Stereochemistry and Mechanism of the Wittig Reaction. Diastereomeric Reaction Intermediates and Analysis of the Reaction Course

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Abstract: Individual diastereomeric 1,2-oxaphosphetanes have been directly observed in the Wittig olefination reaction by use of high-field NMR spectroscopy at low temperature, permitting detailed evaluation of these intermediates. Reactions of benzaldehyde with ylide **4** and with ylide **11** were monitored over time to gain the first intimate kinetic perspective of the Wittig reaction. Complete kinetic data are presented, along with the specifics of our analysis. In a number of instances, the reaction of nonstabilized phosphorus ylides with aldehydes showed a noncorrespondence between the relative proportion of *cis*- and *trans*-oxaphosphetanes at low temperature (prior to significant alkene formation) and the final proportion of *Z* and *E* alkenes, resulting in an exaggerated production of *E* alkene (a phenomenon termed "stereochemical drift" for convenience). Thus, there was a measure of thermodynamic control in these reactions. For triaryl ylide **4**, equilibration readily occurred with the aromatic aldehyde, benzaldehyde, in the presence of lithium salt. The shift to the more stable trans isomer (**6a**, R = Ph) with **4** and benzaldehyde was found to be concentration dependent, presumably because of competitive sequestration of lithium cation by the THF solvent. Such stereochemical drift also occurs in the absence of lithium if the *trans*-oxaphosphetane contaminates the cis isomer to a significant extent, reflecting an interaction of some kind between the two different oxaphosphetanes during their decomposition (a process termed "diastereomeric synergism"). In the case of trialkyl ylide **11**, both an aromatic and an aliphatic aldehyde, benzaldehyde and pivaldehyde, showed drift to the *trans*-oxaphosphetane (**6a** and **6d**, R = *n*-Bu); in fact, the *E* alkene became nearly the exclusive product (*Z*/*E* = 8:92 and 1:99, respectively). The above-mentioned rate studies, entailing low-temperature ^{1}H, ^{13}C, and/or ^{31}P NMR spectroscopic measurements, indicate that the equilibration of *cis*- to *trans*-oxaphosphetane arises from a larger rate of reversion of the *cis*-oxaphosphetane to ylide and aldehyde. Crossover experiments involving deprotonation of diastereomerically pure β-hydroxyphosphonium salts **7a** and **8a** (R = Ph), followed by the addition of 4-chlorobenzaldehyde, supported our overall viewpoint, as did a double-label crossover experiment. A single-crystal X-ray analysis of threo salt **8a** (R = Ph) was performed to unambiguously confirm the stereochemistry. Low-temperature ^{31}P NMR investigations of semistabilized and stabilized phosphorus ylides are also described. Unfortunately, these latter studies did not offer any direct evidence for the existence of oxaphosphetane or betaine intermediates. A general discussion of the Wittig reaction mechanism is presented.

Since its inception about 30 years ago, the Wittig reaction for olefination of aldehyde and ketone functionalities using phosphorus ylides has assumed a key position in the armamentarium of organic chemists.[1] Although considerable mechanistic discussion on the Wittig reaction has transpired, intimate mechanistic details still remain to be elucidated.[2]

The most useful tool for probing the Wittig reaction process probably is stereochemistry. Originally, little attention was paid to stereochemistry since several olefins were obtained as *Z*/*E* mixtures, suggesting that the reaction might not be generally stereoselective.[3] However, it was soon discovered that the type of ylide and the exact reaction conditions play key roles in determining reaction stereochemistry.[1] For example, nonstabilized phosphorus ylides react with aldehydes to give largely *Z* alkenes, except under special conditions,[4,5] and stabilized ylides give predominantly *E* alkenes, but semistabilized ylides generally give a mixture of *Z*/*E* alkenes with a ratio around 50:50. From a historical perspective, the Wittig reaction has become widely recognized and applied because of (1) the ease of obtaining carbon–carbon double bonds in a predictable location and (2) the high stereoselectivity available in the preparation of less thermodynamically stable *Z* alkenes with lithium salt-free, nonstabilized ylides.

Several proposed mechanisms for the Wittig reaction have attracted interest.[2] All of these seek to answer two key questions: (1) what intermediates predominate as the reaction proceeds from ylide and carbonyl compound to alkenes and phosphine oxide and (2) what mechanistic factors govern the resulting stereochemistry. In a classical formulation of the reaction, a phosphorus ylide combines with an aldehyde or unsymmetrical ketone to afford two dipolar betaine intermediates, which collapse to *Z* and *E* alkenes and phosphine oxide via very transient oxaphosphetane species (Figure 1).[1b,4a] However, the pioneering NMR studies of Vedejs' group in the 1970's indicated that 1,2-oxaphosphetanes can be reasonably persistent and that they should be considered as more important intermediates than betaines.[2d,6] Whether oxaphosphetanes are formed directly, or via betaines, is still unknown.

To rationalize stereochemical data, Bestmann has suggested that oxaphosphetane intermediates, presumably cis rich at the outset, can open to zwitterions (Figure 1), which are free to rotate to the thermodynamically more stable threo isomers before decomposing to products.[2b,c,7] The loss of the initial stereochemistry

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(1) For general reviews of the Wittig reaction or selected aspects of it, see: (a) Gosney, I.; Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; pp 7–153. (b) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (c) Bestmann, H. J. *Pure Appl. Chem.* **1980**, *52*, 771. (d) Trippett, S. *Quart. Rev.* **1963**, *17*, 406. (e) Trippett, S. *Pure Appl. Chem.* **1964**, *9*, 255. (f) Maercker, A. *Org. React.* **1965**, *14*, 270. (g) LeBigot, Y.; Delmas, M.; Gaset, A. *Inf. Chim.* **1984**, *251*, 123. (h) Bergelson, L. D.; Shemyakin, M. M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 250. (i) Bestmann, H. J. *Pure Appl. Chem.* **1979**, *51*, 515.

(2) (a) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821. (b) Reference 1c and references cited therein. (c) Bestmann, H. J. *Bull. Soc. Chim. Belg.* **1981**, *90*, 519. (d) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823. (e) Olah, G. A.; Krishnamurthy, V. V. *Ibid.* **1982**, *104*, 3987. (f) McEwen, W. E.; Beaver, B. D.; Cooney, J. V. *Phosphorus Sulfur* **1985**, *25*, 255.

(3) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318.

(4) (a) Schlosser, M.; Christmann, K. F. *Justus Liebigs Ann. Chem.* **1967**, *708*, 1. (b) Schlosser, M.; Muller, G.; Christmann, K. F. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 667.

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(6) (a) Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778. (b) Vedejs, E.; Snoble, K. A. J.; Fuchs, P. L. *J. Org. Chem.* **1973**, *38*, 1178.

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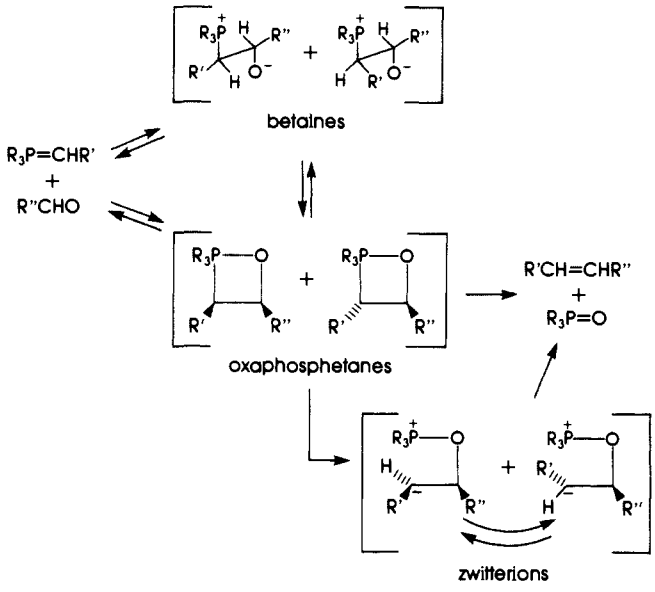


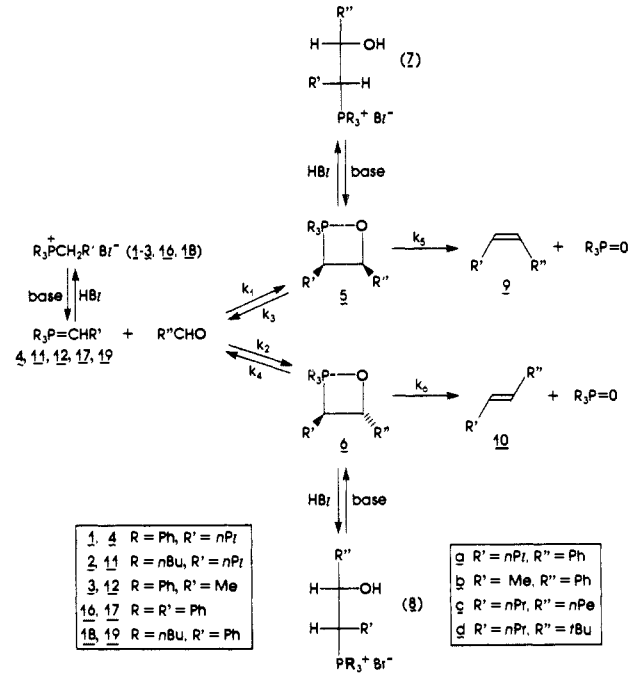
Betaines, oxaphosphetanes and zwitterions as potential intermediate species in the Wittig reaction.

Figure 1. General mechanistic schematic of the Wittig reaction between a phosphonium ylide and an aldehyde, showing betaines, oxaphosphetanes, and zwitterions as potential intermediates.

during the reaction could account for the greater amount of *E* alkene observed with stabilized ylides, in which case the zwitterion would be longer lived because of stabilization of the anionic charge. In the reaction of nonstabilized phosphorus ylides with aldehydes, Schlosser has speculated that *cis*-oxaphosphetanes (and *Z* alkenes) are preferred with triphenylphosphorus ylides, whereas *trans*-oxaphosphetanes (and *E* alkenes) are preferred with trialkylphosphorus ylides because of distinct interactions between the three stationary ligands on the phosphorus (phenyl vs. alkyl) and an approaching aldehyde.[2a,8] Such an analysis assumes that the original cis/trans oxaphosphetane ratio is predominantly conserved on decomposition to olefins, i.e., that there is no intervening stereomutation.[9] McEwen et al. have suggested a mechanism for the reaction of salt-free ylides involving spin-paired diradical intermediates,[2f] and a single-electron transfer (SET) mechanism, more relevant to reactions of sterically hindered ketones, has been postulated by Olah and Krishnamurthy,[2e]

We supposed that major insight into the stereochemical aspects of the Wittig reaction would result if individual diastereomeric oxaphosphetanes could be monitored directly. Thus, we embarked on a series of low-temperature NMR studies. Preliminary communications have reported the successful detection of both oxaphosphetane diastereomers by ^{31}P and ^{13}C NMR, as well as the first examination of a reaction-rate profile.[10,11] Significantly, we observed in several instances a noncorrespondence between the relative proportion of originally formed oxaphosphetane diastereomers and the proportion of *Z* and *E* alkenes. This "stereochemical drift" afforded more *E* alkene than expected from the initial amount of *trans*-oxaphosphetane present.[10,11] Through a combination of high-field ^1H, ^{13}C, and ^{31}P NMR spectroscopy, we followed the time course of the Wittig reaction, intimately studying two systems: Ph_3P=CH-*n*-Pr (**4**) and PhCHO with LiBr present and *n*-Bu_3P=CH-*n*-Pr (**11**) and PhCHO under salt-free conditions (Scheme I).[11] Thus, the stereochemical drift was connected with an exaggerated rate of reversion of the *cis*-oxaphosphetane to ylide and aldehyde ("retro-Wittig" reaction), relative to the reversal rate for the trans isomer and competitive with the rates of alkene formation.[11] Deprotonation experiments with erythro and threo β-hydroxyphosphonium salts confirmed that *cis*-oxaphosphetane **5a** (R = Ph) reverts with much greater facility than *trans*-oxaphosphetane **6a** (R = Ph).[12]

Scheme I



We now present full details of our Wittig reaction studies, which focus on the following: (1) stereochemical drift and its concentration dependence, (2) enhanced reversibility of *cis*-oxaphosphetanes compared to *trans*-oxaphosphetanes, (3) kinetic studies and crossover experiments, (4) reactions of semistabilized and stabilized ylides, and (5) cooperative interaction between *cis*- and *trans*-oxaphosphetanes.

Reaction of Nonstabilized Ylides with Aldehydes

In the course of our investigation of anomalous *E* stereoselectivity in reactions of ylides bearing anionic groups,[5] we became convinced that a study of the Wittig intermediates (oxaphosphetanes), particularly both diastereomers, was essential. Consequently, we explored the applicability of ^{31}P NMR at low temperature, which had been effectively employed by Vedejs for probing Wittig intermediates, albeit without resolution of diastereomeric pairs.[2d] This technique is especially useful because ^{31}P is 100% abundant and has a wide chemical shift dispersion. The use of broad-band proton decoupling on a high-field NMR instrument (145.8 MHz for ^{31}P) generally furnishes sharp, well-resolved singlets for ^{31}P-containing compounds, even at diminished temperatures.

Observation of *cis*- and *trans*-Oxaphosphetanes by NMR. Our earliest experiments involved the reaction of butylidenephosphorane **4** and benzaldehyde (with LiBr present) because this system modeled our work on ylides bearing anionic groups (Scheme I).[5] In the reaction of **4**, we observed a pair of sharp singlets in the P(V) region attributed to *cis*- and *trans*-oxaphosphetanes, **5a** and **6a** (R = Ph).[10] This exciting finding prompted us to conduct an in-depth study of the Wittig reaction, with an orientation toward low-temperature NMR experiments.

Treatment of phosphonium bromide **1** with Li hexamethyldisilazide (HMDS), NaHMDS, or *n*-BuLi gave ylide **4**, characterized by a sharp singlet at 11.8 ppm. The cation had no influence on the ylide chemical shift, in accord with the prior reports[13] that phosphorus ylides (except for Ph_3P=CH_2) do not

(7) Also, see the discussion in McEwen, W. E.; Cooney, J. V. *J. Org. Chem.* **1983**, *48*, 983.
(8) Schneider, W. P. *J. Chem. Soc., Chem. Commun.* **1969**, 785.
(9) For example, see: ref 1b, 2a, and 4a.
(10) Reitz, A. B.; Mutter, M. S.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1984**, *106*, 1873.
(11) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 1068.
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interact significantly with lithium ion. Condensation of **4** with benzaldehyde or hexanal in THF at −78 °C (LiBr present) produced two sharp singlets between −60 ppm and −65 ppm, which disappeared at temperatures between −35 and −10 °C, while a signal for $Ph_3P{=}O$ at 28.0 ppm (LiBr complex) arose. These reactions were homogeneous; no undissolved solids were evident.

In experiments with **4** and benzaldehyde in the presence of Li salt, the two peaks assigned to **5a** and **6a** (R = Ph) resonated at −61.4 ppm and −63.8 ppm. The **5a**:**6a** (R = Ph) ratio at low temperature varied from ca. 50:1 to 3:1 depending on the concentration of the THF solution, which ranged from 1.0 to 0.015 M (vide infra).[14] After recording the ^{31}P NMR spectrum, the solutions were allowed to warm to 23 °C, whereupon the alkenes, **9a** and **10a**, were analyzed by GLC. The *Z*/*E* alkene ratio varied between 40:60 to 98:2, respectively. In most cases, there was a greater proportion of *E* olefin on workup than had been reflected by the original amount of *trans*-oxaphosphetane. This "stereochemical drift" was found to be concentration-dependent in THF, being greatly attenuated at high dilution (e.g., 0.015 M; vide infra). Nevertheless, at normal operating concentrations there was clearly an element of thermodynamic control in this reaction, as a consequence of *cis*/*trans*-oxaphosphetane equilibration.

Reaction of **4**, prepared from **1** and NaHMDS in THF at −78 °C, with benzaldehyde gave only a single peak at −61.9 ppm (at least 98% of one isomer), assigned to **5a** (R = Ph). Decomposition of this solution yielded a 96:4 ratio of *Z*/*E* alkenes, **9a** and **10a**, indicating little stereochemical drift. This result is consistent with the expected prevalence of *Z* alkene and *cis*-oxaphosphetane in the salt-free Wittig reaction, given syn elimination of $Ph_3P{=}O$.[15] It should be noted, however, that there has been speculation on oxaphosphetane decomposition entailing anti elimination of the elements of $Ph_3P{=}O$,[16] which would reverse our oxaphosphetane assignment (however, this issue is resolved in discussion below).

Ylide **4**, generated from **1** with LiHMDS in THF, combined with hexanal at −78 °C (as mentioned briefly above) to give oxaphosphetanes **5c** and **6c** (R = Ph) in a 5.8:1 ratio, which was maintained precisely in the alkene products, **9c** and **10c**. The absence of stereochemical drift here is an outgrowth of very slow equilibration of oxaphosphetanes relative to the rate of alkene formation. Since the ratio of **5c** and **6c** (R = Ph) was ca. 1.7:1 when oxaphosphetane decomposition was 90% complete, we estimate that the *cis*-oxaphosphetane produced alkene about three times faster than the trans isomer.

To gather unambiguous evidence for the structures of **5a** and **6a** (R = Ph), the intermediates were trapped as *erythro*- and *threo*-β-hydroxyphosphonium salts, **7a** and **8a** (R = Ph), by acidolysis[4a,17] with HBr at *low temperature*.[18] Salt **7a** (R = Ph) was prepared in two ways. A 2.6:1 mixture of **5a** and **6a** (R = Ph), from the reaction of **4** and benzaldehyde in THF (LiBr present), was quenched with anhydrous HBr at −78 °C to yield a 2.6:1 mixture of **7a** and **8a** (R = Ph), appearing as two singlets in the ^{31}P NMR spectrum at 25.4 and 23.1 ppm ($CDCl_3$), respectively. Fractional recrystallization of this mixture supplied pure **7a** (R = Ph) (δ ^{31}P 25.4). Alternatively, pure **7a** (R = Ph) was prepared more conveniently (with just a single recrystallization) by HBr treatment of **5a** (R = Ph) derived from a salt-free reaction of **4** and benzaldehyde (NaHMDS as base). Threo salt **8a** (R = Ph) was readily obtained via a trans-selective Schlosser procedure, as follows.[19] The mixture of oxaphosphetanes formed by condensation of **4** and benzaldehyde (LiHMDS as base) was treated with 1.0 molar equiv of *n*-BuLi at −40 °C. After 15 min, HBr was introduced at −40 °C to capture the metalated ylide, i.e., lithio β-oxido ylide,[20] affording threo salt **8a** (R = Ph). After one recrystallization, **8a** (R = Ph) was obtained diastereomerically pure (one ^{31}P NMR peak at 23.1 ppm). The 360-MHz ^1H NMR spectra of salts **7a** and **8a** (R = Ph) corroborated their isomeric purity at greater than 99%. The Schlosser-type equilibration should have yielded threo salt **8a** (R = Ph), given the predominance of *E* alkene from this process. Additionally, separate deprotonation of **8a** (R = Ph) with NaHMDS generated exclusively *E* alkene.

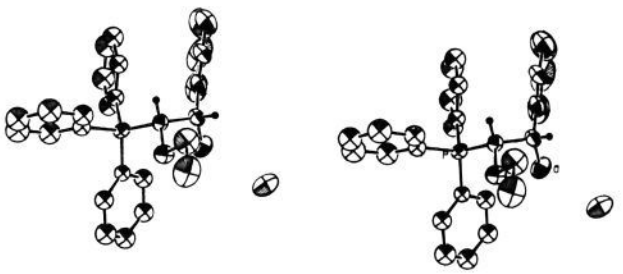

Figure 2. Stereoview of **8a** (R = Ph) (ORTEP representation). Thermal ellipsoids for non-hydrogen atoms represent 35% probability.

We performed a single-crystal X-ray structure determination on **8a** (R = Ph) to assign the stereochemistry unequivocally. An ORTEP representation of **8a** (R = Ph) is depicted in Figure 2; clearly, the molecule possesses the threo configuration. In the crystal lattice, the bromine atom is closer to the hydroxyl group than to the phosphonium center, possibly indicating some weak hydrogen bonding. The triphenylphosphorus moiety adopts a three-bladed propeller conformation, and the O–C5–C4–P grouping possesses a staggered conformation with a gauche arrangement of hydrogen atoms (H4 and H5) and an anti arrangement of the *n*-propyl and phenyl substituents.

Compounds **7a** and **8a** (R = Ph) were individually deprotonated with NaHMDS in THF at −78 °C to furnish oxaphosphetanes **5a** and **6a** (R = Ph), respectively, which appeared as singlets in the ^{31}P NMR spectrum at −62.2 and −64.4 ppm. Examination of the solutions after they had been warmed to room temperature revealed *Z*/*E* olefin ratios of 99:1 (**5a**, R = Ph) and 0:100 (**6a**, R = Ph). Thus, the oxaphosphetanes decomposed with syn elimination of $Ph_3P{=}O$, and, under these conditions (Na base, −78 °C → 23 °C), there was no loss of stereochemistry in the overall process (cf. ref 15).

We also examined the reactions of nonstabilized triphenylphosphonium ylides related to **4** containing anionic groups at the end of the ylidic chain.[5] Although results from these studies were already communicated,[5] we mention in summary that these ylides react with benzaldehyde to give mixtures of pentavalent phosphorus species, whose ^{31}P NMR signals are analogous in chemical shift to those of **5a** and **6a** (R = Ph).

In various $^{31}P\{^1H\}$ NMR spectra, diastereomeric oxaphosphetanes **5a** and **6a** (R = Ph) appeared as singlets separated by 2–3 ppm around −61 and −64 ppm, respectively. However, the peaks for oxaphosphetanes **5b** and **6b** (R = Ph), from the reaction of ylide **12** (from salt **3** and LiHMDS) and benzaldehyde, were much closer together (not base line resolved).[10] The diminutive chemical shift difference between **5b** and **6b** (R = Ph) of ca. 0.4 ppm may be ascribable to the small methyl substituent.[5] For reactions with either *n*-BuLi or LiHMDS in THF, the two peaks, resonating at −61.2 ppm and −61.6 ppm at −35 °C, had a ratio of ca. 5:1, respectively. A ratio of ca. 3:1 was gleaned by quenching the oxaphosphetane mixture with HBr at −35 °C and analyzing the resultant mixture of *erythro*- and *threo*-β-hydroxyphosphonium

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(14) Reitz, A. B.; Nortey, S. O.; Jordan, A. D., Jr.; Mutter, M. S.; Maryanoff, B. E. *J. Org. Chem.* **1986**, *51*, 3302.

(15) For example, see: Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822.

(16) Thacker, J. D.; Whangbo, M.-H.; Bordner, J. *J. Chem. Soc., Chem. Commun.* **1979**, 1072.

(17) Piskala, A.; Rehan, A. H.; Schlosser, M. *Coll. Czech. Chem. Commun.* **1983**, *48*, 3539.

(18) Acid quenching at low temperature (below −30 °C, not at 0 °C[4a]) is important for capturing the original stereochemistry.

(19) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 650. Schlosser, M.; Christmann, K. F. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 126.

(20) (a) These ylides are termed β-oxido ylides because they react as we expect β-oxido ylides to react; however, their true nature in solution is unknown at present.[20b] Since ^{31}P NMR spectra for β- and γ-oxido ylides are rather strange,[5,20b] their gross structure in solution is not simply defined. (b) Vedejs, E.; Meier, G. P. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 56.

bromides (**7b** and **8b**, R = Ph) by 145.8-MHz ^{31}P NMR (δ ^{31}P 23.9 and 23.0, respectively) and 360-MHz ^1H NMR spectroscopy. The ultimate *Z*/*E* alkene ratio (**9b**:**10b**) on workup (of the *n*-BuLi reaction) was 1.9:1, a manifestation of stereochemical drift. Deprotonation of the 3:1 erythro/threo mixture, **7b** and **8b** (R = Ph), with either LiHMDS or NaHMDS in THF at 23 °C also demonstrated significant stereochemical drift; the *Z*- and *E*-β-methylstyrenes (**9b** and **10b**) were formed in 1.1:1 and 2.0:1 ratios, respectively.

Since Wittig reactions of trialkylphosphonium ylides have the special distinction of providing high *E* stereoselectivity,[1a,2a,21] we turned our attention to this area. We hoped to shed some light on the source of this unusual *E* stereoselectivity, a subject which has attracted current interest.[2a,21b] A recent mechanistic proposal by Schlosser and Schaub[2a] was founded on the assumption that the original isomer ratio of Wittig intermediates is not altered by subsequent stereomutation during their decomposition to alkenes (i.e., no stereochemical drift).

Ylide **11** was first prepared by deprotonation of phosphonium salt **2** with *n*-butyllithium in THF in an NMR tube. Addition of benzaldehyde at −78 °C, followed by agitation, resulted in a heterogenous mixture, which was spun in a centrifuge to compact the white precipitate. The clear solution was examined by ^{31}P NMR at −40 °C. No oxaphosphetane signals were detected; only a singlet for *n*-$Bu_3P{=}O$ and absorptions in the P(IV) phosphonium domain, presumably for betaine species, were recorded, Such betaines may be stabilized as LiBr complexes.[4a] The reaction involving *n*-BuLi, conducted in the normal synthetic manner at 23 °C, afforded a modest yield (29%) of styrenes **9a** and **10a** in a 16:84 ratio. Salt-free conditions turned out to be much more rewarding. Ylide **11** was isolated by distillation as a pale yellow, air-sensitive liquid (δ ^{31}P 8.7), usually contaminated with about 5% *n*-$Bu_3P{=}O$ (δ ^{31}P 40.8).[22] Strictly salt-free ylide **11** was mixed with benzaldehyde in THF at −78 °C. The ^{31}P NMR spectrum of this clear solution at −60 °C displayed two sharp singlets at −70.2 and −71.0 ppm in a ratio of 47:53 for oxaphosphetanes **5a** and **6a** (R = *n*-Bu). On warming, it became obvious that the temperature for decomposition of oxaphosphetanes into olefins was elevated relative to the corresponding triphenyl case. Indeed, we observed the downfield oxaphosphetane signal convert almost completely into the upfield signal [**5a**:**5b** (R = *n*-Bu) = 2:98] prior to significant creation of tributylphosphine oxide (and, necessarily, alkenes). The phosphine oxide was not readily evolved, with concomitant depletion of oxaphosphetanes, until the temperature was raised to −5 °C. Rate studies on this reaction will be described later on, Since the initial ratio of 47:53 did not change when a solution was kept for several hours in the NMR probe at −60 °C, we concluded that this represented the kinetic ratio corresponding to initial carbon–carbon bond formation.[11] However, to test this question, a mixture of **5a** and **6a** (R = *n*-Bu) was prepared as above at −78 °C and quenched with gaseous HBr at −78 °C, forming β-hydroxyphosphonium salts **7a** and **8a** (R = *n*-Bu). High-field ^{13}C and ^1H NMR spectra of this mixture revealed precisely a 47:53 mixture of erythro and threo isomers. Additionally, we equilibrated the oxaphosphetanes and quenched the reaction with HBr prior to major formation of alkene. Thus, a reaction of **11** and benzaldehyde at −78 °C was stirred at −20 °C for 20 min, then quenched to give β-hydroxyphosphonium salt containing ≥98% threo isomer **8a** (R = *n*-Bu),

Reaction of **11** with hexanal at −60 °C produced not only pentavalent phosphorus species, **5c** and **6c** (R = *n*-Bu), at −69.3 and −72.8 ppm in a ratio of 14:86 but also a large peak at 32.8 ppm (ca, 30% of the phosphorus-containing material). No change occurred on standing at −30 °C. On warming of the reaction to 23 °C, the peak at 32.8 ppm did not disappear. The abnormal signal is tentatively assigned to the phosphonium enolate of hexanal, a product of acid-base chemistry due to the heightened basicity of ylide **11** vis-à-vis ylide **4**. On workup, the final ratio of alkenes, **9c** and **10c**, was 10:90, indicating a preference for *trans*-oxaphosphetane on initial oxaphosphetane formation and minor stereochemical drift. However, these results might be distorted because of the (alleged) phosphonium enolate. A mixture of **11** and hexanal at −78 °C was quenched with HBr to supply erythro and threo salts, **7c** and **8c** (R = *n*-Bu). The composition was ascertained as 22:78 by a 360-MHz ^1H NMR spectrum and 20:80 by 145.8-MHz ^{31}P and 90.55-MHz ^{13}C NMR spectra. So, the low-temperature ratio of *cis*- and *trans*-oxaphosphetanes representing the carbon–carbon bond-forming step (i.e., kinetic control of stereochemistry) is more likely in the vicinity of 20:80 than 14:86 (disclosing some stereochemical drift).

To avoid the possible problem of enolate formation, we switched to pivaldehyde, which does not possess acidic α protons. An identical reaction with pivaldehyde at −50 °C did not produce any tetravalent phosphorus peaks and gave two pentavalent phosphorus peaks at −70.1 and −74.0 ppm in a ratio of ca. 30:70 for **5d** and **6d** (R = *n*-Bu); ylide **11** was completely consumed. On warming to −15 °C, the oxaphosphetane ratio became 1:99 prior to significant (>5%) production of tributylphosphine oxide (ergo, alkenes **9d** and **10d**). The final ratio of alkenes, **9d** and **10d**, was 4:96, clearly demonstrating stereochemical drift. For confirmation of this behavior, **11** and pivaldehyde were combined at −78 °C and directly quenched with gaseous HBr to obtain salts **7d** and **8d** (R = *n*-Bu). Their respective ratio was established as 43:57 by 360-MHz ^1H and 90,56-MHz ^{13}C NMR spectra and 40:60 by a 145.8-MHz ^{31}P NMR spectrum. This reflects a somewhat greater enrichment in the *cis*-oxaphosphetane, possibly due to the reduced temperature of the quench experiment (similar to what was seen with hexanal, above). The proximity of this ca. 40:60 ratio for pivaldehyde to the 47:53 ratio for benzaldehyde means that there is no more than a minor difference between the initial stereochemistry (that for the C–C bond-forming process) in the reaction of ylide **11** with an aromatic vs. an aliphatic aldehyde. Additionally, a reaction of **11** and pivaldehyde at −78 °C was warmed to −10 °C and held there for 30 min to induce equilibration, but complete conversion to alkenes was avoided. Treatment with HBr at −10 °C yielded the β-hydroxyphosphonium salt material, which contained greater than 98% threo isomer, **8d** (R = *n*-Bu), by ^1H, ^{13}C and ^{31}P NMR spectra.

Concentration Effect in Lithium–Salt Reactions. There are two factors governing olefin stereochemistry in the reaction of nonstabilized phosphorus ylides and aldehydes in the presence of lithium. First, the extent of *trans*-oxaphosphetane formed during the condensation, and, second, the extent to which the ratio shifts to the more stable *trans*-oxaphosphetane before or during decomposition. Since we had encountered the problem of concentration effects in Wittig reactions earlier,[5] we examined the concentration dependence of stereochemistry in the reaction of **4** and benzaldehyde in THF with LiBr present. By varying the amount of THF solvent and monitoring the stereochemistry of oxaphosphetanes by ^{31}P NMR or alkenes by GLC, we obtained data showing a profound concentration effect.[14] Increasing reaction concentration favored *trans*-oxaphosphetane, according to a hyperbolic relationship.[14] Reaction concentration not only has a dramatic impact on the degree of initial *trans*-oxaphosphetane formation but also on the degree of stereochemical drift. At 0.015 M, there is virtually no *trans*-oxaphosphetane, and the alkenes are produced in a *Z*/*E* ratio of 98:2. At 1.0 M, there is a 73:27 ratio of **5a** and **6a** (R = Ph) and a 37:63 mixture of *Z* and *E* alkenes.

This concentration dependence in THF (with LiBr present) should not be underestimated since it has important ramifications on the reproducibility of Wittig reactions. The seriousness of this can be appreciated by comparing two normal reactions, at a concentration of 0.5 and 0.2 M. We obtained 57% *E* alkene at 0.5 M and 42% *E* alkene at 0.2 M, a fairly large disparity. Interestingly, the degree of stereochemical drift became vanishingly small at high dilution. In fact, at high dilution the alkenes were formed with the same *Z* selectivity that is normally seen in lithium salt-free reactions, which suggests that the concentration effect may be associated with the sequestration of lithium by THF.

(21) (a) Bissing, D, E. *J. Org. Chem.* **1965**, *30*, 1296. (b) Meyers, A. I.; Lawson, J. P.; Carver, D. R. *Ibid.* **1981**, *46*, 3119.
(22) Schmidbaur, H.; Tronich, W. *Chem. Ber.* **1968**, *101*, 595.

Bolstering this idea is the absence of a concentration effect in the corresponding Na–salt reaction of **4** and benzaldehyde.[14]

At sufficiently elevated levels of lithium salt, it is possible to intercept oxaphosphetanes as betaine complexes,[2d] In this respect, we combined ylide **4** and benzaldehyde at −78 °C, at the low concentration of 0.03 M, and LiBr dissolved in THF (1.8 M solution) was then added to adjust the LiBr concentration in the mixture to 0.39 M. ^{31}P NMR spectra showed no peaks for **5a** and **6a** (R = Ph); on the contrary, only four peaks in the P(IV) region, between 23 and 30 ppm, were visible, some probably due to betaines. A virtually identical conclusion was reached when addition of LiBr to **4** preceded the addition of benzaldehyde.

The ability of soluble Li salts in the Wittig reaction of nonstabilized ylides to promote the production of *E* alkene at the expense of *Z* alkene has long been recognized; however, it now must be appreciated that this phenomenon can be very concentration dependent, at least in THF.[14] On the basis of the concentration dependency, we were able to distinguish the lithium-catalyzed and lithium-uncatalyzed components of the reaction of **4** and benzaldehyde in THF.[14]

NMR Rate Studies and Kinetic Analysis. The ability to observe individual oxaphosphetane diastereomers directly allowed us to perform the first detailed rate studies on the Wittig reaction, which, in turn, helped us pinpoint the source of the thermodynamic control discussed above. Solutions of oxaphosphetanes, prepared from ylide and aldehyde at −78 °C, were allowed to decompose slowly at a controlled temperature in the NMR probe, while spectra were automatically acquired at set time intervals. We were careful to ensure that (1) relaxation times of the observed nuclei were sufficiently short for accurate integration and (2) the time required for accumulation of the transients for each data point was <5% of $t_{1/2}$, so that a large part of the reaction did not transpire during collection of each timepoint. Consequently, preliminary testing was required before full-blown kinetics experiments could be transacted. We intently studied in THF-d_8 (1) the reaction of **4** and benzaldehyde (with LiBr present) by high-field $^1H/^{31}P$ NMR, (2) the reaction of **4**, enriched at the ylidic carbon with ^{13}C (92 atom %), and benzaldehyde (LiBr present) by high-field ^{13}C NMR, (3) the reaction of **11** and benzaldehyde (salt-free) by high-field $^1H/^{31}P$ NMR, and (4) the reaction of **11** and benzaldehyde, enriched at the formyl carbon with ^{13}C (99 atom %), by high-field ^{13}C NMR, and (5) the reaction of lithium salt-free **4** and [α-^{13}C]benzaldehyde by high-field ^{13}C NMR.

The $^1H/^{31}P$ NMR (360/145.8 MHz) experiments were carried out by repeatedly switching between the ^{31}P and ^1H modes at regular intervals. Thus, we were able to monitor the depletion of oxaphosphetanes and increase of phosphine oxide by ^{31}P NMR and the augmentation of the *Z* and *E* olefins by ^1H NMR. Analysis of the isomeric oxaphosphetanes and the phosphine oxide by integration of their singlets was straightforward; the isomeric oxaphosphetanes could not be readily assayed by ^1H NMR. To assay the alkenes, the upfield vinylic proton of **9a**, a multiplet in the ^1H NMR spectrum at δ 5.65, was integrated relative to the downfield vinylic protons at δ 6.2–6.5, comprising the other vinylic proton for **9a** and the two vinylic protons for **10a**. It was not necessary to proton decouple the ^{31}P NMR because of narrowness of the peaks. This avoided differential heating effects in $^{31}P/^1H$ experiments.

^{13}C NMR (90.5 MHz, proton-decoupled) experiments may be preferable because they avoid switching between different nuclei; however, they demand the introduction of a suitably high level of an appropriate ^{13}C label. The ^{13}C enrichment serves two critical purposes: (1) to afford diagnostic signals for the species of interest in the midst of many undesired, extraneous signals (selective detection and quantitation) and (2) to diminish the number of transients to be accrued for each data point (adjustment of the time frame). Thus, we monitored four ^{13}C-enriched molecules, the oxaphosphetanes and alkenes with time (vide infra).

According to the $^1H/^{31}P$ protocol, three separate sets of data were accumulated at −30 °C for the first two half-lives in the reaction of **4** and benzaldehyde. Here (as in our preliminary communication[11]) we cite an example at 0.36 M with absolute, as opposed to relative, quantitation by use of a sealed capillary holding reference compounds (trimethyl orthobenzoate and trimethyl phosphite).[23] A table containing this set of rate data, for the five observed species over the reaction course, is furnished in the supplementary material.[24] The two other runs were ostensibly similar to this one.

Elaborating on this study, we investigated the same reaction by using ^{13}C-labeled **4**. Quantitation of oxaphosphentanes and alkenes was achieved by integration of the labeled-carbon doublets centered at δ 71.5 ($^1J_{PC}$ = 85.0 Hz) for **5a** (R = Ph) and δ 75.0 ($^1J_{PC}$ = 83.7 Hz) for **6a** (R = Ph) and the labeled-carbon singlets at δ 132.5 for **9a** and δ 130.0 for **10a**. Three separate sets of data were gathered at −30 °C for the first 2–3 half-lives of the reaction. Here (as well as in our communication[11]) we present an example at 0.25 M that encompasses 3 half-lives. A table of complete rate data for the four observed species is in the supplementary material.[24] The other two runs were similar to this one.

Our ^{13}C NMR data have some bearing on the question of whether or not eight-membered ring dimers are present as intermediates in the Wittig reaction, a subject which was broached by Vedejs.[2d] Such dimers could exist as four diastereomers. ^{13}C NMR, with its wide (220-ppm) chemical shift dispersion, should be able to detect these species as a multiplicity of resonances. However, this was not the case. We observed just two pairs of lines for **5a** and **6a** (R = Ph). In further support of the four-membered ring structures, we note that *cis*-oxaphosphetane **5a** (R = Ph) resonates upfield of *trans*-oxaphosphetane **6a** (R = Ph), which agrees with the expected steric effect on the ^{13}C chemical shift.

We also collected data for the reaction of ylide **11** and benzaldehyde. In this case, the two reactions, oxaphosphetane equilibration and alkene formation, did not proceed readily at the same temperature. As discussed previously,[11] a ^{31}P NMR study showed that oxaphosphetane **5a** (R = *n*-Bu) was transformed to **6a** (R = *n*-Bu) with a $t_{1/2}$ of ca. 130 min at −40 °C, while the phosphine oxide remained constant; **6a** (R = *n*-Bu) was transformed to phosphine oxide (thus alkene) with a $t_{1/2}$ of ca. 380 min at −10 °C. A table of rate data appears in the supplementary material.[24] Unfortunately, since oxaphosphetane equilibration and alkene production were highly biased (to the trans/*E* isomer), the measurements of *cis*-oxaphosphetane **5a** (R = *n*-Bu) and, especially, *Z* alkene **9a** are inaccurate at −10 °C.

We thought that a ^{13}C NMR experiment could help here because of the sharp resonances for the labeled alkenes. If precursor phosphonium salt **2** were tagged on one butyl group, the label in ylide **11** would be distributed to the extent of just 25% on the ylidic position (and, quadruple labeling is difficult and expensive). Therefore, we explored the reaction of **11** with benzaldehyde enriched in ^{13}C at the formyl carbon. Oxaphosphetane equilibration was followed at −40 °C for 2 half-lives via the broadened doublets for **5a** (R = *n*-Bu) at δ 68.2 ($^2J_{PC}$ = 13.6 Hz) and the narrow doublets for **6a** (R = *n*-Bu) at δ 71.1 ($^2J_{PC}$ = 13.8 Hz); then the collapse of oxaphosphetanes to alkenes was followed at −10 °C for 3 half-lives via the alkene singlets at δ 129.9 for **9a** and δ 131.1 for **10a**. Rate data are amassed in a table in the supplementary material.[24] Two NMR stacked plots for this reaction are illustrated in Figure 3, and a kinetic plot is depicted in Figure 4.

Before proceeding further, we wish to point out that resonances for *cis*-oxaphosphetanes were generally broadened relative to those for *trans*-oxaphosphetanes or those for other resonances present, whether using ^{13}C or ^{31}P NMR.[14] In reactions containing lithium salt, we tended to ascribe this behavior to complexation of the *cis*-oxaphosphetane, especially since the resonance sharpened under high dilution. However, several lithium salt-free examples (with **11**) indicate that some other cause must be invoked. The

(23) The presence of the references for standardizing quantitation is necessitated by the two different spectral environments; the ^1H and ^{31}P NMR spectra need to be correlated.

(24) See the paragraph at the end of this article regarding supplementary material.

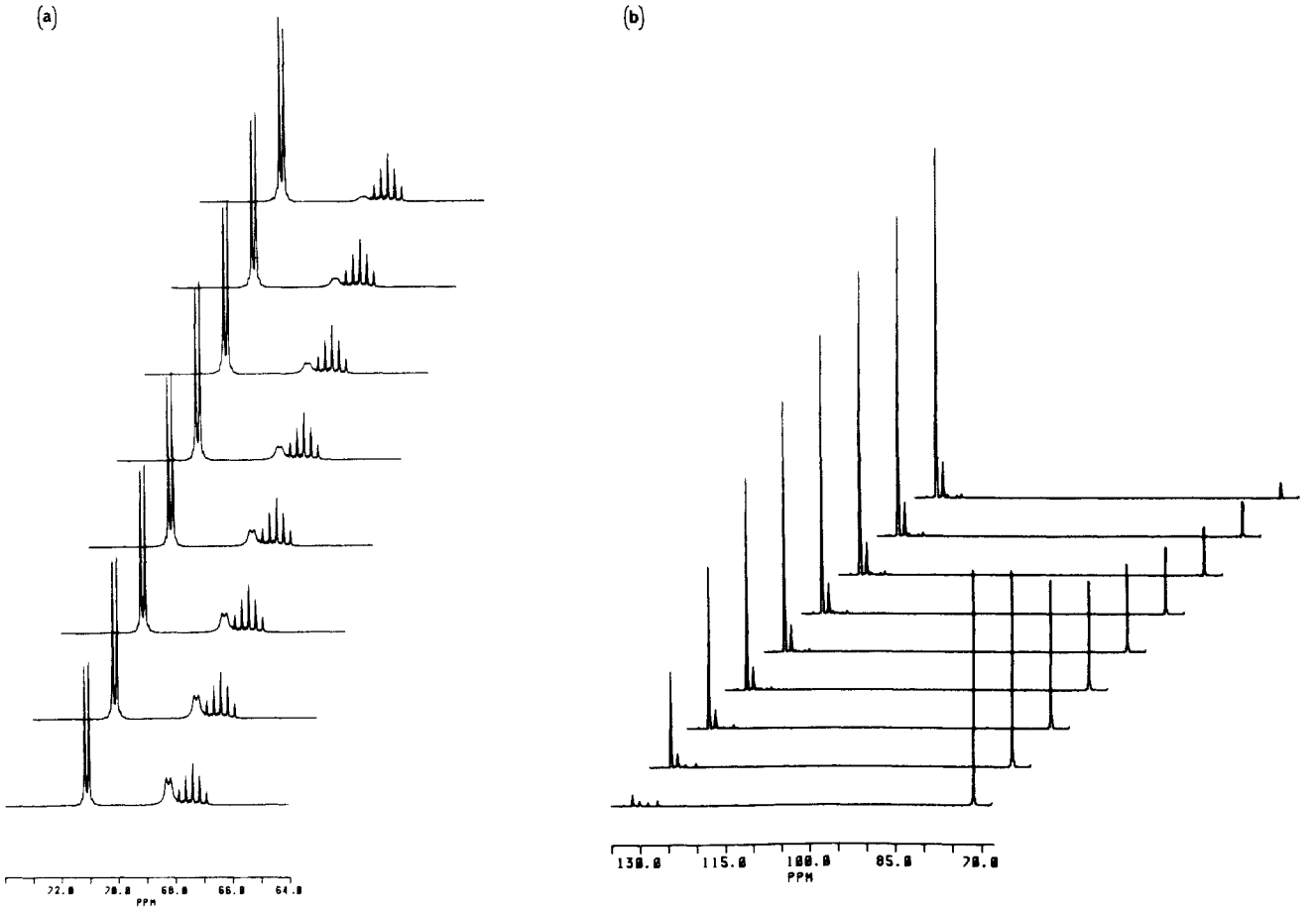


Figure 3. NMR stacked plots for the reaction of **11** with benzaldehyde-α-^{13}C. Panel (a): data collected at −40 °C, representing equilibration of **5a** and **6a** (R = *n*-Bu); time points (from bottom to top) are 14.6, 62.6, 98.6, 134.6, 170.6, 206.6, 242.6, and 350.6 min. Panel (b): data collected at −10 °C, representing formation of alkenes **9a** and **10a**; time points (from bottom to top) are 18.4, 123.4, 213.4, 303.4, 393.4, 483.4, 573.4, 663.4, and 753.4 min.

Table I. Rate Data from Kinetic Experiments[a]

parameter	**4** + PhCHO $^{31}P/^{1}H$ expt	**4** + PhCHO ^{13}C expt	**4** + PhCHO ^{13}C expt ($k_4 = 0$)	**11** + PhCHO ^{13}C expt
k_1/k_2	3.50	5.25	5.01	0.89
k_3	13.9 ± 2.7	9.2 ± 1.8	6.5 ± 0.3	120 ± 30[b]
k_4	0.9 ± 1.3	1.2 ± 0.8	0	4.0[b]
k_5	4.78 ± 0.04	5.68 ± 0.02	5.68 ± 0.02	16.3 ± 0.5[c]
k_6	7.90 ± 0.09	6.78 ± 0.08	6.77 ± 0.08	4.65 ± 0.02[c]
$[\mathbf{5a}]_0$	0.28 ± 0.002	0.210 ± 0.001	0.209 ± 0.001	0.066
$[\mathbf{6a}]_0$	0.08 ± 0.002	0.040 ± 0.001	0.042 ± 0.001	0.074

[a] Rate constants have the units 10^{-5} s^{-1}. Initial concentrations (subscripted with zero) are molar. The error limits represent one standard deviation. Rate constants were determined at −30 °C, except as specified otherwise. The ratio k_1/k_2 applies to the ratio of isomeric oxaphosphetanes at low temperature (−78 to −50 °C), where subsequent reactions are slow. [b] Determined at −40 °C. [c] Determined at −10 °C.

broadening was somewhat temperature-dependent, suggesting a dynamic process of some kind (perhaps oxaphosphetane–betaine interconversion or phosphorus pseudorotation). Currently, we do not understand this broadening phenomenon.

The reaction pathway delineated in Scheme I was considered in our generalized kinetic analysis. Overall, *cis*- and *trans*-oxaphosphetanes equilibrate by some means and decay irreversibly to alkenes and phosphine oxide; both of these are first-order reaction processes. We have assumed that oxaphosphetane equilibration entails reversal to ylide and aldehyde, rather than direct interconversion, which seems reasonable based on crossover reactions (vide infra).[2d,4] (In any event, regardless of the means for epimerization, a similar, albeit not identical, relationship would obtain for the rate constants.) Ylide and aldehyde couple in a second-order reaction to supply *cis*- and *trans*-oxaphosphetanes with rate constants k_1 and k_2. This reaction is exceedingly rapid at low temperatures so rate data cannot be acquired to determine the absolute values for k_1 and k_2. Also, given the fact that neither ylide nor aldehyde could be detected spectroscopically, we have employed a steady-state approximation wherein their rate of disappearance equals their rate of reformation (i.e., k_1 and k_2 are much faster than k_3 and k_4). Therefore, we consider the change in concentration of ylide or aldehyde with time to approximate zero. At low temperature before the oxaphosphetanes undergo any observable changes, the original ratio of *cis*- and *trans*-oxaphosphetanes, which corresponds to k_1/k_2, can be determined. This low-temperature value reflects the ratio of k_1 and k_2 because these rate constants are very much larger than those for the reversal (k_3 and k_4) or decomposition (k_5 and k_6) of oxaphosphetanes (i.e., at low temperature k_3, k_4, k_5, and k_6 are effectively zero). The ratio k_1/k_2 is assumed to be little effected by temperature over the narrow range used for the present analyses. Thus, the rate data were analyzed in terms of equations derived from first-order reaction kinetics,[25] by employing the k_1/k_2 value.

(25) (a) Moore, W. J. *Physical Chemistry*, 4th ed.; Prentice Hall: Englewood Cliffs, NJ, 1972; Chapter 9. (b) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*; Wiley: New York, NY, 1953.

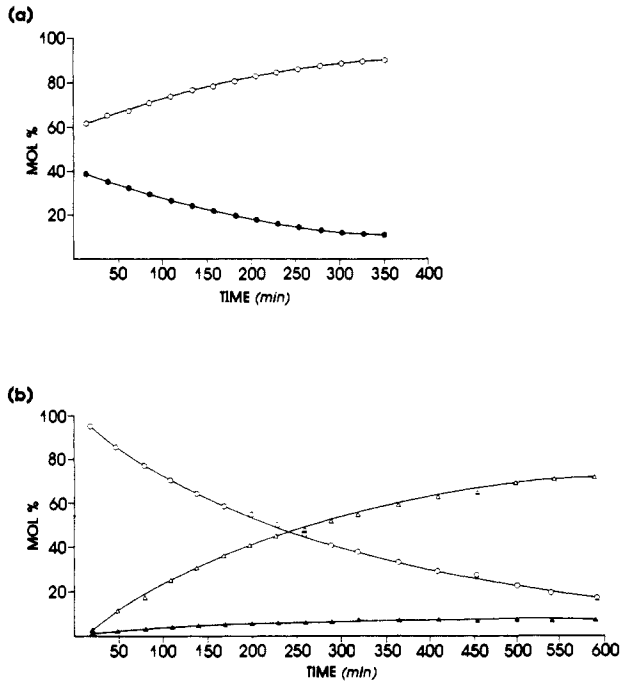


Figure 4. Kinetic plots for the reaction of **11** and benzaldehyde-α-^{13}C, derived from ^{13}C NMR data (THF-d_8). Panel (a) represents the reaction at −40 °C; only every other data point is displayed; legend: (●) **5a** (R = *n*-Bu), (○) **6a** (R = *n*-Bu). Panel (b) represents the reaction at −10 °C; only every other data point is displayed from 0–350 min; legend: (○) **6a** (R = *n*-Bu), (▲) **9a**, (△) **10a**; **5a** (R = *n*-Bu) could not be measured.

The equations are presented in the Experimental Section. Iterative analysis of the experimental data according to the rate equations with a computer program[26] generated the rate constants listed in Table I. In the reaction of **4** and benzaldehyde, the iterative computation gave an estimated k_1/k_2 ratio for the reaction temperature that compared well with the oxaphosphetane cis/trans ratio measured at low temperature, by extrapolation to a "real" $t = 0$ (see Experimental Section).[27] In the reaction of **11** and benzaldehyde, the low-temperature (−40 °C) process had to be dealt with independently and before the other. Once the equilibration was evaluated, the harvested information was applied to the analysis of the high temperature (−10 °C) situation. It should be noted that the absolute numbers extracted from the computational analysis do not necessarily have great significance because of fairly large error limits (see Experimental Section). Nevertheless, the relative values for rate constants in a particular experiment afford a good impression of the degree of competition between the individual processes.

Results for the reaction of ylide **4** and benzaldehyde (LiBr present) were already described in an earlier account, where kinetic plots for the ^{1}H/^{31}P and ^{13}C NMR experiments can be surveyed (these plots are not repeated herein).[11] For this reaction, the rate of depletion of the *cis*-oxaphosphetane (**5a**, R = Ph) was significantly greater than that of the *trans*-oxaphosphetane (**6a**, R = Ph), while alkenes **9a** and **10a** emerged at similar rates (Table I). In the ^{1}H/^{31}P investigation, the *cis*-oxaphosphetane reverted to **4** and benzaldehyde ca. 15 times faster than the *trans*-oxaphosphetane, the *E* alkene (**10a**) formed ca. 1.6 times faster than the *Z* alkene (**9a**), and stereochemical drift was represented by the initial ratio of **5a**:**6a** (R = Ph) of 78:22 vs. a final ratio of **9a**:**10a** of 55:45. In the ^{13}C NMR study, **5a** (R = Ph) reverted to **4** and benzaldehyde ca. 8 times faster than **6a** (R = Ph), **10a** formed ca. 1.2 times faster than **9a**, and the initial value for **5a**:**6a** (R = Ph) was 82:18 compared to a final value for **9a**:**10a** of 72:28. Obviously, the k_3/k_4 ratio, in the range of 8–15 from this data, is a key element in governing the degree of stereochemical drift.

However, an exploration of crossover reactions[12] revealed an even greater disparity between k_3 and k_4, so that the ratio is probably at least in the area of 70 (see next section). In fact, analysis of the data from the ^{31}P/^{1}H NMR kinetic experiment gave a standard deviation for k_4 that encompasses zero. The standard deviation for k_4 in the ^{13}C NMR experiment was smaller but still wide-ranging. Out of curiosity, we analyzed the data from the ^{13}C NMR experiment with k_4 set to zero, to see if this would afford a better picture of the reaction. The results of this analysis showed a much *reduced* standard deviation for k_3 as well as *reduction* of the value of k_3 by ca. 30% (Table I). The values for k_5 and k_6 were little changed by this approximation. The rate of reversion of **5a** (R = Ph) and the rates of decomposition of **5a** and **6a** (R = Ph) to alkenes are within 20% of each other. This signals a dynamic system in which stereochemical drift is caused by the diminished reversal of **6a** (R = Ph) to ylide and aldehyde.

^{13}C NMR results for the reaction of **11** and benzaldehyde, displayed in Figure 4 (only every third data point is shown), indicate that k_3 is ca. 35 times greater than k_4 and that *Z* alkene **9a** forms ca. 3 times faster than *E* alkene **10a** (Table I). Stereochemical drift is marked by a change of the initial ratio for **5a**:**6a** (R = *n*-Bu) of 47:53 to 2:98 and a final **9a**:**10a** alkene ratio of 10:90. Interestingly, although the *cis*-oxaphosphetane is much less favored thermodynamically over the trans (2:98), the *Z*/*E* alkene ratio (10:90) demonstrates a retrenchment of *E* stereoselectivity, connected with k_5 being greater than k_6. At −10 °C, where the alkenes arise at a significant rate, a comparatively rapid underlying equilibrium between **5a** and **6a** (R = *n*-Bu) is proceeding because of the large k_3: $k_3 = 7k_5 = 25k_6$, whereas $k_4 = 0.25k_5 = 0.85k_6$ (k_4 may actually be much smaller than this suggests; vide supra). This sets the stage for a displacement of the stereochemistry as a function of the relative rates. Also, some alkene, preferentially *Z*, is produced early in the reaction (at −40 °C), to the extent of ca. 5%.

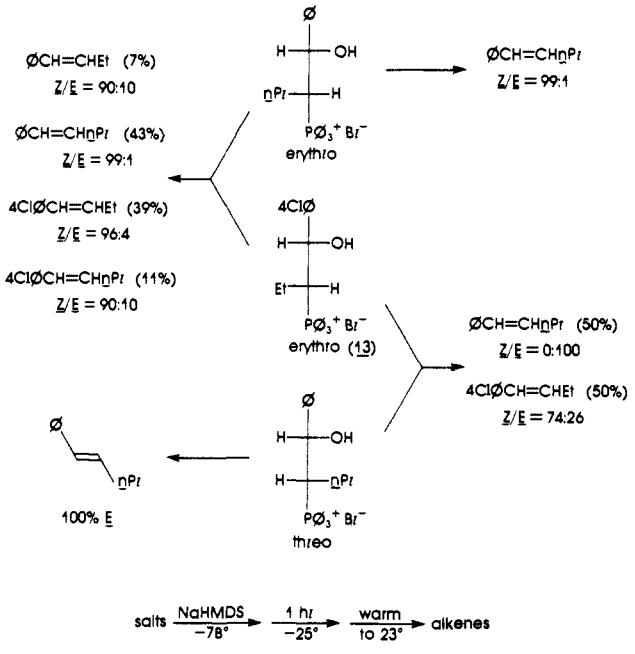
It is interesting to compare the kinetic results for the triphenyl and tributyl systems. For this purpose, we can adjust the rate constants for the tributyl case from −10 to −30 °C, assuming that the rate decreases by a factor of 2.0 for every 10 °C. This provides the following approximate values: $k_3 = 18$, $k_4 = 0.6$, $k_5 = 2.5$, and $k_6 = 0.7\ 10^{-5}\ s^{-1}$. The triphenyl case (−30 °C) has the following rate constants (^{13}C NMR study in Table I): $k_3 = 9.2$, $k_4 = 1.2$, $k_5 = 5.7$, and $k_6 = 6.8\ 10^{-5}\ s^{-1}$. One can appreciate that the tributyl groups relative to the triphenyl groups enhance reversal of the *cis*-oxaphosphetane and diminish reversal of the *trans*-oxaphosphetane by a factor of about 2; also, the tributyl groups detract from the rate of *Z* and *E* alkene development by factors of 2 and 10, respectively. The differences between the two systems are consequential but not striking. Increased stability of oxaphosphetanes bearing alkyl instead of phenyl substituents on phosphorus was mentioned by Bestmann[1i] and was implicit in a paper by Schlosser.[2a]

In correlating our rate data for the tributyl and triphenyl systems, it must be kept in mind that the triphenyl reaction occurred in the presence of lithium salt, while the tributyl reaction was salt-free. To determine if LiBr has any effect on the propensity of oxaphosphetanes to degrade to products, we carried out a rate study on the reaction of **4**, from **1** and NaHMDS, with ^{13}C-labeled benzaldehyde. Since this salt-free reaction supplies only minor amounts of **6a** (R = Ph) and **10a**, we could not examine all of the species quantitatively. ^{13}C NMR data were collected at −25 °C. Oxaphosphetanes **5a** and **6a** (R = Ph) appeared as doublets at 69.2 and 72.3 ppm ($^2J_{PC}$ = 16.4 and 15.3 Hz) in a ratio of ca. 98:2, and olefins **9a** and **10a** appeared as singlets at 129.8 and 131.0 ppm in a ratio of >95:5. The GLC ratio of **9a** to **10a**, after workup, was 99:1, which compares to a 96:4 ratio

(26) Computations were performed with a statistical program for estimating the parameters of nonlinear equations: Metzler, C. M.; Elfring, G. L.; McEwen, A. J. *Biometrics* **1974**, *30*, 562. We employed the 1976 revision, available from the Upjohn Co., Kalamazoo, MI.

(27) Because of the elapsed time (ca. 20 min) for thermal equilibration of the sample in the NMR probe at the reaction temperature, and because of the ca. 3% of reaction that transpired during accumulation of transients for the first data point, the reaction had progressed beyond the true $t = 0$ on acquisition of the first point. The "real" $t = 0$ concentration data were ascertained by iterative computation, wherein an offset in the time scale was introduced into the curve-fitting procedure.

Scheme II



for this reaction at 23 °C (with unlabeled benzaldehyde). The rate of conversion of **5a** to **9a** (k_5) was calculated to be 9.5×10^{-5} s^{-1}, which is rather close to k_5 (5.7×10^{-5} s^{-1} at −30 °C) for the reaction containing LiBr.

Crossover Experiments. Reversibility of intermediates in the Wittig reaction has been detected previously by crossover experiments, in which an adduct from an aldehyde and ylide was treated with a different ylide or aldehyde.[2d,4] Alkene products resulting from reaction of components of the original adduct (either ylide or aldehyde segment) and the added ylide or aldehyde had to arise from reversible dissociation of the first adduct before its decomposition to alkene. (Of course, in the case of addition reactions formation of adduct ought to be corroborated in some way.) With this protocol, it has been established that oxaphosphetanes derived from aromatic aldehydes are freely reversible, but those from aliphatic aldehydes generally are not.[2d,4a,28]

With diastereomerically pure erythro and threo salts (**7a** and **8a**, R = Ph) in hand, we were poised to explore some interesting crossover reactions.[12] Threo isomer **8a** (R = Ph) did not experience any reversion to ylide and aldehyde, within our limits of detection (GLC). On deprotonation of **8a** (R = Ph), *E* alkene was faithfully generated, and no crossover products were discovered. By contrast, **7a** (R = Ph) on deprotonation suffered significant stereochemical drift to *E* alkene (in the presence of Li, but not Na) and there was an abundance of crossover products. Remarkably, mixtures of **7a** and **8a** (R = Ph) decomposed to alkene with stereospecificity that was different from what would be expected based on their separate reactivity. There appears to be a synergistic interaction of the threo isomer with the erythro isomer, causing the latter to undergo more stereochemical drift than would be predicted if the erythro isomer were alone.[12]

The properties of **7a** and **8a** (R = Ph) on deprotonation to oxaphosphetanes **5a** and **6a** (R = Ph), followed by decomposition to alkenes (**9a** and **10a**) and phosphine oxide, can be readily appreciated by a fascinating set of double-label crossover experiments involving mixtures of erythro and threo salts composed of different aldehyde and ylide fragments (**7a** and **8a**, R = Ph; **13**) (Scheme II). Deprotonation of an erythro–threo mixture, **13** and **8a** (R = Ph), with NaHMDS provided only direct products (i.e., no crossed alkenes) with the erythro-derived alkene evincing substantial stereochemical drift. On the other hand, an erythro–erythro combination, **13** and **7a** (R = Ph), gave a complex mixture containing all possible alkenes, with very little stereochemical drift in the direct products but a small amount in the crossed products. It is manifest that the presence of *trans*-oxaphosphetane (from deprotonation of the threo salt) induced stereochemical drift in the *cis*-oxaphosphetane (from deprotonation of the erythro salt). In the erythro–threo case, crossed alkenes were not realized because the *trans*-oxaphosphetane (from **8a**, R = Ph) did not undergo reversal to aldehyde and ylide at a rate sufficiently competitive relative to the rate for genesis of alkenes. In the erythro–erythro case, contrarily, crossed alkenes were realized because the two different (but very similar), intermingled *cis*-oxaphosphetanes (from **7a**, R = Ph, and **13**) suffered competitive reversal.

We also pursued the crossover characteristics of **7a** and **8a** (R = *n*-Bu). A sample highly enriched in **8a** (R = *n*-Bu) was gleaned from a mixture of **5a** and **6a** (R = *n*-Bu), after equilibration at −20 °C for 20 min and quenching with HBr (erythro/threo = 2:98). A syrup replete with **8a** (R = *n*-Bu) was deprotonated by NaHMDS in THF at −78 °C, treated with 4 molar equiv of 4-chlorobenzaldehyde, and allowed to warm to 23 °C. GLC analysis revealed no crossover products. On the other hand, the same experimental protocol with a 47:53 mixture of **7a** and **8a** (R = *n*-Bu) produced a large quantity of crossed alkenes (totaling ca. 40%), which exhibited stereochemical drift (Z/E = 16:84). Direct Wittig reaction involving ylide **11** and benzaldehyde (2 molar equiv) at −78 °C, followed by addition of 5 molar equiv of 4-chlorobenzaldehyde and warming, led to a significant amount (ca. 60%) of crossed alkenes (Z/E = 12:88) (the ratio of **9a**:**10a** was 13:87). Unfortunately, testimony for reversibility of *trans*-oxaphosphetane (**6a**, R = *n*-Bu) again could not be harvested from a crossover experiment with a *threo*-β-hydroxyphosphonium salt (**8a**, R = *n*-Bu). Nevertheless, some reversal of **6a** (R = *n*-Bu) may be suggested by the kinetics studies, particularly the retrogression of *E* alkene stereoselectivity from the level of *trans*-oxaphosphetane.

Reactions of Semistabilized and Stabilized Ylides

To extend our studies, we also investigated ylides bearing groups that delocalize the high electron density on the carbanion carbon α to the phosphorus atom. Such ylides, classified as semistabilized or stabilized depending on the degree of charge delocalization, have been the subject of numerous mechanistic and kinetic studies.[1,30] Of course, we hoped to be able to detect stable Wittig intermediates from these ylides at low temperature, if not individual diastereomers.

Stabilized ylide **14**, a reagent often used in the preparation of α,β-unsaturated esters,[1a] would not combine readily with benzaldehyde in THF at −40 °C, but reaction did occur at −20 °C, as judged by ^{31}P NMR. No short-lived intermediates were detected; we only found singlets due to unreacted **14** (δ 16.5) and triphenylphosphine oxide (δ 23.3) as the reaction progressed. Altogether, the course of reaction was monitored for a 3-h period with incremental increases of temperature from −20 to 10 °C, whence ylide **14** was substantially depleted. The cinnamic ester was produced in good yield (83%, isolated) with a preponderance of the *E* isomer (Z/E = 3:97).

To boost nucleophilicity of the ylide and thereby elevate the reaction rate, we switched to the corresponding tributylphosphorus ylide **15**. As conjectured, this ylide easily reacted with benzaldehyde at temperatures as low as −50 °C. At −40 °C, the ylide (δ ^{31}P 20.1) disappeared with a $t_{1/2}$ of 60 min in a unimolecular fashion, while tributylphosphine oxide (δ ^{31}P 44.4) and (presumably) the cinnamic ester developed. Workup of the mixture yielded

(28) (a) Anderson, R. J.; Henrich, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327. (b) Reversibility has been demonstrated for an oxaphosphetane derived from an aliphatic aldehyde in only two instances: in a reaction of a triphenyl phosphorus ylide bearing an oxido substituent[29a] and in a reaction of a diphenylalkylallylide.[29b]

(29) (a) Reitz, A. B.; Maryanoff, B. E. *J. Chem. Soc., Chem. Commun.* **1984**, 1548. (b) Vedejs, E.; Fang, H. W. *J. Org. Chem.* **1984**, *49*, 210.

(30) Semistabilized ylides: (a) Jones, M. E.; Trippett, S. *J. Chem. Soc. C* **1966**, 1090. (b) Johnson, A. W.; Kyllingstad, V. L. *J. Org. Chem.* **1966**, *31*, 334. (c) Allen, D. W.; Ward, H. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1980**, *35b*, 754. Stabilized ylides: (d) Speziale, A. J.; Bissing, D. E. *J. Am. Chem. Soc.* **1963**, *85*, 3878. (e) Giese, B.; Schoch, J.; Rüchardt, C. *Chem. Ber.* **1978**, *111*, 1395. (f) Rüchardt, C.; Panse, P.; Eichler, S. *Ibid.* **1967**, *100*, 1144. (g) Froyen, P. *Acta Chem. Scand.* **1972**, *26*, 2163.

the cinnamic ester with a 6;94 Z/E ratio. In the case of ylides **14** and **15**, the rates of addition of ylide to aldehyde (k_1 and k_2) had to be slowed considerably relative to the rates of their decomposition to alkenes (k_5 and k_6), precluding the observation of key reaction intermediates.

$Ph_3P{=}CHCOOMe$ (**14**) $Ar_3P{=}CHPh$ (**20**)

$(n\text{-}Bu)_3P{=}CHCOOMe$ (**15**) $Ph_3P{=}CHAr$ (**21**)

Ph = phenyl Ar = 4-methoxyphenyl

Semistabilized benzylidene ylide **17**, prepared from **16** by using either a sodium or lithium base, reacted instantly with benzaldehyde at temperatures as low as −100 °C (!). This reactivity was based on the loss of ylide color (red-orange) as well as the instantaneous depletion of ylide in the ^{31}P NMR spectrum (δ 7.0). ^{31}P NMR analysis at −100 °C did not afford any evidence for Wittig intermediates, be they oxaphosphetanes or betaines, in several experiments. No P(V) signals were ever seen, but transient peaks between 20 and 30 ppm were occasionally recorded. Generation of triphenylphosphine oxide (δ 22.9) and the associated Z/E stilbenes was usually very rapid at −100 °C. After warming this reaction to 23 °C, we obtained a 56% isolated yield of Z and E stilbenes in a 63:37 ratio.

With ylide **17**, the high rates for olefin formation (k_5 and k_6) interfered with the observation of reaction intermediates. Despite the adverse circumstances, we also tried to muster evidence for intermediates by quenching reaction mixtures at low temperature. Addition of anhydrous HCl to a reaction of **17** and benzaldehyde at −100 °C led to isolation of some organic salt, but this substance proved to benzyltriphenylphosphonium chloride (obtained in low yield) rather than the desired β-hydroxyphosphonium salt. The assorted negative results from experiments with **17** and benzaldehyde are consistent with a reported failure to observe crossed products in deprotonation of a β-hydroxyphosphonium salt derived from a benzylidene ylide (viz. *erythro*-$MePh_2PCH(Ph)CH(OH)Ph^+I^-$, **22**) during exposure to *m*-chlorobenzaldehyde (Li salt present).[31] However, a fine line exists between the success or failure of reactions of semistabilized ylides in engendering substantial crossed products. For instance, semistabilized ylide $Ph_2MeP{=}CHC(Me){=}CH_2$, in the presence of lithium salt, was shown to experience crossover with benzaldehyde and cyclohexanecarboxaldehyde.[29b]

Since we expected a tributyloxaphosphetane species to be more resistant to expulsion of alkene and phosphine oxide than a triphenyl compound (see above), the reaction of ylide **19** (generated from **18** and NaHMDS) and benzaldehyde at −95 °C was studied. Again, no transient intermediates were captured by ^{31}P NMR; only tributylphosphine oxide was observed. Nonstabilized ylides with a tri(*p*-methoxyphenyl)phosphorus group give relatively stable intermediates in reactions with aldehydes;[32] however, with ylide **20** we did not detect reaction intermediates at −80 °C by ^{31}P NMR.

We supposed that an ylide with a benzylidene group more akin to an alkylidene group might deliver positive results. The *p*-methoxy derivative, **21**, from phosphonium salt and NaHMDS, reacted with benzaldehyde instantly at −90 °C (color vanished). Only the emergence of $Ph_3P{=}O$ was recorded by ^{31}P NMR at −90 °C.

In comparing the semistabilized and stabilized ylides, the rate of junction with benzaldehyde was not a problem in the former series, as the semistabilized ylides reacted exceedingly fast. However, Wittig adducts from semistabilized ylides and benzaldehyde still could not be easily perceived because such molecules apparently fragment rapidly to alkenes and phosphine oxide.[33a] Although intermediates in reactions of semistabilized or stabilized ylides have defied detection or trapping, significant information has nonetheless been acquired. Jones and Trippett studied the behavior of *erythro*-$MePh_2PCH(Ph)CH(OH)Ph^+I^-$ (**22**), prepared by reacting *trans*-stilbene oxide with $NaPPh_2$, followed by MeI alkylation.[30a] Deprotonation of **22** with base presumably generated a *cis*-oxaphosphetane via an *erythro*-betaine, providing a means for exploring the adduct of a benzylidene ylide and an aldehyde.[30a] The reaction afforded alkene product comprised of both Z and E stilbenes, the exact proportion of which depended on solvent and temperature. In THF at 24 °C, with *n*-BuLi as the base, the Z/E ratio was 93:7, and a crossover experiment was positive. Vedejs and Fuchs[15] generated the betaine of **22** in THF and found ≥98% stereospecificity at 25 °C, even though LiI was present. They observed such high stereospecificity for other systems, as well, showing that decomposition of Wittig intermediates to alkenes is a syn stereospecific process.[15] The stereomutation and crossover noticed by Trippett and Jones,[30a] associated with reversal of Wittig intermediates, was accentuated by hydroxylic agents; so, the minor reversal in THF may have been related to technical factors.[33b] We have deprotonated **22** (≥99% erythro) with LiHMDS in THF at 23 °C and found Z/E stilbenes in a ratio of 94:6.

In a final attempt to observe oxaphosphetanes for a semistabilized ylide case, we deprotonated **22** in THF at −100 °C with NaHMDS in an NMR tube. No oxaphosphetane or betaine signals were detected by ^{31}P NMR, but $Ph_2MeP{=}O$ was rapidly generated.

Discussion of Mechanistic Aspects

Observing Diastereomeric Adducts. The ability to follow diastereomeric reaction intermediates in the midst of a Wittig reaction is extremely useful for analyzing the course of the reaction. Certainly, it is possible to determine the intermediate state of the Wittig reaction by quenching with acids, such as anhydrous HBr. However, direct spectroscopic observation is preferable for studies of reaction time-course. In the work reported here, we have often found a close correspondence between results from quench experiments and NMR experiments; so, the methods can be used interchangeably for gaining a snapshot of a reaction. The NMR method is useful for situations where reaction dynamics are of paramount interest, while the acid-quench method is useful for a simple, quick glance at a reaction.

With the NMR method we have studied some intimate details of the Wittig reaction of nonstabilized ylides for the first time. However, we have only conducted limited work on a sparse collection of systems, There is still important work to be done, and answers to be found. For example, can k_1 and k_2 be independently assessed by some means? Can intermediates be detected in the reaction of stabilized or semistabilized ylides? Can experimental data be obtained to gauge the relative significance of oxaphosphetanes and betaines as first-formed species in the Wittig reaction, that is, the importance of a one-step vs. a two-step mechanism? Can an explicit understanding of the origins of high cis selectivity be achieved? Hopefully, some of these questions will yield to future investigations.

Oxaphosphetanes vs. Betaines. The relative importance of oxaphosphetanes vs. betaines, as intermediates, has been of persistent concern. Although direct experimental evidence for betaines in the reaction of nonstabilized ylides and carbonyl compounds is lacking, contrary to the facile detection of oxaphosphetanes, betaines can still have a meaningful, albeit transient, existence. In certain nonpolar solvents, in the presence of lithium salts, reactions of nonstabilized phosphorus ylides and aldehydes precipitate betaine–lithium halide complexes;[4a] but, free, distinct betaine species have not otherwise been demonstrated in the Wittig reaction.[17] Various low-temperature NMR studies have shown a substantial concentration of oxaphosphetanes in reactions of nonstabilized phosphorus ylides; no tetravalent phosphonium species have been observed, except for the reaction of $Ph_3P{=}CH_2$

(31) McEwen, W. E.; Beaver, B. D. *Phosphorus Sulfur* **1985**, *24*, 259.
(32) Wittig, G.; Weigmann, H.-O.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 676.

(33) (a) In a preliminary examination of the reaction of **17** (from **16** and NaHMDS) and $PhC(O)CF_3$, we observed a transient singlet by ^{31}P NMR (−100 °C) at −60.7 ppm. This putative oxaphosphetane accounted for only 15% of total phosphorus, the remainder being $Ph_3P{=}O$. (b) McEwen and Beaver[31] did not observe stereochemical drift or crossover in low-temperature deprotonation studies with **22**; this is probably related to the reduced reaction temperature (cf. ref 12 and 30a).

in the presence of lithium salt.[2d]

Are oxaphosphetanes formed directly from a phosphorus ylide and aldehyde (or ketone) in a more or less synchronous cycloaddition reaction, or are betaines intermediates en route to oxaphosphetanes? Unfortunately, there is little or no experimental evidence to conclude whether betaines or oxaphosphetanes are the first-formed intermediates.

Giese[30e] and Schlosser[17] have discussed this problem at length. Giese et al.[30e] referred to differential degrees of bonding in a four-centered transition state, containing atoms with partial charges. Whether the P–O or C–C bonds were more advanced, hinged mainly on electronic factors of the substituents. So, there would be a spectrum of transition-state structures, with conventional betaines at one end and true oxaphosphetanes somewhere near the center.

Schlosser and co-workers[17] suggested that substituent effects provide no real answer. They made an important assertion that before one considers betaines, per se, it is necessary to consider the betaine conformation involved, gauche or anti, Because the conformer with an anti arrangement was thought to be too high in energy, they maintained that the gauche conformer is the one that matters (based on electrostatic considerations). Their view of the energetics placed the gauche betaine above the oxaphosphetane, but when the former traverses to the latter the transition state could nearly resemble an oxaphosphetane. A dynamic equilibrium between betaine and oxaphosphetane was also entertained. Still, we are constrained to simply wonder about which comes first on the reaction coordinate.

A recent theoretical study of the Wittig reaction (4-31G* level) by Volatron and Eisenstein has furnished a nice energy profile.[34] In the reaction of $H_3P{=}CH_2$ and CH_2O, the activation energy to form oxaphosphetane (axial oxygen) is ca. 7 kcal/mol, while that to form betaine is ca. 32 kcal/mol. The betaine (anti form) is not an intermediate, rather it rests at the apex of the profile leading to PH_3 and ethylene oxide. The oxaphosphetane (ax O) is 3 kcal/mol less stable than the PH_3/epoxide products; however, there is a formidable energy barrier for this pathway. The activation energy for decomposition of oxaphosphetane (equatorial O) to $H_3P{=}O$ and ethylene is ca. 29 kcal/mol, which compares to ca. 39 kcal/mol for reversal to ylide and formaldehyde. The alkene and phosphine oxide are favored thermodynamically over the phosphine and epoxide by ca. 14 kcal/mol. It is interesting to note that gauche betaine was not found in this reaction and that the cyclic intermediate forms easily.

These results[34] are in substantial agreement with earlier ab initio SCF (STO-3G) calculations on a model Wittig reaction of $H_3P{=}CH_2$ and formaldehyde.[35] The 1980 study revealed an essentially concerted reaction pathway, not involving betaine species. The oxaphosphetane, which formed through a very small energy barrier, was a local minimum on the energy surface.

MNDO calculations have been performed on the reaction of $H_3P{=}CHMe$ or $Me_3P{=}CHMe$ with CH_3CHO.[1c,36] A transition state entailing advanced C–C bond formation was deemed most germane, others being much higher in energy. In this model, a P–O gauche transition state was clearly preferred to a P–O anti one (by at least 4 kcal/mol). Betaines were found to be much higher in energy than oxaphosphetanes, by ca. 20 kcal/mol. Stereochemically, an "E" transition state was favored over a "Z" by ca. 1 kcal/mol, and *trans*-oxaphosphetane was predicted to be more stable than the *cis*-oxaphosphetane by 1.3 kcal/mol (see subsection on stereoselectivity, below).

Unfortunately, theoretical calculations do not take account of medium effects. Solvation would be important in stabilizing the anti betaine, or metal halide adducts thereof, perhaps making it a viable intermediate. Also, one may find it difficult to accept theoretical results that attempt to predict diastereoselectivity related to an energy difference of ca. 1 kcal/mol. Besides having the transition states unsolvated, the computations disregard entropy and probably have an intrinsic error exceeding 1 kcal/mol.

One experimental area suitable for reaping information on the relevance of betaine intermediates in solution phase is the deprotonation of β-hydroxyphosphonium salts. This entry into the Wittig reaction manifold is compelled to proceed through an acyclic, charge-separated species (betaine), which can be relatively stable in benzene when complexed with lithium halide, as described by Schlosser and Christmann.[4a] Thus, one can imitate a betaine reaction pathway and see how it compares with a direct reaction of ylide and aldehyde. For the most part, few distinguishing or unique features have been recorded from comparative studies of direct and deprotonation routes in ether solvents. Therefore, one may be tempted to acknowledge the importance of a betaine route. However, Schlosser and Christmann[4a] found that deprotonation of relevant β-hydroxyphosphonium salts in benzene, followed by reprotonation after 30 h, results in a 50% recovery of the starting salt, with a modified erythro/threo ratio. We repeated such an experiment and obtained virtually the same observation. A suspension of **7a** (R = Ph) in benzene was treated with *n*-BuLi, and the mixture was quenched with HBr to give a 3:1 mixture of **7a** and **8a** (R = Ph) in 70% yield. By contrast, direct combination of ylide **4** (from salt **1** and *n*-BuLi) and benzaldehyde in benzene gave a 68% yield of alkenes **9a** and **10a**, after only 15 min. This is consistent with literature reports that lithium-salt reactions between nonstabilized ylides and aldehydes in benzene or toluene afford moderate to good yields of alkenes.[1a,37] In nonpolar media, at least, it appears that the direct reaction produces oxaphosphetanes immediately and that these would be subsequently attacked by lithium halide to form betaine complexes, if such complexes were to be formed at all. Reactions in a polar milieu, such as THF, may not behave in the same fashion.

In the Wittig reaction of nonstabilized ylides, since oxaphosphetanes are the only observable intermediates and, perhaps, even the first-formed intermediates, it is tempting to postulate a four-centered, cycloaddition mechanism. However, given the electronic characteristics of the two reactants, ylide and carbonyl compound, true synchrony in bond making is highly improbable. In such reactions, C–C bonding is expected to be more advanced over P–O bonding in the transition state for oxaphosphetane formation, resulting in a skewed cyclic array with a quadrilateral geometry approaching that of a regular trapezoid.[2d]

Decomposition of Oxaphosphetanes to Alkenes. It is clear from our results that oxaphosphetanes can decompose in two directions: back to ylide and aldehyde or onward to alkenes and phosphine oxide. To be sure, both processes have been discussed and determined on previous occasions.[2d,4,28a,30a] These reaction pathways represent a dynamic state, balanced by the relative rates for each step. Failure to detect reversibility does not mean that it is nonexistent, just that its rate is noncompetitive with the forward reaction.

The mechanism for collapse of oxaphosphetanes to final products has been addressed. Bestmann[1c,1i,36] has promoted the hypothesis that a stepwise path, with a focusing of negative charge on carbon and positive charge on phosphorus, is operative (a sort of E2H mechanism). This idea has been used to rationalize the high *E* stereoselectivity observed with stabilized ylides. However, it fails to explain the significant differences in alkene stereochemistry between aromatic and aliphatic aldehydes (the former generating much more *E* alkene). Also, a recent study by Vedejs and Hara provides evidence against C–P bond heterolysis.[38]

The ab initio work of Volatron and Eisenstein[34] supports oxaphosphetane decomposition that is "concerted (supra, supra) in a geometric sense, the four heavy atoms being coplanar," with

(34) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1984**, *106*, 6117.
(35) Höller, R.; Lischka, H. *J. Am. Chem. Soc.* **1980**, *102*, 4632.
(36) Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 85.

(37) (a) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1977**, *42*, 2362. (b) Bergelson, L. D.; Barsukov, L. I.; Shemyakin, M. M. *Tetrahedron* **1967**, *23*, 2709. (c) Bergelson, L. D.; Vauer, V. A.; Varsukov, L. I.; Shemyakin, M. M. *Tetrahedron Lett.* **1964**, 2669.
(38) (a) Vedejs, E.; Hara, S. *J. Org. Chem.* **1986**, in press. We thank Professor Vedejs for a preprint of this paper. (b) Given this view, the CNDO study of Trindle et al. (see: Trindle, C.; Hwang, J.-T.; Carey, F. A. *J. Org. Chem.* **1973**, *38*, 2664), which supports a stepwise fragmentation with advanced cleavage of the oxaphosphetane P–C bond, has reduced significance.

an activation energy of ca. 29 kcal/mol. In the same vein, the ab initio calculations of Höller and Lischka[35] showed a concerted reaction with an ca. 25-kcal/mol barrier for dissociation into ethylene and phosphine oxide. Based on our kinetics measurements, the activation energies ($\Delta G^{\ddagger}$) for decomposition of **5a** and **6a** (R = Ph) at −30 °C are 18.9 and 18.8 kcal/mol, respectively (^{13}C NMR data), and the activation energies for **5a** and **6a** (R = *n*-Bu) at −10 °C are 19.0 and 20.8 kcal/mol.[39] These values are lower than, but still in reasonable accord with, those from the theoretical work. The discrepancy may be connected with solvation in the experimental reactions as well as an appreciable, positive entropy of activation.[40]

Oxaphosphetane Pseudorotational Isomers. Bestmann has emphasized that the first oxaphosphetane(s) produced from condensation of an ylide and aldehyde should have an axial P–O bond.[1c,e,36] To fragment to products, this oxaphosphetane form must pseudorotate to one possessing an axial P–C (where this carbon is to be eliminated).[41] This is related to the general rule of "apical entry/apical departure" for reactions involving pentacoordinate (trigonal bipyramidal) phosphorus. Various ab initio calculations[34,35,42] have indicated only a small energy difference between the two pseudorotameric arrangements. Bestmann has mentioned the detection of different pseudorotameric oxaphosphetanes.[36] However, in our research we have not found any evidence for pseudorotational isomers at temperatures usually as low as −50 to −80 °C. We do not know the pseudorotational form of the oxaphosphetanes that we normally have recorded by NMR. But, we do not feel that the particular form has much bearing on the attendant chemistry, because rapid interconversion probably makes both forms readily available.

Origin of Stereoselectivity in the Wittig Reaction. The Wittig reaction can be viewed as a subset of the class of reactions involving attack of a nucleophile on a carbonyl group. This consideration does not, by itself, simplify our attempt to understand the source of stereoselectivity. For example, the addition of a simple acetylide nucleophile to a 4-substituted cyclohexanone gives a stereochemical result (preferential axial addition) that is not easily explained with current knowledge, which prompted Trost to state recently that "... as central and widely used...a reaction as the addition of nucleophiles to a carbonyl group remains a mystery".[43]

For a nonsynchronous Wittig reaction with advanced C–C bond formation, erythro vs. threo stereoselectivity about the C–C bond appears relevant to the stereoselection process. Seeking an understanding, we could try to analogize the Wittig reaction with the addition of prochiral enolates/enol ethers or crotyl organometallics to prochiral carbonyl compounds, areas which have received considerable attention.[44,45] But, stereochemical rationalizations even in these areas can have their own aura of ambiguity.[44,45] For understanding or predicting diasteroselectivity of a reaction, it must be appreciated that a fairly large bias for one product may only represent a relatively small difference in free energy of activation ($\Delta\Delta G^{\ddagger}$) between diastereomeric transition states. For instance, a heavily biased mixture with a 95:5 product ratio (at 25 °C) corresponds to an energy difference of only about 1.7 kcal/mol. So, although qualitative models for predicting stereochemistry may be developed, based chiefly on intuition, it is quite another story to achieve a quantitative paradigm (based on empirical force field or ab initio calculations, for example).

In lithium salt-free Wittig reactions, nonstabilized ylides react with aldehydes to give mainly *Z* alkenes. Recently, this has been rationalized in terms of (1) substituent steric interactions in a nonsynchronous cycloaddition mechanism[2d] or (2) a steric effect of the stationary ligands on phosphorus in a four-centered cyclic transition state.[2a] One can also explain the preference for *Z* alkene (under kinetic control) by having the ylide and aldehyde line up in the transition state with an anti arrangement of the oxygen and phosphorus atoms and an anti arrangement of the bulky ylide and aldehyde substituents (erythro configuration), which diminishes the overall steric interactions. This latter (classical) mechanism involves an anti betaine, which has been calculated (vide supra) to be very high in energy. However, given the inherent limitations of theoretical calculations (mentioned earlier), this explanation should not be discarded because of calculations alone. (It is conceivable that a solvent with a dielectric constant of only 5.0 could sufficiently stabilize an anti betaine.[46]) According to the classical mechanism, the diastereoselectivity would be determined in the transition state leading to the anti betaine, where the critical C–C bond is forged. Taking all of this together, a clear-cut explanation for *Z* alkene, *erythro*-betaine, or *cis*-oxaphosphetane diastereoselectivity is still elusive.

Inclusive rules for stereoselectivity in the Wittig reaction are difficult to formulate. The normally high stereoselectivity for *cis*-oxaphosphetane in the salt-free reaction of a triphenylphosphorus ylide in THF (90–98% cis) is compromised by the presence of lithium salt at moderate to high concentrations (75–85% cis). Of course, there may be an even greater disparity for *Z* alkene stereoselectivity between these two conditions (90–98% *Z* vs. 35–85% *Z*, respectively) because of stereochemical drift with aromatic aldehydes. By comparison, a salt-free tributylphosphorus ylide affords even lower levels of the *cis*-oxaphosphetane (30–45% cis) and *Z* alkene (2–15% *Z*). Then, there are the cases of semistabilized and stabilized ylides. Triphenyl semistabilized ylides rarely give high stereoselectivity for either alkene isomer (50 ± 30% *E*), and stabilized ylides give high *E* alkene selectivity (>90% *E*). However, since there is no guarantee of kinetic control in these reactions (possible reversal of Wittig intermediates[30a,38a]), nothing can be concluded about their intrinsic stereoselectivity. Special cases further confuse attempts at standardization. For instance, the reaction of a fluorophosphoranium tri-*n*-butylphosphorus-stabilized ylide with aldehydes produces much more *E* alkene with aliphatic (e.g., *Z*/*E* = 6:94) than with aromatic aldehydes (e.g., *Z*/*E* = 87:13).[47] Also, semistabilized ylides with a mixture of phenyl and alkyl groups on phosphorus (e.g., $Ph_2MeP{=}CHC(Me){=}CH_2$) can show high *E* stereoselectivity.[29b]

For the "salt-free" reaction of a nonstabilized ylide with an aldehyde, presuming a cycloaddition mechanism, an explanation

(39) Evaluated by using the rate constants in the Eyring equation: $\Delta G^{\ddagger} = 4.576T(10.319 + \log T - \log k)$.

(40) The transition state for decomposition has more disorder than the starting compound, so $\Delta S^{\ddagger}$ has a positive value. Through the $-T\Delta S^{\ddagger}$ term, an experimental $\Delta G^{\ddagger}$ would be reduced from a calculated $\Delta G^{\ddagger}$, since the latter does not contain an entropy component (that is, it is basically identical to $\Delta H^{\ddagger}$).

(41) It should be kept in mind that the constellation of acceptable oxaphosphetane pseudorotamers excludes diequatorial (and, of course, diaxial) disposition of the four-membered ring, because of energetics associated with angle strain.

(42) Bestmann, H. J.; Chandrasekhar, J.; Downey, W. G.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Commun.* **1980**, 978.

(43) Trost, B. M. *Science (Washington, DC)* **1985**, *227*, 908. Also, for background information, see: Juaristi, E.; Cruz-Sanchez, J. S.; Ramos-Morales, F. R. *J. Org. Chem.* **1984**, *49*, 4912 and ref 3–13 cited therein. Nguyen, T. A. *Top Curr. Chem.* **1980**, *88*, 145.

(44) Additions of enolates or enol ethers: (a) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256 and ref 1–6 cited therein. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Part B. (d) Evans, D. A.; Nelson, J. V.; Vorgel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (e) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, *21*, 4607. (f) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *Ibid.* **1982**, *23*, 2387. (g) Shenvi, S.; Stille, J. K. *Ibid.* **1982**, *23*, 627. (h) Labadie, S. S.; Stille, J. K. *Tetrahedron* **1984**, *40*, 2329. (i) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598. (j) Yamamoto, Y.; Maruyama, K. *Ibid.* **1982**, *104*, 2323. (k) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309.

(45) Addition of crotyl organometallics and related reagents: (a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. Yamamoto, Y.; Maruyama, K. *J. Synth. Org. Chem.* **1982**, *40*, 332. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (c) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. (d) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. (e) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970 and references cited. (f) Hoffmann, R. W.; Kemper, B. *Tetrahedron* **1984**, *40*, 2219.

(46) E.g., see ref 25a, Chapter 10, pp 429–430.

(47) Cox, D. G.; Gurusamy, N.; Burton, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 2811.

for cis stereoselectivity can be put forth. There may be an important steric role for the unreactive substituents on phosphorus, as described by Schlosser and Schaub.[2a] (Although the thermodynamic control inherent in some of their Z/E alkene ratios was inadvertently ignored,[2a] we found that there still is a stereochemical distinction between salt-free reactions of ylides with triphenyl vs. trialkyl substitution.) The following borrows from their model[2a] and from that of Vedejs et al.[2d] In a four-centered transition state with early C–C bond formation, the ylidic carbon would follow a perpendicular trajectory en route to the carbonyl carbon, and the C=O axis would be skewed vs. the C=P axis.[2d] The substituents on the incipient stereogenic carbon centers of the skewed, four-atom array would adopt a locus of least steric resistance relative to each other and relative to the collection of substituents on the incipient pentacoordinate phosphorus, which may adopt a trigonal bipyramidal (local D_{3h}) or tetragonal pyramidal (local C_{4v}) geometry. The high preference for *cis*-oxaphosphetane with triphenylphosphorus nonstabilized ylides and aldehydes may arise from steric crowding of one face of the skewed, incipient oxaphosphetane by a single phenyl group, particularly its ortho positions.[2a] This key phenyl group would be oriented by interactions with the other phenyl ligands on phosphorus, as part of a three-bladed, propeller-type conformation. Thus, the substituent on the developing stereogenic carbon atom from the aldehyde would favor a quasi-equatorial environment, then the substituent from the ylide must adopt a quasi-axial environment. However, our examination of molecular models did not convince us of a strong preference (>20:1) for a quasi-axial ylide substituent.

Conclusion

We have studied the Wittig reaction of nonstabilized ylides and aldehydes in some detail by using NMR spectroscopy, by quenching intermediate oxaphosphetanes with HBr, and by deprotonation of β-hydroxyphosphonium salts. Reactions of ylide **4** and benzaldehyde, in the presence of lithium salt, demonstrated "stereochemical drift" and a pronounced concentration dependence of stereochemistry. Stereochemical drift was not just associated with the presence of lithium salt, as indicated by deprotonation of erythro/threo mixtures of β-hydroxyphosphonium salts, in the vicinity of 1:1, with a sodium base. A cooperative interaction between *cis*- and *trans*-oxaphosphetanes, which augments stereochemical drift, was documented. Thus, in a salt-free reaction of ylide **4** and benzaldehyde, we suggest that little stereochemical drift occurs because of the initial high bias (≥98%) for *cis*-oxaphosphetane. The aliphatic aldehyde, hexanal, exhibited straightforward behavior in its reaction with **4**. Reactions of trialkyl ylide **11** with benzaldehyde or pivaldehyde showed significant stereochemical drift (cis/trans = ca. 1:1 and 1:2; Z/E = 1:9 and 1:24, respectively).

Kinetic measurements and crossover experiments indicated that *cis*-oxaphosphetanes are much more inclined to undergo reversal to ylide and aldehyde than the corresponding *trans*-oxaphosphetanes. Since we determined the rates at which the *cis*- and *trans*-oxaphosphetanes (of a pair) generate alkenes, we were able to attribute the degree of stereochemical drift to the relative rates for oxaphosphetane reversal.

Experiments to evaluate reactions of semistabilized and stabilized phosphorus ylides did not provide key information, since intermediates (oxaphosphetanes or betaines) could not be observed. Without the ability to measure the intermediates, it is impossible to frame mechanistic conclusions. One might propose that stabilized ylides react with aldehydes to give mainly E alkenes because of thermodynamic control, but this will remain mere speculation until intermediates can be viewed or trapped.[48] It is a corollary that the determination of Z/E alkene ratios, alone, in the Wittig reaction, cannot yield a sound mechanistic/stereochemical picture.

(48) Indeed, as Vedejs has aptly asserted,[2d] since high Z selectivity can be maintained in a reversible Wittig reaction, high E selectivity is not, ipso facto, sufficient evidence for thermodynamic control through reversibility in reactions of stabilized ylides.

Experimental Section

General Information and Procedures. Proton NMR spectra were recorded on a Varian EM-360 (60-MHz), Varian EM-390 (90-MHz), or Bruker AM-360 WB (360-MHz) spectrometer with $CDCl_3$ as solvent and Me_4Si as internal reference, unless otherwise noted. Proton-decoupled ^{13}C NMR spectra were obtained on a JEOL FX-60Q (15.1-MHz, by using INEPT to determine carbon type) or a Bruker AM-360 WB (90.56-MHz, by using DEPT to determine carbon type) spectrometer in $CDCl_3$ with Me_4Si as internal reference, unless otherwise noted. ^{13}C NMR assignments are based on carbon type, J_{PC} values, and standard chemical shift criteria; the reported multiplicities represent ^{31}P–^{13}C couplings.[49] ^{31}P NMR spectra were acquired on a Bruker AM-360 WB instrument at 145.8 MHz, generally with broad-band proton decoupling; chemical shifts are reference against external 85% H_3PO_4. Abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; br, broad.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Melting points were acquired on a Hoover capillary melting point apparatus and are corrected. Preparation and transfer of ylides and other air-sensitive materials were conducted under argon. THF was reagent grade and used as purchased; it was degassed with argon prior to use.

GLC analyses were conducted on a Perkin-Elmer 3920B instrument with a flame-ionization detector, by using a Hewlett-Packard Model 3392A integrator. The column employed was a 3% SE-30 on Chromosorb Q column ($^1/_8$ in. × 6 ft). The ratio of **9c**:**10c** was determined after conversion to the corresponding epoxides with excess *m*-chloroperbenzoic acid, followed by GLC analysis on the above column. The identities of the alkenes were authenticated by GLC/MS and/or comparison to known samples with known stereochemical composition.

[α-^{13}C]Benzaldehyde was purchased from MSD Isotopes (99.3 atom %) and [1-^{13}C]1-butanol was obtained from Stohler/KOR (99 atom %). We thank Dr. Bruce Beaver (Naval Research Laboratory) for a generous sample of **22**, which we recrystallized from chloroform–hexane, mp 195–210 °C (lit.[30a] mp 222–224 °C); 360-MHz ^1H and 90.56-MHz ^{13}C NMR spectra were satisfactory (≥99% erythro). Preparations of (methoxycarbonyl)tributylphosphonium bromide (**15**, mp 94–96 °C), [1-^{13}C]butyltriphenylphosphonium bromide (mp 241–242.5 °C), benzyltris(4-methoxyphenyl)phosphonium chloride (**20**, mp 115–122 °C), benzyltributylphosphonium chloride (**18**, mp 164–164.5 °C), and (4-methoxybenzyl)triphenylphosphonium chloride (**21**, mp 241.5–242.5 °C) are presented in the microfilm supplement.[24] The ^{13}C-labeled salt had an isotopic content of 95–98%, as determined by high-field ^1H and ^{13}C NMR.[24]

Typical Conditions for Wittig Reactions. A known quantity of the appropriate phosphonium bromide was suspended in THF under nitrogen or argon and treated with 1.1 molar equiv of the appropriate base, typically LiHMDS or NaHMDS dissolved in THF (1 M solutions of LiHMDS and NaHMDS are available from Aldrich). After 15 min, the clear red or orange solutions were carefully transferred to a 10-mm NMR tube. Those solutions containing NaBr were centrifuged prior to transfer of the solvent. A vortex plug was inserted above the solution in the NMR tube. The middle of the plug held a capillary tube containing trimethyl phosphite as a phosphorus standard (if ^{31}P NMR was being run) and THF-d_8 (if the THF-d_8 was not the solvent in the reaction solution). Additionally, trimethyl orthobenzoate was used as an external standard in the instances where ^1H NMR data were being accumulated, and hexamethyldisilazane was used for ^{13}C NMR studies. Alternatively, the standard was placed in a 5-mm NMR tube, coaxially disposed in the 10-mm sample tube. Aldehyde (1 molar equiv) was carefully added via syringe, under a stream of argon, past drilled ridges on the side of the vortex plug into the reaction solution cooled to either ca. −100 °C (pentane in liquid nitrogen) or −78 °C (dry ice/acetone). The aldehyde was thermostated on the side of the NMR tube, and the solution was mixed by gentle shaking. The vortex plug was then tightly fitted, and the tube was capped, thoroughly mixed (vortex mixer), and quickly inserted into the NMR probe precooled to the desired temperature.

Deprotonation NMR Experiments. The β-hydroxyphosphonium salt was combined with THF-d_8 in a 5-mm or a 10-mm NMR tube. The mixture was cooled to −78 °C, treated slowly with 1.1 molar equiv of NaHMDS (1 M in THF), allowed to cool for ca. 2 min, and agitated to effect reaction. The precipitate was packed by centrifugation at −78 °C. For the 10-mm tube, a vortex plug was inserted. Thus, for example, salts **7a** and **8a** (R = Ph) were independently converted to oxaphosphetanes

(49) (a) For ^{13}C NMR data on phosphonium salts, see: Gray, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7736. (Note: data for compounds 10 and 11 in Tables III and IV.) (b) We have recorded the ^{13}C NMR spectrum (15.1 MHz) of *n*-$Bu_4P^+Br^-$ δ 13.29 (CH_3), 18.91 (d, J = 48 Hz, CH_2P), 23.58 (d, J = 4.9 Hz, CH_2CH_2P), 23.75 (d, J = 15.5 Hz, CH_3CH_2).

5a and **6a** (R = Ph). For **5a** (R = Ph): ^{31}P NMR (−78 °C) δ −62.2; 360-MHz ^{1}H NMR (−40 °C) δ 0.40 (t, Me), 5.19 (dd, PhCH, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 11.8 Hz), 5.30 (complex m, CH, $^2J_{PH}$ = ca. 12 Hz). For **6a** (R = Ph): ^{31}P NMR (−78 °C) δ −64.4; 360-MHz ^{1}H NMR (−40 °C) δ 0.61 (t, Me), 4.26 (dd, PhCH, $^3J_{HH}$ = 5.9 Hz, $^3J_{PH} \leq$ 2 Hz), 4.94 (d of d of t, CH, $^2J_{PH}$ = ca. 12 Hz). [Please note that we made a misstatement regarding these PhCH signals in a recent paper: Maryanoff, B. E.; Reitz, A. B. *Phosphorus Sulfur* **1986**, *27*, 167.]

NMR Spectroscopic Measurements and Rate Studies. NMR spectra were recorded in Fourier transform mode on a Bruker AM-360 WB spectrometer operating at 360.13 MHz for proton, 145.78 MHz for phosphorus, and 90.56 MHz for carbon. ^{31}P{^{1}H} NMR experiments were performed with a THF-d_8 internal deuterium lock, and an external reference of 85% H_3PO_4 adjusted to 0 ppm from ambient probe temperature to −30 °C [note: the accuracy of the ^{31}P chemical shifts at temperatures from −45 to −100 °C may be ±2 ppm due to temperature shifts relative to the reference, which could only be accurately measured down to −30 °C]. Various parameters were as follows: 10-μs pulse, equivalent to a 26° flip angle; 4.66-s recycle time, ±85 ppm; 4.33-s recycle time, ±171 ppm. ^{13}C{^{1}H} NMR experiments were conducted with THF-d_8 as an internal deuterium lock and reference at 67.4 ppm. A 5-μs pulse, equivalent to a 27° flip angle, with a 3.66-s total recycle time, for a spectral width of ±138 ppm, was employed. ^{1}H NMR experiments in a 5-mm probe were performed with THF-d_8 as an internal deuterium lock and reference at 1.73 ppm; a 3-μs pulse, equivalent to a 40° flip angle, with a 22.7-s recycle time, was used. For spectra acquired in a 10-mm probe (observing on the decoupler coil, of a broad-band probe tuned to observe ^{31}P or ^{13}C), we employed a 5-μs pulse (∼11° flip angle) and a 5.36-s recycle time. β-Hydroxyphosphonium salts were measured in $CDCl_3$ with an internal deuterium lock and referenced at 7.24 ppm. For **7a** and **8a** (R = Ph), and for **5a** (R = Ph), J_{PH} values were confirmed by two-dimensional homonuclear (^{1}H) decoupled COSY experiments. J_{PH} values for **6a** (R = Ph) were established by proton double irradiation.

Kinetic Studies. The T_1 Null method was used to determine relaxation parameters to assure accurate integration. To ascertain temperature, the chemical shift of neat methanol was measured immediately before each experimental series; temperature was maintained by using the Bruker variable temperature unit at ±1 °C. Data acquisition was automated with standard Bruker software. ^{13}C{^{1}H} NMR spectra were measured with a 3.9-min total acquisition time, corresponding to <5% of $t_{1/2}$, with all other acquisition parameters as shown above. These data sets were correlated to hexamethyldisilazane as an internal standard (isolated in a capillary) to monitor changes due to instrumental variability over the time course of the experiment; temperature was held constant for each series at −40, −30, −25, −15, or −10 °C. ^{31}P{^{1}H} or ^{31}P coupled NMR experiments were conducted with a 1.2-min total acquisition time, corresponding to <5% of $t_{1/2}$; all other acquisition parameters were as shown above. These data sets were correlated to trimethylphosphite as an internal standard (isolated in a capillary) to monitor changes due to instrumental variability over the time course of the experiment; temperature was held constant for each series at −40, −30, or −10 °C. ^{1}H NMR data were obtained with a 2.5-min total acquisition time, corresponding to <5% of $t_{1/2}$; all other acquisition parameters were as shown above. These data sets were correlated to trimethyl orthobenzoate as an internal standard (isolated in a capillary) to monitor changes due to instrumental variability over the time course of the experiment; temperature was held constant for each series at −30 or −10 °C. For the ^{1}H/^{31}P studies, experiments with and without broad-band decoupling during the ^{31}P acquisition were conducted.

Tri-*n*-butylbutylidenephosphorane (11).[22,50] Tetra-*n*-butylphosphonium bromide (6.8 g, 20 mmol, 98% assay, commerical material dried at 0.1 torr/40 °C for 60 min) was placed in a flask under nitrogen with 60 mL of dry THF. The mixture was stirred at 0 °C while being treated with 13.0 mL of *n*-butyllithium in hexane (1.02 molar equiv, 1.6 M). Stirring was continued for 15 min, and then the pale yellow solution was transferred under a stream of argon into a one-necked flask.

The solvent was removed on a rotary evaporator equipped with a dry ice condenser, at ca. 0.5 torr. Argon was admitted from an inflated balloon. The residue was distilled in a Kugelrohr apparatus at 0.1 torr, giving a nearly colorless liquid at a pot temperature of ca. 110 °C. Argon was admitted, and the sample was quickly transferred into a tared flask. The pale yellow distillate, which weighed 4.15 g (80%), was stored in the flask with a septum cap under positive argon pressure. This material is very air-sensitive. ^{31}P NMR indicated 95% desired ylide (δ ^{31}P 8.7) and 5% *n*-Bu_3PO (δ ^{31}P 40.8).

Quenching of Wittig Reactions with HBr. A. Reaction of Ylide 4 and Benzaldehyde To Give *erythro*- and *threo*-(1-Hydroxy-1-phenyl-2-pentyl)triphenylphosphonium Bromide (7a/8a, R = Ph). To a suspension of salt **1** (4.0 g, 10 mmol) in 30 mL of THF was added *n*-butyllithium (6.88 mL of a 1.6 M solution in hexane, 11 mmol). After 15 min, the clear, red solution was cooled to −78 °C and treated with benzaldehyde (1.01 mL, 10 mmol). After 10 min, HBr gas was introduced causing a voluminous precipitate to form. The solution was further treated with 50 mL of dry ether; the precipitate was collected and dried to give 4.2 g (83%) of white powder. Analysis by 360-MHz ^{1}H NMR indicated a ratio of ca. 2.3:1 of erythro:threo isomers, based on integration of their respective C*H*OH resonances. ^{31}P NMR ($CDCl_3$, −40 °C) δ 25.2 (erythro, 72%), 23.5 (threo, 28%).

B. *erythro*-(1-Hydroxy-1-phenyl-2-pentyl)triphenylphosphonium Bromide (7a, R = Ph). Butyltriphenylphosphonium bromide (4.0 g, 10 mmol) was suspended in 19 mL of THF in a centrifuge tube and was then treated with NaHMDS (11 mL of a 1 M THF solution). After stirring for 30 min, the solution was centrifuged, and the clear, red liquid was transferred under argon to a three-necked flask and cooled in a dry ice/acetone bath. Benzaldehyde (1.0 mL, 1 molar equiv) was added slowly, dissipating the red color. After 10 min at −78 °C, HBr gas was introduced. Ether was added, and the resultant solid was filtered and recrystallized from acetone/$CHCl_3$/hexane. The large white crystals weighed 2.24 g (44%), mp 223–224.5 °C: ^{13}C NMR (15.1 MHz) δ 14.0 (1, C_5), 23.4 (d, 1, C_4, J_{CP} = 10.7 Hz), 27.8 (1, C_3), 45.1 (d, 1, C_2, J_{CP} = 43.0 Hz), 68.7 (d, 1, C_1, J_{CP} = 3.9 Hz), 118.6 (d, 2, α CP (Ar), J_{CP} = 83.0 Hz), 126–135 (20, Ar), 140.8 (d, 1, HOCH-*C* (Ar), J_{CP} = 13.7 Hz); ^{1}H NMR (360 MHz) δ 0.47 (m, 3 H, CH_3), 0.79 (m, 2 H), 1.48 (m, 2 H), 2.11 (m, 2 H), 3.53 (m, 1 H, H_2, J_{PH} = 9.7 Hz), 5.37 (dd, 1 H, H_1, J_{HH} = 2.0 Hz, J_{PH} = 9.2 Hz), 5.88 (br s, 1 H, OH), 7.2 (m, 3 H), 7.38 (d, 2 H, *J* = 7.2 Hz), 7.6 (m, 6 H), 7.75 (m, 9 H); ^{31}P NMR ($CDCl_3$) δ 25.4. Anal. Calcd for $C_{29}H_{30}BrOP$: C, 68.91; H, 5.98; Br, 15.81. Found: C, 69.01; H, 6.26; Br, 15.37. None of the threo isomer (see below) could be detected by ^{13}C or ^{1}H NMR.

C. *threo*-(1-Hydroxy-1-phenyl-2-pentyl)triphenylphosphonium Bromide (8a, R = Ph). Butyltriphenylphosphonium bromide (10.0 g, 25 mmol) was suspended in 30 mL of THF under nitrogen and treated with a solution of *n*-BuLi in hexane (1.1 molar equiv, 17.3 mL of a 1.59 M solution). After 15 min, the nearly clear, red solution was cooled to −78 °C, and benzaldehyde (2.5 mL, 1 molar equiv) was added, discoloring the solution. The solution was then warmed to −45 °C, and an additional equiv of *n*-BuLi in hexane (15.7 mL) was slowly added.[10] The solution turned black, and after 15 min, 20 mL of 9% HBr/HOAc was added. The color was again dissipated. Trituration with hexane produced a large batch of white crystals, which were recrystallized from CH_2Cl_2/hexane to give 7.5 g (59%) of **8a** (R = Ph), mp 250–253 °C: ^{13}C NMR (15.1 MHz) δ 13.8 (1, C_5), 22.4 (d, 1, C_4, J_{CP} = 12.7 Hz), 31.5 (1, C_3), 45.3 (d, 1, C_2, J_{CP} = 45.9 Hz), 71.2 (d, 1, C_1, *J* = 3.9 Hz), 119.4 (d, 3, α CP (Ar), J_{CP} = 84.0 Hz), 125–135 (20, Ar), 141.8 (d, 1, HOCH-*C* (Ar), J_{CP} = 4.9 Hz); ^{1}H NMR (360 MHz) δ 0.79 (t, 3 H, *J* = 7.2 Hz), 1.5 (m, 4 H), 2.1 (m, 2 H), 3.88 (m, 1 H, H_2, J_{PH} = 13.9 Hz), 5.24 (dd, 1 H, H_1, J_{HH} = 5.6 Hz, J_{PH} = 19.6 Hz), 6.48 (d, 1 H, *J* = 6 Hz, OH), 7.1 (m, 5 H), 7.5–7.8 (m, 15 H); ^{31}P NMR ($CDCl_3$) δ 23.1. Anal. Calcd for $C_{29}H_{30}BrOP$: C, 68.91; H, 5.98; Br, 15.81. Found: C, 68.37; H, 6.09; Br, 16.16. Less than 1% of the erythro isomer (**7a**, R = Ph) was observed by ^{13}C and ^{1}H NMR.

D. Reaction of Ylide 12 and Benzaldehyde To Give *erythro*- and *threo*-(1-Hydroxy-1-phenyl-2-propyl)triphenylphosphonium Bromide (7b and 8b, R = Ph). *n*-Butyllithium (6.88 mL of a 1.6 M solution in hexane, 1.1 molar equiv) was added to a suspension of salt **3** (3.71 g, 10 mmol) in 30 mL of THF. After 15 min, the solution was cooled to −78 °C and treated with benzaldehyde (1.0 mL, 1 molar equiv). After 10 min, HBr gas was introduced, to give a voluminous precipitate. The solution was warmed to 23 °C, ether was added (50 mL), and the precipitate was collected and dried in vacuo. The solid was dissolved in $CHCl_3$, and the solution was filtered from a small amount of insoluble material and treated with Et_2O. The precipitate was collected and dried (3.5 g, 73%). Analysis of 360-MHz ^{1}H NMR and 145.8-MHz ^{31}P NMR spectra indicated a ratio of ca. 3.0:1 for the erythro and threo diastereomers: ^{1}H NMR[4a] (360 MHz) δ 1.27 (m containing a sharp dd, 3 H, J_{HP} = 18.8 Hz, J_{HH} = 7.1 Hz, erythro and threo CH_3), 3.6–3.9 (m, 1 H, erythro and threo C*H*CH_3), 4.81 (dd, 0.28 H, threo C*H*-OH, *J* = 9.0, 9.0 Hz), 5.44 (dd, 0.72 H, erythro C*H*-OH, *J* = 7.9, 2.0 Hz), 7.1–7.3 (m, 5 H, erythro and threo Ar), 7.5–8.0 (m, 15 H, erythro and threo Ar); ^{31}P NMR ($CDCl_3$, −35 °C) δ 23.94 (erythro, 80%), 23.05 (threo, 20%).

E. Reaction of Ylide 11 and Benzaldehyde To Give *erythro*- and *threo*-(1-Hydroxy-1-phenyl-2-pentyl)tri-*n*-butylphosphonium Bromide (7a/8a, R = *n*-Bu). Distilled ylide **11** (1.1 mL, ca. 1.0 g, 3.8 mmol) was added to 20 mL of dry THF at −60 °C under argon. Benzaldehyde (0.45 g, 4.7 mmol) was added, the reaction was stirred for 20 min at −60 °C, and anhydrous HBr was introduced to quench the reaction. The solvent was evaporated, and the oil was dissolved in CH_2Cl_2. This solution was

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rinsed with 5% aqueous Na_2SO_4 and concentrated to a tan syrup (1.8 g). ^1H NMR (360 MHz) showed a dd at δ 5.23 (J = 6.3, 14.6 Hz) PhC*H* of the threo salt (**8a**, R = *n*-Bu) and a dd at δ 5.57 (J = 8.1 and 1.5 Hz) for PhC*H* of the erythro salt (**7a**, R = *n*-Bu), in a 53:47 ratio. ^{13}C NMR (15.1 MHz) showed a d at δ 67.6 (J = 3.9 Hz) for CHOH of **7a** (R = *n*-Bu) and a d at δ 71.0 (J = 3.8 Hz) for CHOH of **8a** (R = *n*-Bu), in a 1:1.1 ratio. ^1H NMR (360 MHz) δ 0.60 (m, 1.4 H, erythro CH_3), 0.83 (t, J = 7.2 Hz, 1.6 H, threo CH_3), 0.90–1.05 (complex m, 9 H, $3CH_3$), 1.2–1.7 (complex m, 13 H, 3 CH_2CH_2P + 3 CH_2CH_3 + 0.5 CH_2 (centered at δ 1.28, threo), 1.93 (m, 1 H, 0.5 CH_2, erythro), 2.1–2.7 (complex m, 8 H, 3 CH_2P + CH_2), 5.23 and 5.57 (see above), 7.2–7.5 (m, 5, Ar); ^{13}C NMR (15.1 MHz) δ 13.4, 13.7, 13.8 (m, CH_3), 18.94 (d, J = 44.8 Hz, erythro CH_2P), 20.92 (d, J = 45.9 Hz, threo CH_2P), 22.0–25.1 (complex m), 28.7 (C_3), 39.3 (d, J = 43.0 Hz, erythro C_2), 40.8 (d, J = 44.9 Hz, threo C_2), 67.6 and 71.0 (see above), 125.7–129.0 (complex m, Ar CH), 141.0, 141.9, 142.0, 142.5 (4° C in Ph).

F, Reaction of Ylide 11 and Benzaldehyde To Give *threo*-(1-Hydroxy-1-phenyl-2-pentyl)tri-*n*-butylphosphonium Bromide (8a, R = *n*-Bu), A solution of distilled ylide **11** (928 mg, 3.6 mmol) in 3 mL of THF was cooled in a dry ice/acetone bath and treated with PhCHO (360 μL, 1 molar equiv). The clear solution was allowed to warm to −20 °C and kept at that temperature for 20 min. HBr gas was introduced, and the solution was treated with ether, whereupon a yellow oil precipitated (2 g). This oil was washed with dry ether and dried in vacuo. It contained predominantly the threo isomer (≥98%): ^{13}C NMR (15.1 MHz) δ 13.6 (3, *n*-Bu_3P^+), 14.0 (m, CH_3 at C_5), 20.6 (d, J = 40.0 Hz, CH_2P), 22–25 (complex m, CH_2), 29.2 (C_3), 41.2 (d, C_2, J_{CP} = 45 Hz), 71.4 (d, C_1, J_{CP} = 4.9 Hz), 126.5 (2, Ar CH), 128.2 (1, Ar CH), 128.8 (2, Ar CH), 142.4 (d, 1, J = 4.9 Hz, HOCH-*C* Ar); ^1H NMR (360 MHz) δ 5.23 (d, 0.98 Hz, threo C*H*OH), 5.57 (d, 0.02 H, erythro C*H*OH). The threo–erythro ratio is ca. 98:2.

G, Reaction of Ylide 11 and Pivaldehyde To Give *erythro*- and threo-(3-Hydroxy-2,2-dimethyl-4-heptyl)tri-*n*-butylphosphonium Bromide (7d/8d, R = *n*-Bu), Ylide **11** (0.33 mL, 1.15 mmol) was added to 4 mL of THF under nitrogen. The solution was cooled to −78 °C, and pivaldehyde (0.12 mL, ca. 0.95 molar equiv) was added. The reaction was stirred for 15 min at −78 °C and then treated with excess HBr gas. Hexane (10 mL) and dry ether (10 mL) were added, causing an oil to separate. The supernate was decanted, and the oil was rinsed twice with 5 mL of dry ether. The oil was dried in vacuo to afford 0.50 g of pale yellow syrup, which contained 90–95% **7d/8d** (R = *n*-Bu) and 5–10% **2**, from unreacted **11**: ^{13}C NMR (90.56 MHz) δ 13.46 (CH_3 of *n*-BuP), 14.33 (CH_3 at C_7), 18.44 (d, J = 45 Hz, erythro CH_2P), 19.04 (d, J = 48 Hz, CH_2P of *n*-Bu_4P^+, 5–10 mol %), 20.80 (d, J = 47.5 Hz, threo CH_2P), 21.97 (d, J = 6.0 Hz, threo CH_2CH_2P), ca. 23.0 (threo CH_2 ?), 23.7–25.5 (complex m), 26.18 (threo CH_3 of *t*-Bu), 26.88 (erythro CH_3 of *t*-Bu), 30.79 (CH_2), 31.94 (CH_2), 36.22, 36.25 (pair of s, threo and erythro C_2), 37.29 (d, J = 12.4 Hz, erythro C_4), 37.82 (d, J = 52.8 Hz, threo C_4), 72.00 (d, J = 3 Hz, erythro CHOH), 76.4 (d, J = ca. 3 Hz, threo CHOH, nearly under $CDCl_3$ peak). Comparison of peaks at δ 20.80 and δ 18.44 gave threo/erythro = 1.29 (ca. 57:43); comparison of peaks at δ 26.18 and δ 26.88 gave threo/erythro = 1.31 (ca. 57:43); ^1H NMR (360 MHz) δ 0.85–1.1 (m, CH_3 for *t*-Bu and *n*-Bu, C_7, 25 H), 1.2–1.8 (m, 21 H), 2.1–2.6 (m, 10 H), 3.887 (dd, J = 3.5, 6.5 Hz, threo C*H*OH, 0.48 H), 3.973 (d, J_{PH} = 15.7 Hz, erythro C*H*OH, 0.36 H), 4.75 (br s, OH), erythro/threo ratio of 43:57, ca. 10% *n*-$Bu_4P^+Br^-$ present; ^{31}P NMR δ 29.92 (*n*-Bu_4P^+, 8%), 32.65 (threo, 55%), 36.24 (erythro, 37%).

H, Reaction of Ylide 11 and Pivaldehyde To Give Mainly *threo*-(3-Hydroxy-2,2-dimethyl-4-heptyl)tri-*n*-butylphosphonium Bromide (8d, R = *n*-Bu), The procedure was identical with that in part G, except, after the reaction was stirred at −78 °C for 15 min, it was allowed to stir in an ice–salt bath at −10 °C for 30 min. The yellow oil (0.40 g) contained essentially one isomer, **8d** (R = *n*-Bu): ^{13}C NMR (90.56 MHz) δ 13.45 (CH_3 of *n*-BuP), 14.32 (C_7), 20.98 (d, J = 47.4 Hz, CH_2P), 22.10 (d, J = 6.4 Hz, CH_2CH_2P), 22.96 (CH_2), 23.6–24.7 (complex m), 26.29 (threo C_1), 27.0 (erythro C_1, 1–2% by comparison with the peak for threo C_1 at δ 26.29), 30.94 (CH_2), 32.01 (CH_2), 36.29 (threo C_2), 38.19 (d, J = 50.6 Hz, C_4), 76.4 (d, J = ca. 3 Hz, nearly under $CDCl_3$); ^1H NMR (360 MHz) δ 0.85–1.05 (m), 1.3–1.8 (m), 2.1–2.5 (m), 3.855 (dd, J = 3.6, 6.7 Hz, threo C*H*OH), 6.25 (br s, OH); ^{31}P NMR δ 29.92 (*n*-Bu_4P^+, 1.2%), 32.65 (threo, 98.8%); no erythro isomer was detected by ^1H or ^{31}P NMR.

I, Reaction of Ylide 11 and Hexanal To Give *erythro*- and *threo*-(5-Hydroxy-4-decyl)tri-*n*-butylphosphonium Bromide (7c/8c, R = *n*-Bu), The procedure was identical with that described in part G, except 0.14 mL of hexanal (ca. 0.95 molar equiv) was used, and 0.45 g of pale yellow syrup was obtained: ^{13}C NMR (90.56 MHz) δ 13.35 (CH_3 of *n*-BuP), 13.91 and 14.00 (CH_3 at C_1 and C_{10}), ca. 18.5 (d, J = ca. 45 Hz, erythro CH_2P), 18.92 (d, J = 47.3 Hz, *n*-Bu_4P^+), 20.13 (d, J = 46.4 Hz, threo CH_2P), 22.3–22.9 (m), 23.5–25 (complex m), 29.2 (CH_2), 31.6 (CH_2), 35.78 (d, J = 11.2 Hz, erythro C_6), 36.71 (d, J = 7.1 Hz, threo C_6), 37.29 (d, J = 44.1 Hz, erythro C_4), 39.40 (d, J = 46.6 Hz, threo C_4), 67.10 (d, J = 4.3 Hz, erythro C_5), 70.07 (d, J = 4.4 Hz, threo C_5). Comparison of the signals at δ 35.78 and δ 36.71 and δ 37.28 and δ 39.40 gave an ca. 20:80 erythro/threo ratio. Comparison of the signals at δ 18.92 and δ 20.13 indicated that 70% of the material was *n*-Bu_4P^+, presumably due to aldehyde enolate formation. ^1H NMR (360 MHz) δ 0.78 (t, erythro CH_3, 0.75 H), 0.8–0.95 (m, 15 H), 1.2–1.6 (m, 23 H), 2.1–2.4 (m, 10 H), 3.94 (m, threo C*H*OH, 0.2 H), 4.15 (m, erythro C*H*OH, 0.05 H), 6.33 (br s, OH). Integration of the baseline-separated multiplets at δ 3.94 and δ 4.15 gave a 22:78 erythro/threo ratio. ^{31}P NMR δ 29.87 (*n*-Bu_4P^+, 65%), 33.39 (threo, 28%), 34.40 (erythro, 7%).

J, *erythro*-[1-Hydroxy-1-(4-chlorophenyl)-2-butyl]triphenylphosphonium Bromide (13), A suspension of propyltriphenylphosphonium bromide (3.85 g, 10 mmol) in 5 mL of THF in a centrifuge tube was treated with NaHMDS (10 mL of a 1 M solution in THF). After having been stirred for 15 min, the red, cloudy solution was centrifuged, and the red supernatant was transferred under argon to a flask which was then cooled to −78 °C. The solution was treated with 1.41 g of 4-chlorobenzaldehyde (10 mmol), dissipating the red color. After 20 min, HBr gas was added, and the solution was warmed to room temperature. The solution was triturated with ether, and the precipitate was collected. This solid was dissolved in $CHCl_3$, filtered to remove a small amount of undissolved solid, and precipitated with hexane. The material was further recrystallized from CH_2Cl_2/hexane to give 1.2 g of large white crystals (23%), mp 145–147 °C: ^{13}C NMR (90.56 MHz) δ 14.8 (d, 1, C_4, J_{CP} = 11.7 Hz), 19.2 (1, C_3), 46.3 (d, 1, C_2, J_{CP} = 43 Hz), 68.4 (1, C_1), 118.8 (d, 3, α CP (Ar), J_{CP} = 84.0 Hz), 128–135 (20, Ar), 139.8 (d, 1, HOCH-*C* (Ar), J_{CP} = 14.6 Hz); ^1H NMR (360 MHz) δ 0.40 (t, 3 H), 1.65 (m, 2 H), 2.13 (m, 2 H), 3.51 (m, 1 H, CHP), 5.34 (m, 1 H, C*H*OH), 6.18 (br s, 1 H, OH), 7.22 (d, 2 H, J = 8.3 Hz), 7.42 (d, 2 H, J = 8.4 Hz), 7.6–7.9 (m, 15 Hz). Anal. Calcd for $C_{28}H_{27}ClBrOP$: C, 63.95; H, 5.14; Br, 5.90. Found: C, 63.73; H, 4.78; Br, 5.88. Based on ^1H NMR data, relative to those for **7a** and **8a** (R = Ph), the erythro configuration was assigned. No threo isomer was detected by either ^{13}C or ^1H NMR.

Crossover Experiments, These experiments were conducted by using the standard protocol.[12] A 1:1 molar ratio of **13** and either **7a** or **8a** (R = Ph), 40 mg total, was suspended in THF (70 μL) under nitrogen. The solution was cooled to −78 °C and carefully treated with 1 M NaHMDS (THF, 85 μL, 1.1 molar equiv). The solution was kept at −25 °C for 1 h, then allowed to warm slowly, and treated with water. The products were extracted into ether, washed twice with water, dried ($MgSO_4$), filtered, and concentrated. The alkenes were analyzed by GLC and GLC/MS to determine the isomer ratios, which are listed in Scheme II.

The crossover experiments described with **7a** and **8a** (R = *n*-Bu) were conducted in the same manner. As an example, the crossover of a 1.13:1 mixture of **8a**:**7a** (R = *n*-Bu) with 4-chlorobenzaldehyde follows. A solution of the 1.13:1 mixture (25 mg, 0.054 mmol) dissolved in 90 μL of THF was cooled to −78 °C. A 1 M solution of NaHMDS in THF (60 μL, 1.1 equiv) was added, followed by 4-chlorobenzaldehyde (30 mg, 0.21 mmol). The solution was allowed to warm slowly to room temperature over 1 h. Water was added, and the products were extracted into ether, washed twice with H_2O, dried ($MgSO_4$), filtered, and concentrated. GLC and GLC/MS revealed a 1:3 mixture of (*Z*)- and (*E*)-β-propylstyrenes (ca. 50%) and a 1:6 mixture of (*Z*)- and (*E*)-1-(4-chlorophenyl)-1-butenes (ca. 50%).

Kinetic Analysis of Rate Data, In the analysis of kinetic data for the reactions with benzaldehyde, we have assumed that equilibration of intermediate oxaphosphetanes occurs by reaction reversal. (If equilibration were occurring by some other process, such as epimerization, a similar relationship would be obtained for the rate constants.) The equations used in analyzing the NMR data, according to Scheme I, are depicted below (eq 1–5). It should be recognized that lithium salts (LiX) may affect the rate of reaction of ylide and aldehyde.[14] Thus, k_1 and k_2 should be considered as $k_1 = k_1' + Lk_1''$ and $k_2 = k_2' + Lk_2''$, where L represents the concentration of LiX, which remains constant in any particular reaction.

$$d[A]/dt = d[Y]/dt = k_3[C] + k_4[T] - (k_1 + k_2)[Y][A] \quad (1)$$

$$d[C]/dt = k_1[Y][A] - k_3[C] - k_5[C] \quad (2)$$

$$d[T]/dt = k_2[Y][A] - k_4[T] - k_6[T] \quad (3)$$

$$d[ZA]/dt = k_5[C] \quad (4)$$

$$d[EA]/dt = k_6[T] \quad (5)$$

Y = ylide C = *cis*-oxaphosphetane ZA = *Z* alkene

A = aldehyde T = *trans*-oxaphosphetane EA = *E* alkene

Since neither the ylide nor aldehyde could be detected, we have used a steady-state approximation wherein their disappearance is rapid relative to their formation (i.e., k_1 and k_2 are much greater than k_3 and k_4); so, the change in their concentration with time is zero (i.e., $d[Y]/dt = 0$). At −78 °C, the low temperature of mixing, oxaphosphetanes are completely formed but they are not interconverting or decomposing to alkenes. Thus, k_3, k_4, k_5, and k_6 are nearly equal to zero and analysis of eq 2 and 3 affords the ratio $R = [C]/[T] = k_1/k_2$. This ratio is assumed to be independent of temperature, within experimental error. Substitution of R and eq 1 into eq 2 and 3 provided the general eq 6 and 7, which were used along with eq 4 and 5 to calculate the rate constants (k_3, k_4, k_5, and k_6) as well as [C] and [T] at $t = 0$ (using the program NONLIN).[26]

$$d[C]/dt = \{R/(1 + R)\}k_4[T] - \{1/(1 + R)\}k_3[C] - k_5[C] \quad (6)$$

$$d[T]/dt = \{1/(1 + R)\}k_3[C] - \{R/(1 + R)\}k_4[C] - k_6[T] \quad (7)$$

The exact starting time ("real" $t = 0$) was unknown because the first data points were collected after the sample was allowed to equilibrate in the NMR probe at the reaction temperature for ca. 20 min (the sample had to be warmed from −78 to −30 °C in the probe and then stabilized). Thus, an offset in the time scale was introduced such that the sum of weighted, squared deviations between fitted curve and observed data was minimized via iterative calculations.

X-ray Crystallographic Analysis. Data were collected on an Enraf-Nonius CAD4 diffractometer (Mo K_α radiation, $\lambda = 0.71073$ Å) and programs were part of the Enraf-Nonius Structure Determination package, as revised in 1982, and implemented on a PDP 11/34 computer. Crystals of **8a** (R = Ph) were grown from methylene chloride/hexanes (3:1). The crystal used for the analysis, an irregular one cut from a larger crystal, measured 0.3 × 0.3 × 0.25 mm^3.

threo-(1-Hydroxy-1-phenyl-2-pentyl)triphenylphosphonium bromide (**8a**, R = Ph): $C_{29}H_{30}POBr$, mol wt 505.43; orthorhombic, $a = 10.108$ (3) Å, $b = 15.004$ (4) Å, $c = 16.912$ (4) Å, $V = 2565$ (3) Å^3; $d_{calcd} = 1.308$ g/cm^3 for $Z = 4$ molecules/unit cell, space group $Pca2_1$. Of 3301 unique reflections collected up to $2\theta = 56.7°$, 1170 had $I > 2\sigma(I)$ and were used for the subsequent structure analysis (data corrected for Lorentz and polarization factors, but not for absorption). The bromine position was determined by Patterson techniques; the other non-hydrogen atoms were determined from subsequent difference Fourier maps. Final anisotropic refinement of non-hydrogen atoms (benzene carbons were only refined isotropically, and hydrogens were not included) gave $R = 0.061$ and $R_w = 0.063$, where $R = (\Sigma||F_o| - |F_c||)/\Sigma|F_o|$, $R_w = [\Sigma(|F_o| - |F_c|)^2/\Sigma F_o^2]^{1/2}$, and the function minimized was $(\Sigma|F_o| - |F_c|)^2$. A figure showing the crystallographic numbering system and tables of atomic positional parameters, thermal parameters, bond distances, bond angles, and torsional angles are collected in the supplementary material.[24]

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Supplementary Material Available: Figure showing **8a** (R = Ph) with the crystallographic numbering system; tables of bond distances, bond angles, torsional angles, and positional and thermal parameters, for **8a** (R = Ph); complete rate data used in the kinetic analyses; experimental procedures for the preparation of some phosphonium salts (21 pages). Ordering information can be found on any current masthead page.

Kinetics of Ozonation. 5. Reactions of Ozone with Carbon-Hydrogen Bonds

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Abstract: Rates of ozonation for 10 ethers, 2 aldehydes, and 2 saturated hydrocarbons are reported in carbon tetrachloride solvent, over a 36–60 °C temperature range. More limited data are reported in acetonitrile. The resulting activation parameters are inconsistent with a mechanism involving prior complexation of ozone with an α oxygen atom or with hydrogen-atom abstraction. Of the mechanisms previously proposed in the literature, a hydride abstraction and the concerted insertion of ozone into a C–H bond are most consistent with our kinetic data. A comparison of rate constants in carbon tetrachloride to rate constants measured in acetonitrile indicates that the effect of solvent polarity is small, so either an ionic mechanism must involve a high degree of ion pairing or an insertion mechanism involves a dipolar contribution.

Ozone is a reactant of considerable interest in organic chemistry, largely due to its reactions with alkenes.[1] A growing body of work, however, has been reported on the reactions of ozone at carbon–hydrogen bonds.[2-19] Special attention has been given to the reactions of ozone at activated C–H bonds, such as the α hydrogens of alcohols, ethers, and aldehydes and at benzylic positions;[2,3] however, some saturated hydrocarbons also have been studied.[2,3] In a number of cases, the initial products have been

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