627-49-6; $Me_2NPCl_2$, 683-85-2; tetraethylphosphonium chloride, 7368-65-2; tetrabutylphosphonium chloride, 2304-30-5; 5*H*-dibenzophosphole, 244-87-1; *P*-phenyldibenzophosphole, 1088-00-2; *P*-ethyl-*P*-phenyldibenzophospholium iodide, 113686-87-6; *P*-ethyldibenzophosphole, 16523-77-6; *P,P*-diethyldibenzophospholium iodide, 113460-10-9; *P*-ethyl-*P*-(dimethylamino)dibenzophospholium iodide, 113686-88-7; *P*-ethyl-*P*-(dimethylamino)iodo dibenzophosphorane, 113687-05-1; 2,2′-dibromobiphenyl, 13029-09-9.

# Mechanism of the Wittig Reaction: The Role of Substituents at Phosphorus

**E. Vedejs* and C. F. Marth**

*Contribution from the S. M. McElvain Laboratory of Organic Chemistry, Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706.* *Received July 29, 1987*

**Abstract:** The variation in Wittig reaction stereochemistry is attributed to dominant kinetic control in nearly all cases. Formation of cis or trans oxaphosphetanes is the decisive step, and this occurs by an asynchronous cycloaddition. An interplay of 1,2 and 1,3 steric interactions decides which diastereomeric oxaphosphetane will be favored. For $Ph_3P{=}CHCH_3$, the best transition state is the puckered four-center arrangement **2a** having a pseudoequatorial aldehyde alkyl group R′ and pseudoaxial α-methyl. This geometry results from the unusual steric consequences associated with having an $sp^3$-hybridized atom (phosphorus) as one of the reacting centers in a cycloaddition process and is increasingly favored when R′ is bulky. A trend toward the trans diastereomer **5** occurs if the nearest phosphorus ligand can orient a compact face toward the aldehyde, or if the aldehyde R′ group has at least one α-hydrogen. These conditions are satisfied in the exceptionally trans selective ylide **10**, even for tertiary aldehydes, as a result of bond angle preferences and geometric constraints due to the 5-membered ring. In contrast, **7** is constrained to react via the cis-selective puckered geometry and affords exclusively the *Z* alkene. Nonstabilized or "moderated" ylide reactions involve early transition states having phosphorus in a distorted square-pyramidal geometry. Stabilized ylides react via a productlike geometry, and kinetic trans selectivity is easily understood on the basis of oxaphosphetane-like steric interactions.

We have reported several striking examples of contrasting kinetic cis/trans selectivity in the Wittig step leading to oxaphosphetanes.[1-3] The steric factors that control selectivity will now be considered, together with an overall mechanistic interpretation of the Wittig reaction. The discussion is based on a number of experimental observations summarized under the generalizations in Table I. Most of this information is recent and comes from the accompanying paper[1] or from related studies by Maryanoff et al.[5] The rest is included to facilitate the evaluation of mechanistic proposals in this paper and elsewhere. (See Table I.)

**Background.** The old ionic mechanism (betaine intermediates assumed) for the Wittig reaction was proposed on the basis of reasonable analogy and the limited experimental evidence available at the time regarding Wittig intermediates.[14a] However, the two-step mechanism is difficult to reconcile with generalizations 1, 3, and 5, as well as with the results of recent theoretical investigations,[15] or with the absence of substantial solvent effects on cis/trans selectivity in the reactions of nonstabilized ylides.[6]

The alternative mechanistic category involves asynchronous cycloadditions. The first recognizable depiction of a four-center addition process (involving $Ph_3P{=}CPh_2$ and a carbonyl group of ketenes or isocyanates) was published by Staudinger and Meyer and predates the betaine mechanism by more than 30 years.[16] Much later, a cycloaddition process was proposed for the reactions of stabilized ylides + aldehydes, based on the results of kinetic studies.[17] Details of stereochemistry or transition-state geometry were not discussed in this work. The notion that a four-center transition state could explain kinetic selectivity for cis-disubstituted oxaphosphetanes first appeared in the communication that also described the detection of oxaphosphetanes (1973).[18] The most important feature of the proposed geometry was the nonplanar arrangement of ylide and aldehyde π-systems. A subsequent full

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(2) Vedejs, E.; Marth, C. *Tetrahedron Lett.* **1987**, *28*, 3445.
(3) Vedejs, E.; Huang, W. F. *J. Org. Chem.* **1984**, *49*, 210. Kinetic selectivity has now been proved for salt-free conditions (ref 4).
(4) Vedejs, E.; Fleck, T., unpublished results.
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(7) Schlosser, M.; Christmann, K. F. *Justus Liebigs Ann. Chem.* **1967**, *708*, 1. For recent refinements in stereocontrol, see: Schaub, B.; Jeganathan, S.; Schlosser, M. *Chimia* **1986**, *40*, 246.
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(9) Vedejs, E.; Fleck, T.; Hara, S. *J. Org. Chem.* **1987**, *52*, 4637.
(10) (a) Vedejs, E.; Snoble, K. A. J.; Fuchs, P. L. *J. Org. Chem.* **1973**, *38*, 1178. (b) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822. (c) α-branched example: Crouse, G. D.; Paquette, L. A. *J. Org. Chem.* **1981**, *46*, 4272.
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(12) Anderson, R. J.; Henrick, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327. $Li^+$ present may obscure oxaphosphetane stability issues in this case.
(13) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 650. Schlosser, M.; Christmann, F. K.; Piskala, A.; Coffinet, D. *Synthesis* **1971**, 29. Schlosser, M.; Tuong, H. B.; Schaub, B. *Tetrahedron Lett.* **1985**, *26*, 311. $Li^+$ may obscure oxaphosphetane stability in these examples.
(14) (a) Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *87*, 1318. Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654. Trippett, S. *Q. Rev., Chem. Soc.* **1963**, *17*, 406. Maercker, A. *Org. React. (N.Y.)* **1965**, *14*, 270. Johnson, A. W. *Ylide Chemistry*; Academic: New York, 1966. Reucroft, J.; Sammes, P. G. *Q. Rev., Chem. Soc.* **1971**, *25*, 135. Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (b) McEwen, W. E.; Beaver, B. D. *Phosphorus Sulfur* **1985**, *24*, 259.
(15) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1987**, *109*, 1.
(16) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
(17) Froyen, P. *Acta Chem. Scand.* **1972**, *26*, 2163. Aksnes, G.; Khalil, F. Y. *Phosphorus Relat. Group V Elem.* **1973**, *3*, 37 and 79. Giese, B.; Schoch, J.; Ruchardt, C. *Chem. Ber.* **1978**, *111*, 1395.
(18) Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778.

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**Table I.** Mechanistic Generalizations in the Wittig Reaction

| generalization | exceptions | insufficient data |
|---|---|---|
| (1) salt-free betaines or any other ionic intermediates cannot be detected[6] | none | |
| (2) oxaphosphetanes are the initial intermediates (low-temperature, salt-free conditions)[6] | none | moderated or stabilized ylides[3,5] |
| (3) salt-free Wittig reactions are not reversible; olefins are formed under kinetic control[1] | aromatic aldehydes, dependent on ylide substituents and conditions[5-8] | branched ylides; α-monosubstituted aldehydes |
| (a) ylides + $RCH_2CHO$ or $R_2CHCHO$($Ph_3P{=}CHCH_3$, $Ph_2EtP{=}CHCH_3$, $Bu_3P{=}CHC_3H_7$, $Ph_2CH_3P{=}CHC_6H_5$, [Et]DBP=$CHCH_3$, $Ph_2CH_3P{=}CHCO_2C_2H_5$, etc)[1,5,9,10] | | branched ylides, α-monosubstituted aldehydes |
| (b) ylides + $R_3CCHO$ ($Ph_3P{=}CHCH_3$, $Ph_2EtP{=}CHCH_3$, [Et]DBP=$CHCH_3$, etc.)[1,5] | $Et_3P{=}CHCH_3$ + $R_3CCHO$;[1] $Bu_3P{=}CHC_3H_7$ + $R_3CCHO$[5] | moderated or stabilized ylides |
| (4) reversal in the exceptional cases is restricted to cis-disubstituted oxaphosphetanes[1,5] | none | stabilized ylides[9] |
| (5) cis-disubstituted oxaphosphetanes decompose to alkenes faster than do the trans isomers[1,5] | none | |
| (6) for a given ylide, the kinetic % cis oxaphosphetane is higher for $R_3CCHO$ than for $R_2CHCHO$ or $RCH_2CHO$[1] | none | moderated, stabilized ylides |
| (7) oxaphosphetane decomposition occurs with stereochemistry corresponding to a "syn" cycloreversion[1,5,10] | none | |
| (8) trans-disubstituted oxaphosphetanes are strongly favored thermodynamically in cases of spontaneous or catalyzed equilibration[1,5,11,13] | none | moderated, stabilized ylides |

paper emphasized the steric advantages of nonplanar cycloaddition transition states for bulky reactants,[6] but there was no evidence to indicate the extent of phosphorus or carbon rehybridization, and these important issues were left open. The ambiguity regarding phosphorus and carbon geometry resulted in transition-state diagrams that have proven difficult to interpret. As alternative cycloaddition proposals began to appear,[19,20] the opportunity for at least a partial consensus seemed at hand. A paper from this laboratory proposed[3] that further refinements of transition-state geometry might agree to use trigonal-bipyramidal phosphorus geometry, as specified in the two other mechanistic rationales which had been developed in detail.[19,20] This would require relatively advanced transition states with extensive rehybridization at phosphorus and carbon. However, recent findings do not support an advanced transition state, and reevaluation of these proposals is necessary.

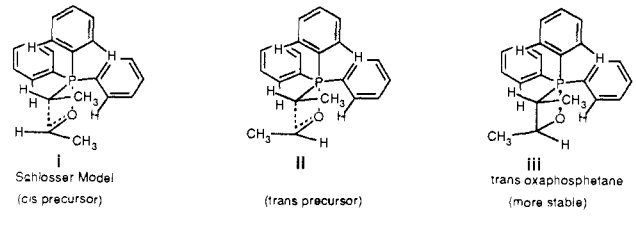
**The Case for an Early Transition State.** There are now several proven examples of partially reversible Wittig reactions.[1,5] In each case, the trans-disubstituted oxaphosphetane is strongly favored (generalization 8). Earlier, there had been a number of reports describing a connection between *E* olefin selectivity and equilibration in Wittig intermediates induced by the presence of alkoxide, or by other means.[11-13] These examples did not necessarily prove a thermodynamic preference for the trans-disubstituted oxaphosphetanes because there could have been a kinetic advantage for *E* olefin formation from the trans oxaphosphetane. However, this scenario has been disproved by recent studies (generalization 5): cis oxaphosphetanes decompose consistently faster.[1,5] It follows that trans-disubstituted oxaphosphetanes are more stable than the cis isomers. Therefore, the transition state for the reaction of aldehydes with cis-selective ylides such as $Ph_3P{=}CHCH_3$ cannot be productlike! If phosphorus rehybridization were relatively advanced, the transition state would have to feel the thermodynamic advantage of the trans oxaphosphetane. Since C–C bonding is advanced relative to P–O bonding, there is probably substantial pyramidalization at carbon, but phosphorus geometry must be close to tetrahedral.

To help visualize the relevant geometric factors, X-ray structures (Cambridge data files) of stable oxaphosphetanes[21] have been imported into the MACROMODEL program[22c] and modified to include representative alkyl groups at phosphorus in place of the stabilizing substituents. The structures have been converted into stereo plot files, and the three-dimensional representation (WIMP output) is shown in Figure 1. The examples illustrate the trapezoidal oxaphosphetane geometry and unusual bond angles that result from long P–O and P–C bonds. Also, these stereo diagrams indicate the severe crowding which is inherent in the cis-disubstituted oxaphosphetanes when a tertiary aldehyde group (*tert*-butyl) is present, even in the case where phosphorus has relatively compact methyl substituents. The trans isomer is clearly less congested, regardless of phosphorus substituents, and would be favored in a late transition state reaction. However, trans selectivity does not in any way assure a late transition state as will be shown shortly.

**The Case for a Nonplanar Transition State in the Cis-Selective Reaction.** In the following discussion, *E* or *Z* selectivity refers to empirical olefin geometry, while the terms "cis-selective" or "trans-selective" are reserved for oxaphosphetane geometry resulting from kinetic control. To aid visualization of the subtle interplay of steric factors, stereo drawings are used extensively (stereo viewer recommended) and the aldehyde substituents of R'CHO are represented with or without alkyl hydrogens, or in

(19) Bestmann, H. J.; Roth, K.; Wilhelm, E.; Eberhard, W.; Bohme, R.; Burzlaff, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 876. Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 85 and references therein.

(20) (a) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821. (b) The original paper (ref 20a, above) includes the following summary: "Although referring only to a transition state, model [i] suggests that also in the ground state a cis-disubstituted oxaphosphetane may be sterically less congested and hence thermodynamically more stable than its trans isomer. This appears to be the case indeed. Since it is actually the trans-disubstituted oxaphosphetane iii that is more stable (Table I), we believe that Schlosser et al. have underestimated the interactions between the aldehyde alkyl group and the ortho phenyl positions in i vs ii. The trans precursor transition state ii corresponding to the Schlosser geometry is productlike and should be more stable than i.




(21) Ul-Haque, M.; Caughlan, C. N.; Ramirez, F.; Pilot, J. F.; Smith, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 5229.

(22) (a) NMR studies: Albright, T. A.; Schweizer, E. E. *J. Org. Chem.* **1976**, *41*, 1168. Ostoja Starzewski, K. A.; Tom Dieck, H. *Phosphorus Relat. Group V Elem.* **1976**, *6*, 177. Albright, T. A.; Gordon, M. D.; Freeman, W. J.; Schweizer, E. E. *J. Am. Chem. Soc.* **1976**, *98*, 6249. Schmidbaur, H.; Tronich, W. *Chem. Ber.* **1968**, *101*, 3556. X-ray studies: Bart, J. C. J. *J. Chem. Soc. B* **1969**, 350. Schmidbaur, H.; Schier, A. S.; Frazao, C. M. F.; Muller, G. *J. Am. Chem. Soc.* **1986**, *108*, 976 and references therein. (b) For a theoretical treatment, see: Bestmann, H. J.; Kos, A. J.; Witzgall, K.; Schleyer, P. v. R. *Chem. Ber.* **1986**, *119*, 1331. (c) The programs were kindly provided by Prof. W. C. Still (MACROMODEL) and Prof. K. Steliou (MODEL).

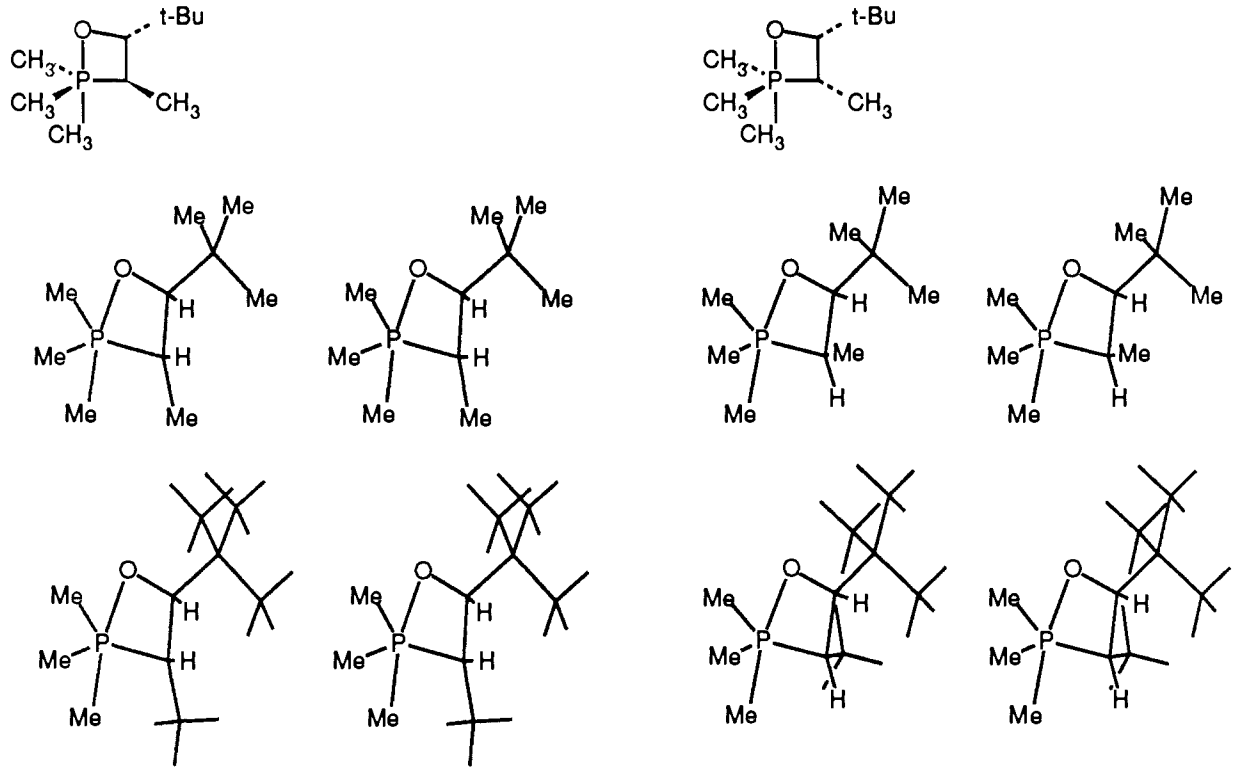


**Figure 1.** Oxaphosphetane geometry (use stereo viewer or direct visual technique: focus eyes 50 cm away; insert figure ca. 35 cm away and refocus eyes slightly until images overlap.

abbreviated form where three-dimensional issues are less important. This technique allows realistic illustration of transition-state proposals and is *not* to be interpreted as molecular mechanics or modeling. Bond angle designations are based on the oxaphosphetane as indicated at the top of Figure 2; angles labeled $B_3$ or $B_4$ refer to developing basal bonds, while bond angles to the eventual apical carbon are labeled $A_1$ or $A_2$. The discussion begins with the behavior of salt-free ylides.

Given that the cis-selective Wittig transition state is a cycloaddition process,[6,15,18-20] the simplest geometry would be a planar four-center arrangement for the carbonyl and ylide P=C bonds. Recent theoretical considerations are consistent with a planar geometry, but they do not evaluate the steric effects of representative substituents.[15,19,23]

Why would a nonplanar transition state be favored in any case? Simply stated, the reason is that a planar geometry encounters more severe van der Waals interactions between sterically demanding substituents than a nonplanar or puckered one, *especially* in an early transition state. The interactions are most obvious with tertiary aldehydes, which consistently react with the highest trend for cis oxaphosphetanes. Figure 2 presents computer-generated stereo drawings of several possible transition-state geometries for the hypothetical reaction of $Me_3P{=}CHCH_3$ with pivaldehyde. We must again emphasize that the overall structures were NOT generated by empirical force field methods to avoid any implication of an energy minimization in the absence of reliable parameters. The ylide geometry was built from the X-ray coordinates of representative ylides in the Cambridge data files, accessed, and then modified to incorporate the $\alpha$-methyl group by using the MACROMODEL and MODEL programs.[22c] According to solution evidence, phosphorus ylides have a planar $\alpha$-carbon, but X-ray studies have revealed examples of pyramidal as well as planar ylides.[22a] The solution geometry is more relevant to the Wittig transition state, and partial $\alpha$-carbon pyramidalization is necessary in any event. As an approximation, somewhat arbitrary $\alpha$-carbon bond angles of 115° (compressed from the ylide values of ca. 120°) were used, and the ylide P–C bond length was modified accordingly for ca. 50% rehybridization. Tetrahedral phosphorus geometry was modified for ca. 33% rehybridization (Figure 2; C–P–C angle $B_3$ expanded from ca. 109° to 113°; angles $A_1$ and $A_2$ contracted to 103°) as an approximation of the asynchronous cycloaddition/early transition state concepts. Methyl groups were incorporated at phosphorus to avoid rotamer population issues. The pivaldehyde fragment was built by using MACROMODEL and was then modified for ca. 50% rehybridization at carbon (bond angles compressed from 120° to 115°; bond distances adjusted likewise). The individual fragments were then brought together for "docking" in various geometries. Those illustrated in Figure 2 are proposed as the best approximations of puckered or nearly planar geometries that allow approach of the reactants to within C–C bonding distances in the range 1.8–2.2 Å and P–O distances of 2.2–2.6 Å. Bond distances were chosen to be no larger than those recently calculated for the hypothetical $H_3P{=}CH_2$ reaction,[15] on the basis of the view that a more highly substituted ylide will react via a somewhat advanced transition state involving closer approach of reactants. Structure A depicts a *planar* cis-selective geometry with the best compromise of 1,2 and 1,3 alkyl vs *tert*-butyl interactions, while B illustrates a planar trans-selective approach. "Docking" of the ylide and aldehyde has also been performed in puckered geometries (C, cis-selective; D, trans-selective).

The difference in steric interactions between A, B, C, and D is substantial. Puckered cis-selective C has virtually no interactions of ylide substituents with the *tert*-butyl group at C–C bonding distances in the range of 1.8 Å or greater. The specific geometry C allows at least 3-Å separation between all of the carbons except those involved in the C–C bond forming step. By comparison, planar A has severe methyl–methyl interactions while the planar trans-selective B or puckered D are intermediate between these extremes. The puckered geometry C sacrifices some orbital overlap relative to planar alternatives, but the advantage in steric interactions is clear.

The kinetic selectivity in the closest known ylide analogy ($Et_3P{=}CHCH_3$ + $PhCH_2(CH_3)_2CCHO$) is 3:1 cis/trans while the analogous $Bu_3P{=}CHC_3H_7$ affords a ca. 1:1 mixture.[1] These observations suggest a relatively delicate balance between C and

(23) (a) Bestmann, H. J.; Chandrasekhar, J.; Downey, W. G.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Commun.* **1980**, 978. (b) Holler, R.; Lischka, H. *J. Am. Chem. Soc.* **1980**, *102*, 4632. (c) Trindle, C.; Hwang, J.-T.; Carey, F. A. *J. Org. Chem.* **1973**, *38*, 2664.

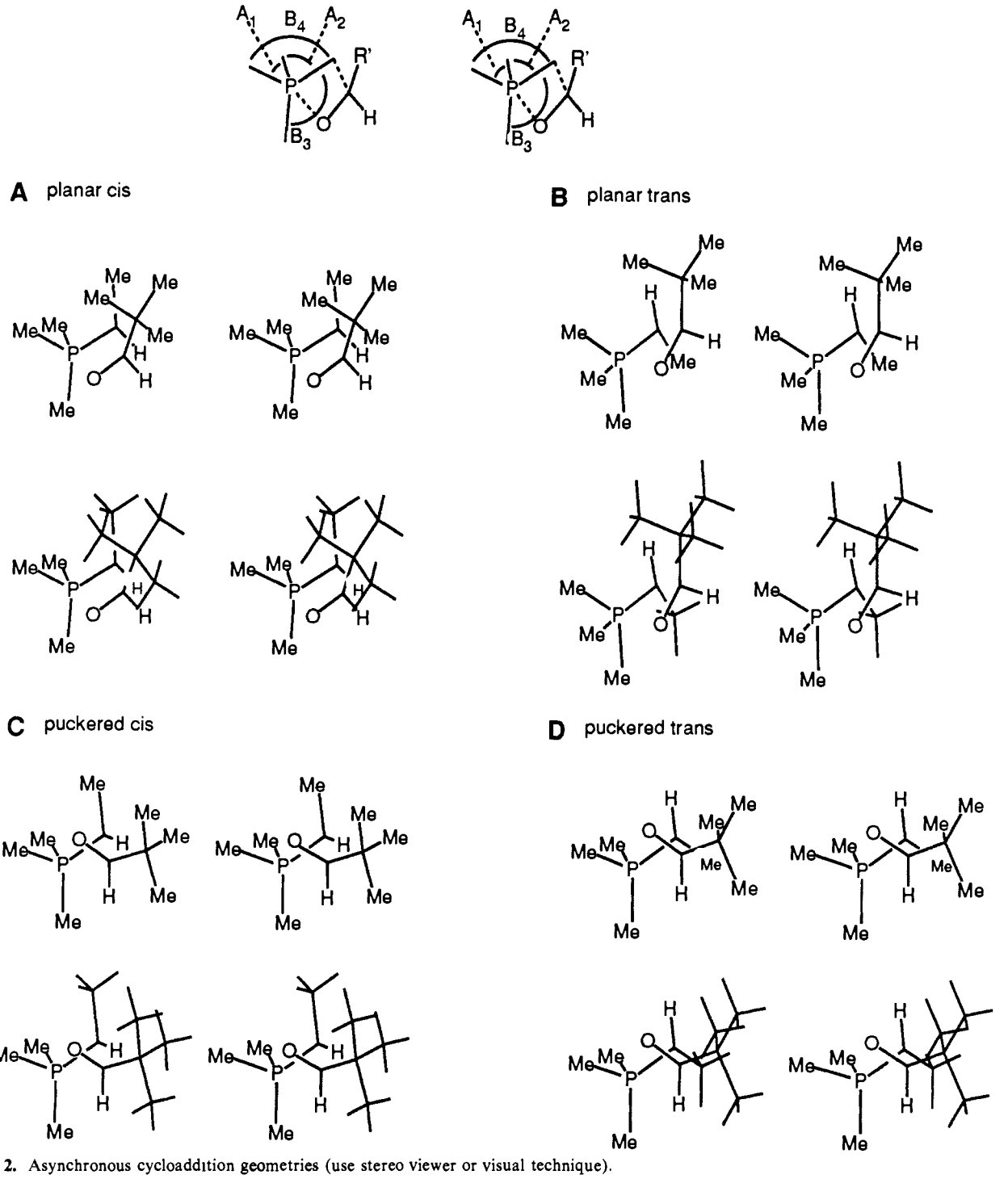



**Figure 2.** Asynchronous cycloaddition geometries (use stereo viewer or visual technique).

B or other trans-selective geometries. Substituents are still relatively compact, and the compromise between steric advantages vs reduced overlap in puckered four-center transition states is easily altered. However, "docking" analysis indicates that as the profile of phosphorus substituents closest to the aldehyde increases, there is a progressive exaggeration of the advantages of a puckered transition state. The advantages become less apparent, however, as phosphorus is modified to trigonal-bipyramidal geometry, or when the bulk of the aldehyde substituent decreases.

The qualitative docking argument can be duplicated with simple Dreiding models (tetrahedral phosphorus as an approximation; C–H bonds included as van der Waals spheres to exaggerate the interactions) or with CPK models. The steric advantages of C are easily seen, but the price in decreased overlap can only be deduced from empirical trends. In the case of $Et_3P{=}CHCH_3$, there is a shift from cis selectivity with the tertiary aldehyde **1** (3:1) to trans selectivity with unbranched $PhCH_2CH_2CHO$ (2:1).[1] However, the steric factors that favor puckered four-center geometries become strongly dominant in the more familiar $Ph_3P{=}CHCH_3$ series as discussed in the next section.

**Transition-State Geometry. Specific Examples.** As in our previous papers,[6,18,24] the cis-selective transition state **2a** is drawn with a puckered 4-membered ring having the aldehyde substituent in a pseudoequatorial orientation, as far as possible from phosphorus ligands (Figure 3). The nonplanar (developing) oxa-

(24) In the original paper, the asynchronous cycloaddition was compared to the 2s + 2a geometry for 2 + 2 cycloaddition reactions (ref 18). The difference between **2a** and the 2s + 2a geometry is subtle and involves the degree of pyramidalization and the position of the aldehyde hydrogen. There is no reason to believe that any cycloaddition process of phosphorus ylides is forbidden by orbital symmetry. We have removed the 2s + 2a terminology to avoid the misconception (ref 20a, ref 23b) that symmetry rules are the reason why puckered **2a** is proposed. The argument depends on steric factors alone.

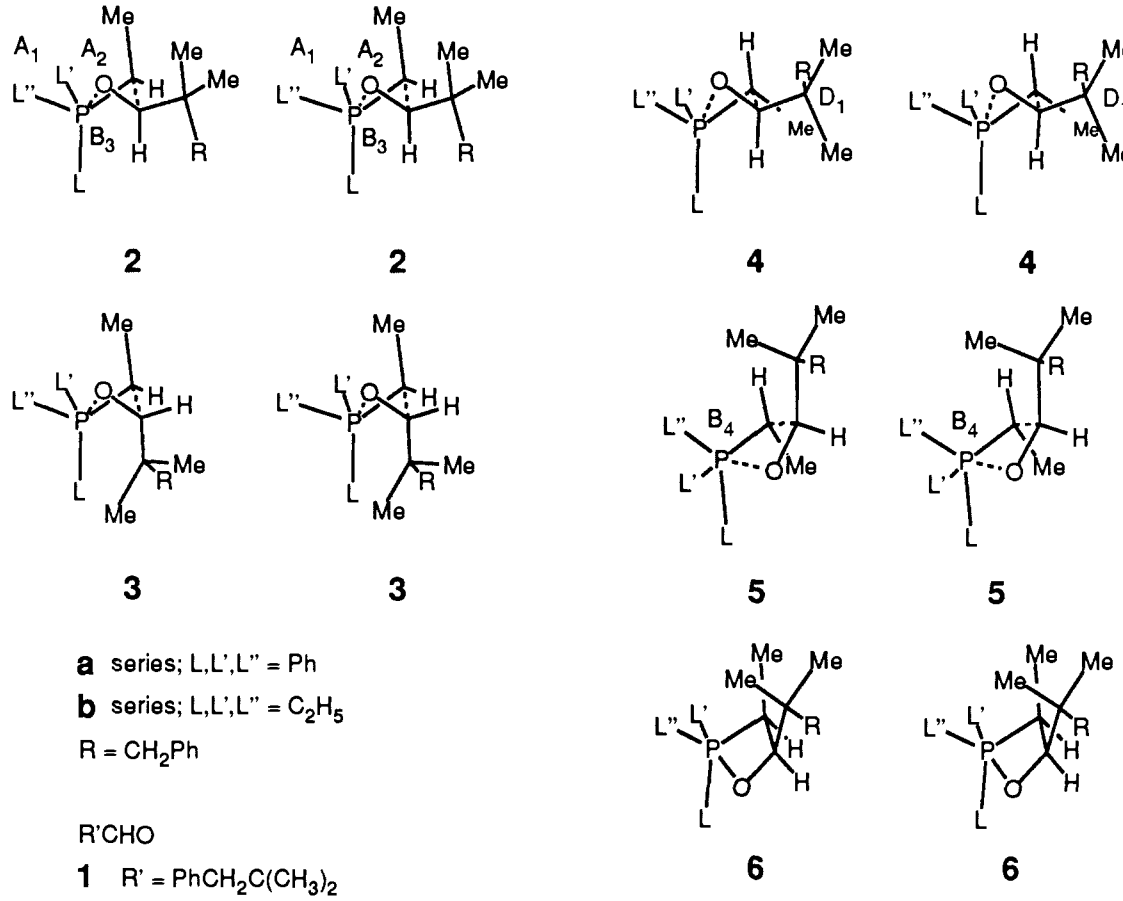



Figure 3. Developing bond angles. Apical: $A_1$, $A_2$. Basal: $B_3$, $B_4$. Dihedral: $D_1$.

phosphetane transition state **2a** allows maximum separation between aldehyde and phosphorus substituents and also the ylide $\alpha$-$CH_3$ substituent. Formally, $\alpha$-$CH_3$ is "pseudoaxial" with respect to the developing ring, but there are no severe 1,3 interactions because the other "pseudoaxial" site is occupied by oxygen lone pair electrons. An alternative puckered geometry **3a** is clearly less favorable because pseudoaxial aldehyde tertiary alkyl encounters one of the *P*-phenyl groups (L) in a pseudoaxial orientation. We introduce the *pseudoequatorial* and *pseudoaxial* terminology to help clarify the previously proposed geometry for $Ph_3P{=}CHCH_3$ reactions.[6] The geometry is the same, but a far more detailed proposal is now possible, and the role of phosphorus substituents and bond angles can be specified with greater certainty.

The trans-selective variation **4a** is less stable because $\alpha$-$CH_3$ and tertiary alkyl are nearly in the same (pseudoequatorial) plane. These interactions can be reduced by increasing the dihedral angle marked $D_1$ in the diagram (**4a**), but the result is a more nearly planar four-center arrangement **5a**. This involves increased 1,3 interactions with L", the nearby phenyl substituent at partially rehybridized phosphorus. If the transition state were late, this interaction would be reduced because the relevant L"–Me distance must increase as phosphorus hybridization changes from $sp^3$ to $dsp^3$ and the bond angle $B_4$ approaches 120°. This is why the *final product* is always more stable as the trans-disubstituted oxaphosphetane. However, in an early transition state **5a**, angle $B_4$ is relatively compressed. There is little flexibility to decrease $\alpha$-$CH_3$ 1,2 interactions in **4a** without increasing the L"–Me 1,3 interactions. Phosphorus rehybridization is not far along and is closer to tetrahedral than to trigonal bipyramidal geometry. As the aldehyde approaches and rehybridization proceeds, the bond angles $A_1$ and $A_2$ (structure **2a**) must decrease. In the final oxaphosphetane, these angles approach 90° but the transition-state geometry at phosphorus most closely resembles a distorted square pyramid with $A_1$ and $A_2$ = ca. 103°. A least motion path from **2a** to the oxaphosphetane **6a** is apparent upon comparison of relevant bond angles, but this occurs after the transition state and does not affect selectivity.

The origin of substituent effects can now be considered. As already mentioned, replacement of phenyl groups in $Ph_3P{=}CHCH_3$ by ethyls results in decreased cis selectivity with the tertiary aldehyde and a switch to moderate trans selectivity with the unbranched aldehyde.[1] This is not a case where late transition state arguments can apply. The reaction with the bulky aldehyde **6** should be less exothermic and therefore the transition state would be more productlike than in the unbranched case, but the major product is still the less stable cis oxaphosphetane. The transition state in both the $Ph_3P$ and the $Et_3P$ ylide cases is early, and the change in selectivity can be understood by comparing **2b** (cis-selective) and **5b** (trans-selective). The 1,3 interactions that destabilize **5b** depend on the bulk of the aldehyde, and also on the profile of the nearest phosphorus ligand L". When *P*-phenyls are replaced by ethyls, the 1,3 interaction with L" decreases and the cis selectivity with tertiary aldehyde is reduced as the stability of **5b** improves relative to **2b**. A further decrease in 1,3 interactions occurs if the aldehyde R'CHO has an $\alpha$-hydrogen (R' unbranched or singly branched at the $\alpha$-carbon). Under these circumstances, it is possible to orient R' such that a C–H bond points toward phosphorus ligands. The trend toward **5b** is also increased if the nearest phosphorus ligand L" is compact, and the combination results in a modestly trans-selective reaction under kinetic control in the case of the unbranched aldehyde.

The strongest evidence for the proposed transition-state geometry comes from a comparison of ylides having two *P*-aryl substituents and systematically varied geometric constraints (Table II). Under conditions of kinetic control, $Ph_2EtP{=}CHCH_3$ is nearly identical with $Et_3P{=}CHCH_3$ in cis/trans selectivity with the unbranched aldehyde (ca. 1:2; $PhCH_2CH_2CHO$) but is moderately more cis-selective (6:1 cis/trans) with the tertiary aldehyde.[1] For now, it is not necessary to define exactly what combination of the many possible arrangements at phosphorus is involved with the less symmetrical $Ph_2EtP{=}CHCH_3$. There

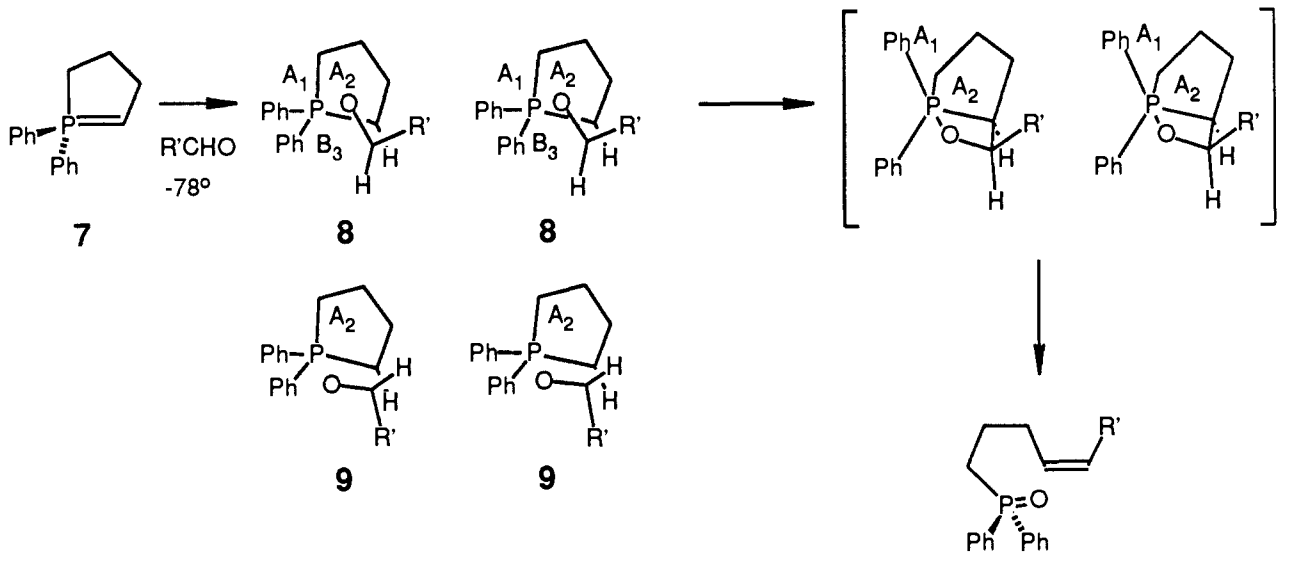
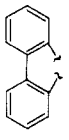
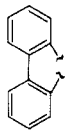
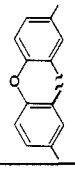



**Figure 4.**

**Table II.** $Ar_2ZP{=}CHR$ $Z/E$ Selectivity with Aldehydes[a]

| | $Ar_2$ | Z | R | $Ph(CH_2)_2CHO$, $Z/E$ | $PhCH_2C(Me)_2CHO$, $Z/E$ |
|---|---|---|---|---|---|
| 1. | $Ph_2$ | Ph | Me | 16:1[b] | >99:1[b] |
| 2. | $Ph_2$ | *t*-Bu | Me | 17:1[c] | 99:1[c] |
| 3. | $Ph_2$ | *i*-Pr | Me | 1:4.6[c] | 1:1[c] |
| 4. | $Ph_2$ | Et | Me | 1:2.3[b] | 5.7:1[b] |
| 5. | $Ph_2$ | $(CH_2)_3$ | | >98:2[c,d] | >99:1[c,d] |
| 6. |  | Ph | Me | 1:1[c] | 9:1[c] |
| 7. |  | Et | Me | 1:18[b] | 1:9[b] |
| 8. |  | Et | Me | 1:6[c] | 1:1[c,d] |

[a] Results from ref 1 unless indicated otherwise. [b] >98% kinetic control proved; see ref 1 for details. [c] Dominant kinetic selectivity is assumed by analogy. [d] Results from this work.

are several subtle issues to consider, but it is clear that replacement of a single *P*-phenyl group by ethyl is responsible for the decreased cis selectivity. *Further replacement of phenyls by ethyls makes little difference* (Table III). On the other hand, there is a striking effect observed when a single phenyl is replaced by an alkyl chain that is conformationally restricted by incorporation into a ring, as in the phospholane **7**.[25] Reaction of **7** with either the tertiary or the unbranched aldehydes gives exclusively the *Z* alkenes (Table II). This is the most highly *Z*-selective ylide known! It happens also to form one of the most reactive oxaphosphetanes as the intermediate cannot be detected prior to decomposition to alkenes (−78 °C). Rapid cycloreversion to alkenes is probably associated with the release of bond angle strain in the 5-membered phosphorus ring.[26] Proof for kinetic control in this series therefore rests on generalization 8 and on the extraordinarily low temperature for olefin formation.

(25) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1981**, *46*, 459.
(26) Allen, D. W.; Nowell, I. W.; Oades, A. C.; Walker, P. E. *J. Chem. Soc., Perkin Trans. 1* **1978**, 98. Allen, D. W.; Hutley, B. G.; Polasik, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 619.

The presence of a strained 5-membered ring in **7** greatly simplifies the problem of selecting the favored transition state substituent pattern at phosphorus. As mentioned above with regard to structure **2a**, the bond angles $A_1$ and $A_2$ undergo some compression, even in an early transition state. This factor will allow partial release of ring strain in **7** if the phosphorus ring is placed to span the bond angle $A_2$ as shown in structure **8**. No other arrangement can incorporate the ring without an *increase* in bond angle strain. Analogues of **4** or **5** are destabilized because the phospholane C–P–C bond angle would have to span the position $B_3$ and would therefore have to increase, but planar transition states such as **9** are especially difficult. The geometric constraint places the closest *P*-phenyl substituent in the path of the approaching aldehyde oxygen. This result dramatically illustrates the consequences of having an $sp_3$ hybridized atom (P) as part of a 2 + 2 cycloaddition transition state. One of the phenyl groups projects forward and must interfere with planar cycloaddition geometries. The trans-selective pathways no longer compete, and the striking contrast between **7** and $Ph_2EtP{=}CHCH_3$ is thereby explained.

One final example will be described in detail. This involves the *P*-ethyldibenzophosphole ylide **10** ([Et]DBP=$CHCH_3$), which reacts with exceptional kinetically controlled trans selectivity.[2] The same bond angle strain argument applies to the phosphole ring, but this time the ylide $\alpha$-carbon is not constrained and the consequences are remarkable. The phosphole ring must now span the compressed bond angle marked $A_1$ in Figure 2. This results in a choice between **11** (cis-selective) or **12** (trans-selective) shown in Figure 5. The steric interactions in the puckered (cis-selective) geometry **11** are not much affected by the incorporation of a phosphole ring by comparison with **2a**. The pseudoaxial $CH_3$ group experiences the usual 1,3 lone pair interaction, the gauche 1,2 interaction with aldehyde alkyl, and a somewhat modified 1,2 interaction with the adjacent aryl group. However, in **12** there are major new advantages over **5a**. The important 1,3 interaction with phosphorus ligands is reduced by structural constraints; the aldehyde methyls face the aryl $\pi$-system and are farther removed from the ortho aryl C–H bonds. Furthermore, the $\alpha$-$CH_3$ group experiences much smaller 1,2 interactions with the nearby *P*-ethyl group. Due to the constrained aromatic rings of the phosphole, the *P*-ethyl group is less restricted in terms of accessible rotamers and can easily turn C–H bonds toward the congested oxaphosphetane. The combination of 1,2 and 1,3 steric advantages and of better overlap favors **12** and results in excellent trans selectivity with aldehydes having at least one $\alpha$-CH bond (**12a**). Even in the case of tertiary aldehydes (**12b**), kinetic trans selectivity is still in the useful range (ca. 9:1 trans/cis), but **11** becomes somewhat more competitive. This is the same trend consistently seen with tertiary aldehydes (generalization 6) in all of the ylide systems.

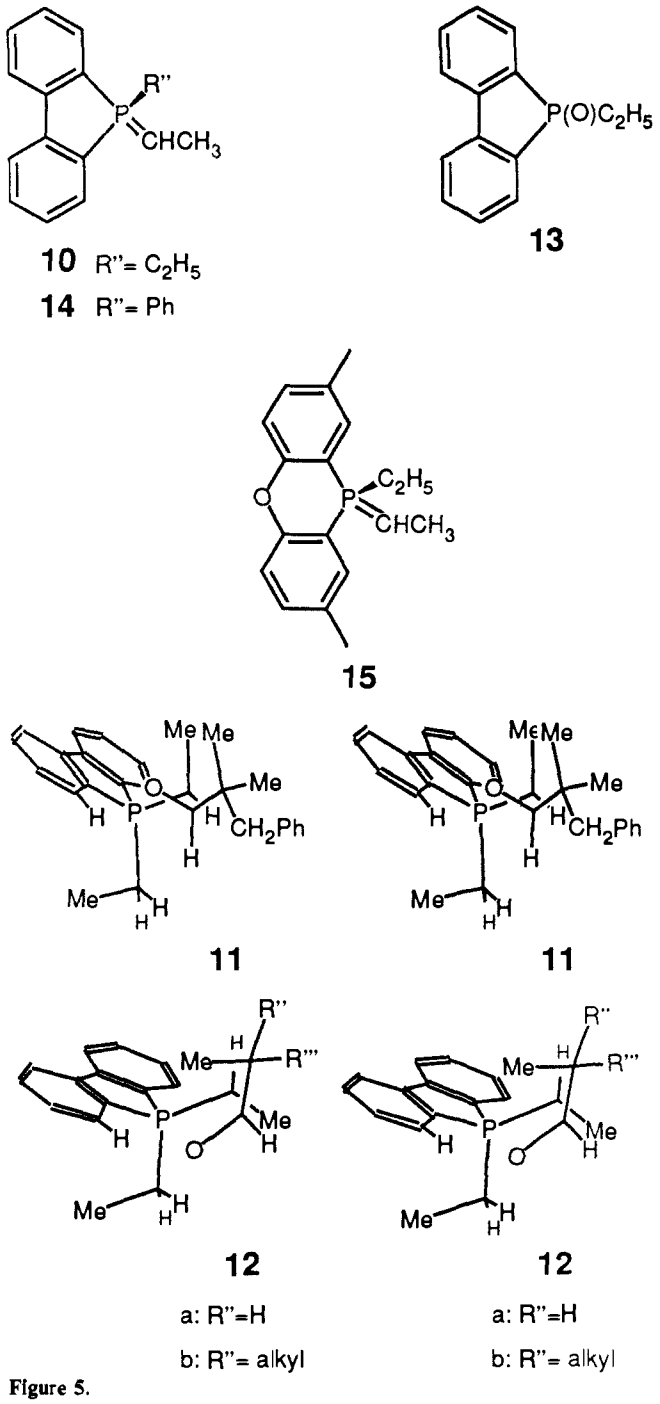



Figure 5.

The initial cycloaddition process between the aldehyde and the [Et]DBP ylide **10** is still very fast at −70 °C due to partial release of strain. If anything, the transition state should come even earlier than for the strain-free ylides. However, the decomposition step leading to alkenes and the phosphine oxide **13** is now exceptionally slow because **13** retains the strained phosphorus ring.[26] Nevertheless, the process is under total kinetic control in both examples studied.[1,2]

Due to the highly congested environment of the four-center Wittig transition state, all of the steric effects are interdependent. The relative bond angles and the shape, rather than bulk, of substituents can be critical, and subtle changes in phosphorus ligands can quickly degrade the high trans selectivity observed with **10**. Replacement of the *P*-ethyl group by a phenyl (ylide **14**) results in a nonselective reaction with $PhCH_2CH_2CHO$ while the reaction with $PhCH_2C(CH_3)_2CHO$ becomes cis selective (6:1)![1] The shape of the phenyl ring results in added steric demands within the developing oxaphosphetane and destabilizes geometries similar to **12**.

A modest increase in phosphorus ring bond angles also has a detrimental effect on trans selectivity. Thus, the *P*-ethyl dibenzooxaphosphorinan ylide **15**[27] reacts with reduced 6:1 trans selectivity with the unbranched aldehyde and with no selectivity in the case of the tertiary aldehyde. These *trends* are predicted by using our model, but their magnitude is remarkable at first glance. Intuition developed in relatively noncongested ring systems (monosubstituted cyclohexanes, A values, etc.) is not easily adjusted to the frame of reference that is relevant to oxaphosphetanes. These are steric interactions at close quarters, and a certain amount of confrontation is required to allocate available space to the substituents.

Two examples will be mentioned briefly to underscore the importance of *P*-ligand shape rather than bulk. In the reaction with unbranched $PhCH_2CH_2CHO$, the cyclohexyl derivative $C_6H_{11}(Ph)_2P{=}CHCH_3$ is trans-selective (3:1)[28] even though cyclohexyl is at least as bulky as phenyl. In contrast, a very compact alkynyl substituent in $(PhC{\equiv}C)(Ph)_2P{=}CHCH_3$ results in a highly cis-selective reaction (>15:1)![28] The symmetrical alkynyl group probably fits well into the *L'* position in **2** because it can best tolerate the contraction in bond angles ($A_1$, $A_2$, etc.) in all directions and thereby promotes cis selectivity by placing *P*-phenyls (L, L'') close to the aldehyde. The reasons for the trans selectivity of the cyclohexyl analogue are more complex and probably are related to the ability of cyclohexyl to rotate one C–H bond toward the developing C–C bond, but the important conclusion is that *interactive* steric effects involve all of the substituents near the oxaphosphetane. Similar phenomena are the likely source of variations among the series of ylides (Table IV) having systematically varied *P*-phenyl vs *P*-isopropyl substituents.

**Extrapolations.** Several predictions can be made from the asynchronous cycloaddition model described above for the preparatively important $Ph_3P{=}CHX$ family of ylides. For example, α-heteroatom substituents such as X = OR should promote a trend toward kinetic trans selectivity because **17** (replace X by OR) will be destabilized by lone-pair repulsions while **16** will be favored by reduced bulk of X = OR, which tends to minimize 1,2 eclipsing interactions.[29] A related electronic effect should disfavor kinetic cis selectivity of moderated ylides (X = $CH{=}CH_2$ or $C_6H_5$).[3] A vinyl group in the pseudoaxial orientation will encounter repulsive oxygen lone pair–π-electron interactions. In an early transition state, this factor is especially pronounced because the moderated ylide has increased electron density along the conjugated π-system. Decreased steric demand of the $sp^2$ hybridized α-carbon will favor **16** (X = $CH{=}CH_2$ or $C_6H_5$, etc.) or puckered analogues, and the result is a trend toward trans selectivity. Experimentally, $Ph_3P$-derived moderated ylides are nonselective while the more compact $Ph_2MeP$ analogues react with excellent *E*-olefin selectivity.[30]

The intuitive connection between the phrase "moderated ylide" and a less reactive ylide is probably incorrect: there is no indication that $Ph_3P{=}CHCH{=}CH_2$, for example, is less reactive than a "nonstabilized" ylide. Indeed, the opposite may be true because the allylic ylide may have a higher HOMO,[31] which implies greater reactivity in the cycloaddition process. It is likely that alterations in kinetic selectivity are neither due to a later transition state nor to Wittig reversal in the moderated ylides[4] but result from the same interplay of 1,2 vs 1,3 interactions as in the nonstabilized ylides.

A combination of electronic and steric factors suggests that carbonyl-stabilized ylides should resemble moderated ylides and

(27) See the Experimental Section.

(28) Vedejs, E.; Ruggeri, R.; Haselow, K. unpublished results.

(29) Enol ether *E*/*Z* ratios in the range of 1–2:1 have been repored: Brewer, J. D.; Elix, J. A. *Aust. J. Chem.* **1972**, *25*, 545. Also, Gut, S. Ph.D. Dissertation, University of Wisconsin, 1987 (personal communication from Gut, S. and Trost, B. M.).

(30) (a) For leading references to the stereochemistry of $Ph_3P{=}CHCH{=}CH_2$, see ref 3. (b) For a tabulation of *E*/*Z* ratios, see: Gosney, I.; Rowley, A. G. *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic: New York, 1979; p 17. (c) Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.*, in press.

(31) Ostoja Starzewski, K. A.; Bock, H. *J. Am. Chem. Soc.* **1976**, *98*, 8486.

**Table III.** $Z/E$ Selectivity as a Function of *P*-Phenyl Replacement by *P*-Ethyl: $Ph(CH_2)_2CHO$ Substrate[a]

| ylide: | $Ph_3P{=}CHMe$ | $Ph_2EtP{=}CHMe$ | $PhEt_2P{=}CHMe$ | $Et_3P{=}CHMe$ |
|---|---|---|---|---|
| $Z/E$: | 16:1[b] | 1:2.3[b] | 1:1.8[c] | 1:2[d] |

[a] Results from ref 1 unless indicated otherwise. [b] >98% kinetic control proved; see ref 1 for details. [c] Dominant kinetic selectivity is assumed by analogy. [d] Kinetic control in an analogous case ($Bu_3P{=}CHC_3H_7$ + hexanal) is proved (ref 5).

**Table IV.** $Z/E$ Selectivity as a Function of *P*-Phenyl Replacement by *P*-Isopropyl; $Ph(CH_2)_2CHO$ Substrate[a]

| ylide: | $Ph_3P{=}CHMe$ | $Ph_2$-*i*-$PrP{=}CHMe$ | Ph-*i*-$Pr_2P{=}CHMe$ | *i*-$Pr_3P{=}CHMe$ |
|---|---|---|---|---|
| $Z/E$: | 16:1[b] | 1:4.6[d] | 2.6:1[d] | 1:2[c,d] |

[a] Results from ref 1 unless indicated otherwise. [b] >98% kinetic control proved; see ref 1 for details. [c] Reference 28. [d] Empirical $E/Z$ ratio; analogous isopropyl ylides have not been tested to establish kinetic control in oxaphosphetane formation.

should prefer trans-selective transition-state geometries. However, there is a second issue to consider. The greatly diminished reactivity of stabilized ylides requires a more productlike transition state, similar to **16** but with relatively advanced rehybridization at phosphorus approaching trigonal bipyramidal geometry. This change reduces 1,3 interactions due to the increase in basal bond angle $B_4$ as mentioned earlier. Conventional interpretations of stabilized ylide reactions have attributed *E*-olefin selectivity to equilibration of intermediates, but we have proved that the high *E* selectivity of $Ph_2CH_3P{=}CHCO_2C_2H_5$ is a kinetic phenomenon.[9] Further studies are needed, but the prediction is clear: stabilized ylides must react with kinetic trans selectivity via a productlike four-center process.

Experimentally, the issue of trans selectivity can be very complex. In the case of nonstabilized ylides, there are isolated cases where spontaneous or catalyzed isomerization of cis oxaphosphetanes is responsible for this trend.[1,5,11-13] There are numerous other examples where trans selectivity originates from steric factors in an early transition state.[1,2,3] By analogy to the stabilized ylides, there may also be nonstabilized ylides that are sufficiently hindered to react via relatively late transition states. This would of course promote a trend toward trans selectivity. Such a situation is possible with branched ylides, but systematic studies have not yet been performed to probe this issue in aldehyde Wittig reactions.

In the case of ketone Wittig reactions, puckered **19** is destabilized by pseudodiaxial R–Ph interactions, and adduct geometries similar to **18** are likely. The mediocre $E/Z$ selectivity that is normally seen[32a] is understandable in view of the substantial and more evenly balanced 1,2 interactions. In cases where the two ketone substituents differ drastically in bulk (for example, steroid $C_{17}$ ketones),[32a] the advantages of puckering the cycloaddition transition state may increase, and there can be a trend toward the *Z*-selective puckered geometry **19**. On the other hand, there are cases of high *E*-olefin selectivity, which are more in accord with nearly planar **18**.[32c]

Similar trends would be expected for $\alpha$-alkoxy ketones[33] but for somewhat different reasons. A preference for maximum separation of unshared electron pairs (Reetz/Cornforth-like carbonyl environment)[34,35] places additional steric demands on the system, and as usual, this results in a puckered transition state, **21**. There are no serious 1,3 interactions introduced in **21** due to the alkoxy group, but in the alternative **20**, the separation of oxygen lone pairs is a conformational restriction which causes increased 1,3 interactions (Ph–Me). In effect, one of the ketone alkyl groups becomes considerably more demanding than the other, and the result is a preference for *Z*-olefin formation.

Overall, our model makes the sweeping generalization that very few salt-free Wittig reactions involve significant equilibration of intermediate stereochemistry. There is extensive evidence to support this statement,[1,5,9,10] but the issue has often been misinterpreted.[37] The reasons for this may be appreciated by examining the rare control experiments in the old literature[8,38] and by comparing the cautious wording in the original publications with the generalizations that evolved over several years in the review literature based on the same data.

**Alternative Interpretations.** The other detailed cycloaddition proposals in the literature contain some features that should be retained pending further study, while other aspects are not consistent with experimental evidence (for example, trigonal-bipyramidal phosphorus).[19,20] Schlosser et al. have drawn attention to the importance of phosphorus substituents.[20] However, Schlosser's "leeward approach" argument invokes a special propeller-like arrangement of *P*-phenyl groups to explain the cis selectivity of $Ph_3P{=}CHCH_3$. This part of the rationale is more likely the coincidental result, rather than the source, of cis selectivity since $Ph_2(t\text{-}Bu)P{=}CHCH_3$, [Ph]DBP=$CHCH_3$, and even $Et_3P{=}CHCH_3$ are kinetically cis-selective with tertiary aldehydes without being capable of the specific propeller arrangement. A similar problem arises with constrained ylides such as **7** (highly cis-selective). If the gearlike interaction of three phenyls is dominant in the $Ph_3P{=}CHCH_3$ case, why would the relatively compact **7** be more cis selective? We view the Schlosser geometry as productlike, a feature that will favor the trans instead of the cis oxaphosphetane.[20b] Schlosser's description of transition-state geometry with $dsp^3$ phosphorus is reasonable for late transition state reactions involving the trans-selective stabilized ylide systems. Staggered *P*-phenyl groups are well established in $Ph_3P$-containing molecules, and related arrangements are expected in all of the alternatives **2a–5a** whether or not the reactions are cis-selective.

The Bestmann rationale[19] includes a detailed analysis of the pseudorotation processes in the oxaphosphetane decomposition step that is qualitatively consistent with currently available evidence. Pseudorotation issues could be important in addition to the bond angle strain arguments mentioned earlier for the drastic differences in oxaphosphetane decomposition rates between **7** and **10**. On the other hand, Bestmann's rationale includes a role for stereochemical equilibration, and a zwitterionic intermediate **22**, both of which have been ruled out by a number of control experiments,[1,5,10] even in an example where X = $CO_2C_2H_5$.[9] Another problem is the incorporation of the Dunitz trajectory.[19] This concept refers to approach of an anion in a nucleophilic addition process[39] and cannot apply in the same way to issues of cycloaddition stereochemistry.

On the other hand, the "quasi-betaine" component of the Bestmann arguments regarding stereochemistry may be relevant to ylides having sufficiently strong donor groups at phosphorus to promote the betaine mechanism. There is no example where this mechanism has been established, but the unusual ylide $(Me_2N)_3P{=}CHCH_3$ used for the synthesis of nearly pure *E* alkene

(32) (a) Wovkulich, P. M.; Uskokovicz, M. R. *J. Org. Chem.* **1982**, *47*, 1600. (b) Krubiner, A. M.; Gottfried, N.; Oliveto, E. P. *J. Org. Chem.* **1968**, *33*, 1715. (c) Schmit, J. P.; Piraux, M.; Pilette, J. F. *J. Org. Chem.* **1975**, *40*, 1586.

(33) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.

(34) Reetz, M.; Kesseler, K. *J. Org. Chem.* **1985**, *50*, 5435. Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112.

(35) The Felkin–Anh terminology could be used to describe carbonyl facial selectivity, but its original formulation is more appropriate for stepwise nucleophilic attack rather than for cycloaddition (ref 36).

(36) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(37) For example, the statement "...betaine formation is reversible in most, if not all, cases..." appears on p 27 in the otherwise very useful compilation of ref 30b.

(38) Bissing, D. E.; Speziale, A. J. *J. Am. Chem. Soc.* **1965**, *87*, 2683. Boskin, M. J.; Denney, D. B. *Chem. Ind.* (*London*) **1959**, 330.

(39) See Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413 and references therein.

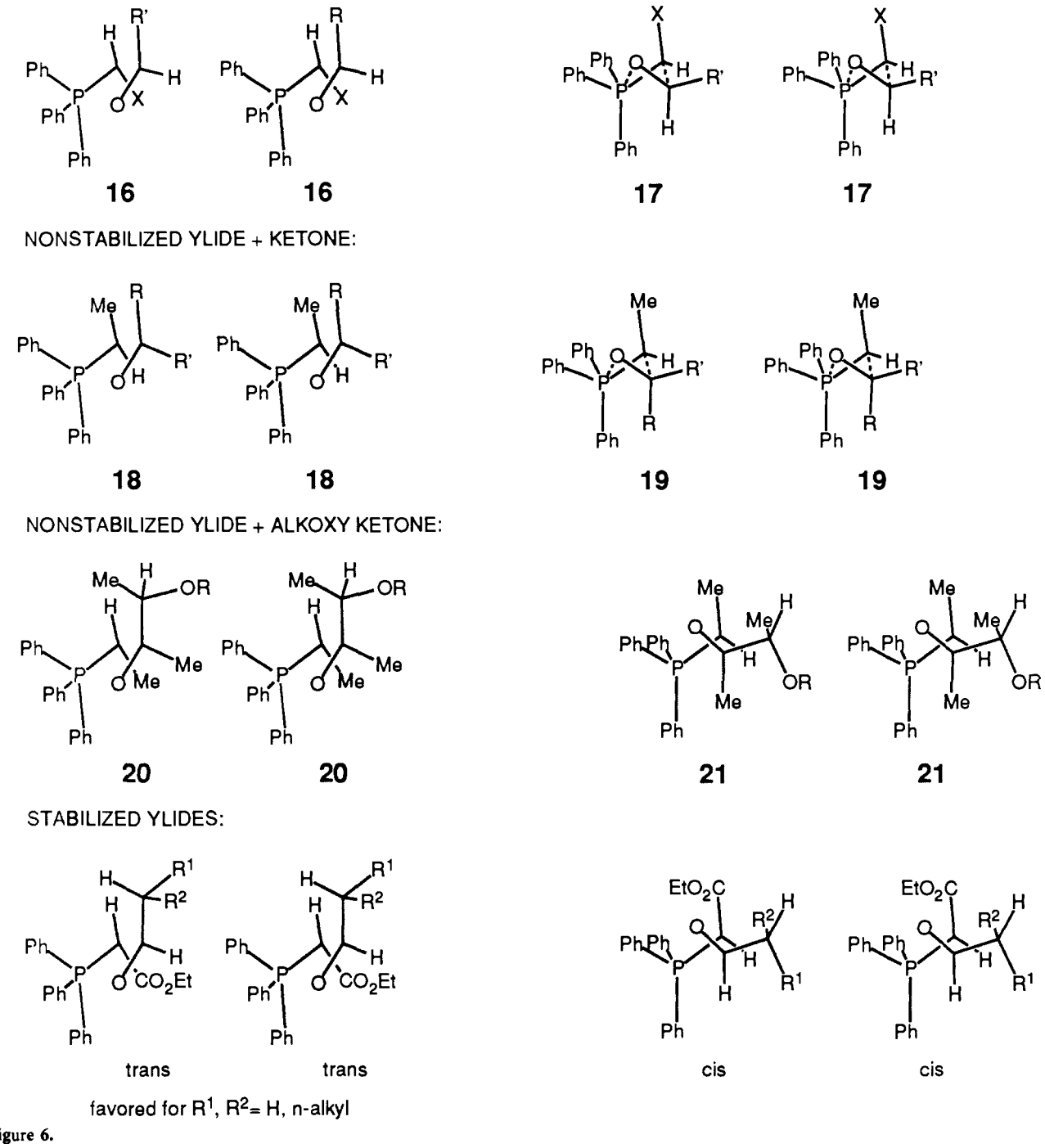



Figure 6.

from the tertiary aldehyde **1**[1] might be a possible candidate for the ionic pathway. Alternatively, the Bestmann rationale could apply to Wittig reactions in the presence of a lithium ion if it can be shown that the catalytic effect of $Li^+$ favors a stepwise rather than a cycloaddition mechanism. These were the usual conditions of the original Wittig reaction, and they often produce lithium halide–betaine adducts.[14] Since the ionic intermediates are more stable under these conditions, we see little reason to argue against at least some contribution from the ionic (betaine–LiX adduct) pathway for the lithium ion catalyzed component.[40] Lithium-containing Wittig reactions are known to occur with reduced kinetic selectivity in the case of $Ph_3P{=}CHR$.[6,11b] Interestingly, the lithium ion effect also decreases the selectivity of certain ylides which are inherently trans-selective.[3] These issues require further study, but it is clear that the catalyzed and uncatalyzed mechanisms compete depending on lithium ion concentration. The lithium ion catalyzed process occurs with relatively low selectivity compared to the uncatalyzed reaction component.[11b]

(40) The "anti betaine" (positive phosphorus and negative oxygen at a 180° dihedral angle) is least plausible due to the absence of solvent effects on cis/trans selectivity (see ref 6). Calculations indicate that the anti betaine is not a minimum on the energy surface (ref 15), but this of course refers only to the gas phase where ionic structures will be least likely. For similar conclusions regarding the "anti betaine", see: Piskala, A.; Rehan, A. H.; Schlosser, M. *Collect. Czech. Chem. Commun.* **1983**, *48*, 3539.

## Conclusion

There have been many attempts to define a simple scheme that explains the origins of Wittig cis/trans selectivity.[14,19,20] However, accumulating evidence makes it increasingly clear that there is no single dominant Wittig transition state geometry. The many different ylides that undergo this remarkably general olefination reaction cannot be expected to fit one simple pattern regardless of conditions and substituents; a continuum of related mechanistic

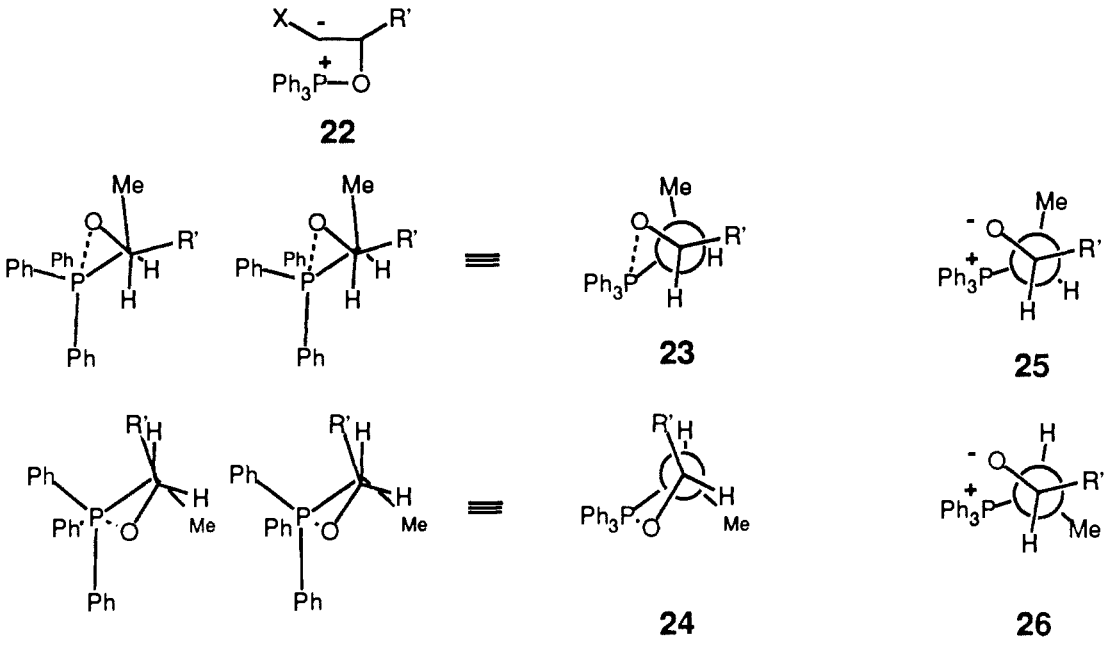



**Figure 7.**

variants is more likely. To make this complex problem manageable, we have emphasized the limiting geometries, **2** (puckered; cis-selective) and **5** (planar; trans-selective), but there will be intermediate cases. Typical nonstabilized or moderated ylides react via early transition states and under kinetic control. The subtle interplay of 1,2 and 1,3 steric interactions is responsible for cis or trans selectivity, and puckered transition states are increasingly important as the 1,3 interactions associated with bulk $\alpha$ to the carbonyl group become dominant. These 1,3 interactions can be suppressed (or exaggerated) by careful selection of phosphorus substituents and geometric constraints.

For salt-free nonstabilized ylides, the cis-selective transition state **2a** can be approximated by the projection **23**, which neglects phosphorus bond angles and substituent profiles. Since 1,3 interactions between R′ and phosphorus substituents are dominant in the cis-selective examples, these large groups are kept apart in an intuitively reasonable way. To the extent that details are included in **23**, this representation is not much different from a conventional Newman projection of the hypothetical "syn betaine" **25**[40] (cis-selective). The Newman projections focus only on 1,2 interactions, which by themselves do not explain selectivity. Should not the diastereomeric "betaine" **26** (trans-selective) have been preferred because it benefits from reduced gauche interactions (Me–H rather than Me–O) relative to **25**? This analysis fails because it ignores the nature of the 1,3 interactions, their interdependence with 1,2 interactions, and the three-dimensional consequences associated with a developing 4-membered ring.

A projection representation of the trans-selective transition state **5** is illustrated by diagram **24**, again without including important features involving the phosphorus ligands. Increased eclipsing relative to **26** can be seen, and the two structures differ in the placement of the aldehyde alkyl group R′. A trend toward trans selectivity is observed when proximity of the R′ group and phosphorus is possible without severe 1,3 interactions in the four-center transition state. The importance of this requirement is completely lost in the "syn betaine" representation **26** (or semantic variants of this geometry) because R′ appears to be far from phosphorus. Why is **24** less favorable than **23**? Again, this is difficult to see in the Newman projection diagram, but the stereo view is more clear. A cycloaddition process involving a tetrahedral center is very different from the more familiar situation where only $sp^2$ centers are involved. The developing P–O bond must avoid the *P*-Ph group that projects forward, and this results in 1,3 interactions between *P*-Ph and R′. As might be expected, it is difficult to adjust the phosphorus ligands to favor nearly eclipsed transition-state arrangements similar to **24** (corresponding to an early transition state **5**), especially if R′ has no $\alpha$-hydrogen. However, this becomes possible with the constrained system **10**. The latter is the first nonstabilized ylide with synthetically useful kinetic trans selectivity toward tertiary as well as unbranched aldehydes.

In the specialized case of stabilized ylides, trans selectivity results from dominant productlike 1,2 interactions; 1,3 interactions are less important due to the increase in basal bond angles in trigonal-bipyramidal phosphorus compared to the distorted square-pyramidal arrangement in **5**. The projection diagram of this situation is identical with **24**, but there are important differences at phosphorus with respect to hybridization. Contrary to long-standing assumptions, the *E* selectivity of irreversible stabilized ylide reactions with aliphatic aldehydes is actually higher than in the corresponding reaction with benzaldehyde, where some reversal can be detected.[9] We do not imply that all stabilized ylide reactions are irreversible, but the assumption of reversal without suitable control experiments is not justified.

The projections **23** and **24** are included to simplify comparisons with the old betaine rationale and with other mechanistic proposals. It would be helpful if future mechanistic discussions would specify how they differ from **23** (**2**) or **24** (**5**) in *geometry*. The projection diagrams may also be useful for pedagogic purposes. However, the more detailed representations **2** and **5** are necessary to understand the origin of the remarkable substituent effects on Wittig selectivity. These are subtle issues that depend on phosphorus bond angles and on the profiles of those groups that are forced into confrontation.

## Experimental Section

**1,1-Diphenylphospholanium Bromide[25] (Precursor to 7).** This phosphonium salt was prepared by reaction of diphenylphosphine (0.87 mL, 5 mmol) with 1,4-dibromobutane (0.72 mL, 6 mmol) in 5 mL of $CH_3CN$ in the presence of potassium carbonate. The reaction was stirred for 3 days at room temperature and was worked up as follows: all solvents were evaporated, the residue was washed with ether, dissolved in chloroform, and filtered. Chloroform was removed, and the salt was recrystallized from $CH_3CN$ to give white crystals in 63% yield, mp 163–165 °C (lit.[25] mp 163–164 °C).

**Wittig Reactions of Ylide 7.** The ylide was formed from the carefully dried salt (above) and reacted with aldehydes (0.9 equiv) under standard conditions (THF/potassium *tert*-butoxide, 0.9 equiv).[1] A nonaqueous workup to isolate the alkenylphosphine oxide was performed as follows: KI salts were removed by centrifugation, the solvent was removed, and the oil was taken up in ether/methylene chloride. The solution was passed through a short silica gel plug to give the pure product.

Tertiary aldehyde **1** gave a single alkene, (7-phenyl-6,6-dimethylhept-4-en-1-yl)diphenylphosphine oxide (>99% cis), in 97% yield: oil;

analytical TLC (silica gel F254), 1:1 ether/methylene chloride, $R_f$ 0.50; MS, exact mass calcd for $C_{27}H_{31}OP$ 402.2105, found 402.2111, error 1.4 ppm; IR ($CDCl_3$, $cm^{-1}$) 1600 (C=C), 1450 (C=C), 1200 (P=O); 500-MHz NMR ($CDCl_3$) $\delta$ 7.74–7.10 (15 H, m), 5.28 (1 H, dt, $J$ = 12.1, 1.7 Hz), 5.11 (1 H, dt, $J$ = 12.1, 7.1 Hz), 2.59 (2 H, s), 2.21–2.15 (2 H, m), 2.11 (2 H, dtd, $J$ = 7.2, 7.2, 1.7 Hz), 1.66–1.59 (2 H, m), 1.06 (6 H, s).

In an attempt to intercept the oxaphosphetane intermediate, a solution of ylide **7** (THF 0.1 M) was cooled to −78 °C, and tertiary aldehyde **1** in THF at the same temperature was added by using a chilled cannula. The reaction mixture was stirred for 10 s and quenched into HCl/MeOH at −78 °C. Workup with methylene chloride[1] and analysis by $^{31}P$ NMR indicated formation of the usual alkene product ($\delta$ 31.2, 22.4 parts), the oxide of 1-phenylphospholane ($\delta$ 59.0, derived from cleavage of the starting phosphonium salt by unknown nucleophiles, 10 parts), a minor unknown ($\delta$ +51, 2 parts), and recovered phospholanium salt ($\delta$ 42.9, 1 part).

Hydrocinnamaldehyde gave a single alkene, (7-phenylhept-4-en-1-yl)diphenylphosphine oxide (>98% cis by $^1H$ and $^{13}C$ NMR), in 91% yield: oil; analytical TLC (silica gel F254), 1:1 ether/methylene chloride, $R_f$ 0.50; MS, exact mass calcd for $C_{25}H_{27}OP$ 374.1793, found 374.1799, error 1.5 ppm; IR ($CDCl_3$, $cm^{-1}$) 1200 (P=O), 1600 (C=C); 500-MHz NMR ($CDCl_3$) $\delta$ 7.73–7.11 (15 H, m), 5.44 (1 H, dtt, $J$ = 10.8, 7.3, 1.5 Hz), 5.30 (1 H, dtt, $J$ = 10.8, 7.3, 1.5 Hz), 2.60 (2 H, t, $J$ = 7.7 Hz), 2.31 (2 H, dtd, $J$ = 7.3, 7.3, 1.5 Hz), 2.20–2.15 (2 H, m), 2.07 (2 H, dt, $J$ = 7.5, 7.5 Hz), 1.67–1.59 (2 H, m).

**10-Ethyl-2,8-dimethyldibenzooxaphosphorinane.** An adaptation of a procedure by Doak and Freedman was used.[41] Di-*p*-tolyl ether[42] (4.27 g, 1.0 equiv), phosphorus trichloride (7.5 mL, 4.0 equiv), and aluminum trichloride (3.45 g, 1.2 equiv) were added to a 25-mL round-bottom flask fitted with a condenser, and the reaction mixture was heated to reflux for 24 h. Aluminum salts, which made isolation of the chlorophosphine difficult, were removed by addition of phosphorus oxychloride, which reacted exothermically and formed a complex with the aluminum salts.[43] The large amount of solid material was washed with ether/hexane, the solution was filtered, and solvent was removed under vacuum. The residue was taken up in toluene and filtered again to remove remaining solids, giving a solution of 10-chloro-2,8-dimethyldibenzooxaphosphorinane in low yield plus a large amount of the oxide, which formed upon workup. To this solution was added 2 equiv (based on starting $PCl_3$) of ethylmagnesium iodide (prepared from magnesium metal and ethyl iodide in ether). The reaction mixture was heated at reflux for 0.5 h, cooled, and worked up under $N_2$ as described in the previous paper for phosphines.[1] 10-Ethyl-2,8-dimethyldibenzooxaphosphorinane: oil; analytical TLC (silica gel F254), 10% ether/hexane, $R_f$ 0.63; MS, exact mass calcd for $C_{16}H_{17}OP$ 256.1013, found 256.1014, error 0.4 ppm; 270-MHz NMR ($CDCl_3$) $\delta$ 7.23–6.99 (6 H, m), 2.32 (6 H, s), 1.57 (2 H, q, $J$ = 7.7 Hz), 0.85 (3 H, br s); $^{31}P$ NMR ($CDCl_3$) $\delta$ −54.2.

**10,10-Diethyl-2,8-dimethyldibenzooxaphosphorinanium Iodide (Precursor to 15).** The phosphine (above) was taken on directly and alkylated with approx 3 equiv of neat ethyl iodide at room temperature for 2 days. The EtI was evaporated, and the residue was crystallized from acetonitrile to give the pure phosphonium salt in 10% yield (based on di-*p*-tolyl ether) for the three steps: solid, mp 276–278 °C (crystallized from acetonitrile); formula $C_{18}H_{22}OIP$; 270-MHz NMR ($CDCl_3$) $\delta$ 8.62 (2 H, d, $J$ = 13.8 Hz), 7.57 (2 H, dd, $J$ = 8.5, 1.6 Hz), 7.30 (2 H, dd, $J$ = 8.5, 5.5 Hz), 3.57 (4 H, dq, $J$ = 12.2, 7.4 Hz); 2.57 (6 H, s), 0.95 (6 H, dt, $J$ = 21.6, 7.4 Hz); $^{31}P$ NMR ($CDCl_3$) $\delta$ 9.9. Anal. Calcd: C, 52.44; H, 5.38. Found: C, 52.26; H, 5.44.

**Wittig Reactions of Dibenzooxaphosphorinane Ylide (15).** The dry phosphonium salt from above (1.0 equiv) and a large excess of commercial sodamide (from Aldrich, ca. 5 equiv) were transferred inside a glovebag to a dry 40-mL centrifuge tube with stir bar. The tube was sealed with a septum and parafilm, and enough THF was added via syringe to form a 0.1 M solution. The reaction was allowed to stir for 2 h under nitrogen. After the ylide was formed, the $N_2$ line was removed, the septum hole was covered with silicone grease, and the solution was clarified by centrifugation. The supernatant solution containing the salt-free ylide was transferred via cannula to a dry round-bottomed flask at −78 °C, and a THF solution of the aldehyde (0.70 equiv) was slowly added. The reaction was stirred for 5 min at −78 °C, and the solution was transferred into a thick-walled tube and sealed. The sealed tube was heated 15 min at 75 °C to decompose the oxaphosphetane. The products were isolated and analyzed as described in the previous paper.[1] Hydrocinnamaldehyde gave 5-phenyl-2-pentene in 77% yield, 1:6 $Z/E$. In the case of the tertiary aldehyde **1**, a 1:1 $Z/E$ mixture of 4,4-dimethyl-5-phenyl-2-pentenes was formed in 85% yield.

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**Registry No. 1**, 1009-62-7; **7**, 113705-06-9; 1,1-diphenylphospholanium bromide, 43017-36-3; (*cis*-7-phenyl-6,6-dimethylhept-4-en-1-yl)diphenylphosphine oxide, 113705-05-8; 1-phenylphospholane oxide, 4963-91-1; hydrocinnamaldehyde, 104-53-0; (7-phenylhept-4-en-1-yl)diphenylphosphine oxide, 113705-07-0; di-*p*-tolyl ether, 1579-40-4; phosphorus trichloride, 7719-12-2; 10-chloro-2,8-dimethyl-10*H*-phenoxaphosphine, 65654-60-6; 10-ethyl-2,8-dimethyl-10*H*-phenoxaphosphine, 113705-08-1; 10,10-diethyl-2,8-dimethyl-10*H*-phenoxaphosphinium iodide, 113705-09-2; (*Z*)-5-phenyl-2-pentene, 16487-65-3; (*E*)-5-phenyl-2-pentene, 16091-23-9; (*Z*)-4,4-dimethyl-5-phenyl-2-pentene, 113460-12-1; (*E*)-4,4-dimethyl-5-phenyl-2-pentene, 113460-11-0.

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