Mechanism of Wittig Reaction: Evidence against Betaine Intermediates

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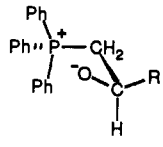
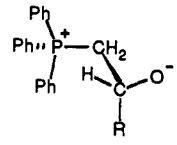
Abstract: The ratio of oxaphosphetane pseudorotamers **8** and **9** obtained from the Wittig reaction of ylide **7** and hydrocinnamaldehyde has been determined at −95 and −109 °C (conditions where the interconversion of isomers by pseudorotation is slow) to be in the range of 2.7–6.5:1. The same products **8** and **9** are obtained by the independent generation of betaine **11** from the hydroxyphosphonium salt **10**, but in a different ratio of 1:1.1–4.2, depending on conditions. The thermodynamic ratio of **8** to **9** at equilibrium is 1.8:1. Therefore, the Wittig reaction must involve a mechanism other than the betaine pathway. An asynchronous cycloaddition process is consistent with the available evidence.

Over much of its history, the Wittig reaction has been described as a stepwise ionic process.[1] The hypothetical betaine intermediates **1** were never observed, but lithium halide adducts **2** could be isolated in some of the early Wittig experiments when alkyllithium reagents were used to make the starting ylide from the phosphonium salt. Lithium-free betaines **1** could be generated independently, and their conversion to alkenes was established in several cases. It was correctly assumed that oxaphosphetanes were intermediates in both the Wittig reaction and in the betaine generation experiments. Although there was no basis for ruling out alternative mechanisms, the intermediate formation of betaines appeared to be consistent with the available evidence and the intuitive rationale became widely accepted.[1,2]

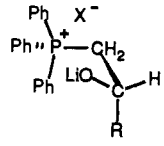
Objections to the ionic mechanism were raised when solvent effects indicated a nonpolar transition state for reactions of stabilized ylides.[3] Shortly thereafter (1973), oxaphosphetanes were detected as the only observable intermediates in several typical Wittig reactions of nonstabilized ylides.[4] These findings did not rule out any mechanisms, and proved only that oxaphosphetanes are more stable than lithium-free betaines **1**. However, there



1 syn



1 anti



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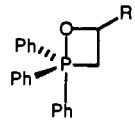

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was no longer a clear need to invoke an ionic intermediate on the way to the covalent oxaphosphetane. These and other considerations stimulated the first correlation of Wittig stereochemistry via a cycloaddition process.[4] The rationale has been modified and debated,[5-7] and a detailed proposal has appeared that uses asynchronous cycloaddition terminology and that recognizes a continuum of 4-center transition-state geometries. This hypothesis attributes stereoselectivity to a combination of steric effects and varying degrees of rehybridization at phosphorus, depending on ylide substitution.[7b]

No comparable attempt has been made to update the betaine rationale. Conversion of independently generated **1** to **3** is now extensively documented, and it is known that cyclization is too fast for NMR detection of the transient intermediate.[8] Under these circumstances, the intermediacy of betaines in the Wittig reaction remains a possibility that is not easily proved nor disproved. Theoretical studies of the $H_3P{=}CH_2 + H_2C{=}O$ system have found no energy minimum corresponding to the closed shell representation **1**, but the hypothetical gas phase environment is biased against zwitterions.[9] Reactions of Wittig intermediates that were originally believed to involve betaine species in solution (for example, the formation of oxidoylides in the presence of strong base) have been explained by the observation that oxaphosphetanes are rapidly cleaved by lithium halides to give betaine adducts **2**.[4,10] On the other hand, this evidence does not rule out **1** as a transient intermediate on the way to **3**. Thus, neither the calculations nor the experimental evidence available to date can resolve the issue of stepwise vs 4-center processes in solution.

We have devised a test for the betaine mechanism based on phosphorus stereochemistry. In principle, the Wittig reaction of eq 1 (Scheme I) can form three oxaphosphetane pseudorotamers **4**–**6** with oxygen in the favored apical position.[11,12] The same pseudorotamers can also be generated independently from a β-hydroxy phosphonium salt by reaction with base (eq 2).[8,13] Since eq 2 is obliged to proceed via the betaine, the ratio of **4**–**6** from

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(2) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44. Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318.

(3) (a) Froyen, P. *Acta Chem. Scand.* **1972**, *26*, 2163. (b) Aksnes, G.; Khalil, F. Y. *Phosphorus Relat. Group V Elem.* **1972**, *2*, 105. Aksnes, G.; Khalil, F. Y. *Ibid.* **1973**, *3*, 37, 79, 109.

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(5) Bestmann, H. J. *Pure Appl. Chem.* **1979**, *51*, 515. Bestmann, H. J. *Pure Appl. Chem.* **1980**, *52*, 771. Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 85.

(6) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821.

(7) (a) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823. (b) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948. (c) Vedejs, E.; Fleck, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 5861.

(8) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(9) (a) Trindle, C.; Hwang, J.-T.; Carey, F. A. *J. Org. Chem.* **1973**, *38*, 2664. (b) Holler, R.; Lischka, H. *J. Am. Chem. Soc.* **1980**, *102*, 4632. (c) Bestmann, H. J.; Chandrasekhar, J.; Downey, W. G.; Schleyer, P. von R. *J. Chem. Soc., Chem. Commun.* **1980**, 978. (d) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1987**, *109*, 1.

(10) Vedejs, E.; Meier, G. P. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 56.

(11) Solid state evidence: Ul-Haque, M.; Caughlan, C. N.; Ramirez, F.; Pilot, J. F.; Smith, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 5229. Bestmann, H. J.; Roth, K.; Wilhelm, E.; Bohme, R.; Burzlaff, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 876.

(12) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1989**, *111*, 1519.

(13) (a) Vedejs, E.; Marth, C. F.; Ruggeri, R. *J. Am. Chem. Soc.* **1988**, *110*, 3940. (b) For the stereochemistry of DBP ylide Wittig reactions, see: Vedejs, E.; Marth, C. F. *Tetrahedron Lett.* **1987**, *28*, 3445.

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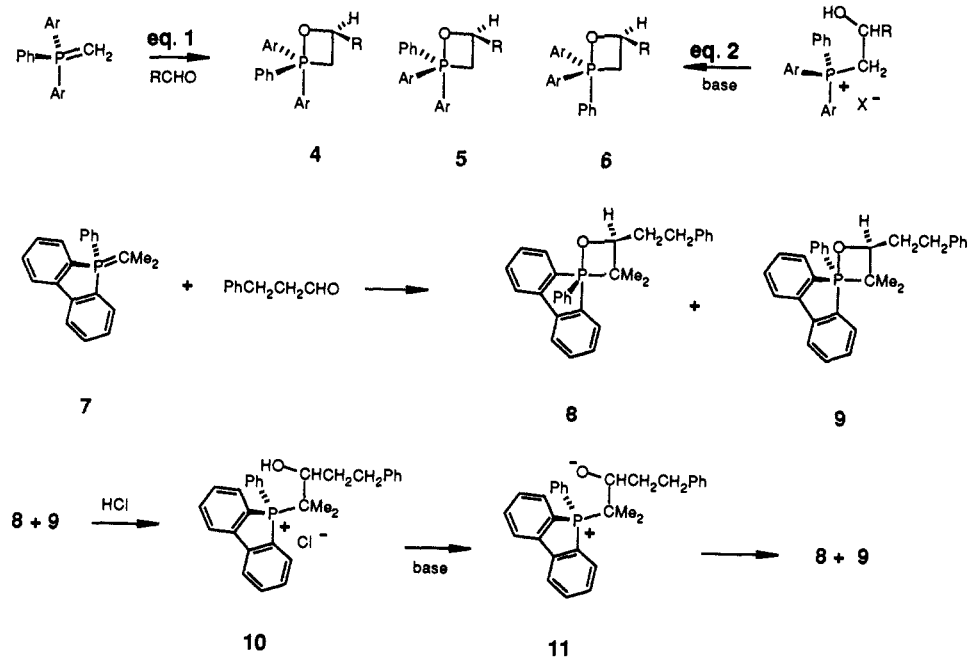
Scheme I



this experiment would constitute a "fingerprint" of the transient ionic intermediate. It does not matter whether the syn or the anti betaine is formed initially because the ratio of **4–6** is controlled at the cyclization step, via the syn rotamer. If the same *kinetic* fingerprint is obtained from both the Wittig reaction (eq 1) and from eq 2, then the betaine can be an intermediate in both cases. Conversely, a different ratio would prove that the Wittig pathway from the ylide to the oxaphosphetane involves another mechanism.

For Scheme I to succeed, interconversion of **4–6** by pseudorotation or by any other means must be slow on the *laboratory time scale*. This requirement is difficult to satisfy with typical Wittig reagents $PhAr_2P{=}CRR'$ (Ar = substituted phenyl) because pseudorotation of relevant oxaphosphetanes is fast even on the NMR time scale.[12] However, incorporation of the dibenzophosphole (DBP) unit (Ar_2P = DBP) strongly retards oxaphosphetane pseudorotation (half-lives of the order of 0.5 h at −78 °C).[12] The influence of the 5-membered ring on pseudorotation is well-precedented in earlier studies of pentavalent phosphorus species.[14] Another advantage of DBP oxaphosphetanes is that product analysis is simplified. Only two pseudorotamers are likely because the structure corresponding to **6** with Ar_2P = DBP is destabilized by ring strain (ring C–P–C angle ca. 94°).[12] The DBP series was therefore selected for detailed study.

For a meaningful mechanistic test, the ratio of oxaphosphetane pseudorotamers from both eq 1 and eq 2 must be different from the thermodynamic ratio. Our earlier investigations of DBP oxaphosphetanes had found no example where both pseudorotamers corresponding to **4** and **5** could be detected by direct NMR methods.[12,13] Several known Wittig reactions of aldehydes with $Ph_2EtP{=}CHCH_3$, (Ph)DBP=$CHCH_3$, (Et)DBP=$CHCH_3$, or (CH_3)DBP=CH_2 could have afforded two or more pseudorotamers in principle, but in each case a single pseudorotamer was strongly favored regardless of conditions or of the technique used to make the oxaphosphetane. Thus, a difference between the thermodynamic and kinetic ratio of pseudorotamers could not be determined in the above examples.

We have now found that treatment of the salt-free isopropylidene ylide **7** with hydrocinnamaldehyde does produce two observable pseudorotamers **8** (major) and **9** (minor) under equilibrium conditions. The isomers were easily resolved by ^{31}P or ^1H NMR below −35 °C (slow exchange; toluene-d^8; δ ^{31}P −63.0, (**8**) −62.2 ppm (**9**); δ ^1H 3.44, (C_4–H, **8**) 3.75 ppm (9); 1.52 and 0.45 ppm (C_3-Me, **8**), 1.55 and 0.49 ppm (9)). A knowledge of the stereochemical identity of **8** and **9** is not essential for interpretation of the key experiments to be described later, but a tentative assignment has been made as follows. In the course of our prior investigations of DBP oxaphosphetanes, we have observed numerous examples of C_3-Me chemical shifts in the range of 0.4–1.0 ppm, but we have never before encountered a signal in the vicinity of 1.5 ppm which is seen for both **8** and **9**.[12,13] We attribute the unusual downfield chemical shift to deshielding of one of the C_3-Me groups by the free rotor *P*-phenyl substituent. Irradiation of the downfield methyl signals results in a 5% NOE enhancement of the C_4-methine proton signal (3.75 ppm) in the minor isomer **9**, and only a 1% enhancement in the 3.44 ppm methine signal of the major isomer **8**. Furthermore, irradiation at 0.5 ppm causes a 3.5% enhancement of the 3.44 ppm signal of the major isomer **8** vs a 1.7% enhancement of the 3.75 ppm signal of **9**. If the assignment of methyl chemical shifts is correct, then the C_4–methine proton in the major isomer is anti to the *P*-phenyl group, and the evidence supports the assignment of the structure **8** to the more stable isomer.

As expected, no NMR signals corresponding to any of the other conceivable pseudorotamers were detected. The assignment of structures **8** and **9** follows from an analysis of ^{13}C–^{31}P coupling constants and other NMR criteria as discussed in an earlier publication.[12] Thus, the quaternary *P*-phenyl carbons of **8** and **9** can be assigned to signals at 137.6 (J = 134 Hz) and 137.7 ppm (J = 131 Hz), respectively ($CDCl_3$ solution, −33 °C). Both signals

Table I. Selected ^{13}C NMR Signals of Oxaphosphetanes **8** and **9**[a]

carbon	**8** chemical shift, ppm (J_{P-C}, Hz)	**9** chemical shift, ppm (J_{P-C}, Hz)
DBP (equatorial *PC*)[b]	132.2 (126)	135.0 (129)
DBP (quaternary *C*)[b]	149.6 (<2)	149.8 (<2)
DBP (quaternary *C*)[b]	144.8 (17)	144.3 (17)
DBP (quaternary *C*)[b]	138.8 (12)	138.8 (12)
C_6H_5 (quaternary *PC*)[b]	137.6 (134)	137.7 (131)
oxaphosphetane *PC*$_3$	67.0 (88)	67.6 (87)
oxaphosphetane *C*$_4$	71.3 (16)	72.7 (16)
C_3-*C*H_3	17.1 (5.3)	24.4 (5.4)
C_3-*C*H_3	21.5 (<2)	17.9 (<2)
C_4-*C*–CPh	34.7 (13)[c]	36.3 (<2)[d]
C_4-C–*C*Ph	33.1 (<2)	33.0 (<2)[d]

[a] Proton-decoupled carbon spectra in $CDCl_3$ at −33 °C; chemical shifts reported relative to TMS. [b] Selective detection of quaternary carbons using Bruker QUAT-D pulse sequence. [c] Assigned to C_4–*C*. [d] Assignment no confirmed.

(14) Hellwinkel, D. *Chimia* **1968**, *22*, 488.

Table II. Initial Oxaphosphetane Ratios: Wittig Reaction

entry	base	solvent	8:9
1	$NaNH_2$[a,b]	d^8-toluene	3.3:1.0
2	$NaNH_2$[a,c]	Et_2O	6.5:1.0
3	KHMDS[a,c]	THF	2.9:1.0
4	KHMDS[a,c]	Et_2O	3.1:1.0
5	KHMDS[c,d]	CH_2CL_2	2.7:1.0[e]

[a] Salt-free ylide **7** preformed from the phosphonium iodide and base at 20 °C, followed by centrifugation to remove salts and cooling to the indicated temperature; final concentration, 0.075–0.1 M. [b] Aldehyde added at −95 °C and products observed at −78 °C by ^{31}P NMR. [c] Aldehyde added at −109 °C and products observed at −78 °C by ^{31}P NMR. [d] Salt-free ylide prepared as for *a*, in ether solution; after solvent removal under high vacuum, the ylide was dissolved in CH_2Cl_2 at −78 °C to make a 0.1 M solution and the solution was used at once. [e] Average of two experiments, range 2.5–2.9:1.

contain the characteristically large phosphorus–carbon coupling expected for equatorial sp^2 carbon, as does one of the quaternary carbons of the DBP subunit in each pseudorotamer (Table I). The C_3 (oxaphosphetane) carbon also couples strongly to phosphorus, but the *J* value is smaller (ca. 87–88 Hz) because this carbon is sp^3-hybridized. The NMR signals of the two isomers **8** and **9** are very similar in chemical shift and in appearance, and these signals also resemble the spectra of other DBP-derived oxaphosphetanes.[12,13] The relative magnitude and similarity of coupling constants and chemical shifts among these examples can be understood only if the DBP unit spans equatorial and apical sites in the trigonal-bipyramidal structures.

Interconversion of **8** and **9** by pseudorotation was slow on the laboratory time scale, $t_{0.5}$ = ca. 3 h at −79 °C. Rate constants were obtained from the rate of equilibration at −79 and −69 °C and also from line-shape analysis in the temperature range of 8–39 °C.[15] The resulting activation parameters are $\Delta G^* = 14.6 \pm 0.3$ kcal/mol, $\Delta H^* = 15.9 \pm 1$ kcal/m, and $\Delta S^* = 4.3 \pm 4$ eu, and they are consistent with data observed for other DBP oxaphosphetanes.[12] The equilibrium ratio of **8**:**9** is 1.8:1 at −78 °C. We were not able to determine a reliable kinetic ratio of **8** and **9** from the Wittig reaction of **7** at −78 °C, probably due to the difficulty of controlling the exotherm. However, when the reaction of **7** and hydrocinnamaldehyde was performed in ether at −109 °C, adducts **8** and **9** were formed in a distinctive and reproducible ratio of 6.5:1 (Table II entry 2). Similar experiments in other solvents gave lower ratios in the vicinity of 3:1 for **8**:**9**. We believe that these variations arise primarily from differences in our ability to control exotherms from heat of mixing and heat of reaction, but we cannot prove this assertion due to the technical difficulty of the experiments.

The critical comparison with independent betaine generation could now be performed (Table III). Betaine **11** was prepared by treatment of a suspension (in ether) or a solution (in CH_2Cl_2) of the β-hydroxy phosphonium salt **10** with a solution of potassium hexamethyldisilazide in ether or in THF and produced the same two oxaphosphetanes **8** and **9**. Exothermic cyclization of the betaine is reflected by the modest ratios (1:1.1 in CH_2Cl_2; 1:4.2 in ether) of **8**:**9** formed via deprotonation of **11**. Since these ratios differ from the equilibrium ratio (ca. 1.8:1), and even more so from the initial Wittig ratios (2.7–6.5:1), the conventional betaine mechanism[1] can play at most a minor role in the Wittig reaction of **7**.

Alternate descriptions of hypothetical Wittig intermediates continue to appear in the literature.[16–19] One variation can be represented by the diradicals **12** or **13** derived from initial C–C

Table III. Initial Oxaphosphetane Ratios from the Betaine: Deprotonation of **10**[a]

entry	base	solvent	temp, °C	8:9
1	KHMDS	THF	−109	1.0:3.3
2	KHMDS	Et_2O	−109	1.0:4.2
3	tBuOK	THF	−109	1.0:1.8
4	KHMDS[b,c]	CH_2Cl_2	−95	1.0:3.0
5	KHMDS[b,d]	CH_2Cl_2	−78	1.0:1.1[e,f]

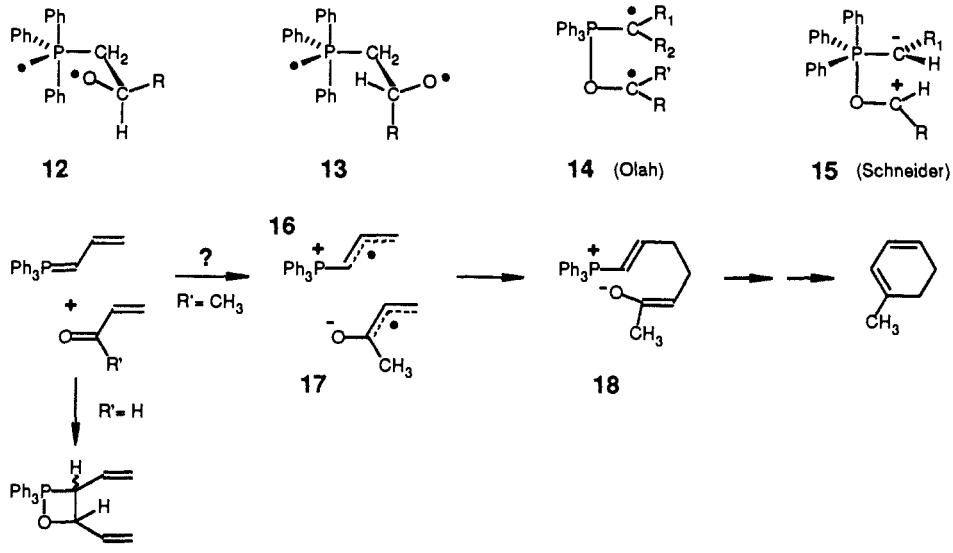
[a] Deprotonations of the suspended salt in a stirred 8-mm NMR tube, final concentration 0.075–0.1 M unless noted otherwise; observation within 2 min at −78 °C by ^{31}P NMR. [b] KHMDS was prepared in THF, 0.7 M, and added to a solution of **10** in CH_2Cl_2 to make a final concentration of 0.02 M; deprotonation of CH_2Cl_2 may precede deprotonation of **10**. [c] Some suspended **10** may be present. [d] Homogeneous condition were assured by using ca. 2-fold excess of solvent over the amount needed for a saturated solution at −78 °C. [e] Deprotonation of the dissolved salt under homogeneous conditions. [f] Two experiments, identical results within 5% integral error.

bonding.[17,20] Technically, **1-syn** and singlet diradical **12** (or **1-anti** and **13**) are different structures in the sense that a ground state differs from the excited state. The distinction involves subtle details of geometry and electron distribution. Since both the zwitterionic and diradical representations contribute to the actual structure of unsymmetrical "1,4-diradicaloids",[21] it is by no means clear which representation (**1-syn** or **12**) would best describe the hypothetical ground state "betaine". There is no evidence to suggest that two distinct electronic structures such as **1-syn** and **12** would have sufficient lifetimes to display unique chemical reactivity on the time scale of Wittig or betaine generation experiments. Pending proof to the contrary, we shall assume that internal conversion between **1-syn** and **12** or **1-anti** and **13** is fast compared to bond rotation or cyclization under the conditions of the betaine generation experiment. There would be no practical distinction between the formal diradical or zwitterion representations under these circumstances, and both would be ruled out as Wittig intermediates by our stereochemical test in the case of ylide **7**.

Similarly, we shall argue that the hypothetical P–O bonded structure **14** (Olah et al., 1982;[18] McEwen et al., 1989, 1990[19]) is the same for practical purposes as the earlier zwitterionic representation **15** (Schneider, 1969[16]). Schneider's paper is noteworthy as one of the first to present a logical argument for stereochemical control in cis-selective Wittig reactions. However, subsequent observations have raised serious obstacles to any Wittig rationale based on initial P–O bonding. It is well-known that aldehydes are far more reactive in the Wittig reaction than are ketones.[7a] Since diradicaloid **14** ≈ **15** should be stabilized when R′ is alkyl or aryl relative to the case where R′ = H, the decreased reactivity of ketones would have to be explained by arguing that conversion of **14** ≈ **15** to the oxaphosphetane is rate-limiting. In that case, characteristic byproducts should be formed when the α-substituents are capable of intercepting radicals. However, carbonyl compounds with R = cyclopropyl undergo the Wittig reaction without any reported complications due to radical-induced ring cleavage.[22] Unexceptional Wittig olefinations are known even in the case of highly strained *bicyclobutyl ketones*.[23] Furthermore, α-alkylthio or α-alkylseleno ketones and aldehydes react normally,[24] as do ylides $Ph_3P{=}CHCH_2SnBu_3$.[25] Radical

(15) Stephenson, D. S.; Binsch, G. *J. Magn. Reson.* **1978**, *32*, 145. DNMR5 program: Stephenson, D. S.; Binsch, G. *Quantum Chemistry Program Exchange* **1978**, *11*, 365.
(16) Schneider, W. P. *J. Chem. Soc., Chem. Commun.* **1969**, 785.
(17) McEwen, W. E.; Beaver, B. D.; Cooney, J. V. *Phosphorus Sulfur* **1985**, *25*, 255.
(18) Olah, G. A.; Krishnamurthy, V. V. *J. Am. Chem. Soc.* **1982**, *104*, 3987.
(19) McEwen, W. E.; Ward, W. J. *Phosphorus Sulfur* **1989**, *41*, 393. McEwen, W. E.; Ward, W. J. *J. Org. Chem.* **1990**, *55*, 493.
(20) In addition to **12** or **13** several other C–C bonded diradicaloid geometries are conceivable, depending on phosphorus hybridization and ligand arrangement. The subtle options for diradical geometry have not been discussed previously and nothing is known regarding the details of this energy surface or the size of barriers between species that differ in electron distribution or hybridization.
(21) Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 92.
(22) Selected examples: Cupas, C.; Watts, W.; Schleyer, P. *J. Chem. Soc., Chem. Commun.* **1964**, 2503. Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1967**, 638. Baldwin, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 5910. Zimmerman, H. E. *J. Am. Chem. Soc.* **1974**, *96*, 1459. Zimmerman, H. E. *J. Am. Chem. Soc.* **1974**, *96*, 4630. Matsuo, T.; Mori, K.; Matsui, M. *Tetrahedron Lett.* **1976**, *17*, 1979.
(23) Heldeweg, R. F.; Hogeveen, H.; Schudde, E. P. *J. Org. Chem.* **1978**, *43*, 1912.

Scheme II



fragmentation with loss of the heteroatom could have occurred at the stage of the hypothetical intermediates **14** ≈ **15** (R = C–S or C–Se, R_1 = CH_2Sn, etc.), but no such reactions have been reported. One paper does mention possible radical reduction products and suggests a single-electron-transfer (SET) pathway leading to **14** (R_1 = R_2 = Me).[18] However, the reaction appears to require the presence of lithium ion,[26] and no connection to the Wittig pathway has been demonstrated.

The conjugate addition reactions of α,β-unsaturated ketones[27] and esters[28] with allylic ylides are more likely candidates for some variant of an SET mechanism. Thus, allylidenetriphenylphosphorane reacts with α,β-unsaturated ketones to give cyclohexadiene products derived from dominant C–C bonding at the ylide γ-carbon.[27] Since the same ylide reacts with enals or with *saturated* ketones to give normal Wittig products derived from bonding at the α-carbon, a delicate balance of mechanisms is apparent. We suggest that the "abnormal" γ-coupling process may be due to a competing SET pathway. In the case of enones, this process would afford the radical ions **16** and **17**, and coupling to give **18** would be the logical result (Scheme II). A similar pathway might also explain the cyclopropanation of unsaturated carbonyl substrates that is occasionally observed.[29] Although there is no direct experimental evidence to indicate an SET pathway in the above examples, the empirical correlation between allylic ylide γ C–C bond formation and a low-lying π^*-orbital in the enone or enoate substrates provides some support. According to our interpretation, enals prefer the normal Wittig pathway with allylidenetriphenylphosphorane because the 4-center process is favored by the small steric demand of the aldehyde.

Conclusions

Our stereochemical test does not necessarily disprove mechanisms via "intermediates" with lifetimes that are short compared to the time scale of bond rotation. In one possible variation, Yamataka et al. have suggested that SET might occur in the normal Wittig pathway with carbonyl and ylide groups placed in a geometry that resembles a puckered oxaphosphetane.[30] There can be subtle theoretical and kinetic distinctions between this process and a formal cycloaddition, but the product-determining step will be subject to similar if not identical steric effects. To avoid semantic distinctions among Wittig rationales that invoke subtle differences in geometry, we suggest that the phrase "4-center mechanism" be used to describe variations that feature advanced C–C bonding, partially rehybridized phosphorus, and oxygen placed within conceivable P–O bonding distance.

High energy intermediates such as **1-anti** became established in the literature because of attempts to explain the remarkable cis selectivity of $Ph_3P{=}CHCH_3$.[1] Only recently has it been realized that this selectivity phenomenon is by no means a characteristic property of phosphorus ylides. Simple ylides such as $Et_3P{=}CHCH_3$ are virtually unselective.[6,13a] DBP ylides can be highly *E*-selective,[13] and the stabilized ylide $Ph_3P{=}CHCO_2Et$ can be either *E*-selective or *Z*-selective, depending on the solvent and the substrate.[31] All of these reactions are now known to occur under dominant if not exclusive kinetic control.[13a,31b] Wittig stereochemistry is a complicated phenomenon that is controlled by several factors[7b,c] and cannot be explained by using general concepts that do not include a specific role for the substituents. No evidence remains to support the conventional betaine pathway that is featured in virtually all textbooks.[32] Further development of stepwise mechanisms (including ionic,[1] diradicaloid,[16-19] or single-electron-transfer variations[18,30]) should begin with evidence that intermediates exist and that they are capable of cyclization to oxaphosphetanes.

Experimental Section

***P*-Isopropyl-*P*-phenyldibenzophospholium Iodide.** *P*-Phenyldibenzophosphole[13a] was dissolved in 2 mL of THF and added to 3.0 equiv (2.2 mL) of isopropyl iodide (dried over P_2O_5 and distilled). The reaction was sealed in a glass tube and heated to 120 °C for 7 h, forming a light yellow oil. The tube was cooled and opened, and all volatile material was removed, first under a stream of N_2 and finally under high vacuum. Crystallization gave 1.51 g (83% yield) of *P*-isopropyl-*P*-phenyldi-

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(30) The Yamataka proposal features rapid C–C coupling by the radical ion pair and rate-limiting cyclization to the oxaphosphetane. We thank Prof. Yamataka for informing us of the results of additional heavy atom isotope studies that may suggest this scenario in certain cases. See also: Yamataka, H.; Nagareda, K.; Hanafusa, T.; Nagase, S. *Tetrahedron Lett.* **1989**, *30*, 7187.

(31) (a) Tronchet, J. M. J.; Gentile, B. *Helv. Chim. Acta* **1979**, *62*, 2091. Valverde, S.; Martin-Lomas, M.; Herradon, B.; Garcia-Ochoa, S. *Tetrahedron* **1987**, *43*, 1895. (b) See ref 7a and 13a for proof that oxaphosphetanes derived from stabilized as well as nonstablized ylides decompose to *E* or *Z* alkenes without significant reversal or loss of stereochemistry.

(32) A rare exception: Ege, S. N. *Organic Chemistry*; D. C. Heath and Co., Boston, MA, 1984; p 855.

benzophospholium iodide: solid, mp 158–161 °C (crystallized from acetonitrile/THF); 270-MHz NMR ($CDCl_3$) δ 8.50–7.64 (13 H, m), 5.12 (1 H, d of septets, J = 12.7, 7.1 Hz), 1.26 (6 H, dd, J = 20.7, 7.1 Hz), ^{31}P NMR ($CDCl_3$) δ 36.9. Anal. Calcd: C, 58.62; H, 4.69; found: C, 58.99; H, 5.00; formula $C_{21}H_{20}IP$.

β-Hydroxy Phosphonium Salt 10 from Ylide 7 and Hydrocinnamaldehyde. Salt **10** was isolated from a low-temperature quench of the standard salt-free Wittig reaction[13a] of *P*-isopropyl-*P*-phenyldibenzophospholium iodide as follows: the ylide was formed by stirring the suspended phosphonium salt (690 mg, 1.6 mmol) and excess $NaNH_2$ (ca. 5 equiv) in 30 mL of Et_2O for 6 h at room temperature, nitrogen atmosphere throughout. After removal of solids by centrifugation, the salt-free ylide solution was cooled to −78 °C and 1.0 equiv (0.21 mL) of hydrocinnamaldehyde in 5 mL of ether was added. The ylide color disappeared rapidly upon addition of a full equivalent of aldehyde. After the reaction was stirred at −78 °C for 15 min, a small amount of precipitate was present, which was allowed to settle. The reaction was then quenched by cannula transfer into a solution of 3 equiv of HCl in 30 mL of methanol at −78 °C. All solvents were evaporated, and the residue was dried by azeotropic distillation with toluene, triturated with THF, and crystallized to give the β-hydroxy phosphonium chloride **10** in 80% yield: solid, mp 212–214 °C (crystallized from CH_3CN); 500-MHz NMR ($CDCl_3$) δ 8.69 (1 H, dd, J = 8.0, 8.0 Hz), 8.59 (1 H, dd, J = 7.7, 7.3 Hz), 8.31–8.20 (4 H, m), 8.01–7.95 (2 H, m), 7.83–7.51 (5 H, m), 7.27–7.08 (5 H, m), 3.85 (1 H, br s), 3.31 (1 H, ddd, J = 14.2, 10.7, 4.3 Hz), 2.80–2.742 (1 H, m), 2.00–1.94 (2 H, m), 1.66–1.60 (1 H, m), 1.27 (3 H, d, J = 20.8 Hz), 1.25 (3 H, d, J = 20.8 Hz), ^{31}P NMR ($CDCl_3$) δ 34.6. Anal. Calcd: C, 76.17; H, 6.41; Cl, 7.49; found: C, 76.18; H, 6.39; Cl, 7.03; formula $C_{30}H_{30}OClP$.

NMR Spectra: General Instrumental Procedures. ^{31}P NMR. All VT NMR work was performed on a Bruker AM-500 instrument using a 5- or 10-mm broad-band probe. Samples were run in 5-mm NMR tubes (unless noted otherwise). For deuterated solvents, the spectra were run locked on deuterium and tuned with use of the lock signal. For nondeuterated solvents, high resolution could be achieved by tuning on the ^1H FID (observed by using the decoupler coils), and spectra were run unlocked. All ^{31}P and ^{13}C NMR spectra were run with proton decoupling, using the composite pulse decoupling (CPD) sequence WALTZ-16 at a decoupler power level of 20 H, to minimize line widths and sample heating. ^{31}P chemical shifts were referenced relative to triphenylphosphine oxide at δ +28.7 ppm in $CDCl_3$ (room temperature) or at δ +23.4 ppm in THF (room temperature), based on 85% H_3PO_4 at δ = 0 ppm. All ^1H NMR VT NMR work was performed on a Bruker AM-500, 500-MHz proton frequency, using a 5-mm proton or broad-band probe. Samples were run in toluene-d_8, unless noted otherwise.

Kinetic Oxaphosphetane Generation. Oxaphosphetanes 8 and 9 via Wittig Reaction (Table II). Ylides were generated with the use of conditions designed to match as closely as possible the conditions of independent betaine generation. For that reason, ylides were not purified to ensure that the same base-derived byproducts would be present. A typical procedure for the $NaNH_2/Et_2O$ experiment follows. The dry, finely powdered DBP salt **10** (140 mg, 0.32 mmol) and 3 equiv of $NaNH_2$ powder (Aldrich) were suspended in 3.2 mL of dry Et_2O. The reaction was stirred at room temperature for 6 h under N_2 to form the ylide **7**. The reaction was clarified by centrifugation and the ca. 0.1 M ylide solution was removed via cannula. One half of the ylide solution was transferred to a dry 8-mm NMR tube through a septum. This NMR sample was cooled to −109 °C with a THF/liquid nitrogen cold bath. In order to avoid solid THF residue on the outside of the NMR tube, the sample was not placed directly in the THF–liquid nitrogen slush. Instead, a small vial of Et_2O was placed into the cold bath and the NMR tube was cooled in the ether bath to −109 °C. A small, specially fitted Teflon stirring rod was introduced into the NMR tube through the septum. After everything had cooled to the desired temperature, hydrocinnamaldehyde (0.15 mmol, 0.9 equiv) in 0.5 mL of ether was carefully added by syringe over the precooled ylide solution. This procedure could be accomplished without significant mixing of layers. After all components had equilibrated to −109 °C (ca. 1 min), the layers were quickly mixed with the stirring rod for 1 min. The sample was placed in the NMR probe at −78 °C and rapid magnet shimming on the ^1H FID was performed. The first ^{31}P NMR spectrum was obtained in 2–4 min.

For the reactions in THF or ether using KHMDS as base, the ylide was formed from the salt at room temperature (stirred under nitrogen for 0.5 h) with the use of 0.95 equiv of KHMDS (1.2 M in THF; 0.7 M in ether) in the appropriate solvent for 1 equiv of the salt. All other conditions remained the same. The ylide solutions contained <5% of phosphine oxide signals. When toluene was used as solvent, the only change in procedure was that the mixing of ylide and aldehyde was done at −95 °C, since toluene freezes at −98 °C. For the kinetic Wittig reactions in CH_2Cl_2, the ylide was generated in ether with $NaNH_2$ as described above. After centrifugation, the ether solution was cooled to −78 °C, and the solvent was removed at high vacuum. CH_2Cl_2 was added to the ylide residue to make a 0.1 M solution, and this solution was kept at −78 °C at all times. The ylide was placed in an 8-mm NMR tube, hydrocinnamaldehyde was added, and the solutions were mixed at −95 °C to form the oxaphosphetane (Table II).

The oxaphosphetanes **8** and **9** are stable at room temperature and appear to crystallize from ether, mp ca. room temperature. Despite massive effort, suitable crystals for X-ray analysis could not be obtained. The solid material that was isolated could be redissolved without difficulty at −78 °C, but NMR spectra revealed the usual equilibrium mixture of pseudorotamers. Apparently, both pseudorotamers are present in the solid, and the crystals are disordered. NMR: −33 °C (slow exchange), toluene-d_8 δ ^{31}P −63.0 (**8**) −62.2 ppm (**9**); δ ^1H (partial) C_4-H, 3.44 (J_{P-C} = 3.0 Hz, **8**), 3.75 ppm (J_{P-C} = 18 Hz, **9**); C_3-Me **8**, δ 1.52 (J_{P-C} = 22 Hz, **8**) and 0.45 ppm (J_{P-C} = 27 Hz, **8**); 1.55 (J_{P-C} = 23 Hz, **9**) and 0.49 ppm (J_{P-C} = 26 Hz, **9**).

Oxaphosphetanes 8 and 9 via β-Hydroxy Phosphonium Salt Deprotonation (Table III). The dry phosphonium chloride **10** (70 mg, 0.15 mmol) was placed in an NMR tube, and 1.5 mL of solvent (THF or Et_2O) was added. The sample was fitted with a specially designed Teflon stirring rod, the tube was cooled to −109 °C as before, and 1.0 equiv of base (KHMDS or tBuOK in THF, KHMDS in Et_2O) was added via syringe on top of the phosphonium salt layer. After all components had cooled, the suspended phosphonium salt **10** and the base were stirred in the NMR tube for 2–4 min. The sample was placed in the NMR probe and examined as described above.

For deprotonation under homogeneous conditions, the β-hydroxy phosphonium salt **10** was dissolved by stirring in 5 mL of CH_2Cl_2 at room temperature for 1 h. The solution was then cooled to −78 °C and filtered at this temperature through a cotton plug in a pipet immersed in a dry ice/acetone bath. A second 5 mL of CH_2Cl_2 was added to ensure that all of the phosphonium salt was in solution. The solution of salt **10** was ca. 0.02 M, as judged by ^{31}P NMR integration of a known volume of solution plus added triphenylphosphine as reference. The solution was transferred via cannula to an 8-mm NMR tube. A solution of 0.95 equiv of KHMDS in THF (1.2 M) was then added at −78 °C without mixing layers. After ca. 30 s, the layers were stirred and the spectrum was recorded within ca. 1 min. The identity of the anion that actually deprotonates the hydroxyl group is unknown under these experimental conditions, due to the high kinetic acidity of dichloromethane. Attempts to prepare a solution of the anion in dichloromethane without the phosphonium salt present gave a clear solution at −78 °C, but color developed upon standing or upon warming. Thus, the critical experiment was performed by using the in situ technique as described above.

Kinetic Studies of Oxaphosphetane Pseudorotation. Pseudorotation rate constants were calculated from the rates of equilibration of **8** and **9** at −79 °C and −68.7 °C, $k = 4.84 \times 10^{-5}$ s^{-1} and 3.85×10^{-4} s^{-1}. A second series of rate constants was defined by ^{31}P line-shape analysis.[15] The following data points were obtained: +8 °C, 45 s^{-1}; 24.5 °C, 135 s^{-1}; 28.7 °C, 168 s^{-1}; 39.1 °C, 372 s^{-1}, $\Delta G^* = 14.6 \pm 0.3$ kcal/mol; $\Delta H^* = 15.9 \pm 1$ kcal/mol; $\Delta S^* = 4.3 \pm 4$ eu for interconversion of **8** and **9**.

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