The Wittig Olefination Reaction and Modifications Involving Phosphoryl-Stabilized Carbanions. Stereochemistry, Mechanism, and Selected Synthetic Aspects

BRUCE E. MARYANOFF* and ALLEN B. REITZ

Chemical Research Department, Janssen Research Foundation, Spring House, Pennsylvania 19477

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Contents

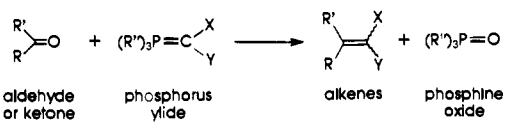
I. Introduction

There was a time in organic chemistry when the olefination of ketones and aldehydes was faced with some trepidation. Because of limited synthetic methods, as recently as 30 years ago, the chemist had to contend with two isomer problems, that of double-bond position and that of double-bond geometry. Landmark papers[1,2] published by Wittig and co-workers in the early 1950s disclosed a means for the preparation of alkenes with unambiguous positioning of the double bond, based on the reaction of aldehydes or ketones with phosphonium ylides (eq 1). Because of its effectiveness and generality, the Wittig reaction became widely used and thereby changed the course of olefin synthesis for all time.[3] Indeed, the development of the Wittig reaction helped to usher in the modern era of organic synthesis, wherein positional selectivity, stereoselectivity, and chemoselectivity are of paramount importance to, and under the sensitive and responsive control of, the synthetic practitioner.[4]

The 1960s witnessed major advances in the Wittig reaction and in Wittig-style olefinations. The stereochemistry and mechanism of the Wittig reaction were investigated, and a complementary reaction involving phosphoryl-stabilized carbanions was developed. Although several reviews have documented the state of the Wittig and related reactions, up to as recently as 1985,[5–17] key recent facets, especially in the areas of stereochemistry and mechanism, have inspired us to compose this article. Our emphasis will be placed on information added to this topic from 1978 to the present. Also, we will present new synthetic highlights from this period of time to provide a full, up-to-date discussion. This review will be limited to reactions of aldehydes and ketones; it will not deal with ester- or amide-type substrates.[18]

II. Phosphonium Ylides

The conventional Wittig reaction entails the reaction of a phosphonium ylide with an aldehyde or a ketone (eq 1). This olefination method has enjoyed wide-



(1)

spread prominence and recognition because of its simplicity, convenience, and efficiency.[5–14] Yet, despite such venerable attributes, the attractiveness of the Wittig reaction in synthesis may often hinge on effective stereocontrol.[7,11,12,19] High selectivity for (*Z*)- or (*E*)-alkenes is available, depending on the particular circumstances, such as the type of ylide, type of carbonyl compound, or reaction conditions.[8,11]

Phosphorus ylides have been loosely classified according to their general reactivity. "Stabilized" ylides have strongly conjugating substituents (e.g., COOMe, CN, or SO_2Ph) on the ylidic carbon and usually favor the production of (*E*)-alkenes, "semistabilized" (or "moderated") ylides bear mildly conjugating substituents (e.g., Ph or allyl) and often give no great preference one way or the other, and "nonstabilized" ylides lack such functionalities and usually favor (*Z*)-alkenes. Of course, there are notable, if not glaring, exceptions to these generalized stereoselectivities, some of which will

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Bruce Maryanoff was born in Philadelphia, PA, in 1947 and has resided in that region for most of his life. He received his B.S. (1969) and Ph.D. (1972, with Professor Robert Hutchins) degrees from Drexel University. After postdoctoral studies with Professor Kurt Mislow at Princeton University (1972–1974), he joined the staff of McNeil Laboratories (renamed McNeil Pharmaceutical in 1980). Following reorganization of the Johnson & Johnson Pharmaceutical Sector in 1987, he became part of the Belgium-headquartered Janssen Research Foundation (JRF) Worldwide. He now holds the position of Distinguished Research Fellow in the laboratories of JRF–US in Spring House, PA. His major research interests have entailed stereochemistry and mechanisms of organic reactions, conformational analysis, monosaccharide chemistry, heterocyclic chemistry, selective reduction processes, and drugs for treating disorders of the central nervous system. He has published over 80 scientific papers, is an inventor on 15 U.S. Patents, and was recipient of the 1984 Section Award of the American Chemical Society, Philadelphia Section. He dedicates this review to his wife Cynthia.

Allen Reitz was born in Alameda, CA, in 1956. He received his B.A. degree (1977) from the University of California at Santa Barbara and his Ph.D. degree (1982) from the University of California at San Diego, working with Professor Murray Goodman. After a 1-year postdoctoral stint with Dr. Maryanoff at McNeil Pharmaceutical, he was appointed to the medicinal chemistry staff. He is currently a Principal Scientist in the Janssen Research Foundation at Spring House, PA. His major research interests include development of new synthetic methods, stereocontrol in cyclization reactions, and synthesis of monosaccharides for therapeutic applications. He has ca. 30 scientific publications to his credit. He dedicates this review to Evelyn, his wife of 10 years, with whom he has two children, Darryl and Meredith.

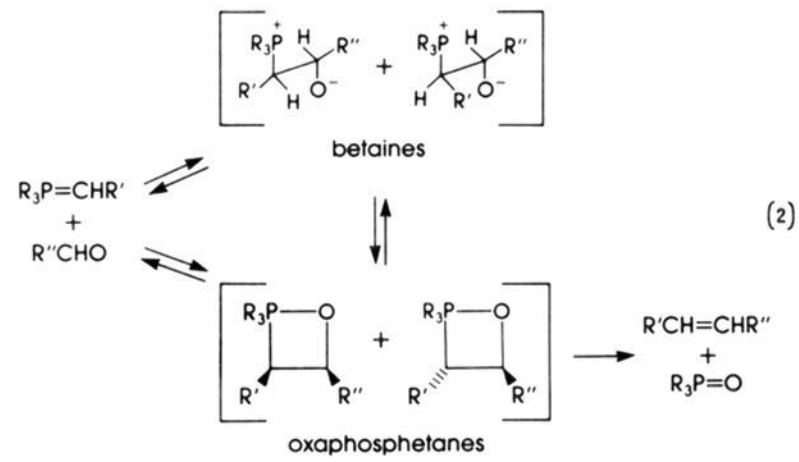
emerge in the subsequent discourse.

A. Stereochemistry and Mechanism

The nonstabilized class of phosphorus ylides is particularly significant mechanistically in that the thermodynamically less stable (*Z*)-alkene is often produced preferentially.[8,11,12,14,19,20] In fact, a certain mystique has persisted with respect to this high preference for contrathermodynamic (*Z*)-alkenes in, for example, reactions of triphenylphosphorus nonstabilized ylides with aldehydes. This characteristic has attracted the curiosity of chemists for decades and stimulated attempts to arrive at a truly satisfying mechanistic explanation. The other two classes of ylides are also interesting from a mechanistic standpoint. For example, one may wonder: Is the strong preference for the (*E*)-alkenes with many stabilized ylides a consequence of kinetic or thermodynamic control? To define the source of such stereocontrol, organic chemists have resorted to mechanistic studies and the pursuit of reaction intermediates. These two subjects will be addressed in section II.A.

1. 1,2-Oxaphosphetanes and Betaines as Intermediates

Regarding intermediates in the reaction, Wittig first mentioned a four-membered cyclic phosphorane (a 1,2-oxaphosphetane) early on;[1] however, he soon came to favor a zwitterionic phosphorus betaine (eq 2).[2,21]



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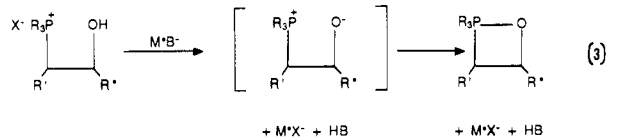
This view gained broad acceptance in the mid 1960s,[5,6,9,22–26] and by 1970 the mechanism of the Wittig reaction was commonly expressed in terms of two steps: (1) nucleophilic addition of the phosphorus ylide to the carbonyl compound to give a betaine species and (2) irreversible decomposition of the betaine to give alkene and phosphine oxide (eq 2).[5–9,22–26] Although the 1,2-oxaphosphetane was widely considered to be a transition state between betaine and final products, rather than a distinct intermediate, two reviews were careful to present the oxaphosphetane as a possible intermediate.[7,9]

Greater weight had been placed on the dipolar betaine intermediate because of certain experimental observations: (1) the formation in situ of stable adducts between betaines and lithium halide salts, (2) the trapping of betaines as β-hydroxy phosphonium salts by addition of acid at low temperature, and (3) the pronounced effect of lithium salts on alkene stereochemistry.[2,5,6,8,9,22–26] However, in 1973 Vedejs reported for the first time that oxaphosphetanes are the sole observable intermediates by ^{31}P NMR spectroscopy in conventional reactions of nonstabilized ylides at low temperature.[27] Vedejs' positive observations, along with the lack of evidence for *uncomplexed* betaines, revolutionized impressions about the Wittig reaction mechanism for most organic chemists. Subsequent work by the Vedejs group, reported in 1981,[20] established 1,2-oxaphosphetanes as principal intermediates in a variety of reactions involving nonstabilized phosphorus ylides and aldehydes or ketones. In the 1980s, Maryanoff and co-workers extended the oxaphosphe-

tane paradigm by detecting and quantitating the short-lived diastereomeric intermediates in Wittig reactions of nonstabilized ylides and aldehydes.[28-32] In general, the ^{31}P NMR signal for pentacoordinate phosphorus in oxaphosphetanes occurs far upfield (e.g., from −50 to −80 ppm) relative to the reference (at 0 ppm), while the signal for tetracoordinate phosphorus in a betaine would be expected to occur downfield (e.g., from 10 to 50 ppm).

The relative importance of oxaphosphetanes vs betaines as intermediates has been a persistent concern. To date, true betaines have never been observed directly in any Wittig reaction. The precipitates formed in certain lithium salt reactions[22] are really betaine–lithium halide adducts, which should not be confused with "salt-free" (i.e., uncomplexed) betaines. Such complexes can arise by the addition of a lithium salt (mild Lewis acid) across the P–O bond of a preformed oxaphosphetane,[20] as opposed to direct formation. By the same token, the production of β-hydroxy phosphonium salts on treatment of Wittig reactions with acid at low temperature can be attributed to oxaphosphetanes, which are readily cleaved by addition of HX across the P–O bond.[20,22,31] Even in cases where the betaine must be generated first, such as in deprotonation of a β-hydroxy phosphonium salt with base (eq 3), only oxaphosphetane species have been noted by NMR spectroscopy.[31,33,34]



(3)

Since the course of the Wittig reaction virtually demands an oxaphosphetane stage, the question arises: Does a betaine precede the oxaphosphetane stage (Wittig reaction of three distinct steps: ylide + aldehyde → betaine → oxaphosphetane → alkene) or is the oxaphosphetane formed directly from ylide and aldehyde? From the body of experimental data, Vedejs[20,34b] has argued that a four-centered transition state leading directly to oxaphosphetane is more likely. Also, several theoretical studies have strongly favored oxaphosphetanes over betaines.[10b,12,35,36]

In calculations for the reaction of $H_3P{=}CH_2$ and CH_2O (4-31G* level), the activation energy to form oxaphosphetane (axial oxygen) is ca. 7 kcal/mol, while that to form betaine is ca. 32 kcal/mol.[35] 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 (axial 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 with 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.

The results of earlier ab initio SCF (STO-3G) calculations on a model Wittig reaction of $H_3P{=}CH_2$ and formaldehyde are in substantial agreement.[36] This 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 MeCHO.[10b,12] 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).

(a) *Decomposition of Oxaphosphetanes.* In principle, oxaphosphetanes can fragment in two directions: to ylide and aldehyde (retro-Wittig reaction) or to alkene and phosphine oxide. In practice, both of these processes have been recorded, and their relative proportion appears to be dependent on oxaphosphetane structure, particularly the substituents appended to the ring, and on reaction conditions, such as in response to the presence of lithium salts.[20,22,23,31,34,37-40] On the whole, these reaction pathways represent a dynamic state that is balanced by the relative rates for the various processes (e.g., see section II.A.2.b). Failure to detect reversal experimentally does not necessarily mean that it is nonexistent, just that its rate is noncompetitive with the forward reaction, the facility of which poses an obstacle to complete elucidation of the Wittig reaction mechanism in many cases.

Generally, oxaphosphetanes are thermally unstable; they readily disintegrate to alkene and phosphine oxide below room temperature. Reasonable decomposition rates for various oxaphosphetanes derived from nonstabilized ylides have been documented at −30 to 0 °C.[20,30,31,34a] The adduct from $MeCH{=}PPh_3$ and PhCHO (presumably mostly cis oxaphosphetane because of the salt-free conditions) was reported to have a half-life at −8 °C of ca. 30 min, and at 20 °C of ca. 1.5 min; oxaphosphetanes from $CH_2{=}PPh_3$ were found to be much more transient.[20] Decomposition of oxaphosphetanes derived from cyclobutanone and 2-norbornanone was the most retarded, requiring temperatures in excess of 0 °C.[20] We have performed rate studies on the decomposition and interconversion of cis and trans oxaphosphetanes,[30,31] details of which will be described in section II.A.2.b.

In the case of semistabilized ylides, oxaphosphetanes have generally not been detected even at temperatures as low as −100 to −80 °C,[31,34c] and there probably can be little hope for oxaphosphetanes from stabilized ylides. This, of course, presents a problem for mechanistic studies on these ylides, which is discussed further in section II.A.3. An exceptional case, in which oxaphosphetanes from semistabilized ylides have been observed, is mentioned there as well.[34c]

Some oxaphosphetanes are stable enough to be isolated; examples of these are presented in section II.A.1.c.

The mechanism of collapse of an oxaphosphetane to ylide and aldehyde is presumably the opposite of direct condensation, given microscopic reversibility. The mechanism for decomposition of an oxaphosphetane to alkene and phosphine oxide is a separate issue of considerable interest.[10,12,35,36,40-42] Is this process concerted or stepwise, syn or anti, in nature? Bestmann has

promoted the hypothesis of a stepwise path with the concentration of negative charge on carbon and positive charge on phosphorus, in a sort of E2 elimination mechanism.[10,12] This could account for the high *E* stereoselectivity of stabilized ylides, where the opportunity for epimerization by bond rotation would be enhanced. Trindle et al., in a CNDO study,[41] proposed a stepwise fragmentation with advanced cleavage of the oxaphosphetane P–C bond, in concurrence with Bestmann's view. However, entry into the Wittig manifold for a stabilized ylide by the deprotonation route (q.v. eq 3) has provided evidence against such heterolysis of the carbon–phosphorus bond (details are in section II.A.3).[40] Additionally, a similar lack of reversibility has been observed in deprotonation experiments with the β-hydroxy phosphonium salt diastereomers from the $Ph_2MeP{=}CHPh$/benzaldehyde system under most conditions (refer to section II.A.3).[23,31,43,44] Although an anti elimination of $Ph_3P{=}O$ from oxaphosphetanes was proposed by Thacker et al.,[42a] this has been invalidated by stereochemical results: diastereomeric oxaphosphetanes generally afford alkenes with retention of configuration (corresponding to syn elimination).[20,23,31,43,44] In most instances where stereomutation has been registered, it has proceeded in an energetically downhill direction to trans oxaphosphetane/(*E*)-alkene and has been attributed to equilibration by reversal.[31,34,45]

The ab initio work of Volatron and Eisenstein[35] supports oxaphosphetane decomposition that is "concerted (supra, supra) in a geometric sense, the four heavy atoms being coplanar", with an activation energy of ca. 29 kcal/mol. Similarly, the ab initio calculations of Höller and Lischka[36] showed a concerted reaction with an ca. 25 kcal/mol barrier for dissociation of oxaphosphetane into ethylene and phosphine oxide. Thus, the theoretical work[35,36] may be more in accord with a concerted decomposition mechanism.

Vedejs and Marth have discussed oxaphosphetane decomposition and its relationship to pseudorotation (see next section).[42b] The barrier to pseudorotation could govern the rate of decomposition if bond reorganization at phosphorus were rate determining; however, as indicated in section II.A.1.b, this is not the case for the systems derived from nonstabilized ylides studied thus far. The transition state from oxaphosphetane → alkene was viewed by Vedejs and Marth as an asynchronous cycloreversion with advanced P–C bond breaking.[42b]

(*b*) *Oxaphosphetane Pseudorotational Isomers.* Bestmann has emphasized that the first oxaphosphetane(s) produced from condensation of an ylide and aldehyde should have an axial (apical) P–O bond.[10,12] To fragment into products, this oxaphosphetane conformation must pseudorotate to one possessing an axial P–C bond, where this carbon is the one to be eliminated.[46,47] This idea is related to the general rule of "apical entry/apical departure" for nucleophilic substitution reactions at pentacoordinate (trigonal bipyramidal) phosphorus.[46]

Although various ab initio calculations[35,36,48] have indicated only a small energy difference between the two pseudorotameric arrangements, the known apicophilicity for electronegative oxygen should cause the initial (P–O axial) oxaphosphetane form to predominate.[46] For a very simplified oxaphosphetane, Bestmann's ab initio MO calculations, with a split-valence 4-31G basis set, gave an energy difference between axial and equatorial P–O forms of 7.6 kcal/mol, with the former being more stable.[10b,48]

Bestmann mentioned the detection of different pseudorotameric oxaphosphetanes,[12] but this has not been followed up in the primary literature. In our research, no evidence has been found for pseudorotational isomers at temperatures often as low as −50 to −80 °C.[31] We did record some temperature-dependent broadening of NMR resonances for cis oxaphosphetanes, relative to the trans form, which was accentuated in going from −20 to −60 °C.[31] This suggests a dynamic process, perhaps connected with oxaphosphetane pseudorotation. In the usual situation, the pseudorotational form of the oxaphosphetanes recorded by NMR methods in our work[28-32] and the work of Vedejs[20,34a] has not been proven. It is likely, however, that the oxaphosphetane species under observation were axial P–O forms (as expected from the apicophilicity rule[46]) and that they rapidly interconvert on the NMR time scale (sufficient to make both axial and equatorial P–O forms available to the alkene-forming step). In fact, the sizable P–C one-bond coupling constants of 85.0 and 83.7 Hz reported[31] for two standard, ^{13}C-labeled oxaphosphetanes (viz., **26a** and **26b** in eq 7) support a strong predominance of the axial P–O conformer.[49a]

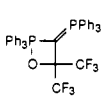
Vedejs and Marth also reported fast pseudorotation for a standard, unconstrained oxaphosphetane at ca. −80 °C.[42b] However, by employing a dibenzophosphole (DBP) ligand on phosphorus, which is known to elevate markedly the barrier for pseudorotation in phosphoranes,[49b] they were able to observe oxaphosphetane pseudorotamers for the first time (by ^1H and ^{13}C NMR at low temperature). Thus, the oxaphosphetane from condensation of $(DBP)MeP{=}CH_2$ and 3-pentanone displayed two sets of ^1H NMR signals at ca. −50 °C for the ring methylene and the ethyl protons, which coalesced around room temperature. Line-shape analysis afforded an activation free energy of 13.1 kcal/mol. For this oxaphosphetane, the ^{13}C NMR data defined a structure having an axial P–O bond and an axial aryl substituent; the pseudorotation rate (5.6×10^3 s^{-1}) at 43 °C differed from the decomposition rate (7.3×10^{-5} s^{-1}) by an enormous margin, corresponding to $\Delta G^{\ddagger}$ = 11.5 kcal/mol. By extrapolation, the pseudorotation rate for an unconstrained oxaphosphetane was estimated to be ca. 3×10^3 s^{-1} at ca. −80 °C. The Vedejs–Marth paper indicates that barriers to pseudorotation should not be rate limiting in the conventional Wittig reactions involving nonstabilized ylides.[42b]

(*c*) *Isolable Oxaphosphetanes.* As mentioned earlier, the 1,2-oxaphosphetanes generally observed to date are rather unstable species.[20,31,34] However, certain oxaphosphetanes are sufficiently robust to be detected, if not isolated, *above 0 °C.*[20,34a,50-53,56,58,60-62]

Vedejs et al.[20] indicated that adducts from cyclobutanone and 2-norbornanone are stable above 0 °C, but isolation was not performed. However, a crystalline oxaphosphetane was obtained from the reaction of *p*-chlorobenzaldehyde with $CH_2{=}PPh_3$ and characterized; the solid readily decomposed at 20 °C. This oxaphosphetane (along with several others) was characterized by 270-MHz ^1H NMR [toluene-d_8: δ 4.03 (dd,

2, $H_3/H_{3'}$, J = 7 Hz, $^2J_{PH}$ = ca. 16 Hz), 4.55 (dt, 1, H_4, both J = 7.0 Hz, $^3J_{PH}$ = 6.6 Hz)] and 40.5-MHz ^{31}P NMR (−68 ppm).[20]

Birum and Matthews[50a] isolated stable oxaphosphetane 1 (mp 155–157 °C (dec); ^{31}P NMR: 7.3 and −54 ppm) from the reaction of hexafluoroacetone with $Ph_3P{=}C{=}PPh_3$. Heating of 1 above 110 °C yielded $Ph_3P{=}C{=}C(CF_3)_2$ and $Ph_3P{=}O$, in completion of the Wittig olefination process.



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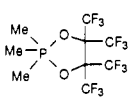

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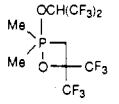

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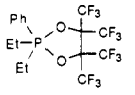

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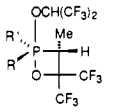
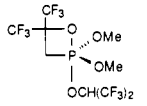


5a R = Et, R' = Ph (major)

5b R = Ph, R' = Et (minor)

5c R = R' = Ph

5d R = R' = Et

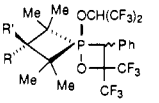


6

Ramirez and co-workers also obtained stable oxaphosphetanes by using hexafluoroacetone.[51-53] Oxaphospholane 2, from Me_3P and hexafluoroacetone, rearranged to oxaphosphetane 3[54] on heating at 80 °C (mp 45 °C; ^{31}P NMR: −24 ppm); further heating of 3 at 120 °C produced $(CF_3)_2C{=}CH_2$ and phosphinate $Me_2P(O)OCH(CF_3)_2$, as expected.[51] Ramirez synthesized and pyrolyzed a series of oxaphosphetanes analogous to 3.[51] 1,3,2-Dioxaphospholane 4 was particularly interesting in that its thermolysis generated two diastereomeric oxaphosphetanes, **5a** and **5b**, in unequal proportion (^{31}P NMR: −30 and −21 ppm, respectively), each of which underwent further thermolysis to the same olefin, $(CF_3)_2C{=}CHMe$. The relative amount of the diastereomers varied with the age of the sample, especially at elevated temperatures.[52a,55] This was eventually ascribed to contaminants since scrupulously purified samples of **5a** and **5b** did not stereomutate prior to decomposition, although they did equilibrate readily on treatment with $(CF_3)_2CHOH$.[55c] The group on the ring carbon and the ligands on phosphorus influenced the rate of oxaphosphetane decomposition; the order of stability was **3 < 5d < 5a/5b < 5c**.

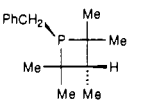
Stable oxaphosphetanes with additional alkoxy substituents on phosphorus (e.g., **5** with one alkoxy or two alkoxy ligands for R and R') were also prepared by Ramirez and co-workers.[52b,d] Derivatives diastereomeric by virtue of the groups on phosphorus were readily equilibrated above 100 °C under $(CF_3)_2CHOH$ catalysis. Methoxide displacement chemistry on **6** (^{31}P NMR: −36 ppm), involving substitution at the phosphorus center and ligand permutation, was also studied.[52d]

Oxaphosphetane **7a**, strained by virtue of two four-membered rings fashioned into a spirocyclic array, was prepared (from trans phosphetane 8 and hexafluoroacetone) and isolated by Oram and Trippett (^{31}P NMR: −10 ppm).[56,57] This molecule decomposed above 70 °C to the expected olefin, $PhCH{=}C(CF_3)_2$, and the cis phosphinate **9a**, which reflected the phosphetane ring geometry shown in **7a**, given retention of configuration at phosphorus. On treatment with hexafluoropropanol at room temperature, **7a** slowly isomerized to afford another stable oxaphosphetane, suggested to be **7b**;



7a R = H, R' = Me

7b R = Me, R' = H



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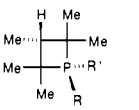
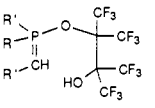


9a R = O, R' = OCH(CF3)2

9b R = OCH(CF3)2, R' = O



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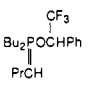

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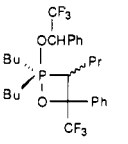

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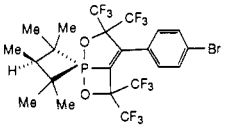
after 18 h, an equilibrium mixture was obtained (**7a**:**7b** = 1:10). Thermal degradation of this final mixture gave the cis and trans phosphinates, **9a** and **9b**, in a 1:10 ratio.

Ramirez drew an important conclusion in his 1968 paper[51] that his observations pointed to 1,2-oxaphosphetanes as intermediates in the Wittig olefination reaction. Mechanistically, he proposed that the oxaphospholane rearrangement proceeds to oxaphosphetane via ylide **10** in what is tantamount to a Wittig reaction wherein the carbonyl compound is delivered intramolecularly. Furthermore, Ramirez[51] speculated that the previously reported[58] reaction of tributylphosphine and $PhC(O)CF_3$, which produces two isomers of $PrCH{=}C(CF_3)Ph$ (Z/E = 1:3), actually involves a Wittig-like condensation of ylide **11** with a second mole of ketone to give two diastereomeric oxaphosphetanes (**12**) that are "isomers at carbon" [of the ring[59]]. Experimental support for oxaphosphetanes, diastereomeric at the ring carbon, in this reaction was supplied later [2.5:1 ratio; ^{31}P NMR: −23 ppm (major) and −21 ppm (minor)].[52a] Apparently, Ramirez' revelation had little impact on mechanistic thinking about the standard Wittig olefination reaction.

A single-crystal X-ray analysis was performed on **5c** (mp 70 °C); the molecular structure appeared as depicted here.[53] X-ray crystal structures for two unusual, ring-fused oxaphosphetanes, **13**[60] and **14**,[61] have been



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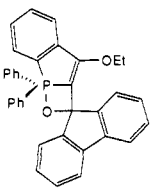

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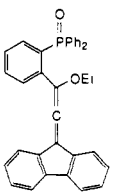

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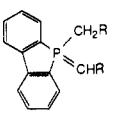
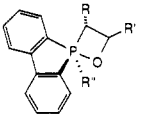


16a R = Me

16b R = Pr



17 a: R = Me, R' = CH_2CH_2Ph, R'' = Et

b: R = Me, R' = $C(Me)_2CH_2Ph$, R'' = Et

c: R = $CH{=}CH_2$, R' = c-Hx, R'' = Me

d: R = $CH{=}CH_2$, R' = c-Hx, R'' = Ph

reported more recently. Compound **13** is structurally interesting in that there are three small rings incorporating the same pentacoordinate phosphorus atom and a phosphetane ring bridging two equatorial positions.[60] Bestmann found that **14**, which is quite resistant to thermal decomposition, proceeded on heating to allene

15 and fluorenone. He suggested that this behavior of 14 confirms the fact that ligand rearrangement about phosphorus, to give an axial nucleofuge, occurs in the course of the Wittig reaction (see section II.A.1.b); with 14, the required pseudorotation is presumably retarded by the rigidity of the molecular skeleton.[61]

Recently, Vedejs disclosed relatively stable oxaphosphetanes containing the dibenzophosphole moiety.[34a,62] Salt-free ylides **16a** and **16b** reacted readily with aldehydes at −78 °C, and the resulting oxaphosphetanes (e.g., **17a** and **17b**) were very resistant to decomposition. Thermal fragmentation to alkene and phosphine oxide occurred over 5–10 h at 70 °C or ca. 30 min at 110 °C.[62] For the oxaphosphetane from (DBP)MeP=CH_2 and 3-pentanone, a $\Delta G^{\ddagger}$ for decomposition of ca. 25 kcal/mol was ascertained.[42b] Vedejs and Marth suggested that such oxaphosphetane stability results from the narrow bond angle (ca. 94°) for the C–P–C unit of the dibenzophosphole group (e.g., **17**), which better accommodates the trigonal-bipyramidal phosphorus (spanning axial and equatorial positions) than the tetrahedral phosphorus of ylide or phosphine oxide. No attempts to isolate and characterize such stable oxaphosphetane compounds have been reported.[34a,62] (As will be discussed later in sections II.A.4 and II.B.1.e, this procedure has afforded alkenes with unusually high *E* stereoselectivity.)

The use of dibenzophosphole stabilization was nicely applied to the observation of oxaphosphetanes derived from semistabilized ylides, such as **17c** and **17d**.[34c] These were still very fleeting species, so further details surrounding them are reserved for section II.A.3.

2. Nonstabilized Ylides

As mentioned above, there has been a mystique associated with the high preference for the contrathermodynamic (*Z*)-alkene in reactions of triphenylphosphonium nonstabilized ylides with aldehydes. For more than two decades, organic chemists have tried to identify the specific factors involved in such stereocontrol. Thus, stereochemistry has served as the premier probe for acquiring mechanistic information on the Wittig reaction and, coincidentally, it has led to a deeper understanding of the mechanism. The pronounced *E* stereoselectivity in reactions of aldehydes with trialkylphosphonium ylides, and with triphenylphosphorus ylides bearing anionic groups, has merited considerable interest as well.

We will review these major facets of nonstabilized ylide chemistry in this section, with a strong emphasis on results that have emanated from our research group over the years 1981–1986. This encapsulation of our work will be projected in a narrative fashion from a personal perspective. Although relevant work of other investigators will also be cited here, as deemed appropriate, in-depth elaboration on that material is reserved for section II.A.4.

(a) Observation of Oxaphosphetane Diastereomers by ^{31}P NMR. By 1982, 1,2-oxaphosphetanes were well-accepted intermediates, at least for Wittig reactions of nonstabilized ylides,[10,20,63,64] However, their existence had not been exploited to address one of the fundamental issues of the Wittig reaction—namely, stereochemistry. For many years, researchers have measured the ratios of (*Z*)- and (*E*)-alkenes from diverse Wittig reactions to develop an understanding of the stereochemistry for the initial carbon–carbon bond-forming step.[7,8,11] Such *Z*/*E* ratios were frequently presumed to have a 1:1 correspondence with the ratios of the primary Wittig intermediates (cis/trans oxaphosphetanes or erythro/threo betaines). It turns out that this presumption may or may not be true, depending on the specific case under consideration. Indeed, throughout this article, we will make a point of delineating different cases. In any event, it seemed to us that the observation and measurement of diastereomeric oxaphosphetanes in the course of the reaction would do well to establish the original stereochemistry of the carbon–carbon bond-forming step.

Our desire to detect and quantitate diastereomeric Wittig intermediates stemmed from a study of anomalous stereochemistry caused by anionic groups on the ylidene chain of phosphorus ylides.[28,65] In 1980, amidst a project concerning the synthesis of leukotriene analogues, we reacted **18** with benzaldehyde, under "lithium salt" conditions. Surprisingly, the resulting mixture of 6-phenyl-5-hexenoic acids (**19**; eq 4) was chiefly composed of the (*E*)-olefin acid (**19a**:**19b** = 12:88).[65a] Ylide **18**, commonly employed in the synthesis of prostaglandins and related compounds, is recognized to combine with aliphatic aldehydes in a highly *Z*-selective fashion.[66] Therefore, some special factor had to be contributing to the high *E* stereoselectivity with benzaldehyde.

$$Ph_3\overset{+}{P}(CH_2)_4COOH\ Br^- \xrightarrow[2)\ PhCHO]{1)\ LiN(TMS)_2} PhCH=CH(CH_2)_3COOH \qquad (4)$$
$$Z/E = 19a/19b = 12:88$$

$$Ph_3\overset{+}{P}(CH_2)_3CH_3\ Br^- \xrightarrow[2)\ PhCHO]{1)\ LiN(TMS)_2} PhCH=CH(CH_2)_2CH_3 \qquad (5)$$
$$Z/E = 21a/21b = 50:50$$

$$Ph_3\overset{+}{P}(CH_2)_3CH_3\ Br^- \xrightarrow[\substack{LiOC(O)nC_5H_{11}\\ 2)\ PhCHO}]{1)\ LiN(TMS)_2} PhCH=CH(CH_2)_2CH_3 \qquad (6)$$
$$Z/E = 58:42$$

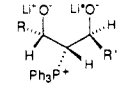
A similar reaction of reference ylide **20**, which lacks the carboxylate group, gave alkenes **21a** and **21b** in a 50:50 ratio (eq 5), implicating the carboxylate of ylide **18** in the anomalous *E* stereoselectivity. Additionally, results with **20**, benzaldehyde, and lithium hexanoate (eq 6) suggested that anomalous *E* stereoselectivity depends on an intramolecular carboxylate group.[28]

Exaggerated *E* stereoselectivity had been reported in several papers from 1970 to 1980 for β- and γ-oxido ylides,[67–72] which are analogous to our carboxylate ylides by virtue of the metallo-anionic substituent. Corey[69] discussed the anomalous *E* stereoselectivity of β-oxido ylides in terms of preferential formation of a *rac*-dioxido phosphonium intermediate, such as **22**, which would be

$Ph_3P=CH(CH_2)_3COO^-Li^+$ (16)

$Ph_3P=CHR$: 20 R = nPr; 25 R = Me

$Ph_3P=CH(CH_2)_nO^-Li^+$: 23 n = 4; 24 n = 2



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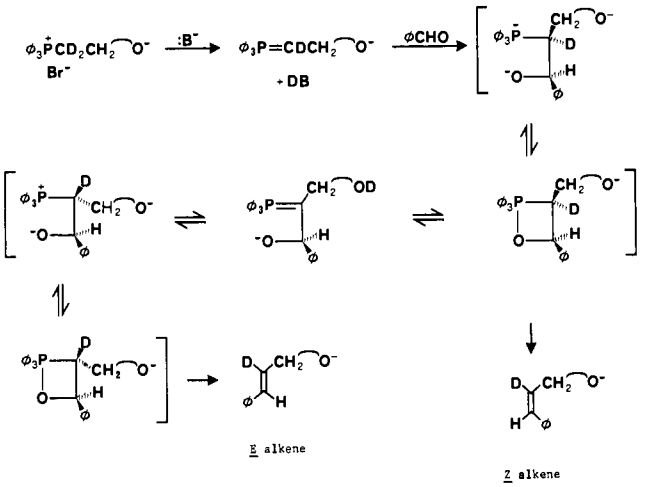
more inclined to eliminate the (*E*)-alkene (vide infra).[28] Alternatively, the atypical *E* stereoselectivity of γ-oxido ylides was rationalized by a mechanism involving internal proton exchange,[70,71] analogous to the intermolecular exchange in the *E*-selective Wittig equilibration

SCHEME I



process described by Schlosser.[73-75] Accordingly, the basic alkoxide group would equilibrate the Wittig intermediates, be they betaines or oxaphosphetanes, by transfer of a proton (or deuteron) from the stereogenic carbon atom next to phosphorus to the oxygen atom, prior to excision of the alkene (e.g., see Scheme I).

Our early data militated against the internal proton-transfer mechanism.[65a,b] First, the carboxylate group in δ-carboxy ylide **18** is only weakly basic, possibly making it inadequate for proton exchange. Second, the enhanced production of (*E*)-alkene was substantially dispelled in going from an aromatic to an aliphatic aldehyde, a change that should have little bearing on proton transfer. Third, ϵ-oxido ylide **23** did not give surplus amounts of (*E*)-alkene with aliphatic aldehydes, although it did with aromatic aldehydes.[65b,76] These apparent discrepancies spurred us to launch a systematic study of the effect of anionic or nucleophilic substituents on the stereochemistry of the Wittig reaction. The project encompassed reactions of carboxy, oxido, and amino phosphorus ylides with varying distances between the nucleophilic and ylide centers, the use of α-deuterated ylides as mechanistic probes, and the use of ^{31}P NMR spectroscopy for assessing the original stereochemistry of carbon–carbon bond formation.[28]

In reactions with aldehydes, triphenylphosphorus ylides bearing anionic groups, such as oxido or carboxylate, on the ylidene side chain show a shift in stereochemistry of the alkene products toward the *E* isomer (relative to reference reactions; Figure 1). This shift in stereochemistry is often stronger with aromatic aldehydes than with aliphatic aldehydes and is highly dependent on the distance between the anionic and phosphorus centers (Figure 1).[28] For carboxylate ylides, the anomalous shift to the *E* direction, compared with references, is also independent of whether the ylides are generated via lithium, sodium, or potassium bases, although the amount of *E* selectivity is more pronounced with lithium present.[28]

To define a mechanism for the anomalous *E* stereoselectivity, we substituted α-deuterated ylides[28,77] into certain reactions (Table I). If a proton-transfer process were responsible for equilibrating a first-formed, cis-rich mixture of oxaphosphetanes (or erythro-rich mixture of betaines) to a trans-rich (or threo-rich) mixture, then considerable deuterium could be lost to an appropriate proton source (Scheme I). With 5 mol equiv of hexamethyldisilazane present, full equilibration would afford alkenes having a statistical H/D isotopic distribution of 83:17. The reference reaction with benzaldehyde (Table I, entry 1) showed a normal (*Z*)/(*E*)-alkene ratio and retention of deuterium at the 85% level. With benzaldehyde, oxido and carboxylate ylides (entries 2 and 3) showed anomalous *E* stereoselectivity and 70–75% deuterium in each alkene; with hexanal, the oxido ylide (entry 4) behaved similarly. These observations exclude intramolecular base-induced equilibration (Scheme I) as a major factor in the anomalous *E* stereoselectivity.[28] Additional support for this understanding derives from the observation of *E* selectivity when a methyl group replaced the potentially exchangeable proton.[69a,b,75a,c]

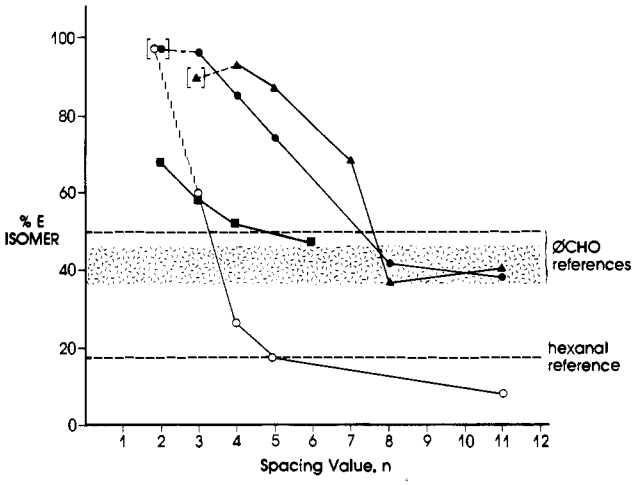


Figure 1. Variation of alkene *Z*/*E* ratio with the distance of the nucleophilic group from the ylide center. Each reaction involved a phosphonium salt, an aldehyde, and LiHMDS in THF under standard conditions, except for those in brackets (see ref 28). Symbols: (●) $Ph_3P{=}CH(CH_2)_nO^-Li^+$ (n = 2–5, 8, 11) and PhCHO; (▲) $Ph_3P{=}CH(CH_2)_{n-1}COO^-Li^+$ (n = 3–5, 7, 8, 11) and PhCHO; (■) $Ph_3P{=}CH(CH_2)_nNMe_2$ (n = 2–4, 6) and PhCHO; (○) $Ph_3P{=}CH(CH_2)_nO^-Li^+$ (n = 2–5, 11). Reference reactions with **20** are indicated.[28] The lines connecting the points are present as an aid to the viewer.

TABLE I. **Proton–Deuterium Exchange Experiments**

$$Ph_3P{=}CD(CH_2)_nX \xrightarrow[-78\ °C]{RCHO} \xrightarrow[5\ equiv]{HN(TMS)_2} RCH{=}CD(CH_2)_nX$$

R	phosphonium salt	base (equiv)	*E*/*Z* ratio	% D in alkenes[a]
Ph	$Ph_3P^+CD_2$-$(CH_2)_2CH_3\,Br^-$	*n*-BuLi (1.0)	38/62	85
Ph	$Ph_3P^+CD_2(CH_2)_2OH\,Br^-$	*n*-BuLi (2.1)	88/12	70
Ph	$Ph_3P^+CD_2$-$(CH_2)_3COOH\,Br^-$	*n*-BuLi (2.1)	80/20	75
n-C_5H_{11}	$Ph_3P^+CD_2(CH_2)_2OH\,Br^-$	*n*-BuLi (2.1)	61/39	70

[a] Statistical H/D distribution: 17% D, 83% H.

The inordinate shift to *E* isomer could be due primarily to reversibility of Wittig intermediates (retro-Wittig reaction), facilitated by the metallo-anionic substituent. During reversible regeneration of ylide and aldehyde from intermediate adducts, trapping of the ylide with a different, but similarly reactive, aldehyde is possible. Such crossover experiments had already shown that betaines or oxaphosphetanes from aromatic aldehydes experience significant reversal, whereas those from aliphatic aldehydes do not.[20,22,39]

Since the short-chain oxido ylides exhibited striking anomalous *E* stereoselectivity with aliphatic aldehydes,

we sought to determine if this is affiliated with reversibility.[65d] Experiments with ylides **18** and **20**, which fail to show anomalous *E* stereoselectivity with aliphatic aldehydes, did not show crossed products. On the contrary, γ-oxido ylide **24**, which manifests strong anomalous *E* stereoselectivity, gave a considerable amount of crossed alkenes.[28,65d] This first example of a reversible Wittig intermediate derived from an aliphatic aldehyde and a nonstabilized triphenylphosphorus ylide logically suggests that the metalloxido group facilitates reversal of the intermediate species to ylide and aldehyde.

At this juncture, we realized that additional insight into the reaction mechanism for anionic ylides would require an evaluation of diastereomeric intermediates. Vedejs[20,27] had employed ^{31}P NMR spectroscopy to detect oxaphosphetanes directly in the Wittig reaction at low temperature; however, resolved resonances for the individual cis and trans species were generally not observed.[78] We first examined a standard case involving **20**, which is related to ylide **25**, studied by Vedejs.[20] Ylide **20** was generated from butyltriphenylphosphonium bromide and lithium hexamethyldisilazide[79a] (LiHMDS) in THF and reacted with benzaldehyde at −78 °C in an NMR tube (0.5 M). The proton-decoupled, 145.8-MHz ^{31}P NMR spectrum revealed *two, baseline-separated singlets* at −61.4 and −63.8 ppm in a 75:25 ratio, which represented oxaphosphetanes **26a** and **26b** and slowly disappeared on standing at −30 °C (structures are presented in eq 7). After warming to 25 °C, analysis of the alkenes showed a *Z*/*E* ratio of 59:41 (**21a**:**21b**). Surprisingly, the product ratio did not coincide with the ratio of isomeric oxaphosphetanes at −78 °C, where the 75:25 ratio of **26a**:**26b** reflects the stereochemistry of the original carbon–carbon single bond. For convenience, we have referred to this phenomenon as "stereochemical drift".[79b]

Under lithium salt free conditions (NaHMDS as base[79a]), ylide **20** reacted with benzaldehyde at −78 °C to give a >98:2 ratio of **26a**:**26b** (sharp singlet at −61.9 ppm and eventually a 96:4 ratio of (*Z*)- and (*E*)-β-propylstyrenes, **21a** and **21b**. Here, high *Z* stereoselectivity and little stereochemical drift are realized.

The lithium salt reaction of **20** with hexanal at −78 °C produced cis and trans oxaphosphetanes (at −59.7 and −64.3 ppm) in a 5.8:1 ratio, which was perfectly retained in the product alkenes (*Z*/*E* = 5.8:1). Again, there is an absence of stereochemical drift, which was entirely expected in this case since intermediates in Wittig reactions of nonstabilized triphenylphosphorus ylides and aliphatic aldehydes normally are not reversible and do not equilibrate significantly.[20,39]

We were now poised to explore reactions of anion-bearing ylides and determine whether the presence of anionic groups has a greater influence on the initial formation of oxaphosphetanes or on the extent of oxaphosphetane equilibration by retro-Wittig reaction. Ylides **18**, **23**, and **24** were separately reacted with benzaldehyde in THF at −78 °C, dissipating the red ylide color, and the resultant solutions were assayed by ^{31}P NMR.[28] The spectrum for lithio carboxy ylide **18**, at −45 °C and 0.25 M, depicted two oxaphosphetane resonances at −59.5 and −62.0 ppm in a 1:1.2 ratio; at 0.125 M, we measured a cis/trans ratio of 8:1.[80] The use of sodium or potassium ions gave cis/trans ratios of 2.2:1 (−55 °C) or 6:1 (−80 °C), respectively.[80b] On warming, these reactions yielded a disproportionate amount of (*E*)-alkene (*Z*/*E* = ca. 10:90) relative to the original cis/trans ratios, independent of the cation. Thus, the initial stereochemistry of the Wittig reaction of **18** is much more biased toward cis oxaphosphetane than the ultimate (*Z*)/(*E*)-alkene ratio would indicate, such that the stereochemistry of carbon–carbon bond formation is more consistent with expectations.

Reactions of lithio ylide **18** with aliphatic aldehydes bolster this view. With hexanal at 0.125 M and −80 °C, we observed a pair of singlets at −59.8 and −64.5 ppm in a 2.7:1 ratio for cis and trans oxaphosphetanes, respectively. A similar reaction of **18** with nonanal at 25 °C afforded alkenes with a *Z*/*E* ratio of 2.7:1.

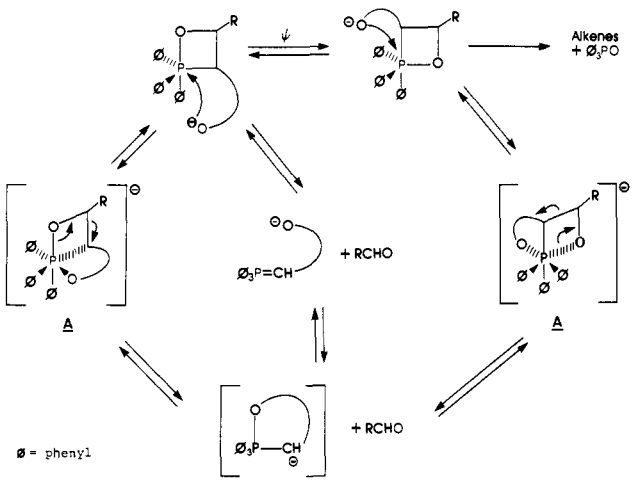
The ^{31}P NMR spectrum for lithio oxido ylide **24** and benzaldehyde at −80 °C (0.5 M) displayed two major singlets at −61.0 and −63.6 ppm, attributed to cis and trans oxaphosphetanes. The initial cis/trans ratio of 1:2.2 changed to a 1:14 ratio on standing at −55 °C for 30 min, reflective of robust stereochemical drift. The corresponding preparative reaction at 25 °C gave a *Z*/*E* ratio of 1:24. The NMR spectrum of lithio oxido ylide **23** and benzaldehyde at 0.17 M at −55 °C revealed an 8:1 ratio of resonance lines at −59.5 and −62.0 ppm for cis and trans oxaphosphetane. Here, the preparative reaction at 25 °C showed a (*Z*)/(*E*)-alkene ratio of 1:6. Thus, anomalous *E* stereoselectivity with ylides **18**, **23**, and **24** appears to be associated with facilitated reversibility of intermediate oxaphosphetanes.

Further substantiation of this point was obtained from HBr quenching experiments (see section II.A.2.d). Lithio oxido ylide **24** and benzaldehyde were stirred at −78 °C for 15 min, and then treated with dry HBr to yield a mixture of the corresponding erythro and threo β-hydroxy phosphonium salts in a 2:1 ratio. However, when the same reaction was allowed to stand for 20 min at −45 °C, a temperature too low for equilibration of regular oxaphosphetane diastereomers such as **26a** and **26b**, quenching provided a 1:1 ratio of salts. And, from a reaction maintained for 20 min at −30 °C, the isolated phosphonium salts comprised a 1:4 erythro/threo mixture (NMR analysis).

Altogether, our results show that anomalous *E* stereoselectivity occurs with ylides bearing anionic substituents, as amino substituents are not especially effective, and that it is attributable in the main to enhanced reversibility of oxaphosphetane intermediates. The pronounced effect of chain length between the anion and ylide centers suggests a dependency on intramolecular cyclization.

The following hypothesis constitutes one possible mechanistic rationale. The interconversion of cis and trans oxaphosphetanes by reversal to ylide and aldehyde may be promoted by the anionic moiety "biting back" onto phosphorus to generate a transient hexacoordinate phosphate intermediate or a hexacoordinate transition state in a sort of intramolecular S_N2 reaction (see Scheme II).[46c,81] The critical cyclization would impart a dependency on ring size or chain length, with larger rings being disfavored. Also, the ease of reversibility would be related to the type of nucleophile, with the stronger ones being more effective. This model can accommodate the reactivity order oxido > carboxylate

SCHEME II



> amino and the decrease in anomalous *E* stereoselectivity with increase in chain length. However, it may not be the best construct to explain results from reactions of β-oxido ylides, some of which are discussed below. In that case, the hexacoordinate species or state would, perforce, unfavorably juxtapose two four-membered rings.

Another possible influence, perhaps acting as an overlay on this process, is facilitation of reversal by lithium salts, which will be mentioned later in section II.A.2.c. In this case, the anionic groups might serve to amplify equilibration through reversal by bringing lithium ion into close proximity to the reaction sphere. Intermolecular aggregation may also play an important role.

Within the context of enhanced reversibility, it is important to consider the chemistry of β-oxido ylides (also see section II.B.1.g).[69,73-75] In one mode of the β-oxido ylide route to alkenes, a simple triphenylphosphonium ylide is condensed with an aldehyde (first component) at low temperature to produce a Wittig intermediate, which is deprotonated (*n*-BuLi or PhLi) and condensed with another aldehyde (second component), all in the cold. When the new intermediate is decomposed to alkene and phosphine oxide by warming, the oxygen atom of the *first* aldehyde is retained in the alkene while that of the *second* aldehyde is eliminated.[69,75a,c] Corey et al. tested this regiocontrol by reacting Ph_3P=CHMe sequentially with PhCHO (first component) and PhCDO (second component), from which they isolated (*E*)-PhCD=C(Me)CH(OH)Ph exclusively (74% yield); predictably, the reverse sequence gave (*E*)-PhCH=C(Me)CD(OH)Ph.[69b] On the contrary, when formaldehyde was used as the second component, the opposite regiochemistry was found (the oxygen of formaldehyde was retained), and the olefin was strongly biased to the *Z* geometry.[69b] Thus, treatment (−78 °C) of heptanal with Ph_3P=CHMe and then *n*-butyllithium generated a fairly stable β-oxido ylide, which was warmed to 0 °C, combined with dry paraformaldehyde, and warmed to 25 °C to furnish (*Z*)-Me$(CH_2)_5$CH=C(Me)CH_2OH.[69b] This outcome was confirmed by Schlosser and Coffinet, who also conducted an inverse protocol, addition of formaldehyde and then hexanal, to obtain a 36:64 mixture of (*Z*)- and (*E*)-Me$(CH_2)_4$CH=C(Me)CH_2OH.[75b]

To rationalize the distinctive regio- and stereochemistry, Corey invoked a dioxido phosphonium intermediate (**22**) having a *dl*-like, as opposed to a *meso*-like, configuration (true *dl* and *meso* when R = R′).[69a,b] The sense of stereochemistry for the three stereogenic centers in **22**, first aldehyde (R) erythro and second aldehyde (R′) threo (relative to the central stereocenter), would be established at once by the mode of addition of the second aldehyde to the β-oxido ylide. Lithium salt bridging in the β-oxido ylide may contribute to the high stereocontrol by helping to differentiate sterically the pathways for approach of the electrophile.[28,69a] The decomposition of **22** in the observed direction, to an (*E*)-alkene comprising the second aldehyde, was presumably caused by a much greater propensity for expulsion of phosphine oxide from the threo subunit via a trans oxaphosphetane.

In a MeCHO–MeCHO sequence, addition of acetic acid at −78 °C deposited a solid that was characterized as a *dl*-β,β′-dihydroxy phosphonium bromide salt, corresponding to **22** (R = R′ = Me).[69a] Deprotonation of this salt with 2 equiv of methyllithium produced MeCH=C(Me)CH(OH)Me with a *Z*/*E* ratio of 7:93, as expected. A small amount of material believed to be the meso isomer was isolated and deprotonated also to give mostly (90–95%) (*Z*)-MeCH=C(Me)CH(OH)Me. Additionally, the PhCHO–PhCHO sequence afforded an analogous chloride salt, which yielded (*E*)-PhCH=C(Me)CH(OH)Ph exclusively on treatment with *n*-butyllithium.

On the basis of our studies, we propose an alternative model for consideration. The β-oxido ylide could cycloadd to an aldehyde to give predominantly a cis oxaphosphetane, related to a *meso*-dioxido phosphonium intermediate, which equilibrates to the *dl*-form (**22**) through reiterative cycloreversion–cycloaddition. In this portrayal, the erythro relative stereochemistry for the centers arising from the original β-oxido ylide piece would be stereochemically invariant to the retro-Wittig process. Exclusive olefination of the second aldehyde may relate to its containment in an oxaphosphetane assembly, while the oxido group (from first aldehyde) is enveloped by interaction with lithium ion and lithium salts. No new betaine subunit would form during addition of the second aldehyde, and quenching with acid at low temperature would still supply β,β′-dihydroxy phosphonium salts.

The peculiar results with formaldehyde as the second component probably relate to its noncompetiveness in the olefin-forming step. Formaldehyde cycloaddition may be followed by a rapid opening of this more vulnerable oxaphosphetane (due to less substitution on carbon) by lithium salt[20] to give a dioxido phosphonium intermediate, which then prefers to lose phosphine oxide from the other end. A more tightly bound complex at the sterically less encumbered, formaldehyde-derived oxygen may be responsible for this preference. However, it is unclear why the (*Z*)-alkene forms, as equilibration via the retro-Wittig process ought to take place. This description is consistent with the production of an equimolar mixture of CH_2=C(Me)CD_2OH and CD_2=C(Me)CH_2OH when operating on Ph_3P=CHMe with CH_2O–CD_2O or CD_2O–CH_2O.[75d] In fact, Schlosser and Tuong reported a major ^{31}P NMR resonance (−55 ppm) in this reaction (at −80 °C), suggestive

TABLE II. Data from the Reaction Rate Studies[a]

parameter	Ph_3P=CHPr + PhCHO[b]	Ph_3P=CHPr + PhCHO[b,c]	Bu_3P=CHPr + PhCHO[b]	Bu_3P=CHPr + t-BuCHO[d]
k_1/k_2	5.25	5.01	0.89	0.69
k_3	9.2 ± 1.8[e]	6.5 ± 0.3[e]	14.4 ± 0.8[e]	15 ± 1[f]
k_4	1.2 ± 0.8[e]	0	0.49 ± 0.22[e]	1.0 ± 0.3[f]
k_5	5.68 ± 0.02[e]	5.68 ± 0.02[e]	9.3 ± 0.9[g]	h
k_6	6.78 ± 0.08[e]	6.77 ± 0.08[e]	5.21 ± 0.07[g]	2.7 ± 0.1[i]

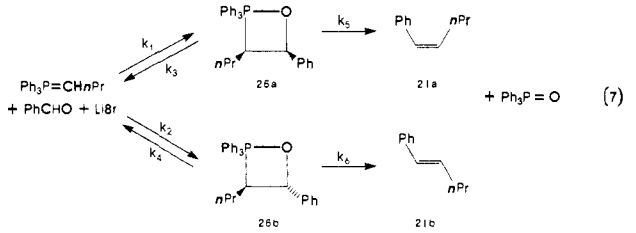
[a] Rate constants are expressed in units of 10^{-5} s^{-1}. [b] ^{13}C NMR experiment with labeled ylide. [c] The value of k_4 was arbitrarily set to zero in the computational analysis. [d] ^{31}P NMR experiment. [e] The rate constant is for −40 °C. [f] The rate constant is for −55 °C. [g] The rate constant is for −10 °C. [h] The rate constant could not be determined because of insufficient concentration of cis oxaphosphetane. [i] The rate constant is for −15 °C.

of an oxaphosphetane intermediate.[75d]

(b) Reaction Rate Profiles by NMR Spectroscopy. The ability to detect individual oxaphosphetane diastereomers by NMR permitted the investigation of stereochemical detail over the full course of the Wittig reaction of *nonstabilized ylides* for the first time.[30,31] Although rate studies have been performed on reactions of *stabilized ylides* with aldehydes, by measurement of the disappearance of starting materials or appearance of products,[6,7,13] betaine or oxaphosphetane intermediates have not been observed.

The first detailed rate studies on the reaction of nonstabilized phosphorus ylides involved three reaction systems (in THF): (1) the reaction of ylide **20** and benzaldehyde with LiBr present (by ^{31}P and ^{1}H NMR; by ^{13}C NMR), (2) the salt-free reaction of **20** and benzaldehyde (by ^{13}C NMR), and (3) the salt-free reaction of trialkylphosphorus ylide **27** with benzaldehyde (by ^{31}P and ^{1}H NMR).[30,31] Rate data were collected in the NMR probe by monitoring the reaction at a suitable low temperature for at least 2 half-lives. The disappearance of oxaphosphetanes was recorded by ^{31}P NMR or ^{13}C NMR of a ^{13}C-enriched sample, and the appearance of alkenes was recorded by ^{1}H NMR or ^{13}C NMR, respectively. Since the reaction of ylide and aldehyde was virtually instantaneous at −78 °C, this stage could not be analyzed by NMR techniques. Recently, we have also studied the rate of reaction for ylide **27** and pivalaldehyde (by ^{31}P NMR).[82a] Rate constants for the three different Wittig reactions are presented in Table II.

A set of ^{31}P–^{1}H NMR results for the reaction of **20** and benzaldehyde (LiBr present) is illustrated in Figure 2. It is readily apparent that the cis oxaphosphetane (**26a**) vanishes much faster than the trans (**26b**) and that the (*Z*)- and (*E*)-alkenes are produced at nearly the same rate. Also, stereochemical drift is evident in that the initial ratio of **26a**:**26b** is 78:22 (extrapolation), whereas the final alkene ratio (**21a**:**21b**) is 55:45. We suggest that the cis and trans oxaphosphetanes interconvert by reversal, which causes a bias to the trans oxaphosphetane (eq 7). Computational analysis of the rate data furnished a set of rate constants (10^{-5} s^{-1}): k_3 = 13.9, k_4 = 0.9, k_5 = 4.8, and k_6 = 7.9 (with k_1/k_2 = 3.5).



(7)

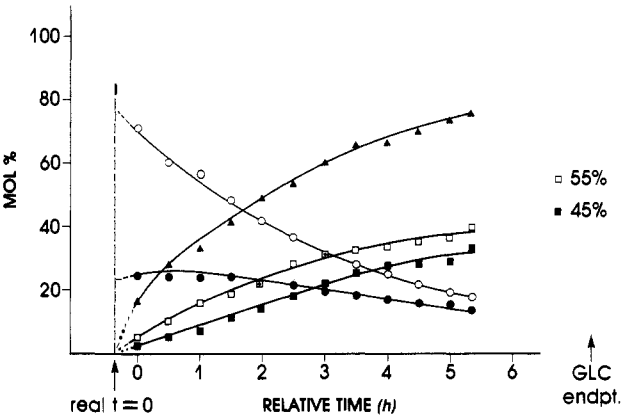


Figure 2. Rate profile for the reaction of **20** with PhCHO (LiBr present) at −30 °C in THF-d_8 (0.36 M). Only every third data point, determined by using ^{31}P and ^{1}H NMR, is shown. Symbols: (○) cis oxaphosphetane **26a**: (●) trans oxaphosphetane **26b**; (□) (*Z*)-alkene **21a**; (■) (*E*)-alkene **21b**: (▲) Ph_3P=O. A GLC analysis is shown for the alkenes after warming the reaction to 25 °C.

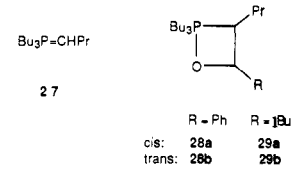
Similar results were obtained by using ^{13}C NMR spectroscopy with ylide **20**, ^{13}C-labeled at the α position of the butylidene group.[30] In this case, the stereochemical drift entailed a change from **26a**:**26b** = 84:16 to **21a**:**21b** = 72:28. Computational analysis provided the reaction rate constants (10^{-5} s^{-1}): k_3 = 9.2, k_4 = 1.2, k_5 = 5.7, and k_6 = 6.8 (with k_1/k_2 = 5.2) (see Table II).

Since the standard deviation in k_4 was very large, we tested the fit of the ^{13}C NMR data set computationally with k_4 = 0 and found that the values for k_1/k_2, k_3, k_5, and k_6 were little changed. This emphasizes that in the data set cis oxaphosphetane **26a** reverses much faster than the trans, **26b**. Indeed, the relative rate of reversal for the trans oxaphosphetane is deemed minimal. Although the difference in rate, reflected by k_3/k_4, came out to be in the range of 8:1 to 15:1 in the free-floating computational analysis, we believe that k_4 is actually at least 70–100 times smaller than k_3, a point that is reinforced by deprotonation and crossover experiments with β-hydroxy phosphonium salts (see section II.A.2.d).

The salt-free reaction of **20** and benzaldehyde-α-^{13}C in THF was monitored at −25 °C by the ^{13}C NMR method. Since this reaction generates only minor amounts of trans oxaphosphetane (**26b**) and (*E*)-alkene (**21b**), all of the species could not be quantitated. The initial ratio of **26a** and **26b** of 98:2 remained constant as the reaction progressed to alkenes, present in a final *Z*/*E* ratio of >95:5 by NMR and 99:1 by GLC. The rate of conversion of **26a** to **21a** was calculated as k_5 = 9.5 × 10^{-5} s^{-1}, which compares closely with k_5 in the LiBr-containing reaction (at −30 °C).

Distilled ylide **27** (strictly salt free) was combined with benzaldehyde-α-^{13}C in THF, and the reaction was

followed with time by ^{13}C NMR. The early ratio of cis



and trans oxaphosphetanes (**28a** and **28b**) of 47:53 at −60 °C eventually shifted to a 2:98 ratio.[82b] This equilibration process was reasonably well paced at −40 °C. However, the alkenes **21a** and **21b** were formed more slowly than for the corresponding triphenyl reaction, so it was necessary to record the latter process at −10 °C (final Z/E = 10:90). The data supplied the following rate constants (10^{-5} s^{-1}): k_3 = 14.4 and k_4 = 0.5 at −40 °C; k_5 = 9.3 and k_6 = 5.2 at −10 °C (Table II).[31,82c] The overall stereochemistry, a direct outgrowth of the competitive rates, is particularly governed by the large k_3/k_4 ratio of ca. 30 (i.e., trans oxaphosphetane **28b** reverts much less readily than cis isomer **28a**). Notably, this ratio is quite consistent with the reaction rate profile delineated later (section II.A.4.b).

A comparison of the kinetic results for the triphenyl and tributyl systems indicates no striking differences. Assuming that the rate changes by a factor of 2.0 of every 10 °C, we can adjust the rate constants for the tributyl case (Table II) from −40 and −10 °C to −30 °C. This provides new, approximate values of $k_3 = 29 \times 10^{-5}$, $k_4 = 1.0 \times 10^{-5}$, $k_5 = 2.3 \times 10^{-5}$, and $k_6 = 1.3 \times 10^{-5}$ s^{-1}. It is evident that tributyl substitution relative to triphenyl substitution augments reversal of the cis oxaphosphetane by a factor of ca. 3 and diminishes the rate of formation for (*Z*)- and (*E*)-olefin by factors of 2 and 5, respectively (cf. data for the triphenyl case in Table II).

Wittig reactions of trialkylphosphorus ylides warrant a special distinction because of their high *E* stereoselectivity under salt-free conditions.[11,12,34,63,83] The above rate study with **28** links the high *E* stereoselectivity to stereochemical drift, not to the original carbon–carbon bond formation. This property is further manifested in the reaction of pivalaldehyde with ylide **27** (salt free). At −50 °C, cis and trans oxaphosphetanes **29a** and **29b** were obtained in an approximately 30:70 ratio, which shifted to a 1:99 ratio on warming (−20 °C); the final (*Z*)/(*E*)-alkene ratio was 4:96. Quenching with HBr at −78 and −10 °C afforded 40:60 and 2:98 mixtures of the corresponding erythro and threo β-hydroxy phosphonium salts, respectively, which essentially reflects the above cis/trans oxaphosphetane ratios. This patent stereochemical drift via oxaphosphetane equilibration *in a Wittig reaction of an aliphatic aldehyde* appears to be a consequence of the trialkyl substitution on phosphorus (see section II.B.1.e). In a ^{31}P NMR rate study on the reaction of ylide **27** and pivalaldehyde,[82a] the initial 40:60 cis/trans mixture of oxaphosphetanes at −55 °C (in THF-d_8) shifted in favor of the trans isomer with $k_3 = 1.5 \times 10^{-4}$ s^{-1} (Table II). Conversion of the trans oxaphosphetane (cis/trans > 2:98) to $Bu_3P{=}O$ proceeded at −15 °C with $k_6 = 2.7 \times 10^{-5}$ s^{-1} ($t_{1/2}$ = 7.0 h). This system displays the fastest rate of cis oxaphosphetane reversion of the three that we have investigated.

Thermodynamic control in salt-free reactions of nonstabilized ylides with aliphatic aldehydes appears to be limited to the case where $R_3P{=}CHR'$ (R and R' = alkyl) is paired with a tertiary aldehyde (see section II.B.1.e).[34a,82a]

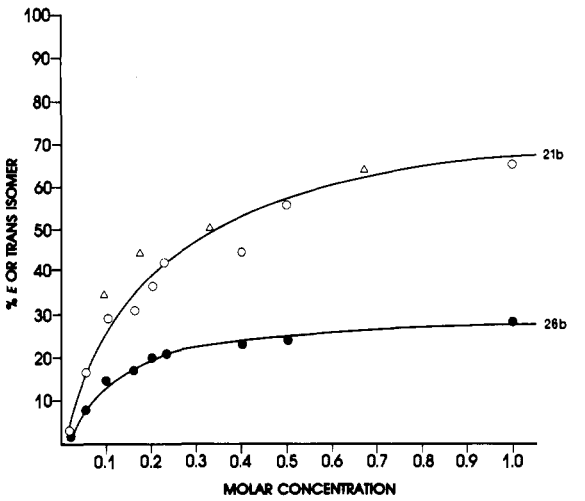


Figure 3. Plot of the relative levels of **26b** and **21b** vs concentration for the reaction of **20** with PhCHO in the presence of LiBr (THF). The data points in each set define a hyperbolic function (lines connecting the data points are present as an aid to the viewer). Symbols: (●) percent **26b** from ^{31}P NMR at −40 °C; (○) percent **21b** (from NMR experiments) by GLC analysis; (△) percent **21b** (from experiments at 23 °C) by GLC analysis.

(*c*) *Concentration Effects on Reaction Stereochemistry.* We were prompted to study the effect of concentration on stereochemistry because of problems in obtaining reproducible stereochemical results for the reaction of **20** and benzaldehyde.[28,32] In the LiBr reaction of **20** with benzaldehyde in THF, the ratio of oxaphosphetanes **26a** and **26b** (by NMR) and alkenes **21a** and **21b** (by GLC) were recorded at diverse concentrations (Figure 3). There is a striking concentration dependence of the stereochemical distribution at the level of oxaphosphetanes and alkenes. The proportion of trans oxaphosphetane and (*E*)-alkene increased with respect to increasing concentration, approaching limiting values in a hyperbolic fashion. The difference between the two curves represents the stereochemical drift, which is concentration dependent and more accentuated at higher concentrations. At 0.015 M there is virtually no **26b** and the (*Z*)/(*E*)-alkene ratio is 98:2, a situation analogous to the reaction of **20** and benzaldehyde *under lithium salt free conditions*. We have related this behavior to sequestration of lithium ion by the solvent.[32]

It is well-known that lithium salts can exert a profound effect on alkene stereochemistry in the Wittig reaction.[11,20,22] We found that lithium bromide has a pronounced, stereoselective impact on *initial oxaphosphetane formation*. For the original carbon–carbon bond-forming step, there are two rate constants, k_1 and k_2, which are too large for direct measurement. Relying on the relative amounts of **26a** and **26b**, determined at temperatures too low for interconversion, the competition between these two forward reactions was evaluated. In the presence of lithium ion, each pathway is comprised of two components, the lithium-dependent ("catalyzed"; defined by k_1'' and k_2'') and lithium-independent ("uncatalyzed"; defined by k_1' and k_2') reactions. Given the concentration dependence in THF, we derived the relative rates of these distinct processes.[32] For the reaction of **20** and benzaldehyde

in THF with LiBr, the catalyzed and uncatalyzed rate constants (assuming a first-order reaction in ylide, aldehyde, and LiBr[6,7,13]) have the following relative rank: $k_1'' = 5.2$ and $k_2'' = 2.5$ mol^{-2}·dm^6·s^{-1}; $k_1' = 1.0$ and $k_2' < 0.02$ mol^{-1}·dm^3·s^{-1} (eq 7).

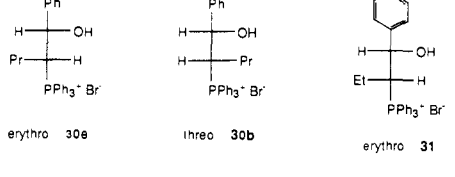
(*d*) *Deprotonation Route to Diastereomeric Oxaphosphetanes and Crossover Experiments.* Individual erythro and threo β-hydroxy phosphonium salts can be obtained by acidification of diastereomeric oxaphosphetanes, derived from nonstabilized ylides, at low temperature.[20,22,31,34a] Below the point where equilibration takes place, the ratio of salts will parallel the ratio of oxaphosphetane isomers. Thus, this method is effective for capturing the initial stereochemistry of carbon–carbon bond formation in the Wittig reaction. However, it should be kept in mind that systems with a propensity for enhanced reversibility must be quenched at a *low enough temperature*, e.g., as indicated for the reaction of ylide **24** and benzaldehyde in section II.A.2.a.

In specific cases, it is possible to separate the mixture of diastereomeric salts by recrystallization to get pure erythro and threo forms. The process may be facilitated by enriching the oxaphosphetane mixture in the first place by appropriate choice of reaction conditions. For example, a salt-free condensation will often give mainly cis oxaphosphetane (thus, erythro salt), and a Schlosser modification[73–75] will generate mostly trans oxaphosphetane (thus, threo salt). Unfortunately, certain salts tend to be refractory to crystallization.

An alternative route encompasses nucleophilic addition of R_2P^- to suitable cis- or trans-disubstituted oxiranes, with stereospecificity, followed by alkylation of the resultant β-hydroxy phosphines.[23,34a,40,62] In this procedure, any necessary isomer enrichment could be performed at the hydroxy phosphine stage, thereby avoiding problems with noncrystalline salts or mixtures that are resistant to fractional crystallization. This method has been used for the study of reactions involving stabilized and semistabilized ylides, since intermediates *cannot* be trapped with acid in such reactions.[20,23,31,40]

β-Hydroxy phosphonium salts can be deprotonated to reenter the Wittig reaction manifold (eq 3). In this capacity, diastereomerically pure salts are advantageous for probing stereochemical features that would be otherwise inaccessible. Indeed, this route affords the only good way to produce diastereomerically pure oxaphosphetanes in solution.

Consequently, we obtained salts **30a** and **30b** by treating various mixtures of **26a** and **26b** with HBr and prepared samples with >99% diastereomeric purity.[29,31] At this point, threo salt **30b** was rigorously identified by single-crystal X-ray analysis.[31]



Deprotonation of either **30a** or **30b** with NaHMDS in THF at −78 °C in an NMR tube gave essentially one, stereochemically correspondent oxaphosphetane, resonating at −62.2 or −64.4 ppm, each of which liberated β-propylstyrenes stereospecifically on warming (Z/E ratios of 99:1 or 1:99). Strangely, although deprotonation of a 45:55 mixture of **30a** and **30b** afforded oxaphosphetanes **26a** and **26b** in a 45:55 ratio, the resultant alkenes comprised a 25:75 Z/E mixture. This type of stereochemical drift appears to be connected with a synergistic interaction between diastereomeric oxaphosphetanes.[45] As such, the effect is, in fact, dissipated on increasing dilution.[45]

Deprotonation of erythro salt **30a** with LiHMDS at 23 °C showed substantial stereochemical drift to **21b**, while deprotonation of threo salt **30b** gave exclusively (*E*)-alkene. This is consistent with reversal only of the cis oxaphosphetane **26a** to ylide **20** and benzaldehyde. If **26b** (from **30b**) were to revert to **20** and benzaldehyde, these elements should recombine with some production of **26b** and (*Z*)-alkene. The degree of reversibility for **26b** from the kinetic results must be adjusted to account for the lack of reversal of **26b** from deprotonation of **30b**.

The deprotonation of individual erythro and threo β-hydroxy phosphonium salts can add another dimension to the crossover test.[31,45] Thus, salt **30a** or **30b** was deprotonated at −78 °C in THF to give **26a** or **26b**, 4-chlorobenzaldehyde (4 mol equiv) was added to trap any released ylide **20**, and the mixture was allowed to warm slowly to 23 °C. The erythro salt, **30a**, provided mixtures of direct and crossed products with either LiHMDS or NaHMDS [amount of crossed products: 6% (Z/E = 76:24) and 21% (Z/E = 85:15), respectively], but the threo salt did not give crossed products. This evidence confirms that trans oxaphosphetane **26b** does not revert competitively to **20** and benzaldehyde.

A similar crossover experiment with a 56:44 mixture of **30a** and **30b**, involving NaHMDS in THF, afforded a 41:59 ratio of **21a** and **21b** (78% yield) and an 84:16 ratio of *Z* and *E* crossed alkenes (16% yield). Since deprotonation of **30a** at −78 °C gave an 96:4 Z/E ratio, there is an enhancement of stereochemical drift with a pair of diastereomeric oxaphosphetanes (i.e., synergism).[45]

A pair of double-label crossover experiments provided additional support.[31] Deprotonation of an erythro–threo mixture, **31** and **30b**, with NaHMDS provided only direct products, with the alkene derived from **31** reflecting substantial stereochemical drift. By contrast, an erythro–erythro combination, **31** and **30a**, provided a complex mixture of all possible alkenes, with hardly any (*E*)-alkene in the direct products and just a small amount in the crossed products. It certainly seems that the trans oxaphosphetane from **30b** induces stereochemical drift in the cis oxaphosphetane from **31**. In the erythro–threo case, crossed alkenes were not realized because oxaphosphetane **26b** does not revert to aldehyde and ylide at a rate competitive with alkene formation. In the erythro–erythro case, crossed alkenes were realized because the two cis oxaphosphetanes suffered competitive reversal, thereby exchanging the ylide and aldehyde segments.

3. Stabilized and Semistabilized Ylides

Semistabilized and stabilized ylides have been the subject of numerous mechanistic and kinetic studies,[6,7,23,34c,38a,b,40,43,44,84] almost all of which have lent no

firm evidence for oxaphosphetanes or betaines as intermediates. Overall, kinetic studies have indicated that the rate-determining step is initial condensation of the ylide and aldehyde, with any intermediate adducts decomposing to alkenes too rapidly for their detection, and that the reaction is first order in each reactant. Effects of substituents on reaction rates have been examined.[38a,84c,e,g] Since much of the mechanistic and stereochemical work precedes 1980 and has been reviewed or discussed elsewhere,[6-8,11,85a] the present treatment will be limited. We will only address newer findings of mechanistic relevance.

Our ^{31}P NMR experiments on Wittig reactions of diverse ylides **32–37** at low temperature (down to −100 °C) did not reveal any oxaphosphetanes or betaines.[31]

$Ph_3P=CHCO_2Me$	$(n\text{-}Bu)_3P=CHCO_2Me$	$Ph_3P=CHPh$
32	**33**	**34**
$(n\text{-}Bu)_3P=CHPh$	$Ar_3P=CHPh$	$Ph_3P=CHAr$
35	**36**	**37**

Ar = 4-methoxyphenyl

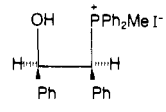
Stabilized ylide **32** reacted too sluggishly with benzaldehyde at −40 °C to be suitable for the study of intermediates. However, ylide **33**, with augmented nucleophilicity,[6,11,84i] readily attacked benzaldehyde at −40 °C; the ylide disappeared with a half-life of 60 min and tributylphosphine oxide was cleanly formed. In ^{31}P NMR experiments with benzylidene ylides **34–37** at −80 to −100 °C, the ylide vanished rapidly and the phosphine oxide appeared; there were no signals for Wittig intermediates. A ^{13}C NMR experiment on the reaction of ylide **34** with benzaldehyde-α-^{13}C in THF-d_8 at −90 °C was also negative for intermediates. The only positive note emerged from the reaction of $Ph_3P=CHPh$ (**34**) with $PhC(O)CF_3$ at −100 °C, where a transient ^{31}P singlet at −60.7 ppm was observed (see section II.B.1.a). Although this key signal accounted for only 15% of total phosphorus (the remainder being $Ph_3P=O$) and needs corroboration, the result suggests a promising future approach for studying oxaphosphetanes in the Wittig reaction of semistabilized ylides. Use of this solitary perfluoroalkyl group to stabilize the oxaphosphetane species is a direct outgrowth of the observations of Ramirez[51-53] and Trippett[56] (see section II.A.1.c). More recently, Ward and McEwen detected a ^{31}P NMR signal at −68.7 ppm in the reaction of *t*-BuCHO and $Ph_2MeP=CHPh$ at −78 °C (uncorroborated).[84k]

In another attempt to detect Wittig intermediates for a benzylide system, we deprotonated erythro salt **38** in THF with NaHMDS at −100 °C in an NMR tube.[31] Although an erythro betaine is an obligatory species in this reaction, no signals for any betaines, or oxaphosphetanes, were recorded by ^{31}P NMR; only a signal for $MePh_2P=O$ was seen.

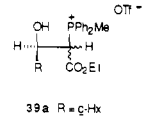
Significantly, Vedejs and Fleck employed the dibenzophosphole (DBP) moiety to stabilize oxaphosphetanes derived from semistabilized ylides (see section II.A.1.c) and thereby observed such species by ^{31}P NMR.[34c] The reaction of $(DBP)PhP=CHCH=CH_2$ with cyclohexanecarboxaldehyde at −78 °C produced unstable phosphorane **17d** ($\delta(^{31}P)$ −72), which decomposed at −50 °C to (*E*)-c-HxCH=CHCH=CH_2 (*Z*/*E* = 1:99) with a half-life of ca. 10 min. The cis oxaphosphetane was not detected, suggesting that the reaction proceeded under kinetic control. This point was confirmed by deprotonation of *threo*- and *erythro*-$(DBP)MePCH(CH=CH_2)CH(OH)$-c-$Hx^+OTf^-$ with NaHMDS at −78 °C, which generated either **17c** ($\delta(^{31}P)$ −74.3) or its cis isomer (not pictured; $\delta(^{31}P)$ −75.6). There was no interconversion of diastereomers up to the temperature for decomposition to diene and phosphine oxide ($t_{1/2}$ for **17c** at −45 °C was 60 min; $t_{1/2}$ for the cis isomer at −50 °C was 70 min), and each diastereomer afforded the respective *E* or *Z* diene with >95% stereospecificity. A cis oxaphosphetane comprising a benzylide unit was also produced by the deprotonation route ($\delta(^{31}P)$ −76.0) and monitored; it decomposed within 10 min at −20 °C to (*Z*)-c-HxCH=CHPh. Condensation of c-HxCHO with $(DBP)MeP=CHPh$ yielded c-HxCH=CHPh with a *Z*/*E* ratio of 3:97. In contrast to this high *E* stereoselectivity, $Ph_3P=CHCH=CH_2$ and $Ph_3P=CHCH=CH_2$ are hardly selective, and their Ph_2MeP counterparts show more moderate *E* selectivity (see section II.B.1.e).

It seems reasonable to extrapolate the kinetic control principle to other reactions of semistabilized ylides and aldehydes. As such, Vedejs and Fleck concluded that the trend for enhanced *E* double-bond stereoselectivity with semistabilized (or "conjugated") ylides emanates from the decreased steric demands of the vinyl or benzyl group, relative to corresponding alkyl groups, in the crowded Wittig transition state.[34b,c]

Vedejs' group has performed deprotonation studies with β-hydroxy phosphonium salts (**39**) related to sta-



38 (erythro)



39a R = c-Hx
39b R = Ph

bilized ylide reaction systems.[34c,40] For the case of an aliphatic aldehyde (cyclohexanecarboxaldehyde), the erythro salt (*erythro*-**39a**) produced (*Z*)-alkene (c-$HxCH=CHCO_2Et$) stereospecifically.[40] This signifies the absence of reaction reversal and the presence of kinetic control in the *E*-selective addition of a stabilized ylide (here $Ph_2MeP=CHCOOEt$) to an aliphatic aldehyde. Thus, in the common *E*-selective reactions of stabilized ylides there is apparently no need to invoke (1) equilibration of Wittig intermediates by a retro-Wittig process, (2) the Bestmann mechanism (see section II.A.1.a), or (3) exchange of the proton α to phosphorus in Wittig intermediates. For an aromatic aldehyde (PhCHO), deprotonation of β-hydroxy phosphonium salts (viz., **39b**) gave considerable reversibility of the intermediates, at a rate much faster than alkene production, which allows for some degree of thermodynamic control in the associated Wittig reaction.[40,85b] In cases where some stereomutation did occur, deuterium-labeling studies supported *betaine reversal*, as opposed to oxaphosphetane equilibration by C–P bond cleavage (Bestmann mechanism).[34c]

In reactions of aliphatic aldehydes with ester-stabilized ylides, at least, the prevalence of (*E*)-alkene is presumably due to threo or trans stereoselectivity in the initial carbon–carbon bond-forming process. This outcome can be rationalized by using a model[34b] involving a much later, four-centered transition state that more closely resembles the oxaphosphetane products

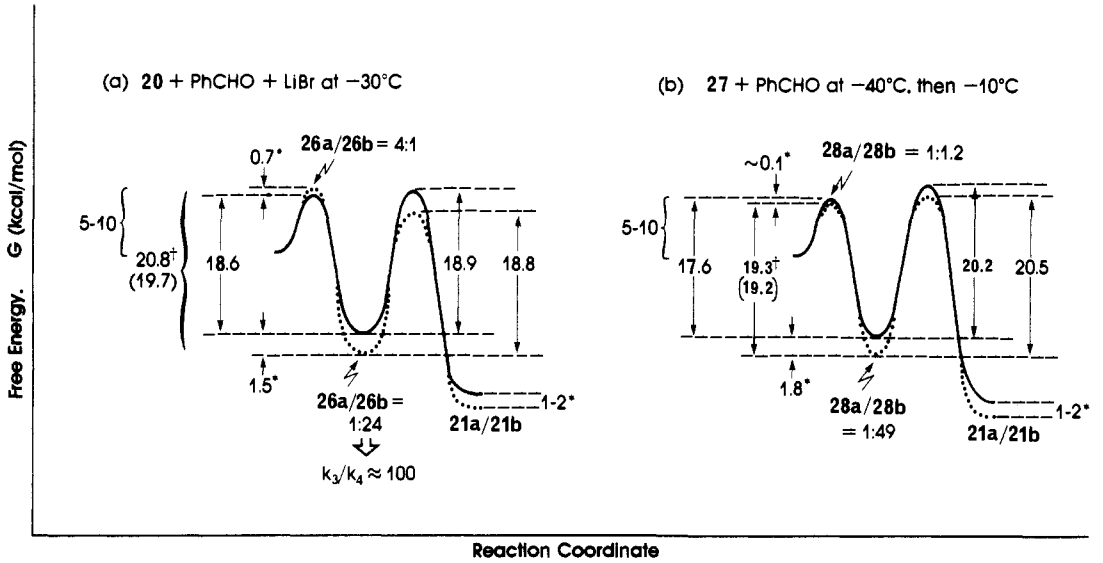


Figure 4. Free energy profiles for (a) reaction of **20** and benzaldehyde at −30 °C in THF-d_8 (0.25 M) with LiBr present and (b) reaction of **27** and benzaldehyde at −40/−10 °C in THF-d_8 (0.14 M). An asterisk denotes a ΔG value for a ratio of isomers, as indicated (the ΔG value of 1–2 kcal/mol for **21a** and **21b** is a guess). In panel a the solid line represents **26a** and **21a**, while the dotted line represents **26b** and **21b**; in panel b the solid line is for **28a** and **21a**, while the dotted line is for **28b** and **21b**. Since the measured k_4 values may be inexact,[30,31] we chose to show calculated free energy values, which are denoted by a dagger [panel a: 20.8 = 18.6 + 0.7 + 1.5 kcal/mol; panel b: 19.3 = 16.6 + 1.8 − 0.1 kcal/mol]. The experimental free energy values of 19.7 and 19.2 kcal/mol are given in parentheses.

with trigonal-pyramidal phosphorus.[34c]

4. General Discussion

(*a*) *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 with anhydrous HBr, as mentioned earlier. However, direct spectroscopic observation better lends itself to monitoring reaction progress and reaction time course. We have generally found a close correspondence between results from HBr-quench experiments and NMR experiments; so, the methods can be used interchangeably for garnering snapshots 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.[28,31,32,82a] Vedejs and co-workers have further tapped the power of NMR to glean answers to some long-burning mechanistic questions.[34,42b] However, 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 in the reaction of stabilized and semistabilized ylides be bolstered enough for easy examination? 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? Hopefully, some of these questions will yield to future research.

(*b*) *Reaction Coordinates.* The ab initio calculations of Volatron and Eisenstein[35] and Höller and Lischka[36] support concerted oxaphosphetane decomposition with an activation energy of 25–29 kcal/mol. On the basis of our rate measurements, the activation energies ($\Delta G^{\ddagger}$) for decomposition of **26a** and **26b** are 18.9 and 18.8 kcal/mol (^{13}C NMR data), and the activation energies for **28a** and **28b** at −10 °C are 20.0 and 20.5 kcal/mol.[86a] Although these values are lower than those from the theoretical work, they are still in reasonable accord. Solvation phenomena, as well as an appreciable activation entropy in the experimental reactions,[86b] could account for the discrepancy between the experimental (solution phase) and theoretical (gas phase) results.

Given these activation energies and the $\Delta G^{\ddagger}$ values for oxaphosphetane reversal (from rate data; section II.A.2.b) and assuming a one-step condensation process (i.e., no betaines or relatively unstable betaines), we can construct reaction coordinate plots for these Wittig reactions (Figure 4). Activation energies for the direct condensation step are crudely estimated in the vicinity of 5–10 kcal/mol for the purpose of illustration, with the oxaphosphetane ratios (k_1/k_2) at low, subequilibration temperatures suitably reflected. This range of $\Delta G^{\ddagger}$ for the initial stage is reasonable considering the very rapid reaction of ylide and aldehyde at −80 to −100 °C and the theoretical calculations.[35,36] The diagrams depict a comparison of the cis/*Z* and trans/*E* reaction paths and of the triphenyl and tributyl systems.

From the reaction profile in Figure 4a, reversal of trans oxaphosphetane **26b** ($\Delta G^{\ddagger}$ = 20.8 kcal/mol) is much less facile than reversal of cis oxaphosphetane **26a** ($\Delta G^{\ddagger}$ = 18.6 kcal/mol). The relationship of k_3 to k_4 could not be accurately assessed because of the error content in k_4.[30,31] Nevertheless, in Figure 4a the value for $\Delta G^{\ddagger}$ of 20.8 kcal/mol for k_4 is established by reasonably assuming a ratio of 1:24 for **26a**:**26b** at equilibrium (ΔG = ca. 1.5 kcal/mol; $\Delta G^{\ddagger}$ = 18.6 + 0.7 + 1.5 = 20.8 kcal/mol). This affords a value of ca. 100 for k_3/k_4, which is consistent with the results of crossover experiments (i.e., $k_3/k_4 > 70$). The reaction profile in Figure 4b also shows the less facile reversal of trans vs cis oxaphosphetane, **28b** vs **28a**, with $\Delta G^{\ddagger}$ = 19.2 and 17.6 kcal/mol. Since the $\Delta G^{\ddagger}$ values from k_3 and k_4 are consistent to within ±0.1 kcal/mol when free energy

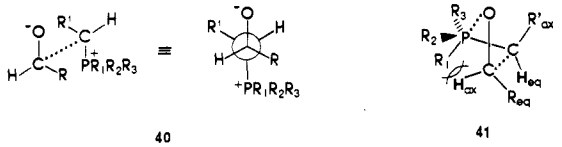
values from the isomer ratios are considered (i.e., 17.6 + 1.8 − 0.1 = 19.3 kcal/mol vs 19.2 kcal/mol), a value of ca. 30 for k_3/k_4 is reinforced.

One detail not represented in the reaction profile is pseudorotation at the oxaphosphetane pentacoordinate phosphorus (q.v. sections II.A.1.b and II.A.1.c).[31,42b] Probably, the oxaphosphetanes formed first from ylide and aldehyde will have an axial (apical) P–O bond and the four-membered ring spanning axial–equatorial sites. Fragmentation to products will entail prior pseudorotation to a conformer with an axial P–C bond,[10,12] given the rule of "apical entry/apical departure" for reactions involving pentacoordinate (trigonal bipyramidal) phosphorus.[46] The strongly favored pseudorotameric form represents the well on the reaction coordinate; it should interconvert freely with other forms of much higher energy en route to products.

(c) *Source of Stereoselectivity.* One of the great mysteries associated with the Wittig reaction relates to stereocontrol. Indeed, many chemists have been eager for years to understand the source of the high preference for contrathermodynamic (*Z*)-alkenes in salt-free reactions of nonstabilized triphenylphosphorus ylides and aldehydes. Generally, *Z* stereoselectivities in excess of 10:1 have been experienced! However, when the phenyl groups of the ylide are replaced by various alkyl groups (*t*-Bu, cyclohexyl, ethynyl, butyl), the great preference for (*Z*)-alkene (under kinetic conditions) is substantially diminished, if not lost.[30,31,34a]

From various studies, the intermediacy of oxaphosphetanes in reactions of nonstabilized ylides and aldehydes is pretty much the rule now. Many types of these reactions are under kinetic control, whereupon the initial ratio of cis and trans oxaphosphetanes reflects the original stereochemistry for C–C bond formation. One outstanding exception is the reaction of trialkylalkylidenephosphoranes with certain aldehydes, which is dominated by thermodynamic factors. Significantly, this observation indicates that trans oxaphosphetanes are probably much more thermodynamically stable than their cis counterparts, in general, which implies that a cis-selective transition state is inconsistent with a product-like geometry. An early, reactant-like transition state for the coupling of ylide and aldehyde is also suggested from the low activation energy for the reaction. The same viewpoint would pertain to reactions of alkylidenetriphenylphosphoranes as well.

Classically, the substantial preference for (*Z*)-alkene in reactions of nonstabilized triphenylphosphoranes (under kinetic control) was rationalized by an anti arrangement of the aldehyde oxygen and ylide phosphorus groups in an erythro betaine-like transition state.[8,11] In this aldol-type condensation, the aldehyde and ylide substituents would adopt a favorable anti orientation (viz., **40**).[87] Although theoretical calculations have



40

41

signified that an anti betaine is exceedingly high in energy,[12,35,36] which is inconsistent with the obviously low activation energy for oxaphosphetane formation, the calculations do not take account of charge stabilization by solvation. A one-step, nonsynchronous cycloaddition mechanism has gained broad acceptance in recent years.[20,27,31,34,35,43,63]

The key for explaining cis oxaphosphetane stereoselectivity here resides in the geometry of the four-centered cyclic array and the interaction of the appended ring substituents. Vedejs has recently developed a model involving a four-centered transition state with early C–C bond formation in which the ylidic carbon attacks the carbonyl group with the C=O axis skewed relative to the C=P axis (viz., 41).[20,34b] Given the importance of substituents on phosphorus, alkyl vs aryl, the substituents on the incipient pentacoordinate phosphorus define a critical steric environment. The substituents on the incipient stereogenic carbon centers of the skewed, four-atom array adopt a locus of least steric resistance relative to each other and to the substituents on phosphorus (viz., 41), which does not possess a trigonal-bipyramidal geometry at this juncture. The very high preference for cis oxaphosphetane in reactions between triphenylphosphorus nonstabilized ylides and aldehydes would arise from steric crowding of one face of the formative oxaphosphetane, perhaps by a single phenyl ring (R_1 = Ph in 41) that is positioned by interactions with the other two phenyl ligands (R_2 = R_3 = Ph in 41). The substituent on the developing stereogenic center of the aldehyde would favor a quasi-equatorial orientation, requiring the substituent of the ylide carbon to adopt chiefly a quasi-axial orientation (as in 41) to rationalize the high cis selectivity.[34b] Basically, this model relies on a subtle balance of 1,2 and 1,3 steric interactions between substituents on the four-centered array. By contrast, the model of Schlosser and Schaub[63] comprises a late transition state, with trigonal-bipyramidal phosphorus, and employs one of the phenyl rings on phosphorus as a steric guide for the cycloaddition stereochemistry ("leeward approach").[63] To account for the high *E* stereoselectivity in reactions of stabilized ylides, Vedejs considered an analogous model but with a later transition state involving trigonal-bipyramidal phosphorus (increased basal C–P–C bond angles),[34b,c] which contrasts with the Bestmann mechanism for *E* stereoselectivity that hinges on stereomutation at the carbon α to phosphorus amidst alkene formation (see section II.A.1.a).[10] Currently, Vedejs' model seems to be the most useful construct for explaining the strong cis oxaphosphetane preference in many reactions of triphenylphosphorus nonstabilized ylides, and the strong *E* stereoselectivity in (kinetic) reactions of stabilized ylides.[34b,c,87] The two transition state extremes were summarized as puckered for cis selectivity and planar for trans selectivity.[34b] For detailed discussions, we invite interested readers to consult the original papers.[10,34b,c,63]

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 (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 trialkylphosphorus ylide affords even lower levels of the cis

oxaphosphetane (30–45% cis) and (*Z*)-alkene (2–15% *Z*).

Besides the effect of salts[8,11,32] (both cation and anion[84k]) on stereochemistry, there are also the effects of solvent, additives, concentration, and temperature to consider.[32,88] As it is not our purpose to delve deeply into this area here, we merely offer some examples for illustration. Concentration effects in lithium salt reactions were already discussed in section II.A.2.c. In the lithium salt reaction of PhCHO and $Ph_3P{=}CHPr$, *Z*/*E* ratios varied widely on changing the solvent from toluene to ether to THF to 2,5-Me_2-THF to DMSO.[32] In the reaction of $Ph_3P{=}CHMe$ with PhCHO at −75 °C, the additives $(Me_3Si)_2NH$, NH_3, DMSO, *t*-BuOH, and MeOH (2 equiv) resulted in alkene *Z*/*E* ratios of 90:10, 90:10, 90:10, 80:20, and 44:56, respectively (the ratio without additive was ca. 92:8).[88] From a variety of data, Schlosser et al. generally concluded that THF, 1,2-dimethoxyethane, ethyl ether, and *tert*-butyl methyl ether are solvents of choice with respect to furnishing a higher yield and *Z* stereoselectivity, while protic solvents such as alcohols and DMSO should be avoided.[88]

In the sodium salt reaction of $AcO(CH_2)_8CHO$ and $Ph_3P{=}CHEt$ in THF, the *Z*/*E* ratio ranged from 98:2 to 90:10 with temperatures ranging from −78 to +60 °C.[79c] Two other examples of temperature effects are the following: (1) in the lithium salt reaction of PhCHO and $Ph_3P{=}CH(CH_2)_3COO^-Li^+$ in THF, the *Z*/*E* ratio varied from 23:77 to 10:90 in going from −78 to +120 °C (the reaction at 120 °C was performed in a sealed pressure flask).[65a] (2) The salt-free reaction (in THF) of $Ph_3P{=}CHMe$ and hexanal at temperatures ranging from −100 to +25 °C afforded *Z*/*E* ratios ranging from 96:4 to 87:13; a corresponding series with PhCHO afforded ratios ranging from 92:8 to 86:14.[88]

Now, let us consider semistabilized and stabilized ylides. Semistabilized ylides rarely give high alkene stereoselectivity in either direction (50 ± 30% *E*), and stabilized ylides often give high (*E*)-alkene selectivity (>90% *E*).[8,11] If kinetic control is absent in the reaction, then one can conclude little about intrinsic stereoselectivity. However, Vedejs et al.[40,85b] have fortunately shed some light on this point. Wittig intermediates corresponding to reaction of $Ph_2MeP{=}CHCO_2Et$ with cyclohexanecarboxaldehyde showed negligible stereomutation en route to olefin products, while intermediates for the benzaldehyde case showed some stereomutation (see section II.A.3). The bias for (*E*)-olefin with stabilized ylides under kinetic control can be ascribed to a much later transition state within the context of Vedejs' recent mechanistic model, as mentioned above.[34b,c]

Special cases tend to confuse attempts at standardization. For example, a fluorophosphoranium–tributylphosphorus stabilized ylide produces much more (*E*)-alkene with aliphatic (e.g., *Z*/*E* = 6:94) than with aromatic aldehydes (e.g., *Z*/*E* = 87:13).[89a] Semistabilized ylides possessing a combination of phenyl and alkyl groups on phosphorus, such as $Ph_2MeP{=}CHC(Me){=}CH_2$, can express high *E* stereoselectivity.[89b] Aldehydes or ketones bearing neighboring ether substituents can manifest enhanced or inverse stereoselectivity vs a standard Wittig reaction (see section II.B.1.c). Various Wittig reactions with unusual stereochemistry, by virtue of the carbonyl or ylide component, are discussed in detail in section II.B.1.

(*d*) *Phosphorus Ylides vs Sulfur Ylides, Silyl Carbanions, etc.* In the addition of carbanion reagents to carbonyl compounds, the type of atom connected to the nucleophilic carbon can decisively govern the reaction course. Although phosphonium and sulfonium ylides are structurally analogous, their chemistry with simple aldehydes is not analogous. Sulfonium ylides, instead of giving an alkene and a phosphine oxide, produce an epoxide and a sulfide. Of course, thermodynamics can readily explain this disparity: e.g., the P=O group is energetically much more stable than the S=O group. The Peterson olefination, a silicon-based equivalent of the Wittig reaction, involves the reaction of a silyl carbanion with an aldehyde or ketone to give alkenes, with elimination of $R_3SiO^-M^+$.[90] This reaction is presumably driven by the affinity of silicon for oxygen. Although the Peterson reagent involves a carbanionic reagent and thus has a mechanism akin to the condensation of phosphoryl-stabilized carbanions, it is isosteric with the Wittig process.

Theoretical calculations have been conducted on the reaction of a sulfur ylide with an aldehyde, in comparison with the Wittig reaction.[35] In the reaction of $H_3S{=}CH_2$ and CH_2O, the activation energy to generate oxathietane (axial O) is 3.5 kcal/mol, while that for betaine is ca. 12 kcal/mol. Again, the betaine (trans) resides at the pinnacle en route to products, H_2S and ethylene oxide. The oxathietane requires 39 kcal/mol of activation to eliminate $H_2S{=}O$ and ethylene, possibly because of the need to cleave an equatorial S–C bond (no stable oxathietane with an equatorial oxygen was located), which compares to only ca. 16 kcal/mol for reversal to starting reagents. The sulfide and epoxide are favored over the alkene and sulfoxide by nearly 40 kcal/mol! In reactions of the phosphorus and sulfur ylide, the cyclic intermediate forms easily, but the energetics dictate alkene production for the phosphorus system and epoxide production for the sulfur system by a wide margin.

Trindle et al.[41] have considered the Peterson olefination in a CNDO study. In the decomposition of $XCH_2CH_2O^-$ to XO^- and ethylene (X = H_3P^+ or H_3Si) four-centered intermediates were evaluated. The stabilization of an oxaphosphetane relative to a betaine was greater than the stabilization of an oxasiletanide relative to a silylethoxide. Thus, they suggested that a four-membered-ring species is less important in the Peterson reaction sequence.

Reaction of an α-(trimethylsilyl) phosphonium methylide with a carbonyl compound could occur via two competitive pathways, involving elimination of phosphine oxide or silanoxide. Benzaldehyde was reported to react with $Me_3SiCH{=}PPh_3$ only in the customary Wittig manner, providing an *E*/*Z* mixture of (trimethylsilyl)styrenes and $Ph_3P{=}O$;[91] however, benzophenone and acetone react anomalously.[92–94]

The Peterson reaction generally shows little stereoselectivity.[90] Although the erythro and threo adducts (β-hydroxy silanes) decompose to alkenes by stereospecific syn elimination (under basic conditions), the reaction in most cases is presumably under kinetic control (irreversible) with erythro and threo β-oxido silane adducts being formed in nearly equal amounts;

the diastereoselectivity is generally unperturbed by environmental factors.[90,95,96] A study of the reaction of lithio benzyl silanes and benzaldehyde showed a mild influence of the silicon substituents on the stilbene stereochemistry: trimethylsilyl gave a Z/E ratio of 43:57 and triphenylsilyl gave a ratio of 66:34, representing two ends of a narrow spectrum.[95] In a related study of the Wittig reaction involving Ar_3P=CHPh reagents and benzaldehyde (in ethanol), increased steric bulk also slightly favored (Z)-stilbene (Ar = p-tolyl, Z/E = 40:60; Ar = o-tolyl, Z/E = 70:30).[97] But, great disparities between the stereochemistry of corresponding stabilized silicon and phosphorus reagents are frequently the rule. For example, the lithio carbanions of Me_3SiCH_2CN and Ph_3SiCH_2CN show a preference for (Z)-alkenes in reactions with aldehydes,[98,99] while Ph_3P=CHCN (behaving like a standard ylide) strongly favors (E)-alkenes.[100-102]

Recently, Hudrlik[103] has examined chemistry surrounding [bis(trimethylsilyl)methyl]lithium. This reagent (generated with t-BuLi in THF/HMPA) was first reported by Gröbel and Seebach to react with benzaldehyde to yield a 1:1.4 mixture of (Z)- and (E)-β-(trimethylsilyl)styrenes (other aldehydes behaved similarly).[104] However, deprotonation of β-hydroxy silane $PhCH(OH)CH(SiMe_3)_2$, corresponding to the putative β-oxido silane intermediate, with strong bases (KH or NaH in THF, t-BuLi in THF/HMPA) led almost completely to the E isomer (98–99% E); Hudrlik obtained similar results with the hexyl analogue (Ph replaced by n-hexyl).[103,105] Since a β-oxido silane is obligatory in this deprotonation route, such a species may not be very important in the Peterson direct-addition regime. Thus, conventional Peterson reactions may proceed predominantly via a cycloaddition mechanism involving 1,2-oxasiletanide intermediates, in analogy to the Wittig reaction.

Boeckman and Chinn have studied a related bis(silyl) carbanion in the direct-addition route.[106] Intriguing stereochemical results were realized in the reaction of stabilized silyl carbanion $(Me_3Si)_2CCO_2$-t-Bu^- with various aldehydes, which the reader may examine in the original source.

There are some stereochemical similarities and differences between sulfonium and phosphonium ylide systems. Reaction of Ph_2S=CHMe with benzaldehyde (Li salt present; in THF) gave a 1:1 ratio of isomeric β-methylstyrene oxides,[107] analogous to the ratio of styrenes in the corresponding Wittig reaction.[28,31] However, reaction of Ph_2S=CHEt with an aliphatic aldehyde gave a 1:1 ratio of cis/trans epoxides,[108] while a related Li salt Wittig reaction, such as Ph_3P=CHPr and hexanal,[31] favors (Z)-alkene to the extent of 5.8:1. Ylide Me_2S=CHPh combined with diverse benzaldehydes to yield stilbene oxides highly enriched in the cis isomer,[109] whereas Ph_3P=CHPh usually has resulted in (Z)/(E)-olefin mixtures in the vicinity of 50:50 (±30%).[8,11] In the case of stabilized sulfonium ylides, simple aldehydes were unreactive.[110]

A comparison of stereoselectivities across related systems, such as reactions of aldehydes with phosphorus ylides, sulfur ylides, and silyl carbanions, can be an interesting exercise. But, more extensive studies are required to derive any mechanistic sense. At the moment, there is a dearth of carefully controlled comparative studies. Future work on these systems, and related carbon nucleophiles, could prove rewarding from both a mechanistic and synthetic standpoint. A recent example points to the potential here. The "boron-Wittig" reaction of [1-(dimesitylboryl)ethyl]lithium and benzaldehyde showed high erythro stereoselectivity for the initial adducts, which suffered stereochemical drift on warming in analogy to comparable Wittig reactions to afford an alkene mixture enriched in E isomer **21b**.[111] Pelter and co-workers demonstrated boron-Wittig reactions that are stereocontrolled for either (Z)- or (E)-alkene, depending on the way the first-formed erythro adduct is treated.[112]

Arsonium ylides can generate alkenes and/or epoxides in reactions with carbonyl compounds.[113] The nature of the ylide, carbonyl compound, and reaction conditions can affect the product distribution and diastereoselectivity.[113,114] In general, stabilized arsonium ylides tend to give alkenes, while nonstabilized ylides tend to give epoxides,[113] and there is usually a marked propensity for trans epoxides or (E)-alkenes.[113-115] Semistabilized arsonium ylides have produced nearly stereorandom epoxides from aldehydes (Li salt, THF).[115f] In the reaction of Ph_3As=CHPh with benzaldehyde or acetaldehyde, epoxides predominated in the presence of lithium salt (Z/E = 17:1 or 3.7:1, respectively), whereas (E)-alkene predominated under salt-free conditions.[114d] Still and Novack[114a] developed conditions for optimum production of trans epoxides from nonstabilized arsenic ylides and aldehydes. Interestingly, Still found that a carboxylate group in the ylide (i.e., as in $Ph_2(t\text{-Bu})As{=}CH(CH_2)_3COO^-$) exerted a profound influence on stereoselectivity, in analogy with the corresponding Wittig reactions (see sections II.A.2.a and II.B.1.g); however, the effect went in the opposite direction, in favor of the cis epoxide.[114a,116]

(e) *Miscellaneous Mechanistic Material.* There are some kinetic and mechanistic papers that may have been underexposed or neglected in the narrative discourse of section II.A. We will address aspects of these here.

{i} *Single-Electron Transfer and Diradicals.* Olah and Krishnamurthy investigated the reaction of adamantanone and benzophenone with isopropylidenetriphenylphosphorane and found evidence for an initial one-electron-transfer mechanism.[117] Whereas adamantanone coupled cleanly with methylenetriphenylphosphorane (n-BuLi; refluxing THF or ether), the isopropylidene reagent did not. With the latter reagent, adamantanone was recovered intact at low temperatures, but at higher temperatures (e.g., refluxing toluene) there was a high yield of adamantan-2-ol. Methylidene- and (diphenylmethylene)triphenylphosphorane also gave adamantanone reduction in hot toluene. Similar chemistry was recorded with $Me_2C{=}PPh_3$ and benzophenone. Therefore, these researchers proposed an initial one-electron transfer from the ylide to the ketone, under certain conditions, to generate a tight radical ion pair, which is possibly in equilibrium with a P–O covalently bound diradical species. The pair then couples to engender the usual Wittig reaction cascade. Confirmation was obtained by the detection of bibenzyl and methyldiphenylmethanes, originating from toluene-derived benzyl radicals and benzyl cations that dimerize, and by demonstration of a catalytic na-

ture. Olah and Krishnamurthy[117] suggested that the Wittig reaction may generally involve an underlying one-electron-transfer process, which either partitions to the normal cascade or causes reduction of the ketone to an alcohol. With sterically hindered systems at higher temperatures in hydrogen-donor solvents, the ketone reduction chemistry would be prevalent.

Yamataka et al. have carefully examined the reaction of benzophenone and $Ph_3P{=}CMe_2$ in THF (Li salt free) at 0 °C by ^{31}P NMR.[118] The initial condensation step was slow enough for study and measurement; thus, rate constants for the forward (k_1 = 1.3 × 10^{-3} L·mol^{-1}·s^{-1}) and reverse (k_2 = 4.0 × 10^{-4} L·mol^{-1}·s^{-1}) oxaphosphetane-forming step were obtained, along with that for the irreversible alkene-forming step (k_3 = 7.0 × 10^{-4} s^{-1}). A carbonyl carbon kinetic isotope effect (^{12}C vs ^{14}C) of 1.053 ± 0.002 and aromatic substituent effects (ρ = +1.40) were also determined. The results indicate that the carbonyl carbon is significantly changing its geometry in the transition state of the rate-determining condensation step, which rules out an electron-transfer mechanism under these conditions.

Yamataka et al. also briefly reinvestigated the reaction of $Me_2C{=}PPh_3$ and benzophenone at higher temperatures.[118] With *n*-butyllithium as base in toluene, they found the desired alkene ($Ph_2C{=}CMe_2$) and benzhydrol, in agreement with Olah and Krishnamurthy.[117] However, with phenyllithium or $NaN(TMS)_2$ only the alkene was obtained (excellent material balance). As the single-electron reduction process appears to depend on the base employed, its relevance to the Wittig reaction mechanism, in general, is definitely limited.

A spin-paired diradical mechanism for the salt-free, *Z*-selective Wittig reaction was suggested by McEwen et al.[13,84k] In their scheme, a P–O covalently bound diradical (vide supra) with erythro stereochemistry exists en route to cis oxaphosphetane. They also proposed that a spin-paired diradical could participate in the olefin-forming stage. The reader is directed to the original article for relevant arguments.

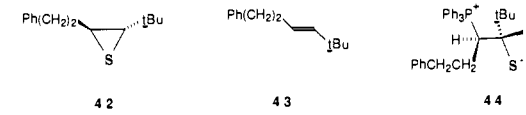
{ii} Effects of Aromatic Substituents. Linear free-energy relationships have been determined for the reaction of triphenylphosphorus ylides with aromatic carbonyl partners substituted on para and meta ring positions; ρ values have ranged from ca. +1.0–1.4 for nonstabilized ylides to ca. +2.4–2.8 for stabilized ylides).[38a,75,84c,d,g,118] This is consistent with the increased reactivity of nonstabilized ylides, where an earlier transition state is anticipated. Reactions of benzaldehyde with $(p\text{-}XC_6H_4)_3P{=}CHCO_2Et$ gave ρ values in the vicinity of +2.5–3.0.[84c,d] Ortho substitution in the carbonyl component gave aberrant rates, being slower due to steric interference.[118]

Ortho substitution on *P*-aryl groups of semistabilized ylides ($Ar_3P{=}CHPh$) has induced differences in (*Z*)/(*E*)-alkene ratios.[44,97,119] In most of the comparisons, however, the differences were not especially demonstrative *in energetic terms*. Whereas an *o*-methyl substituent tilted the isomer ratio in favor of (*E*)-stilbene with *n*-butyllithium in THF, it showed a proclivity for (*Z*)-stilbene with LiOEt in ethanol or NaOEt in ethanol.[119] McEwen and Beaver found that bis(*o*-methoxyphenyl)methylbenzylidene ylide and benzaldehyde tended to give more (*Z*)-stilbene with *n*-butyllithium in THF (also true for pivalaldehyde), but more (*E*)-stilbene with potassium metal.[44] A nonstabilized ylide bearing the 2,6-dimethoxyphenyl group delivered a disproportionate amount of (*E*)-styrenes in reactions with assorted benzaldehydes (KO-*t*-Bu in THF).[120] McEwen ascribed these anomalous stereochemical results to a through-space donation of electron density to the phosphorus atom (2p–3d overlap).[44,120] It is also conceivable that the abnormal displacement of the isomer ratio toward (*E*)-alkene may be associated, at least in part, with enhanced reaction reversal (in analogy to results with trialkyl nonstabilized ylides; see sections II.A.2.b and II.B.1.e).

Some isolated examples of Wittig reactions with $Ar_3P{=}CHR$ reagents are mentioned in section II.B.1.e.

{iii} Thiocarbonyl and Selenocarbonyl Reactants. Wittig reactions involving thio- and selenocarbonyl compounds could be an interesting and useful area of study; however, little stereochemical or mechanistic work has been executed here. One reason for this, in particular, is the scarcity of suitable thio and seleno reactants.

Vedejs et al. generated monomeric thiopivalaldehyde, $Me_3CCH{=}S$, reacted it with $Ph_3P{=}CH(CH_2)_2Ph$ (KO-*t*-Bu as base in THF; −78 → 20 °C), and obtained trans episulfide **42** instead of (*Z*)-alkene **43** (which was



42 43 44

arrived at by stereospecific desulfurization of **42** with *n*-BuLi).[121] If one assumes that the episulfide is formed by intramolecular S_N2 displacement of Ph_3P by the mercaptide group (inversion of configuration at carbon), then the betaine progenitor of **42** must have the erythro stereochemistry, as shown in **44**. Therefore, the initial carbon–carbon bond-forming step would have proceeded with the same stereochemistry, and same high stereoselectivity, as corresponding Wittig reactions of pivalaldehyde and its congeners (lithium salt free or not).[20,27,34a,122a] The standard Wittig reaction with triphenylphosphorus ylides, of course, transpires predominantly via a cis oxaphosphetane (observed at diminished temperatures), which decomposes to an (*E*)-alkene with retention of configuration. Can one construe from this stereochemical parallelism that the thiopivalaldehyde condensation may involve a first-formed 1,2-thiaphosphetane (mainly cis) in a cycloaddition mechanism? In such a case, the thiaphosphetane would lack a tendency to eliminate alkene (mainly *Z*) and $Ph_3P{=}S$, preferring to convert to a betaine. It might prove interesting to study this type of reaction by ^{31}P NMR or acid-quench experiments at low temperature to check for potential intermediates.

In a brief study, benzylidene- and ethylidenephosphoranes were found to react with sulfur to give dimeric alkenes (see selenium analogy below).[122b] Ylide $Ph_3P{=}CHPh$ produced only the *E* isomer of stilbene.

Stabilized phosphonium ylides, $Ph_3P{=}C(R')CO_2R''$, react with episulfides in hot toluene to give dimeric alkenes, maleate/fumarate derivatives, enriched in the *E* isomer.[122c] The reaction was presumed to encompass (1) ylide-induced sulfur extrusion to give Ph_3P, $R'C(S)CO_2R''$, and $RCH{=}CH_2$ and then (2) condensation of the thioketoester with ylide to give $Ph_3P{=}S$ and

dimeric alkenes. (The ylides themselves decomposed to maleate/fumarate derivatives at much higher temperatures.) A stereoselectivity of ca. 14:1 in favor of dimethyl fumarate was achieved in the reaction of styrene episulfide with $Ph_3P{=}CHCO_2Me$; the E/Z ratio was reduced to (2–3):1 with either $Ph_3P{=}CHCO_2Et$ or $Ph_3P{=}C(Me)CO_2Me$. Okuma et al. confirmed the proposed mechanism by condensing thioaldehyde $MeO_2CCH{=}S$, made independently, with $Ph_3P{=}CHCO_2Me$ to give dimethyl maleate/fumarate (no ratio was reported).[122c]

Reactions of phosphorus ylides with elemental selenium have been described just recently.[123] Heating of $Ph_3P{=}CHR$ with Se_n afforded $Ph_3P{=}Se$ and a selenoaldehyde, trapped by [4 + 2] cycloaddition reactions.[123] In the absence of diene scavenger $Ph_3P{=}CHPh$ gave $PhCH{=}Se$, which combined with ylide to give $PhCH{=}CHPh$ (mostly E), possibly via a 1,2-selenaphosphetane intermediate that extrudes $Ph_3P{=}Se$;[123] $Ph_3P{=}CHCO_2Me$ and selenium afforded dimethyl fumarate (only E).[123a] Interestingly, $Ph_3P{=}Se$ reacted with the phosphorus ylide to induce a similar dimerization, so that the reaction could be performed in a catalytic mode (i.e., ylide and a catalytic quantity of selenium or phosphine selenide).[123b] With an assortment of ylides, the catalytic procedure furnished alkenes RCH=CHR (R = Ph, Me, Et, *n*-Bu, and *n*-Hx) with a remarkably constant Z/E isomer ratio of ca. 15:85. The E stereoselectivity here with R = alkyl is opposite to that seen in the corresponding normal Wittig reactions (lithium salt free or not).[11,20,31,34b] The mechanistic significance of the stereochemistry is uncertain since two disparate processes are possible. Diastereomeric selenaphosphetanes may be formed first in a predominantly cis arrangement, but then may suffer stereomutation competitive with alkene elimination. Alternatively, the reaction may proceed chiefly via a thermally unstable trans episelenide, which can decompose stereospecifically to (E)-alkene, as suggested for the reaction of thiopivalaldehyde.[121]

B. Selected Synthetic Aspects Involving Stereochemistry

1. Wittig Reactions with Anomalous Stereochemistry

When a 1,2-disubstituted or trisubstituted carbon–carbon double bond is desired in a target molecule, the synthetic organic chemist thinks of stereochemistry in carbonyl olefination reactions from the point of view of predictability. What reactions and what conditions will afford the best stereoselectivity for the purpose at hand, not to mention a good yield? As such, it is important for the chemist to be cognizant not only of standard or general stereochemical protocols but also of less common protocols that may be used to special advantage (or, alternatively, that may be wisely avoided because they would subvert the desired strategy). In this section, we provide information on Wittig reaction situations that depart significantly from the norm (generally defined at the end of section II.A.4.c) or that may offer a distinct and extraordinary benefit. We have intentionally avoided discussion of the myriad effective applications of standard stereochemical formulas, such as (1) high E stereoselectivity for di- and trisubstituted olefins in reactions of stabilized ylides (e.g., $Ph_3P{=}C(Me)CO_2R$) with aldehydes or (2) high Z stereoselectivity in reactions of salt-free nonstabilized ylides (e.g., $Ph_3P{=}CHR$) with aldehydes (as in the synthesis of prostaglandins, thromboxanes, leukotrienes, pheromones, and the like), which pervade the chemical literature. Synthetic applications of such common Wittig procedures have been well treated by Maercker (up to 1965),[7] Gosney and Rowley (up to 1977),[11] and Bestmann and Vostrowsky (up to 1980).[12] We will focus on information published from 1978 through 1987.

Much experience with the Wittig reaction indicates that *structural features* of the carbonyl component (aldehyde or ketone) or ylide component can drastically influence stereochemical outcome. In fact, there are specific cases where alteration of customary stereochemistry has proven quite useful. Our subsequent discussion of these "aberrant" Wittig reactions should have an enduring value to the synthetic chemical community.

(*a*) *Bulky Aldehydes and Unsymmetrical Ketones.* Reactions of simple triphenyl nonstabilized ylides with bulky aliphatic aldehydes, such as *t*-BuCHO, under salt-free or Li salt conditions show enhanced (Z)-alkene stereoselectivity vs similar reactions with RCH_2CHO.[11,12,20,27,31,34a,b] With RR′R″CCHO, the amount of Z isomer falls in the range of 96–99% (salt free) or 90–98% (Li salt); with RCH_2CHO, the amount of Z isomer is 85–95% or 70–85%, respectively. This aspect is illustrated by the olefination (lithium salt, THF) of 1-(methylseleno)-1-formylcyclopropane, which gave Z/E = 92:8 with $Ph_3P{=}CH(CH_2)_5Me$ and Z/E = 98:2 with $Ph_3P{=}CHPh$.[124a]

Unsymmetrical ketones with similar substituents appended to the carbonyl group generally afford poor stereoselectivity.[11,12] However, a large bias for one alkene isomer can be realized when one of the groups is much bulkier than the other, such as in the reaction of methyl isopropyl ketone with $Ph_3P{=}CHMe$ under lithium salt conditions (Z/E = ca. 1:9)[124b] or in the highly Z-selective olefination of 17-keto steroids with $Ph_3P{=}CHR$ under salt-free conditions (Z/E = ca. 9:1).[124c]

Aliphatic acylsilanes, such as $BuC(O)SiMe_3$, react with $Ph_3P{=}CHR$ (R = alkyl) under lithium salt conditions to give (Z)-vinylsilanes (cis R and $SiMe_3$) almost exclusively (96–98% Z).[124d,e] Soderquist and Anderson examined the reaction of $BuC(O)SiMe_3$ and $Ph_3P{=}CHPr$ at −90 °C by ^{31}P NMR and detected an intermediate oxaphosphetane (−65.7 ppm), which decomposed to products at ca. −50 °C.[124d] The condensation step appeared to be irreversible and betaine–lithium halide complexes were not appreciably involved. A steric explanation for this remarkably high Z selectivity in the presence of dissolved lithium salt was posed.[124d]

Trifluoromethyl ketones have also been olefinated with high stereoselectivity in certain circumstances.[125] Although $Me_2C{=}CHCH_2CH_2C(O)CF_3$ reacted with a nonstabilized ylide under salt-free conditions to deliver a Z/E ratio of just 75:25,[125a] a similar reaction under lithium salt conditions gave a Z/E ratio of 89:11.[125b] Analogously, $MeC(O)CF_3$ afforded Z/E ratios of 90:10 and 95:5 in two reactions with nonstabilized ylides involving lithium salt.[125b] In reactions of the trifluoromethyl ketones, Camps et al.[125a,b] noted that the ylide color disappeared rapidly but little alkene was pro-

duced, prior to warming at 100 °C, which reasonably suggests the formation of stable oxaphosphetane intermediates (see section II.A.1.c). Condensation of $MeC(O)CF_3$ with $Ph_3P{=}CHCO_2Me$ gave a highly *E*-rich product mixture (*Z*/*E* = 5:95), while condensation of this ketone with $(MeO)_2P(O)CHCO_2Me^-$ was not remarkably stereoselective under different conditions.[125a] A strong bias for (*E*)-olefin was evident as well in various reactions of $MeC(O)CF_3$ and $PhC(O)CF_3$ with stabilized ylides.[125c]

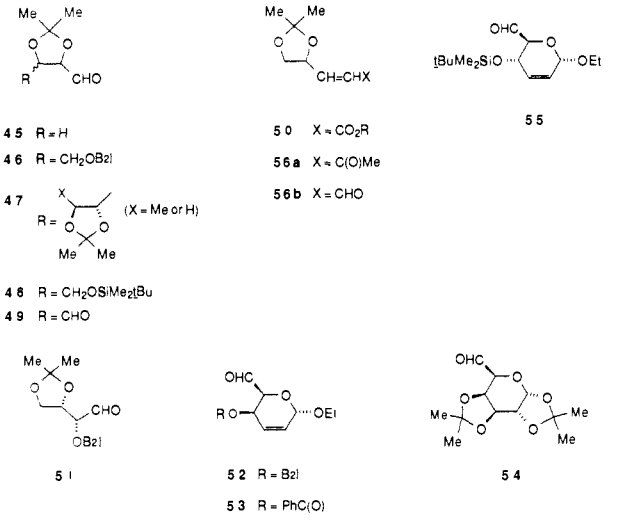
The stereochemical influence of α-alkoxy and α-hydroxy groups on one of the ketone substituents is discussed in sections II.B.1.c and II.B.1.d.

(*b*) *Conjugated Aldehydes and Ketones.* Aromatic and vinylic aldehydes are prone to deliver more (*E*)-alkene than aliphatic aldehydes deliver.[11,12,20,28,31,32] This effect is usually minor under salt-free conditions, but is pronounced for nonstabilized ylides under lithium salt conditions (especially in a nonpolar solvent) presumably because of enhanced stereochemical drift.[31,32] In contrast to the stereorandomness of unsymmetrical aliphatic ketones, reactions of aryl alkyl ketones with nonstabilized ylides under salt-free conditions gave high *Z* selectivity.[126]

The effect of aromatic substituents on stereocontrol in some reaction classes is only modestly addressed in this article (see section II.A.4.e), because the subject has been substantially reviewed elsewhere.[7-9,11]

(*c*) *Reactants with Oxygen-Containing Groups Adjacent to the Carbonyl Group.* α-Alkoxy substituents on aldehydes or ketones can result in abnormal Wittig reaction stereochemistry, depending on circumstances. In this subsection, we have collected and organized such reactions, which are widely dispersed in the literature, in an attempt to dispel the current disarray of data in the area. This chronicle should assist in identifying subject matter worthy of further serious study.

In certain reactions of stabilized phosphonium ylides with α-alkoxy aldehydes, one may realize a special synthetic advantage by the obtainment of highly *Z*-rich alkene mixtures. Most of the reactions of stabilized ylides with 2,3-isopropylideneglyceraldehyde (**45**, *R* or



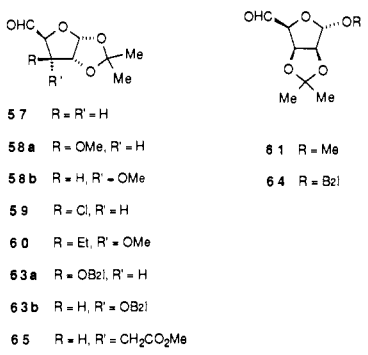
S configuration) and homologous carbohydrates (**46–49**), nicely exemplify the phenomenon.[127-140] With $Ph_3P{=}CHCO_2R$ (R = Me or Et) and **45**, the acrylate products (**50**; formed in good yields) have shown *Z*/*E* ratios ranging from 6:94 (methylene chloride with catalytic acetic acid[131]) to ca. 90:10 (methanol at 0[128-131,139] or 25 °C[127]).[141] Various congeners of **45**, namely **46–48**, behaved similarly, with *Z*/*E* ratios of 6:1 for **46**[128] and 7:1 for **47** (X = Me)[135] in methanol, but 1:3 for **47** (X = H) in benzene (80 °C)[140a] and 1:2 for **48** in methylene chloride.[137a] In analogy, (2*R*,3*R*)-dialdehyde **49** combined with $Ph_3P{=}CHCO_2Me$ in methanol (−78 → 20 °C) to yield a mixture of diacrylates enriched in the *Z*,*Z* isomer (*Z*,*Z*/*Z*,*E*/*E*,*E* = ca. 12:10:1).[140b] Significantly, in the reactions of **45–49** the configurational integrity of the stereogenic center α to the carbonyl was largely, if not completely, maintained.

Valverde et al. reacted a constellation of α-alkoxy aldehydes with $Ph_3P{=}CHCO_2Me$ in methanol at room temperature.[135] *Z* stereoselectivities exceeding 10:1 were found with compounds **51–54**. Although the *Z*/*E* ratios for **52** and **53** even approached 100:1, the ratio for **55** was surprisingly reversed (*Z*/*E* = 1:3.5)! Besides the broad dependence of stereoselectivity on substrate, there also was a great variation with solvent and temperature. To illustrate, **54** gave (*Z*)/(*E*)-acrylate ratios of 10:1, 22:1, 35:1, and >100:1 in 2-propanol at 25 °C, ethanol at 25 °C, methanol at 0 °C, and methanol at −8 °C, respectively; and MeCH(OBzl)CHO gave *Z*/*E* ratios of 3.7:1, 1:1, and 1:2 in methanol, toluene, and methylene chloride, respectively. In general, anhydrous methanol and diminished temperature were preferred for high *Z* stereoselectivity and good yields; contamination by a small amount of water was deleterious.

Curiously, the reaction of MeCH(OBzl)CHO with $Ph_3P{=}C(Me)CO_2Me$ in methylene chloride at room temperature exhibited an even higher *E* selectivity (*Z*/*E* = 1:15) than the analogous reaction involving $Ph_3P{=}CHCO_2Me$ (*Z*/*E* = 1:1.7).[142] This α substituent effect turns out to be fairly general. Indeed, it was also found for the reaction of $Ph_3P{=}C(Me)CO_2Et$ with both **45** (*Z*/*E* = ca. 1:100)[140c] and EtCH(OCHO)C(Me)(OBzl)-CHO.[143]

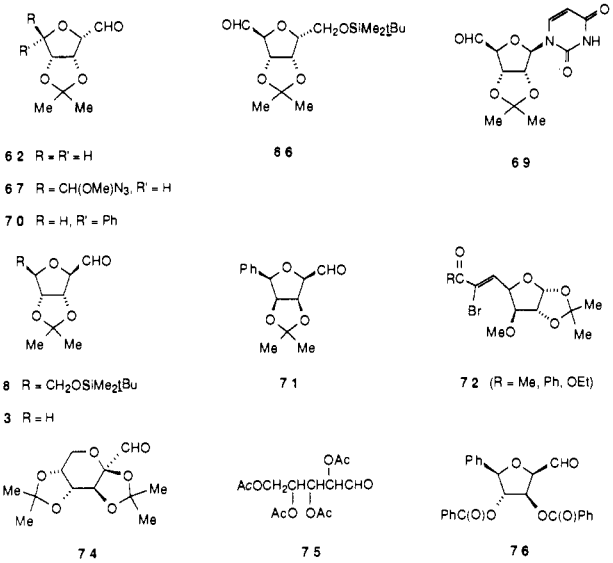
For reactions of **45** and $Ph_3P{=}CHC(O)Me$, Leonard and Ryan reported that a mixture of *Z*/*E* isomers, (*Z*)- and (*E*)-**56a**, is invariably obtained.[136a] The isomer ratio was said to span from 1:1 to 1:14, depending on solvent and temperature; however, the only result disclosed was a 1:1 ratio for methylene chloride at room temperature. Other workers reported a *Z*/*E* ratio of ca. 1:2.5 for this reaction[136b] and *Z*/*E* ratios of 1.3:1 and 1:3.6 for the reaction of **45** with $Ph_3P{=}CHC(O)Et$ in methanol or methylene chloride, respectively.[136c] As indicated above, methyl branching in the ylide, viz., $Ph_3P{=}C(Me)C(O)Me$, again strongly accentuated *E* selectivity; in fact, only (*E*)-enone was detected.[136b]

Fortunately, for purposes of our insight, Tronchet and Gentile have described more detailed results for reactions of $Ph_3P{=}CHC(O)Me$ with a series of aldehydo sugars (**57–62**).[144] Examination of each compound in three solvents, chloroform, benzene, and dimethylformamide (DMF), revealed a dramatic dependence of stereoselectivity on both the substrate and the medium (Table III). Compounds **57**, **58b**, and **60**, which lack a polar group on the β carbon in a syn orientation to the aldehyde, gave exclusively the (*E*)-enone, regardless of solvent. However, **58a**, **59**, **61**, and **62** departed from *E* stereoselectivity to varying degrees, especially in chloroform. Tronchet and Gentile[144] were thus inspired to investigate the reaction of **58a** with $Ph_3P{=}CHCO_2Et$



57 R = R' = H
58a R = OMe, R' = H
58b R = H, R' = OMe
59 R = Cl, R' = H
60 R = Et, R' = OMe
63a R = OBzl, R' = H
63b R = H, R' = OBzl
65 R = H, R' = CH_2CO_2Me

61 R = Me
64 R = Bzl



62 R = R' = H
67 R = CH(OMe)N_3, R' = H
70 R = H, R' = Ph

66

69

68 R = CH_2OSiMe_2tBu
73 R = H

71

72 (R = Me, Ph, OEt)

74

75

76

in seven different solvents. This portrayed a remarkable solvent effect on stereoselectivity (solvent, Z/E ratio): DMF, 14:86; benzene, 20:80; hexane, 46:54; acetone, 47:53; carbon tetrachloride, 53:47; chloroform, 60:40; methanol, 92:8.

Brimacombe reported high Z selectivity for reactions of **54**, **63a**, and **64** with $Ph_3P{=}CHCO_2Me$ (MeOH, 4 °C), but not for the reaction of **63b** (Z/E = ca. 1:1).[145] The first two results are in precise agreement with those for **54**[135] and **58a**,[144] and the last two are consistent with the observations in ref 135 and 144. There was an absence of anomalous Z selectivity in the reaction of **66a** with a complex keto phosphorane agent,[146a] and in the reaction of related substrate **65** with $Ph_3P{=}CRCO_2Me$ (R = Me or Et).[146b]

Considering the experiments of Valverde et al.,[135] Tronchet and Gentile,[144] and Brimacombe et al.,[145] the structural requirements for the aldehyde reagent have come into focus. An α-alkoxy aldehyde is probably necessary, *but not sufficient*, for a substantial departure from E stereoselectivity with the stabilized ylides. For high Z selectivity, two other requirements are apparent: (1) a polar or donor group on the carbon β to the aldehyde group that is capable of adopting a syn or cis orientation relative to the aldehyde group, and (2) an anhydrous alcoholic solvent. To explain this phenomenon, a betaine mechanism has been suggested.[135,144] An anti betaine with an erythro configuration could be stabilized through solvation and chelation of the charged groups in a supramolecular ensemble.[135,144] Regardless of the reason, the occurrence of high Z stereoselectivity in reactions of stabilized ylides with certain aldehydes has a profound significance within the broader context of the Wittig reaction mechanism. This

TABLE III. Z/E Ratios for Reactions of 57–62 with $Ph_3P{=}CHC(O)Me$

compd	$CHCl_3$	benzene	DMF
57	only E	only E	only E
58a	30:70	5:95	ca. 1:90[a]
58b	only E	only E	only E
59	25:75	7:93	5:95
60	only E	only E	only E
61	43:57	21:79	3:78[a]
62	38:62	15:85	3:87[a]

[a] Some minor epimerization occurred at the carbon α to the aldehyde group, which accounts for the unrepresented material.

stereochemistry implies the reaction of a stabilized ylide involving principally cis oxaphosphetane (and/or erythro betaine), substantially *under kinetic control*, which concurs with some observations made by Vedejs (section II.A.3).[34c,40] Consequently, the anomalous stereochemical data further undermine the applicability of epimerization mechanisms (e.g., see section II.A.1.a).

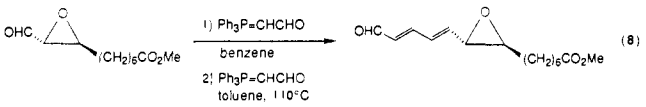
Other, related examples of stabilized ylide reactions follow. Fleet and Seymour reacted aldehydes **66–68** with $Ph_3P{=}CHC(O)Me$ in methylene chloride to furnish enone products having respective Z/E ratios of >6:1 (probably), 1:4, and >6:1 (probably); the reaction of **68** with $Ph_3P{=}CHCO_2Me$ also gave a preponderance of (*Z*)-alkene.[147] The decent Z selectivity with **66** and **68** occurred despite the presumably inauspicious anti arrangement of the β-alkoxy group relative to the aldehyde. However, reaction of uridine derivative **69** with an assortment of stabilized ylides afforded E adducts exclusively, possibly owing to the reaction conditions employed.[148a] Compounds **70** and **71**, with favorably disposed oxygen substituents, also showed a high preference for (*Z*)-acrylates with $Ph_3P{=}CHCO_2Me$.[148d] An α,β-epoxy aldehyde system gave moderate Z selectivity (4.3:1) with $Ph_3P{=}CHCO_2Me$ in methanol.[135] Branched, stabilized ylides $Ph_3P{=}C(Br)COR$, where R = Me, Ph, or OEt, reacted with **58a** in DMSO to afford mainly (*Z*)-alkenes, **72**, which is expected in the dipolar aprotic solvent (the outcome corresponds to the above pattern as the carbonyl moiety is in a trans geometry).[148b] The reaction of $Ph_3P{=}CHCN$ with **63a** in DMSO gave a (*Z*)/(*E*)-acrylonitrile ratio of >95:5, whereas reaction of this ylide with **73** in benzene gave a 1:2 ratio;[148c] $Ph_3P{=}CHCN$ and **45** in acetonitrile resulted in a Z/E ratio of 1:4.[148e] Further investigation of the solvent effect with $Ph_3P{=}CHCN$ would be worthwhile. Only the (*E*)-acrylate or (*E*)-vinylphosphonate was formed on combining **74**, an educt in which the β-alkoxy is anti to the aldehyde group, with $Ph_3P{=}CHCO_2Et$ ($CHCl_3$)[149b] or $Ph_3P{=}CHP(O)(OPh)_2$ (DMSO[149] or $CHCl_3$[149b]).

In the reaction of **73** and $Ph_3P{=}CHCN$ in DMSO, higher E selectivity (e.g., Z/E = 14:86) was fostered by using an excess of ylide and benzoic acid as an additive.[148c] It is noteworthy that carboxylic acid additives can be generally exploited to enhance E stereoselectivity in reactions between stabilized ylides (e.g., $Ph_3P{=}CHCO_2Me$) and aldehydes, particularly when there is a proclivity for the Z isomer due to neighboring oxygen-containing substituents.[131,150]

Since tetraacetylarabinose **75** gave very high E selectivity in refluxing benzene, one might suppose that an α-acyloxy group does not engender anomalous Z stereoselectivity.[140a] However, the more rigid, cyclic

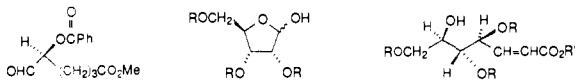
dibenzoate **76** furnished a 5:1 Z/E ratio (methanol, 20 °C).[151]

Reactions of $Ph_3P{=}CHCHO$ with α-alkoxy aldehydes, used in various synthetic enterprises,[128,145,152,153] have customarily produced (E)-alkenes almost exclusively. In the preparation of (E)-**56b**, Katsuki et al.[128] favored reacting **45** with $Ph_3P{=}CHCHO$ because of the excellent Z/E ratio of 1:50 (toluene, 0 °C, 90%). Brimacombe et al. homologated **54**, **63a**, **63b**, and **64** to the corresponding enals with good yields and high E stereoselectivity (refluxing benzene).[145] α-Benzoyloxy aldehyde **77** was also olefinated with high E selectivity.[152a] (E,E)-Dienal epoxides have been obtained in moderate yields by employing a two-step tandem addition of $Ph_3P{=}CHCHO$ to α,β-epoxy aldehydes (e.g., eq 8).[153]



γ-Hydroxy- and δ-hydroxy aldehydes exist predominantly as cyclic hemiacetals;[154] nevertheless, they participate well in Wittig reactions, especially with stabilized phosphoranes.[155,156] Such Wittig reactions initially generate α,β-unsaturated olefins, which can be isolated and characterized under controlled conditions. However, since these conjugated alkenes may be subject to Michael-type cyclization on exposure to bases, including excess ylide, they often proceed directly to cyclic ethers (tetrahydrofurans or tetrahydropyrans).[155-158] This constitutes the "Wittig–Michael" route to C-glycosides. We will be concerned here mainly with the stereochemistry of the alkenes that are formed prior to the cyclization event.

Corey's first total synthesis of leukotriene C-1 began with the condensation of tribenzoyl-D-ribose **78** and



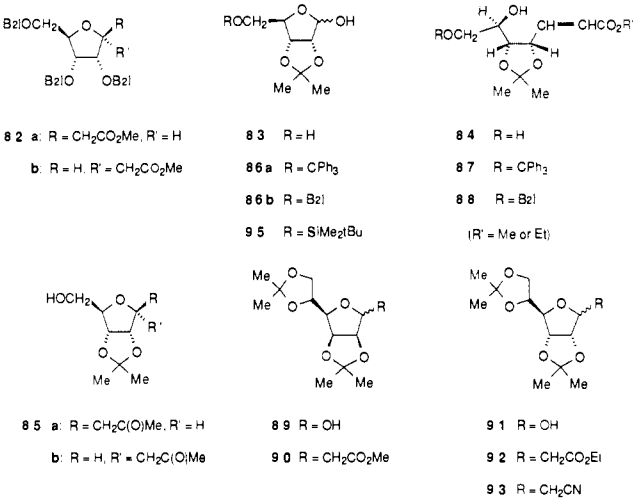
77

78 R = C(O)Ph
80 R = Bzl
104 R = H

79 R = C(O)Ph
81 R = Bzl
(R' = Me or Et)

$Ph_3P{=}CHCO_2Et$ in refluxing 1,2-dimethoxyethane (DME) with a trace of benzoic acid to afford uncyclized ester **79** (R′ = Et) with a Z/E ratio of 14:86.[150a] Closely related tribenzyl-D-ribose **80** gave an ca. 2:1 Z/E mixture of acrylates **81** with $Ph_3P{=}CHCO_2Me$ in refluxing acetonitrile, reflecting anomalous Z selectivity.[150d,159] Neither (Z)-**81** nor (E)-**81** (R′ = Me) appeared to cyclize spontaneously; rather, cyclization had to be induced with base (e.g., methanolic NaOMe). Interestingly, Ohrui et al. found that (Z)-**81** (R′ = Me) generated pure β-C-glycoside **82a**, whereas (E)-**81** (R′ = Me) gave a 3:2 mixture of **82a** and α-C-glycoside **82b**, even though the equilibrium ratio for **82a**:**82b** is ca. 3:1.[159,160]

2,3-Isopropylidene-D-ribofuranose derivatives have received greater attention.[159,161,162] Reaction of **83** with $Ph_3P{=}CHCO_2Me$ in benzene (reflux, 28 h) afforded a mixture of acrylates **84** (R′ = Me) enriched in the Z isomer.[161d] A similar reaction of **83** with $Ph_3P{=}C(Me)CO_2Me$ or $Ph_3P{=}C(Me)CN$ in refluxing acetonitrile furnished intermediate alkenes, suggested to be a Z/E mixture (no assay), which cyclized readily to the β-C-furanosides on treatment with NaOMe in methanol.[161e] Sun et al. did not observe alkenes in the condensation of **83** with $Ph_3P{=}CHC(O)Me$; rather, **85a** and **85b** were obtained directly in a 7:3 (kinetic) ratio (1:4 thermodynamic ratio).[161e] Earlier, Moffatt's group had found that **83** led only to cyclic products with $Ph_3P{=}CHCO_2Me$ or $Ph_3P{=}CHCN$ (refluxing acetonitrile) in incredible $\beta{:}\alpha$ ratios of 22:1 or ca. 50:1, respectively.[159] Under the same conditions, the corresponding trityl system **86a** gave cyclic products with lower stereoselectivity for the β form ($\beta{:}\alpha$ = 3:1).[159,162a-c] Chu et al. isolated acrylate **87** (R′ = Et), suggested to be a Z/E mixture, and closed it down to the cyclic species with potassium *tert*-butoxide.[161b] More importantly from the standpoint of anomalous stereochemistry, Freeman and Robarge prepared analogue **88** (R′ = Et) from **86b** in methylene chloride and proved a high bias for the Z isomer.[161g] Diisopropylidenemannose, **89**, reacted with $Ph_3P{=}CHCO_2Me$ to give furanosides **90** with a 1:1 anomeric ratio, and diisopropylideneallofuranose, **91**, reacted with $Ph_3P{=}CHCO_2Et$ or $Ph_3P{=}CHCN$ to give anomeric mixtures of **92** or **93** (ca. 3:1 β rich).[159] In a synthesis of KDO, Collins et al. managed to isolate (85% yield) alkene **94**,



82 a: R = CH_2CO_2Me, R′ = H
b: R = H, R′ = CH_2CO_2Me

83 R = H
86a R = CPh_3
86b R = Bzl
95 R = $SiMe_2tBu$

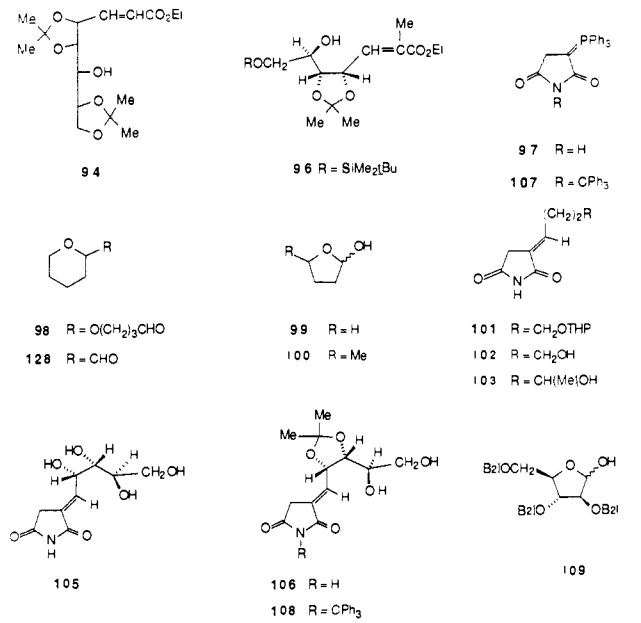
84 R = H
87 R = CPh_3
88 R = Bzl
(R′ = Me or Et)

85 a: R = $CH_2C(O)Me$, R′ = H
b: R = H, R′ = $CH_2C(O)Me$

89 R = OH
90 R = CH_2CO_2Me

91 R = OH
92 R = CH_2CO_2Et
93 R = CH_2CN

mainly the E isomer, from **89** with $Ph_3P{=}CHCO_2Et$ (benzene); the carbomethoxy ylide gave some α- and β-C-furanosides along with **94**.[161c] The reaction between



94

96 R = $SiMe_2tBu$

97 R = H
107 R = CPh_3

98 R = $O(CH_2)_3CHO$
128 R = CHO

99 R = H
100 R = Me

101 R = CH_2OTHP
102 R = CH_2OH
103 R = CH(Me)OH

105

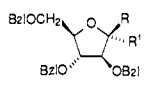
106 R = H
108 R = CPh_3

109

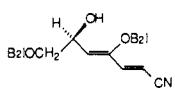
95 and $Ph_3P{=}C(Me)CO_2Et$ (methylene chloride) gave **96** enriched in the *E* isomer (*Z*/*E* = 1:9, 85% yield),[161h] as would be expected from the above results, not in the *Z* isomer as was first reported.[161a]

Barrett et al., in a total synthesis of showdomycin, studied reactions of stabilized ylide **97**.[161f] Reactions of **97** with model aldehyde partners **98–100** produced (*E*)-succinimide adducts **101–103** with high stereocontrol. An optimum yield of **103** of 83% was gleaned in wet acetic acid at a concentration of 0.6 M over 65 h. Ylide **97** coupled with unprotected D-ribose, **104**, in refluxing THF to give **105** (*E* isomer) in 75% yield and with protected ribose **83** in DME at 60 °C for 290 h to give **106** in 52% yield.[161f] Reaction of ylide **107** with **83** generated not only **108** but also, inexplicably, a considerable amount of the corresponding *Z* isomer (*Z*/*E* = 1:1.8, 30% yield, methylene chloride).

Tribenzyl-D-arabinose **109** combined with $Ph_3P{=}CHCO_2$-*t*-Bu in methylene chloride to give a 3:2 mixture of (*Z*)/(*E*)-alkenes (92% yield).[163] Heating of **109** with $Ph_3P{=}CHCO_2Me$ in acetonitrile furnished cyclic products of **110** and **111** in β:α ratios ranging from 1:9



110 R = CH_2CO_2Me, R' = H
111 R = H, R' = CH_2CO_2Me
112 R = CH_2CN, R' = H
113 R = H, R' = CH_2CN



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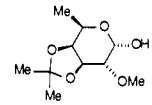
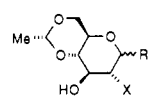
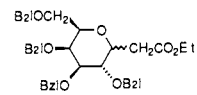


115



116 R = OH, X = NHAc
117a R = X = OH
117b R = $CH_2C(O)CH_2CO_2Et$, X = OH



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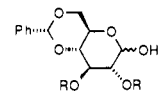
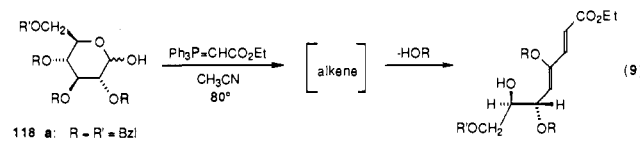


121a R = Ac
121b R = Bzl

to 1:5; no alkene intermediates were detected.[164] Reaction of **109** and $Ph_3P{=}CHCN$ gave a 1:(2–3) mixture of **112** and **113**, which produced diene **114** (*E*,*Z* stereochemistry confirmed by ^1H NMR coupling and NOE) on treatment with hexamethyldisilazide base, via elimination of the 3-benzyloxy group.[164,165]

Reactions of 2-deoxyribose derivatives with $Ph_3P{=}CHCO_2Et$ in refluxing THF have led solely to (*E*)-alkenes, as might be expected from the absence of an α-alkoxy substituent.[166]

Protected D-fucopyranose **115**[167a] or D-acetamidoglucopyranose **116**[167b] coupled with $Ph_3P{=}CHCO_2Et$ in refluxing acetonitrile to give an ca. 2:1 or a 1:3 mixture of (*Z*)/(*E*)-alkenes in good yield.[167c] On the contrary, attack of masked D-glucopyranose **117a** with $Ph_3P{=}CHCO_2Me$ rendered just the corresponding (*E*)-alkene (presumably).[168] Only cyclized products **117b** were found on treatment of **117a** with $Ph_3P{=}CHC(O)CH_2CO_2Et$.[161e] D-Glucopyranoses **118a** and **118c** generated only diene products **119a** and **119c**, by anti elimination of ROH in situ, instead of monoalkenes or *C*-glycosides, as shown in eq 9; **118b** gave a mixture of **119b** and cyclized product.[169] (Note: The first paper[169a] made erroneous structure assignments that were corrected by the later papers.[169b,c]) In contradistinction, tetrabenzyl derivatives of D-manno-, D-altro-, and D-allopyranoses furnished only normal monoalkenes,

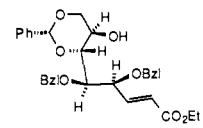


118 a: R = R' = Bzl
b: R = R' = Ac
c: R = Ac, R' = Bzl

119

(9)

while tetrabenzyl-D-galactopyranose furnished only the *C*-glycoside, **120**.[169b,c] Interestingly, benzylidene glucopyranoses **121a** or **121b** provided *C*-glycosides or a mixture of monoalkenes (no isomer ratio) and *C*-glycosides, respectively. A clean conversion of **121b** to **122** was reported by Reed et al. (82% yield, largely *E*



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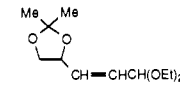

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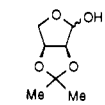


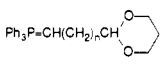
124

isomer).[170a] The appearance of conjugated dienes is a new facet of the reaction of glycosides with stabilized ylides. The extent of this side pathway seems to depend on the stereochemistry of the substrate, restriction of conformational freedom in the substrate, type of stabilized ylide, and presence of excess ylide or strong base.[164,165,169–171]

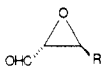
In concluding the discussion of stabilized ylides and lactols bearing α-alkoxy substituents, we emphasize the following. The factors influencing the alkene stereochemistry are not well understood because many of the reactions have not been examined effectively at the alkene stage. Also, the relationship between alkene stereochemistry and *C*-glycoside stereochemistry is poorly understood. Deliberate, systematic studies of the "Wittig–Michael" sequence are needed to eliminate these deficiencies of knowledge. [Note added in proof: A very interesting paper on the stereochemistry of reactions of stabilized ylides with lactols has recently appeared (Webb, T. H.; Thomasco, L. M.; Schlachter, S. T.; Gaudino, J. J.; Wilcox, C. S. *Tetrahedron Lett.* **1988**, *29*, 6823). A dramatic influence of a free γ-hydroxy group was determined.]

The stereochemistry of reactions of nonstabilized and semistabilized ylides with α-alkoxy aldehydes is usually more commonplace. In some cases, the *Z*/*E* ratios simply parallel, more or less, those anticipated for aldehydes lacking an α-alkoxy moiety; however, proximate oxygen-containing functionalities can sometimes play an influential role in these reactions.

Compound **45** reacted with $Ph_3P{=}CHCH(OEt)_2$ under Bestmann's protocol[172a] (THF, Li salt free) to give alkenes **123** with a *Z*/*E* ratio of 17:1,[128] which compares with ratios of 11.5:1, 24:1, and 19:1 for hexanal, *t*-BuCHO, and PhCHO, respectively.[172a] Treatment of $(EtO)_2CHCHO$ with $Ph_3P{=}CHPr$ (THF, salt free) gave a normal *Z*/*E* ratio of 19:1.[172b] Reaction of **45** with $Ph_3P{=}CHPr$[173a] or $Ph_3P{=}CH(CH_2)_{14}Me$[173b] (both with THF and Li salt) or with $Ph_3P{=}CH(CH_2)_3COO^-Na^+$ (DMSO, salt free)[153c] was stated to produce only the (*Z*)-alkene.[173c] In the synthesis of leukotrienes Cohen et al.[174a] exposed **124** to ylide **125a** (THF, Li salt), as a substitute for $Ph_3P{=}CHCH_2COO^-$ (which was unsuccessful), to obtain the desired (*Z*)-alkene exclusively. A strongly *Z*-selective olefination was also realized from (*Z*)-$Ph_3P{=}CHCH_2CH{=}CH(CH_2)_3CO_2Me$ and an al-



125 a: n = 1
b: n = 4



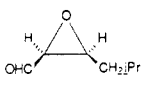
126 R = $i(CH_2)_3CO_2Me$
127 R = nC_5H_{11}

dehyde related to **54** en route to the eicosanoid trioxilin B_3.[174b]

There seems to be a hint of improved *Z* selectivity with α-alkoxy aldehydes and nonstabilized ylides, relative to unsubstituted aldehydes. Indeed, this concept has been clearly substantiated in one series by Bernstein and co-workers.[175] Under lithium salt conditions in THF (−78 → 0 °C), $Ph_3P{=}CHCH_2Ph$ combined with heptanal to give an 80:20 *Z*/*E* ratio of alkenes and with benzaldehyde to give a 56:44 ratio, as expected. However, reaction of this ylide with epoxy aldehyde **126** afforded a surprisingly high *Z* stereoselectivity of >95:5.[175] More impressively, this anomalous *Z* stereocontrol was evinced, to an even greater degree, with trialkyl ylide $(c\text{-}Hx)_3P{=}CHCH_2Ph$: heptanal, 62:38; benzaldehyde, 13:87; **126**, >95:5.[175b] Other possible examples of such anomalous *Z* stereocontrol with α,β-dialkoxy aldehydes (such as **47**, X = Me or H) and nonstabilized ylides are discussed in section II.B.2. Certainly, the phenomenon deserves further attention as it may boast heretofore unappreciated generality, useful for strategic synthetic planning.

This pattern was absent, however, in a similar comparison with semistabilized ylide $Ph_3P{=}CHC{\equiv}CSiMe_3$ (Li salt, THF, −78 → 0 °C): cyclohexanecarboxaldehyde, *Z*/*E* = <1:10, benzaldehyde, 1:2.7; **127**, <1:10.[176] On the contrary, reaction of this propargyl ylide with α-alkoxy aldehyde **45** or **128** resulted in a *Z*/*E* ratio (−78 °C) of 4.4:1 or 1:1.4, respectively.[177] There was a decided temperature effect in that **45** gave a 1.25:1 ratio at −40 °C and **128** gave a 1:2.9 ratio at 0 °C.[177] Nevertheless, anomalous enhancement of *Z* selectivity is evident.

Nonstabilized ylide $Ph_3P{=}CH(CH_2)_2OSiMe_3$ and epoxy aldehyde **129** (THF, Li salt) favored (*Z*)-alkene (*Z*/*E* = ca. 10:1)[178a] more than the analogous reaction of $Ph_3P{=}CHCH_2C(Me)_2OSiMe_3$ and **130** (*Z*/*E* = 85:15).[70] Surprisingly, the reaction of labile aldehyde **131** with nonstabilized ylide **125b**, generated with NaH in DMSO–THF, produced only (*E*)-alkene (section II.B.2).[178b]



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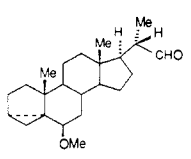

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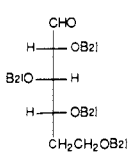

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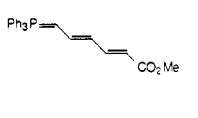

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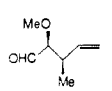

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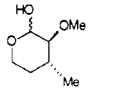

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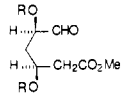
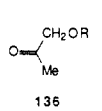


135 R = $SiMe_2tBu$

Semistabilized ylide **132**, created in situ from $Ph_3P{=}CHCH{=}CH_2$ and methyl 3-chloroacrylate,[179] added to **45** to give a *Z*/*E* ratio of 1.8:1 at the new double bond.[180] This is close to the 1:1.5 *Z*/*E* ratio obtained for the reaction of **132** and isobutyraldehyde.[179]

Ylide $Ph_3P{=}CHPh$ reacted with **133** (THF, 0 °C, Li salt) to give a 1:2 (*Z*)/(*E*)-alkene ratio, but with structurally related lactol **134** to give a 1:10 ratio.[181] Remarkably, the latter transformation afforded a *Z*/*E* ratio of <1:40 with KH in DMSO.[181] Aldehyde **135** furnished mainly the (*E*)-alkene under similar conditions.[182] The reaction of **57** with $(2,4\text{-}Cl_2C_6H_3)CH{=}PPh_3$ (KO-*t*-Bu, THF–DMF) gave a normal 4:1 *Z*/*E* product mixture,[183] as did the reaction of $(EtO)_2CHCHO$ with $Ph_3P{=}CHPh$ (THF, salt free).[172b] Sugar **63a** condensed with $Ph_3P{=}CHPh$ abnormally, supplying a >95:5 (*Z*)/(*E*)-alkene ratio.[149]

α-Alkoxy ketones can also demonstrate anomalous stereoselectivity in Wittig reactions. Still's group studied ethylidenation of various ketones **136** by using



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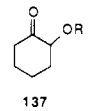

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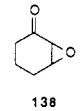
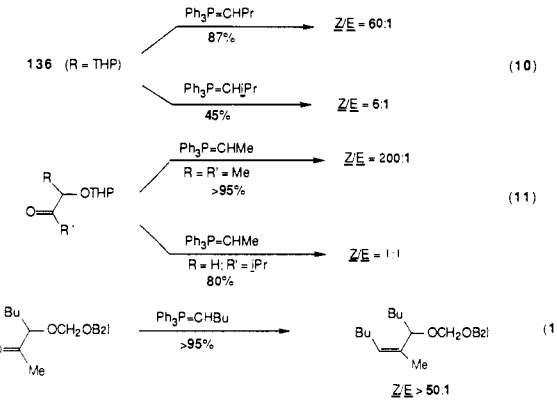


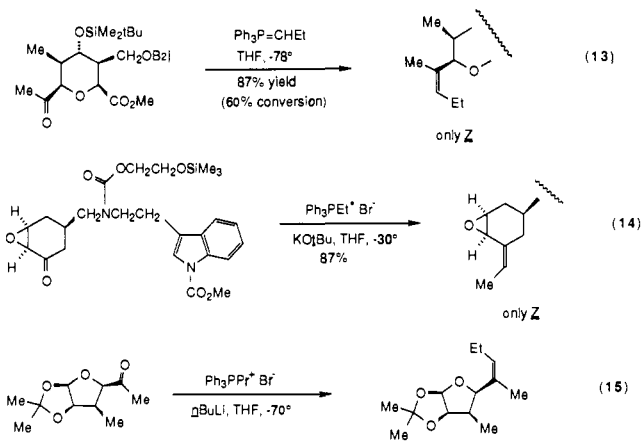
138

$Ph_3P{=}CHMe$ at −78 °C.[184] With $KN(TMS)_2$ in HMPA/THF, R = OTHP, CMe_2OMe, CPh_3, $SiMe_2$-*t*-Bu, or Bzl gave *Z*/*E* ratios of 41:1 (83% yield), 30:1, 18:1, 14:1, or 12:1, respectively. With R = THP, diverse conditions still led to decent *Z* stereoselectivity: THF and $KN(TMS)_2$, 29:1; HMPA/THF and *n*-BuLi, 28:1; THF and *n*-BuLi, 11:1; ether and *n*-BuLi, 5:1. Under the $KN(TMS)_2$–HMPA/THF protocol, there was some dependence of stereocontrol (and yield) on the structure, particularly steric properties, of the ylide or ketone (eq 10–12). A marginal, but significant, increase in *Z*



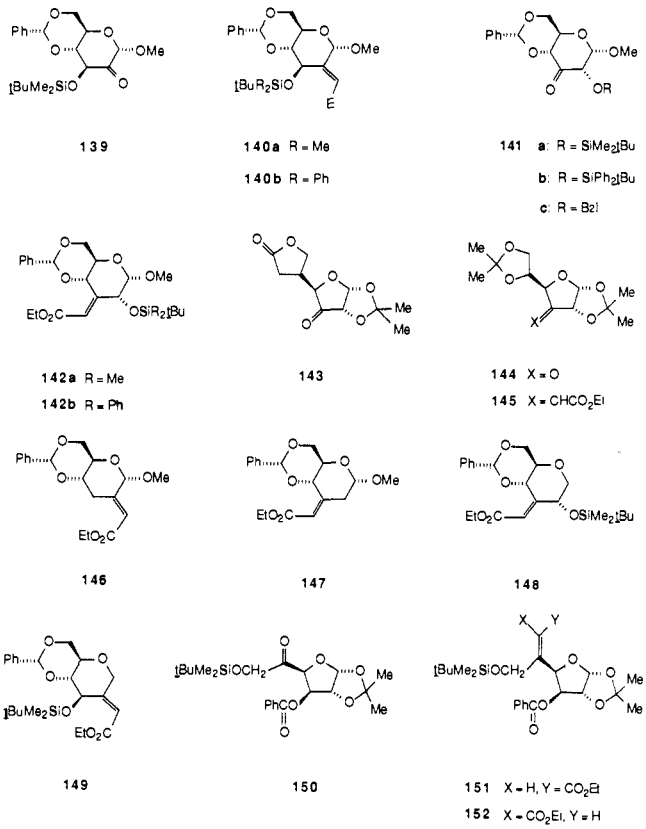
selectivity was realized by employing phosphonium fluoborate salts instead of the halide salts. Sreekumar et al. effectively applied this chemistry to a stereocontrolled synthesis of α-santalol.[184] Reaction of $Ph_3P{=}CHCH_2NBu_2$ with **136** (R = Ac) under Still's conditions gave exclusively the trisubstituted (*Z*)-alkene.[185a] However, Stork and Atwal obtained only a 3:1 *Z*/*E* ratio from addition of **136** (R = allyl) to $Ph_3P{=}CH(CH_2)_3OTHP$.[185b] Some more recent applications are presented in eq 13,[186a] 14,[186b] and 15.[143]

Koreeda et al. studied Still's process with 2-oxygenated cyclohexanone derivatives.[187] Ethylidenation of ketones **137** with R = Ac, Me, Ph, $SiMe_2$-*t*-Bu, or Bzl under lithium salt free conditions (THF) gave *Z*/*E* ratios of 6:1, 8:1, 10:1, 26:1, or 36:1, respectively; under lithium salt conditions, **137** with R = Me, Ph,



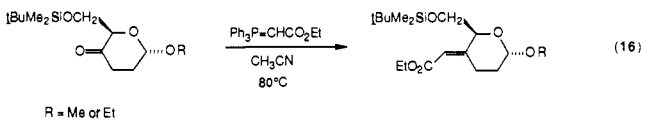
$SiMe_2$-*t*-Bu, or Bzl gave poorer *Z* selectivities of 2.6:1, 5:1, 7.6:1, or 1.1:1. Epoxycyclohexanone **138** also delivered good *Z* stereocontrol (*Z*/*E* = 6:1) under salt-free conditions.

Some keto sugars have provided templates for unusual stereochemistry with stabilized ylides.[188,189] Reaction of **139** with $Ph_3P{=}CHCO_2Et$ in refluxing ace-



tonitrile generated only (*E*)-alkene adduct **140a** (E = CO_2Et) in a yield of 90%.[188a,b] Analogous 3-keto sugar **141a** also gave only one isomer, **142a** (76%),[188b] whereas the corresponding 2-benzyloxy derivative **141c** surprisingly gave both alkene isomers in equal amounts.[188a] A similar stereorandomness was observed for the reaction of 3-keto furanose **143** with $Ph_3P{=}CHCO_2Me$,[146b] while congener **144** just led to about a 3:1 ratio of alkenes **145**.[189b] More recently, Wood and Rashid reported that **139** and **141a** each react with $Ph_3P{=}CHCO_2R$ (R = Me or Et) to furnish a single product, namely **140a** (E = CO_2Me or CO_2Et).[189a] Since treatment of ketone **139** with base (triethylamine; hot acetonitrile) afforded a 4:1 (presumably equilibrium) mixture of **139**:**141a**, they suggested that the stereoconvergence to **140a** is kinetic in nature.[189a] That is, under the reaction conditions equilibration of **139** and **141a** occurred and **139** combined with ylide at a much faster rate than did **141a**. In an attempt to circumvent this problem, Wood and Rashid employed a larger, less labile silyl group. Thus, ketone **141b**, in a slow reaction, gave rise to desired alkene **142b** and rearranged alkene **140b** in a 3:1 ratio. Although the discrepancy between these two sets of results[188a,b,189a] is unresolved, the stereochemical outcome is unambiguous.

Fraser-Reid and associates also obtained 2-deoxypyranoses **146**–**149** exclusively from the corresponding ketones.[188a,b] Interestingly, with **146** and **147** the stereocontrol inverts from *E* to *Z*, and with **148** and **149** the ester group changes from anti to syn vs the silyloxy substituent. A similar high stereoselection was found in the conversion of a 4-keto sugar to its acrylate derivative (eq 16).[188a,c] With ylide $Ph_3P{=}CHCO_2Et$ in

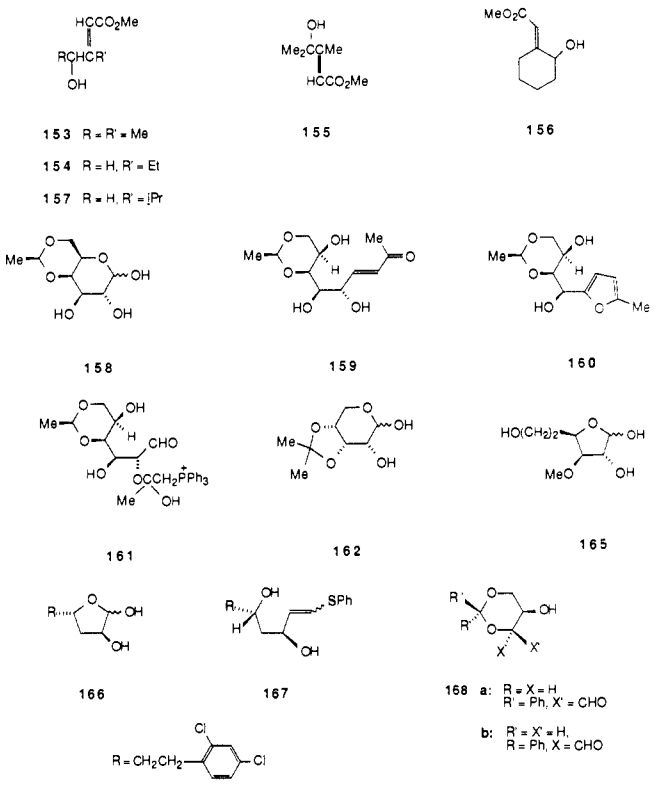


hot acetonitrile, keto furanose **150** demonstrated reasonably good stereoselectivity (**151**/**152** = ca. 4.5:1), despite the carbonyl group now being exocyclic; indeed, in DMSO at 23 °C, **150** demonstrated excellent stereoselectivity (**151**/**152** > 10:1).[146b]

As Fraser-Reid so aptly affirmed,[188b] a satisfactory rationale for the special stereochemistry arising from Wittig reactions of carbalkoxy-stabilized ylides and α-alkoxy ketones is less than obvious. A better understanding of scope and limitations through judicious experimentation would help to counter this shortfall.

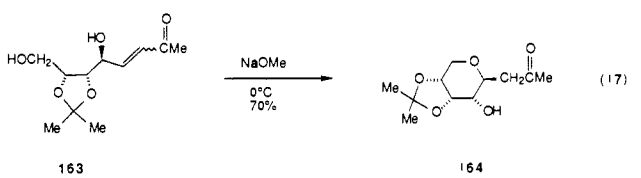
(*d*) *Reactants with a Free Hydroxy Group near the Carbonyl.* When a free hydroxy group is present in the carbonyl reactant, it may be deprotonated to some extent to form an alkoxide, depending on the base strength of the ylide. The oxido moiety will be paired with the metal of the base employed to generate the phosphorus ylide and/or with the phosphonium conjugate acid. In the case of stabilized ylides, it is doubtful that a full-fledged alkoxide would be obtained; indeed, the hydroxy group may retain its chemical integrity for the most part. Some enolate of the ketone or aldehyde, perhaps an enediolate, may also coexist. Whatever the specific circumstances, when the hydroxyl is proximate to the reaction center, as with α-hydroxy carbonyl compounds, it may exert a strong effect on reaction stereochemistry. With the hydroxy group intact, this could be viewed as an analogy with the chemistry in the previous section (II.B.1.c). But, there could be a uniqueness here due to the possibility of hydrogen bonding. Moreover, if the oxido species were significantly populated, then an entirely new factor would come into play.

Garner and Ramakanth have conducted the only investigation of α-hydroxy carbonyl compounds,[190] albeit some isolated reports have appeared as well.[160c,161f,183,191] In Garner's work, both acyclic and cyclic α-hydroxy ketones reacted, at an accelerated pace, with carbomethoxy-stabilized ylides to yield (*E*)-alkenes.[190] Good yields of (*E*)-alkenes **153** and **156** were obtained from the corresponding ketones and $Ph_3P{=}CHCO_2Me$ in refluxing acetonitrile (78% and 94%), but only fair



yields of **154**, **155**, and **157** were realized (43%, 23%, and no reaction). The poor results in the latter two examples denote a sensitivity of the reaction to steric hindrance around the carbonyl site. The use of $Bu_3P{=}CHCO_2Me$ raised yields somewhat in the difficult cases. Reactions of $Ph_3P{=}CHCO_2Me$ with trimethylsilyl ethers of 3-hydroxy-2-butanone and 2-hydroxycyclohexanone were very sluggish and underproductive (10% and 49%); the former was stereorandom and the latter gave only (*E*)-alkene.

As mentioned before, D-ribose has been coupled with ylide **97** to produce **105** (75% yield), exclusively as the *E* isomer.[161f] In the reaction of **158** and $Ph_3P{=}CHC(O)Me$, Olejniczak and Franck obtained not only (*E*)-alkene **159**, but also furan **160**, possibly because of an intramolecular Wittig condensation of **161**.[191b] Treatment of D-ribose acetonide **162** with $Ph_3P{=}CHC(O)Me$ in acetonitrile gave alkene **163**, a mixture of geometric isomers, which was cyclized to β-*C*-glycopyranoside **164** (eq 17); further reaction of **164** with



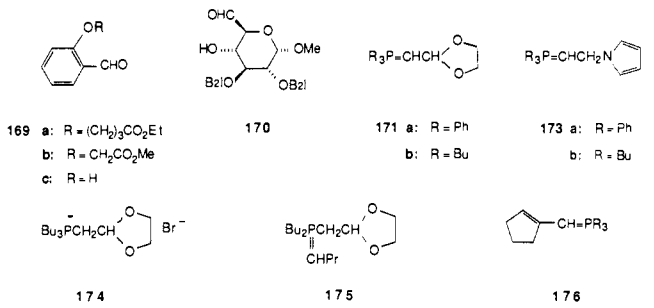
(17)

$Ph_3P{=}CHCO_2Me$ in acetonitrile gave a 3:2 mixture of (*Z*)/(*E*)-acrylate adducts, as expected.[160c] Addition of $Ph_3P{=}CHCO_2Me$ to furanose **165** (EtOAc) yielded only the (*E*)-acrylate (75%).[191c] Cyclic hemiacetal **166** combined with salt-free $Ph_3P{=}CHSPh$ in DMF/DMSO to give a 2:1 ratio of (*Z*)/(*E*)-vinyl sulfides **167**.[183]

Stabilized ylides $Ph_3P{=}CHX$ (X = COOR or CN) gave (*E*)-alkenes, as expected, in reactions with $HSCH_2CHO$ (released from the cyclic dimer in situ).[191a]

α-Alkoxy-β-hydroxy aldehyde **168a** failed to show the predicted *E* selectivity in a Schlosser–Wittig betaine–ylide process with a nonstabilized phosphorane (see section II.B.1.g), perhaps because of interference by the neighboring metallo oxido group in the aldehyde unit.[192a] However, it is extraordinary that diastereomeric aldehyde **168b** reacted with an anion-bearing nonstabilized ylide, $Ph_3P{=}CHCH_2CO_2^-Li^+$, to render exclusively the (*E*)-alkene product (THF–DMSO).[192b]

Although **169a** and $Ph_3P{=}CH(CH_2)_{10}Me$ (dimsylsodium in DMSO) gave a 1:1 mixture of (*Z*)/(*E*)-β-undecylstyrenes, as anticipated,[28,65a] 2-hydroxybenzaldehyde (**169c**) and $Ph_3P{=}CH(CH_2)_5Me$ gave a 2.3:1



mixture of β-hexylstyrenes; 4-hydroxybenzaldehyde gave a 7:1 *Z*/*E* mixture with the former ylide.[192c] Reaction of **169c** and $Ph_3P{=}CH(CH_2)_5Me$ (*n*-BuLi, THF) led to solely the *E* isomer (58% yield), while **169b** and $Ph_3P{=}CH(CH_2)_{10}Me$ afforded a 2:1 *Z*/*E* ratio; 4-hydroxybenzaldehyde gave a 1:2.7 mixture. With lithium ion present, the proximate phenolate group appears to strongly affect reaction stereochemistry.

Reaction of β-hydroxy aldehyde **170** with an excess of ylide **171a** supplied a 7:1 *Z*/*E* mixture of adducts (dimsylsodium, DMSO/THF; 70%).[192g] Benzaldehyde gave an 8:1 ratio under the same conditions; however, only a 3:1 mixture was produced in straight DMSO and, oddly enough, only *E* adduct was produced with *n*-butyllithium in THF. A rationale for this conspicuously high *E* selectivity with benzaldehyde is not yet evident.

Fairly normal stereoselectivity has been observed in several reactions of sugar-derived β-hydroxy aldehydes with nonstabilized ylides (salt-free or lithium salt conditions) or stabilized ylides.[153b,166b,c,192d-f]

Some other Wittig reactions of hydroxy carbonyl compounds are located in sections II.B.1.g and II.B.2.

(*e*) *Variation of the Phosphorus Ligands of the Ylide.* Of the phosphorus ylides used or studied by chemists over the years, the triphenyl class has vastly preponderated. Thus, the results for reactions of these ylides have become, more or less, the paradigm by which reactions of other ylide types are judged. Replacement of all three phenyl ligands by alkyl ligands can significantly augment ylide reactivity[6,11,84i,192h] (section II.A.3) and definitely has a profound stereochemical consequence (section II.A.2.b).[11,12,31,34,63,83,175b,193] Probably, the first report of enhanced *E* stereoselectivity with trialkyl ylides was that of Bestmann and Kratzer, in which three cyclohexyl groups were connected to phosphorus.[193g] Some examples from the trialkyl ylide area, and from reports germane to the exchange of one or two phenyl ligands for alkyl ligands, will be elaborated upon here.

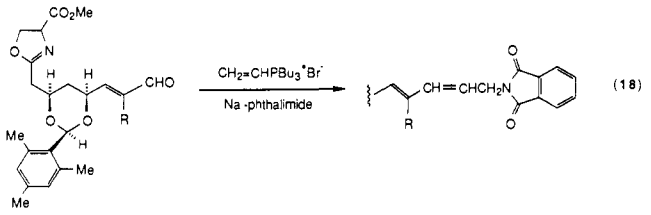
Schlosser and Schaub[63] reacted $Ph_3P{=}CHMe$ and $Et_3P{=}CHMe$ under salt-free conditions in THF at 25 °C with a series of four aldehydes; heptanal, pivalaldehyde, benzaldehyde, and 4-chlorobenzaldehyde (Table IV). Of the eight combinations, three (high-

TABLE IV. Z/E Ratios for Reactions of Ph_3P=CHMe and Et_3P=CHMe with Various Aldehydes

ylide	heptanal	*t*-BuCHO	PhCHO	4-ClC_6H_4CHO
Ph_3P=CHMe	86:14	98:2	87:13	88:12
Et_3P=CHMe	33:67	*10:90*	*17:83*	*4:96*

lighted in Table IV) experience some influence of stereochemical drift.[31]

Meyers and colleagues have assembled allyl amines[83b,193a] and *N*-allylpyrroles[193b] by addition of nitrogen nucleophiles to vinyl phosphonium salts and reaction of the resultant ylides with aldehydes. Ylide Ph_3P=$CHCH_2$-phth, derived by using sodium phthalimide (phth), combined with benzaldehyde or cinnamaldehyde to give a 73:27 or 79:21 ratio of (*Z*)/(*E*)-alkenes.[83b] Addition of 0.6 mol equiv of LiBr to these reactions resulted in a 26:74 or 38:62 ratio, respectively. With benzaldehyde, a 26:74 alkene ratio was also obtained when Li-phth was employed directly. Ylide Bu_3P=$CHCH_2$-phth (Na-phth, THF) delivered much better *E* stereoselectivity. For example, benzaldehyde, cinnamaldehyde, 1-naphthyl-CHO, furfural, and $PhCH_2CH_2CHO$ gave Z/E ratios of 0:100, 17:83, 19:81, 9:91, and 25:75, respectively. Homologation of **172a** proceeded in low yield and with a disappointing Z/E ratio of 35:65 (eq 18).[193a] Results with aldehyde



(18)

172 a: R = H
b: R = Me

172b were more auspicious: a 51% yield of pure *E,E* isomer. In contrast, the corresponding triphenylphosphorane chemistry did not provide any homologated product.

The sodium salt of pyrrole engendered analogous triphenyl and tributyl ylides **173a** and **173b**, which converted aldehydes into alkenes with good yields and a similar stereochemical profile.[193b] Reaction of **173a**/**173b** with benzaldehyde, PhCH=C(Me)CHO, or hexanal gave Z/E ratios of 90:10/9:91, 78:22/1:99, or 97:3/57:43, respectively.

Conjugated (*E*)-alkenes were produced in good yields from the reaction of aromatic, heteroaromatic, or cinnamyl aldehydes with **174** and sodium ethoxide in DMF at 90 °C.[193c] Since the desired phosphorus ligand was transferred selectively and since the procedure essentially did not employ an excess of **174**, two possibilities surface: (1) deprotonation of the correct side chain of **174** may have been facilitated by the oxygen substituents and/or (2) the desired ylide **171b** may be stabilized relative to **175** by these substituents.

Reaction of $(c\text{-}Hx)_3P$=$CHCH_2Ph$ (Li salt, THF) with benzaldehyde or heptanal afforded Z/E ratios of 13:87 or 62:38, more or less predictably.[175b] However, reaction of this ylide with epoxy aldehyde **126** surprisingly gave a >95:5 (*Z*)/(*E*)-alkene ratio.

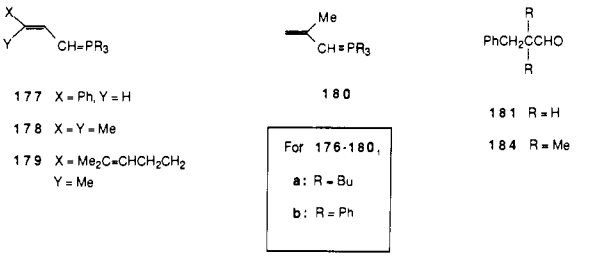
Semistabilized ylide **176b**, prepared in situ from 1-nitromethylcyclopentene, Ph_3P, and a palladium(0) catalyst, reacted with benzaldehyde (*n*-BuLi, THF/MeOH) with poor stereoselectivity (Z/E = 55:45).[193d] However, this situation could be rectified by use of the related tributyl ylide, **176a**. Thus, reaction of **176a** (prepared in situ; Li salt or salt free, THF/MeOH) and benzaldehyde gave exclusively the (*E*)-alkene. Very high *E* selectivity was also obtained with other aldehydes, such as *p*-anisaldehyde (>95% *E*), cinnamaldehyde (>95% *E*), and heptanal (Z/E = 7:93).

TABLE V. Z/E Ratios for Reactions of Allylides 176–180 with Various Aldehydes

ylide	base	PhCHO	heptanal or 181[a]	c-HxCHO	*t*-BuCHO
176a	BuLi	>95% *E*	8:92	>95% *E*	>95% *E*
176b	BuLi	55:45	42:58	27:73	85:15
177a	BuLi	40:60		18:82	37:63
	KO-*t*-Bu	42:58		5:95	
177b	BuLi	48:52		54:46	83:17
	KO-*t*-Bu	75:25		30:70	
178a	BuLi	29:71		15:85	23:77
	KO-*t*-Bu	22:78		5:95	
178b	BuLi	60:40		44:56	>95% *Z*
	KO-*t*-Bu	78:22		20:80	
179a	BuLi	15:85		12:88	15:85
179b	BuLi	70:30		34:66	78:22
180a	BuLi	16:84	8:92*	>95% *E*	
	KO-*t*-Bu	16:84	8:92*		
180b	BuLi	31:69	29:71*	10:90	
	KO-*t*-Bu	55:45	39:61*		

[a] Aldehyde 181 is denoted by an asterisk.

In a more extensive study, Tamura et al. subjected a large variety of isolated allylic phosphonium salts to olefination reactions.[193e] They compared ylides **176a** and **176b** in reactions with heptanal, isovaleraldehyde, cyclohexanecarboxaldehyde, and pivalaldehyde (Li salt, THF). The former ylide invariably gave strong *E* selectivity (>92% *E*), whereas the latter varied considerably (Table V). For the most part, ylides **177a–179a**



and **177b–179b** afforded similar stereoselectivities within *each* category; **180a** and **180b** were a little more unusual (Table V). Some notable highlights are as follows: (1) **177a** and **178a** gave a 5:95 Z/E ratio with c-HxCHO by using KO-*t*-Bu vs ca. 15:85 by using *n*-BuLi, whereas **180a** gave >95% *E* selectivity with c-HxCHO by using *n*-BuLi; (2) **177b** and **179b** gave reasonable *Z* selectivity (Z/E = 83:17 and 78:22) with pivalaldehyde (*n*-BuLi), while **178b** gave exceptional *Z* selectivity (>95% *Z*); (3) **180a** gave excellent *E* selectivity with aldehyde **181** (Z/E = 8:92) and c-HxCHO (>95% *E*); (4) **180b** gave good *E* selectivity with c-HxCHO (Z/E = 10:90). The authors interpreted these stereochemical results with the assistance of Vedejs' recent steric model.[34b]

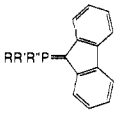
Taylor and Martin prepared heteroarylidenephosphoranes by displacement of halide or $MeSO_2^-$ from π-deficient nitrogen heterocycles (Het-X) with R_3P=CHR′ (R = Bu, R′ = Ph; R = Ph, R′ = H).[193f] One type of ylide bore three butyl groups (viz., **182**, R

TABLE VI. *Z/E* Ratios for Reactions of 181 and 184 with Various Salt-Free Nonstabilized Ylides

ylide	$Ph(CH_2)_2CHO$ (181)	$PhCH_2CMe_2CHO$ (184)
Et_3P=CHMe	33:67	10:90
Et_2PhP=CHMe	36:64	56:44
Ph_2EtP=CHMe	30:70	85:15
Ph_3P=CHMe	94:6	>99:1
Ph_2-*i*-PrP=CHMe	18:82	50:50
Ph_2-c-HxP=CHMe	25:75	
Ph_2-*t*-BuP=CHMe	94:6	99:1
$Ph_2(PhC{\equiv}C)P$=CHMe	93:7	
16a	6:94	10:90
16b	5:95	8:92
185	32:68	90:10
186	14:86	50:50

= Ph), but no results for reactions of it with aldehydes were reported; transformations involving related triphenylphosphoranes, with R′ = H, gave just (*E*)-alkenyl heterocycles.

182



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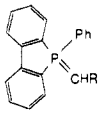


185 R = Me

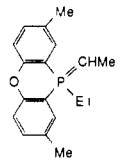
190 R = C(O)Ph

191 R = CO_2Me

An appreciation for the effect of different phosphorus ligands on the rate of ylide–aldehyde condensation can be gleaned from a study of fluorenylidenephosphoranes (viz., **183**) by Froyen.[84f] The triethyl ylide reacted with 4-nitrobenzaldehyde 2500 times faster than the triphenyl ylide (in benzene). The $PhEt_2P$ and Ph_2EtP ylides reacted at 55% and 4% of the rate of the triethyl ylide reaction. Interestingly, the E_a value for the triphenyl ylide (10.3 kcal/mol) was dramatically larger than the values for the other ligand combinations (4.1, 5.1, and 4.7 kcal/mol).

Vedejs has investigated the effect of monotonic variation of the phosphorus ligands in the ylide, from triethyl to triphenyl, on reaction stereoselectivity under salt-free conditions in THF.[34a] Representative primary and tertiary aliphatic aldehydes **181** and **184** were paired with Et_3P=CHMe, Et_2PhP=CHMe, Ph_2EtP=CHMe, or Ph_3P=CHMe (Table VI).[34a] The bulky aldehyde, **184**, manifested a tendency toward (*Z*)-alkene with three of the ylides, but conspicuously not with Et_3P=CHMe. This outstanding result derives from stereochemical drift,[31] from cis to trans oxaphosphetane, in the reaction of **184** with Et_3P=CHMe, as documented in the related reaction of ylide **27** and pivalaldehyde.[31,82a] Of the eight reaction combinations, only the pairing of Et_3P=CHMe and **184** was found to exhibit significant stereochemical drift; the seven other reactions proceeded under kinetic control.[34a]

Diphenylalkylphosphoranes $Ph_2(t\text{-Bu})P$=CHMe and $Ph_2(PhC{\equiv}C)P$=CHMe reacted with **181** to give much enhanced *Z* selectivity compared to Ph_2EtP=CHMe (Table VI). On the contrary, $Ph_2(i\text{-Pr})P$=CHMe and Ph_2(c-Hx)P=CHMe were slightly more *E* selective than the reference ylide.[34a,b] Bridging of the two phenyl rings into a dibenzophosphole entity, as in **16a**, **16b**, and **185**, caused a shift to *E* selectivity relative to corresponding ylides Ph_2EtP=CHMe and Ph_3P=CHEt (Table VI).[34a,b,62] Significantly, the enhanced *E* stereoselectivity with bridged ylides such as **16a** was shown to be under kinetic control on the basis of deprotonation experiments with relevant β-hydroxy phosphonium salts. The effect of bridging on stereochemistry was considerably attenuated with **186**, a congener of **16a** (Table VI).[34a,b] Nevertheless, certain dibenzophosphole ylides are quite useful for the stereoselective synthesis of (*E*)-alkenes.[62]



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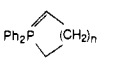
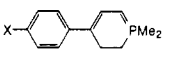


187 e: n = 2

b: n = 3



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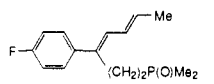

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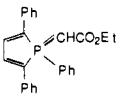

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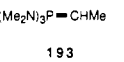


193

Ylide **187a**, in which a pair of alkyl ligands is bridged, was also explored.[34a,b] In a dramatic turnabout, **187a** (salt free, THF) gave exclusive *Z* selectivity with aldehydes **181** and **184**. A low-temperature (−78 °C) HBr-quench experiment did not capture oxaphosphetane intermediates, suggesting that they may be inordinately unstable in this case. By the same token, Muchowski and Venuti had demonstrated earlier virtually complete *Z* stereocontrol for **187a** and RO-$(CH_2)_6$CHO (R = OAc or THP) with KO-*t*-Bu in THF in their preparation of $RO(CH_2)_6CH{=}CH(CH_2)_3P(O)Ph_2$ for use as an olefination reagent (see section III.B).[194a] Homologous ylide **187b** showed somewhat diminished *Z* selectivity with **181** (*Z*/*E* = 88:12) and **184** (*Z*/*E* = 82:18) under salt-free conditions, while the *Z*/*E* ratio with PhCHO was 45:55.[85b] Yamamoto et al. briefly examined **187b**, but by using *n*-butyllithium in THF.[194b] In this work, benzaldehyde, 4-(dimethylamino)benzaldehyde, and cinnamaldehyde furnished *Z*/*E* ratios of 32:68, 0:100, and 35:65, respectively.

With regard to the work discussed in the last three paragraphs, Vedejs and co-workers proposed a new transition-state model to rationalize the stereochemistry for Wittig reactions of nonstabilized phosphorus ylides with aldehydes (see section II.A.4.c).[34b]

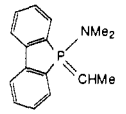
Semistabilized, cyclic allylides **188** added to benzaldehydes to furnish solely (*E*,*E*)-dienes **189** (*n*-BuLi, THF).[195] Vedejs and Huang studied some acyclic allylides under various conditions.[89a] Reaction of Ph_3P=CHCH=CHMe (chiefly *E*) with cyclohexanecarboxaldehyde or 3-phenylpropanal (**181**) gave a diene *Z*/*E* ratio of ca. 1:1, while Ph_2MeP=CHC(Me)=CH_2 gave a 1:16 or 1:2.4 ratio, respectively (*n*-BuLi, THF). Salt-free reactions of $Ph_2(Me_2C{=}CHCH_2)P$=CHCH=CMe_2 ($NaNH_2$, THF) delivered the best stereochemical performance, in the *E* direction: benzaldehyde, *Z*/*E* < 1:15; c-HxCHO, 1:40; 3-phenylpropanal, <1:15.

Stabilized phosphoranes with bridged phenyl rings, **190** and **191**, were briefly studied by Wilson and Tebby.[196] In benzene, **190** gave *Z*/*E* ratios of 28:72 or 22:78 with acetaldehyde or benzaldehyde, whereas Ph_3P=CHC(O)Ph was more *E* stereoselective with both aldehydes (*Z*/*E* = 12:88). These two ylides, and **191** and

$Ph_3P{=}CHCO_2Me$ (**32**), reacted with benzaldehyde with similar rates.

Bridged "divinyl" phosphorane **192** reacted with acetaldehyde somewhat sluggishly to afford a low yield of (*Z*)/(*E*)-crotonates in a ratio of 24:76 (benzene solvent); $Ph_3P{=}CHCO_2Et$ gave an 11:89 ratio.[197]

Ylide **193** and bulky aldehyde **184** combined with nearly exclusive *E* selectivity.[34] With **181** or **184**, ylide **194** gave *Z*/*E* ratios of 4.6:1 or 24:1, which were less *E* selective than ratios obtained with ylides **16a** (1:18 and 1:9) and **185** (1.2:1 or 9:1).



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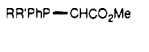
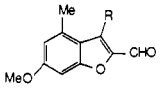


195 a: R = Ph, R' = Fc
b: R = R' = Fc



196

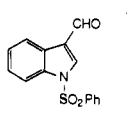
The (*Z*)/(*E*)-alkene ratio for the reaction of semistabilized ylides $Ar_3P{=}CHPh$ with benzaldehyde in ethanol decreased in the series Ar = 2-furyl (63:37), 2-thienyl (54:46), phenyl (50:50), 4-methoxyphenyl (33:67), 3-thienyl (35:65), 3-furyl (30:70), and 1-methyl-2-pyrrolyl (22:78).[84b] In reactions of benzaldehyde or acetaldehyde with $Ar_3P{=}CHCO_2Et$, the 2-furyl group also supplied more (*Z*)-alkene (by ca. 20%) relative to phenyl.

The reactions of ferrocenyl (Fc) ylide **195a** or **195b** with benzaldehyde proceeded at nearly the same rate as the reaction of $Ph_3P{=}CHCO_2Me$ did.[198a] With either ferrocenyl ylide, the ratio of (*Z*)/(*E*)-methyl cinnamates was substantially better (*Z*/*E* = 4:96) than that achieved with $Ph_3P{=}CHCO_2Me$ (*Z*/*E* = 15:85). The stereochemistry with ylides **195a** and **195b** was virtually identical (*Z*/*E* = ca. 5:95) to that experienced with $Bu_3P{=}CHCO_2Me$ (**33**).[31,83a]

Schaub et al. investigated the effect of exchanging all three phenyl groups in $Ph_3P{=}CHMe$ with aryl or heteroaryl groups.[198b] When hexanal was the substrate, *Z* stereoselectivity was enhanced by replacement of phenyl (*Z*/*E* = 96:4) with 2,6-difluorophenyl (99:1), 2-tolyl (98:2), or 2-thienyl (99:1). When benzaldehyde was the substrate, enhancement of *Z* selectivity occurred by replacing phenyl (*Z*/*E* = 92:8) with 2,6-difluorophenyl (99:1). For reactions involving $Ph_3P{=}CHPr$, such special effects were virtually dissipated.

(f) Presence of Polar α Substituents in the Ylide. α-Alkoxy and α-thioalkoxy phosphonium ylides have been used for one-carbon homologation of aldehydes and ketones.[199] Unfortunately, the alkene stereochemical information in many instances was discarded amidst the drive to attain the ultimate synthetic target. Many of the isolated reports that contain stereochemical data are presented here.

Aldehyde **196** (R = H) united with $Ph_3P{=}CHOMe$ (NaOEt/EtOH) to yield a 1:2 ratio of (*Z*)/(*E*)-alkenes (54%); **196** (R = Cl and OMe) gave ca. 1:1 mixtures.[200] Reaction of **197** with $Ph_3P{=}CHOMe$ (*n*-BuLi, THF) furnished a 1:3 ratio of (*Z*)/(*E*)-vinyl ethers (80%).[200] A conjugated enol ether, with a *Z*/*E* ratio of ca. 3:7, was produced by condensation of **198** and $Ph_3P{=}CHOMe$ (DMSO–THF).[201] Lactol **199** was converted to **200** (87% yield), with a *Z*/*E* ratio of nearly 1:2, by using $Ph_3P{=}CHOMe$ (KO-*t*-Bu, THF).[202] The natural fungicide strobilurin A (**202**), along with its 9-*E* isomer **203**,



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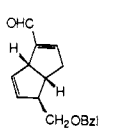

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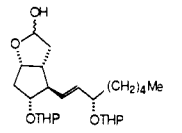

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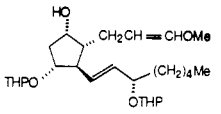

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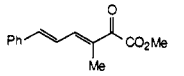

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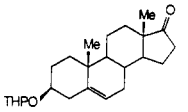

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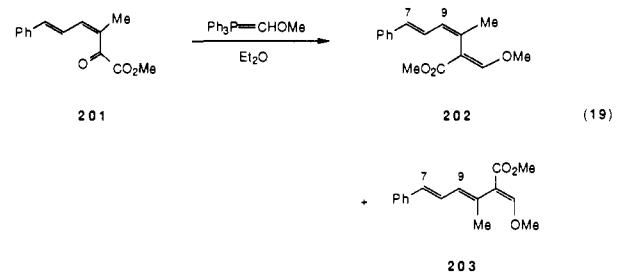
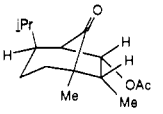
was synthesized from ketone **201** (eq 19; PhLi as base); high *E* stereoselectivity was obtained for the newly formed double bond in both products.[204] Similar



201 202 (19)

203

treatment of ketone **204** afforded **203**, with high *E* selectivity and without stereomutation of any other double bonds.[204,205] Reaction of pregnenolone derivative **205** with $Ph_3P{=}CHOMe$ (potassium *tert*-amylate, toluene) provided a 1:4 *Z*/*E* mixture of vinyl ethers in quantitative yield.[206] Homologation of **206** (*n*-BuLi,



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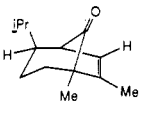

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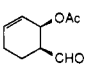

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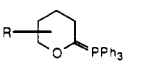

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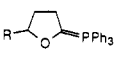
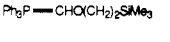


210 (R = H or OMe)



211

ether), followed by deacetylation, gave a 1:3 mixture of hydroxy enol ethers; homologation of **207** led to a 2:1 mixture of isomers (stereochemistry unassigned).[207] Attempted conversion of **208** into the enol ether by using $Ph_3P{=}CHOMe$, generated with *n*-butyllithium, was complicated by transylidation[7] and ensuing butylidene transfer to the substrate.[208] Trost and Verhoeven overcame the problem by employing *tert*-butyllithium as the base (ether; *Z*/*E* = 2:3; 88% yield).[208]

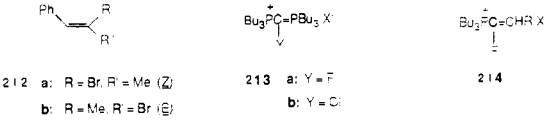
Cyclic phosphoranes **209** or **210** have proven useful in the synthesis of spiro ketal molecules, but no isomer ratios for the alkene intermediates are available.[209] Phosphorane **211** (made by using dimsylsodium in DMSO) has been successfully applied to the one-carbon homologation of aldehydes and ketones.[210] The enol ethers had *Z*/*E* ratios in the vicinity of 1:1, and the (trimethylsilyl)ethyl protecting group was easily removed from the products under mild conditions.[210]

Z/*E* isomer ratios were reported for the vinyl sulfides derived from addition of $Ph_3P{=}CHSMe$ to sugar aldehydes **58**, **63**, and **64** (NaH, DMSO): 68:32 (41% yield), 55:45 (52%), and 89:11 (70%), respectively.[148c] As mentioned in section II.B.1.d, $Ph_3P{=}CHSPh$ at-

tacked **166** to afford (*Z*)/(*E*)-vinyl sulfides **167** in a 2:1 ratio.[183]

The synthesis of vinyl halides is readily effected via Wittig olefination with Ph_3P=CHX (generally, X = F, Cl, Br). Schlosser and Zimmermann described a convenient preparation of vinyl fluorides by the agency of Ph_3P=CHF (PhLi, ether–THF).[211] For example, hexanal was transformed into a 45:55 *Z*/*E* mixture of $Me(CH_2)_4CH$=CHF (58%); benzaldehyde gave a 50:50 mixture of PhCH=CHF (65%).[211a] Vinyl chlorides were synthesized from aldehydes or ketones and Ph_3P=CHCl in good yields (KO-*t*-Bu, *t*-BuOH); benzaldehyde, nonanal, 2-methylcyclohexanone, and acetophenone furnished *Z*/*E* ratios of 54:46, 56:44, 8:92, and 44:56, respectively.[212] When the ylide was generated by using NaOEt in ethanol, diminished reactivity was seen. Olefination of 2-methylcyclohexanone under NaOEt/EtOH conditions resulted in an altered *Z*/*E* ratio of 56:44. Extended reflux of the aldehyde reactions gave acetylenes in good yield, due to elimination of HCl.[212] Addition of Ph_3P=CHCl to $PhSeCH_2CHO$ (*n*-BuLi, THF) provided $PhSeCH_2CH$=CHCl with a *Z*/*E* ratio of 40:60.[213]

In 1965, Wolinsky and Erickson employed Ph_3P=CHBr, generated by deprotonation of the phosphonium salt with phenyllithium, to make symmetrical vinyl bromides from ketones in good yields.[214a] Sometimes, halogen–metal exchange took place, whereupon methylenated derivatives were also produced (cf. ref 223m). The use of potassium *tert*-butoxide (THF, −60 → 25 °C) can obviate this predicament, as demonstrated for the clean conversion of Me_2C=$C(CH_2)_2C$(O)Me to Me_2C=$C(CH_2)_2C$(Me)=CHBr in 81% yield (*Z*/*E* = 1:3).[214b] Smithers assembled vinyl bromides by using Ph_3P=CRBr, where R = H, Me, or Et. In this study, the ylides were created by halogen–metal exchange between $Ph_3PCRBr_2{}^+Br^-$ and *n*-butyllithium (THF, −40 °C).[214c] Ph_3P=CHBr added to benzaldehyde in 44% yield (*Z*/*E* = 1:1) and to pivalaldehyde in poor yield, albeit with high stereoselectivity (*Z*/*E* = 98:2). Ph_3P=C(Me)Br afforded trisubstituted olefins with respectable stereocontrol in some cases: benzaldehyde, *Z*/*E* >95:5 (40%; **212a**/**212b**); heptanal, 87:13



212 a: R = Br, R' = Me (*Z*)
b: R = Me, R' = Br (*E*)

213 a: Y = F
b: Y = Cl

214 (X = Cl or Br)

(55%); pivalaldehyde, 25:75 (16%); MeOCH=CHCHO, 87:13 (30%). In contrast, the ethyl-substituted ylide showed little stereochemical preference with benzaldehyde or heptanal. Interestingly, in the reaction of Ph_3P=C(Me)Br and benzaldehyde, use of DMF solvent seriously eroded the high *Z* selectivity (*Z*/*E* = 57:43) and resulted in a poor yield. Bestmann and Bomhard generated Ph_3P=CHBr by desilylation of $Ph_3PCH(SiMe_3)Br^+Br^-$ with CsF and condensed it with benzaldehyde *in DMF* to supply **212a** and **212b** in a 96:4 ratio (15%).[215a] This novel technique also allowed the facile preparation of Ph_3P=C(Me)I, which condensed with benzaldehyde to give PhCH=C(Me)I with an incredible *Z*/*E* ratio of 99:1 (35%).[215b] Bestmann and Arenz carried out reactions of aldehydes with Ph_3P=CRBr (R = Et or *n*-pentyl), formed via the above-mentioned halogen–metal exchange route.[216] Their results were generally consistent with those of Smithers; the best stereochemical bias, *Z*/*E* = 1:7, was achieved by pairing the pentyl ylide and 2-methylpentanal.[216]

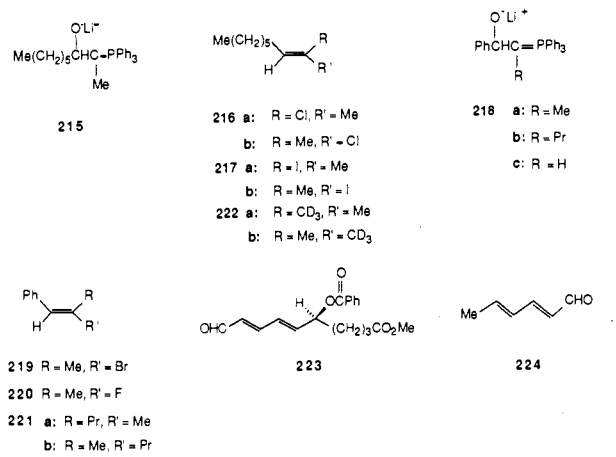
In dealing with α-halo ylides, we must address the fascinating observations that have been made with unusual fluorophosphorane **213a**,[217] which may be viewed as a stabilized phosphorus ylide.[89b] Reaction of **213a** (Li salt free) with benzaldehyde in methylene chloride afforded an 87:13 mixture of (*Z*)/(*E*)-vinylphosphonium salts **214** (R = Ph), the stereochemistry of which is opposite from the norm. A methoxy or nitro substituent on the para position of the benzaldehyde caused an erosion of *Z* stereoselectivity (*Z*/*E* = 83:17 or 57:43, respectively); *o*-methyl gave *exclusively Z product*, whereas *o*-methoxy gave a *Z*/*E* ratio of 77:23. On the other hand, the aliphatic aldehydes hexanal or cyclohexanecarboxaldehyde reacted with very high *E* stereoselectivity (*Z*/*E* = 3:97 or 0:100), which concurs with accepted concepts.[89b] An attempt to effect similar chemistry with ylide **213b** and benzaldehyde was unsuccessful, as no reaction occurred.[218] To account for the anomalous *Z* stereoselectivity, Cox et al. proposed an intramolecular, through-space, charge-transfer complex involving one of the Bu_3P groups in **213a** and the π electrons of the aromatic ring of the benzaldehyde (see ref 89b for a full discussion).

Cleavage of various fluoro vinylphosphonium salts, such as **214**, with hydroxide brought forth the corresponding vinyl fluorides with predominant retention of configuration at the sp^2 carbon (note: inversion of priority with regard to *Z*/*E* assignment).[89b,217,219]

(*g*) *Presence of Anionic Groups in the Ylide.* In section II.A.2.a of this review, we discussed stereochemistry and mechanism associated with phosphorus ylides bearing anionic groups on the ylidene side chain fairly extensively. This topic has been treated in our primary papers[28,65] as well. Also, the review by Gosney and Rowley[11] has effectively addressed the chemistry of β-oxido ylides. Therefore, this section will concentrate on synthetic applications, with an emphasis on material published from 1979 to 1987.

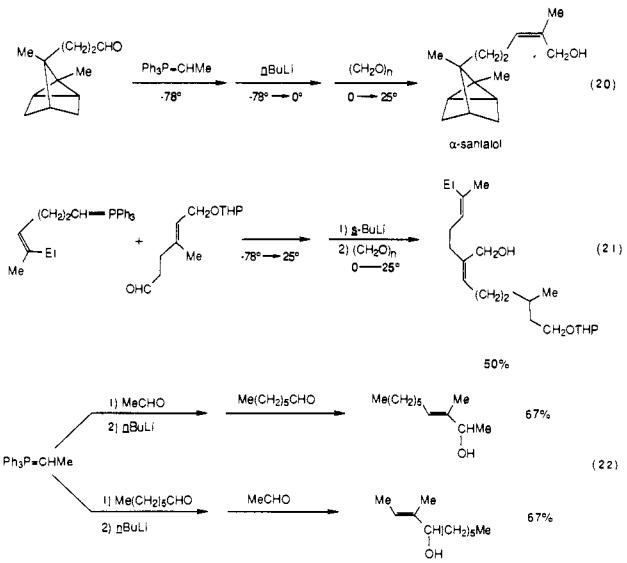
As stated earlier, the "betaine–ylide reaction" is a modification of the Wittig reaction that entails addition of a strong base to the Wittig intermediates at low temperature (prior to their collapse to products) and often leads to a high proportion of (*E*)-alkene.[11] The *E* stereoselectivity may be attributed to (1) equilibration of metalated intermediates via stereomutation at the carbon α to phosphorus to give threo betaine or trans oxaphosphetane[22,73] [thermodynamic control] or (2) highly selective addition of the proton electrophile to the metalated species to give threo/trans species[69b] [kinetic control]. Schlosser and co-workers were the first to devise this process,[22,73] and they subsequently applied it to other electrophiles in the so-called "SCOOPY" reaction.[74,75] Corey and co-workers also introduced methodology involving the addition of different electrophiles to the betaine–ylides.[69b-e]

Besides the proton or deuteron, electrophiles can be halogenating reagents, reactive alkyl halides, aldehydes, and epoxides. In this manner, trapping of betaine–ylides has led to the stereoselective synthesis of diverse trisubstituted alkenes.[69,74,75] For example, reaction of **215** with *N*-chlorosuccinimide (NCS), $PhICl_2$, or $Hg(OAc)_2$/LiI–I_2 furnished **216a**/**216b** in a 3:97 *Z*/*E* ratio



(ca. 50%), **216a/216b** in a 95:5 ratio (ca. 50%), or **217a/217b** in a 98:2 ratio (ca. 40%), respectively;[69c] reaction of **218a** with bromine or $FClO_3$ furnished **219** (23%) or **220** (37%) with high *E* selectivity.[74] Brominating agents and iodine have given poor yields of vinyl halides.[69c] Alkyl halides were poor reagents[69a] as well, but methyl iodide did combine to a reasonable extent.[69a,75a] Thus, **218b** was transformed by MeI into a 22:78 mixture of **221a** and **221b** (56%),[75a] and **215** by CD_3I into a 1:1 to 3:1 mixture of **222a** and **222b** (50%), depending on conditions.[69a] Schlosser et al. found that nearly equal amounts of isomeric disubstituted alkenes were formed from halogenating agents and **218c**, an ylide devoid of an alkyl substituent on the ylidic carbon.[75a] Curiously, the direction of addition to the betaine–ylides is similar for all of the electrophiles discussed so far, with the glaring exception of NCS.

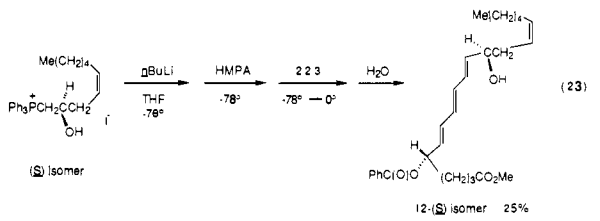
This technique reaches its apex in the highly stereoselective synthesis of trisubstituted (*Z*)-allylic alcohols, whereupon formaldehyde is the electrophile.[69,75b-d] This important protocol, first disclosed by Corey et al. in 1970,[69b] is illustrated by two applications concerning key steps from the stereocontrolled synthesis of α-santalol (eq 20)[69b] and Cecropia juvenile hormones (eq 21).[69d] Surprisingly, (*E*)-allylic alcohols are garnered



when higher aldehydes are used as the electrophile because the elimination of phosphine oxide then takes place from the freshly assembled oxaphosphetane; i.e., it encompasses the *new* carbon–carbon linkage (e.g., eq 22).[69b] In any event, it should be noted that the *direction of addition* of all aldehydes to betaine–ylides fits the common pattern for almost every electrophile examined (vide supra). For the (*E*)-allylic alcohol synthesis, the minimum stereoselectivity would probably be around 1:10 (*Z*/*E*), which was obtained for the acetaldehyde–acetaldehyde addition sequence.[69a]

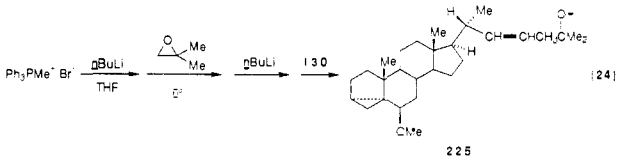
The betaine–ylide protonation method, which is capable of giving (*E*)-olefins with up to 99.5% isomeric purity, has been exploited in several synthetic endeavors.[191c,221] Ohashi et al.[191c] have indicated that usual *E* stereoselectivity[221j] can be counteracted by the presence of a proximate hydroxy group in the aldehyde component (viz., **168**). Also, a distant oxido group in the ylide, as with $Ph_3P{=}CH(CH_2)_nO^-Li^+$ (n = 7 or 9), has been reported to cause some erosion of *E* stereoselectivity.[221c,d] However, Schlosser et al.[221b] have asserted that difficulties in the (*E*)-alkene synthesis, especially when metallo oxido groups are present, can be avoided by using "self-prepared" phenyllithium for ylide and betaine–ylide generation. In this case, the organolithium solution contains a substantial amount of complexed lithium bromide, whereas there is only a small quantity of lithium salt in commercial solutions. A large proportion of THF in the reaction medium may also help, as may the addition of extraneous lithium bromide. Schlosser's group was able to derive (*Z*)/(*E*)-alkene ratios ranging from 3:97 to 1:99 (69–78%) in reactions of $Ph_3P{=}CH(CH_2)_nO^-Li^+$ (where n = 2, 3, 5, and 7) and aliphatic aldehydes (also (*E*)-butenal).[221b] Presumably, their γ-oxido ylide reaction (n = 2) would have given a fairly strong bias for (*E*)-alkene without the PhLi-induced equilibration, albeit not as extreme as ca. 98% *E* (vide infra).[28]

As an alternative, a convenient and expedient means of accessing β-oxido ylides is deprotonation of preformed β-hydroxy phosphonium salts, prepared by alkylation of triphenylphosphine. This approach permits the use of very specialized ylides. Thus, homochiral ylide units have been linked with aldehydes to obtain nonracemic compounds with high stereoisomeric purity. Unfortunately, reactions of aldehydes by this route have too often given modest yields (25–50%) of the highly *E*-enriched allylic alcohols; even worse yields would be predicted in the absence of a lithium base.[28] A number of synthetic applications, especially in the area of prostaglandins, HETE's, and leukotrienes, have been reported.[66-68,173a,222] An example from a synthesis of the 12(*S*) and 12(*R*) forms of 6-(*E*)-leukotriene B is depicted in eq 23.[222c] In this paper, a better yield (78% of *E*,*E*,*E* adduct) was achieved in the reaction of the (*R*)-phosphonium ylide with sorbaldehyde, **224**.[222c]

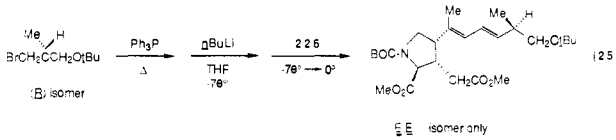


γ-Oxido ylides have been used in the production of homoallylic alcohols.[70-72,178b,221c,223] Salmond et al. were the first to demonstrate that olefins substantially biased to the *E* isomer could be readily obtained from aldehydes by using a γ-lithio oxido ylide. In the example

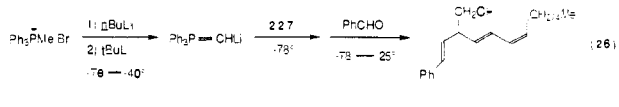
presented in eq 24, the crude product, **225**, had a Z/E



ratio of 15:85; moreover, there was no epimerization at the stereocenter adjacent to the original aldehyde group (75–85% isolated yield of (*E*)-**225**).[70] A Z/E ratio of 85:15 for the reaction of **130** with masked ylide $Ph_3P{=}CHCH_2C(OTMS)Me_2$ confirmed the requirement for a lithio oxido substituent to get high *E* selectivity.[70] Under lithium salt free conditions, no preference for (*E*)-homoallylic alcohols was seen; also, yields were rather uninspiring.[28,223a] Even with lithium salt present, this procedure can be disappointingly inefficient with respect to yield.[72,223r] Another synthetic example is depicted in eq 25.

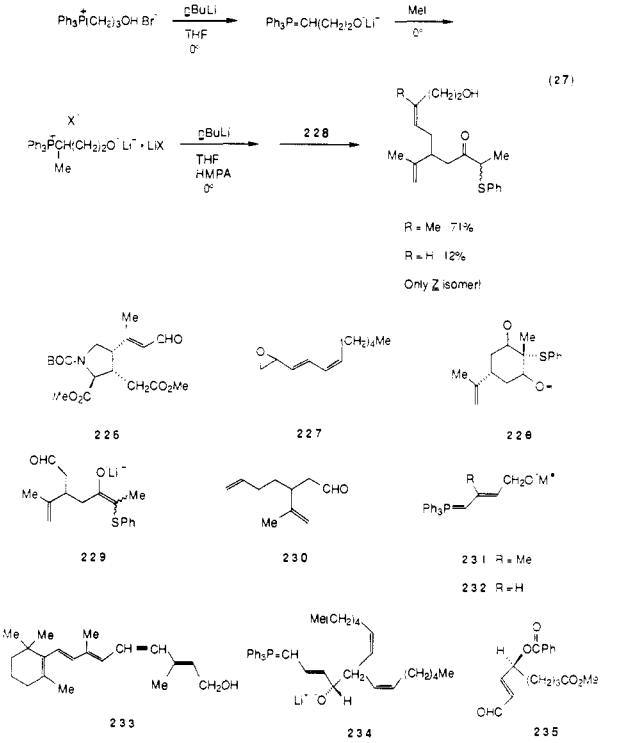


There are two common avenues to γ-oxido ylides: (1) double deprotonation of a preformed γ-hydroxy phosphonium salt and (2) addition of a simple phosphorus ylide to an epoxide, followed by 1 equiv of base; two rarer avenues are (3) addition of base to an oxaphospholane,[28] which can be isolated from the reaction of a γ-hydroxy phosphonium salt with 1 equiv of base,[28,225a] and (4) condensation of an α-lithio ylide (or its synthetic equivalent) with an epoxide (e.g., eq 26).[223l,m] For one system, benzaldehyde and $Ph_3P{=}CH(CH_2)_2O^-Li^+$, procedures 1–3 led to virtually identical consequences, with Z/E = 4:96; the corresponding hydroxy ylide, $Ph_3P{=}CH(CH_2)_2OH$, supplied a Z/E ratio of 73:27.[28]



Alkyl substitution on the γ position of the ylide serves to augment (*E*)-alkene formation. Thus, hexanal was attacked by $Ph_3P{=}CH(CH_2)_2O^-Li^+$, $Ph_3P{=}CHCH_2CH(Me)O^-Li^+$, or $Ph_3P{=}CHCH_2C(Me)_2O^-Li^+$ to give Z/E ratios of 42:58, 25:75, or 19:81.[28] This trend is consistent with a mechanism for anomalous *E* stereoselectivity involving enhanced reversibility, as proposed in Scheme II (section II.A.2.a), since it reflects the classical *gem*-dimethyl effect, which implicates a cyclic process.[224]

A paper by Caine and Crews suggests that the presence of a metallo oxido group in the aldehyde substrate, a lithio enolate in this case, may interfere with the expected *E* stereoselectivity.[223n] Thus, $Ph_3P{=}C(Me)(CH_2)_2O^-Li^+$ reacted with **228** via retro-aldol substrate **229**, to yield two (*Z*)-alkenes (eq 27). By contrast, addition of the same ylide to aldehyde **230** gave a 1:1 Z/E ratio.



A solid–liquid phase-transfer technique involving $Ph_3P(CH_2)_3OH^+Br^-$ and potassium carbonate in 2-propanol that gives good yields of olefin from aromatic aldehydes has been described.[223q] The homoallylic alcohols were enriched in the *E* isomer in the range of 64–87%. This probably is not anomalous *E* stereoselectivity from the γ-hydroxy group since a similar *E*-rich mixture was observed with benzaldehyde and $Ph_3P{=}CHPr$ in methanol.[225b] More usual *Z* stereoselectivity was obtained with aprotic solvents (toluene or 1,4-dioxane).[225b,c]

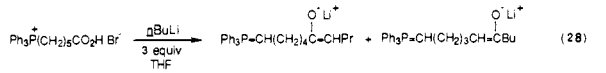
δ-Lithio oxido ylides also can show anomalous *E* stereoselectivity, but it is attenuated. For example, $Ph_3P{=}CH(CH_2)_3O^-Li^+$ combined with benzaldehyde or hexanal to give alkenes with a 15:85 or 41:59 ratio, whereas $Ph_3P{=}CHBu$ gave a 50:50 or 82:18 ratio, respectively.[28] An ε-lithio oxido ylide afforded abnormal *E* selectivity to a slight degree with benzaldehyde, but not at all with hexanal.[28] Schaub et al. obtained good yields of (*Z*)-alkenols (97–98% *Z*) from aliphatic aldehydes and sodio oxido ylides having long ylidene chains (4–11 carbon atoms between oxygen and phosphorus).[226] Phosphoranes with such long ylidene chains have been employed by others to synthesize (*Z*)-alkenes.[152a,221c,d,227]

One interesting report deals with the synthesis of dienols by using δ-oxido allylidenephosphoranes.[227e] A highly selective synthesis of 2(*E*),4(*Z*)-dienols from aldehydes was achieved with ylides **231** and **232** (M = K), generated from the corresponding hydroxy phosphonium salts with $KN(TMS)_2$.[227e] Thus, retinoid **233** was obtained from β-ionylidene acetaldehyde with a Z/E ratio at the 11-position of 83:17 (40% yield); use of *n*-butyllithium as base gave a Z/E ratio of 37:63 (31%). Results for the reaction of hexanal or benzaldehyde with **231** (M = K or Li) or **232** (M = K or Li) were as follows (THF; **231**-K, **231**-Li, **232**-K, **232**-Li): 2*E*,4*Z*/2*E*,4*E* (hexanal) = 91:9, 78:22, 95:5, 81:12*; 2*E*,4*Z*/2*E*,4*E* (PhCHO) = 83:17, 18:82, 83:17, 49:32*, respectively (the asterisk indicates the presence of other

isomers to make 100%). There appears to be some anomalous E stereoselectivity in these reactions, but its extent is difficult to gauge.

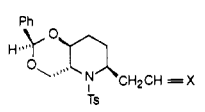
Corey et al.,[152a] en route to (5S,12S)-diHETE, united analogous lithio oxido ylide **234** and aldehyde **235** under careful conditions to get the desired tetraene ester in ca. 25% yield with an unpleasant Z/E ratio of ca. 1:1 (at the newly formed double bond).

Treatment of 6-(triphenylphosphonio)hexanoic acid bromide with 3 equiv of n-butyllithium might be expected to give rise to a mixture of ylide enolates, as shown in eq 28. This reagent was used by Holmes et

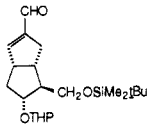


(28)

al. to olefinate **236** into a Z/E mixture (ratio unspecified) of butyl ketone derivatives **237** in 46% yield.[227d] Further information on this type of Wittig reaction would be valuable.



236 X = O
237 X = $CH(CH_2)_4C(O)Bu$



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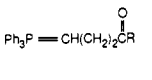
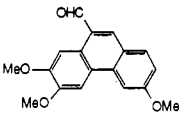


239 R = OEt
240 R = O$^-K^+$

Carboxyalkylidenephosphoranes have been widely exploited in organic synthesis, especially for prostaglandin and thromboxane derivatives,[66] for leukotrienes, and for arachidonic acid metabolites.[228] Conditions have usually involved the use of NaH or dimsylsodium in DMSO and, regardless of whether the carboxy ylide was being coupled with a free aldehyde or with a lactol, the new double bond almost always was highly enriched in the Z direction. Anomalous E stereoselectivity was first observed for a carboxy ylide in 1981, with the quintessential prostaglandin ylide, $Ph_3P{=}CH(CH_2)_3CO_2^-$, and aromatic aldehydes.[65a] Later reports further established this phenomenon, which occurs solely with aromatic or vinylic aldehydes and is pronounced with ylides having one to three carbon atoms between the ylidic and carboxy carbons.[28,229] The anomalous E selectivity is evident with lithium, sodium, or potassium as counterion.[28] By way of illustration, although **238** reacted with carbethoxy ylide **239** to afford a normal Z/E ratio of 87:13, potassio carboxy ylide **240** afforded *a 1:12 ratio* (KO-t-Bu, THF, 25 °C; excellent yields).[229d] Weinreb and colleagues obtained a 1:3 Z/E mixture from the reaction of $Ph_3P{=}CH(CH_2)_3CO_2^-Li^+$ with **241** in THF (60%) en route to the alkaloid cryptopleurine.[229c] Addition of this same ylide to **242** gave styrenes with a Z/E ratio of 1:2.5, and addition of $Ph_3P{=}CH(CH_2)_2CO_2^-Li^+$ to **242** gave a 1:6 Z/E ratio,[229a] in agreement with the chain-length effect described by Maryanoff et al.[28]

As mentioned in section II.B.1.d, addition of β-hydroxy aldehyde **168b** to $Ph_3P{=}CHCH_2CO_2^-Li^+$ furnished only the (*E*)-olefinic acid,[192b] instead of the anticipated Z-rich product,[28,230] which points to participation of the β-lithio oxido group of the aldehyde fragment in the reaction mechanism. This is related



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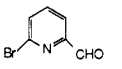

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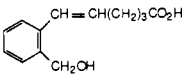

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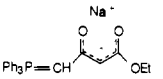

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to the experience of Caine and Crews,[223n] but in the reverse sense.

At this juncture, some comment on the use of $Ph_3P{=}CHCH_2CO_2^-$ is warranted. Although successful condensation of this ylide (Na^+ salt) with ketone educts by a coaddition procedure has been reported (NaH, 1:1 DMSO–THF, 0 °C),[230b] reactions with aldehydes can be very problematic.[28,174a,192b,231] We and others have realized little or no alkene product under a variety of reaction regimes. Fortunately, Baker et al.[192b] have just disclosed a set of conditions (n-BuLi, 1:4 DMSO–THF, −5 °C, normal addition) that afforded a respectable yield of alkene (69% isolated) from aldehyde **168b**. We have confirmed the viability of their procedure with an aromatic aldehyde (unpublished results; 60% isolated yield, Z/E = 13:87).

There are some exceptions to anomalous E stereoselectivity with carboxy ylides.[232] Morris and Wishka reported that $Ph_3P{=}CH(CH_2)_3CO_2^-Li^+$ combines with **243** to give a 4:1 (*Z*)/(*E*)-alkene mixture (THF, room temperature).[232a] The π-deficient electronic character of the pyridine ring may detract significantly from anomalous E stereoselectivity, in line with the reported effect of aromatic substituents.[65a] For example, Z/E ratios of 35:65 and 41:59 were obtained with 4-cyano- and 4-nitrobenzaldehyde, respectively, compared to 13:87 with benzaldehyde.[65a] Also, the pyridine nitrogen may be involved in coordination of lithium ion. In another exception, reaction of the $Ph_3P{=}CH(CH_2)_3CO_2^-Li^+$ and lactol **244** supplied styrenes **245** with a Z/E ratio of 65:35.[232b] Here, interference by the neighboring oxido group in the aldehyde apparently depreciates the level of E stereoselectivity.

Semistabilized ylides with a $Ph_2(CH_2CH_2COO^-)P{=}$ unit gave increased E stereoselectivity relative to corresponding triphenylphosphorus ylides; also the phosphine oxide byproduct was conveniently water soluble.[229f] The authors attributed the enhanced E selectivity to Schlosser-type equilibration induced by the anionic substituent; however, this message is clouded by the absence of a control experiment with Ph_2(alkyl)P=CHR. Indeed, results with germane model ylides[34c,89a] (cf. sections II.A.3 and II.B.1.e) indicate that there is no anomalous E stereoselectivity in these carboxylate ylide reactions; the E-biased isomer ratios are a consequence of kinetic control.[229f] A reagent employing this technique offered just a modest advantage in the synthesis of diacetylenic analogues of leukotriene A_4 methyl ester.[229g]

(Dialkylamino)alkylidenephosphoranes essentially do not display anomalous E stereoselectivity.[28] When the ylide has the shortest chain possible, as with $Ph_3P{=}CHCH_2NR_2$, a minor departure from normal stereoselectivity is observed,[28,233] which may be ascribed to an inductive effect of the electronegative substituent. On

the contrary, lithio amido ylides, such as $Ph_3P{=}CHCH_2NR^-Li^+$, do engender unusually high levels of (*E*)-alkene.[28,234] An *E*-rich alkene mixture was even obtained with an aliphatic aldehyde in the union of pivalaldehyde with $Ph_3P{=}CHCH_2NBzl^-Li^+$ (*Z*/*E* = 18:82, 88% yield).[234]

Some interesting observations have been made with phosphoranes in which a stabilized enolate is directly connected to the ylidic carbon.[235a,b] Of course, stabilized ylides should produce (*E*)-alkenes with high stereoselection. However, if the stabilizing carbonyl group is part of a conjugated enolate system (e.g., **246**), the stereochemical outcome can be altered.[235a] Thus, ylide **246** converted propanal, undecanal, pivalaldehyde, or *trans*-**46** into Δ^4-unsaturated 3-keto carboxylates comprised of 85%, 86%, 98%, or ca. 90% (*Z*)-alkene, respectively.[235a,c] Curiously, benzaldehyde or *p*-anisaldehyde yielded only 25% or 13% (*Z*)-alkenes, the opposite of what one might expect.

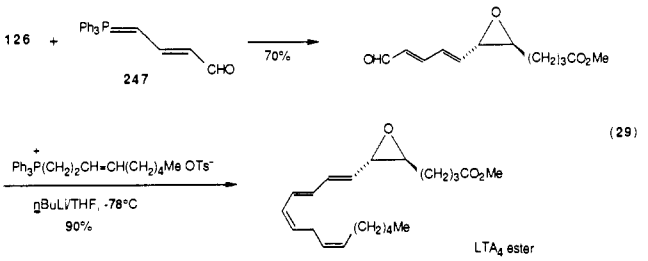
"Diylides" are ylides that are metalated on an α carbon of one of the other phosphorus substituents, e.g., $Ph_2(RLiCH)P{=}CHR$.[236,237] Although such compounds have been employed for years by Schmidbauer and colleagues as bidentate ligands in metal coordination complexes,[236] their application to olefination of carbonyl compounds has been studied only recently.[237] Lithio diylides have enhanced nucleophilicity, in a similar vein to α-lithio ylides.[223l,m] Therefore, for example, $Ph_2(LiCH_2)P{=}CH_2$ reacted with the highly sterically hindered ketones fenchone and di-*tert*-butyl ketone to give alkene products in good yield.[237b] Diylides from lithiation of a free benzyl group in $PhCH_2R_2P{=}CHPh$ were added to benzaldehyde to give predominantly (*E*)-stilbene in good yield;[237a] a 5:95 *Z*/*E* ratio was realized in the reaction of $Ph(PhCH_2)_3P^+Br^-$ with 2 mol equiv of both *n*-butyllithium and benzaldehyde. Cristau and co-workers performed reactions with lithio diylides corresponding to nonstabilized, semistabilized, and stabilized systems.[237b] With heptanal, $Ph_2(MeLiCH)P{=}CHMe$ afforded a 40:60 mixture of (*Z*)/(*E*)-alkenes in 98% yield, and $Ph_2(PhLiCH)P{=}CHPh$ afforded a 25:75 mixture of styrenes in 95% yield; with benzaldehyde, the latter diylide gave a 15:85 ratio of (*Z*)/(*E*)-stilbenes in 98% yield. The stabilized versions appeared to have insufficient reactivity.

2. Selected Synthetic Applications (1979–1987)

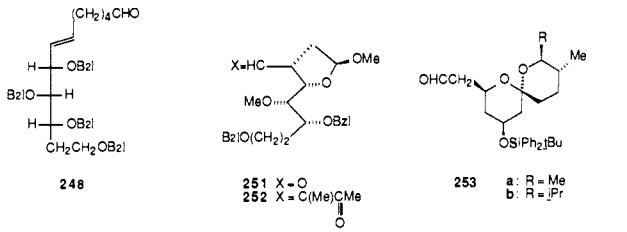
To convey an appreciation of the significance of the Wittig reaction in organic synthesis, we offer in this section a sampling of synthetic applications of recent vintage (1979–1987). We will concentrate on syntheses that have benefited especially well from the use of this reaction. Information divulged in other parts of this review will generally not be repeated. The various applications of the Wittig reaction in synthesis have been discussed effectively by Gosney and Rowley up to 1978[11] and by Bestmann and Vostrowsky up to ca. 1980.[12] Also, this topic was treated by Le Bigot et al.[14]

By now, the reader should be impressed by the convenience, facility, and versatility of the Wittig reaction. In fact, these venerable attributes are aptly supported by the frequent use of the Wittig reaction for fabrication of carbon–carbon *single bonds*. That is, the reaction seems to have been favored even when the carbon–carbon double bond is not ultimately desired (in which case it has been eradicated in the second part of a two-step procedure, entailing carbonyl olefination and double-bond reduction).

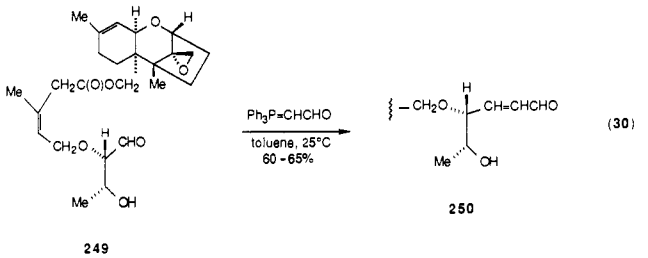
Three Wittig condensations, one of which was described in section II.B.1.g, were elegantly interwoven into a synthesis of homochiral leukotriene A methyl ester from D-glucose.[191e] The two yet-unmentioned reactions are shown in eq 29. Ylide **247**,[238] stabilized by the vinylogous formyl group, furnished nearly complete *E* stereoselectivity (ca. 2:98).



Tatsuta et al. used two tandem Wittig reactions in the synthesis of macrolide antibiotic A26771B, the first of which was broached in section II.B.1.c.[178b] That one was extraordinarily *E* selective for a nonstabilized ylide process, presumably because of the α- and β-alkoxy groups in aldehyde **131**. The second reaction involved the fusion of aldehyde **248** with a γ-oxido ylide, obtained by treating $Ph_3P(CH_2)_2CH(Me)OH^+I^-$ sequentially with NaH/DMSO and *n*-butyllithium/hexane (66%); the alkene group was then hydrogenated. Much lower yields were experienced when a sufficient quantity of just one type of base was used.



In the synthesis of two macrocyclic trichothecanoids, baccharin B5 and roridin E, Still et al. performed a Wittig reaction on **249** with $Ph_3P{=}CHCHO$ to get **250** (eq 30), the *E* isomer of which was a precursor for a

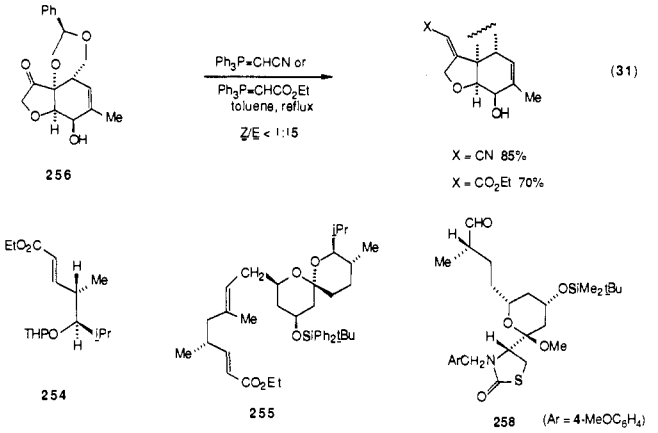


phosphonate-based macrocyclization (see section III.A.5).[239] They found a less than satisfying 1:4 *Z*/*E* ratio, which departs from the nearly exclusive *E* selectivity expected in standard reactions of this stabilized ylide (see section II.B.1.c and ref 11). Most probably, the α-alkoxy and β-hydroxy substituents in **249** are responsible for this erosion of *E* stereoselectivity, as discussed in sections II.B.1.c and II.B.1.d.

Two Wittig reactions were used in the enantiospecific total synthesis of the macrolide antibiotics carbomycin and josamycin (leucomycin A_3).[191c] One of these, con-

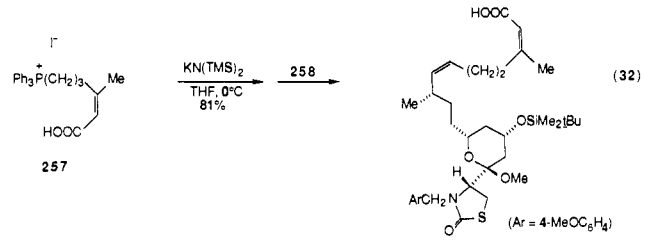
cerning substrate **165**, was mentioned in section II.B.1.d. Here we note that the reaction of **251** with an α-branched stabilized ylide, $Ph_3P{=}C(Me)C(O)Me$, was claimed to yield solely the *Z* isomer of **252**. This result is odd given the information put forth in section II.B.1.c. Since the double-bond stereochemistry was destroyed by hydrogenation in the next step of the synthesis, there are no subsequent compounds available to corroborate the assignment.

The area of milbemycins/avermectins has benefited from stereoselective Wittig reactions.[240] Two research groups established the *E* trisubstituted double bond at C14–C15 of (+)-milbemycin β_3 by reacting $Ph_3P{=}C(Me)CO_2Et$ with **235a**;[240c,d] **253b** was similarly homologated en route to the C11–C31 fragment of milbemycin D.[240a] Crimmins and co-workers also used $Ph_3P{=}CHCO_2Et$ to construct **254** and **255** from the corresponding aldehydes[240a,c] and were able to olefinate ketone **256** with high *E* stereocontrol (eq 31).[240b] Danishefsky et al. similarly twice transformed aldehydes into *E* double bonds in the synthesis of avermectin A_{1a}.[240]



(31)

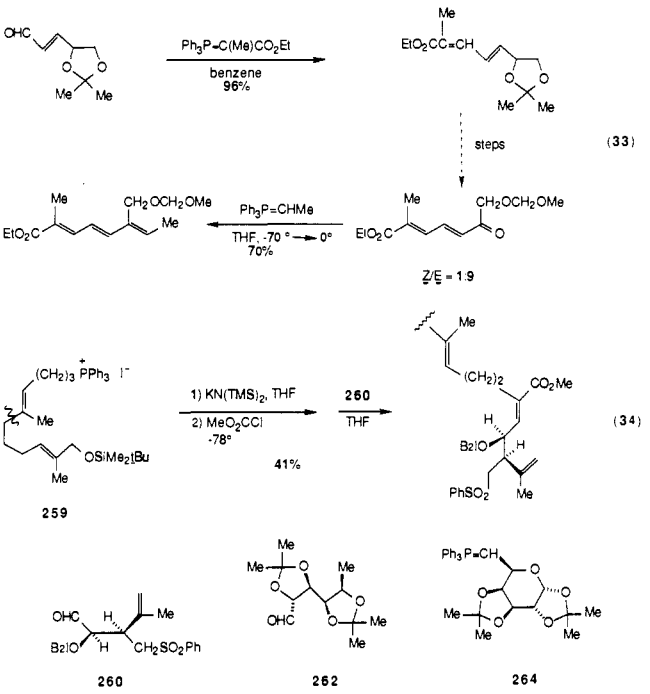
The synthesis of (+)-latrunculin B relied on *Z*-selective coupling of **257** and **258** as a key step (eq 32).[241] The carboxylate functionality did not cause the stereoselectivity to deviate from that which was expected for an aliphatic aldehyde under salt-free conditions (cf. section II.B.1.g).



(32)

Two Wittig reactions were employed in the synthesis of the spirotetronic acid portion of kijanolide (eq 33).[242] The first one gave only a marginally biased *Z*/*E* ratio of ca. 7:3; the second represented an extension of the *Z*-selective ketone olefination reported by Still and co-workers.[184]

Marshall and Cleary had an *E*-selective Wittig coupling as one of the key steps in their synthesis of 7-(8)-desoxyasperdiol (eq 34).[243] The stabilized ylide was generated in situ by adding 2 mol equiv of base to phosphonium salt **259**, followed by methyl chloroformate. A higher yield of (*E*)-alkene (76%) was obtained in the reaction of **260** with $Ph_3P{=}C(Me)CO_2Me$.



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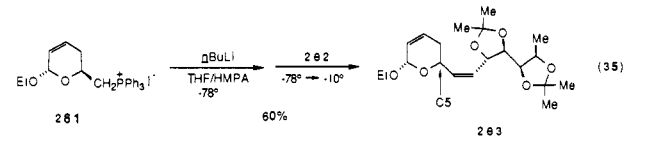
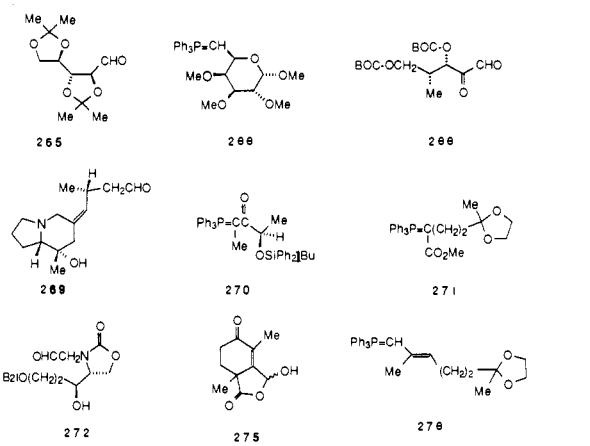
(34)

A convergent synthesis of (−)-anamarine from D-glucose relied on linkage of the ylide from **261** with **262** (eq 35).[244] Since ylide formation with such a β-alkoxy



(35)

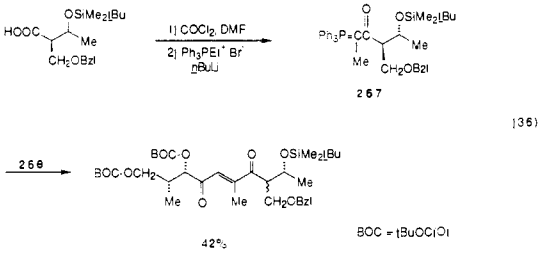
phosphonium salt is prone to elimination chemistry,[245] care must be exercised in the choice of reaction conditions. Secrist and Wu devised a recipe for extracting good yields out of this type of Wittig condensation,[245c] an adaptation of which was used by Lichtenthaler et al.[244] to obtain only the *Z* adduct, **263** (accompanied by ca. 10% of the C5 epimer, presumably reflecting ylide susceptibility to alkoxide elimination and readdition). The excellent *Z* stereoselectivity in this sequence (eq 35) had to be discarded since the (*E*)-alkene (obtained via isomerization) was the actual target. Although the atypically intense *Z* selectivity (under lithium salt conditions) may be associated with having an α,β-dialkoxy aldehyde as a reactant (see section II.B.1.c), Secrist and Wu found that related ylide **264** combines with either D-arabino aldehyde **265** or pentanal to give



only the (*Z*)-alkene (benzaldehyde gave more normal

Z/E stereoselectivity of 1.7:1 with **264** and 10:1 with **266**).[245c] Further study with simple nonstabilized ylides is needed to clarify the effect of α- and β-alkoxy groups in the aldehyde on alkene stereochemistry.

Ireland and Smith used three E-stereoselective Wittig reactions with carbethoxyphosphoranes in synthesizing the 3-acyltetramic acid antibiotic (+)-streptolic acid.[246] The condensation of keto phosphorane **267** and keto aldehyde **268** was an integral part of a synthetic approach to Bu-2313, also a 3-acyltetramic acid (eq 36).[247]



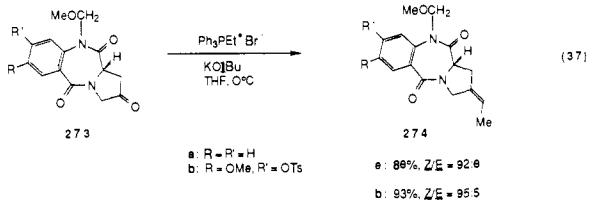
(36)

Labile **268** was generated by Swern oxidation (oxalyl chloride, DMSO, Et_3N) of a diol precursor and coupled directly with the ylide in a general Swern–Wittig route to (E)-enediones.[248] The stereochemistry of the carbon α to the carbonyl in **267** was scrambled in the process.

In their enantioselective synthesis of pumiliotoxin B, Overman et al. installed half of the side chain with >99% E stereoselectivity by reacting **269** (containing a free hydroxy group) and **270** (71%).[249]

Ylide **271** added smoothly to α-carbamyl aldehyde **272** (84%), with normal E stereoselectivity, in the early stage of an enantiospecific synthesis of acromelic acid A.[250a] Similarly, (R)-BOC-NHCH(Me)CHO and $Ph_3P{=}C(Me)CO_2Me$ combined to give a 5:95 Z/E mixture of alkenes in 98% yield.[250b]

Outstanding Z stereocontrol was realized in the conversion of ketones **273** to **274** (eq 37).[251] However, the

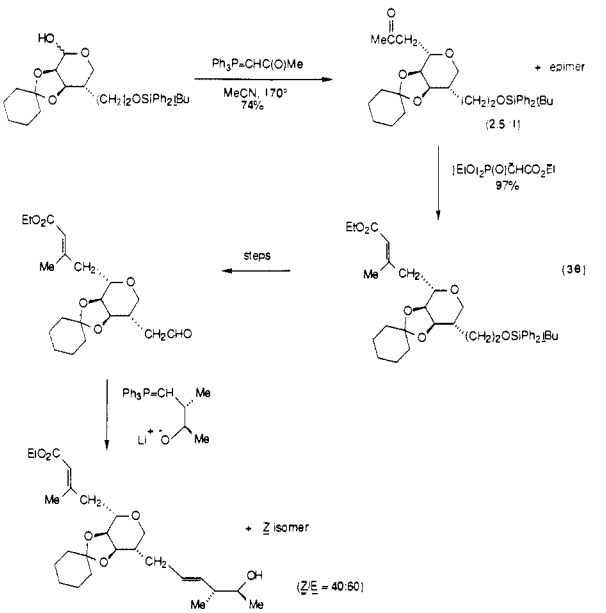


(37)

olefin stereochemistry had to be inverted to attain the E orientation present in the antiviral, antitumor antibiotics prothracarcin and tomaymycin. The stereochemical outcome here may be analogous to that obtained with α-alkoxy ketones, discussed in section II.B.1.c.

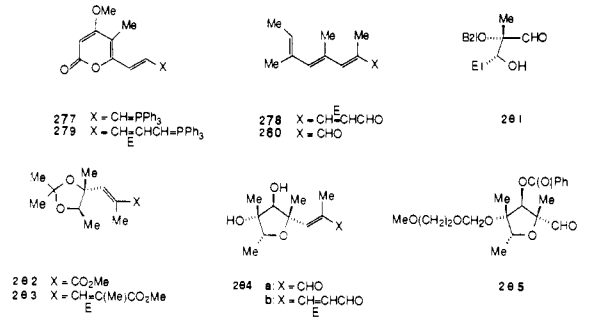
The ester side chain of pseudomonic acid C was established by using two standard olefination reactions, involving a Wittig reagent and a phosphonate carbanion; the homoallylic alcohol side chain was established by using an anomalous E-selective Wittig reaction with a γ-oxido ylide (eq 38).[72]

In the synthesis of trisporol B, reaction of lactol **275** with (E)-ylide **276** (n-BuLi, THF, −78 → 0 °C) furnished a 61% yield of conjugated trienone with only an E arrangement for the two exocyclic double bonds. However, the corresponding (Z)-ylide gave a 1:1 mixture of 7E,9Z and 7E,9E products (53%), possibly due to isomerization of the ylide.[252a] Later, Takabe and White discovered that the sodium carboxylate salt of **275** (NaH, THF–HMPA, 0 °C) would condense with the

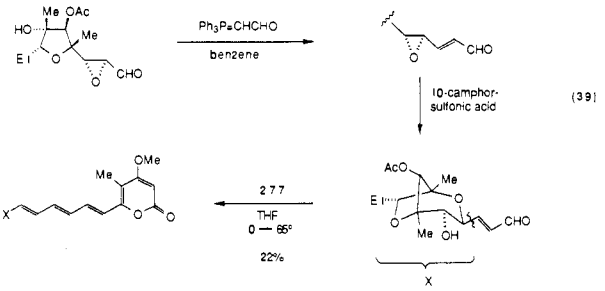


(Z)-ylide rapidly to supply a mixture of acids enriched in the 7E,9Z isomer (7E,9Z/7E,9E = 3.5:1) in much better yield (89%).[252b]

Several Wittig reactions were crucial to the total synthesis of the carotenoid prolycopene.[214b] Another molecule with extended conjugation, citreomontanin, also was constructed with a series of Wittig reactions; however, the condensation of **277** and **278** in the ultimate step gave a less than satisfying Z/E ratio of 2:3 (n-BuLi, THF, −78 → 25 °C).[253] A related approach by Patel and Pattenden involved coupling of **279** and **280** to give a mixture of adducts somewhat enriched in the desired E isomer.[254]



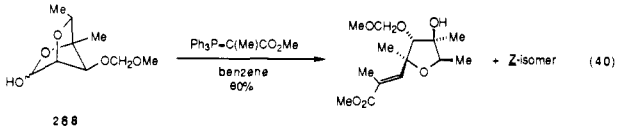
A synthesis of congeneric aurovertin B from D-glucose contained three Wittig reactions.[255] One of these was a normal E-selective condensation of $Ph_3P{=}C(Me)CO_2Et$ with **281**, which has α-alkoxy and β-hydroxy groups (see section II.B.1.d). The other two reactions are delineated in eq 39.



(39)

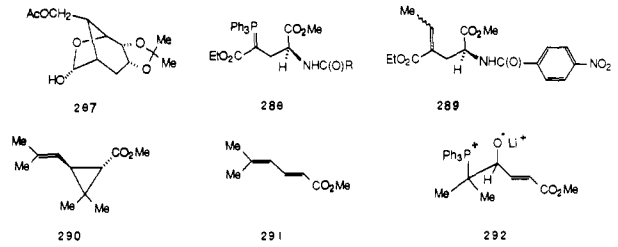
In the synthesis of related mycotoxin citreoviridin, Nishiyama et al. capitalized on five Wittig reactions.[256a]

They prepared **282** from its corresponding aldehyde and $Ph_3P{=}C(Me)CO_2Me$ (benzene, reflux, 64%), and then **283** from its corresponding aldehyde (79% overall from **282** for three steps). Diene ester **283** was converted to (+)-citreoviral **284a** (42%), which was homologated to **284b** by using a third Wittig reaction involving $Ph_3P{=}CHCO_2Et$. Linkage of **284b** with phosphorane **279**, formed by the agency of one Wittig step,[257] produced (−)-citreoviridin in a meager yield of ca. 10% (NaH, THF, 0 °C). Two other syntheses of this photolabile molecule (*dl*-[256b] and (+)-citreoviridin[256c]) contained only one stereogenic Wittig procedure, along with a key phosphonate-based olefination (see section III. A.3). Williams and White[256b] obtained virtually exclusive *E* selectivity with **285** and $Ph_3P{=}C(Me)CO_2Et$ (93% yield), and Suh and Wilcox[256c] obtained a 1:15 *Z*/*E* ratio with bicyclic lactol **286** (eq 40), despite the α and β oxygen-containing substituents in the carbonyl component (see section II.B.1.c).



286

Semistabilized ylide $Me(CH_2)_2CH{=}CHCH{=}PPh_3$ added to bicyclic lactol **287** to give only the (*E*,*E*)-diene stereochemistry (*n*-BuLi, THF, 23% yield) en route to *dl*-palitantin.[258]



287 **288** **289**

290 **291** **292**

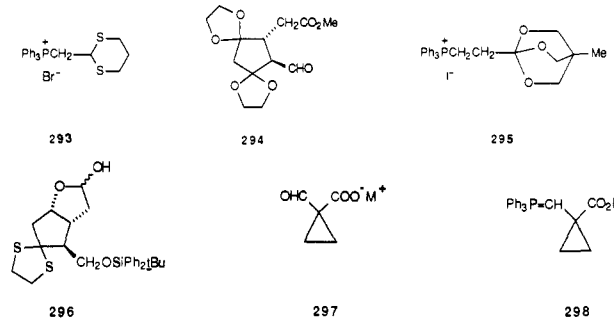
Z-selective Wittig reactions with ylides of the $Ph_3P{=}CHCH(OR)_2$ variety were crucial to pyranoside homologation leading to tripyranoside precursors for ansamycins (see section II.B.1.d).[192g]

Baldwin et al. prepared novel isolable ylides **288**, useful as synthons for unsaturated glutamic acids, by ring opening of aziridine-2-carboxylates with $Ph_3P{=}CHCO_2Et$.[259] β-Amido ylide **288** (R = 4-nitrophenyl), obtained in 49% yield, reacted normally with acetaldehyde to afford a 1:12 mixture of (*Z*)/(*E*)-γ-ethylidene (2*S*)-glutamates **289** (75%).

Treatment of $MeO_2CCH{=}CHCHO$ with excess $Ph_3P{=}CMe_2$ yielded chrysanthemic ester **290**; however, reaction of $Ph_3P{=}CMe_2$ with dienoic ester **291**, a product from 1 equiv of $Ph_3P{=}CMe_2$ and the same aldehyde, did not form a trace of **290** (lithium salt, THF).[260] To rationalize this result, Devos and Krief[259] suggested that **290** arises by addition of a second ylide unit to the carbon–carbon double bond of a lithio betaine species (viz., **292**), a yet-undecomposed intermediate in the first step. Experiments supporting this idea were discussed.

Of course, the Wittig reaction has been broadly applied in the synthesis of arachidonic acid metabolites, such as prostaglandins, prostacyclins, thromboxanes, leukotrienes, HETE's, and diHETE's.[11,12,66,228,261] Since many of the salient methods have already been encapsulated in these sources, our presentation will be severely restrained.

Phosphonium salt **293**, obtained by treating $[Ph_3PCH{=}CHPPh_3]^{2+}2Br^-$ with triethylamine and 1,3-propanedithiol, reacted with **294** (KO-*t*-Bu, THF)



293 **294** **295**

296 **297** **298**

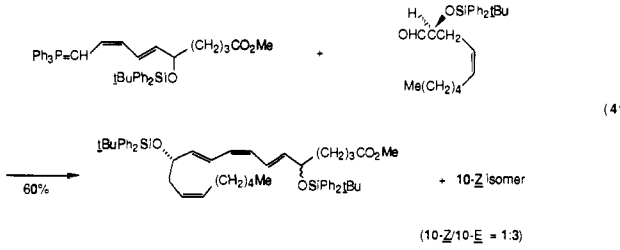
to give a 1:3 mixture of (*Z*)/(*E*)-alkenes in 70% yield.[262] This strong bias toward the (*E*)-alkene, which was readily separated and transformed into a doubly masked prostaglandin-like molecule, is special considering the salt-free conditions. (Installation of the α side chain involved a conventional Wittig reaction with $Ph_3P{=}CH(CH_2)_3COO^-$.)

Corey and Shimoji introduced reagent **295** for construction of the α side chain of prostaglandin D2 and its metabolites.[263] The ylide from **295** (dimsylsodium, DMSO) combined with lactol **296** to yield only the (*Z*)-alkene (90%). (The β side chain was crafted by a typical phosphonate coupling.) Additional results for reactions of aldehydes with the ylide from **295** have recently appeared.[231b]

Installation of the acid side chain in prostacyclin analogues by addition of $Ph_3P{=}CH(CH_2)_3COO^-$ to bicycloalkanones has resulted in only modest stereoselectivity at best (although enrichment can be achieved by crystallization or chromatography).[202,264] Another approach to carbaprostacyclins involved reaction of **238** with $Ph_3P(CH_2)_3CO_2R^+Br^-$ (section II.B.1.g).[229d]

The syntheses of arachidonic acids bearing cyclopropane units benefited greatly from the use of various *Z*-selective Wittig reactions.[265] Reactions involving formyl carboxylate **297** were well behaved, but those involving ylide **298** had their *Z* selectivity compromised.

The Wittig reaction in eq 41 (lithium salt, toluene,



−78 °C) was superior to the related reactions based on phosphonate or sulfone reagents.[266] To explain the slightly *E*-rich product mixture compared to reference reactions, a steric model predicated on betaine intermediates was proffered. This depiction is unwarranted, given the minor difference in free energy; also, it does not concur with recent mechanistic information (section II.A).

Considering the current vintage of review articles on leukotrienes[228] and the appearance of various examples in other parts of this article, we will not address further

synthetic work in this area. The remainder of this section will deal with miscellaneous Wittig reaction techniques.

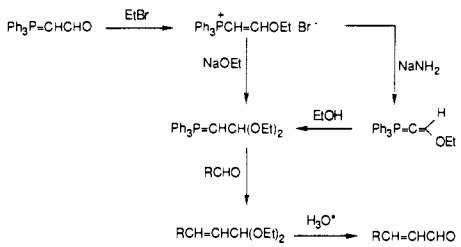
The Wittig reaction has been exploited in myriad intramolecular cyclization strategies.[267]

Wittig reagents bound to polymeric supports have proven useful in simple synthetic transformations.[268] An advantage here is elimination of the sometimes troublesome phosphine oxide. Alkene stereochemistry can be influenced by this technique to some extent.

Wittig reactions that are sluggish, particularly because of steric hindrance in the ketone and/or ylide component, can be accelerated and driven more to completion under high pressures (7–15 kbar).[269]

Addition of cuprates $R_2Cu^-Li^+$, where R = alkyl, alkenyl, or aryl, to $Ph_3PCH{=}CH_2{}^+Br^-$ afforded phosphorus ylides useful for olefination chemistry.[270] Ylide $Me(CH_2)_4CH{=}PPh_3$, made by transfer of a butyl group from the cuprate, reacted in THF with benzaldehyde or hexanal to give Z/E ratios of 50:50 (82%) or 77:23 (30%), respectively.[270a] In these reactions, addition of HMPA greatly accentuated Z stereoselectivity (97:3 or 92:8, respectively). (*Z*)-1-Hexenyl cuprate was used with PhCHO or hexanal to prepare (*Z*,*Z*)-1,4-pentadienes in 30% or 50% yield, respectively, with a Z/E ratio of 87:13 or 90:10 (for the new double bond). Two applications of the pentadiene route were described.[270b]

Bestmann and co-workers have reported a nice method for the stereoselective synthesis of Z α,β-unsaturated aldehydes, which is illustrated in eq 42.[172a] Yields of this two-carbon homologation[271] were generally respectable, and Z/E ratios generally ranged between 90:10 and 97:3.



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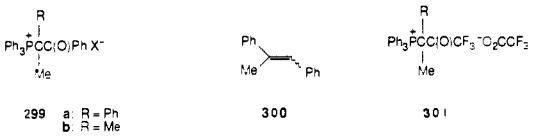
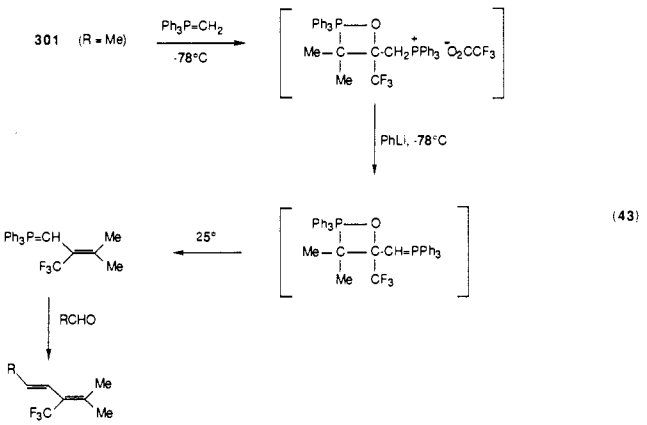
Reduction of keto phosphonium salt **299a** with lithium or sodium borohydride led to **300** with a (*Z*)/



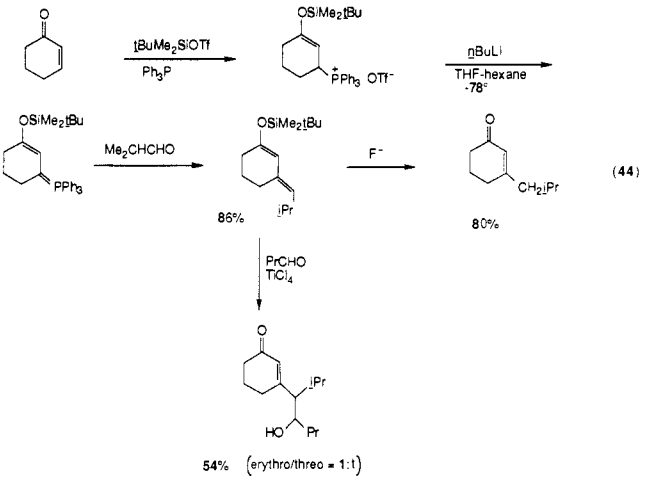
(*E*)-alkene ratio of 89:11 (80% yield), whereas addition of $Ph_3P{=}CMePh$ to benzaldehyde gave a Z/E ratio of 20:80.[272] This demonstrates a new avenue to betaine and oxaphosphetane species, related to the deprotonation of β-hydroxy phosphonium salts. However, this procedure has the added attraction of stereoselective synthesis by reduction of the prochiral keto group with an appropriate reducing agent. Some well-chosen experiments in this area could prove mechanistically intriguing.

Belletire and Namie[272] were unable to harvest a good yield of tetrasubstituted alkene by adding *n*-butyllithium to **299b**, presumably because of steric hindrance. However, analogous phosphonium salts with a perfluoroalkyl group, such as **301**, reacted with phenyllithium to furnish tetrasubstituted alkenes in yields of 40–70%.[273a] For R = alkyl, benzyl, or propyl, the Z/E ratios were 45:55, 13:87, or 55:45, respectively. Salts such as **301** also combined with $Ph_3P{=}CH_2$ en route to dienes as shown in eq 43.[273b] With benzaldehydes (R = Ph) only (*E*)-diene was produced in 55% yield.



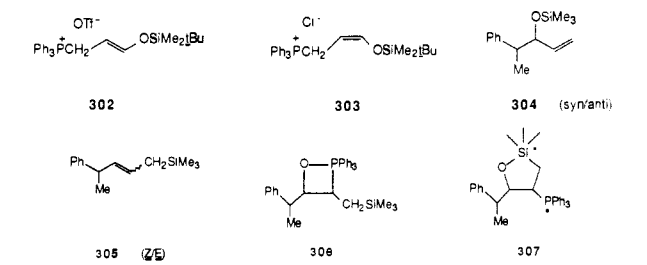
(43)

Phosphoniosilylation of enones has generated complex phosphonium salts for use in Wittig olefination (e.g., eq 44).[274] The silyloxy diene, highly biased to the



(44)

E isomer (Z/E = 1:13), was converted readily to the corresponding enone and was also subjected to a vinylogous, Lewis acid promoted aldol-type condensation. Allylphosphonium salts **302** and **303**, both prepared

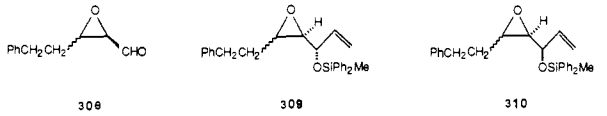


from acrolein, also coupled well with isobutyraldehyde in what amounts to a three-carbon homologation method. Although each siloxy diene product retained the stereochemistry of the original salt, the newly created double bond had a Z/E ratio of 1:1. This process, with $Et_3P{=}CHCH{=}CHOSiMe_2$-*t*-Bu, provided a key diene for a Diels–Alder cycloaddition en route to a forskolin intermediate.[274b] It should be noted that Martin and Garrison introduced a related three-carbon homologation method involving (*E*)-$MeOCH{=}CHCH{=}PPh_3$,[275a]

which effectively served a recent total synthesis of forskolin that featured a key intramolecular Diels–Alder reaction.[275b]

β-Silyl and β-stannyl phosphoranes transform aldehydes not only into allylsilanes and allylstannanes, as would be expected,[276] but also into silyl ethers of allyl alcohols.[277] Addition of $Ph_3P{=}CHCH_2SiMe_3$ to PhCH(Me)CHO provided a 2:1 ratio of **304** and **305**, because of partitioning between two pathways, one encompassing an oxaphosphetane (viz., **306**) and one silyl migration from carbon to oxygen, perhaps via cyclic siliconate **307**.[277b] The product distribution was sensitive to (1) reaction conditions, (2) constitution of the ylide, (3) structure of the aldehyde, and (4) silicon substituents.[277] Thus, PhCH(Me)CHO and $Ph_3P{=}C(Me)CH_2SiMe_3$ produced only the Wittig adduct, whereas PhCH(Me)CHO and $(o\text{-anisyl})_3P{=}CHCH_2SiMe_3$ produced only the allylic silyl ether.[277b] The alkenylation product from $(p\text{-anisyl})_3P{=}CHCH_2SiMe_3$ and PhCH(Me)CHO, favored by 10:1, exhibited a syn/anti diastereoselectivity of 15:1 (vs 3:1 for addition of vinylmagnesium bromide); 2-methylpentanal afforded only alkenylation product, but the syn/anti selectivity (2.7:1) was much poorer (erythro preferred).[277b,278] α-Alkoxy aldehydes participated in anti-selective alkenylation (erythro preferred).[277d,278] A highly stereoselective synthesis of (*Z*)-allyltrimethylsilanes from aliphatic aldehydes was realized by use of $(o\text{-tolyl})_3P{=}CHCH_2SiMe_3$ under lithium salt conditions.[277f]

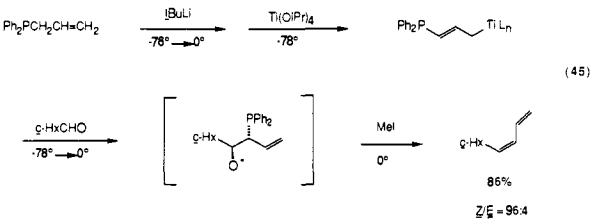
From a synthetic perspective, several rewarding results were encountered. For example, $Ph_3P{=}CHCH(Me)SiMePh_2$ propenylated PhCH(Me)CHO, steroid **130**, and MeCH(OBzl)CHO with high *E* stereoselectivity (*Z*/*E* ratio at least 1:30) and with erythro/threo diastereoselectivities of 15:1, 10:1, and >50:1, respectively (79%, 45%, and 60% yields).[277a] Vinylation of α,β-epoxy aldehydes proceeded with high erythro stereoselectivity when the formyl and larger β substituent were oriented cis.[277e] By way of illustration, although $(p\text{-anisyl})_3P{=}CHCH_2SiMePh_2$ converted *trans*-**308** to a 1.5:1 erythro/threo mixture (*trans*-**309**/*trans*-**310**), it converted *cis*-**308** to a 13:1 mixture (*cis*-**309**/*cis*-**310**).



306 309 310

The intervention of a silyl migration pathway in the Wittig reaction process may have a profound significance relative to the Wittig reaction mechanism. Does this detour reflect the capture of a transient betaine species present on the Wittig reaction coordinate? Or does the silicon just insert into the strained, weak P–O bond of an exclusive oxaphosphetane intermediate?

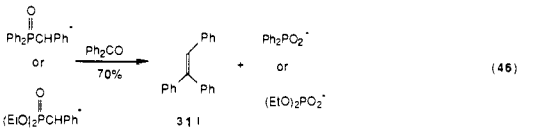
Yamamoto and co-workers devised a useful synthesis of (*Z*)-1,3-dienes, which consists of a Wittig-type reaction through methylation of an intermediate β-oxido phosphine (eq 45).[279] An interesting mechanistic point surfaces from this chemistry.[279a,b] So far as this process is expected to involve an erythro betaine (after methylation) and a cis oxaphosphetane, for a system representing a semistabilized ylide (i.e., allylide), an absence of reversibility in that class of direct Wittig reaction is suggested. This is analogous to experiments with systems comprising semistabilized and stabilized



ylides,[34c,40] albeit reaction conditions for the titanium-mediated sequence do not mirror a standard Wittig protocol.

III. Phosphoryl-Stabilized Carbanions

Horner and co-workers were the first to react phosphoryl-stabilized carbanions with aldehydes and ketones to produce olefins;[280,281] the carbanions used were derived from either diphenylphosphine oxides or diethyl benzylphosphonate. In these studies, benzylic carbanions were found to combine with benzophenone to give **311** in good yields (eq 46). However, the special ad-



vantages of phosphonates in alkene synthesis were not demonstrated until later. Indeed, the 1961 paper by Wadsworth and Emmons served to popularize this method in the organic synthetic community.[282] In the ensuing years, there has been confusion about whom to credit for this class of reaction, as the names "Horner", "Wadsworth", "Emmons", "Wadsworth–Emmons", and "Horner–Wittig" have appeared as descriptors with regularity. Horner was the first to use phosphine oxides;[280,281] however, since his group[281] only examined a single phosphonate reagent, Wadsworth and Emmons can also lay claim to developing the phosphonate modification of the Wittig reaction.[282] For the purposes of our current discussion, phosphonate-mediated olefinations will be referred to as the "Horner–Wadsworth–Emmons" (more concisely "HWE") reaction, and the phosphine oxide variant will be called the "Horner" reaction.

Wadsworth authored a key[283] review in 1977 on the use of phosphoryl-stabilized carbanions as olefin-forming reagents.[15] Additional reviews have appeared, which impart excellent literature coverage up to the end of 1977.[16,284] Our survey is intended to cover important new aspects of these reactions that have appeared from 1978 to the end of 1987, with particular emphasis on stereochemistry and mechanism. This overview will also address noteworthy synthetic applications from the last 10 years.

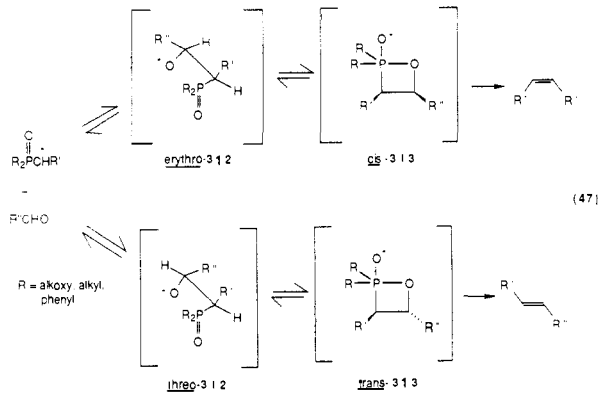
Among the various phosphoryl-stabilized carbanions that have been applied to olefination are those containing phosphonate, phosphine oxide, phosphonamide, and thiophosphonate functionalities. Phosphonates, the most commonly employed class, will be considered first and in the greatest detail. Synthetic applications of the Horner reaction (involving phosphine oxides), which have increased noticeably in the past decade, will be discussed next. Phosphoryl reagents, in comparison to phosphoranes, offer several advantages, which have been adequately described elsewhere.[15,16,282,284] In brief, the water-soluble phosphate, phosphinate, or thio-

phosphate byproducts facilitate isolation and purification of the desired products; the customary increased reactivity of phosphoryl-stabilized reagents permits their condensation with relatively unreactive carbonyl compounds; and reaction conditions are often available for the preparation of alkene mixtures enriched in either the *Z* or *E* direction.

A. Phosphonate Carbanions

1. Mechanistic Aspects

The mechanism for the HWE reaction, related to that of the Wittig reaction (section II), is shown in eq 47 for

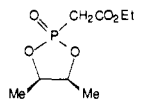


(47)

an aldehyde (R″CHO) condensation. The phosphoryl-stabilized carbanion attacks the carbonyl in a stepwise manner, to give oxyanion intermediate **312**, which then decomposes via a transient four-centered intermediate, **313**, to yield olefin. The stereochemistry is determined by a combination of the stereoselectivity in the initial carbon–carbon bond-forming step and, perhaps, reversibility of intermediates (e.g., **312** and **313**). Although direct observation of intermediates in the HWE reaction has not been generally possible, there are several kinetic and spectroscopic studies that shed light on the course of this process. There are also several reports that demonstrate the reversible dissociation of originally formed HWE aldolates, and these will be discussed later (see sections III.A.3.b and III.A.3.d). In reactions of phosphine oxides, investigated in detail by Warren and colleagues (section III.B), *erythro*-**312** and *threo*-**312** can be captured by protonation and isolated as stable β-hydroxy phosphine oxides, examples of which have been independently and stereospecifically decomposed to the respective (*Z*)- and (*E*)-alkenes.

The HWE reaction is generally restricted to phosphonates bearing an α substituent that can stabilize a carbanion (e.g., COO^-, CO_2Me, CN, aryl, vinyl, SO_2R, $P(O)(OR)_2$, SR, OR, and NR_2). The absence of such groups usually results in poor yields of alkene products. In difficult cases, anion **312** is resistant to decomposition to olefin;[16,284] however, new methods for inducing elimination have recently appeared (see section III.2.a).

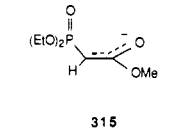
Pentacoordinate adducts have not been observed spectroscopically for the reaction of such anions with carbonyl compounds. One report claimed detection of **313** by NMR amidst treatment of cyclic phosphonate **314** with benzophenone.[285] Although signals for pentacoordinate phosphorus were not observed by ^{31}P NMR at −25 °C, in conjunction with formation of alkene product from the anion, a peak (at −34 ppm) attributed to the same was seen at a higher temperature, namely 0 °C. Unfortunately, no other evidence was presented to support the structure, and no data were supplied to confirm an intermediate in the reaction, as opposed to a side product.



314

(*a*) *Reaction Rate Studies.* Careful rate studies have been conducted by Larsen and Aksnes on the HWE reaction.[286,287] The reactions of several phosphonate reagents with sodium ethoxide and para- and meta-substituted benzaldehydes were studied by monitoring levels of aldehyde and alkene by UV spectroscopy. The reaction was found to be first order in aldehyde, ethoxide, and phosphonate, and third order overall, with the rate-limiting step being the initial condensation of phosphonate with aldehyde. The precise isosbestic point indicated that there was no discernible accumulation of intermediates. Cyclic phosphonate **314** reacted about 20 times faster than acyclic counterpart $(EtO)_2P(O)CH_2CO_2Et$. The enhancement was attributed to a more pronounced release of ring strain on conversion from the tetrahedral to the pentacoordinate state at phosphorus with carbanions derived from **314**.[286] An order of magnitude decrease in rate was seen with phosphinate $EtO(Ph)P(O)CH_2CO_2Et$, relative to $(EtO)_2P(O)CH_2CO_2Et$,[287] and phosphine oxide $Ph_2P(O)CH_2CO_2Et$ reacted generally 35 times slower than the phosphinate. This may be explained by the relative ease with which the reaction from the phosphinate can achieve a pentacoordinated state relative to the phosphine oxide.

(*b*) *Spectroscopic Studies.* The nature of anions derived from phosphoryl-stabilized reagents has been extensively investigated by Seyden-Penne, Corset, and their colleagues via IR and NMR spectroscopy.[288-292] Species **315** and **316** were observed as slowly intercon-



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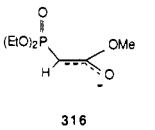

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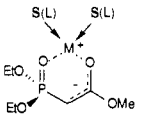

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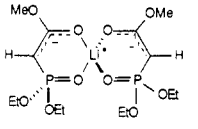

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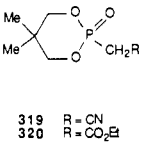
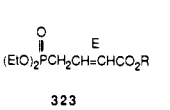


319 R = CN
320 R = CO_2Et



323

verting, planar species when the potassium counterion was complexed in THF, pyridine, or DMSO by [2.2.2]cryptand.[288,289] In the absence of cryptand, a solvated chelate structure, **317**, was observed in all three solvents (e.g., Li^+/DMSO, 0.5 M), which may coexist with free ion (K^+/DMSO, 0.5 M) or aggregates (Li^+ or K^+/THF, 0.5 M).[291,292] In acetonitrile (Li^+ base), triplet ions **318** have also been characterized.[291] With a deficiency of base (Li^+ cation, THF or MeCN), aggregates **317**, **318**, and other partially characterized intermediates appeared.[291] This information is useful for understanding pK_a values and chemical reactivity.[291] Similar effects were seen with $(EtO)_2P(O)CH_2C(O)Me$,

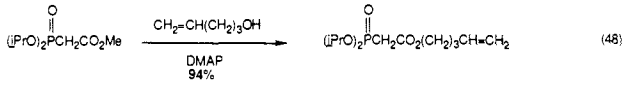
$(EtO)_2P(O)CH_2C(O)NMe_2$, and $(EtO)_2P(O)CH_2CO_2Me$.[292]

Cyclic phosphonates **314**, **319**, and **320**, and their corresponding anions, have also been studied spectroscopically.[290] The anion derived from **314** was too unstable for a careful evaluation; however, **319** and **320** were examined thoroughly. Although phosphonates **319** and **320** exist mainly in a conformation with an equatorial P=O bond, the axial conformer becomes more prevalent subsequent to anion formation, possibly because of an anomeric effect.[290]

2. Preparation of Phosphonate Reagents

Phosphonates can be readily prepared by the Arbusov[293] or the Michaelis–Becker[294] reactions. Several additional methods, worthy of note, have appeared in the past 10 years. Only references that bear on the preparation of phosphonates suitable for the HWE reaction are included.

An efficient ester-exchange reaction has been developed by Takano and associates for the preparation of differentially substituted phosphonoacetates.[295] For example, heating of phosphonate **321** and 4-penten-1-ol with a catalytic amount of 4-(dimethylamino)pyridine (DMAP) resulted in transesterification to give **322** (eq 48). With isopropyl phosphonates, alkoxy exchange at phosphorus was minimized.



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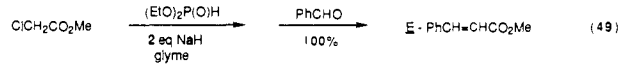
321 322

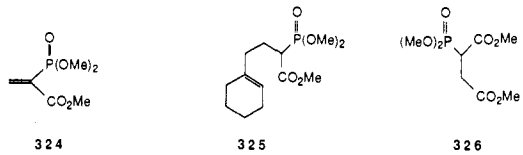
Alternatively, different ester groups can be incorporated by reaction of $(MeO)_2P(O)CH_2COCl$ with alcohols. This acid chloride was used by Meyers in a synthesis of *N*-methylmaysenine.[296] Floyd and Fritz[297] prepared the acid chloride in situ by treatment of $(MeO)_2P(O)CH_2CO_2H$, obtained from the methyl ester,[298] with oxalyl chloride and converted it to an ester; crotonate esters **323** were similarly constructed.[297] A dicyclohexylcarbodiimide (DCC) coupling was employed to place a complex carbon skeleton in the carboxylic ester of a phosphonoacetate in 86% yield en route to brefeldin A.[299]

A novel, in situ HWE process was reported by Brittelli.[300] Treatment of a 2-halo carboxylic acid with a dialkyl phosphite, a carbonyl component, and sodium hydride in glyme led to high yields of acrylic acids in one step. A Michaelis–Becker reaction occurred initially to generate a phosphonate, which was transformed into the unsaturated acid. For example, 2-bromopropionic acid and benzaldehyde were forged into (*E*)-PhCH=C(Me)CO_2H in good yield (82%). 2-Bromobutyric acid and isobutyraldehyde gave *i*-PrCH=C(Et)CO_2H with a 3:7 *Z*/*E* ratio, a result that is more *E*-selective than anticipated considering the steric effects in this system.[301] α,β-Unsaturated esters and amides were also obtained in high yield, as demonstrated by the synthesis of (*E*)-methyl cinnamate (eq 49).



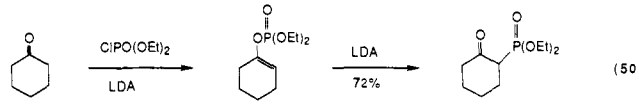
(49)

Snider and Phillips[302] have reported $EtAlCl_2$-catalyzed ene reactions of 2-phosphonoacrylates to yield α-carbalkoxy phosphonates. For example, methylenecyclohexane reacted with vinylphosphonate **324** to give



324 325 326

phosphonate **325** in 71% yield. This technology was useful for situating functionalities in an appropriate position for intramolecular olefinations (section III.A.5).[302] Phosphonosuccinates (e.g., **326**) have been prepared by a Michael-type reaction of triethyl phosphite and dimethyl maleate.[303] β-Keto phosphonates were realized by treatment of readily obtained enol phosphates with strong base.[304] This oxygen to carbon phosphorus migration is especially suited for the synthesis of phosphonates bearing a cyclic ketone, such as in the preparation of **327** from cyclohexanone (eq 50).[304]



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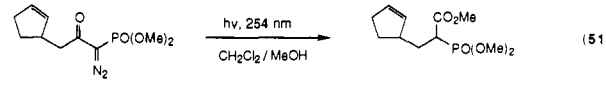
Dialkyl formylphosphonates, such as $(EtO)_2P(O)CH(Me)CHO$, were produced in good yields by condensation of lithio alkylphosphonates with DMF.[305] A photoinduced Wolff rearrangement of α-diazo β-keto phosphonates in the presence of an alcohol afforded α-substituted phosphonates, as in the conversion of **328** to **329** (eq 51).[306a]



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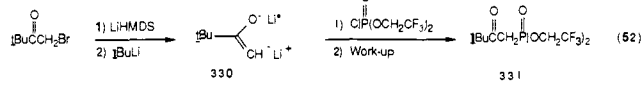
328 329

The Arbuzov synthesis of β-keto phosphonates does not work well, so several other methods have been developed to access these compounds, such as the reaction of $(EtO)_2P(O)CHR'COCl$ with cuprates[306b] and $(RO)_2P(O)CH_2Cu$ with acid chlorides.[306c] β-Keto phosphonates can also be prepared by the union of dianions such as **330**, derived from α-bromo ketones, with dialkyl chlorophosphates (eq 52).[307] This proce-



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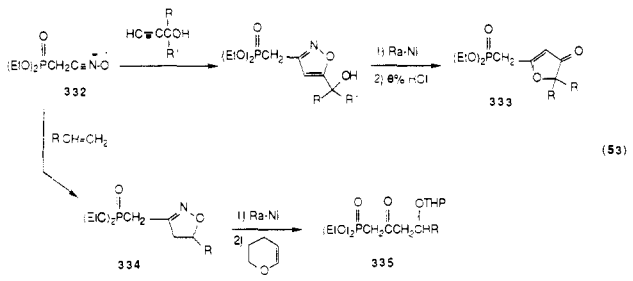
330 331

dure was extended to the preparation of bis(2,2,2-trifluoroethyl) phosphonates (e.g., **331**), important reagents that may be difficult to make by an Arbuzov reaction involving poorly nucleophilic tris(2,2,2-trifluoroethyl) phosphite. The reaction is apparently limited to α-halo ketone starting materials lacking α protons on the opposite side of the carbonyl group.

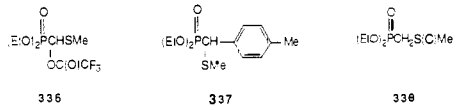
Nitrile oxide **332** is a versatile reagent that has been used by Tsuge and colleagues to build functionalized phosphonates.[308-310] In the synthesis of geipavarin, **332** added to propargylic alcohols to give isoxazoles, the elements of which were synthetically transposed to furanone phosphonate reagents **333** (70–90% from **332**, eq 53).[308] Alternatively, cycloaddition of **332** with terminal olefins resulted in isoxazolines **334**,[309] which were reductively cleaved to 4-hydroxy-2-oxo phosphonates **335**.[310]

α-Methylthio phosphonates, such as **337**, have been prepared by acid-mediated condensation of trifluoro-



(53)

acetate **336** with aromatic[311,312] and vinylic compounds.[312] Compound **336**, generated by $[CF_3C(O)]_2O$-induced Pummerer rearrangement of sulfoxide **338**, was typically not isolated; rather, it was transformed in situ to **337**. Reaction of β-nitrostyrene with $(EtO)_2POSiMe_3$

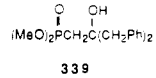


in the presence of $TiCl_4$, followed by zinc reduction, led to cyano phosphonates such as $PhCH(CN)PO(OEt)_2$.[313] Treatment of nitriles, nitroalkanes, and esters with 2 mol equiv of base, followed by diethyl chlorophosphate, engendered new phosphonate reagents.[314]

3. Different Types of Phosphonates in Synthesis

(*a*) *Nonstabilized Phosphonates.* Normally, phosphonate carbanions must bear a carbanion-stabilizing group on the α carbon in order to be effective partners in the HWE reaction, as mentioned earlier; however, there are some notable exceptions. For example, an expedient choice of reaction conditions can lead to good yields of terminal methylenes, such as in the reaction of $PhC(O)CH_2SBzl$ and $(EtO)_2P(O)CH_2^-Li^+$ to give $Ph(BzlSCH_2)C{=}CH_2$.[315] Nonstabilized phosphonate anions can undergo self-condensation to give stable dimers. This process is dependent on steric and electronic factors.[316] A study on the relative acidity and stability of a series of nonstabilized phosphonates has appeared.[316]

In a similar vein, β-hydroxy phosphonates such as **339**, readily formed from phosphonate anions and carbonyl compounds, can be decomposed to alkenes by the agency of either fluoride ion[317a] or weak bases, such as potassium carbonate in aqueous DMF[317b] The al-

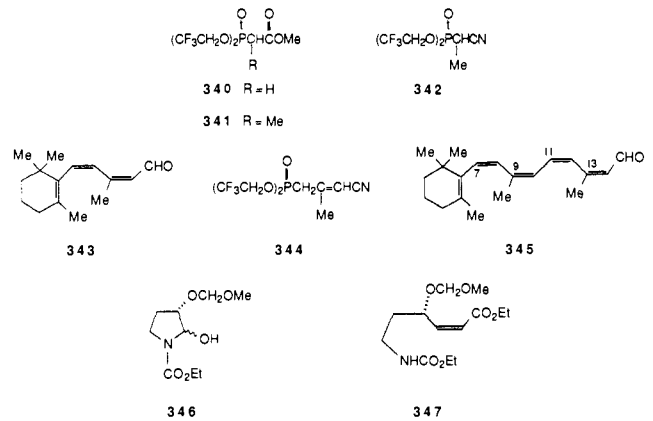


kenes formed can be either alkyl- or aryl-substituted. Stronger bases such as KO-*t*-Bu, NaH, or KH were not effective. A variety of mild bases, for example sodium phenoxide, gave 60–80% yields of alkenes.[317b] This constitutes a two-step method for the preparation of olefins from phosphonates that lack α electron-withdrawing groups, similar to chemistry of phosphine oxides described later (section III.B).

Silyl phosphonates $(MeO)_2P(O)CH(R)SiMe_3$ (R = H, Me) were heated at 250 °C with aldehydes or ketones to give good yields (68–100%) of alkenes, without addition of base.[318] The reaction probably proceeded via thermal 1,3-silyl migration to give $Me_3SiO(MeO)_2P{=}CH_2$, which was the actual olefinating reagent. As discussed in section III.A.3.e, if the reactive species were $(MeO)_2P(O)CHSiMe_3^-$, then the products would have been vinylphosphonates.

(*b*) *Phosphonates Bearing an α-Carbonyl or α-Cyano Group.* The following discussion presents details of important synthetic advances pertaining to types of α-carbonyl- or α-cyano-stabilized phosphonates. Some of these reagents will also be mentioned in the context of newer reaction technologies or intramolecular reactions (sections III.4 and III.5).

{*i*} *Cis-Selective Reactions of Bis(2,2,2-trifluoroethyl) Phosphonates.* Still and Gennari discovered that bis-(2,2,2-trifluoroethyl) phosphonates can supply mainly (*Z*)-alkenes in HWE reactions with aldehydes.[319] Phosphonate **340** combined with octanal (KHMDS,



18-crown-6, THF) to give a 12:1 ratio of (*Z*)/(*E*)-alkenes. Moreover, a >50:1 *Z*/*E* ratio was observed in a similar reaction of **340** with benzaldehyde.[319] The high *Z* selectivity in such reactions was attributed to an increase in the rate of elimination of the originally formed adduct, relative to equilibration of intermediates, which is similar to the rationale suggested for the *Z* stereoselectivity of **314**. Good levels of *Z* selectivity were also obtained with α-methyl carbanion **341**. Reaction of **341** with benzaldehyde afforded a 30:1 ratio of *Z*/*E* isomers (>95% yield), which contrasts with the 1:22 *Z*/*E* ratio recorded for the analogous reaction of $(EtO)_2P(O)CH(Me)CO_2Et$. This new variant of the HWE reaction has attained widespread recognition in synthesis.[320–333] One example of its utility is represented by Danishefsky's synthesis of *N*-acetylneuraminic acid.[320]

Still's method has been extended to phosphonates other than those bearing an α-carbalkoxy group. α-Cyano phosphonate **342** and an α,β-unsaturated aldehyde rendered only (*Z*)-alkene,[322] which is surprising when one considers that cyano-stabilized phosphonates exhibit poor stereoselectivity in typical HWE reactions.[15] Combination of **343** and allylic phosphonate **344**, followed by reduction of the nitrile with diisobutylaluminum hydride (DIBAL), produced **345** as a mixture of four stereoisomers (7,9-*Z*/7,9,11-*Z*/7,9,13-*Z*/*all*-*Z* = 21:66:7:6). Of this mixture, 72% of the material comprised the *Z* geometry at the newly formed bond (C-11).[331] In another interesting application,[332] reaction of hemiaminal **346** with **340** produced only (*Z*)-alkene **347** (55% yield).[334]

{*ii*} *α-Carbonyl-Stabilized Phosphonates.* The stereoselectivity of HWE olefinations of $(EtO)_2P(O)CH_2CO_2Et$ was studied in a systematic fashion with benzaldehyde and aliphatic aldehydes.[335] By far the major products were (*E*)-acrylates, although some of the (*Z*)-olefin was formed (up to 16% *Z*) with the aliphatic aldehydes.[335] The fact that phosphonate **314** was

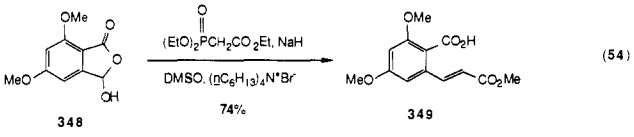
moderately *Z*-selective (65–70% *Z*),[335] as previously demonstrated,[336-337] was explained by a postulated decrease in reversibility of intermediates in reactions of **314**. A Roussel group has systematically examined the reactions of cyclic phosphonates, such as **314** and **320**, in their work on pyrethrin insecticides.[338] For example, high levels of (*Z*)-alkenes (>95%) were obtained (Li^+ counterion, –20 °C) by using **314** (*tert*-butyl ester) with an aldehyde.[338]

There are occasionally situations in which, for one reason or another, only phosphonates are satisfactory for a given purpose, relative to their phosphorane counterparts. As an example, the anion from $(EtO)_2P(O)CH_2CO_2Et$ attacked **118a** to give either an alkene or a *C*-glycoside, depending on the solvent, whereas the stabilized phosphorane led to diene products (see section II.B.1.c).[339a]

A valuable means of homologating carboxylic esters by two carbons into α,β-unsaturated esters has been developed by Takacs et al.[339b] Reduction of $Me(CH_2)_4CO_2Me$ with DIBAL to the aldehyde was conducted in the presence of a phosphonate carbanion. The aldehyde then underwent a HWE process to produce (*E*)-$Me(CH_2)_4CH{=}CHCO_2Me$. This one-pot procedure minimized further reduction of the ester to the alcohol and resulted in good yields (60–80%) of products with *E* stereochemistry.[339b]

Another one-pot procedure involves the condensation of α-lithio alkylphosphonates with diethyl carbonate, followed by treatment with aldehydes.[340] The ethyl acrylates obtained were typically in the *E* configuration.[340]

Trost et al. determined that opening of hydroxy phthalides, such as **348**, with $(EtO)_2P(O)CHCO_2Et^-Na^+$ in DMSO was not reproducible.[341] However, a good yield of olefin **349** was realized by addition of 1 mol % of tetra-*n*-hexylammonium bromide to the phosphonate anion, prior to the addition of the aldehyde component (eq 54). Although the reason for the dramatic improvement is unknown, this technique should prove valuable in other applications.



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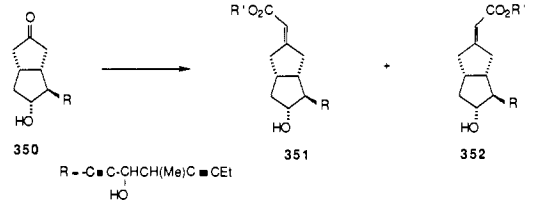
The direct preparation of acrylic acids has been achieved by use of $(EtO)_2P(O)CH_2CO_2H$,[298,342] or $(EtO)_2P(O)CH_2CO_2SiMe_3$[343] followed by mild hydrolysis. Both methods appear superior to the previously reported[344a] use of $(BzlO)_2P(O)CH_2CO_2H$. Phosphonates $(EtO)_2P(O)CH_2CO_2SiMe_3$ and $(EtO)_2P(O)CH_2CO_2H$ produced the *E* isomer with aldehydes, in high yield, whereas with ketones they produced a mixture containing up to 30% of the *Z* isomer.[342,348] In a competition experiment between heptanal and 2-butanone, $(EtO)_2P(O)CHCO_2SiMe_3^-Li^+$ readily discriminated in favor of the aldehyde; there was a 99% yield of (*E*)-$Me(CH_2)_5CH{=}CHCO_2H$ and no ketone adduct.[343]

Reaction of glutaraldehyde or succinaldehyde with 1 mol equiv of a HWE reagent in an aqueous medium (potassium carbonate base) resulted in intramolecular aldolization to give five- or six-membered cycloalkenols.[344b]

Rehwinkel[345] and Gais[346] have recently explored the stereoselectivity of phosphonates bearing asymmetric auxilliary groups on the carboxylic ester. The HWE reaction of ketone **350** with $(MeO)_2P(O)CHCO_2Me^-K^+$ was essentially stereorandom, giving a 3:2 ratio of **351** (R′ = Me) and **352** (R′ = Me) in 90% yield (eq 55).[345]



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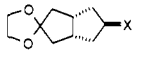
A number of chiral ester groups were then incorporated into the HWE reagents, and the stereoselectivity was examined. The highest ratio was attained for the reagent derived from (+)-8-phenylneomenthol, which furnished an 88:12 ratio of the 8-phenylneomenthyl esters of **351** and **352**. Phosphonates containing (+)- and (–)-8-phenylmenthol delivered equal but opposite stereoselectivity (86:14 and 15:85 ratios of **351** and **352**, respectively).[345] Reaction of the (+)-8-phenylmenthol-derived reagent with *meso*-ketone **353** favored one stereoisomer of **354** (90% ee; 93% yield).[346]

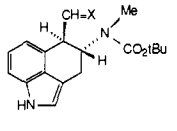


353 X = O

354 X = $CHCO_2R'$

Trisubstituted alkenes, the stereochemistry of which is often difficult to control in olefination, can be readily formed in the HWE reaction either by using α-branched phosphoryl reagents with aldehydes or by using ketones as the carbonyl component.

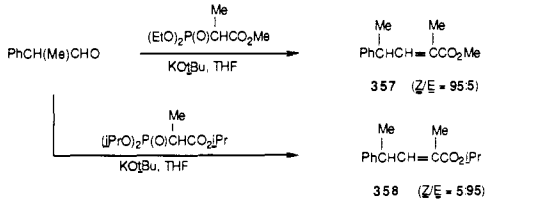
Addition of α-substituted phosphonates to aldehydes typically results in (*E*)-alkenes, although a number of significant nuances have arisen. For example, $(EtO)_2P(O)CH(Me)CO_2Me$ was unexpectedly *Z*-selective in reactions with α-branched aldehydes,[347] as demonstrated in the conversion of **355** to **356**.[348] Although



355 X = O

356 X = $C(Me)CO_2Me$

the yield was low (27%),[348] the *E* isomer of **356** was absent from the crude product. The size of the substituents on the phosphoryl and carboxyl esters can play a pivotal role in governing the stereoselectivity: bulky ester groups favor the *E* isomer, while small ones favor the *Z* isomer. Although 2-phenylpropanal reacted with $(EtO)_2P(O)CH(Me)CO_2Me$ (KO-*t*-Bu, THF) to give a 95:5 ratio of (*Z*)-**357** and (*E*)-**357**, it reacted with (*i*-PrO)$_2$P(O)CH(Me)CO$_2$-*i*-Pr to give a 5:95 ratio of (*Z*)-**358** and (*E*)-**358** (eq 56).[127,349-351]



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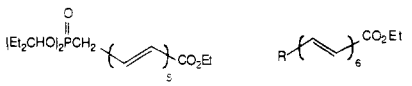
Another instance in which the size of the phosphoryl ester groups are important is the treatment of vinylogous carbethoxy phosphonate **359** with a complex aldehyde (RCHO) to render only *all-E* isomer **360**, even

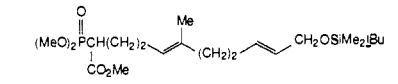


359 360

though the diethyl or dimethyl phosphonates were stereorandom at the new C–C double bond.[352] In this very sensitive polyene system, lithium 2,2,6,6-tetramethylpiperidide (LiTMP) bestowed a higher yield of **360** (68%) than did LDA (20%). In the same context, phosphonate **323** (R = Et) was employed to prepare conjugated polyunsaturated esters,[256b] although a two-step route to this structural type was more efficacious in one example.[353]

Reactions of $(EtO)_2P(O)CH(Me)CO_2Me$ with a linear (non-α-branched) aldehyde or with α,β-unsaturated aldehydes were *E*-selective.[347,354] An α-amido-substituted phosphonate reacted with >1:20 *Z*/*E* stereoselectivity.[355]

Marshall and co-workers found that α-substituted phosphonates with long alkyl chains combine with propanal, decanal, and more complex aldehydes to give only modest *E* selectivity, the *Z* isomer being formed presumably because of an influence of the massive hydrocarbon groups.[323] For example, treatment of **361**



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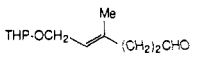

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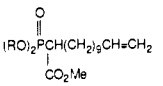


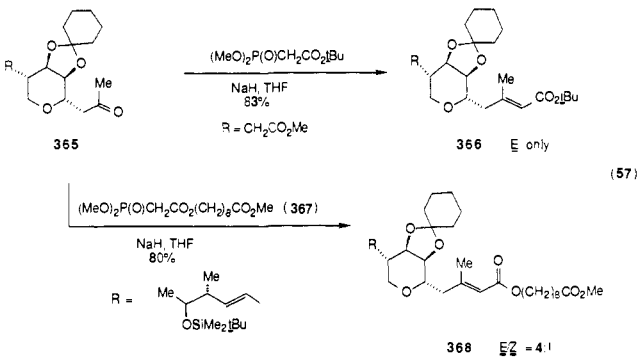
363 R = CH_2CF_3
364 R = Me

with aldehyde **362** (18-crown-6, KHMDS, THF) produced a 45:55 mixture of *Z*/*E*-alkenes in 80% yield. Union of bis(2,2,2-trifluoroethyl) phosphonate **363** with decanal gave an 87:13 ratio of *Z*/*E*-alkenes, an amount of *E* isomer that was higher than anticipated on the basis of Still's paper.[319] These stereochemical discrepancies were ascribed to enhanced reversibility of intermediate aldolates, due to retardation of the alkene-forming step by the long alkyl chain.[323] A crossover experiment involving addition of salt $(MeO)_2P(O)C(Me)CO_2Et^-K^+$ to a preformed adduct of nonanal and phosphonate **364** at −78 °C provided some support for this hypothesis (ca. 10% crossed product from nonanal). In a recent paper by Weigele and coworkers, a long-chain phosphonate (dimethylphosphoryl esters) combined with an aldehyde to give a 79:21 mixture of *Z*/*E* isomers (74% yield).[356a]

Branched carboxylate $[(EtO)_2P(O)C(Me)COO]^{2-}\cdot 2Li^+$ reacted with aromatic and linear aldehydes to afford only (*E*)-alkenes. Its reactions with α-branched aldehydes were only slightly less *E*-selective.[356b]

α-Fluoro phosphonate reagents have been added to a variety of aldehydes to proffer (*E*)-α-fluoro esters with high stereoselectivity.[221c,357-359] An example is the combination of isobutyraldehyde with $(EtO)_2P(O)CH(F)CO_2Me$, which yielded 90% of $PrCH{=}C(F)CO_2Me$ with a *Z*/*E* ratio of ca. 2:98 (*n*-BuLi, THF, −78 °C).[357] This outstanding *E* stereoselectivity, attributed to electronic effects,[357] has been applied to the synthesis of fluorinated insect sex pheromones[221c] and visual pigments.[358] Reactions of the diphenylphosphonyl ester reagent showed a considerable erosion of *E* stereoselectivity.[357] For acid targets, use of $(EtO)_2P(O)CH(F)CO_2H$ obviates the need for ester hydrolysis.[360a] Treatment of this compound with 2 mol equiv of *n*-butyllithium generated the dianion, which coupled with aromatic aldehydes to produce (*Z*)-alkenes, but with aliphatic aldehydes there was only a slight preference for (*E*)-alkenes.[360a] Phosphonates $(RO)_2P(O)CH(F)COR'$, prepared by addition of organometallic reagents to $(RO)_2P(O)CH(F)COCl$, are useful for generating α-fluoro enones.[360b] α-Bromo[361] and α-chloro[229d] phosphonates, from phosphonate carbanions and an *N*-halosuccinimide, have been used to synthesize vinyl halides en route to prostaglandin analogues.[229d,361] In the reaction of $(EtO)_2P(O)C(Br)C(O)R^-Na^+$ with an aldehyde only the (*Z*)-vinyl bromide was isolated (60% yield);[361] however, high stereoselectivity is unlikely to be general as $(MeO)_2P(O)C(Cl)C(O)R^-Na^+$ combined with a similar aldehyde to give a *Z*/*E* ratio of 39:61 (80% yield).[229c] With more bulky phosphoryl esters, such as in $(i\text{-PrO})_2P(O)C(Cl)C(O)R^-Na^+$, the proportion of (*Z*)-alkene was improved (*Z*/*E* = 73:27, 78%).[229d]

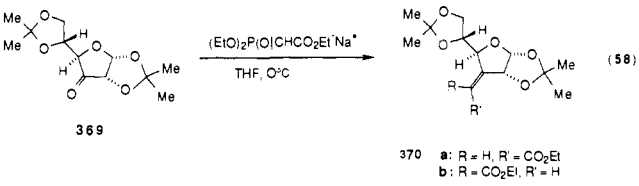
In contrast to aldehydes, reactions of ketones with unbranched phosphonate reagents are often just moderately *E*-selective.[362-364] However, $(MeO)_2P(O)CHCO_2\text{-}t\text{-}Bu^-Na^+$[365] and ketone **365** provided **366**, which was contaminated with only a trace of the *Z* isomer,[364] again indicating that bulky groups can induce high *E* selectivity (eq 57). Phosphono carboxylate **367** coupled with ketone **365** in the synthesis of a 1:4 mixture of (*Z*)/(*E*)-**368**;[366] this ratio may reflect the presence of a long alkyl chain, similar to effects described above.



365 366 E only (57)

368 E:Z = 4:1

Ketones that are unreactive to Wittig olefination, particularly sterically hindered ones, may succumb to the corresponding phosphonate reagent. For example, although protected glucose **369** was inert to the $Ph_3P{=}CHCO_2Et$, it readily combined with $(EtO)_2P(O)CHCO_2Et^-Na^+$ to give a mixture of **370a** and **370b** (eq 58).[189b] In the olefination of **369**, the size of the

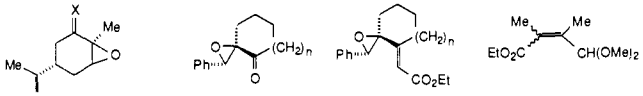


369 (58)

370 a: R = H, R' = CO_2Et
b: R = CO_2Et, R' = H

ester group in the phosphonate influenced the stereochemistry: $(RO)_2P(O)CHCO_2R'^-Na^+$ gave ratios of

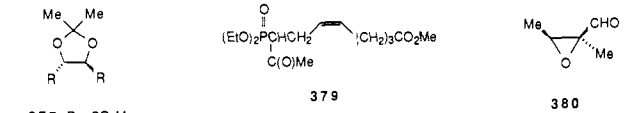
370a/370b of 73:27, 81:19, and 90:10 for R′ = Me, Et, and *t*-Bu, respectively.[189b,367a] Choice of solvent can also play a role in determining the final product ratios. In benzene, >95% *E* selectivity was seen for reaction of $(EtO)_2P(O)CHCO_2Et^-Na^+$ with a seven-membered-ring ketone in a pseudoguaiane synthesis; in ethanol, a 1:3 *Z*/*E* ratio was obtained.[367b] Phosphonates and cyclohexanones can react with pronounced stereoselectivity, depending upon the substituents on the ring. For example, treatment of ketone **371** with $(EtO)_2P(O)CHCO_2Et^-Na^+$ resulted in a 1:9 ratio of (*Z*)/(*E*)-**372**.[368] In a related vein, a 1:5 or 3:4 mixture of (*Z*)/(*E*)-**374** or (*Z*)/(*E*)-**375** was generated by condensation of $(EtO)_2P(O)CHCO_2Et^-Na^+$ with **373** (*n* = 1) or **373** (*n* = 0), respectively.[369]



371 X = O
372 X = $CHCO_2Et$
373
374 (n = 1)
375 (n = 0)
376

Occasionally, tetrasubstituted alkenes have been obtained by the HWE reaction,[370,371] such as in the formation of **376** (*Z*/*E* = 78:22) from $(MeO)_2CHC(O)Me$ and $(EtO)_2P(O)C(Me)CO_2Et^-$.[370]

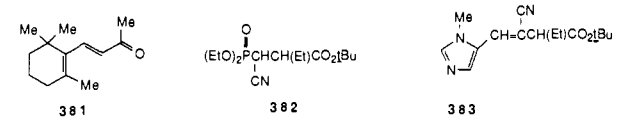
The presence of oxygenated groups α and β to a carbonyl often leads to cis stereoselectivity in reactions with stabilized phosphoranes (section II.B.1.c). In general, treatment of such substrates with phosphonate carbanions results in the *E* isomer, although there are some exceptions. Isopropylideneglyceraldehyde (**45**) combined with $(EtO)_2P(O)CHCO_2Me^-Na^+$ to yield the (*E*)-alkene isomer (**50**, R = Me, 95%).[131] With **45**, a 1:40 *Z*/*E* mixture arose from use of $(EtO)_2P(O)CH_2CO_2Et$ in toluene,[128] and a <1:120 mixture arose from use of $(i\text{-}PrO)_2P(O)CHCO_2Et^-K^+$ in THF.[127,141b] Trost and Mignani recently reported that $(MeO)_2P(O)CHCO_2Me^-Li^+$ reacts with **45**, in the presence of *acetic acid* in THF, to furnish only (*Z*)-**50** (R = Me).[132,141c] This remarkable outcome probably deserves further study to determine if it can be extended to other HWE reactions. *E*,*E* isomer **378** was prepared in a two-step sequence from **377**: reduction of the esters with DIBAL followed by HWE reaction of the dialuminate with $(EtO)_2P(O)CHCO_2Me^-Na^+$ (51% of *E*,*E* isomer, 3% of *Z*,*E* isomer).[140b] Aldehyde **48** coupled with $(MeO)_2P(O)CHCO_2Me^-Na^+$ to yield only the *E* ester in 95% yield.[137]



377 R = CO_2Me
378 R = $CH{=}CHCO_2Me$ (E)
379
380

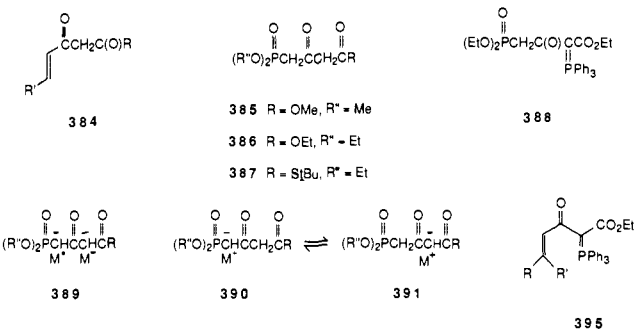
Other than Trost's finding that acetic acid can reverse the customary HWE stereoselectivity with **45**,[132,141c] there is a scarcity of examples of high *Z* stereoselectivity with α-oxygenated carbonyl compounds.[372a] Treatment of MeCH(OBzl)CHO with $(EtO)_2P(O)CHCO_2Et^-Na^+$ resulted in an expected 1:19 *Z*/*E* ratio of alkenes.[142] Alternatively, coupling of $(MeO)_2P(O)CHCO_2Me^-Na^+$ with the same aldehyde gave a 1:1 *Z*/*E* mixture. Use of Still's procedure[319] $[(CF_3CH_2O)_2P(O)CHCO_2Me^-K^+]$ resulted in a 5:1 *Z*/*E* ratio with MeCH(OBzl)CHO and an 8:1 *Z*/*E* ratio with $MeCH(OCH_2OBzl)CHO$.[142] Phosphonate **379** and aldehyde **45** gave a 1:2.3 *Z*/*E* ratio of alkenes.[372b] The rather poor *E* stereoselectivity can be ascribed to the long hydrocarbon chain in the phosphonate (cf. ref 323). Epoxy aldehyde **380** and $(MeO)_2P(O)C(Me)CO_2Me^-Na^+$ provided high *Z* stereoselectivity (<10% *E* isomer).[373]

{iii} α-Cyano Phosphonates. These reagents are anomalous compared to their carbalkoxy counterparts in that they produce mixtures of *Z* and *E* isomers in the range of 1:4 to 2:1.[15,374,375] A systematic study comparing the stereochemistry obtained by different Wittig-type reagents with α,β-unsaturated aldehydes has been published.[374] In another paper, $(i\text{-}PrO)_2P(O)CHCN^-Na^+$ was determined to be more *E*-selective (*Z*/*E* = 18:82) than the corresponding diethyl phosphonate (*Z*/*E* = 1:2) in reaction with β-ionone (**381**).[375] Rapoport and Compagnone alkylated $(EtO)_2P(O)CH_2CN$ to form reagent **382**, which was reacted (KH) with 1-methyl-5-imidazolecarboxaldehyde to furnish a 2:3 ratio of (*Z*)/(*E*)-**383** (95% yield).[376] Inexplicably, a similar sequence with the analogous carbethoxy phosphonate was unsuccessful.[376] A completely stereoselective preparation of (*E*)-acrylonitriles is offered by analogous phosphine oxide reagents (see section III.B).[377,378]



381
382
383

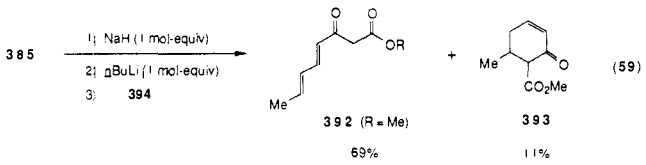
(c) Phosphonates Bearing Both α- and γ-Carbonyl Groups. Phosphonate reagents with both α- and γ-carbonyl groups are useful for the preparation of molecules such as **384**. Several reagents for this purpose, particularly compounds **385**–**388**, have recently been described.[379–367] Phosphonates **386** and **387** were treated with 2 mol equiv of sodium hydride, followed by addition of carbonyl compounds, to give *E*-configured alkenes **384** (R = OEt, S-*t*-Bu) in good yields (50–96%).[379,385] In this reaction, the carbonyl group condensed with the α carbon of the phosphonate, rather than the γ carbon. The potassium salt of **386**, and not the sodium salt, was required in the reaction with substituted benzophenones; good yields were obtained in these systems.[380]



384
385 R = OMe, R″ = Me
386 R = OEt, R″ = Et
387 R = StBu, R″ = Et
388
389
390
391
395

It was originally proposed that dianion **389** is formed and that it reacts selectively at the α carbon.[379–381] An alternative explanation has been offered.[383] Thus, under the original conditions (e.g., 2 mol equiv of NaH),[379,380] monoanion **390**, in equilibrium with γ-monoanion **391**, would be the reactive species.[383] After treatment with the carbonyl compound, the second equivalent of base deprotonates the product, preventing

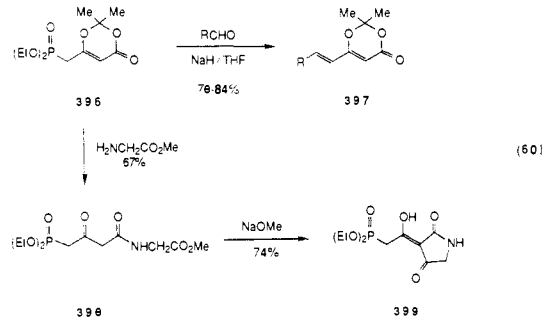
it from protonating yet-unreacted phosphonate carbanion. Dianion **389** is claimed to be formed on treatment of **385** sequentially with 1 mol equiv each of sodium hydride and *n*-butyllithium.[383] The main evidence for the monoanions **390** and **391**, from **385** and 2 mol equiv of sodium hydride, rests with the different reactivity of **389** prepared by the sodium hydride/*n*-butyllithium method. For example, reaction of **389** (NaH/*n*-BuLi) with (*E*)-MeCH=CHCHO (**394**) gave a 69% yield of **392** (R = Me), along with 11% of **393** (eq 59).[383] Cyclohexenone **393** was formed by initial



(59)

attack of **389** at the β carbon, followed by an intramolecular HWE reaction, akin to analogous processes.[381,384] When **385** or **386** was treated according to the original procedure,[379] no **393** was formed, and **392** (R = Me) or **392** (R = Et) was isolated in yields of 47%[383] or 91%.[379] However, in the latter experiment one might have expected **393** to form as well, because γ-ion **391** could have reacted at the β carbon of **394** and then cyclized to **393** (given the second mol equiv of NaH). Furthermore, the presence of lithium in the reaction that afforded **392** and **393** may have prompted **389** to take a different reaction course (to **393**), especially since the nature of the cation is known to have an influence on reactivity.[380] Although the character of the reagents derived from **385** or **386** and 2 equiv of base is left unsettled, the procedure does offer an attractive synthetic route to 3-oxo-4-pentenoates (viz., **384**). Phosphonate **388** reacted with aldehydes with high *E* stereoselectivity, but was less selective with ketones.[386,387] The products (**395**) are Michael acceptors suitable for homologation to complex acyl phosphoranes.

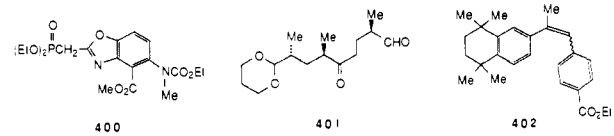
Boeckman and co-workers obtained phosphonate **396**, which olefinated aldehydes (NaH/THF) to give protected alkenes **397** in good yield (eq 60).[388] Nucleo-



(60)

philes such as alcohols, amines, α-hydroxy esters, and α-amino acids added to **396** on heating to yield the corresponding β-keto esters and amides.[389-391] With thermally sensitive reactants, such as glycine methyl ester, ring opening of **396** was catalyzed by acid (eq 60). Treatment of **398** with 1.005 mol equiv of sodium methoxide gave tetramic acid **399**, a strategy employed in the preparation of the tetramic acid fragment of streptolydigin.[389,390] DeShong et al. described the preparation of tetramic acids **399** in low and irreproducible yields by fragmentation of the appropriate 2,5-disubstituted isoxazolium salts.[392] In reaction with simple aldehydes, removal of the NH proton of the tetramic acid moiety of **399** was required for satisfactory HWE condensation.[385b,392]

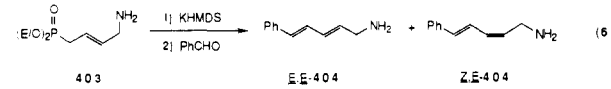
(d) Vinyl- and Aryl-Stabilized Phosphonates. Vinyl and aryl substituents can also stabilize phosphonate carbanions, and these reagents have been employed routinely to prepare styrene, stilbene, or 1,3-diene derivatives.[15,284,393] The reactions generally supply a high proportion of (*E*)-alkene, in contrast to the reactions of allylic or benzylic phosphoranes, which rarely show remarkable stereoselectivity (see section II.A.3). It is interesting to note that the anion from phosphonate **400** (prepared with NaH) reacted with aldehyde **401** without epimerization of the methyl-bearing stereocenters; a 1:19 *Z*/*E* ratio of olefins was realized (79% yield).[394]



Although aryl- and vinyl-stabilized phosphonate reagents generally show robust *E* selectivity, the configurational preference may sometimes be due to product equilibration, which engenders a thermodynamic mixture enriched in the *E* isomer.[395] For example, (*Z*)- and (*E*)-**402** were originally produced as a 35:65 mixture, but this changed on treatment with 0.2 mol equiv of sodium ethoxide (DMSO) over 0.5–4.0 h to a 6:94 *Z*/*E* mixture (74% recovery of **402**).[395] Stereomutation about the carbon–carbon double bond in **402** is a special case, however, as deprotonation and reprotonation of the vinylic methyl group can account for the equilibration.

Addition of a catalytic amount of 15-crown-5 to reactions of aryl- or heteroaryl-stabilized phosphonate carbanions with aromatic aldehydes, involving sodium hydride in THF, has been found to augment the yield of "stilbenes" dramatically.[396-398]

5-Amino-1,3-pentadienes were obtained by a HWE reaction of phosphonate **403** (K salt) with carbonyl compounds.[399] For example, reaction of benzaldehyde with **403** gave an 84% yield of dienes **404** as a 2.5:1 mixture of the (*Z*,*E*)- and (*E*,*E*)-alkenes, isomeric at the double bond originally in **403** (eq 61).[399] Considering

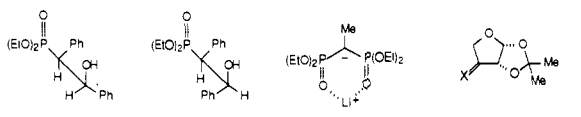


(61)

that the isomeric composition of **403** was *Z*/*E* = ca. 1:9, isomerization must have taken place. In general, reactions of allyl phosphonate reagents are highly *E*-selective (*Z*/*E* < 10); thus, they have been employed in the preparation of polyunsaturated molecules, such as leukotrienes.[393k]

As with α-silyl phosphonium salts,[215a,400a] α-silyl phosphonates can be treated with fluoride ion to release phosphonate carbanions, suitable for HWE reactions.[400b,c] An example is the cesium fluoride promoted condensation of $(MeO)_2P(O)CH(Ph)SiMe_3$ with acetophenone, which afforded Ph(Me)C=CHPh as a 3:1 ratio of *Z*/*E* isomers (67% yield).[400b,c]

Seyden-Penne and Bottin-Strzalko prepared the erythro and threo diastereomers of β-hydroxy phosphonate **405**.[401] In separate experiments, each was treated with base (NaH or KO-*t*-Bu in THF; KO-*t*-Bu in

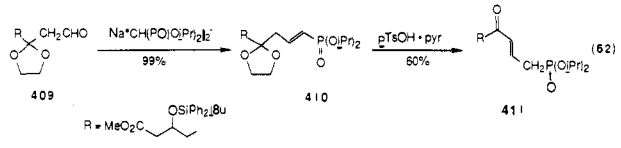


erythro-405 threo-405 406 407 X=O 408 X=CHPO(OEt)$_2$

DMSO) to afford (*E*)-stilbene and/or the starting reagents.[401] Because of the orange color in some of these reactions, which is characteristic of the anion of $(EtO)_2P(O)CH_2Ph$, and the lack of formation of (*Z*)-stilbene in the decomposition of *erythro*-**405**, one can argue that the relative rate for conversion of *erythro*-**405** to stilbene is much slower than the rate for its dissociation to the benzylidenephosphonate anion and benzaldehyde (retro-HWE reaction). This reversibility explains the *E* stereoconvergence and is reminiscent of the reversibility of erythro β-hydroxy phosphonium salts (section II.A.2.d).

(*e*) *Bisphosphonates and Related Reagents.* Vinylphosphonates can be readily prepared by reaction of tetraalkyl methylenebisphosphonates and carbonyl compounds,[402-404] frequently with excellent *E* stereoselectivity. Exposure of bisphosphonate reagents to lithium bases generates stable chelates, like **406**, which have been characterized by NMR, IR, and Raman spectroscopy.[404] Although $[(i\text{-}PrO)_2P(O)]_2CF^-$ coupled with aldehydes to give fluorovinylphosphonates consisting predominantly of the (*E*)-alkene,[405] $[(EtO)_2P(O)]_2CF^-Li^+$[406a] coupled with **407** to give a 2:3 mixture of *Z*/*E* isomers.[406b] Amazingly, the same reactions with $[(EtO)_2P(O)]_2CH^-Li^+$ produced only one stereoisomer, assigned as (*Z*)-**408**.[406b] Bisphosphonate reagents are more reactive than mixed phosphorane–phosphonate reagents, such as $(RO)_2P(O)CH{=}PPh_3$. The former could react with the anomeric carbon of furanose sugars (e.g., **109**) in molecules inert to the mixed reagents.[164,407,408]

Condensation of aldehyde **409** with $[(i\text{-}PrO)_2P(O)]_2CH^-Na^+$ yielded vinylphosphonate **410** (eq 62).[409] On deketalization of **410**, the carbon–carbon double bond migrated into conjugation with the new carbonyl group, establishing molecule **411** for further HWE chemistry.



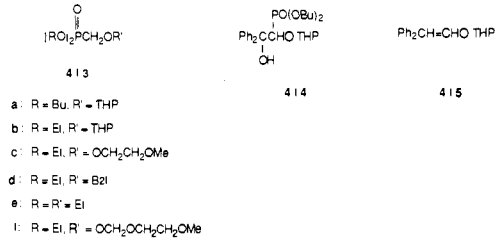
409 410 411 (62)

Reaction of phosphonate carbanions with acyl phosphonates gave mostly (*Z*)-alkenes, whereas analogous reactions with phosphoranes gave (*E*)-alkenes.[410,411] Acyl phosphonates $(EtO)_2P(O)C(O)R$ (**412**; R = Me, Et, Ph, Bzl, or $C_{15}H_{31}$) and $Ph_3P{=}CHR'$ (R' = CO_2Et or CN) linked with nearly exclusive *E* stereoselectivity.[410] Alternatively, **412** (R = Et, Ph, or $C_{15}H_{31}$) and $(EtO)_2P(O)CHCO_2Et^-Na^+$ or $(EtO)_2P(O)CHCN^-Na^+$ gave alkene mixtures enriched in the *Z* isomer.[410] For example, $(EtO)_2P(O)CHCO_2Et^-Na^+$ and **412** (R = Ph) led to $(EtO)_2P(O)C(Ph){=}CHCO_2Et$ in 63% yield, with a 90:10 *Z*/*E* ratio. The HWE reaction was unsuccessful for $(EtO)_2P(O)CH_2Ph$ or for the addition of $(EtO)_2P(O)CHCO_2Et^-Na^+$ to **412** (R = Me or Bzl). Reaction of **314** (NaH, THF) with **412** (R = Ph) provided a 40% yield of olefin with moderate *Z* selectivity (*Z*/*E* = 80:20).[411] A discrepancy in selectivity between the phosphorane- and phosphonate-mediated condensations was also observed in reactions with $MeC(O)CO_2Et$ and $PhC(O)CO_2Et$.[410] The phosphorane reactions gave (*E*)-alkenes, while $(EtO)_2P(O)CHCO_2Et^-Na^+$ yielded mainly (*Z*)-alkenes. The unexpected *Z* stereoselectivity in the latter case was attributed to electronic interactions between the substituents.[410]

There are occasions where the HWE pathway competes with the Wittig[412] or Peterson[94b,413] olefination. Although carbanions from reagents such as $(RO)_2P(O)CH_2X$, where X = $SiMe_3$ or PPh_3, could react with carbonyl compounds to yield either vinylphosphonates, vinylsilanes (X = $SiMe_3$), or vinylphosphonium salts (X = PPh_3), these reactions uniformly create vinylphosphonates. β-Hydroxy phosphonates generally need an electron-withdrawing group on the β carbon in order to fragment to alkene (section III.A.1.a), but the other pathways (Wittig and Peterson) do not and thus proceed to completion. In a study by Carey and co-workers,[94b] $(EtO)_2P(O)CHSiMe_3^-Li^+$ reacted with isobutyraldehyde to give a 2.4:1 *Z*/*E* ratio of $[(Me)_2CH]CH{=}CHP(O)(OEt)_2$ and with benzaldehyde to give only the (*E*)-alkene. By contrast, $(EtO)_2P(O)C(Me)SiMe_3^-Li^+$ and benzaldehyde rendered an 8:1 *Z*/*E* ratio of $PhCH{=}C(Me)P(O)(OEt)_2$.[94b] Stereoselectivity did not follow set trends; however, a truly salient point is the utter absence of vinylsilane products.[94b] One-carbon homologation of carbonyl compounds was nicely achieved with $(EtO)_2P(O)C(SiMe_3)O(CH_2)_2SiMe_3^-Li^+$ (vinylphosphonate stereochemistry not determined).[413]

(*f*) *Heteroatom-Stabilized Phosphonates.* Electronegative elements such as nitrogen, sulfur, oxygen, or the halogens can stabilize phosphonate carbanions sufficiently so that they can be used to olefinate carbonyl compounds.[15,284] This provides a convenient means of preparing enamines, enol ethers, enol thioethers, vinyl sulfones, vinyl sulfonates, and vinyl sulfoxides, often with good stereocontrol. Since some of these products can be hydrolyzed to aldehydes or ketones, a one-carbon homologation procedure for carbonyl compounds emerges.[199]

{*i*} *Oxygen- and Nitrogen-Stabilized Phosphonates.* The formation of enol ethers from phosphonates $(RO)_2P(O)CH_2OR'$ (**413a–f**) and a variety of carbonyl



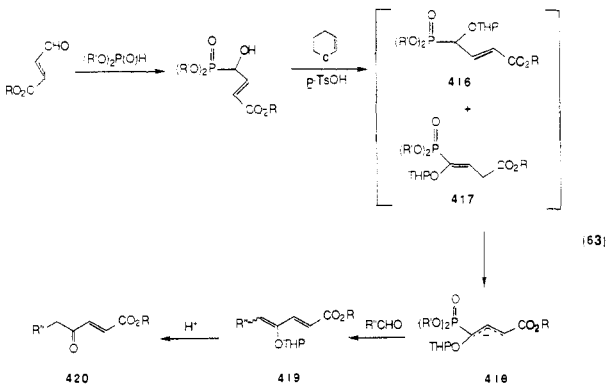
413 414 415

a: R = Bu, R' = THP
b: R = Et, R' = THP
c: R = Et, R' = OCH_2CH_2OMe
d: R = Et, R' = Bzl
e: R = R' = Et
f: R = Et, R' = $OCH_2OCH_2CH_2OMe$

components is facilitated by metal exchange.[414,415] For example, in the initial condensation of **413a** with benzophenone, initial adduct **414** was acidified, isolated, and then treated with a potassium base (KO-*t*-Bu or KH) to produce **415**.[414] In a reaction of propanal with **413d**, a (*Z*)/(*E*)-alkene ratio of 1:4 was observed; analogous reactions of **413d–f** with (*E*)-$Et(CH{=}CH)_nCHO$ (*n* = 1 or 2) led only to the *E* adducts.[415]

Krief et al. added dialkyl phosphites to 4-oxobutenoates and protected the resulting hydroxyl group to give reagents **416** and **417**, the exact ratio of which depended on the ester substituents (eq 63).[416] Anion **418**, prepared by treating **416** and **417** with LDA, and

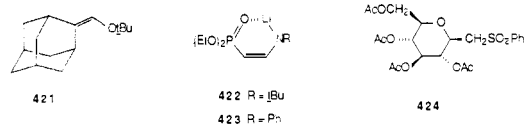
aldehydes conferred tetrahydropyranyl enol ethers **419**, which were then hydrolyzed to unsaturated ketones **420**.[416,417]



(63)

α-Branched phosphonate $(EtO)_2P(O)CH(Me)OEt$ did not react with benzophenone or benzaldehyde, even when the two-step metal-exchange procedure was applied.[418] In contrast, the more stable anion from $(EtO)_2P(O)CH(Ph)OEt$ condensed readily with aldehydes and ketones in good yields.[418] Reaction of $(EtO)_2P(O)C(Ph)OSiMe_3^-Li^+$ with carbonyl compounds (e.g., ArCHO) did not give rise to enol ethers; rather silyl group migration occurred, followed by fragmentation to benzoins (e.g., ArCH(OH)C(O)Ph after workup).[419,420]

An attractive alternative to the direct preparation of enol ethers and enamines from alkoxy- and amino-substituted phosphonate reagents is the use of $(MeO)_2P(O)CH{=}N_2$.[421a] Treatment of this compound with KO-*t*-Bu (LiOH or potassium carbonate also), followed by various carbonyl compounds in the presence of alcohols or amines, delivered the corresponding enol ethers or enamines. Even tertiary alcohols were acceptable: enol ether **421** was obtained in 74% yield. In



the absence of alcohols or amines, $(MeO)_2P(O)CH{=}N_2$ and RCHO afforded terminal acetylenes ($RC{\equiv}CH$).[421b]

The anions of aminomethylphosphonates unite with aldehydes and ketones to furnish the corresponding enamines.[422-425] The separation of the diastereomeric adducts before decomposition offers a route to pure (*Z*)-enamines, which are very difficult to prepare by other means.[424]

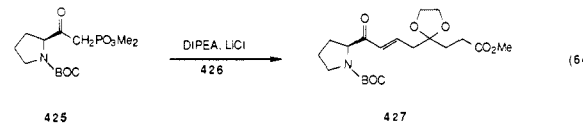
Meyers and colleagues developed an in situ method for homologating aldehydes by two carbons into α,β-unsaturated aldehydes,[426a] as part of a synthetic program directed to streptogramin.[193a] In this method, MeCH=N-*t*-Bu was treated with LDA and then $(EtO)_2P(O)Cl$ to afford chelate **422**, which reacted in situ with RC(O)R′ to yield $RR'C{=}CHCHO$.[426a] For the same purpose, **423** was prepared by treatment of EtOCH=NPh with phosphonate carbanions.[426b] The products, after condensation with the carbonyl compound and imine hydrolysis, were obtained in 42–78% yields.[426b]

{ii} Sulfur-Stabilized Phosphonates. Vinyl sulfides,[427,428] sulfones,[427,429,430] sulfonates,[431-433] and sulfoxides[429,430,434] have been synthesized from the appropriate α-substituted phosphonates, generally with a strong preference for the *E* geometry. For example, (*E*)-vinyl sulfonates were generated from reactions of $(EtO)_2P(O)CH_2SO_2OEt$; however, salt $(EtO)_2P(O)CH_2SO_3^-Bu_4N^+$ was less stereoselective.[431-433] Ketenes condensed with $(EtO)_2P(O)CH_2SO_2Me$ to afford allenic sulfones (e.g., $Ph(Et)C{=}C{=}CHSO_2Me$).[435] Davidson et al. found that $(EtO)_2P(O)CHSO_2Ph^-Na^+$ will attack the anomeric carbon of unprotected monosaccharides to produce *C*-glycosides (via a HWE–Michael sequence), obtainable in either the furanose or pyranose forms depending upon conditions.[436] For example, **424** was synthesized (50% overall yield) by addition of the phosphonate to D-glucose, treatment with sodium methoxide (to convert the original β- and α-furanoses into the β-pyranose), and acetylation.[436]

{iii} Halogen-Stabilized Phosphonates. There are a few examples of successful HWE olefinations involving halogen-stabilized phosphonate carbanions. Compound $(EtO)_2P(O)CF_2^-Li^+$ coupled with a variety of aldehydes and ketones in the synthesis of terminal difluoroalkenes.[437] Similar reagent $(EtO)_2P(O)CCl_2^-$ was generated electrolytically and yielded dichloromethylene adducts.[438] Stabilization of the phosphonate carbanion by adjacent trifluoromethyl groups was observed with $(EtO)_2P(O)C(CF_3)_2^-Cs^+$ (or $MeEt_3N^+$), which formed alkenes with hexafluoroacetone or benzaldehyde in modest yield.[439]

4. Newer Reaction Technologies

(a) Use of Tertiary Amine Bases. Because phosphonate-stabilized carbanions are more basic than their phosphorane counterparts, there are instances where they are incompatible with sensitive substrates,[190] albeit this is not always a problem, even with groups susceptible to epimerization.[440] Some newer methods permit the generation of phosphonate carbanions with tertiary amine bases in the presence of lithium or magnesium salts.[441,442] One protocol entails the use of lithium chloride and either 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or diisopropylethylamine (DIPEA).[441] Reactants that can racemize easily or are base-sensitive usually remain unaffected. Excellent yields (85–100%) have been achieved with typical HWE stereochemistry. Even triethylamine can be used under such conditions.[442] Of the standard organic solvents, DMF proved problematic, presumably because it coordinates with metal cations.[442] These mild conditions for generating phosphonate carbanions have been exploited in several synthetic endeavors,[308,329,443-445] including intramolecular olefinations (section III.5). In one notable case, use of LiCl/DIPEA circumvented racemization in the reaction of **425** with complex aldehyde **426** to produce **427**, a key intermediate en route to norescurinine, despite severe racemization when potassium *tert*-butoxide was used (eq 64).[445] On the other hand, $(EtO)_2P(O)CHCH{=}$



(64)

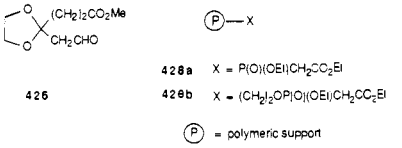
$CHCO_2Et^-Li^+$ reacted to afford (*all-E*)-alkene with a complex aldehyde (LDA as base, 73% yield), while the same reaction with LiCl/DBU gave a much lower yield of product.[446] Regardless of the few instances where a

mild organic base is inadequate, this procedure constitutes a convenient alternative to traditional HWE techniques, especially with base-sensitive substrates.

The effect of organic bases and lithium chloride on phosphoryl-stabilized carbanions has been studied by Seyden-Penne and co-workers, as an extension of their earlier work (section III.A.1.c).[288-292] In the presence of DBU and LiCl in acetonitrile, phosphonate carbanions are aggregates (e.g., monomeric ion pair **317**), small amounts of triplet ion **318**, and other intermediate species.[291] The DBU deaggregates LiCl, deprotonates the phosphonate, and assists proton exchange.[291]

(*b*) *Two-Phase Systems.* Solid–liquid two-phase reaction systems have been used in the HWE reaction, with KOH, NaOH, or potassium carbonate as the base in organic solvents (e.g., toluene or methylene chloride).[447-449] Two-phase liquid–liquid processes, in which the base is dissolved in water, have also been of value.[448,450-452] A method of preparing α-deuterated alkenes, developed by Villieras and Seguineau, entails performing the HWE reaction in 6 M dry potassium carbonate in D_2O.[453] Reaction of $(EtO)_2P(O)CHCO_2Et^-Na^+$ with aqueous formaldehyde and potassium carbonate unexpectedly produced $H_2C{=}C(CH_2OH)CO_2Et$;[451] $H_2C{=}C(CH_2OH)P(O)(OEt)_2$ could also be prepared this way.[452] A review of phase-transfer catalysis in the HWE reaction has appeared.[454] Alumina,[455] KF supported on alumina,[455] magnesium oxide,[456] and zinc oxide[456] have been effective catalysts in the HWE reaction, and there are conditions that favor either HWE or Knoevenagel [e.g., $PhCH{=}C(CN)P(O)(OEt)_2$] products.[455,456] With water and magnesium oxide, the Knoevenagel reaction is suppressed; the addition of HMPA is beneficial in the zinc oxide example of the HWE reaction.[456] A barium hydroxide catalyst (C-200), in the presence of water, also promotes the HWE process to furnish high yields of *E* products rapidly.[457,458] Activated barium hydroxide, sonicated in an organic solvent (e.g., THF) with a small amount of water, is efficacious as well.[459] A gas–liquid process has been effected by passing vaporized carbonyl compound and phosphonate, under pressure, through a thermostated column of potassium carbonate.[460]

(*c*) *Polymer-Bound Phosphonates.* Polymer-bound HWE regents may offer advantages over the soluble reagents in cases where the products are water soluble and difficult to separate from the anionic phosphorus side product.[268] Phosphinate[461] and phosphonate[462] examples exist (**428a** and **428b**, respectively), the former



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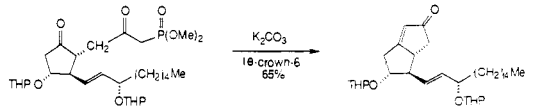
benefiting from polymer-reagent attachment by a P–C bond, which is less apt to cleave from the polymer relative to a more hydrolytically labile P–O linkage. The yields of products obtained with both reagents were not as high as those obtained with soluble phosphonates.

5. Intramolecular Reactions

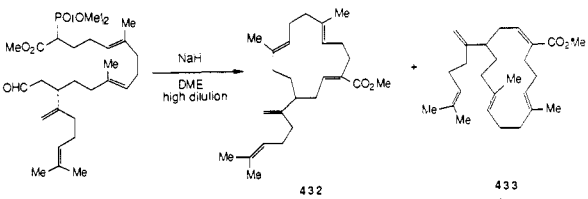
The intramolecular HWE reaction has become an indispensable means of cyclization, particularly for macrocyclic ring systems. A review covering intramolecular Wittig reactions, including those of phosphoranes and phosphoryl-stabilized carbanions, appeared in 1980.[267a] Although the HWE reaction had been used to prepare five- and six-membered rings early on,[15,267a] the first application to macrolide construction (a 16-membered-ring) appeared only as recently as 1978,[463] in a synthesis of vermiculine. Over the past 10 years, the popularity of the intramolecular version has burgeoned, to the point where it has been used to fashion rings containing 5,[240b,463-477] 6,[474,478-481] 12,[482] 13,[483] 14,[483-488] 15,[483,489-491] 16,[463,489,491-495] 18,[489] 20,[496] and 38[497,498] atoms. The diversity in the literature attests to the wide acceptance and general utility of this technique. In the synthesis of the larger ring sizes, often found in macrolides, high-dilution procedures (ca. 0.001 M[269a,494] or syringe pump[483,489]) have usually been required to achieve satisfactory yields. As an illustration of the sensitivity to concentration effects, a reaction that furnished 60% yield of 20-membered macrocycle at 1.4 mM was substantially diverted to dimer at 2.4 mM.[496]

The use of lithium bases in THF with ca. 1% HMPA was advanced as a reliable method for macrolide synthesis,[483] although the commonly employed sodium or potassium cations also provide good yields.[463,465,489] Cyclization has also been effected by mild base (DBU and LiCl)[441,486b,487,490,497] or crown ether catalysis.[239,396-398,465-467,473,482,484,494,495,497] The catalysis by crown ethers is an important discovery, which has proven crucial in some macrocyclizations.[465,466] For example, the use of 18-crown-6, introduced for intramolecular reactions by Aristoff et al.,[464] played an essential role in the conversion of ketone **429** to bicycle **430**, an intermediate in the synthesis of 6α-carbaprostaglandin I_2 (eq 65).[465]



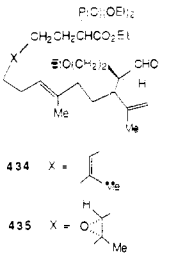
429 430 (65)

The geometry of the new double bond in intramolecular HWE reactions is usually *E*. However, in cases where large rings are being formed, one can often find considerable amounts of the *Z* isomer.[239,483,485,487-489] For example, HWE reaction of **431** produced mainly *Z* isomer **432**, with less of the (desired) *E* isomer **433** (eq 66).[485,488] The stereochemistry, as well as the ease, of



431 432 52% 433 24% (66)

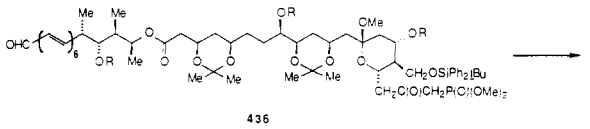
the intramolecular HWE reaction is largely determined by the nature of the carbon chain that forms the ring. By way of illustration, a 1:2 mixture of (*Z*)- and (*E*)-alkene isomers was formed on cyclization of **434**,[486a] whereas only *E* isomer was formed with **435** (61% yield).[486b] The macrocyclic *E* and *Z* stereoisomers are often easily separated by chromatography. In the synthesis of an 18-membered ring, a 1.5:1 ratio of *Z*/*E* isomers was obtained, whereas the undesired *E* isomer was the sole product of the analogous triphenyl-



434 X =

435 X =

phosphorane reaction.[239] Conformational restrictions imposed by sp^2 centers, appended rings, or other substituents often facilitate cyclization, enabling some extraordinary reactions. Polyene precursor **436** was smoothly cyclized to 38-membered product **437** (70–80% yield) in Nicolaou's synthesis of amphotericin B (eq 67).[497,498] This reaction was carried out by using



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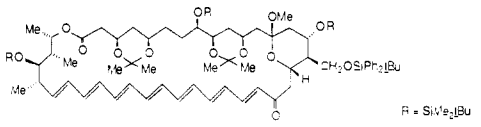
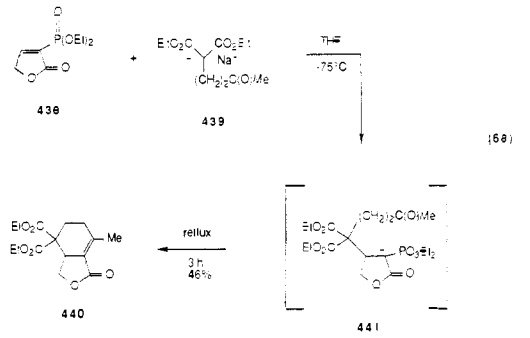


437

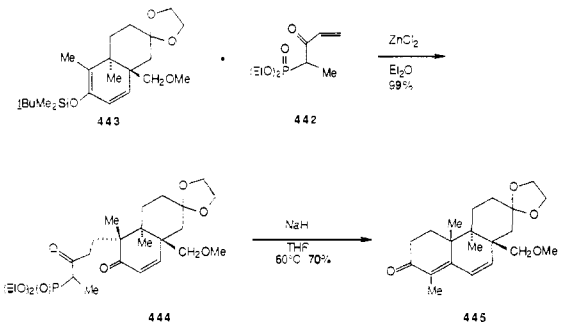
either potassium carbonate/18-crown-6 (in toluene at 0.001 M) or DBU/LiCl (in acetonitrile at 0.01 M). Nicolaou concluded that "the intramolecular keto phosphonate–aldehyde condensation reaction is a most powerful method for constructing macrorings".[498c]

Tandem Michael–HWE sequences provide a means of annulating rings onto existing ring systems. For example, treatment of vinylphosphonate **438** with anion **439** resulted in compound **440** through the intermediacy of phosphonate anion **441** (eq 68).[470] As an alternative



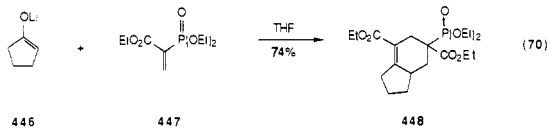
(68)

to the Robinson annulation, **442** was condensed with silyl enol ether **443** to yield **444**, which underwent intramolecular HWE reaction to **445** (eq 69).[478] Addition



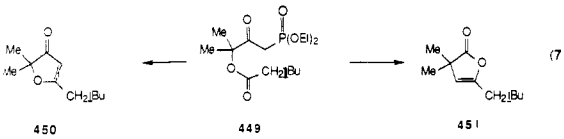
(69)

of two vinylphosphonate molecules in intramolecular cyclizations was observed with enolates, such as **446**, which attacked **447** (2.1 mol equiv) to yield bicyclic adduct **448** (eq 70).[471] The four-membered-ring product that would arise from cycloaddition of only one molecule of **447** to **446** was not formed, due to ring strain.



(70)

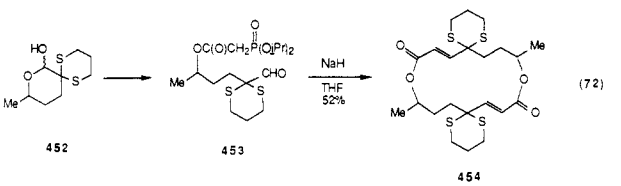
Intramolecular reaction of γ-acyloxy-β-keto phosphonates, such as **449**, produced either 3(2*H*)-dihydrofuranones (**450**) or 2(3*H*)-dihydrofuranones (**451**), depending on conditions (eq 71).[472,473] Compound **450**



(71)

emanated from an intramolecular HWE reaction of the ester functionality; **451** emanated from an unusual structural rearrangement. Treatment of **449** with potassium carbonate in DMF at 110 °C produced **450** in 47% yield.[472,473] Alternatively, when **449** was reacted with sodium hydride in DME and then refluxed, compound **451** was obtained in 59% yield.

Reaction of $(i\text{-PrO})_2P(O)CH_2CO_2Me$ with hemiacetal **452** under conditions of ester exchange (catalytic DMAP) resulted in the formation of phosphono aldehyde **453** (eq 72).[492] Macrocycle **454** was afforded upon dimerization of **453** under basic conditions.

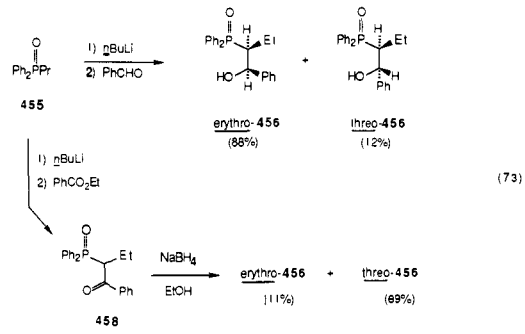


(72)

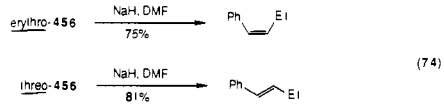
B. Phosphine Oxide Carbanions

A considerable body of work, chiefly by Warren and colleagues, has been conducted over the past 10 years on olefination with phosphine oxide stabilized carbanions. These studies have definitely elevated the status of the Horner reaction in the realm of synthetic chemistry. Horner's original recipe, entailing the one-step reaction of phosphine oxides, potassium *tert*-butoxide, and aldehydes or ketones,[280,281] was used to construct relatively simple alkenes. The disubstituted alkenes formed were stilbenes, presumably of the *E* configuration.[280,281,499] Horner also found that the presence of lithium ion permitted isolation of the intermediate β-hydroxy phosphine oxides,[280,281] and Warren's group has capitalized on these intermediate adducts (see below).

Warren and Buss prepared and separated diastereomeric β-hydroxy phosphine oxides (erythro/threo) by condensing alkyldiphenylphosphine oxides, such as **455**, with aldehydes (eq 73).[499] The relative stereochemistry of the erythro and threo adducts was unequivocally established in one case by an X-ray structure determination of an erythro isomer.[500] The ^1H NMR spectra

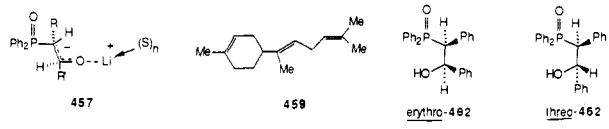


for each pair of diastereomers were distinctive, allowing for facile structure assignment.[500] These adducts have been decomposed stereospecifically, with few exceptions, to the corresponding alkenes via syn elimination of diphenylphosphinic acid (erythro → *Z* and threo → *E*; eq 74).[499,500] The phosphine oxide based approach



(Horner reaction) expands the HWE process to reagents that lack an α-stabilizing substituent. Advancements in methodology for controlling the erythro/threo ratio in the preparation of β-hydroxy phosphine oxides further enhances the utility of this technique.

In many reactions of nonstabilized phosphine oxide carbanions with aldehydes, erythro/threo ratios are not particularly biased toward one isomer; however, certain reaction conditions have been developed to obtain synthetically useful yields of erythro intermediate.[499,501] For example, an 88:12 mixture of *erythro*-**456** and *threo*-**456** was realized on treatment of **455** with *n*-butyllithium in THF with 1 mol equiv of tetramethylethylenediamine (TMEDA), followed by addition of benzaldehyde.[499] Nonpolar solvents resulted in poor selectivity, with *erythro*-**456** and *threo*-**456** being formed in nearly equal amounts.[499] Condensation at low temperature led to greater erythro selectivity. A series of different alkyldiphenylphosphine oxides and aldehydes were reacted to gather a detailed picture of the stereoselectivity in the reaction.[499] Typically, the erythro/threo ratios were 6:1, with the exception of the cyclohexyl cases (i.e., reactions of $Ph_2P(O)CH_2$-c-Hx or c-HxCHO), which were stereorandom. The erythro selectivity probably originates in a transition state resembling **457**, in which the solvent-stabilized oxido



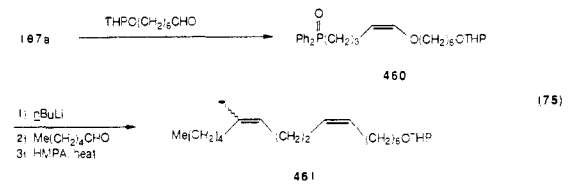
group is anti to the bulky diphenylphosphinyl moiety.[499] The cyclohexyl group, the largest substituent studied, could compete sterically with the diphenylphosphinyl moiety and destabilize this transition state.

Decomposition of β-hydroxy phosphine oxides **456** was best effected with sodium hydride in DMF, or KOH in DMSO (at 50 °C; eq 74).[499] The threo adducts supplied (*E*)-alkenes stereospecifically and in high yields, without exception. Conversely, erythro adducts have displayed variable stereospecificity. Whereas erythro adducts from alkyldiphenylphosphine oxides and aliphatic aldehydes decomposed to (*Z*)-alkenes stereospecifically, similar adducts involving aromatic aldehydes gave a small proportion (2–6%) of the *E* isomer. Moreover, benzyldiphenylphosphine oxides and aromatic aldehydes yielded considerable amounts of the *E* isomer, often in low yields. This loss of stereochemical integrity is an outgrowth of reversible dissociation of the phosphine oxide and aldehyde components from the β-oxido phosphine oxide intermediates.

Kauffmann and Kieper have shown that ortho substitution in diarylphosphine oxides leads to greater erythro/threo ratios on reaction with aldehydes.[502,503] A dramatic effect was evinced with $(o\text{-anisyl})_2P(O)\text{-}CHPr^-Li^+$, which reacted with benzaldehyde to give solely the erythro isomer.[502]

Since direct condensation methods favoring the threo isomer could not be identified, Warren and co-workers developed an alternative approach.[499,505] Acylation of phosphine oxide anions furnished α-keto phosphine oxides, which were reduced with different agents, including sodium borohydride, to yield predominantly threo β-hydroxy phosphine oxides. For example, benzoylation of the anion from **455** produced **458**, which was reduced to a threo-rich mixture of β-hydroxy phosphine oxides (*erythro*-**456**/*threo*-**456** = 11:89).[499] Alternatively, β-keto phosphine oxides, such as **458**, were obtained by oxidation of erythro β-hydroxy phosphine oxides (or erythro and threo mixtures) and reduced to threo salts, which were decomposed to (*E*)-alkenes. It is interesting to note that keto diphenylphosphine oxides (e.g., **458**) can be elaborated by alkylation with a variety of alkyl halides or Michael acceptors into more complex synthons; however, they do not react with carbonyl compounds to furnish enones.[506]

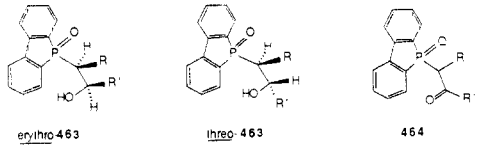
The utility of these indirect methods has been demonstrated by the stereoselective synthesis of alkene natural products.[507] A 1:11 mixture of (*Z*)/(*E*)-alkenes was prepared by the acylation/reduction sequence in the synthesis of a portion of dihydrocompactin;[508] this sequence has also found application in the synthesis of oudemansin A and B.[509] (*E*)-Isosaffrole, (*E*)-anethole, and feniculin have been made in an analogous fashion.[505,507] Trisubstituted alkenes were synthesized stereospecifically by reaction of branched phosphine oxides such as $Ph_2P(O)CH(Me)CH_2CH_2Ph$ with aldehydes or by treatment of phosphine oxides such as **455** with ketones.[507,510] Although the latter approach was utilized to obtain (*Z*)-α-bisabolene (**459**), it was not generally viable because of instability of the intermediate β-hydroxy phosphine oxides. The first approach, coupling of branched phosphine oxides with aldehydes, worked quite well; however, the initial reaction was stereorandom and isomer separation required chromatography.[507,510] An α-branched phosphine oxide was coupled with an aldehyde as a key step in the Merck group's synthesis of the immunosuppressant (-)-FK-506.[511] The two diastereomeric hydroxy phosphine oxides were obtained in a 1:1 ratio (77% overall yield) and separated by chromatography.[511] The sensitivity of the condensation step to reaction conditions can be exploited when a random mixture of alkenes is desired. For example, reaction of **460** (from cyclic phosphorane **187a**) with valeraldehyde gave the desired 1:1 mixture of (*Z*,*Z*)- and (*Z*,*E*)-**461** (en route to gossyplure) by employing THF/ether (1:1) as solvent (eq 75).[194a] Phos-



phorane **187a** was also reacted with heptanal, and the resulting phosphine oxide sulfenylated with dimethyl disulfide, to produce an α-methylthio phosphine oxide (see section II.B.1.e). Phosphorane **187b** was used in a two-step Horner–Wittig sequence.[194b]

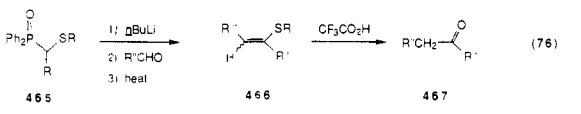
Diastereomerically homogeneous *erythro*-**462** and *threo*-**462** were subjected to crossover and fragmentation experiments.[512] Base-induced decomposition of *threo*-**462** under a variety of conditions gave only (*E*)-stilbene. In marked contrast, *erythro*-**462** decomposed with poor selectivity, typically giving mostly (*E*)-stilbene. The reluctance to form (*Z*)-stilbene is similar to analogous results in the phosphonate series discussed earlier[401] (section III.A.3.d). The stereomutation in the phosphine oxide case was attributed to reversion to benzaldehyde and benzyldiphenylphosphine oxide, the latter being characterized in the reaction mixture.[512] Considerable crossover was detected when *p*-chlorobenzaldehyde was added, again pointing to reversibility of the anion from *erythro*-**462**. Decomposition of *erythro*-**462** with DBU was the best method of preparing (*Z*)-stilbene, although benzyldiphenylphosphine oxide was still formed.[512]

Decomposition of *erythro*-**463** (R = R′ = Ph) with DBU gave (*Z*)-stilbene exclusively in 93% yield.[513] Even under conditions where *erythro*-**462** had decomposed to give mostly (*E*)-stilbene (NaH, DMSO), *erythro*-**463** (R = R′ = Ph) fragmented to an 89:11 mixture of (*Z*)/(*E*)-stilbenes (91% yield).[513] A good measure of selectivity is available in the reduction of α-keto phosphine oxides **464** to furnish mainly *erythro*-**463** or *threo*-**463**.[514] With sodium borohydride, reduction of

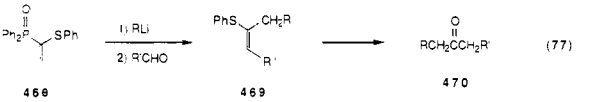


464 [R = Me, R′ = 3,4-(methylenedioxy)phenyl] proceeded with the usual threo selectivity to a 15:85 mixture of erythro/threo adducts.[514] Alternatively, the addition of $CeCl_3$ to the sodium borohydride resulted in an 85:15 mixture of erythro/threo diastereomers, possibly due to chelation control. This reversal of stereoselectivity was much diminished in reductions of $Ph_2P(O)CHRC(O)R'$, as steric interactions of the relatively more mobile phenyl substituents may have destabilized any chelate structure.[514]

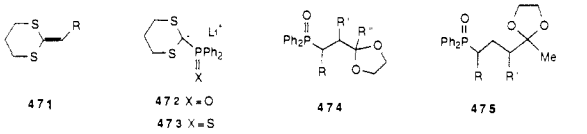
Sulfenylated phosphine oxides **465** have been developed by Warren and co-workers as acyl anion equivalents.[515–517] Reaction of **465** with carbonyl compounds gave vinyl sulfides **466**, which were then hydrolyzed to ketones **467** (eq 76).[515] This process was



a key aspect of a three-component synthesis of ketones in which vinylphosphine oxide **468** was alkylated by a Michael reaction and treated with a carbonyl compound to produce vinyl sulfide **469**, which was hydrolyzed to ketone **470** (eq 77).[516,517]

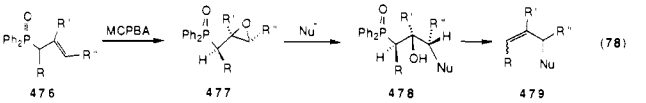


Reagent **472** combined with aldehydes and ketones to give ketene dithioacetals **471**.[518] The diminished reactivity of thiophosphoryl reagent **473** was attributed partly to the greater apicophilicity of oxygen relative to sulfur in the trigonal-bipyramidal oxaphosphetane intermediate.[518]

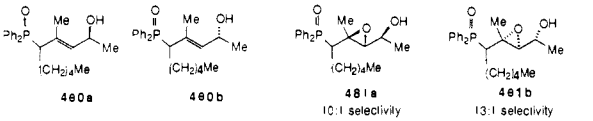


β,γ-[519,520] or γ,δ-unsaturated[521,522] ketones were synthesized with reagents **474** and **475**, respectively. Reaction of anions of **474**, however, displayed poor stereoselectivity, and the diastereomers were difficult to separate;[519] each case was analyzed on an individual basis. Compound **475** rendered greater stereoselectivity in the Horner reaction. Once again, erythro adducts were typically favored in the direct condensation, and threo adducts were favored by the reduction of α-keto phosphine oxides.[521,522]

Epoxidation of allylphosphine oxides **476** proceeded in a highly stereoselective manner (eq 78).[523] The

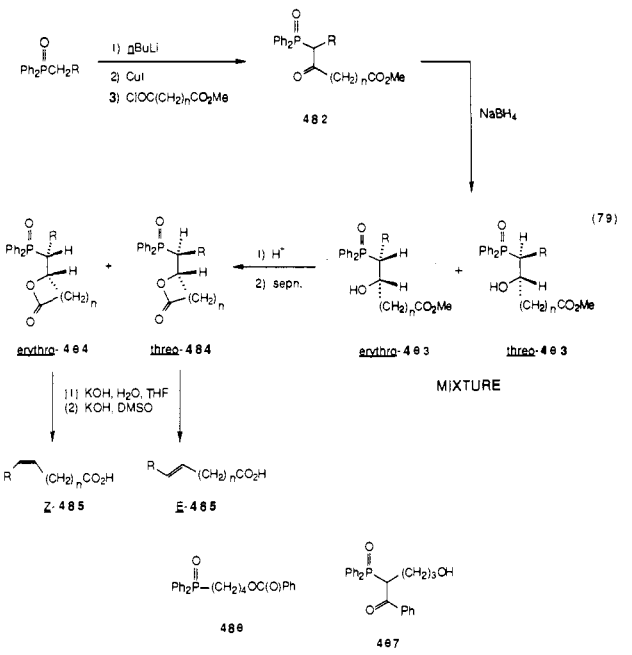


diphenylphosphinyl group introduced sufficient A(1,3) strain to direct MCPBA addition from the opposite face of the carbon–carbon double bond. Epoxides **477** were opened by sulfur nucleophiles (generically "Nu") to yield β-hydroxy phosphine oxides **478** (eq 78). Alkenes **479** were released on decomposition of **478**.[524,525] Epoxidation can also be directed by an allylic hydroxyl group, which overrides the steric encumbrance of the diphenylphosphinyl group. For example, there was >10:1 selectivity in hydroxy-directed MCPBA epoxidations of **480a** and **480b** to **481a** and **481b**, respectively (71 and 87% yields).[524,525]

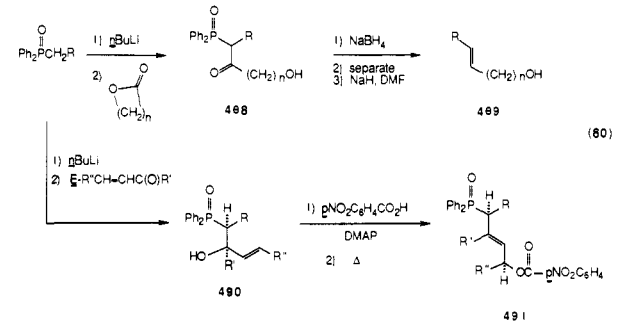


The Horner reaction with $Ph_2P(O)(CH_2)_4COOH$ did not give the predicted unsaturated acids, in contrast to the analogous phosphonium salt.[526] As an alternative, Levin and Warren reduced α-keto phosphine oxides **482** with sodium borohydride to a mixture of *erythro*- and *threo*-**483**, which were converted into **484** and the lactone isomers were separated; treatment with base then delivered (*Z*)- and (*E*)-**485** (eq 79).[526,527] The reduction of **482** was only mildly threo-selective, although the selectivity was chain length dependent, becoming more pronounced as the chain was extended (*n* varied from 2 to 4).[526]

The Horner reaction has been used for the synthesis of alkenols.[528–532] Esters such as **486** underwent trans-



acylation on treatment with base (e.g., LDA; eq 80). Reduction of **487** occurred with mild threo diastereoselectivity.[528,529] Alternatively, alkenols were created by a scheme beginning with phosphine oxide opening of cyclic lactones. The resulting compounds, **488**, were reduced with threo selectivity and decomposed as before, yielding **489**. Condensation of a phosphine oxide



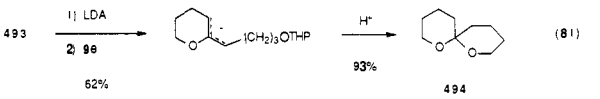
carbanion with an α,β-unsaturated ketone or aldehyde resulted in β-hydroxy phosphine oxides with the usual erythro selectivity (e.g., **490**).[531,532] Conversion to the *p*-nitrobenzoate was followed by a thermal rearrangement to allylically transposed product, **491**.[532] Under these conditions, there was >95% stereospecificity in the rearrangement of the allyl group, starting from either the erythro or threo isomer.[532]

Allylamides and allylamines were obtained from β-amidoalkyl and β-aminoalkyl phosphine oxides, respectively.[533-535] β-Aminoalkyl phosphine oxides arose from Michael-type addition of an amine to $Ph_2P(O)CH{=}CH_2$; β elimination of the nitrogen on forming phosphine oxide anions was not a significant problem.[535]

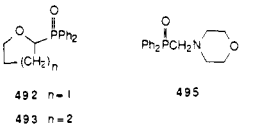
Allylphosphine oxides have been used to prepare dienes and polyenes.[279a,b,356a,536-541] There are some advantages associated with these reagents relative to the allylic phosphoranes: (1) the *E* isomer predominates in the new double bond, (2) erythro intermediates can be isolated and purified to furnish pure (*Z*)-alkenes, and (3) double-bond stereomutation is less likely.[536,539] Occasionally the synthesis of polyenes by the Horner reaction is accompanied by low yields and undesired stereomutation about some of the present double bonds.[536] In the synthesis of milbemycin β_3, Smith and co-workers found that the proper choice of base counterion was essential in controlling the stereochemistry of the new bond.[537a] The use of a sodium counterion led to a 1:7 *Z*/*E* ratio (85–95% yield), whereas substitution with potassium gave a 2:3 *Z*/*E* ratio (74% yield).[537a] The lithio derivatives of $Ph_2P(O)CH(Me)CH{=}CH_2$ and $Ph_2P(O)CH_2CH{=}CH_2$ added to aldehydes with high *E* selectivity (typically >84% *E*);[279a,b] a 1:4 *Z*/*E* ratio was observed in a recent study.[537b]

Reagent $Ph_2P(O)CHPh^-Li^+$ only gave the (*E*)-alkene on treatment with an α-methoxy-substituted aldehyde.[181a] Alternatively, the correspondent α-phenyl-α-keto phosphine oxide was reduced with the expected threo selectivity.[181a] Surprisingly, the threo salts decomposed directly to (*E*)-alkene upon hydride reduction; the β-hydroxy phosphine oxide was isolated when diisobutylaluminum hydride was the reducing agent.[181a]

Enol ethers are easily obtained by the Horner reaction.[542-548] For example, reaction of $Ph_2P(O)CHOMe^-Li^+$ with aldehydes and ketones, which was not stereoselective, was followed by separation of the diastereomeric β-hydroxy phosphine oxides.[542] Independent decomposition of these diastereomers led to pure (*Z*)- and (*E*)-enol ethers.[542] The use of titanium allowed for α addition in the reaction of α-methoxy alkylphosphine oxide carbanions.[545] The resultant diastereomeric β-hydroxy phosphine oxides were separately decomposed to stereoisomeric 2-methoxy dienes.[545] Enol ethers derived from cyclic phosphine oxides **492** and **493** have been converted into spiro ketals such as **494** (eq 81).[546-549] van der Gen demonstrated the utility



of $Ph_2P(O)CH(OR)_2$ for preparing $R'R''C{=}C(OR)_2$ derivatives (45–90% yields); the initial condensation had to be carried out at below −90 °C due to thermal instability of the phosphine oxide component.[550]

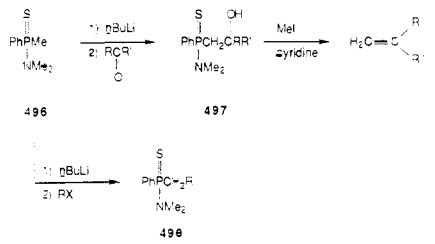


Enamines were produced on reaction of **495** with aromatic and aliphatic aldehydes (72–99%).[551] On the other hand, ketones were fairly unsatisfactory carbonyl components with the α anion of **495**, due to competing enolate formation. To overcome this problem, reagent $Ph_2P(O)CH_2NMePh$ was introduced.[552] The anion from this phosphine oxide is less basic than the corresponding species from **495**, so high yields were realized with ketones (80–92%).[552]

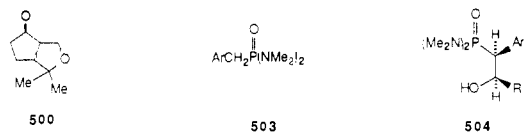
In the course of examining phosphine oxide derived carbanions by NMR, Seyden-Penne and colleagues studied $Ph_2P(O)CH_2CO_2Me$ and $Ph_2P(O)CH(Me)CO_2Me$.[553] Both are *E*-selective with benzaldehyde and isobutyraldehyde, although a potassium base is required for *E* selectivity in the reaction of the second reagent with isobutyraldehyde.[553] In contrast, the analogous phosphonate reagent is not stereoselective in reactions with isobutyraldehyde.[553] By the same token, $Ph_2P(O)CH_2CN$ is more *E*-selective than its phosphonate counterpart.[377]

C. Other Phosphoryl and Thiophosphoryl Carbanions

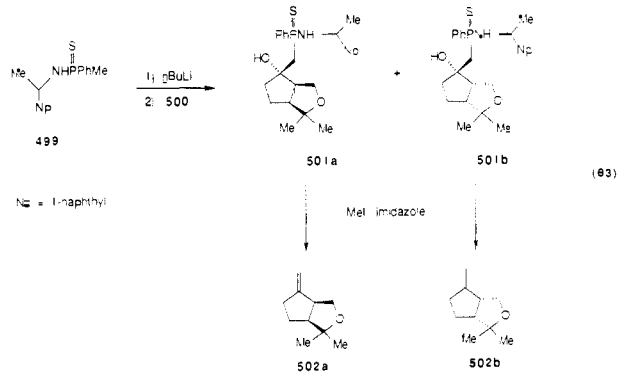
Johnson and Elliot showed that phosphinothioic amide **496** reacts with carbonyl compounds to give stable β-hydroxy adducts **497**, which decompose to alkenes on treatment with methyl iodide and pyridine (eq 82).[554]



Compound **496** could also be alkylated to provide other olefination reagents (e.g., **498**) suitable for preparing tri- and tetrasubstituted alkenes.[554] Since the anion from **496** is more reactive than $Ph_3P{=}CH_2$, it provides an alternative reagent for methylenation of poorly reactive carbonyl compounds. The dianion of phosphinothioic amide **499**, which was resolved with regard to the phosphorus stereocenter, reacted with ketone **500** to

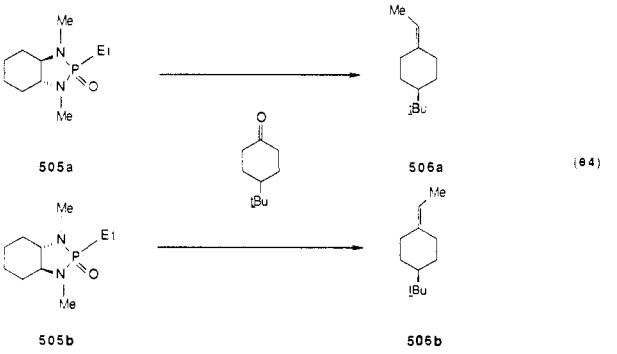


furnish readily separable diastereomers **501a** and **501b** (eq 83). These products were then converted to the two antipodes of hop ether, viz., **502a** and **502b**.[555] This asymmetric synthesis provides a novel means of resolution amidst ketone olefination.[555]



The reaction of the lithium salt of phosphonic diamides **503** with aldehydes was well controlled to give only erythro adducts (**504**).[556a] Highly stereoselective decomposition of **504** produced only (*Z*)-alkenes.[556a] An acid-catalyzed decomposition of **504** to alkenes was also conducted, but the reaction was not stereoselective.[556a] The reaction of $(Me_2N)_2P(O)CH(Me)CN$ with aldehydes was studied by Seyden-Penne and co-workers.[336] Generally, mixtures of *Z* and *E* isomers were obtained, with more of the *E* isomer being formed with Li^+ compared to K^+ (45–88% *E* with Li^+).[336] In a different study, phosphine imines (e.g. $EtPh_2P{=}NPh$) were metalated and reacted with several different aldehydes, resulting in >98:2 erythro:threo selectivity.[556b]

In a remarkable development, Hanessian and colleagues designed and prepared two chiral phosphonic diamides, **505a** (*R,R*) and **505b** (*S,S*).[557,558] These react with the two prochiral faces of substituted cyclohexanones with high diastereoselectivity (eq 84). For



example, reaction of **505a** with 4-*tert*-butylcyclohexanone gave a 95:5 mixture of (*R*)-alkene (**506a**) and (*S*)-alkene (**506b**), whereas reaction of **505b** gave a 5:95 mixture of **506a** and **506b**. Reversibility of hydroxy phosphonamides does not account for the high diastereoselectivity, insofar as alkylation of **505a** and **505b** with alkyl halides (irreversible) produces >80% yields of single, unique diastereomers.[557] This result is similar to the equal but opposite stereocontrol engendered by antipodes of 8-phenylneomenthyl phosphonates as HWE reagents (section III.A.3.b.ii).[345,346]

IV. Concluding Remarks

A. Phosphonium Ylides

The Wittig olefination reaction has found widespread prominence in organic synthesis. Perhaps, this is the case because it has been employed, at one time or another, by nearly every practicing organic chemist. The popularity of this reaction emanates from its simplicity, convenience, efficiency, and versatility, notwithstanding the stereocontrol available under certain circumstances.

To be sure, there has been a mystique associated with the high preference for the contrathermodynamic (*Z*)-alkene in reactions of triphenylphosphorus nonstabilized ylides and aldehydes. This phenomenon has captured the curiosity of chemists for decades, resulting in various attempts to arrive at a satisfying mechanistic explanation. Significant progress toward an understanding has been achieved particularly within the past 10 years. Indeed, the recent transition-state model proposed by Vedejs[34b,c] constitutes a prominent advance in this direction.

In our work, a curious stereochemical finding in the reaction of carboxylate ylide **18** and benzaldehyde induced a systematic study of Wittig reactions involving ylides with nucleophilic groups. For reactions between nonstabilized triphenylphosphorus ylides bearing anionic groups and aldehydes, the extent of anomalous *E* stereoselectivity strongly depended on the type of anionic substituent and the distance between the ylidic and anionic centers. This investigation afforded a series of revelations that culminated in the observation and quantitation of diastereomeric oxaphosphetane intermediates in reactions of nonstabilized phosphorus ylides at low temperature, which, in turn, spurred us to investigate "stereochemical drift", "diastereomeric synergism", and an unexpected concentration dependency in such Wittig reactions. Consequently, we performed the first detailed rate studies with nonstabilized phosphorus ylides, which enabled characteriza-

tion of the different stages of that type of Wittig reaction. Stereochemical drift was attributed largely to the faster rate of reversal of cis oxaphosphetane to ylide and aldehyde, relative to trans oxaphosphetane. Also, a sizable portion of the excess *E* stereoselectivity observed with a trialkylphosphorus ylide and ylides bearing anionic groups was associated with thermodynamic control via reaction reversal (i.e., "retro-Wittig" reaction).

Wittig reactions that experience a significant measure of thermodynamic control are the exception rather than the rule. Our studies and those of the Vedejs group have served to pinpoint those cases that involve thermodynamic control. Of special note is the recent progress made by Vedejs on reactions of stabilized and semistabilized ylides, in which kinetic control was found to be predominant.[34c,40] Deprotonation studies with appropriate β-hydroxy phosphonium salts have been very useful here,[34c,40] but further gains might surface from attempts to stabilize oxaphosphetane intermediates by a judicious choice of substituents (e.g., CF_3 or C_6F_5 on carbon; $Me_2NC_6H_4$ or $C_6H_4O^-$ on phosphorus). In this vein, Vedejs successfully employed the dibenzophosphole group to study oxaphosphetanes derived from semistabilized ylides.[34c]

What directions might be taken in the future? It would be exciting to determine the rate constants for condensation of nonstabilized triphenylphosphorus ylides and aldehydes (k_1 and k_2 in eq 7). Although this step appears to be exceedingly fast, even at depressed temperatures, it might be measured by using a rapid kinetics technique. For example, one can imagine generating an aldehyde by pulse irradiating an inert precursor masked by a photoremovable group in the presence of an ylide and then monitoring the decay of reactants with a pulse from a laser (thereby obtaining a value for $k_1 + k_2$).

An area that has not been explored, to our knowledge, is Wittig reactions in the gas phase. By using distilled ylides and a high-vacuum reactor, it may be possible to conduct gas-phase reactions and compare their stereochemistry with that of reactions in solution phase. Thus, one might find differences between the two reaction types that may relate to solvation phenomena. Also, if a means for obtaining rate data from gas-phase reactions could be devised, then free energy values for such reactions could be related to those from the ab initio calculations.

The intimate studies of Wittig reactions at low temperature have focused, for the most part, on aldehyde rather than ketone substrates. Moreover, the large body of stereochemical data for Wittig reactions is heavily weighted in favor of aldehydes. Nevertheless, intriguing stereocontrol has been reported for some ketones, such as those bearing Me_3Si, CF_3, or α-alkoxyalkyl substituents, as mentioned in sections II.B.1.a–d. Systematic investigations of these and other ketone substrates would certainly be recommended for the future.

Careful investigation of ylides bearing anionic groups provided some thought-provoking stereochemical results. By the same token, the reaction of ylides with carbonyl compounds bearing anionic substituents may also afford some unusual stereochemistry. Given the smattering of anomalous stereochemical results already documented in this area (section II.B.1.d), a systematic, in-depth study would be worthwhile.

Additionally, the intriguing anomalous *Z* stereochemistry arising from the reaction of ester-stabilized ylides with aldehydes bearing proximate ether substituents (section II.B.1.c) beckons for continued examination. In the polar, protic solvents where *Z* selectivity is maximized, a solvent-associated transition-state model may be appropriate. Further work is needed to furnish a clearer understanding in this area.

B. Phosphoryl-Stabilized Carbanions

Olefination reactions based on phosphonate, phosphine oxide, and related carbanions can demonstrate synthetic advantages over phosphonium ylide reagents. As such, the phosphoryl reagents serve a complementary purpose in organic synthesis and have been widely employed.

The degree of reversibility in the HWE reaction is poorly understood at the moment. For example, do the bis(trifluoroethyl) phosphonate reagents (section III.A.3.b) generate (*Z*)-alkenes because equilibration of intermediates is suppressed or because there are other factors (e.g., electronic) that bear on pure kinetic selectivity?

Can the use of phosphonate carbanions be extended to a one-pot procedure for nonstabilized reagents, perhaps by an appropriate choice of reaction conditions or phosphonate ester substituents?

The phosphine oxides are attractive reagents, and high stereoselectivity can be achieved; however, the intermediate β-hydroxy phosphine oxides usually have to be isolated and purified prior to their stereospecific decomposition to alkenes. One-step or one-pot Horner–Wittig procedures that could give essentially pure (*Z*)- and (*E*)-alkenes would be a useful improvement.

Olefinations that embody phosphorus reagents with inherent asymmetry should offer a fertile area for future research. Reagents may be tailored specifically to produce geometrical isomers, as directed by remote stereogenic centers. The results of Hanessian afford a striking prelude to this approach.[557] An understanding of the topological interactions between the carbanion and carbonyl components in such asymmetric syntheses would be a welcome advance.

V. Acknowledgments

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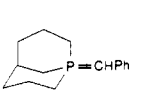
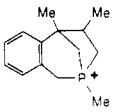


i



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(80) (a) For lithium salt Wittig reactions, such as this, there is a dramatic concentration dependency in THF, which leads to an increase of *cis*-oxaphosphetane and (*Z*)-alkene at lower concentrations.[32] Some differences between (*Z*)/(*E*)-alkene ratios in ref 28 and 65a relate to this issue. (b) Low-temperature oxaphosphetane ratios for reactions of anionic ylides were also variable because of problems with timing of the NMR measurements, temperature control, and precipitate formation.
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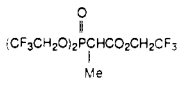

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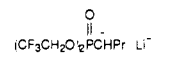

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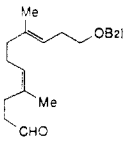
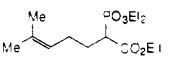


v



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