31</sup>P NMR at -20 °C, and then heated to 80 °C for 2 hours to effect alkene formation.
- [18] The OPA *cis/trans* was either evaluated directly by low temperature <sup>31</sup>P NMR, or inferred from the *syn/anti* ratio of the  $\beta$ -HPS produced by low temperature acid quenching of the OPA intermediate, using <sup>1</sup>H and <sup>31</sup>P NMR.
- [19] B. E. Maryanoff, A. B. Reitz, M. S. Mutter, R. R. Inners, H. R. Almond Jr., R. R. Whittle, R. A. Olofson, *J. Am. Chem. Soc.* **1986**, 108, 7664.
- [20] That is, the initial low temperature OPA *cis/trans* ratio matches the *Z/E* ratio of the alkene that is ultimately produced on warming of the OPA.
- [21] E. Vedejs, C. F. Marth, *J. Am. Chem. Soc.*, **1990**, 112, 3905.
- [22] F. Bangerter, M. Karpf, L. A. Meier, P. Rys, P. Skrabal, *J. Am. Chem. Soc.* **1998**, 120, 10653.
- [23] E. Vedejs, C. F. Marth, *Tetrahedron Lett.* **1987**, 28, 3445.
- [24] E. Vedejs, C. F. Marth, R. Ruggeri, *J. Am. Chem. Soc.*, **1988**, 110, 3940.
- [25] A. B. Reitz, M. S. Mutter, B. E. Maryanoff, *J. Am. Chem. Soc.* **1984**, 106, 1873.
- [26] M. Appel, S. Blaurock, S. Berger, *Eur. J. Org. Chem.* **2002**, 1143.
- [27] Other mechanisms for OPA interconversion may operate in the presence of Li cation and/or iodide anion. A plausible alternative mechanism that may operate in reactions of non-stabilised ylides with *aromatic* aldehydes is initial scission of the P-O bond of the OPA by lithium halide salt to give a betaine-lithium halide complex, which then undergoes C-C bond cleavage to give ylide and aldehyde. Reactions of non-stabilised ylides with *aliphatic* aldehydes appear to be irreversible even in the presence of Li<sup>+</sup>. The fact that the diastereomeric ratios of the alkenes produced in these reactions differ depending on the presence or absence of Li<sup>+</sup> is to do with the effect of Li<sup>+</sup> on the [2+2] cycloaddition step.
- [28] E. Vedejs, G. P. Meier, K. A. J. Snoble, *J. Am. Chem. Soc.* **1981**, 103, 2823.
- [29] The implication of this fact, given that *cis*-OPA is *kinetically* favoured (i.e. predominant in the initial low temperature diastereomeric ratio), is that *trans*-OPA is more thermodynamically stable than *cis*-OPA.
- [30] The reagents were added to a Schlenk flask under an atmosphere of argon in a glove box.
- [31] Tubes connecting the flask to the nitrogen source (a Schlenk manifold in our case) must be dried; this was done in our lab by fitting a syringe barrel and needle to each tube when not in use, and keeping the needles embedded in a sealed flask of dried potassium hydroxide. 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.

- [32] In some cases, other very small signals could also be observed in the OPA region of the  $^{31}\text{P}$  NMR spectrum of the reaction mixture (integrating for *ca.* 1% of the major OPA diastereomer). We attribute these to being a consequence of the interaction of the OPA(s) with residual aldehyde, as has been observed previously,<sup>28</sup> and indeed no such signals were evident if less than 1 equivalent of aldehyde was employed in the reaction.
- [33] See the supporting information for error analysis and plots of the kinetic data.
- [34] M. Schlosser, B. Schaub, *J. Am. Chem. Soc.* **1982**, *104*, 5821.
- [35] In the final  $^1\text{H}$  NMR spectrum, *ca.* 4% of the amount of OPA initially present remained (all of this was *cis*-OPA). The alkene *Z/E* ratio was 86:14 in this spectrum. The maximum final *Z/E* ratio of the alkene was estimated as 88:12 by adding the integrations of the *Z*-alkene and *cis*-OPA in the final spectrum (i.e. assuming all remaining *cis*-OPA would decompose to *Z*-alkene), and expressing this number as a percentage of the total amount of alkene (i.e. the sum of the integrations of the *cis*-OPA, *Z*-alkene and *E*-alkene).
- [36] B. E. Maryanoff, A. B. Reitz *Tetrahedron Lett.* **1985**, *26*, 4857.
- [37] *cis*-OPA has been shown to decompose more quickly than its *trans* diastereomer in the Li salt-free reactions of several ethylides (including **1** and **2**) with  $\text{Ph}(\text{CH}_2)_2\text{CMe}_2\text{CHO}$ ,<sup>24</sup> and of  $\text{Et}_3\text{P}=\text{CHMe}$  with benzaldehyde,<sup>34</sup> and in the Li-present reaction of **4** with hexanal.<sup>19</sup> See also reference 22 for further examples of this phenomenon.
- [38] For example, addition of aldehyde across the P-C bond of the OPA ring (as shown in Scheme 2) would give a six-membered ring (dioxaphospholane), which could decompose in either of two ways to give phosphine oxide, alkene and aldehyde. It is easy to conceive that such an addition could occur in a non-stereoselective manner and, if decomposition occurred as indicated in Scheme 2 route (i), then *E*-alkene would be produced from *cis*-OPA without any involvement of *trans*-OPA. The six-membered ring of Scheme 2 could also form *trans*-OPA (and hence *E*-alkene) by expulsion of the aldehyde that had initially undergone cycloaddition with the ylide, as shown in Scheme 2 route (ii). Both of these possible mechanisms would occur without reversal of the *cis*-OPA to ylide and aldehyde, and would be consistent with the results of crossover experiments. Although there is no obvious reason why such a mechanism would be restricted to reactions of ethylides with benzaldehydes, and it is clear that this mechanism does not operate in the majority of Wittig reactions, in which OPAs decompose stereospecifically,<sup>1-9</sup> it is also clear that ethylides display unusual (and perhaps unique) behaviour in their reactions with benzaldehydes, and thus may undergo processes not available in other Wittig reactions.
- [39] Addition of benzaldehyde across the OPA P-O bond would give a six-membered ring (dioxaphospholane) intermediate (a different one from that in Scheme 2, having a P-C bond & a P-O bond, rather than two P-O bonds), which could decompose to give ylide and two equivalents of benzaldehyde. This could also occur if crossover aldehyde was added, rather than an excess of the original aldehyde.
- [40] This would have particular relevance for crossover reactions in which a reactive aldehyde is added to a solution containing OPA to react with any ylide that is produced by OPA reversal – our implication (as made previously by Vedejs)<sup>24</sup> being that the aldehyde added may not be innocent in the process of stereochemical drift, since its addition involves a perturbation to the reaction that would not otherwise be present.
- [41] We had particular interest in the behaviour of this ylide since it was the only one in our previous study<sup>5</sup> that did not show very high *Z*-selectivity in reactions with *ortho*-heteroatom substituted benzaldehydes – we thus conjectured that it too, as a particularly reactive semi-stabilised ylide, might undergo stereochemical drift in reactions with benzaldehydes.
- [42] There is at present no example of a reaction of a secondary aliphatic aldehyde that undergoes stereochemical drift, i.e. all such reactions are irreversible. The reaction of **12** with aldehyde **17** is almost certainly under kinetic control, and gives alkene with a *Z/E* ratio of 75:25 (unpublished results). Since the product ratio in this reaction is virtually identical to that in the reaction of **12** with 2-bromobenzaldehyde, there is no reason to think that the latter reaction is not under kinetic control.
- [43] Please note that we have used *erythro* and *threo* in place of *syn* and *ant*, respectively, in our previous publications.
- [44] Details on the structure of OPAs produced in Wittig reactions, on OPA pseudorotation rates,<sup>12,21,22</sup> and on the stereospecificity<sup>5,19,21,22,24,25,26</sup> and kinetics<sup>19,22</sup> of the decomposition of OPA intermediates to alkene & phosphane oxide have been reported previously. The OPAs in these reports are usually characterised by  $^{31}\text{P}$  and in some cases  $^1\text{H}$  and  $^{13}\text{C}$  NMR. Two-dimensional NMR techniques have not previously been applied to these intermediates, to our knowledge.
- [45] P.-Y. Renard, P. Vayron, C. Mioskowski, *Org. Lett.* **2003**, *5*, 1661.
- [46] W. Dabkowski, A. Ozarek, S. Olejniczak, M. Cypryk, J. Chojnowski, J. Michalski, *Chem. Eur. J.* **2009**, *15*, 1747.
- [47] Note, however, that reactions of ethylides bearing *P*-fur-2-yl groups are under kinetic control.<sup>22</sup>