Low-Temperature Characterization of the Intermediates in the Wittig Reaction

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Abstract: Nonstabilized salt-free ylides react with aldehydes and nonhindered or strained ketones at −78 °C to give oxaphosphetanes. The Wittig intermediates can be observed by ^{31}P and ^{1}H NMR techniques. In the presence of LiBr, betaine–lithium bromide adducts often precipitate from solution. The oxaphosphetane from PhCHO + CH_2=PPh_3 reacts rapidly with LiBr to give a betaine·LiBr adduct, and the corresponding salt $Ph_3P^+CH_2CHOHPh\ Br^-$ reacts with KH at −40 °C to form the oxaphosphetane. No salt-free betaine has been detected. Lithium bromide is shown to decrease cis selectivity (CH_3CH=PPh_3 + $PhCH_2CH_2CHO$) in the condensation step and not by oxaphosphetane equilibration. Oxaphosphetane reversal to ylide + aldehyde is confirmed for aryl aldehydes but not for aliphatic aldehydes or ketones according to three types of crossover experiments. Rationales for cis selectivity of aldehyde–ylide reactions are discussed. A "crisscrossed" cycloaddition rationale is proposed, aldehyde and ylide planes tilted toward an orthogonal arrangement to minimize steric interactions, to explain cis-alkene formation. Other transition-state geometries having carbonyl and ylide planes roughly parallel are considered more likely for trans-olefin formation or for Wittig reactions of ketones.

During our 1973 study of olefin inversion by the sequence (1) epoxide + $LiPPh_2$ and (2) CH_3I, we attempted to monitor conversion of the presumed phosphorus betaine intermediates into alkenes by ^{31}P NMR,[1,2] In place of the expected signals of tetravalent (betaine) phosphorus in the δ 20–40 range (downfield relative to 85% H_3PO_4), we found pentavalent (oxaphosphetane) intermediates, >50 ppm upfield of H_3PO_4.[1] Betaine signals were also absent in several low-temperature Wittig reactions although oxaphosphetanes were observed easily.[3]

We now describe a more extensive investigation of low-temperature Wittig reactions. In every example, only the pentavalent oxaphosphetane intermediate has been detected in solution. Although our results do not rule out betaines as transient intermediates, we believe that historical tradition is the primary remaining basis for the widespread assumption that betaines are key intermediates in the Wittig reaction.

In fact, true "betaines" have never been observed from any Wittig reaction. Confusion prevails on this point because ylides prepared in the presence of lithium halides ($Ph_3PR^+X^-$ + R′Li) in ether do react with certain carbonyl substrates to give ionic precipitates.[4,5] These precipitates have been characterized as betaine–lithium halide adducts and are not to be confused with the hypothetical *salt-free* betaines. Regrettably, the term "betaine" has been used in reference to both the unobserved salt-free species as well as the noncontroversial lithium halide adducts, a practice which should be abandoned.

Our primary goal here is to establish the nature of Wittig intermediates under salt-free conditions by ^{31}P NMR.[6] The effect of lithium halides on these intermediates will also be described.

^{31}P NMR Observation of Ylides. Nondecoupled ^{31}P spectra of alkyltriphenylphosphonium derivatives are hopelessly broadened by extensive coupling to the aryl protons. By far the best ^{31}P spectra are obtained by using narrow-band aryl H decoupling. With this method, highly characteristic multiplets due to aliphatic proton phosphorus coupling are observable, and low-temperature Wittig intermediates are easily distinguished from typical contaminants. However, great care in decoupler power optimization is essential to minimize off-resonance effects which decrease the apparent coupling constants (see Experimental Section).[7] Accurate J values can only be obtained from proton spectra in most cases.

Low-Temperature Condensation of Ylides and Carbonyl Compounds. Salt-Free Ylides. The most convenient procedure for preparing nearly pure CH_2=PPh_3 or CH_3CH=PPh_3 in our experience is the $NaNH_2$/liquid NH_3 method.[8] Homogeneous 0.1–0.3 M ylide solutions react rapidly with most aldehydes at −78 °C (color end point), although $(CH_3)_3CCHO$ requires ca. 0.5 h for completion. Strained ketones (norbornanone, cyclobutanone) or nonhindered cyclic ketones (cyclohexanone) also react at −78 °C, but typical acyclic ketones require −20 °C or above.[9] In extreme cases (pinacolone, 3-ethyl-2-pentanone), many hours at 20 °C are required for disappearance of ylide color.

For best results, the carbonyl compound must be added slowly to a small excess of ylide. Excess aldehyde or ketone causes the appearance of unknown extraneous signals in the pentavalent phosphorus region in some cases, especially if lithium halides are present. In all salt-free experiments, homogeneous solutions of the intermediates can be obtained in THF, ether, or toluene.

The ^{31}P shifts of Wittig intermediates fall in a relatively narrow range, depending on the substitution on the oxaphosphetane ring (Table I). There can be no doubt that pentavalent phosphorus is involved in each case.[10] We have not specifically proved that the adducts are monomers (four-membered ring rather than eight-membered ring), but oxaphosphetane structures have been established by X-ray methods in related cases where the rates of fragmentation to alkene are unusually slow.[12]

Representative Examples

(1) CH_2=PPh_3 + Aldehydes. *p*-ClC_6H_4CHO vs. $(CH_3)_3CCHO$. In contrast to other aldehydes studied, *p*-chlorobenzaldehyde forms an adduct which can be crystallized from THF solution as a finely divided white solid. Although we have been unable to obtain a sample free of some residual solvent, the filtered material is

(1) Vedejs, E.; Snoble, K. A. J.; Fuchs, P. L. *J. Org. Chem.* **1973**, *38*, 1178.
(2) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822.
(3) Vedejs, E.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1973**, *95*, 5778.
(4) Wittig, G.; Schöllkopf *Chem. Ber.* **1954**, *87*, 1318.
(5) Schloser, M.; Christmann, K. F. *Justus Liebigs Ann. Chem.* **1967**, *708*, 1.
(6) In keeping with current practice and contrary to our initial reports,[1,3] ^{31}P chemical shifts downfield of 85% H_3PO_4 are now assigned positive values; upfield shifts are negative.
(7) The coupling constants reported in ref 3 are significantly smaller than apparent J values obtained under carefully optimized decoupler conditions reported later in this paper.
(8) Wittig, G.; Eggers, H.; Duffner, P. *Justus Liebigs Ann. Chem.* **1958**, *619*, 10.
(9) Pentavalent phosphorus signals are observed in these borderline cases in the usual chemical shift range. Due to the additional experimental complication of competing condensation vs. decomposition, we have not invetigated such systems in detail.
(10) The observation of oxaphosphetanes has been confirmed by Schlosser et al.[11]
(11) Schlosser, M.; Piskala, A.; Tarchini, C.; Tuong, H. B. *Chimia* **1975**, *29*, 341.
(12) Ramirez, F.; Smith, C. P.; Pilot, J. F. *J. Am. Chem. Soc.* **1968**, *90*, 6726. Mazhar-Ul-Hague; Caughlan, C. N.; Ramirez, F.; Pilot, J. F.; Smith, C. P. *Ibid.* **1971**, *93*, 5229. Aly, H. A. E.; Barlow, J. H.; Russell, D. R.; Smith, D. J. H.; Swindles, M.; Trippett, S. *J. Chem. Soc., Chem. Commun.* **1976**, 449. Bestmann, H. J.; Roth, K.; Wilheilm, E.; Böhme, R.; Burzlaff, H. *Angew. Chem.* **u1979**, *91*, 945. For additional NMR studies, see: Gibson, J. A.; Roschenthaler, G. V.; Wray, V. *J. Chem. Soc., Dalton Trans.* **1977**, 1492. Dakternicks, D.; Roschenthaler, G. V.; Sauerbrey, K.; Schmutzler, R. *Chem. Ber.* **1979**, *112*, 2380.

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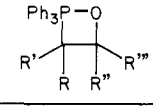
Table I. ^{31}P Characterization of Oxaphosphetanes (Salt-Free Unless Indicated Otherwise)



A. R = R' = H in all Cases

(1) R" = H, R"' = H, δ −63 (t, $J \geq 6$ Hz), toluene[a,b]
(2) R" = H, R"' = $PhCH_2CH_2$, δ −68.3 (unresolved m), THF
R" = H, R"' = $PhCH_2CH_2$, δ −68.1 (unresolved m), THF[a,b]
(3) R" = H, R"' = $(CH_3)_3C$, δ −71 (br d,d, $J \geq 11$, 8 Hz), THF
R" = H, R"' = $(CH_3)_3C$, δ −71 (unresolved), THF[a,b]
(4) R" = H, R"' = Ph, δ −68 (br. t, $J \geq 7$ Hz), THF
R" = H, R"' = Ph, δ −69 (br. t, $J \geq 7$ Hz), toluene[a,b]
R" = H, R"' = Ph, THF[a,c]
(5) R" = H, R"' = p-ClC_6H_4, δ −68 (br t, $J \geq 6$ Hz), THF
(6) R", R"' = $(CH_2)_5$, δ −74 (t, $J \geq 12$ Hz),[d] THF
R", R"' = $(CH_2)_5$, δ −73 (unresolved), THF[a,b]
(7) R", R"' = $(CH_2)_3$, δ −71 (t, $J \geq 8$ Hz), THF
(8) R", R"' = (C_6H_{10}, ketone = norcamphor), δ −73 (t, $J \geq 11$ Hz), THF

B. R = H, R' = CH_3

(1) R" = H, R"' = CH_2CH_2Ph, δ −61 (unresolved m), THF
R" = H, R"' = CH_2CH_2Ph, δ −61 THF[a]
(2) R" = H, R"' = $(CH_3)_3C$, δ −64 (q,d,d, $J \geq 20$, 7, 3 Hz), THF
R" = H, R"' = $(CH_3)_3C$, δ −64 (q,d,d, $J \geq 20$, 7, 3 Hz), THF[a]
(3) R" = H, R"' = n-C_5H_{11}, δ −62 (unresolved m), THF
(4) R" = H, R"' = Ph, δ −61 (br q, $J \geq 24$ Hz), THF
R" = H, R"' = Ph, δ −62 (br q, $J \geq 24$ Hz), THF[a]
(5) R" = H, R"' = p-ClC_6H_4, δ −62 (br q, $J \geq 22$ Hz), THF
(6) R", R"' = $(CH_2)_5$, δ −65 (q,d, $J \geq 24$, 14 Hz), THF
R", R"' = $(CH_2)_5$, δ −66 (q,d, $J \geq 24$, 14 Hz), THF[a]
(7) R", R"' = $(CH_2)_3$, δ −64 (q,d, $J \geq 25$, 14 Hz), THF
(8) R", R"' = (C_6H_{10}, ketone = norcamphor), δ 65, 66, ca. 1:1 ratio[e] (two partially overlapping q,d, $J \geq 23$, 12 Hz), THF

C. R = R' = CH_3

(1) R" = H, R"' = C_6H_5, δ −57 ("septet"−5 maxima, 2 inflection pts−$J \geq 10$ Hz)

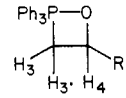
[a] LiBr present. [b] Precipitate formed at −78 °C. [c] Precipitate; no ^{31}P signals. [d] Unresolved at −78 °C, sharp resolution at −25 °C, all experiments at −78 °C and spectra at −40 °C to −50 °C unless noted otherwise. [e] Diastereomeric oxaphosphetanes, decomposition gives 1:1 ratio of olefin isomers.

reasonably stable and survives brief exposure to the atmosphere at room temperature. Spontaneous melting and decomposition to *p*-chlorostyrene occurs within 1–2 min if the solid is placed on a spatula at 20 °C. The proton spectrum (270 MHz, toluene-d_8) shows H_4 at δ 4.55 (dt, $J_{H_4-H_3} = J_{H_4-H_{3'}} = 7$ Hz; $J_{H_4-P} = 6.6$ Hz) and two protons ($H_3 + H_{3'}$) at 4.03 ($J_{H_3-P} = J_{H_{3'}-P} = 16.0$ Hz). The methylene protons are at unexpectedly low field, but similar H_3 shifts are observed with all of the oxaphosphetanes studied. More surprising is the apparent magnetic equivalence of H_3 and $H_{3'}$. However, H_3 and $H_{3'}$ are nonequivalent in other methylide adducts of aromatic aldehydes (PhCHO, p-$CH_3OPhCHO$).

The corresponding pivalaldehyde–methylide adduct is slower to form and does not crystallize. However, excellent 270-MHz proton spectra can be obtained when the condensation is performed in toulene-d_8. The methylene protons of the pivalaldehyde–methylide adduct are well separated, and all of the coupling parameters are apparent from first-order analysis: H_3, 4.10 ppm (ddd, $J_{H_3-P} = 20.5$ Hz, $J_{H_3-H_{3'}} = 15.0$ Hz, $J_{H_3-H_4} = 8.1$ Hz); $H_{3'}$, 3.50 ppm (ddd, $J_{H_{3'}-P} = 12.5$ Hz, $J_{H_3-H_3} = 15.0$ Hz, $J_{H_{3'}-H_4} = 5.5$ Hz); H_4, 3.31 ppm (ddd, J_{H_4-P} = ca. 5 Hz, $J_{H_4-H_{3'}} = 5.5$ Hz, $J_{H_4-H_3} = 8.1$ Hz). Judging from the different values of J_{H_3-P} vs. $J_{H_{3'}-P}$, the spatial orientation of the methylene protons with respect to the O–P–C_3 plane must be unsymmetrical. The four-membered ring is apparently distorted from a planar geometry to accommodate the bulky *tert*-butyl group, in contrast to other oxaphosphetanes.[12]

(13) The adduct of PhCHO + CH_2=PPh_3 does solidify upon solvent removal, but we have not been able to induce crystallization from solvents without contamination by triphenylphosphine oxide.

The phosphorus spectrum of the $ClC_6H_4CHO + CH_2$=PPh_3 adduct consists of a single absorption at −68 ppm. The signal is not resolved clearly, but inflection points indicative of a symmetrical triplet, $J \geq 6$ Hz, are apparent. This behavior is typical of aryl aldehyde adducts with the CH_2P *J* value decreased considerably by off-resonance decoupler effects. The pivaldehyde adduct shows a broadened doublet of doublets at −71 ppm in the aryl-decoupled ^{31}P spectrum, $J \geq 11$ and 8 Hz. Since three different aliphatic H···P coupling constants (20.5, 12.5, ca. 5 Hz) are visible in the proton spectrum, the off-resonance effect apparently obscures the 5-Hz *J* value. Other aliphatic aldehyde–methylide adducts show indications of similar, complex coupling although none has been as well resolved.



(2) CH_2=PPh_3 + Cyclohexanone. This reaction is slower than with ClC_6H_4CHO but faster than with $(CH_3)_3CCHO$. A color end point can be detected if the ketone is added very slowly. The ^{31}P signal of the adduct at −74 ppm is cleanly resolved into a triplet, apparent $J \geq 12$ Hz, by using aryl H decoupling. In general, the ^{31}P multiplets for ketone adducts are much easier to resolve than for aldehyde adducts, presumably because spectra of the latter are broadened by coupling to the methine proton α to oxygen. In the proton spectrum (toluene-d_8), the CH_2 group appears at 3.91 ppm (d, $J_{P-CH_2} = 15.7$ Hz).

(3) CH_3CH=PPh_3 + $(CH_3)_3CCHO$. Adduct formation requires ca. 0.5 h at −78 °C. The adduct does not crystallize, but the solution in toluene-d_8 is sufficiently clean for observation by 100-MHz proton NMR. In addition to strong signals in the methyl region, the solution displays methine absorptions at 3.85 and 4.50 ppm. With phosphorus decoupled, the 3.85-ppm signal is a doublet ($J = 7$ Hz) and must therefore be due to oxaphosphetane H_4. The 4.50-ppm signal (H_3) is a doublet of quartets ($J_{H_3-H_4} = 7$ Hz, $J_{H_3-CH_3} = 8$ Hz). Marginal resolution in the absence of P decoupling obscures the proton phosphorus couplings.

The pivalaldehyde adduct decomposes to give >99% *cis*-4,4-dimethyl-2-pentene, a result which is independent of the presence of lithium halides. A value of 7 Hz for $J_{3,4}$ is consistent with a cis-disubstituted oxaphosphetane.

The ^{31}P spectrum of the pivalaldehyde–ethylide adduct is exceptionally well resolved compared to other aldehyde adducts. With aryl H decoupling, the pentavalent phosphorus signal at −64 ppm appears as a quartet of doublets of doublets (apparent $J_{P-C-CH_3} \geq 20$ Hz, $J_{P-H_3} \geq 7$ Hz, and $J_{P-H_4} \geq 3$ Hz).

(4) CH_3CH=PPh_3 + PhCHO. This adduct can be prepared in the usual way in toluene-d_8. Proton NMR studies with phosphorus decoupling reveal oxaphosphetane H_4 at 5.4 ppm (d, $J = 7.5$ Hz) and H_3 at 5 ppm (methyl-coupled multiplet, partly obscured by minor unknown signals, $J_{3,4} = 7.5$ Hz).

The ^{31}P spectrum of the benzaldehyde adduct consists of a broadened quartet with inflection points characteristic of partly resolved doublet character in each line, δ −61 ($J_{P-C-CH_3} \geq 24$ Hz, $J_{P-CH} < 4$ Hz). Other aldehyde–ethylide adducts are likewise dominated by methyl coupling. With broad-band noise decoupling, the benzaldehyde adduct collapses to a single sharp resonance.

(5) CH_3CH=PPh_3 + Cyclohexanone. As in the case of CH_2=PPh_3 + ketone adducts, much improved resolution is observed with ketone–ethylide adducts relative to the aldehyde analogues. The oxaphosphetane derived from cyclohexanone appears at −64 ppm as a quartet of doublets ($J_{P-C-CH_3} \geq 25$ Hz, $J_{P-CH} \geq 14$ Hz).[7]

(6) $(CH_3)_2C$=PPh_3 + PhCHO. The ^{31}P spectrum displays a broadened septet at −57.4 ppm. Adduct formation occurs normally at −78 °C.

(7) $(CH_3)_2C$=PPh_3 + Cyclohexanone. Combination of the reactants in toluene at −78 °C gives no immediately observable change in the ^{31}P spectrum. Upon being warmed to −30 °C the ylide signal at +9 ppm disappears, but no pentavalent phosphorus signals can be detected. Instead, a broad absorption at +31 ppm

is observed. The ylide color disappears and a fine white precipitate is apparent. After the solution is quenched with aqueous HBr, isopropyltriphenylphosphonium bromide can be isolated.

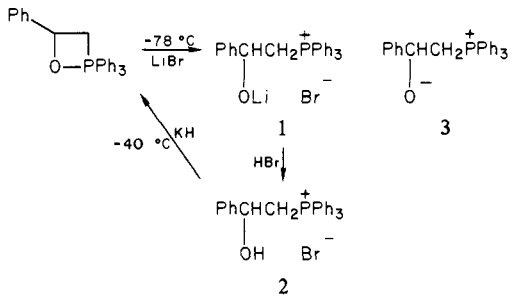
These results suggest that simple enolization has occurred upon addition of cyclohexanone to isopropylidenetriphenylphosphorane. Our findings are consistent with the well-known failure of enolizable ketones to condense with α-disubstituted ylides.[14]

Oxaphosphetane Decomposition Rates The ^{31}P technique is not well suited for quantitative rate studies.[17] Nevertheless, some interesting qualitative observations can be made. Oxaphosphetanes are stable below −35 °C and decompose at −25 °C or above. Methylide adducts decompose considerably faster than do the ethylide-derived oxaphosphetanes.[18] At −25 °C, in order of decreasing rate, methylide adducts of dihydrocinnammaldehyde, cyclohexanone, *p*-chlorobenzaldehyde, and benzaldehyde all decompose with half-lives of the order of ≤0.5 h, with the dihydrocinnammaldehyde adduct decomposing significantly faster than the others. The corresponding ethylide adducts undergo measurable, but very slow (<5%) decomposition over the same time scale. At −8 °C, typical methylide adducts are totally decomposed within a few minutes while the rates of ethylide adduct decomposition are now of the order of $T_{1/2} \approx 0.5$ hr. About 50% of the relatively stable $CH_3CH{=}PPh_3$ + PhCHO adduct survives after 90 s at 20 °C. In the case of ketones, cyclohexanone adducts decompose at about the same rate a aromatic aldehyde adducts, but cyclobutanone- or norbornanone- derived oxpahosphetanes require >0 °C for conversion to the (strained) alkene.

The decomposition rate differences between methylide and ethylide adducts have been verified by internal competition experiments and are undoubtedly real. However, the differences are too small to justify detailed rationalization. Most important, these experiments must not be confused with other reports of adduct decomposition in the presence of lithium halides which often cause precipitation of Wittig intermediates as the betaine–lithium halide adducts.[5] If good complexing agents for Li^+ are present, betaine–lithium halide adducts may decompose below 0 °C. Otherwise, prolonged reaction times at elevated temperatures have been found necessary in extreme cases. In our experience, THF is a sufficient Li^+ scavenger to promote betaine–lithium halide decomposition to alkenes at 0 °C, but ether frequently is not.

The Role of Lithium Halides: General Features. When alkyltriphenylphosphonium bromides are treated with *n*-butyllithium in ether or THF, the lithium bromide is retained in solution. On the basis of ^{31}P–^{13}C coupling data, solutions of $CH_2{=}PPh_3$ + LiBr are best described by the organolithium structure $LiCH_2PPh_3{}^+Br^-$ while solutions of alkyl-substituted ylides $RCH{=}PPh_3$ retain the *J* values of salt-free ylides and therefore interact little, if at all, with the LiBr.[20] Along similar lines, we find that "$CH_2{=}PPh_3$" in toluene prepared from $CH_3PPh_3{}^+Br^-$ + BuLi retains ca. 0.5 mol of the theoretical amount of LiBr after filtration (Br^- analysis) while solutions of $CH_3CH{=}PPh_3$ or alkyl-substituted analogues prepared similarly contain no LiBr.[21] Addition of carbonyl compounds to $CH_2{=}PPh_3$ + LiBr in THF, ether, or toluene generally results in formation of the insoluble betaine–lithium bromide adduct. In some cases (see Table I), the oxaphosphetane structure is also present and can be observed in the ^{31}P spectrum. However, no signals due to the betaine–lithium bromide adducts have been detected in any of our experiments.

A solution of the salt-free oxaphosphetane adduct of $CH_2{=}PPh_3$ + PhCHO reacts at once with equimolar LiBr in THF at −78 °C to give betaine–lithium bromide adduct **1** as a white



precipitate. After dilute HBr workup, the hydroxyphosphonium salt **2** can be isolated in good yield. When pure **2** is stirred with KH at −40 °C in THF, a solution containing ^{31}P signals of the starting oxaphosphetane is obtained. No tetravalent phosphorus signals which might be due to betaine **3** are present. Thus, oxaphosphetanes can be cleaved rapidly by LiBr to give the insoluble (and, in this case, more stable) betaine–lithium bromide adducts. Conversely, betaine **3** prepared independently in the absence of LiBr (KH experiment) is not stable and cyclizes rapidly to the oxaphosphetane. Similar observations have been described by Schlosser et al.,[22] who have also reported a possible example of a soluble betaine–lithium halide adduct ($Bu_3{}^+PCH_2CPh_2OLi\,I^-$).[23]

Lithium salt-containing solutions of $CH_3CH{=}PPh_3$ in ether or THF react with some carbonyl compounds to give precipitates, but the oxaphosphetane is usually present also according to ^{31}P NMR. In toluene solution, $CH_3CH{=}PPh_3$ prepared by the butyllithium method behaves exactly as does salt-free ylide from the sodamide method.

These results show that energy barriers for salt-free betaine cyclization to oxaphosphetanes or for oxaphosphetane cleavage by lithium halides are not large. As mentioned before, reclosure of the betaine–lithium halide adducts to oxaphosphetanes depends on the presence of Li^+ coordinating agents and can be relatively difficult in their absence. Conversely, reactions which are characteristic of betaine-like structures can be slow unless lithium halides or other Lewis acids are present. For example, formation of alkoxyylides from certain oxaphosphetanes + BuLi does not occur at −78 °C unless LiBr is added.[24]

When an excess of a carbonyl component is added to the ylide–lithium bromide solutions, one or two minor new ^{31}P NMR peaks often appear in the pentavalent phosphorus region. Similar behavior is sometimes seen under salt-free conditions if the carbonyl component is not carefully purified prior to use. We have no evidence on the exact structure of these unknown species other than the empirical correlation with excess carbonyl compound and the presence of potential protic or Lewis acids.

Our preliminary communication reported the possible observation of two diastereomeric oxaphosphetanes from ethylide and benzaldehyde.[3] Since this was an experiment conducted in the presence of LiBr, we are now quite certain that the second (minor) pentavalent phosphorus species observed in a narrow temperature range was actually due to interaction of excess benzaldehyde with the oxaphosphetane as discussed above. None of the aldehyde–ethylide derived oxaphosphetanes prepared under the best conditions (salt-free; excess ylide) show any evidence of resolved ^{31}P signals from both cis and trans diastereomers. This is not surprising since the oxaphosphetane chemical shift range is quite small for aldehyde derived adducts.

Lithium Halides and Olefin Geometry. The empirical effect of lithium salts on the stereochemistry of the aldehyde Wittig re-

(14) We are aware of only one report that $Ph_3P{=}C(CH_3)$ can be used for Wittig olefination of an enolizable ketone.[15] With other very closely related substrates, no Wittig products are formed.[16]

(15) Baldwin, S. W.; Gawley, R. E. *Tetrahedron Lett.* **1975**, 3969.

(16) McGuire, H. M.; Odom, H. C.; Pinder, A. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1879.

(17) The Fourier transform technique requires significant time (2–15 min, depending on sample concentration). Other complications include varying degrees of NOE signal enhancement and no better than ±10% peak area reproducibility.

(18) A similar observation has been mentioned by Schlosser although the method has not been specified (ref 19, p 13).

(19) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1.

(20) (a) Albright, T. A.; Schweizer, E. E. *J. Org. Chem.* **1976**, *41*, 1168. (b) Ostoja Starzewski, K. A.; Tom Dieck, H. *Phosphorus* **1976**, *6*, 177. (c) Schmidbaur, H.; Tronich, W. *Chem. Ber.* **1968**, *101*, 3556. (d) Albright, T. A.; Gordon, M. D.; Freeman, W. J.; Schweizer, E. E. *J. Am. Chem. Soc.* **1975**, *98*, 6249. (e) Schmidbaur, H. *Acc. Chem. Res.* **1975**, *8*, 62.

(21) See ref 20a for similar findings.

(22) See ref 11, footnote 7.

(23) Schlosser, M.; Tuong, H. B.; Tarchini, C. *Chimia*, **1977**, *31*, 219.

(24) Vedejs, E.; Meier, G. P., submitted for publication.

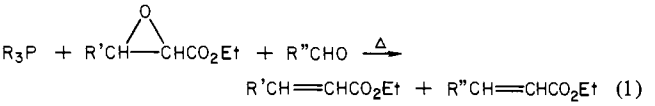
actions is now clear, largely due to the systematic studies of Schlosser et al.[5] However, very little is known regarding the origins of the effect. Unstabilized salt-free ylides $RCH{=}PPh_3$ react with aldehydes to give >90% cis alkenes in polar as well as nonpolar aprotic solvents.[19,25] if the ylide is made from $RCH_2{}^+PPh_3\ X^-$ + butyllithium, the cis:trans ratio is much lower unless strong chelating agents for Li^+ are also present in solution.[5,19,26] Previous studies do not establish whether (1) the stereochemistry is already influenced in the condensation step due to competition by a modified Wittig mechanism involving LiX or (2) whether the oxaphosphetane is formed normally and undergoes partial LiX-induced cis,trans equilibration.[5] Evidence from indirect generation of Wittig intermediates (epoxide + $LiPPh_2$; CH_3I) suggests that (1) is more likely but that (2) may also play a role in special cases. Thus, epoxide deoxygenation via the betaine and oxaphosphetane in the presence of LiI occurs with <1% loss of stereochemistry in a number of examples.[1,2] However, partial loss of stereochemistry can compete under certain experimental conditions if the rate of oxaphosphetane decomposition is unusually slow (*cis*-cyclooctene oxide → *trans*-cyclooctene).[1] Schlosser et al. have also reported some examples of stereochemical equilibration of Wittig intermediates by LiX, but these studies were performed with benzaldehyde adducts which are anomalous in the sense that they appear capable of reversal to the ylide and aldehyde (see next section).[5] The presence of alcohols or alkoxides also promotes oxaphosphetane cis,trans equilibration[27,28] via an α-deprotonation process.

To determine whether (1) or (2) or a combination of both might be responsible for the lithium halide effect on olefin geometry, we have investigated the reaction $PhCH_2CH_2CHO$ + $CH_3CH{=}PPh_3$ in some detail. **Experiment 1**: addition of $PhCH_2CH_2CHO$ to the ylide in THF at −78 °C gives a homogeneous solution, and warming to 0 °C (20 min) results in 5-phenyl-2-pentene, 24:1 cis:trans. **Experiment 2**: salt-free ylide is first combined with 1 equiv of dry LiBr in THF, and the experiment is then repeated exactly as above. A thick white precipitate (betaine–lithium bromide adduct) appears upon addition of the aldehyde. Precipitated solids persist until water is added during workup, but the eventual yield of alkene is the same as in the salt-free experiment. The 5-phenyl-2-pentene is 3:1 cis:trans. Virtually the same cis:trans ratio has been obtained in 5-phenyl-2-pentene from $CH_3CH{=}PPh_3$ made by the butyllithium method ($CH_3CH_2PPh_3{}^+Br^-$).[3] **Experiment 3**: the salt-free oxaphosphetane prepared at −78 °C as in experiment 1 is treated with 1 equiv of dry LiBr in THF to duplicate the concentration of experiment 2. An immediate white precipitate appears upon adding the LiBr. After the solution is warmed to 0 °C as before, the olefin cis:trans ratio is 24:1.

There is no detectable cis,trans equilibration of the oxaphosphetane in THF on this time scale, even though the betaine–lithium bromide adduct is formed whenever LiBr is present. Whether or not other experimental conditions might cause stereochemical equilibration of this or of other oxaphosphetanes is not of great importance. Far more significant is the conclusion that at least 20% of the 5-phenyl-2-pentene is formed by a different mechanism when LiBr is present in the starting ylide than under salt-free conditions.

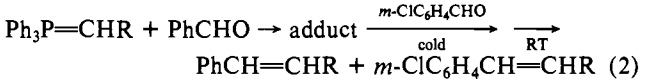
Reversibility of the Wittig Condensation Step. Reversible dissociation of the Wittig intermediate into starting ylide and aldehyde has often been invoked to explain the increasing tendency for trans-olefin formation as the stability of the ylide increases. On the basis of negative "crossover" experiments, it is now generally agreed that intermediates from *aliphatic* aldehydes and nonstabilized ylides do not revert to the starting materials under typical Wittig conditions.[5,19,28]

Even with positive crossover experiments, substantial ambiguities remain. Reversible adduct formation with stabilized ylides is generally accepted, but the only direct evidence on this point comes from the assumed generation of Wittig intermediates in reaction 1 under distinctly atypical conditions.[29a] The same



technique also indicates significant crossover with 4-octene oxide, a system which would have to fragment to a nonstabilized ylide and an aliphatic aldehyde. Since no such fragmentation has been detected from intermediates of aliphatic aldehyde Wittig reactions, the relevance of high temperature epoxide deoxygenation to representative Wittig conditions is open to question.

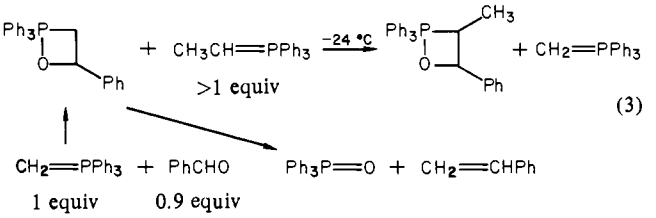
Other examples of crossover have been reported where the Wittig intermediates are formed indirectly (from β-hydroxyphosphonium salts),[5,30] but we are aware of only one series of experiments where crossover has been demonstrated with true Wittig intermediates which are clearly in the oxaphosphetane form. Schlosser et al. have referred to experiments of type 2. Although



full experimental details have not been published, it is clear that crossover is extensive for R = CH_3 and minor, but measurable, for R = H.[5,19]

According to ^{31}P evidence, excess aldehyde may be incorporated into the Wittig intermediate in the presence of Lewis acids. This observation raises some questions regarding crossover with added *m*-ClC_6H_4CHO since potential 1:2 adducts of ylide and aldehyde might have access to crossover mechanisms which do not require formal dissociation of an oxaphosphetane into the original components. We have therefore performed crossover studies which do not depend on the presence of excess aldehyde. Our results corroborate Schlosser's findings: oxaphosphetanes prepared from $CH_3CH{=}PPh_3$ or $CH_2{=}PPh_3$ and aromatic aldehydes are capable of reversible dissociation, but analogues prepared from aliphatic carbonyl compounds are not.

The simplest experiment relies upon ^{31}P NMR monitoring of characteristic oxaphosphetane signals. Sequence 3 establishes



crossover between a salt-free oxaphosphetane and excess ylide. After 35 min at −24 °C, ca. 82% of the original oxaphosphetane has decomposed to triphenylphosphine oxide, 13% survives, and the remainder (5%) is present as the crossover product, the adduct of PhCHO + $CH_3CH{=}PPh_3$. No crossover is seen at −50 °C after 1 h. Similar experiments show that methylide adducts of cyclohexanone and dihydrocinnammaldehyde do not undergo retro-Wittig dissociation competitively with fragmentation to the alkene.

A ^{31}P NMR technique can also be used to demonstrate crossover process 4 (salt-free). In this case, the oxaphosphetanes cannot be distinguished, but the reservoir of excess ylide can be assayed qualitatively for crossover. At temperatures below −30 °C, the excess ylide consists of $CH_3CD{=}PPh_3$, observed as a

(25) Early reports of cis olefinations in typical reactive ylide–aliphatic aldehyde reactions: Bergelson, L. D.; Shemyakin, M. M. *Pure Appl. Chem.* **1964**, *9*, 271 and references therein. Hauser, C. F.; Brooks, T. W.; Miles, M. L.; Raymond, M. A.; Butler, G. B. *J. Org. Chem.* **1963**, *28*, 372.

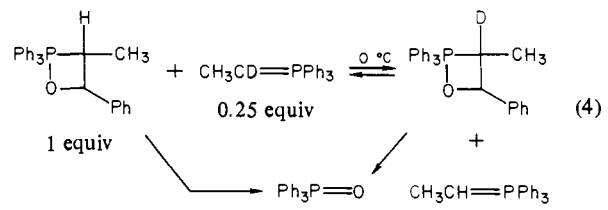
(26) Sonnet, P. E. *J. Org. Chem.* **1974**, *39*, 3793; *Org. Prep. Proced. Int.* **1974**, *6*, 269.

(27) Schlosser, M., Christmann, K.-F., Piskala, A. *Chem. Ber.* **1970**, *103*, 2814.

(28) Anderson, R. J.; Henrick, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327.

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

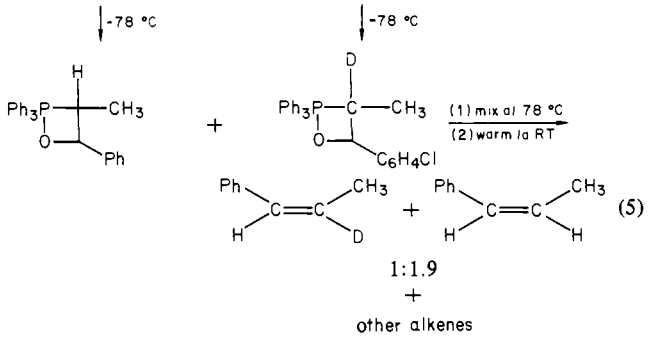
(30) Jones, M. E.; Trippett, S. *J. Chem. Soc. C* **1966**, 1090.



(4)

quartet in the ^{31}P spectrum (J_{CH_3-P} only) and there is no crossover. At 0 °C, crossover occurs competitively with Wittig fragmentation. After 20 min, 75% of the oxaphosphetane has decomposed to $Ph_3P{=}O$ and alkene, and the reservoir of excess ylide now consists of a ca. 1:1 mixture of $CH_3CD{=}PPh_3$ and $CH_3CH{=}PPh_3$ (^{31}P ylide signal is a quintet of protio ylide overlapping the quartet of deuterio ylide).

For final verification, a double-labeling experiment based on analysis of isolated (*Z*)-β-methylstyrene is conclusive (see eq 5).



(5)

In spite of ca. 34% crossover, the β-methyl styrene is nevertheless formed with high cis selectivity (93%). This experiment shows that there is no great kinetic preference for alkene formation by decomposition of a trans-disubstituted oxaphosphetane relative to the cis isomer, contrary to a popular assumption. All of the crossover experiments leave no doubt that the benzaldehyde-derived oxaphosphetanes do revert to the starting materials competitively with alkene formation. If high cis selectivity is maintained in a reversible Wittig condensation, it follows that high trans selectivity should no longer be accepted as sufficient evidence for reversibility in moderated or stabilized ylide condensations. This latter topic deserves more study.

Rationale. The mechanism of the Wittig reaction is controversial. Prior to 1972, it was common practice to rationalize the most diverse ylide condensations by variants of a single mechanism based on betaine intermediates. The first indications to the contrary appeared from kinetic studies with stabilized ylides, experiments which suggested that the transition state has little charge separation.[31] Shortly thereafter, we reported the first evidence that oxaphosphetanes are the low-temperature Wittig intermediates from nonstabilized ylides.[3] Since it is now clear that salt-free betaines are neither stable nor observable by available techniques, their use in mechanistic rationales is not justified until simpler alternatives can be ruled out.

Betaine–lithium halide adducts, on the other hand, are certainly formed in numerous condensations of nonstabilized ylides when dissolved lithium halides are available. Current evidence does not distinguish whether betaine–lithium halide aducts are formed directly from an ionic addition process ($Ph_3P{=}CHR + R'CHO + LiX \rightarrow Ph_3P^+CHRCHR'OLiX^-$) or whether an oxaphosphetane–lithium(+1) complex is formed initially and undergoes ring opening. However, we have shown conclusively that LiBr affects stereochemistry by altering the condensation step (lower cis:trans ratio from $Ph_3P{=}CHCH_3 + PhCH_2CH_2CHO$) and *not* by inducing subsequent cis,trans equilibration of the oxaphosphetane. Therefore, at least some fraction of this condensation process occurs by a different mechanism in the presence of LiX than under salt-free conditions.

The effect of lithium halides on alkene geometry varies in degree depending on the nature of R′ in R′CHO. Aromatic aldehydes show the most dramatic reduction of the cis:trans ratio, a result which may be related to the reversibility of oxaphosphetane formation.[5,19] However, there is no apparent effect of LiX if R′ is a tertiary alkyl group. Selectivity of ≥99% cis has been reported in two cases despite the presence of LiBr.[3,32]

Since the relative rates of potentially competing LiX-catalyzed vs. uncatalyzed condensations are not known in any example, it is not yet possible to deduce the actual cis:trans ratio for the catalyzed process. Without that information, any rationale of the LiX effect on olefin geometry is a pointless exercise. Not even the site of LiX involvement can be specified with certainty. Coordination of Li^+ to the carbonyl group is an obvious possibility, but involvement of an unstable $Ph_3P^+CHRLiX^-$ species analogous to the observable[20] $Ph_3P^+CH_2LiX^-$ has not been ruled out.

There probably is no single unifying mechanism for all Wittig reactions. Ylides behave differently depending on reaction conditions, and changes in ylide structure, stabilization,[33] and carbonyl substrate may well cause significant mechanistic changes. At present, the reactions of nonstabilized, salt-free ylides are by far the most extensively studied and characterized. The remainder of this discussion deals exclusively with salt-free $Ph_3P{=}CHR$, R = alkyl.

The mechanistic puzzle of how the reaction $Ph_3P{=}CHR$ + R′CHO takes place revolves around the preponderant formation of *cis* alkenes. For aliphatic aldehydes, cis selectivity increases from ca. 95% to ca. 99% as R′ is varied from *n*-alkyl to *tert*-alkyl.[3,19,32] Essentially identical results are observed in DMF, Me_2SO, ether, toluene, etc. It is also established that cis-disubstituted oxaphosphetanes are precursors of cis alkenes[34] and that oxaphosphetane dissociation into ylide and aliphatic aldehyde is not a factor.

The absence of solvent effects on stereochemistry suggests a transition state with significant P—O as well as C—C bonding. A cycloaddition rationale for the condensation ArCHO + $Ph_3P{=}CHR$ is also supported by a Hammett study.[11] The value of ρ = ca. +1.1 is reasonable for the carbonyl group as an electron-poor partner in a nonsynchronous 2 + 2 cycloaddition with electron-rich ylide. By comparison, $\rho = -0.7$ has been reported for the electron-rich styrene reactants in the presumed cycloaddition $Ph_2C{=}C{=}O + ArCH{=}CH_2$.[35] The magnitudes of ρ in other cycloadditions are similar, and the sign depends on relative electron demand of the reactants.[36]

The simplest Wittig rationale which accounts for high cis selectivity is a cycloaddition process having the plane of partially rehybridized aldehyde tilted with respect to the ylide plane to minimize nonbonded interactions and also having the C=O and ylide C—P bonds "crisscrossed" to maintain reasonable C···C and P···O bonding distance. Any crisscrossed transition-state geometry between two limiting situations **4** (parallel planes) and 5 (planes tilted 90°) will lead to a cis-disubstituted oxaphosphetne as bonding

(31) Froyen, P. *Acta Chem. Scand.* **1972**, *26*, 2163. Aksnes, G.; Khalil, F. Y. *Phosphorus* **1972**, *2*, 105. *Ibid.* **1973**, *3*, 79. Nesmeyanov, N. A.; Vishtok, E. V.; Reutov, U. A. *Dokl. Akad. Nauk SSSR* **1973**, *210*, 1102.

(32) Salomon, R. G.; El Sanadi, N. *J. Am. Chem. Soc.* **1975**, *97*, 6214 (LiBr present). See: Corey, E. J.; Kwiatkowski, G. T. *Ibid.* **1966**, *88*, 5653 for 98.5% cis selectivity for $(CH_3)_3CCHO$ under salt-free conditions.

(33) For a recent discussion of the role of cycloaddition in stabilized ylide reactions, see: Giese, B.; Schoch, J.; Ruchardt, C. *Chem. Ber.* **1978**, *111*, 1395.

(34) The evidence for retention of carbon geometry is based on epoxide deoxygenation with phosphines[29] or with $LiPPh_2$ followed by quaternization with CH_3I,[1,2,30] experiments where oxaphosphetanes are formed via indirect generation of betaines. The phosphine experiments are salt-free, while the $LiPPh_2$ examples are performed with LiI present throughout. While some caution is appropriate in extrapolating these results to typical Wittig condensations, there is no evidence to suggest any stereochemical result other than retention at carbon. More than 99% retention has been observed in typical cases.[2]

(35) Baldwin, J. E.; Kapecki, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4868.

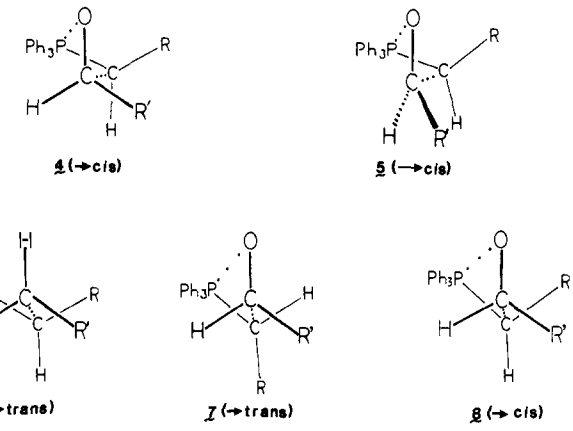
(36) DeWitt, E. J.; Lester, C. T.; Ropp, G. A. *J. Am. Chem. Soc.* **1956**, *78*, 2101. Matthews, D. N.; Becker, E. I. *J. Org. Chem.* **1966**, *31*, 1135; Sustmann, R. *Tetrahedron Lett.* **1974**, 963 and references therein.

proceeds. Crisscrossed arrangements such as **6**, leading to trans-disubstituted oxaphosphetane, are destabilized by increased interaction between ylide R group with the bulkier end of the carbonyl group. However, we see little basis for believing that **4** would be more stable than an alternative parallel transition-state **7** which leads to trans product. More important, the relative stability of parallel transition-state geometries such as **4**, **6**, **7**, **8**, etc. must be sensitive to a change of aldehyde R′ from *n*-alkyl to *tert*-alkyl. Any such change would be expected to favor **7** relative to the others and should decrease cis selectivity. The observed result is a small increase.

If the transition state leading to cis products more nearly resembles **5**, the increase in selectivity for bulky aldehydes is reasonable. Tilting the aldehyde plane minimizes interactions between R′ and the Ph_3P and R substituents of the ylide. As R′ becomes larger, the angle of tilt can increase if necessary until a compromise is reached between minimal R′–ylide interactions vs. increased aldehyde CH–ylide interactions. Competing transition-states **6** or **7** which afford trans-disubstituted oxaphosphetane cannot benefit to the same extent by tilting the aldehyde plane. In both **6** and **7**, the result of tilted geometries would be to increase aldehyde C–H interactions with the bulkier side of the ylide. According to this argument, trans alkenes are formed via a parallel approach as in **7**, and substantial R′-ylide interactions are unavoidable. Tilted cis-alkene precursor **5** would be less destabilized by bulky R′, resulting in a small increase in the cis:trans ratio. The exact transition-state geometry leading to cis products depends on the angle of tilt and the extent of rehybridization, but the approach of reacting components would be largely controlled by a trajectory which maximizes separation between R′ and bulky ylide groups.

At present, there is no theoretical basis for choosing between "parallel" cycloaddition geometries vs. tilted ones. A recent ab initio SCF treatment of hypothetical reaction $H_3PCH_2 + CH_2O$ concludes that a concerted parallel 2 + 2 reaction is feasible.[37] Since the energy difference between tilted **5** and parallel **4**, **6**, **7**, **8**, etc. depends on steric interactions of unsymmetrical, substituted ylides and aldehydes, the ab initio calculation does not address the problem of Wittig stereochemistry. Our preliminary communication noted that limiting crisscrossed geometry **5** with perpendicular aldehyde and ylide planes corresponds formally to the geometry proposed for ketene cycloadditions. The latter can be described as allowed 2s + 2a or 2s + 2s + 2s processes.[35,38] However, we have not suggested that any 2 + 2 cycloaddition of ylides + carbonyl compounds is forbidden.[39] The choice of tilted **5** over parallel **4**, **6**, **7**, **8**, etc. is based on a stereochemical rationale and *not* on orbital symmetry considerations.

Other rationales for aldehyde–ylide cis selectivity have appeared. Condensation via a zwitterionic intermediate with initial P–O bonding was proposed by Schneider in 1969.[40] Although this suggestion now appears unlikely in view of the more recent Hammett study, Schneider was the first to recognize that a nonparallel aldehyde–ylide orientation logically explains the stereochemical result. Bestmann has recently published a Wittig mechanism via a "quasi-betaine" transition state having both C···C and P···O interaction.[41] Stereochemistry is defined in an "approaching complex" along the Dunitz trajectory for nucleophilic addition to the aldehyde. Bestmann has not specified whether a "quasi-betaine" is the same as the transition state of a nonsynchronous cycloaddition or how an "approaching complex" is different from the transition state leading to a salt-free betaine. However, his rendition of the transition state differs from **8** only in that sp^3-bond angles are specified for the carbons. The Dunitz trajectory does not explain why **8** should be strongly favored over **7** or why selectivity should increase as R′ in R′CHO becomes larger.



Certain Wittig reactions of ketones are highly selective in favor of the more hindered alkene.[42] Tilted geometries analogous to **5** should be destabilized because one of the ketone alkyl groups must interact strongly with substituents in the ylide plane. Planar geometries related to **4** or **7** appear more likely, and the ketone analogue of **4** nicely accounts for some of the selective reactions. Systematic studies of ketone adduct stereochemistry, equilibration, and dissociation are needed before detailed rationales can be recommended. In qualitative agreement with the idea that tilted transition states predominate in Wittig reactions of aldehydes while planar geometries are more important for ketones, we have found that various R′CHO differ in relative reactivity by less than a factor of 4, while analogous ketones $R'COCH_3$ differ by a factor of >30.[43]

Conclusion

Oxaphosphetanes are the only Wittig intermediates observable by ^{31}P NMR under salt-free conditions, and they are sufficient intermediates in the sense that no other species are required to account for Wittig olefination. Variations of a crisscrossed cycloaddition transition state having tilted aldehyde and nonstabilized ylide planes effectively rationalize stereochemical results without resorting to nonobserved intermediates. However, other mechanisms are involved to an unknown extent when lithium halides are available and it must not be assumed that ylide–carbonyl reactions can be rationalized by one single scheme regardless of subsitution or conditions.

In the presence of lithium halides oxaphosphetanes can often be observed, but betaine–lithium halide adducts are also formed. With added base or hydroxylic agents, α-deprotonated species of uncertain composition which are equivalent to oxidoylides can be in equilibrium with oxaphosphetanes.[24,27] All labeling, kinetic, and stereochemical results available to date for reactions of nonstabilized alkylidenetriphenylphosphoranes can be rationalized by using the three observable species: oxaphosphetanes, be-

(37) Höller, R.; Lischka, H. *J. Am. Chem. Soc.* **1980**, *102*, 4632. See also: Trindle, C.; Hwang, J. T.; Carey, F. A. *J. Org. Chem.* **1973**, *38*, 2664.

(38) Hassner, A.; Cory, R. M.; Sartoris, N. *J. Am. Chem. Soc.* **1976**, *98*, 7698. Huisgen, R.; Mayr, H. *Tetrahedron Lett.* **1974**, 2969.

(39) The theoretical extrapolation from ketene + ethylene to carbonyl + ylide is long indeed. The double-bond notation "$Ph_3P{=}CH_2$" is used for convenience and not to imply extensive π character. It is generally agreed that ylide bonds are polar and have sp^2 carbon, but the extent of p–d overlap remains uncertain: Bart, J. C. J. *J. Chem. Soc. B* **1969**, 350. Hoffmann, R.; Boyd, D. B.; Goldberg, S. Z. *J. Am. Chem. Soc.* **1970**, *92* 3929. Absar, I.; Van Wazer, J. R. *Ibid.* **1972**, *94*, 2382. Lischka, H. *Ibid.* **1977**, *99*, 353. Strick, A. *Nouv. J. Chim.* **1979**, *3*, 105.

(40) Schneider, W. P. *J. Chem. Soc., Chem. Commun.* **1969**, 785.

(41) Bestmann, H. J. *Pure Appl. Chem.* **1979**, *51*, 515; *Ibid.* **1980**, *52*, 771.

(42) For leading references and recent examples of selective ketone olefinations, see: Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978** *100*, 3435. Sreekumar, C.; Darst, K. P., Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.

(43) Addition of $CH_3CH{=}PPh_3$ to fourfold excess $(CH_3)_3CCHO$ + *n*-$C_5H_{11}CHO$ gives a 4:1 ratio of $C_5H_{11}CH{=}CHCH_3$:$(CH_3)_3CCH{=}CHCH_3$. The corresponding reaction with excess $(CH_3)_3CCOCH_3$ + *n*-$C_5H_{11}COCH_3$ gives only a trace of the pinacolone products, and $(CH_3)_3C(CH_3){=}CHCH_3$:$C_5H_{11}C(CH_3){=}CHCH_3$ is at least 30:1. Methylidenetriphenylphosphorane is less selective toward aldehydes ($C_5H_{11}CHO$:$(CH_3)_3CCHO$, 1.6:1; $C_5H_{11}CHO$:$(C_2H_5)_2CHCHO$, 1.7:1) and comparably selective with ketones ($C_5H_{11}COCH_3$:$(C_2H_5)_2CHCOCH_3$, >30:1; $C_5H_{11}COCH_3$:$(CH_3)_3CCOCH_3$, 20:1) (experiments performed by K. A. J. Snoble and S. P. Singer).

taine–lithium halide adducts, oxidoylide–lithium halide adducts.

Calculations suggest that oxaphosphetanes are transformed into olefins by nonsynchronous cycloreversion (C_α···P bond breaking advanced relative to C_β···O bond breaking.)[37] In systems where C_α has strongly electron-withdrawing substituents, it is conceivable that an intermediate having formal negative charge at carbon might be formed although this has not been proved. However, the labeling evidence cited[41] in support of such an ionic intermediate from oxaphosphetanes lacking electron-withdrawing C_α substituents is not convincing and appears more compatible with intervention of oxidoylide derivatives.

From time to time, unusual stereochemical results are reported for Wittig reactions performed under unique conditions. Caution is appropriate in the interpretation of such results. The generalizations presented in this paper refer to specific conditions and to reactions of nonstabilized ylides with certain aldehydes and ketones. They should not be extended to other situations without performing the necessary control experiments regarding oxaphosphetane stability, reversal, and stereochemical equilibration.

Experimental Section

Ether solvents were dried by distillation from Na/Ph_2CO. Toluene was dried by distilling 20% of the volume, cooling, adding $LiAlH_4$ slowly until H_2 evolution subsided, and then distilling the remainder. Liquid ammonia was dried by distillation from a blue solution of sodium into a flame-dried flask fitted with a Dry Ice condenser.

Instrumental Methods. All ^{31}P spectra were determined by using a Varian XL-100 FT system, deuterium pulse lock. Samples were prepared in 10-mm tubes which were centered inside a 12-mm tube containing sufficient lock solvent for a stable lock signal. This concentric arrangement with a separate lock solvent reservoir sacrifices some resolution because fine tuning does not take into account homogeneity conditions in the sample itself. The benefits include arbitrary choice of reaction solvent. Selective aryl proton decoupling was performed by using the Hetero Hi × 14-20 db decoupler settings, with extensive power level optimization and frequency optimized within ±10 Hz.

Failure to optimize aryl H decoupler power for each case gave signals of unpredictable multiplicity due to off-resonance effects. Coupling due to hydrogens at >4 ppm in the proton spectrum was often obscured even under the best conditions, but higher field proton ^{31}P coupling was generally resolved. Thus, ^{31}P spectra of $(CH_3)_2C{=}PPh_3$ (septet, 9 ppm, $J \geq 10$ Hz) and $CH_2{=}PPh_3$ (t, 20 ppm, $J \geq 6$ Hz) were correctly resolved. However, $(CH_3)_2CHPPh_3Br^-$ gave a signal at 27 ppm ("septet", $J \geq 13$ Hz) with no resolvable coupling from the methine proton which resonates too close to the aryl H decoupler frequency and experiences the greatest off-resonance effect.

Broad-bandwidth noise decoupling was done at maximum power, 800-Hz bandwidth, centered at ca. 5 ppm in the proton spectrum. Chemical shifts are referenced to external 85% H_3PO_4 and are considered accurate to no more than ±1 ppm due to solvent and temperature changes. For any given experiment, the shifts are reproducible to ±0.1 ppm. Temperatures cited for variable-temperature experiments were determined by placing a thermocouple into the lock solvent reservoir (12-mm tube) after equilibrium had been reached.

Proton spectra were recorded at 100 MHz by using the XL-100 system in the CW mode with optional phosphorus decoupling or at 270 MHz (Bruker) without phosphorus decoupling.

Ylide Solutions From Alkyltriphenylphosphonium Bromides + BuLi: Retention of Dissolved LiBr. A specially designed 250-mL round-bottom flask was equipped with nitrogen inlets and outlets controlled by three-way vacuum stopcocks. A single ground-glass port "A" (14/20) was provided for introducing solid reactants, stir bars, etc. A coarse-porosity fritted-glass filter "B" equipped with its own removable receiver flask was fused horizontally to the 250-mL flask so that the frit could contact the solution in the reaction vessel when the latter was tilted. The entire apparatus was oven dried (150 °C) and was then maintained under nitrogen flow with the nitrogen vented through "B".

$CH_2{=}PPh_3$ in THF (BuLi Method). A suspension of 1.23 g (0.35 mmol) of $CH_3{}^+PPh_3Br^-$ in dry THF (28 mL) was placed in the above apparatus and cooled to −78 °C under N_2 flow. Port A wa sealed with a securely wired septum cap and *n*-butyllithium in hexane (2.1 mL, 3.5 mmol) was added by syringe to the stirred suspension. The canary yellow color of ylide appeared at once. After 2 h at −78 °C, the fine suspension was allowed to settle, the Dry Ice bath was removed, and the apparatus was tilted gently until the solution covered the glass frit. Nitrogen pressure caused the solution to pass into the receiver flask (50-mL three-neck, nitrogen-flow through) within 2–3 min unless settled solids were disturbed during the filtration. If the receiver flask was cooled (−20 °C or below), the ylide was obtained as a clear, bright yellow solution. After the solution was warmed to room temperature, the color darkened significantly. Color end point titration of an aliquot with PhCHO in ether or $PhCO_2H$ in THF at −20 °C (syringe techniques) showed the solution to be 0.11 M in ylide. An aliquot of ylide solution was quenched with distilled water sufficient to discharge the color. The total mixture was then evaporated to dryness (0.05 mm, 24 h), and the residue was subjected to elemental analysis: found, 8.13% P, 20.96% Br, ca. 1:1 mole ratio. A sample of ylide was examined by ^{31}P NMR, selective aryl decoupling. The spectrum showed a signal at δ 19.6 (t, $J \geq 6$ Hz).

Solubility of CH_2PPh_3 + LiBr in Toluene. A 15-mL sample of the THF solution of methylide prepared above was placed into a second flask fitted with the usual glass-frit filter attachment. The THF was evaporated (20 °C) by using rapid nitrogen flow, and the last traces were removed under high vacuum. Dry toluene (15 mL) was added to the stirred residue, and the mixture was filtered as usual into a receiver flask. An aliquot was quenched with water as above. Elemental analysis: 14.54% Br, 10.16% P, ca. 0.56 mol of Br/mol of P.

Soluble bromide was also obtained by stirring $CH_3{}^+PPh_3Br^-$ with *n*-butyllithium in toluene ($AgNO_3$ test) although deprotonation of the salt was slow compared to the THF reaction. Salt-containing $CH_2{=}PPh_3$ in toluene gave erratic results with carbonyl compounds and was not used for ^{31}P studies.

Ethylidenetriphenylphosphorane in Toluene (Butyllithium Method). A suspension of ethyltriphenylphosphonium bromide (1.86 g, 5 mmol) in dry toluene (40 mL) was stirred vigorously (paddle stirrer) with *n*-C_4H_9Li (5 mmol, in 3 mL of hexane) for 2.5 h at 20 °C in the usual apparatus. After filtration, a bright orange solution was obtained. By color end point titration of an aliquot with PhCHO at −20 °C, the solution was 0.091 M. A sample was quenched with water as in the methylide examples, and the product was evaporated to dryness (high vacuum). Elemental analysis showed <0.1% Br^-. This ylide solution could be used routinely for ^{31}P experiments, but salt-free ethylide was more conveniently obtained by the $NaNH_2/NH_3$ method.

Isopropylidenetriphenylphosphorane in Toluene (BuLi Method). The same procedure was used as for ethylidenetriphenylphosphorane (above). Thus, $(CH_3)_2CH^+PPh_3Br^-$ (1.16 g) and butyllithium (3 mmol) in toluene (23 mL) gave a deep red solution after filtration, 0.12 M. The ^{31}P spectrum consisted of a septet at δ 9.3 with selective aryl decoupling, $J \geq 10$ Hz. No dissolved bromide could be detected ($AgNO_3$) after quenching with dilute HNO_3.

Salt-Free Methylidenetriphenylphosphorane ($NaNH_2/NH_3$ Method). Representative literature procedures were followed up to the point where liquid ammonia has been allowed to boil off.[8,28] The experiments were carried out in the usual filtration apparatus. The solid residue was then stirred with sufficient dry ether, THF, or toluene (20 °C) to give ca. 0.2 M solution by assuming 100% conversion of phosphonium salt. By titration the THF or toluene solutions were 0.15–0.18 M.

Ether solutions were allowed to evaporate slowly under a nitrogen stream until crytals of the ylide persisted (ca. 10 °C). Cooling to −20 °C gave a mass of dense yellow crystals. The supernatant was withdrawn by syringe, and the crystals were washed with a small amount of cold ether (syringe). Upon being redissolved in ether (0.2–0.25 M by titration) the recrystallized ylide was examined by ^{31}P NMR. A single peak at 20 ppm was observed. Essentially identical spectra were obtained from the initial extracts (THF, ether, or toluene) of "crude" (noncrystallized) ylide. The bright yellow solution in THF was stored at room temperature in a flask under nitrogen, protected by a three-way vacuum stopcock + septum. Aliquots were withdrawn via nitrogen-filled syringe as needed, N_2-flow-through stopcock ports.

Salt-Free Ethylidenetriphenylphosphorane ($NaNH_2/NH_3$). Exactly the same extraction method was used from the solid residue after NH_3 evaporation as for CH_2PPh_3. A sample was crystallized from a saturated ether solution, dense orange rhombs. After the supernatant ether (cannula) was decanted, the sample was dried under vacuum. The proton NMR spectrum of this material consisted of a complex aromatic region, a methyl signal, 2.05 ppm (dd, J = 7, 19 Hz), and the ylide α-proton at 0.88 ppm (dq, J = 18, 7 Hz) (toluene-d_8). A single absorption was seen in the optimized aryl H decoupled ^{31}P spectrum, δ 14.6 (quintet, $J \geq 16$ Hz). Extracts of "crude" ylide were identical by ^{31}P NMR. The off-resonance decoupler effect is responsible for apparent $J_{CH-P} = J_{CH_3-C-P}$ in the ^{31}P spectrum. The effect is more pronounced on J_{CH_3-C-P} because the methyl protons resonate at lower field than the ylide α-proton and are therefore closer to the decoupler frequency.

Procedure for Low-Temperature Wittig Condensation: ^{31}P Experiments. All experiments with salt-free ylides ($NaNH_2/NH_3$) used the same procedure. Solutions of CH_2PPh_3 and CH_3CHPPh_3 in THF (ca. 0.25 M) or toluene (ca. 0.1 M) were prepared by the $NaNH_2/NH_3$ method while $(CH_3)_2CPPh_3$ in toluene was prepared by the butyllithium method. The ylide solution (ca. 2 mL) was transferred into a nitrogen-

flushed septum capped 10-mm NMR tube by syringe. Nitrogen flow through the tube was maintained by using syringe needle inlet and outlet ports. The sample was cooled to −78 °C, and a solution of the carbonyl compound in the same solvent (ca. 0.7 M, calculated to 0.9 equiv relative to ylide) was added via microliter syringe, a drop at a time with continuous shaking and cooling (this could not be done in 5-mm tubes due to inefficient mixing and local exotherms). Residual ylide color was distinctly visible after addition was complete. The nitrogen inlet and outlet needles were removed, and the septum was wrapped with parafilm. Samples containing Wittig adducts could be stored several hours at −78 °C without change.

Depending on sample concentration, 0.25 M or less, 20–500 transients were typically required to obtain a spectrum. Spectra of oxaphosphetanes for best resolution were obtained at −50 °C to −40 °C in a concentration range of 0.1–0.15 M, 200 transients. Qualitative decomposition rates were determined by using concentrations ≥0.2 M to allow total acquisition times of the order of 2-3 minutes, ca. 30 transients. Each sample was stored in an external constant temperature bath for the appropriate time and was then transferred into the NMR probe maintained at −35 °C or below. Triphenylphosphine oxide usually crystallized after ca. 85% decomposition in THF or sooner in ether or toluene. Resolution was usually lost as the Ph_3PO crystallized, but broad-band noise-decoupled spectra were still informative. All noise-decoupled ^{31}P signals of oxaphosphetanes were sharp singlets, width at half-height ca. 0.1 ppm, under salt-free conditions. If precipitates were present, line broadening to 0.5 ppm or more was observed.

Spectra of oxaphosphetanes from LiBr-containing ylides could be obtained in some cases even though precipitated betaine–lithium bromide adducts were present in the NMR tube. Filtration of typical mixtures failed, but centrifugation proved feasible. The supernatant homogeneous solutions showed no signals other than oxaphosphetane absorptions. Precipitates were obtained with $CH_2{=}PPh_3$ + LiBr + carbonyl substrate in ether, THF, or toluene. With $CH_3CH{=}PPh_3$ + LiBr/THF reactions generally became somewhat turbid, but dense precipitates were only observed in ether or toluene.

Observation of Oxaphosphetanes by Proton NMR: General Procedure. In a 10-mL round-bottom flask (flame dried and nitrogen purged) was placed the alkylidenetriphenylphosphorane (0.2–0.3 M in THF, $NaNH_2/NH_3$ method, 1 mL), and the solvent was removed under nitrogen flow at 20 °C. The resulting crystalline mass was dissolved in 1.0 mL of toluene-d_8 (distilled from lithium aluminum hydride) and cooled to −78 °C, and 0.9 equiv of the requisite carbonyl compound in toluene-d_8 was added. After 0.25 h the slightly colored solution was transferred via cannula to an NMR tube (dried at 150 °C for 3 h and purged with nitrogen) cooled to −78 °C. The spectra were taken at −30 °C to −40 °C since lower temperatures caused loss of resolution, most likely due to viscosity effects.

Isolation of Crystalline *p*-Chlorobenzaldehyde–Methylidenetriphenylphosphorane Adduct. In a 10-mL round-bottom flask (flame dried and N_2 purged) was placed methylidenetriphenylphosphorane (0.32 M in THF, 5.0 mL, 1.6 mmol), and the volume was reduced to ca. 2 mL under N_2 flow. The ylide solution was cooled to −78 °C, and *p*-chlorobenzaldehyde (2.36 M in THF, 0.61 mL, 1.44 mmol) was added slowly via syringe. Crystallization began within ca. 15 min, and the mixture became a solid white mass after ca. 0.5 h. The product was stirred with ether, and the resulting slurry was transferred via a large bore cannula into a jacketed fritted-glass funnel precooled to −78 °C under nitorgen. Filtration was effected under N_2 pressure, and the filter cake of microcrystalline (filament-like) solid was washed with cold ether (5 mL, cannula transfer). The proton spectrum of this material in THF-d_8 showed a complex aromatic region and all three protons in an unresolved, overlapping multiplet at 4.6–4.7 ppm. The crystalline material was not sufficiently soluble in toluene-d_8 for a well-resolved spectrum. However, a solution of the same adduct could be made in toluene-d_8 by the general procedure (above) without precipitation of the product: 270-MHz NMR δ, aromatic protons, 7–8 (complex), 4.55 (1 H, dt, J = 7.0, 6.6 Hz), 4.03 (2 H, dd, J = 7, 16 Hz); the 6.6- and 16-Hz couplings are to phosphorus.

The Effect of LiBr on Salt-Free Oxaphosphetanes. Betaine–Lithium Bromide Adduct from the Oxaphosphetane from Benzaldehyde + $CH_2{=}PPh_3$. A solution of salt-free methylidenetriphenylphosphorane ($NaNH_2/NH_3$ method) in THF (0.22 M, 2 mL) was cooled to −78 °C in a 10-mm NMR tube, N_2-flow through. Benzaldehyde in THF (0.6 M) was added dropwise over 2–3 min until the ylide color was barely visible. The usual ^{31}P spectrum was observed (−69 ppm). After 15 min at −78 °C, the yellow color had disappeared and the homogeneous solution had a faint tan color. Dry LiBr (slowly fused with a small Bunsen flame under N_2 flow in a 5-mL flask, 38 mg, 0.44 mmol) was dissolved in ca. 1 mL of dry THF under nitrogen. The solution was then cooled to −78 °C and added by cannula to the stirred Wittig adduct. An immediate white precipitate appeared, and all ^{31}P NMR signals disappeared within 3 min, the minimum acquisition time. After 10 min, the mixture was allowed to reach 0 °C and was stirred with 5% aqueous HBr (20 mL) and extracted twice with chloroform (15 mL); the organic layer was dried (Na_2SO_4) and evaporated (aspirator). The residue crystallized upon trituration with a small amount of THF to give the known hydroxyphosphonium salt $PhCHOHCH_2{}^+PPh_3Br^-$ (140 mg).

Oxaphosphetane from $PhCHOHCH_2{}^+PPh_3Br^-$ + KH. A suspension of the hydroxyphosphonium salt (0.46 g, 1 mmol) in dry THF (6 mL) was stirred at −40 °C (Dry Ice–CH_3CN bath) in a 25-mL three-neck flask equipped with a coarse porosity filter sidearm. A standardized suspension of KH (mineral oil) calculated to contain 45 mg of KH (total base titration) was added by pipette to the stirred mixture under nitrogen. Immediate hydrogen evolution was apparent. After 30 min, the suspended solids were allowed to settle. The fritted-filter side arm was packed with Dry Ice contained in an aluminum foil jacket, and a two-neck receiver flask was cooled similarly. The receiver flask was flushed with N_2, and the apparatus was gently tilted until the THF solution covered the frit. Filtration was slow (ca. 15 min) and required considerable N_2 pressure.

The clear filtrate was transferred to a 10-mm NMR tube (cannula, N_2 pressure), and the ^{31}P spectrum was recorded at −50 °C. The only signals visible were the oxaphosphetane (identical with the PhCHO + $CH_2{=}PPh_3$ adduct, −69 ppm, broadened triplet with selective aryl decoupling, and triphenylphosphine oxide, 23 ppm, singlet, ca. 10% relative intensity compared to oxaphosphetane).

Lithium Bromide Effect on Stereochemistry: $PhCH_2CH_2CHO$ + $CH_3CH{=}PPh_3$. Three parallel experiments were performed by starting with the same solution of salt-free $CH_3CH{=}PPh_3$ ($NaNH_2/NH_3$ method, 0.21 M in THF). Round-bottom 10-mL flasks, equipped with stir bar, septum cap, and nitrogen flow were charged with 2 mL of ylide solution and then cooled to −78 °C. **Experiment 1** was performed by adding a solution of $PhCH_2CH_2CHO$ (distilled, 0.75 M in THF, 0.55 mL) to the ylide at −78 °C until the color end point had been reached. After 10 min at −78 °C, the homogeneous solution was placed in a 0 °C bath and stirred 20 min. Water (5 mL) was then added; the organic product were recovered by extraction with hexane (2 × 10 mL). After being dried ($MgSO_4$) and evaporated (aspirator), the residue was separated by preparative layer chromatography (silica gel, hexane eluent). The hydrocarbon (R_f 0.5) was recovered, 88 mg (60%) by ether extraction. Determination of the cis:trans ratio was done by 270-MHz NMR by using the integrals of cis methyl (upfield) vs. trans methyl signals which were completely resolved (base line separation). The $PhCH_2CH_2CH{=}CHCH_3$ was found to be 96% cis, 4% trans. **Experiment 2:** The ylide solution was combined at −78 °C with a solution of anhydrous LiBr in THF (0.45 mL, 0.93 M), resulting in no color change but in the appearance of a small amount of white suspended material. The mixture was treated with the same volume of $PhCH_2CH_2CHO$ as in experiment 1 (0.55 mL, 0.75 M). A white precipitate appeared at once, but the solution retained a distinct yellow color. After 10 min at −78 °C, the mixture was placed in the 0 °C bath (20 min), resulting in a color change from yellow to pale tan. The usual workup, isolation, and analysis gave 85 mg $PhCH_2CH_2CH{=}CHCH_3$, 76% cis, 24% trans. **Experiment 3** was identical with experiment 1 up to the formation of oxaphosphetane at −78 °C. A solution of anhydrous LiBr in THF (0.45 mL, 0.93 M) was then added by syringe, resulting in an immediate white precipitate. After 10 min at −78 °C, the mixture was warmed to 0 °C (20 min). The precipitate became gummy and, after a few minutes, partly crystalline. After an identical workup as for experiment 1, the alkene $PhCH_2CH_2CH{=}CHCH_3$ (75 mg) was found to be 96% cis.

Crossover Experiments: Double-Labeling Method. Two 50-mL reaction vessels A and B were joined by a glass tube fused such that the contents of one flask could be transferred to the other by tilting the apparatus. Flask A was charged with (α-deuterioethylidene)triphenylphosphorane[44] (10 mL, 0.19 M, 93% d_1) in ether, and flask B with (protioethylidene)triphenylphosphorane (8.1 mL, 0.24 M, 1.91 mmol) in ether, both ylides prepared by the $NaNH_2/NH_3$ method. The apparatus was swept with nitrogen until ether had evaporated, and the orange crystalline ylides were dissolved in dry THF (10 mL for each flask). The apparatus was cooled to −78 °C and *p*-chlorobenzaldehyde (2.36 M in THF) was added dropwise to flask A until a trace of ylide color remained. Benzaldehyde (1.5 mmol in THF) was added to flask B (protio ylide), resulting in an orange solution with ca. 0.4 mmol of excess $CH_3CH{=}PPh_3$. After 15 min at −78 °C, the apparatus was tilted until the contents of flask B emptied into flask A at −78 °C. Stirring was continued at −78 °C for 30 min, and the bath was then removed. After the mixture had reached room temperature, the solvent was removed

(44) See: Heimgartner, H.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1385 for the procedure used to make $CH_3CD_2PPh_3{}^+ Br^-$. The ylide was prepared by using $NaNH_2/NH_3$ in the usual way.[8,28]

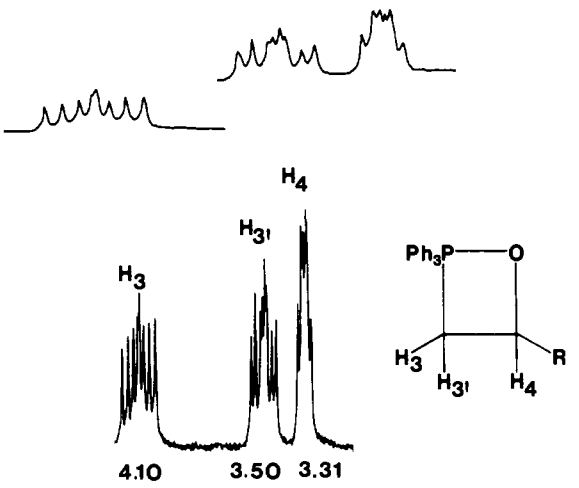


Figure 1. A 270 MHz proton NMR spectrum of the pivalaldehyde–methylidenetriphenylphosphorane adduct (toluene-d_8, R = $C(CH_3)_3$, methine region): lower plot, 3012-Hz sweep width; upper plot, arbitrary expansion.

(aspirator). The residue was taken up in hexane and filtered through a short column of silica gel (40 g) with more hexane to remove triphenylphosphine oxide. The eluant was concentrated, and the olefin mixture was separated by preparative GLPC (15% 20 M carbowax, 210 °C). Four peaks were observed in order of increasing retention time, (*Z*)-1-phenylpropene, (*E*)-1-phenylpropene, (*Z*)-1-(chlorophenyl)-propene, and (*E*)-1-(chlorophenyl)propene. The relative ratio of *Z*:*E* phenylpropenes was 13.5:1 (93% *Z*) and the *Z*:*E* ratio of chlorophenylpropenes was 6:1 (86% *Z*). No attempt was made to establish response factors for phenyl- vs. chlorophenyl-substituted alkenes, so their relative amounts are not known precisely. The (*Z*)-1-phenylpropene peak was collected and examined by 270-MHz NMR. By integral ratio, H_1:H_2 was found to be 1:0.66. Thus, 34% of the (*Z*)-phenylpropene has experienced crossover with deuterio ylide.

To establish the % *d* in (deuterioethylidene)triphenylphosphorane, we repeated the experiment with *p*-chlorobenzaldehyde as the reacting partner. The 1-(*p*-chlorophenyl)propene was collected and examined by 270-MHz NMR; intergration showed H_1:H_2 = 1:0.075, 93% d_1 in both cis and trans isomers.

The extent of crossover in the double label experiment is *not* a measure of the extent of oxaphosphetane dissociation since it cannot measure dissociation–recombination of ArCHO + $CH_3CH{=}PPh_3$. A more informative estimate of extent of dissociation is provided by an experiment by using excess labeled aldehyde, assuming the latter does not perturb the system under study. A solution of the adduct from C_6H_5CHO + $CH_3CH{=}PPh_3$ was prepared by careful color end point titration at −78 °C (0.4-mmol scale). After 15 min at −78 °C, 1.1 equiv of *p*-chlorobenzaldehyde was added and the mixture was allowed to reach 20 °C. By NMR analysis of the combined alkene product mixture, the ratio of (*Z*)-(*p*-chlorophenyl)propene:(*Z*)-phenylpropene was 1.4:1. Thus, dissociation under these conditions is more extensive than is crossover determined by the double-label method. The latter requires dissociation of *both* labeled oxaphosphetane and determines only a lower limit for the extent of dissociation.

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Electron Spin Resonance Characterization of Radicals from 3,4-Dihydroxyphenylalanine: Semiquinone Anions and Their Metal Chelates

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Abstract: Semiquinone radicals generated by photolysis of aqueous solutions of 3,4-dihydroxyphenylalanine have been studied over a pH range from 5–11. The semiquinones have distinctive ESR spectra with five major proton couplings all of which have been measured and assigned. The spectra are strongly influenced by the amino acid side chain, reflecting (i) the presence of the chiral carbon center and (ii) restricted rotation of the methylene protons. The major species detected at neutral pH is suggested to be the semiquinone anion with the amino acid group in the zwitterionic form. Above pH 9 the radical with the amino group deprotonated is found to predominate. It is confirmed that these species also are formed by other oxidative procedures, including autoxidation and enzymic oxidation with tyrosinase. Diamagnetic metal ions (Mg^{2+}, Zn^{2+}, Cd^{2+}, Ca^{2+}, and Sr^{2+}) complex with the semiquinones to give chelate complexes which have been characterized by ESR. With Cd^{2+} and Zn^{2+} steady state concentrations of the metal chelates are very much higher than those of the uncomplexed radicals, allowing hyperfine couplings to ^{111}Cd, ^{113}Cd, and ^{67}Zn to be measured. It is suggested that this ability to chelate metal ions and associated signal enhancement can be useful in the identification of *o*-semiquinone and related species in complex systems.

Catechols and related compounds are widely distributed in nature. There is current interest in the oxidative degradation of these materials, with clear evidence for the toxicity of their degradation products. Examples of phototoxicity,[1] cytotoxicity,[2,3] and antitumor activity[4] have been reported for a number of these compounds. The cytotoxicity is felt[2,3] to reflect (i) production of superoxide and other damaging oxygen radicals and (ii) the ability of product *o*-quinones to react with sulfhydryl groups of sensitive enzymes. Semiquinones derived from the catechols are almost certainly important intermediates; they are readily formed from most catechols during autoxidation[5] and can participate in the formation of both superoxide and *o*-quinone. Enzymic oxi-

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