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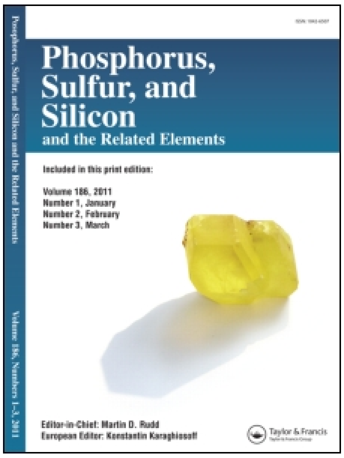

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DELVING INTO THE WITTIG REACTION-STEREOCHEMISTRY AND MECHANISM. STEREOCHEMICAL IDIOSYNCRASIES AND MECHANISTIC IMPLICATIONS[1]

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DELVING INTO THE WITTIG REACTION—STEREOCHEMISTRY AND MECHANISM. STEREOCHEMICAL IDIOSYNCRASIES AND MECHANISTIC IMPLICATIONS[1]

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Non-stabilized triphenylphosphorus ylides bearing anionic groups can react with aldehydes to give alkene mixtures anomalously enriched in the *E* isomer [ref. 7]. To explain this phenomenon, we sought to study both cis and trans oxaphosphetane (OP) intermediates at low temperature. The observation of both intermediates was achieved for the first time by the use of high-field H-1, P-31, and C-13 NMR spectroscopy in various instances. We have monitored some Wittig reactions in detail via NMR-based kinetic measurements of OP's and alkenes. In certain cases, OP's equilibrate, presumably by reaction reversal to aldehyde and ylide, to introduce a measure of thermodynamic control into the Wittig reaction. Thermodynamic control accounts for a large portion of the excess *E* stereoselectivity observed in going from a triphenyl to trialkyl (i.e., butyl) phosphorus ylide. Quenching experiments with HBr and the deprotonation of erythro and threo beta-hydroxyphosphonium salts are also discussed. Attempts to investigate reactions of stabilized and semi-stabilized ylides in an analogous manner were not fruitful.

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The Wittig reaction (generalized in Figure 1) has been known for nearly 35 years,[2] during which time it has achieved recognition as a convenient and effective method for the preparation of a wide variety of alkenes from aldehydes or ketones.[3] Considerable mechanistic discussion has transpired over this period, accompanied by a fair amount of controversy. Early on, the reaction as generally viewed as an aldol-like process with a betaine (Figure 1) as the key intermediate, representing the carbon-carbon bond-forming step. However, the more recent studies of Vedejs' group[4] have shown that only oxaphosphetanes (Figure 1) can be observed spectroscopically as intermediates in the Wittig reaction of non-stabilized phosphorus ylides.[5] Thus, a cycloaddition mechanism has gained credibility.

Stereochemistry is a useful tool for probing organic reaction mechanisms, and this is no less the case for the Wittig reaction. For decades, chemists have tried to rationalize alkene stereochemistry in the Wittig reaction by different mechanistic ideas.[3,4a,6] Certain empirical generalities (for which one can find some exceptions, of course) have evolved: (1) stabilized phosphorus ylides furnish predominantly *E* alkenes, (2) non-stabilized ylides give *Z* alkenes in the main, and (3) semi-stabilized ylides give mixtures with no special preference for *Z* or *E* geometry. It is particularly significant that non-stabilized ylides combine with aldehydes to yield frequently, especially in the absence of Li salt, a high proportion of the less thermodynamically stable *Z* alkene. This stereochemical paradigm has assumed a central position in the long-standing curiosity about the mechanism of the Wittig reaction.

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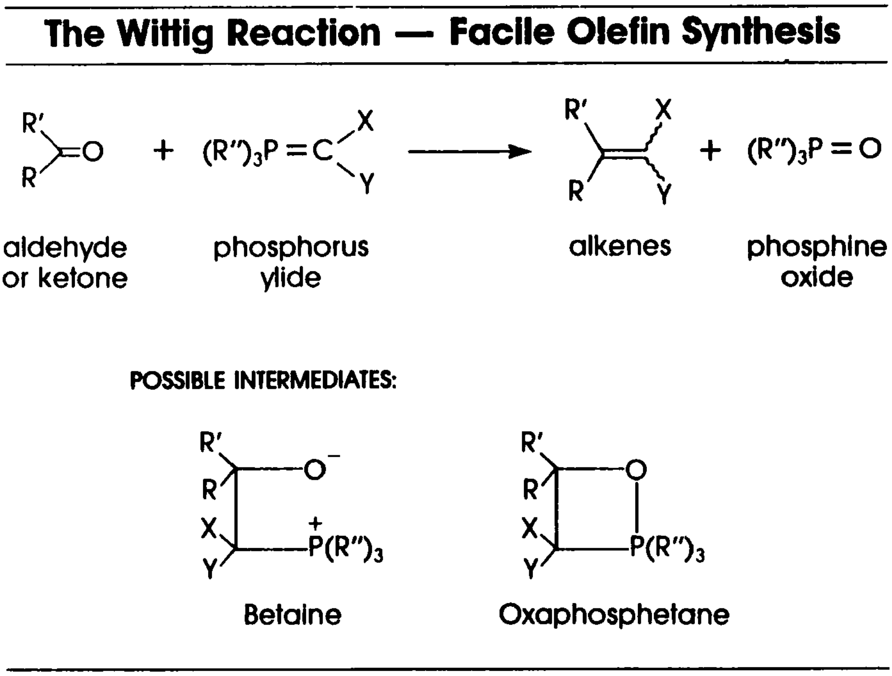

FIGURE 1 General depiction of the Wittig olefination reaction with possible intermediates.

With non-stabilized ylides several common factors have been generally recognized to be important in influencing stereocontrol: (1) presence or absence of lithium salt, (2) polarity of aprotic solvent, especially when Li is present, (3) substituents on phosphorus, e.g., phenyl vs. alkyl, (4) type of aldehyde, e.g., aliphatic vs. aromatic, and (5) temperature of reaction. Over the past four years, we have been investigating systematically another factor that affects stereochemistry: proximate anionic groups on the "ylidene" chain.[7] To summarize our results (with aldehydes only), anionic groups, such as oxido and carboxylate, in the side chain of triphenylphosphorus ylides cause a shift in stereochemistry of the alkene products toward the *E* isomer, apparently regardless of cation (Li, Na, and K). The anomalous *E* stereoselectivity (relative to reference reactions) is highly dependent on the distance between the anionic and phosphorus centers and is often stronger with aromatic than aliphatic aldehydes. Based on experiments involving deuterium-labeled ylides, ^{31}P NMR at low temperature, and crossover products, it was proposed that the metalloanionic group facilitates oxaphosphetane interconversion via reaction reversal; this allows for a degree of thermodynamic control.[7a]

We envision the process depicted in Figure 2 as a possible mechanistic rationale. The intermediate cis and trans oxaphosphetanes are shown in two forms interconvertible by pseudorotation of trigonal bipyramidal phosphorus. The anion-bearing side chain could "bite back" on phosphorus to generate a hexacoordinate intermediate or transition state (intramolecular S_N2 process) en route to reversal to ylide and aldehyde. Although low temperature ^{31}P NMR spectra showed no signals for a hexacoordinate species or a phosphorane anion, the equilibria in Figure 2 can still

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A Mechanistic Rationale for Facilitated Reversal

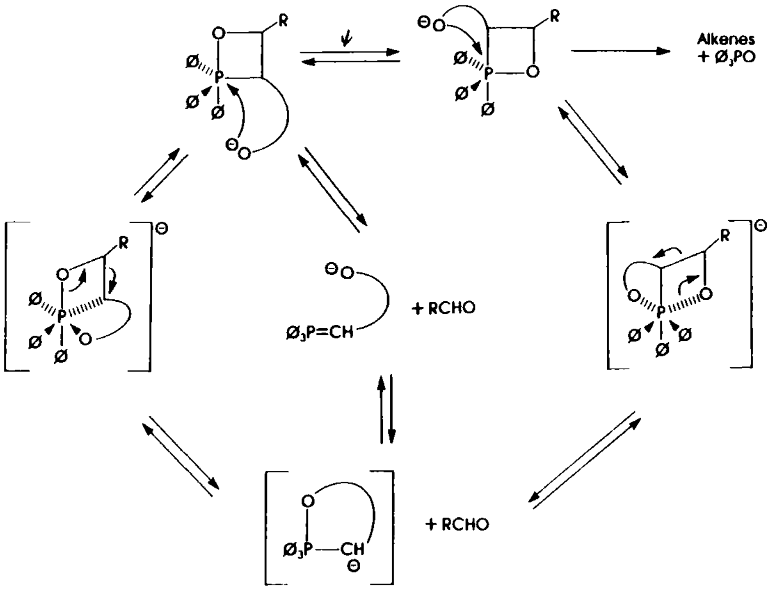

FIGURE 2 Mechanistic proposal to rationalize facilitation of oxaphosphetane reversal by anion-bearing side chains. A chain-length effect should be operative because of the intramolecular cyclization to the hexacoordinate structure. There is no direct evidence for the existence of hexacoordinate species or cyclic phosphorane carbanions as intermediates.

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exist.[7a] It should be noted that this picture is consistent with the decrease of anomalous *E* stereoselectivity with increasing chain length and the crucial presence of an anionic moiety.

To gain an understanding of the source of anomalous *E* stereoselectivity with the anion-bearing ylides, we had to view both diastereomers of the reaction intermediates (oxaphosphetanes) in some manner. Thus, we set out to explore the applicability of high-field ^{31}P NMR (145.8 MHz) at low temperature to this problem.

RESULTS AND DISCUSSION

Non-stabilized phosphonium ylides. Our first experiments involved a standard case, the reaction of benzaldehyde with butylidenetriphenylphosphorane (**1**), produced from *n*-butyltriphenylphosphonium bromide and lithium hexamethyldisilazide (LiHMDS). Thereupon, we observed for the first time individual cis and trans oxaphosphetanes (**2** and **3**, respectively).[8] This reaction is illustrated in Figure 3, along with some appropriate data, and two representative ^{31}P NMR spectra are presented in Figure 4. The spectrum at −78 deg C (top) shows some unreacted ylide and minimal triphenylphosphine oxide, whereas the spectrum at −30 deg C shows

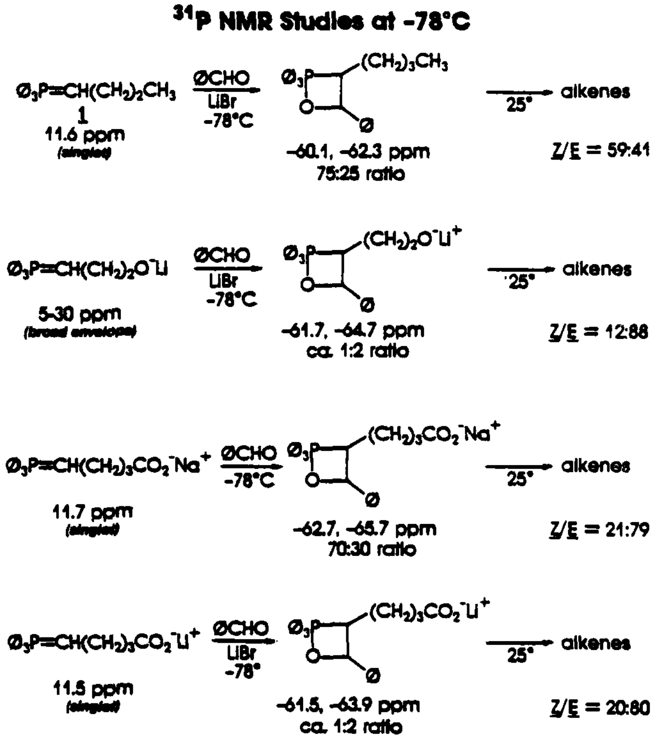

FIGURE 3 Various low temperature P-31 NMR studies illustrating oxaphosphetane cis/trans diastereomers and "stereochemical drift" in the formation of alkenes.

that considerable decomposition of oxaphosphetanes had occurred. Even though the line-widths in these proton-decoupled ^{31}P NMR spectra are naturally broader at -78 deg C than at -30 deg C, baseline separation between the oxaphosphetane resonances is still achieved at the lower temperature (Figure 4). Thus, diastereomeric ratios were easily established by electronic integration for this reaction under various conditions. Notably, the ratio of oxaphosphetanes **2** and **3** (75 : 25) at -78 deg C does not correspond with the ratio of *Z* and *E* alkenes (59 : 41) formed on warming to 25 deg C (GLC analysis of the crude product). This we have termed "stereochemical drift" for convenience and brevity.

Ylide **1**, from deprotonation of the phosphonium salt with NaHMDS (lithium salt-free conditions), joined with benzaldehyde at -78 deg C to give essentially one ($>$ 98%) oxaphosphetane (resonance at -61.9 ppm), the cis isomer. On workup, this reaction yielded beta-propylstyrenes with a *Z*/*E* ratio of 96 : 4, reflecting very little stereochemical drift. Although this salt-free example behaves rather normally, such propriety need not be demonstrated in all salt-free Wittig reactions, as will be discussed later on.

Some reactions of benzaldehyde with anion-bearing ylides are also displayed in Figure 3. Although these data have already been described in a full paper,[7a] we reiterate here the non-correspondence between the oxaphosphetane ratios at low temperature and the alkene ratios determined after warming to 25 deg C. It is

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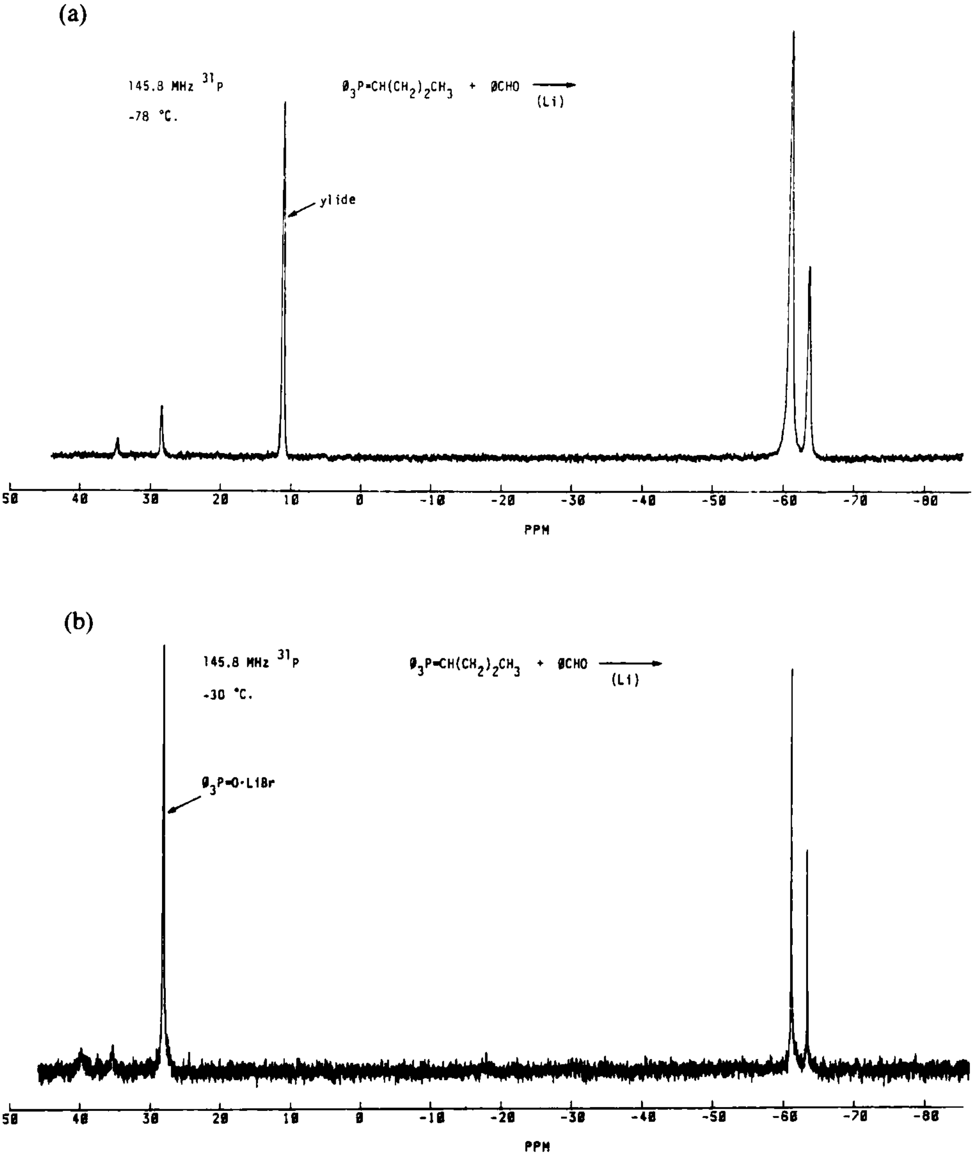

FIGURE 4 Low temperature proton-decoupled P-31 NMR spectra for the reaction of ylide 1 and benzaldehyde. (a) Spectrum at −78 deg C with some excess ylide remaining. (b) Spectrum at −30 deg C showing partial conversion to triphenylphosphine oxide, present as a complex with LiBr.

important to note that stereochemical drift with the anionic ylides is more accentuated, indicating enhanced equilibration of isomeric oxaphosphetanes possibly by reaction reversal (mentioned above).

Low temperature NMR spectroscopy provided a means to monitor the Wittig reaction intermediates and products during the reaction course. Thus, we conducted the first detailed rate studies on the reaction of non-stabilized phosphorus ylides.[9]

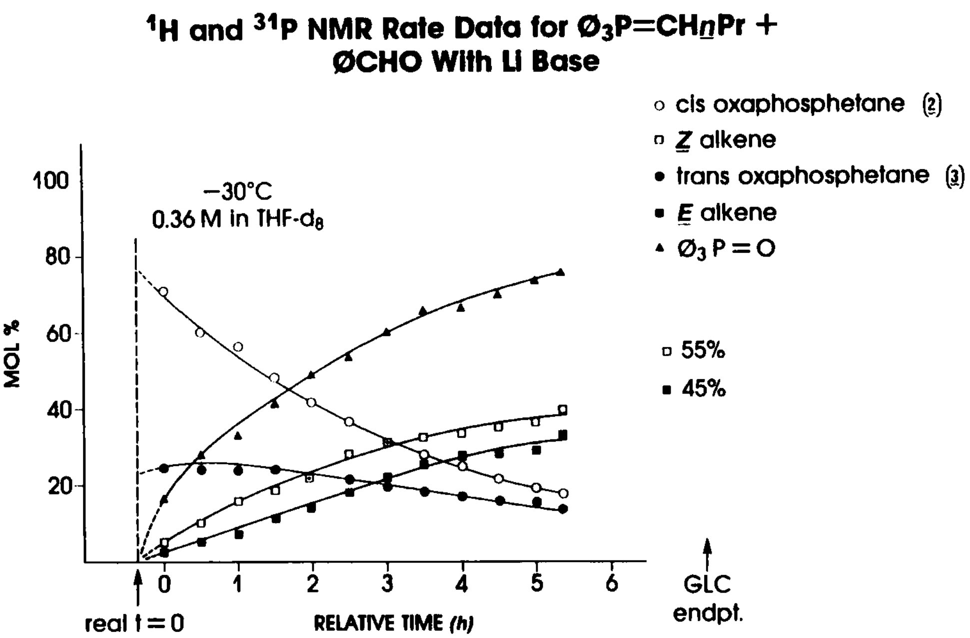

FIGURE 5 Rate profile for the reaction of **1** and benzaldehyde at −30 deg C (0.36 M in perdeuterio-THF), determined by using P-31 and H-1 NMR. Only every third data point is exhibited. The entire data set was fit to previously discussed kinetic equations by use of iterative computations (see ref. 9).

Rate data (only every third data point), acquired on the reaction of **1** and benzaldehyde at −30 deg C in THF-d_8 with LiBr present by using ^{31}P NMR for the phosphorus species (oxaphosphetanes and triphenylphosphine oxide) and ^{1}H (360 MHz) NMR for the alkenes, are depicted in Figure 5. The kinetic equations were solved by using iterative computation and the curves were derived. The rate of decay for the cis oxaphosphetane is obviously greater than that for the trans oxaphosphetane, while the isomeric alkenes arise at similar rates. The stereochemical drift is indicated by the initial oxaphosphetane ratio of 78 : 22 vs. the final alkene ratio of 55 : 45. It is clear that the cis oxaphosphetane is being converted to trans oxaphosphetane at a rate competitive with its decomposition to *Z* alkene. Two 360-MHz ^{1}H NMR spectra of the reaction of **1** and benzaldehyde at −30 deg C, one early on (top) and one after 5 h, are shown in Figure 6. The upper spectrum reveals that oxaphosphetanes **2** and **3** cannot be readily distinguished by ^{1}H NMR; e.g., note the overlap of cis and trans PhC$\underline{H}$ signals. The lower spectrum indicates the discernible alkene resonances, after substantial decomposition of the oxaphosphetanes. An expansion of the vinyl proton region was integrated to obtain the alkene concentrations for each data point in the rate study.

We also used high-field ^{13}C NMR (90.5 MHz) to study this reaction by employing ylide **1** enriched with ^{13}C at the ylidic position (92 atom %). This reduced the complexity of the kinetics experiment because now the probe would not have to be switched to detect all of the relevant species. Rate data (only every third data point) for the reaction at −.30 deg C are displayed in Figure 7. The results are fairly

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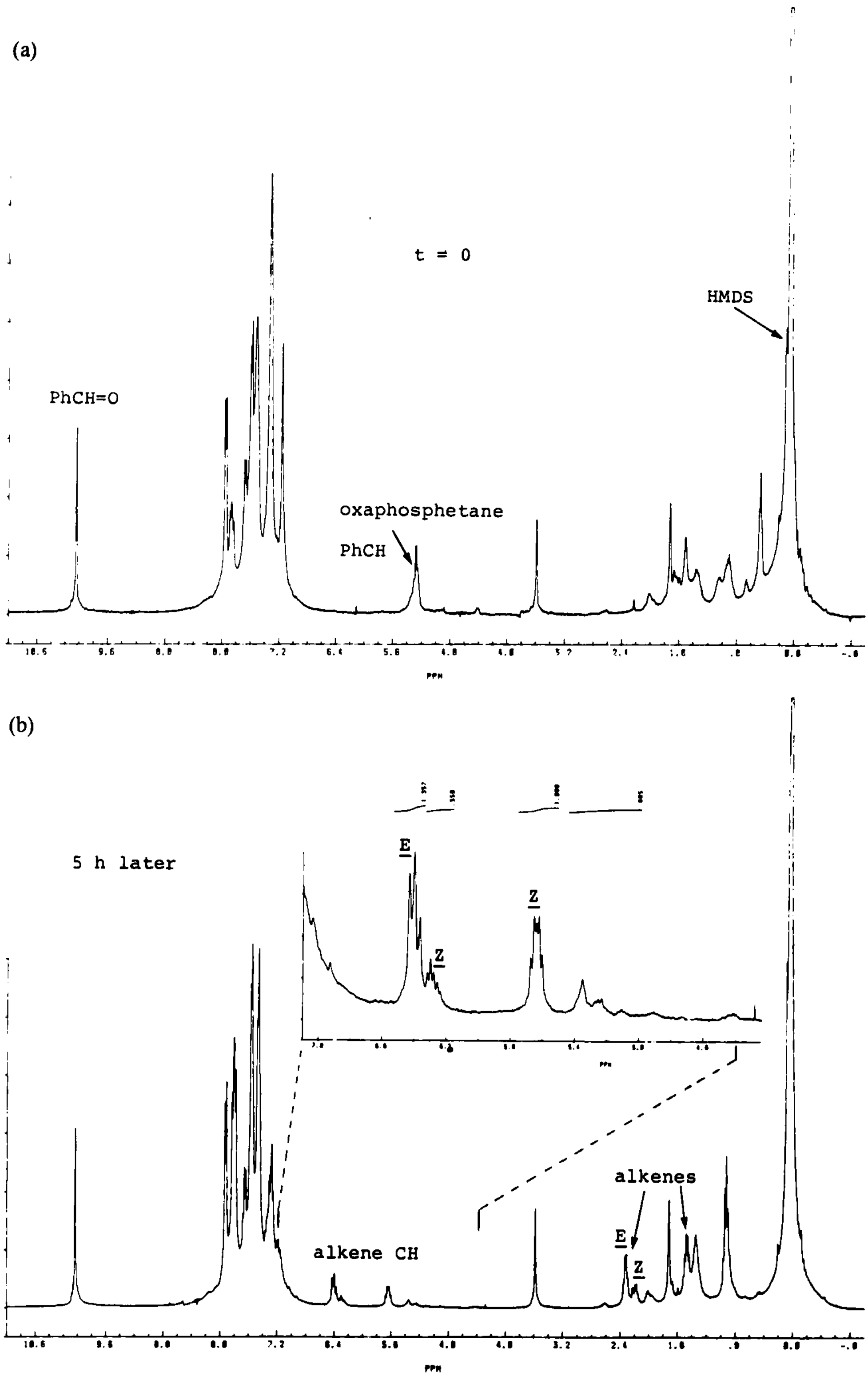

FIGURE 6 Low temperature proton NMR spectra for the reaction of **1** and benzaldehyde from a kinetic experiment. (a) Spectrum of a mixture of cis and trans oxaphosphetanes **2** and **3** at −60 deg C (t = 0). (b) Spectrum late in the course of alkene production. The blow-up/expansion shows the alkene region that was used for quantitation.

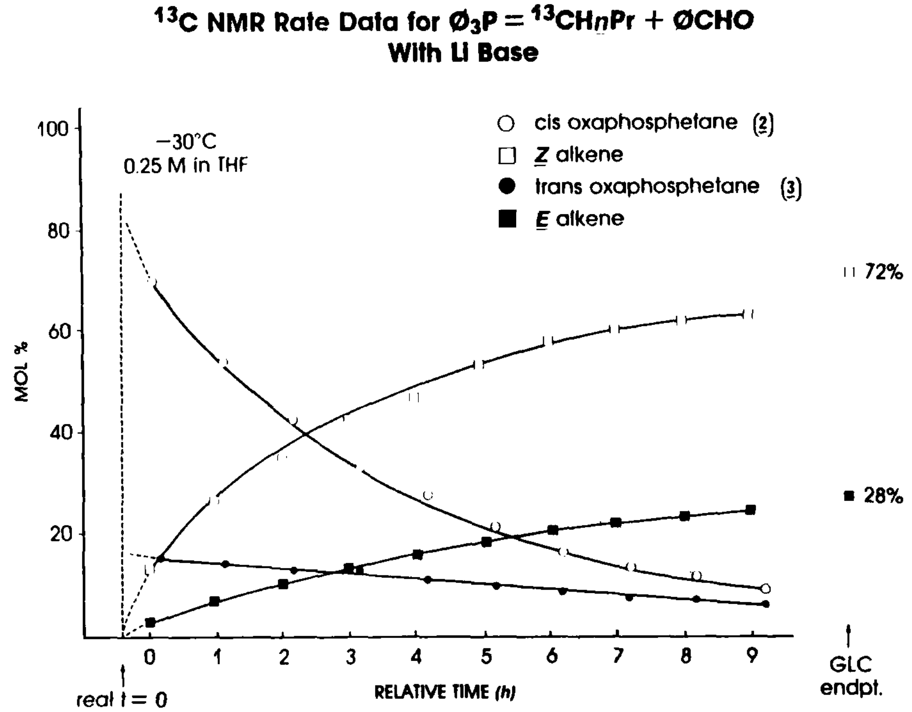

FIGURE 7 Rate profile for the reaction of **1** and benzaldehyde at −30 deg C (0.25 M in perdeuterio-THF), determined by using C-13 NMR. Only every third data point is exhibited. The entire data set was analyzed by iterative computations.

analogous to those obtained in the ^{31}P-^{1}H NMR study. There are some differences between these experiments, which we attribute to effects of concentration (to be discussed below) and, to a lesser extent, isotopic enrichment. Two representative proton-decoupled ^{13}C NMR spectra (key spectral region only) are presented in Figure 8. The oxaphosphetanes appear as a pair of doublets ($^{1}J_{PC}$ = ca. 85 Hz) separated by 3.5 ppm, with the cis isomer upfield of the trans.[10] The alkene resonances emerged from the multitude of aromatic carbon resonances during the course of oxaphosphetane decomposition.

The ^{13}C NMR rate data were analyzed by using kinetic equations representing the reaction profile expressed in Figure 9 and iterative computation to afford the following rate constants (10^{-5} sec^{-1}): $k_3 = 9.2$, $k_4 = 1.2$, $k_5 = 5.7$, and $k_6 = 6.8$.[11] The conversion of cis to trans oxaphosphetane is faster than the reverse reaction by a factor of 8 ($k_3/k_4 = 8$). However, later evidence will show that the difference between k_3 and k_4 is actually much greater than 8;[12] k_3 is probably at least 70–100 times faster than k_4. This is the source of the stereochemical drift.

We have gathered data on the reaction of **1** and benzaldehyde at various concentrations between 0.01 and 1.0 M, where we have recorded the oxaphosphetane cis/trans ratio at low temperature (NMR) and the alkene *Z*/*E* ratio (GLC). As demonstrated in the semi-log plot in Figure 10, the amount of trans oxaphosphetane and the amount of *E* alkene define separate linear functions, which converge at high

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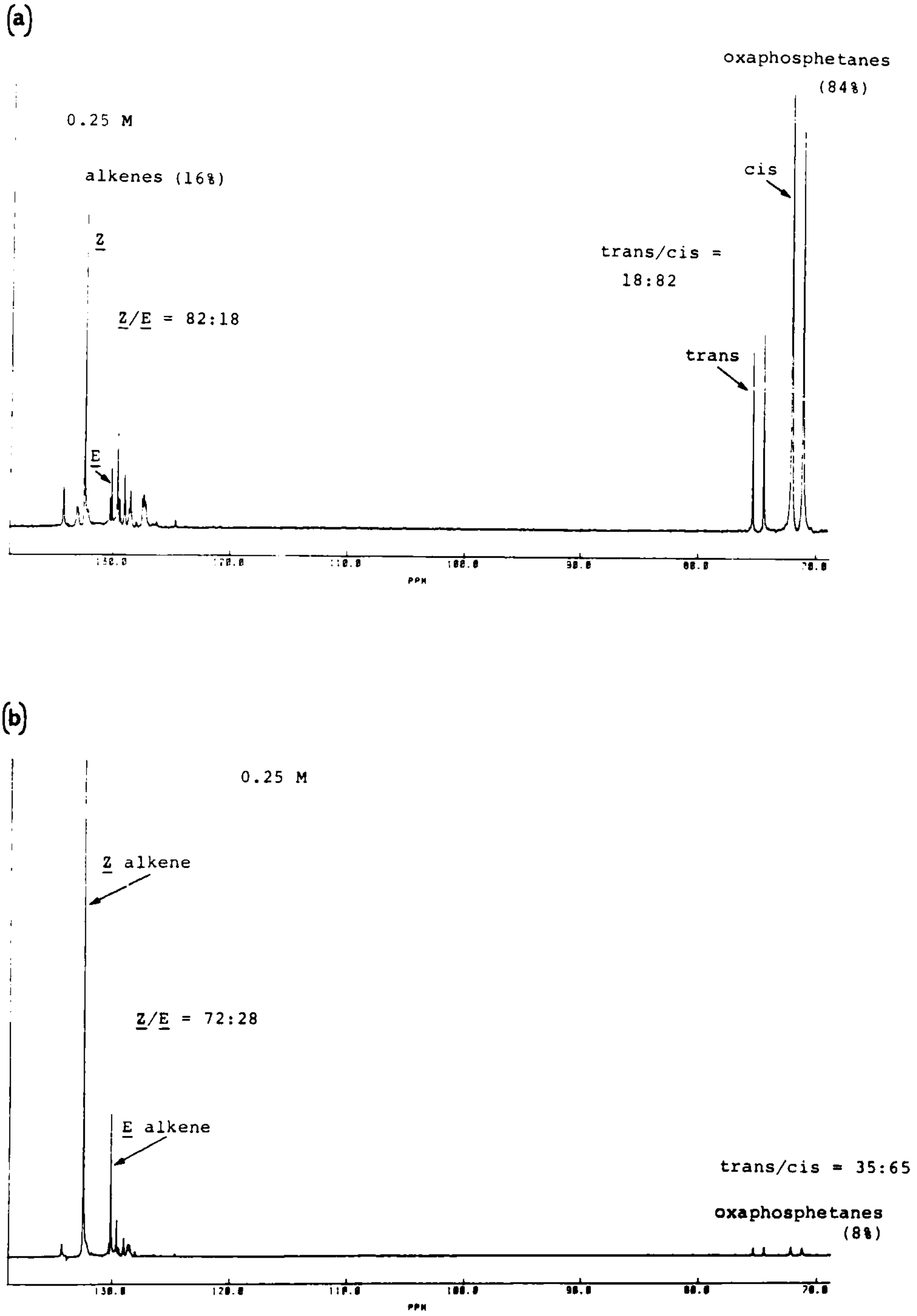

FIGURE 8 Low temperature C-13 NMR spectral segments for the reaction of 1 and benzaldehyde at −30 deg C from a kinetics experiment. (a) Spectrum showing oxaphosphetane isomers 3 and 2 early in the reaction course. (b) Spectrum of the reaction after three half-lives, showing mainly the alkenes.

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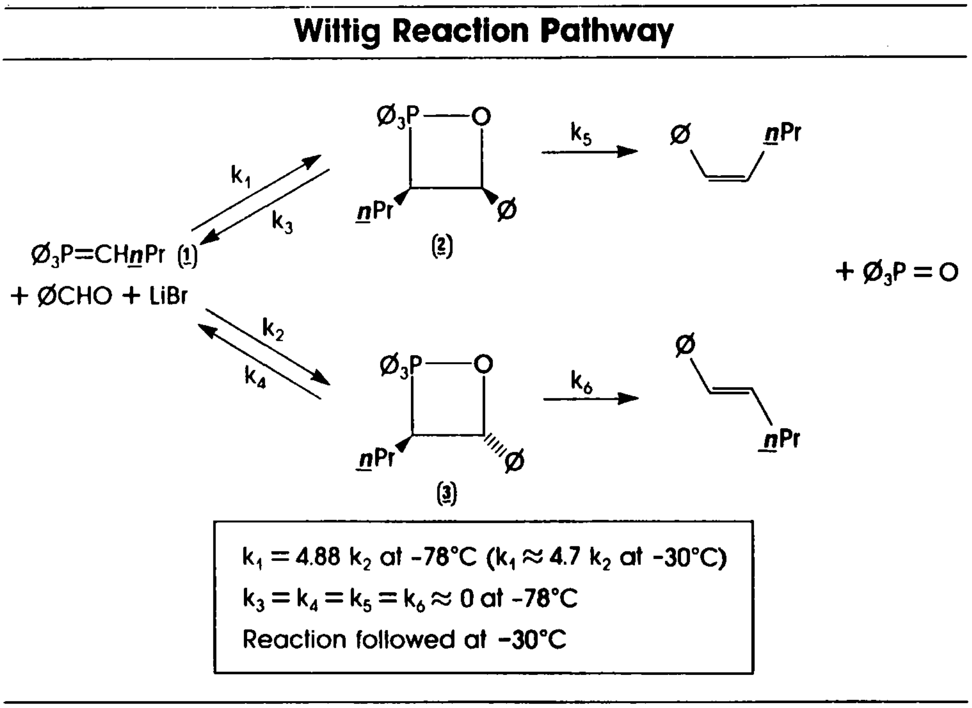

FIGURE 9 Summary of the Wittig reaction process used in the kinetic analysis, with the various rate constants. Reversal of **2** is much faster than reversal of **3** leading to a bias toward **3** and, thus, in the direction of *E* alkene. For more details, see ref. 9.

dilution. The separation between the two straight lines characterizes the degree of stereochemical drift, which becomes vanishingly small in the vicinity of 0.01 M. The analogous lithium salt-free reaction would not be expected to display such dramatic behavior since only as much as 10% of *E* alkene would ever be generated. The concentration dependence is clearly a remarkable finding, which may have far-reaching implications relative to the reproducibility of a particular Wittig reaction in the hands of different synthetic chemists. Considering the alkene line in Figure 10, a concentration of 0.5 M would result in ca. 57% *E* alkene and 0.2 M would result in 42% *E* alkene, quite a considerable disparity. However, concentration dependency in the Wittig reaction has received scant attention in the chemical literature.

The reaction of ylide **1** (from phosphonium salt and LiHMDS) with *n*-hexanal generated cis and trans oxaphosphetanes in a ratio of 5.8 : 1, which is maintained in the product alkenes (Figure 11). The absence of stereochemical drift in this instance is a logical consequence of relatively slow (if not nonexistent) interconversion between diasteromeric oxaphosphetanes. This was anticipated since Wittig reactions of non-stabilized triphenylphosphorus ylides with aliphatic aldehydes generally do not exhibit crossover due to reversibility of intermediates, whereas reactions of aromatic aldehydes do.[4a, 6a, 7d, 13] Since the cis/trans oxaphosphetane ratio was 1.7 : 1 after alkene formation was 90% complete, the cis isomer decomposes to alkene about 3 times faster than the trans isomer.

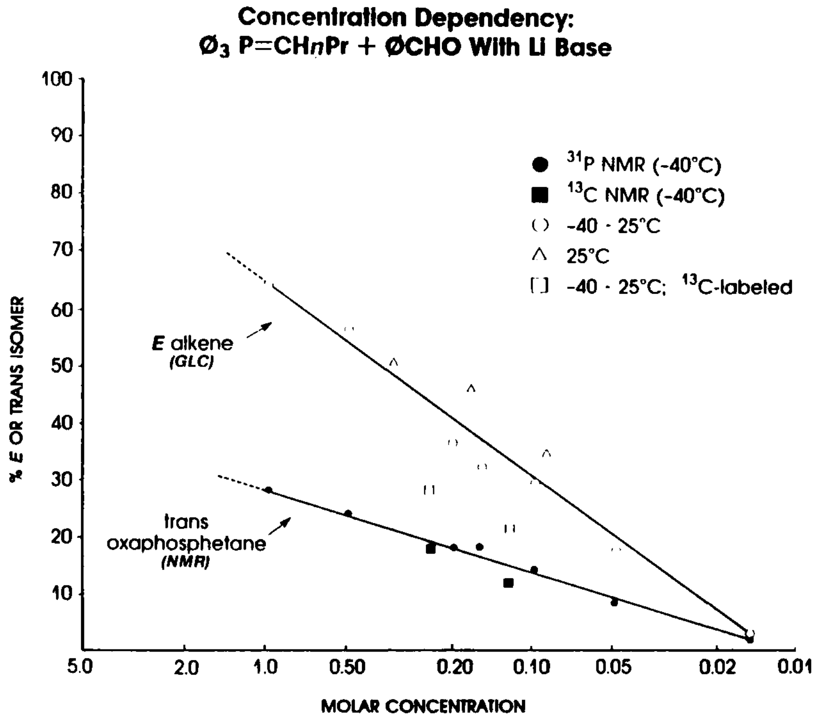

FIGURE 10 Concentration dependence of the Wittig reaction of 1 with benzaldehyde in THF in the presence of LiBr. The amount of trans oxaphosphetane was ascertained by low temperature P-31 NMR before reaction progressed and the amount of *E*-alkene was measured by GLC, after warming to 23 deg C. The lines result from least-squares analysis ($r = 0.95$ or better; the two open-square points, for experiments involving C-13 enriched **1**, were eliminated from the alkene line because of their unusual deviation).

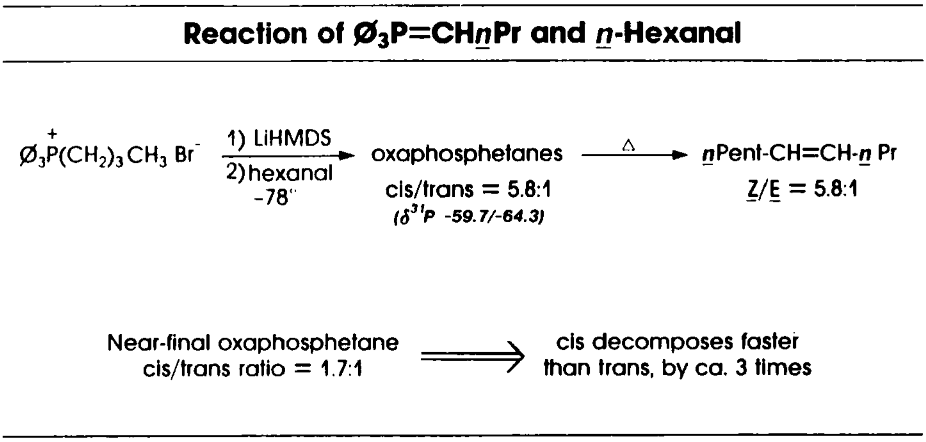

FIGURE 11 Reaction of ylide 1 with hexanal in THF in the presence of LiBr.

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Wittig intermediates, such as oxaphosphetanes, can be trapped by reaction with anhydrous HBr to give beta-hydroxyphosphonium bromide salts, which can be deprotonated to reenter the Wittig reaction manifold.[6a, 6c] Consequently, we quenched a 73 : 27 mixture of **2** and **3**, from the condensation of **1** and benzaldehyde in the presence of LiBr, with HBr at −78 deg C (Figure 12). A mixture of erythro and threo salts, **4** and **5**, was isolated in which the isomer ratio of 73 : 27 was conserved (^{31}P and ^{1}H NMR). This quenching of the Wittig reaction at low temperature offers an effective means for evaluating the oxaphosphetane isomer ratio at any given moment; however, the method is more amenable for single, instantaneous measurements than for continuous monitoring of the progress of a reaction. We also performed a Schlosser-style equilibration[14] of the oxaphosphetane mixture by addition of the strong base *n*-butyllithium at −78 deg C prior to quenching with HBr (Figure 12). The isolated phosphonium salt was greatly enriched (ca. 99%) in the threo diastereomer, **5**, as expected. Recrystallization of this material provided a sample of diastereomerically pure **5**, and fractional crystallization of the 73 : 27 mixture provided a sample of the erythro diastereomer, **4**, with nearly 100% isomeric purity. A single-crystal X-ray analysis of **5** confirmed the threo stereochemistry (Figure 13).[15]

When either beta-hydroxyphosphonium salt (**4** or **5**) was deprotonated with sodium-HMDS in THF-d_8 in an NMR tube, essentially one, stereochemically correspondent oxaphosphetane, was formed; warming furnished alkenes with high stereospecificity (Figure 14).[8] However, when a 45 : 55 mixture of salts **4** and **5** was deprotonated under the same conditions, a 25 : 75 mixture of *Z* and *E* alkenes was realized, despite the fact that the oxaphosphetane ratio (**2** : **3** = 45 : 55) was consistent with the initial ratio of salts.[16] This intriguing example of stereochemical drift is definitely valid, as the results have been repeated several times with deliberately

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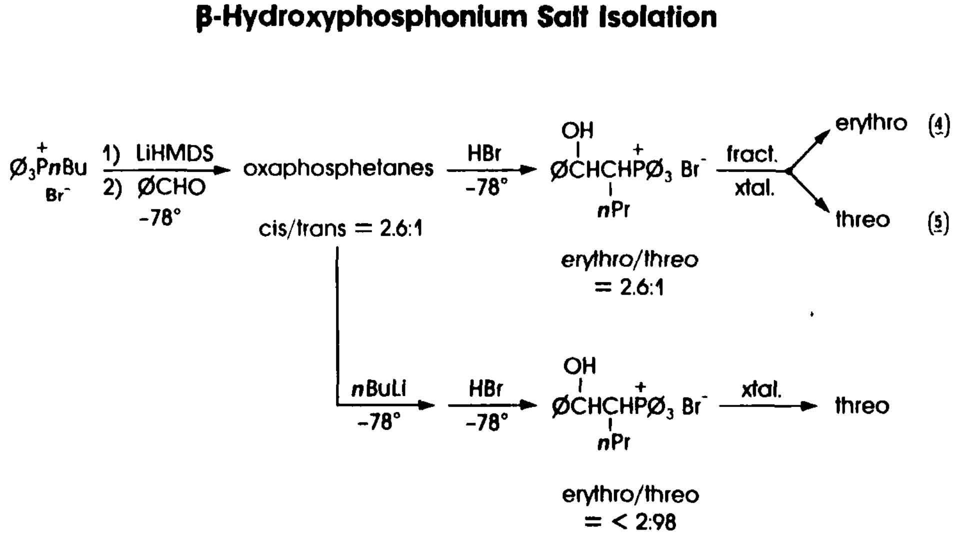

FIGURE 12 Production of beta-hydroxyphosphonium salts by quenching oxaphosphetanes with HBr at −78 deg C. Isolation of the erythro and threo isomers.

X-Ray of Threo Salt

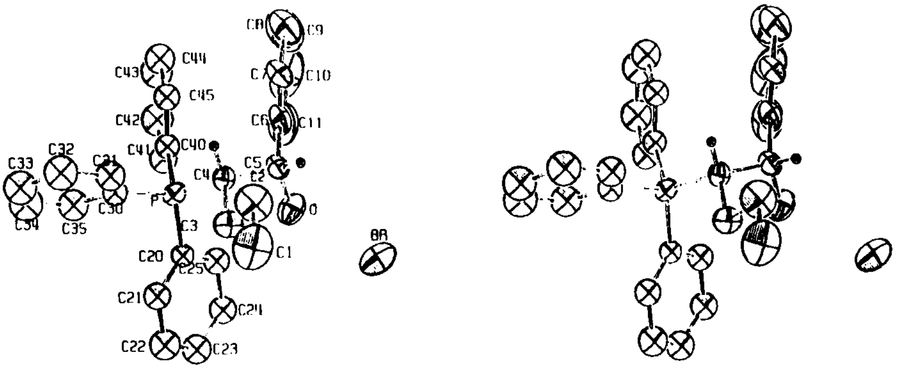

FIGURE 13 Stereoscopic pair (with numbering system) from a single-crystal X-ray analysis of threo diastereomer **5**, courtesy of Prof. R. A. Olofson (The Pennsylvania State University).

constituted mixtures of **4** and **5**. Deprotonation of **4** or **5** with NaHMDS at 23 deg C gave basically the same results. With LiHMDS at 23 deg C, **5** yielded a 1 : 99 mixture of *Z*/*E* alkenes, but **4** yielded a 62 : 38 mixture.[16] By contrast, deprotonation of **4** with LiHMDS at −78 deg C followed by warming to 23 deg C gave an 80 : 20 mixture of alkenes. The occurrence of stereochemical drift with a mixture of diastereomeric salts (thus mixture of oxaphosphetanes), when neither salt expe-

Deprotonation of Hydroxyphosphonium Salts in THF at -40°C

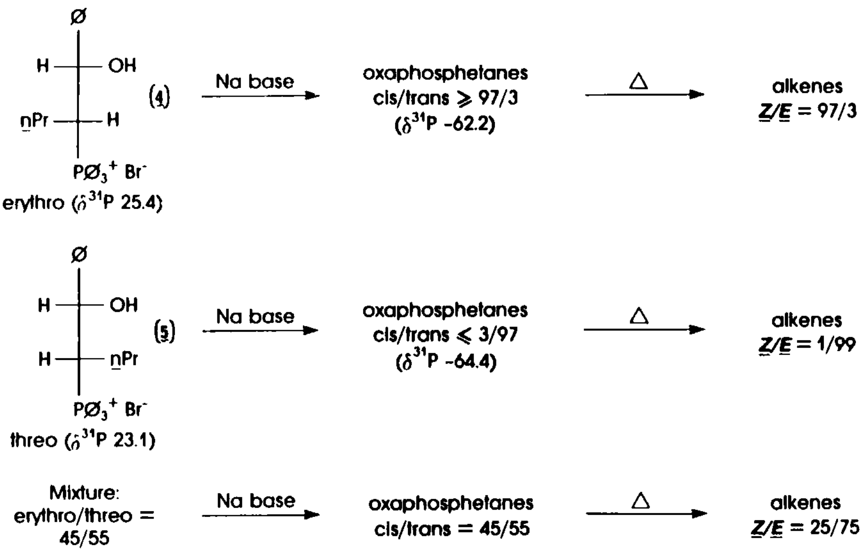

FIGURE 14 Deprotonation experiments on beta-hydroxyphosphonium salts **4** and **5**, conducted at −40 deg C with NaHMDS in THF. Alkenes were obtained by warming the reactions to 23 deg C (ratios from GLC).

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riences drift alone, suggests some type of interaction or cooperativity between diastereomers ("diastereomeric synergism").

Since Vedejs' NMR studies of oxaphosphetanes in the Wittig reaction principally employed ethylidenetriphenylphosphorane (**6**),[4] we carried out a brief examination of its reaction with benzaldehyde (Figure 15). Two oxaphosphetane signals were observed by ^{31}P NMR, but they were only separated by 0.4 ppm.[17] Although this proximity inhibited accurate quantitation (cis/trans = ca. 5 : 1), the corresponding phosphonium salts (from HBr quenching) were easily quantitated by high-field ^{31}P or ^{1}H NMR (erythro/threo = 4 : 1). The ultimate Z/E alkene ratio of 1.9 : 1 in this Wittig reaction reflected substantial stereochemical drift. Deprotonation of the 4 : 1 mixture of beta-hydroxyphosphonium salts with either LiHMDS or NaHMDS at 23 deg C also demonstrated significant stereochemical drift in the formation of the beta-methylstyrenes (Figure 15).

With diastereomerically pure beta-hydroxyphosphonium salts **4** and **5** in hand, we were in an admirable position to explore some interesting crossover reactions.[16] After deprotonation of **4** or **5** at −78 deg C in THF, excess 4-chlorobenzaldehyde (4 mol-equiv) was added, then the reaction was allowed to warm to 23 deg C. In this way the crossover experiments were transacted with each diastereomerically pure oxaphosphetane, **2** or **3**. Experiments involving NaHMDS or LiHMDS as bases are displayed in Figures 16 and 17, respectively (along with appropriate reference reactions). The erythro salt, **4**, gave mixtures of the direct and the crossed products with either base, whereas the threo salt, **5**, did not. Also, we detected benzaldehyde by GLC in the reactions of **4**.

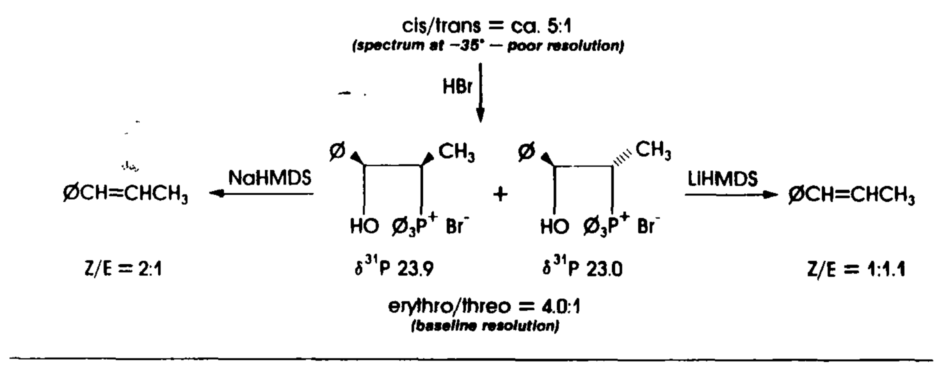

FIGURE 15 Several experiments are represented: Reaction of ylide **6** with benzaldehyde in THF in the presence of LiBr at −78 deg C, followed by warming to 23 deg C; quenching of intermediate oxaphosphetanes with HBr at −35 deg C; deprotonation of a mixture of beta-hydroxyphosphonium salts with two different bases.

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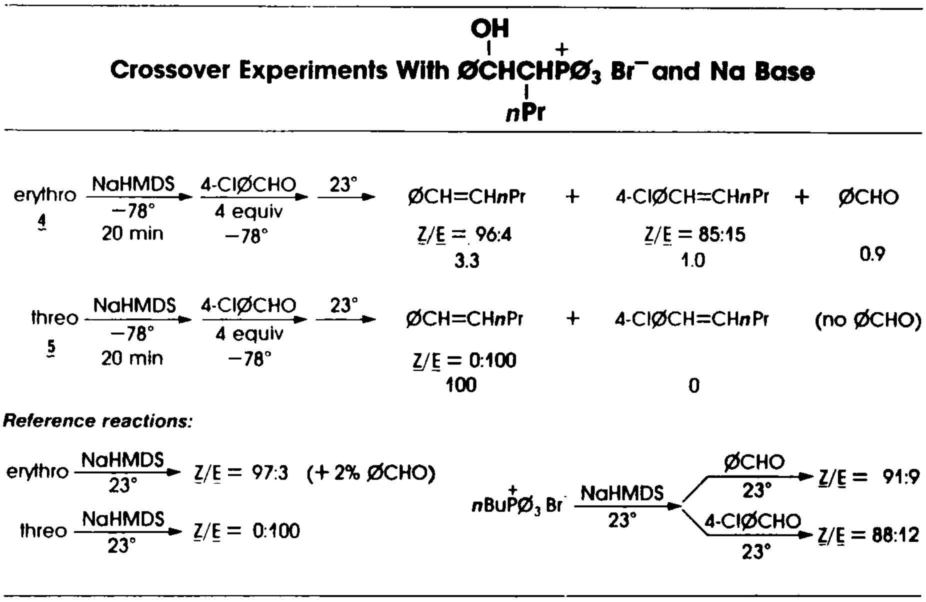

FIGURE 16 Crossover experiments entailing deprotonation of phosphonium salts 4 or 5 with NaHMDS, followed by addition of excess 4-chlorobenzaldehyde. Control reactions are presented, as well.

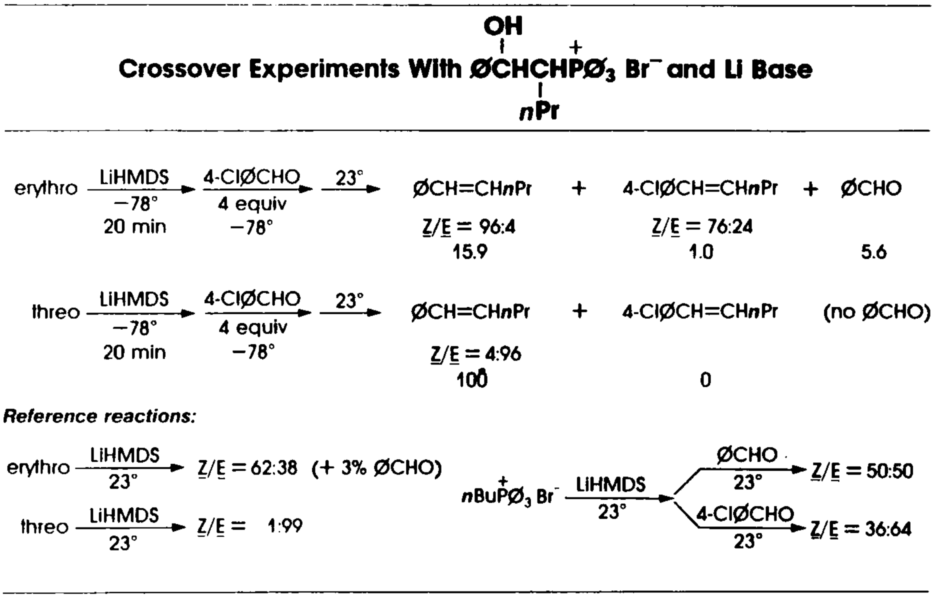

FIGURE 17 Crossover experiments analogous to those in Figure 16, but with LiHMDS.

From the results of deprotonation experiments, the trans oxaphosphetane (3) does not appear to undergo reaction reversal (competitive with alkene formation), whereas the cis oxaphosphetane does. In the kinetic studies we ascertained that the rate of reversion of **2** to ylide **1** and benzaldehyde was 7–15 times as fast as that for **3**,[9] albeit the standard deviation for the rate constant k_4 was rather large. The crossover results indicate that cis oxaphosphetane **2** reverts much faster than trans oxaphosphetane **3**. Moreover, the rate of reversion of **3** (i.e., k_4) must be much slower (by at least a factor of 20) than its rate of decomposition to *E* alkene (i.e., k_6).

A double-label crossover experiment afforded some fascinating results (Figure 18), which support this pattern, as well as the cooperativity phenomenon that was mentioned earlier. Thus, a mixture of erythro and threo salts composed of different aldehyde and ylide fragments (as shown) gave on deprotonation with NaHMDS only direct products (i.e., no crossed alkenes) with the erythro-derived alkene showing substantial stereochemical drift. In distinct contrast, a mixture of different erythro salts (as shown) gave an entire array of the possible alkenes with very little stereochemical drift in the direct products and a small amount of drift in the crossed

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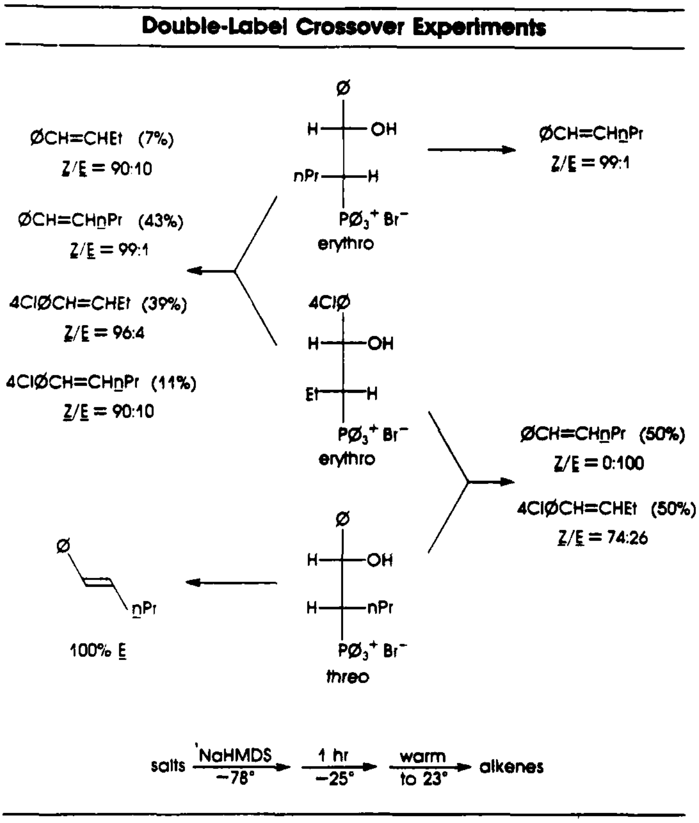

FIGURE 18 Double-label crossover experiments employing NaHMDS. The overall reaction scheme is depicted at the bottom. Amounts in parentheses are relative amounts for that particular reaction.

products. Clearly, the presence of trans oxaphosphetane (from the threo salt) induces stereochemical drift in the cis oxaphosphetane (from the erythro salt). Under this condition, crossed alkenes are not realized because the trans oxaphosphetane does not suffer reversibility at a sufficiently competitive rate. However, crossed alkenes are realized when the two diverse cis oxaphosphetanes are intermixed.

Trialkylphosphorus ylides have been noted to react with aldehydes with particularly high *E* stereoselectivity,[6b,18] and the reason for this behavior has been a subject of speculation.[6b,18b] Therefore, we investigated the stereochemical reactivity of butylidenetri-*n*-butylphosphorane, 7 (Figure 19). When 7 was created from tetra-*n*-butylphosphonium bromide by using *n*-butyllithium and reacted with benzaldehyde at −40 deg C in an NMR tube, we could detect no oxaphosphetane signals by ^{31}P NMR; just peaks in the phosphonium region, presumably for betaines, and a singlet for tri-*n*-butylphosphine oxide were evident. Such betaines may be stabilized by complexation with the LiBr. Conducting this reaction at room temperature in the normal synthetic manner, we obtained a poor (29%) yield of styrenes with a strong preference for the *E* isomer (Figure 19). It seemed that lithium cation presents a problem to this chemistry, so we decided to examine "salt-free" conditions. Thus, the phosphonium salt was treated with *n*-butyllithium in THF and the ylide (7) was isolated as a pale yellow liquid by distillation in vacuo. This ylide, which is highly air-sensitive, was preserved under an argon atmosphere.[19] Ylide 7, now strictly salt-free, was combined with benzaldehyde in THF in an NMR tube at temperatures between −78 and −40 deg C to reveal two sharp singlets for cis and trans oxaphosphetanes at −70.2 and −71.0 ppm in a ratio of ca. 47 : 53, respectively.[20] A ^{31}P NMR spectrum at −50 deg C is presented in Figure 20 (bottom left). A quick purview of the reaction was gotten by elevating the temperature incrementally and collecting some spectral data (Figure 20, center and right). From the center panel it is quite apparent that the oxaphosphetanes equilibrate prior to decomposition to the

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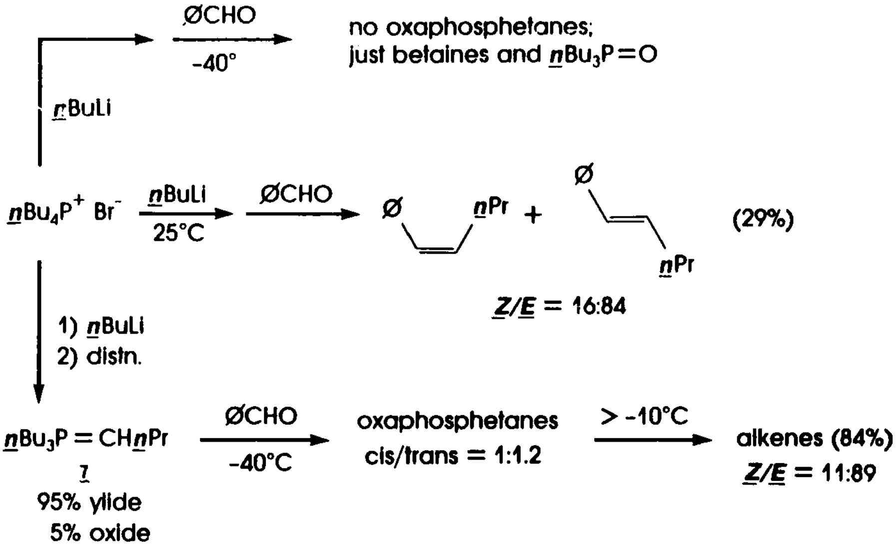

FIGURE 19 Various reactions of ylide 7 with benzaldehyde.

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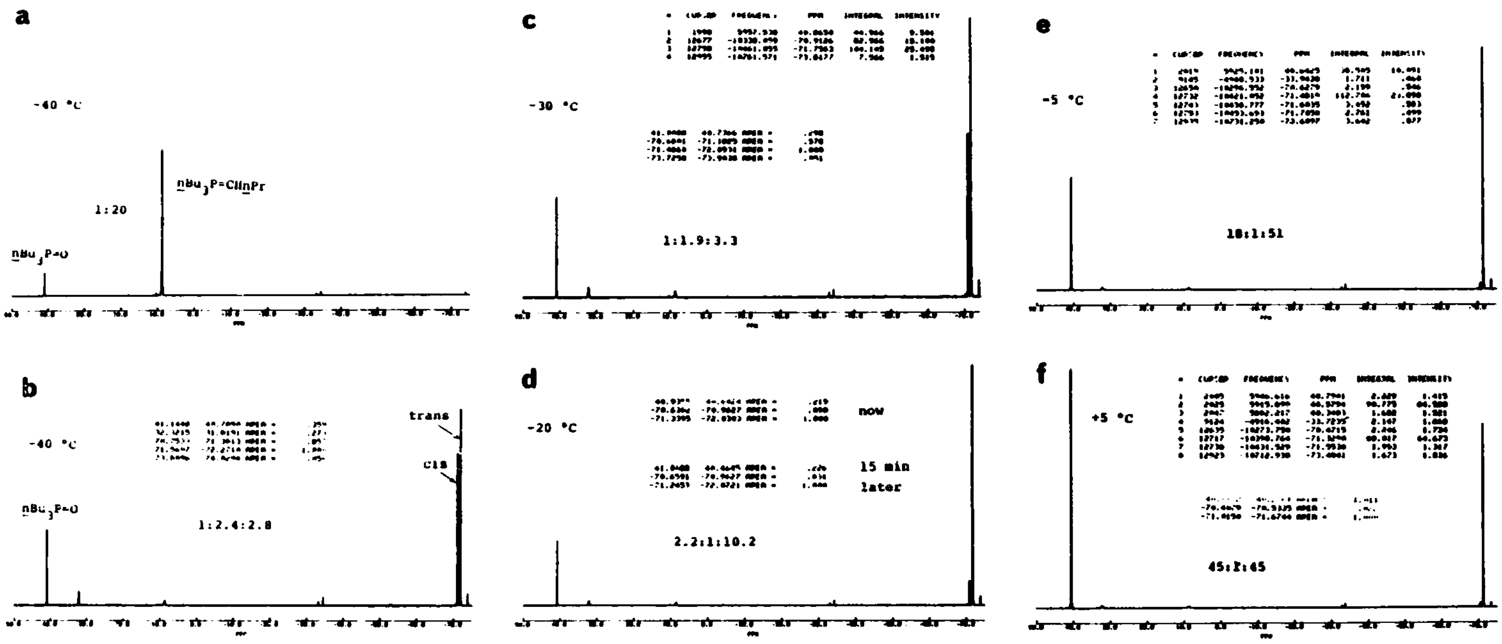

Figure 20 P-31 NMR spectra of the reaction of salt-free **7** with benzaldehyde. (a) Spectrum of ylide **7** at −40 deg C in THF showing 5% of phosphine oxide by integration. (b) Spectrum of ylide **7** treated with benzaldehyde at −78 deg C after thermal stabilization in the NMR probe at −40 deg C: accounting for total phosphorus shows ca. 15% of phosphine oxide; cis/trans oxaphosphetane ratio is 46 : 54. (c) Spectrum of the reaction at a probe temperature of −30 deg C: phosphine oxide accounts for ca. 15% of total phosphorus; the oxaphosphetane ratio is altered. (d) Spectrum at −20 deg C: phosphine oxide still corresponds to ca. 15% of total phosphorus; cis/trans oxaphosphetane ratio has now shifted to 1 : 10. (e) Spectrum at −5 deg C: phosphine oxide makes up ca. 25% of total phosphorus; the cis/trans oxaphosphetane ratio is 1 : 50. (f) spectrum at 5 deg C: phosphine oxide is now ca. 50% of total phosphorus; the cis/trans ratio is ca. 1 : 50.

phosphine oxide (and therefore alkenes). Spectrum (d), recorded at −30 deg C, shows a cis/trans ratio of 9 : 91, while the proportion of tri-*n*-butylphosphine oxide has hardly increased. On further warming (right panel) the proportion of phosphine oxide increased, while the oxaphosphetane ratio was constant at cis/trans = ca. 2 : 98. The completed reaction contained *Z* and *E* alkenes in a ratio of 11 : 89.

The data depicted in Figure 20 illustrate a nearly complete separation between the two processes of oxaphosphetane equilibration and decomposition, which were superimposed in the case of the corresponding triphenylphosphorus ylide, **1**. In separate experiments with ylide **7** and benzaldehyde, we have monitored the equilibration and alkene formation steps with time.[9] Preliminarily, the half-life for equilibration at −40 deg C is ca. 130 min and the half-life for disappearance of oxaphosphetanes at −10 deg C is ca. 380 min. We are now performing a thorough work-up of data from a ^{13}C NMR kinetics experiment involving ylide **7** and benzaldehyde, highly enriched at the formyl group with ^{13}C, to obtain rate constants. In any event, the high *E* stereoselectivity in this type of Wittig reaction (that of a trialkylphosphorus ylide) arises to a large extent from thermodynamic control, rather than kinetic control in the carbon-carbon bond-forming process.

In a similar fashion, ylide **7** was reacted with pivaldehyde at −60 deg C to furnish a 30 : 70 mixtüre of cis/trans oxaphosphetanes (at −70.1 and −74.0 ppm).[9] This ratio changed on warming at −15 deg C to ca. 1 : 99; the final alkene ratio was *Z*/*E* = 4 : 96. The reaction of **7** with hexanal was complicated by a side process presumably entailing acid-base chemistry.[9]

Semi-stabilized and stabilized phosphonium ylides. Given our success in studying intermediates in reactions of non-stabilized ylides with aldehydes, we attempted to pursue the chemistry of semi-stabilized· and stabilized ylides (Figure 21).

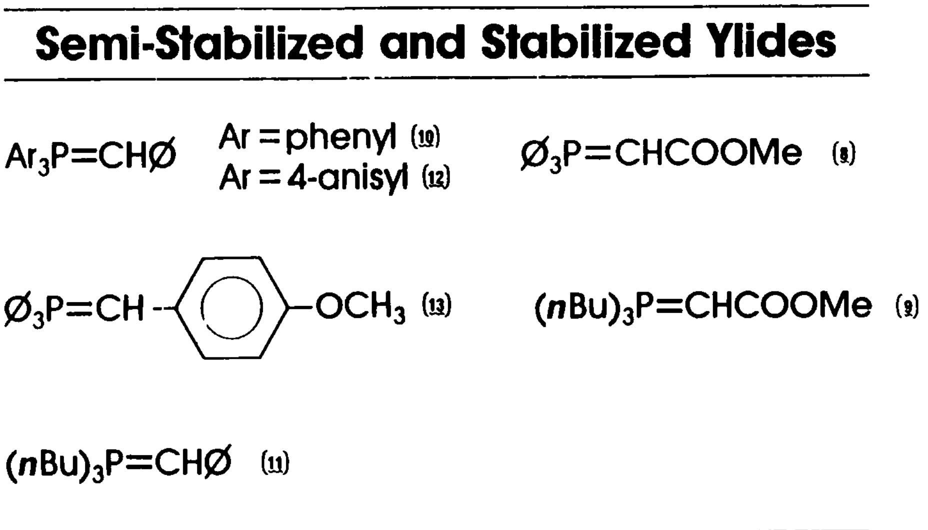

FIGURE 21 Stabilized ylides **8** and **9**; semi-stabilized ylides **10–13**.

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Carbomethoxymethylenetriphenylphosphorane (**8**) would not react with benzaldehyde in THF at −40 deg C, but reaction did take place at −20 deg C, as judged by ^{31}P NMR (Figure 22). Unfortunately, no intermediates were detected; we found just signals for unreacted ylide and triphenylphosphine oxide during the reaction course. The alkene was produced in good yield (83%) with a preponderance (> 95%) of the *E* isomer.

To boost nucleophilicity, and thereby lower the temperature of reaction, we prepared carbomethoxymethylenetri-*n*-butylphosphorane (**9**). This ylide combined with benzaldehyde at −50 deg C and the phosphine oxide was then generated. However, we again did not perceive any intermediates, be they oxaphosphetanes or betaines.

Benzylidenetriphenylphosphorane (**10**) reacted rapidly with benzaldehyde in THF at temperatures as low as −100 deg C, based on the loss of orange ylide color and the formation of triphenylphosphine oxide (NMR). However, ^{31}P NMR analysis at −100 deg C did not reveal any meaningful intermediates. We also tried to obtain evidence for reaction intermediates by quenching reactions between −80 and −100 deg C with HCl. However, we did not obtain any beta-hydroxyphosphonium salts; the salt isolated was benzyltriphenylphosphonium chloride from reprotonation of unconsumed ylide.

Because tributyl oxaphosphetane intermediates would be expected to possess greater stability against decomposition to alkenes and phosphine oxide than the

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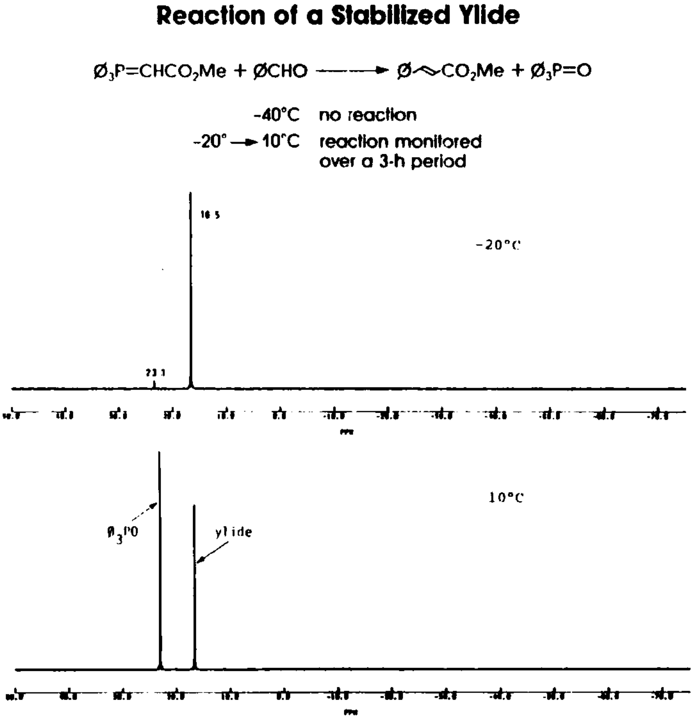

FIGURE 22 P-31 NMR spectra for the reaction of ylide **8** with benzaldehyde.

triphenyl congeners (based on our aforementioned experience), we also studied the corresponding tributyl benzylide, **11**, by ^{31}P NMR at −100 deg C. Again, no transient intermediates were detected while (tributyl) phosphine oxide was evolved. Tri(*p*-methoxyphenyl) ylide **12** also did not afford a glimpse of reaction intermediates at −100 deg C.

We surmised that an ylide with a benzylidene group more akin to an alkylidene group might yield positive results. Thus, we tested *para*-methoxy derivative **13**, wherein the electron density at the ylide center would be closer to that of an alkylidene ylide and, perhaps, the oxaphosphetanes would possess greater stability. But, a low temperature ^{31}P NMR study was not at all rewarding.

CONCLUSION

In the absence or presence of lithium salt, non-stabilized phosphorus ylide **1** reacts rapidly with benzaldehyde or hexanal at −78 deg C to give oxaphosphetanes. Both cis and trans diastereomers can be easily observed by ^{31}P NMR; the oxaphosphetanes can be monitoreed during their decomposition to alkenes. At temperatures exceeding −30 deg C, these oxaphosphetanes decompose relatively quickly, collapsing to alkenes and triphenylphosphine oxide.

By using low temperature phosphorus-proton or carbon NMR, we succeeded in obtaining reaction rate profiles for the condensation of ylide **1** with benzaldehyde. Cis and trans oxaphosphetanes **2** and **3** collapsed to alkenes and triphenylphosphine oxide at similar rates. During this process, oxaphosphetane equilibration involving the siphoning of **2** into **3** occurred competitively. This accounts for the considerable non-correspondence between the alkene Z/E ratio on workup and the initial oxaphosphetane cis-trans ratio. By contrast, stereochemical drift was not manifested by the reaction of **1** with hexanal.

A strong concentration dependence was seen for the lithium-salt reaction of ylide **1** and benzaldehyde. At higher concentrations, a greater proportion of trans oxaphosphetane was produced, with an even greater proportion of E alkene. That is to say, stereochemical drift was accentuated at the higher concentrations. We suggest that the concentration effect on the initial cis/trans oxaphosphetane ratio relates to an interaction of lithium salt in the carbon-carbon bond-forming step of the Wittig condensation. On dilution of the reaction, the THF solvent would compete effectively for the lithium cation, sequestering it and thereby neutralizing its critical contribution to the reaction process. The enhanced stereochemical drift at higher concentration is attributable to the increased presence of the trans oxaphosphetane relative to the cis isomer, a phenomenon of "diastereomeric synergism" that we have characterized by means of deprotonation studies on **4**, **5**, and their mixtures.[16] On deprotonation, mixtures of **4** and **5** in the vicinity of 50 : 50 evince stereochemical drift much in excess of that experienced with **4** or **5** alone. This interaction or "synergism" between diastereomers was unequivocally corroborated through an interesting set of double-crossover experiments.

In single-crossover experiments with **4** or **5** and 4-chlorobenzaldehyde, we discovered that erythro salt **4** suffers crossover, whereas threo salt **5** does not, regardless of the cation present (Li or Na). Consequently, the cis oxaphosphetane (**2**) reverts to

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ylide and aldehyde much faster than the trans (3), probably at least by a factor of 40, which is larger (and more reliable) than the value established from the kinetics studies. Additionally, although 4 showed substantial crossover, there was little attendant stereochemical drift. This salient observation indicates that reversibility of oxaphosphetanes is *not a sufficient condition* for stereochemical drift (rather, it is just a necessary condition).

Ylide 7 also combines rapidly with benzaldehyde at −78 deg C. However, in the presence of lithium salt betaines (probably as Li complexes) are observed, in lieu of oxaphosphetanes. The salt-free reaction does furnish oxaphosphetanes. In this case, equilibration of cis and trans oxaphosphetanes is virtually complete prior to production of alkenes and phosphine oxide. Comparable results were also found for the reaction of 7 with pivaldehyde, an aliphatic aldehyde! This thermodynamic control probably contributes to a large extent to the high *E* stereoselectivity that occurs in reactions of trialkylphosphorus ylides with aldehydes. The trialkyl groups also exert a substantial influence on the carbon-carbon bond-forming process, albeit not as great as previously believed.[6b]

Various benzylidene, semi-stabilized ylides readily combine with benzaldehyde at low temperature (−80 to −100 deg C), but no intermediates are evident. If betaines or oxaphosphetanes exist at some point, then they are much too fleeting relative to their rate of disintegration to phosphine oxide and alkenes. Carbomethoxymethylene, stabilized ylides are much less reactive with benzaldehyde and, again, provide no evidence of intermediates. To gain information on these two classes of ylides in the future, it may be worthwhile investigating the deprotonation of suitable erythro and threo beta-hydroxyphosphonium salts under diverse conditions, as we have done with 4 and 5.[16]

In conclusion, some far-reaching, general messages derive from the work we have described herein. The occurrence of "stereochemical drift" in the Wittig reaction introduces a caveat regarding the use of alkene isomer ratios for determining the initial sterochemistry of carbon-carbon bond formation. Indeed, some mechanistic interpretations about the Wittig reaction in the literature, based exclusively on alkene isomer ratios, may be subject to revision. Further, the occurrence of a strong concentration dependence in the lithium-salt Wittig reaction could easily engender irreproducibility of stereochemical results between different researchers. Careful control of reaction parameters may be required for stereochemical reproducibility.

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11. Derivation of kinetic equations and other details are furnished in the microfilm supplement of ref. 9.
12. The large standard error in k_4 (ca. ±60%) can induce a large error in the ratio of k_3 to k_4.[11]
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15. This affords the first absolute proof of stereochemistry for a threo-erythro pair of beta-hydroxyphosphonium salts.
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19. Ylide **7** generally contained about 5% of tributylphosphine oxide, which could not be eliminated even by very careful handling. A ^{31}P NMR spectrum of **7** at -50 deg C is shown in Figure 20 (top left).
20. This ratio was corroborated by NMR analysis of the beta-hydroxyphosphonium salts from an HBr-quench experiment.

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