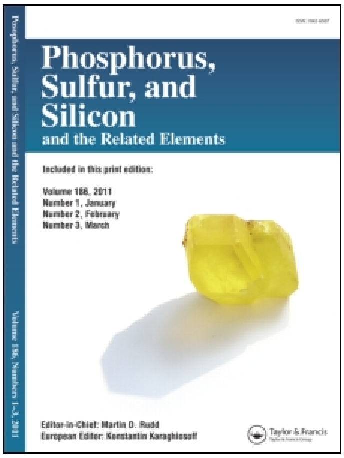

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THE SYNTHETIC UTILITY OF DIOXYPHOSPHORANES IN ORGANIC SYNTHESIS

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Diethoxytriphenylphosphorane, DTPP, prepared by reaction of triphenylphosphine and diethyl peroxide, is a "hydrolytically active" dioxyphosphorane which promotes mild and efficient cyclodehydration of diols to cyclic ethers in neutral media. Simple 1,2-, 1,4-, and 1,5-diols afford good yields of the cyclic ethers but 1,3-propanediol and 1,6-hexanediol give mainly 3-ethoxy-1-propanol and 6-ethoxy-1-hexanol, respectively, with DTPP. Tri- and tetra-substituted 1,2-diols afford the relatively stable 1,3,2-dioxaphospholanes in the presence of DTPP and the reaction conditions dictate whether epoxides, ketones, or allylic alcohols are obtained.

Preparative routes to a majority of σ-phosphoranes can generally be traced to the intermediacy of trivalent phosphorus reagents at some stage. In fact, a common procedure involves "redox" reactions between alkyl, aryl, or aminophosphines and compounds possessing weak heteroatom-heteroatom bond (e.g., —O—O—,[1] —O—S—,[2] —S—S—,[3] —O—Cl,[4] —S—N—,[5] etc.) as well as carbon-halogen[6] and halogen-halogen bonds.[7] Other σ-phosphoranes are conveniently prepared by the reaction of trivalent phosphorus compounds with *o*-quinones and α-diketones,[8] the equivalent of a [4 + 2]cycloaddition reaction. These "organophosphorus reagents"[9] have been particularly effective in promoting mild synthetic transformations such as substitution and condensation reactions. Our current research effort has focused on determining the feasibility of diethoxytriphenylphosphorane, $Ph_3P(OEt)_2$, as an effective cyclodehydrating reagent for a wide variety of diols.

Diethoxytriphenylphosphorane (DTPP), prepared by oxidative addition of triphenylphosphine (TPP) with diethyl peroxide, is a stable, but *hydrolytically active* dioxyphosphorane which has been isolated and spectroscopically characterized.[10] DTPP is isolated by "flash distillation" at 150–160° (0.05 torr) and is stable indefinitely in anhydrous toluene solvent under Ar or N_2 up to 70°. The ^{13}C, ^1H, and ^{31}P NMR spectral parameters described in Chart 1 are in agreement with the pentacoordinated trigonal bipyramidal conformer having diapical ethoxy groups as previously proposed by Denney.[11]

In the ^{13}C NMR spectrum some pertinent phosphorus-carbon couplings are clearly evident. For example, $^2J_{\underline{P}O\underline{C}} = 7.2$ and $^3J_{\underline{P}OC\underline{C}} = 5.5$ Hz attributable to phosphorus coupling to the ethoxy carbons are readily observable while the phosphorus-ipso carbon coupling is also diagnostic. A pentet (δ 2.56, $^3J_{\underline{H}CC\underline{H}} = {}^3J_{\underline{P}OC\underline{H}} = 7$ Hz) is observed for the CH_2 group in the ^1H NMR spectrum ($CDCl_3$) implying

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*Author to whom all correspondence should be addressed.

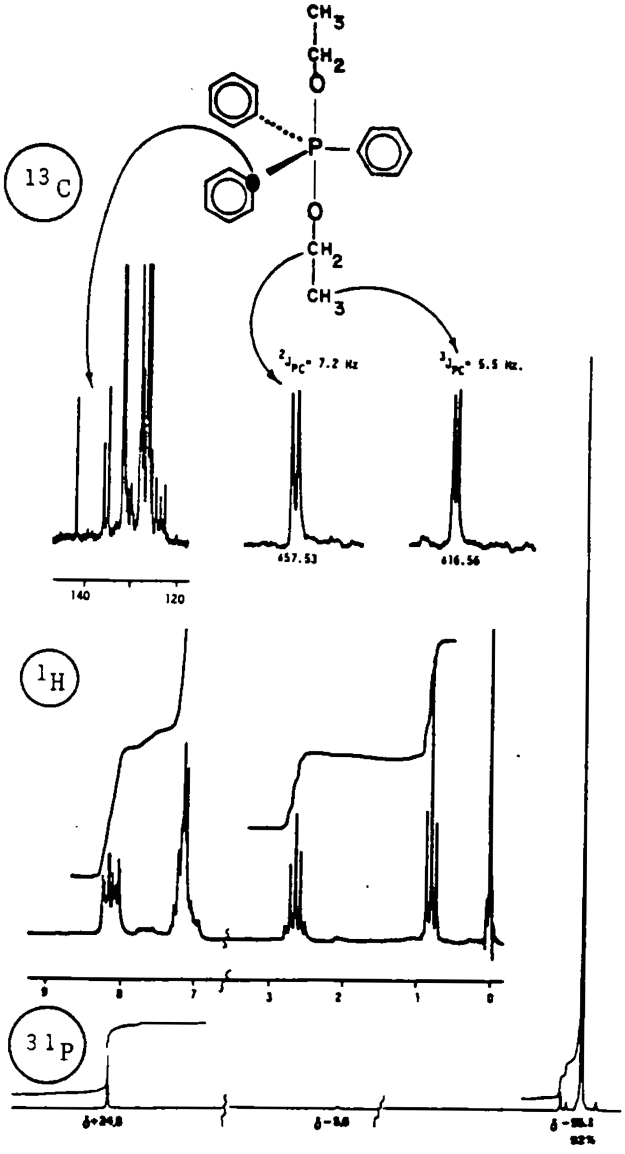
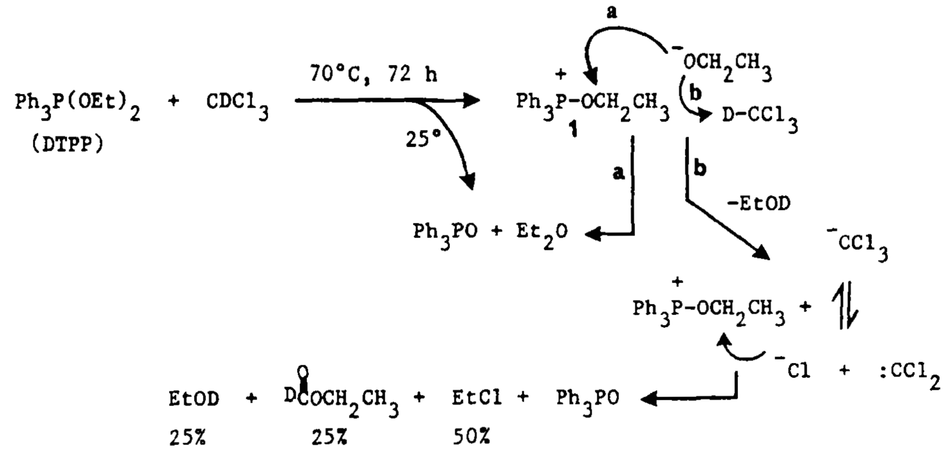


CHART 1 NMR spectra of $Ph_3P(OEt)_2$.

equivalent spin-spin interactions between the attached phosphorus atom and methyl group. Finally, the ^{31}P resonance at δ -55.0 (C_6D_6) is indicative of a σ-dioxyphosphorane having diapical alkoxy groups (Resonances at δ 24.8 and -5.6 are attributable to Ph_3PO and Ph_3P, respectively.).

DTPP slowly decomposes in chloroform solvent at 25°C presumably by irreversible Arbosov collapse of oxyphosphonium ethoxide ion pair **1** to triphenylphosphine oxide (TPPO) and diethyl ether. However, at 70°C, ion pair **1** initiates proton abstraction from $CDCl_3$ and chloride ion, presumably resulting from α-elimination of trichlorocarbanion, displaces TPPO from $Ph_3P^+—OCH_2CH_3$ to give ethyl chloride (50%). The other products, ethanol and ethyl formate, are obtained in nearly equal amounts while only a trace of ethyl ether is observed by ^{13}C NMR analysis (Scheme 1).



SCHEME 1

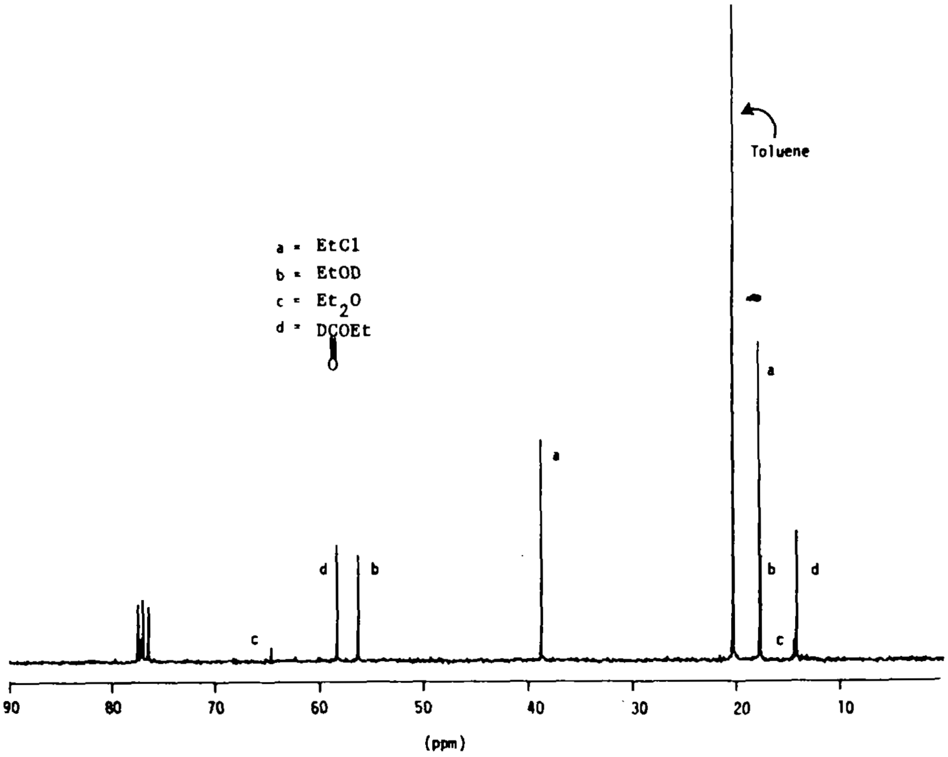
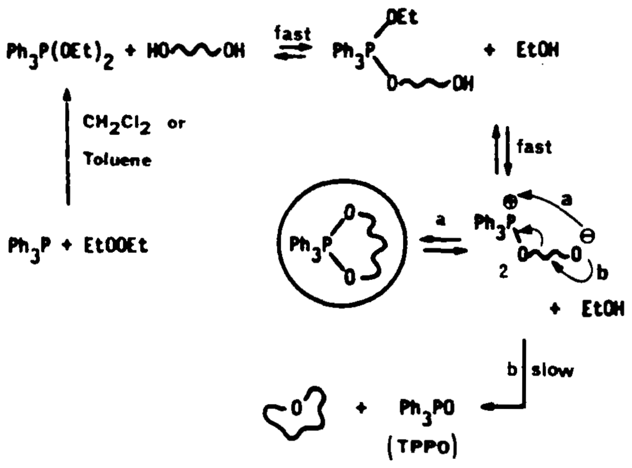


CHART 2 ^{13}C NMR spectrum of the $Ph_3P(OEt)_2$ + $CDCl_3$ reaction mixture.

It is evident that ethyl formate arises from dichlorocarbene insertion into the hydroxyl bond of ethanol followed by slow hydrolysis of the intermediate dichloromethoxyethane ($HCCl_2OCH_2CH_3$).[12]

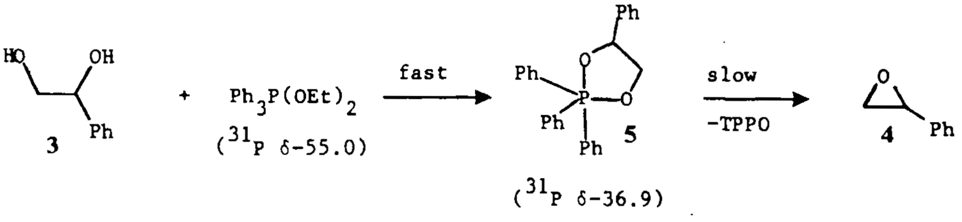
When 1,1,2,2-tetrachloroethane (TCE) and DTPP are combined and stirred at 65°C for 72 h, DTPP is quantitatively decomposed to TPPO by ^{31}P NMR analysis. In fact, ethanol, ethyl chloride, and trichloroethene are also formed in a 1 : 1 : 1 ratio. Apparently, ethoxide anion from ion pair **1** initiates β-elimination of HCl from TCE to form trichloroethene. Accordingly, chloride ion displacement of TPPO from Ph_3P^+—OEt gives ethyl chloride.

DTPP undergoes ligand exchange with compounds containing sufficiently acidic hydrogens via the oxyphosphonium-alkoxide ion pair **1**. If a diol is added to DTPP, the exchange of ethanol by the diol commences to form the prerequisite 1,3,2-dioxaphosphorane-betaine combination. In this way, formation of the cyclic ether by intramolecular displacement of TPPO from betaine **2** can be achieved (Scheme 2).



SCHEME 2 Ligand exchange of DTPP with a diol.

The ligand exchange processes are rapidly accomplished suggesting that intramolecular displacement of TPPO from betaine **2** is rate-limiting. For example, cyclodehydration of phenylethane-1,2-diol (**3**) to phenyl oxirane (**4**) with DTPP was monitered by ^{31}P NMR as a function of time (Chart 3). At 70°C, DTPP (^{31}P δ − 55.0) very quickly undergoes ligand exchange forming 1,3,2-dioxaphospholane **5** (^{31}P δ − 36.9). It is clear that decomposition of **5** is considerably slow, requiring 700 minutes for 95% conversion.



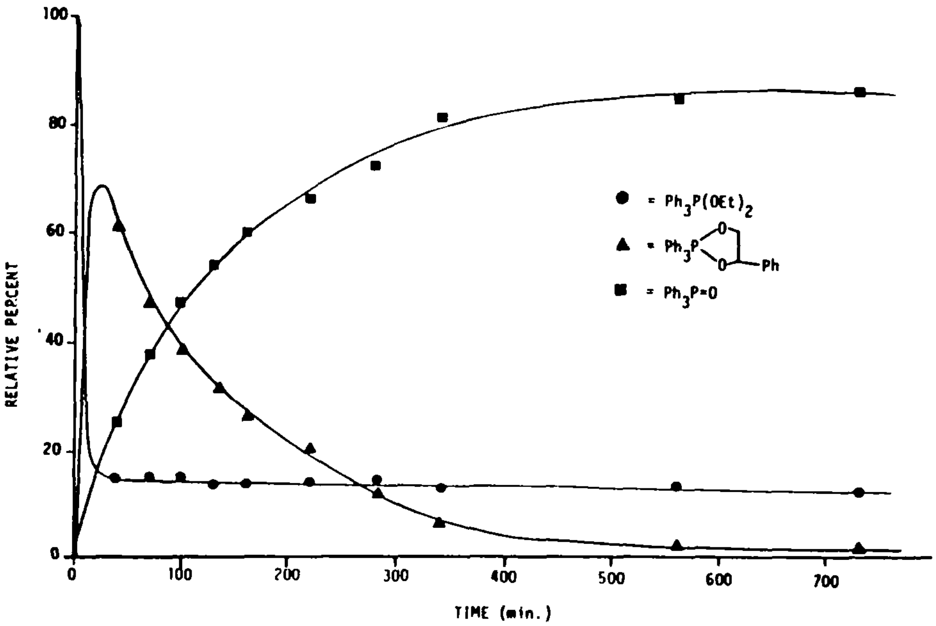


CHART 3 ^{31}P NMR results of the DTPP/phenylethane-1,2-diol cyclodehydration reaction versus time.

To gauge the efficiency with which DTPP promotes cyclodehydration of diols, a series of simple α,ω-diols were examined with the DTPP reagent. 1,2-Propanediol reacts with DTPP in refluxing CH_2Cl_2 or toluene solvent (80–95°C) to give propylene oxide (83–88%). 1,3-Propanediol, on the other hand, reacts with DTPP affording $< 3\%$ oxetane and mainly 3-ethoxy-1-propanol ($> 97\%$). These latter results indicate that while "phosphorylation" of the hydroxyl group does occur, subsequent closure of betaine **2** to the four-membered oxetane is thermodynamically disfavored relative to ethoxide displacement of TPPO from Ph_3P^+—$OCH_2CH_2CH_2O^-$(H).

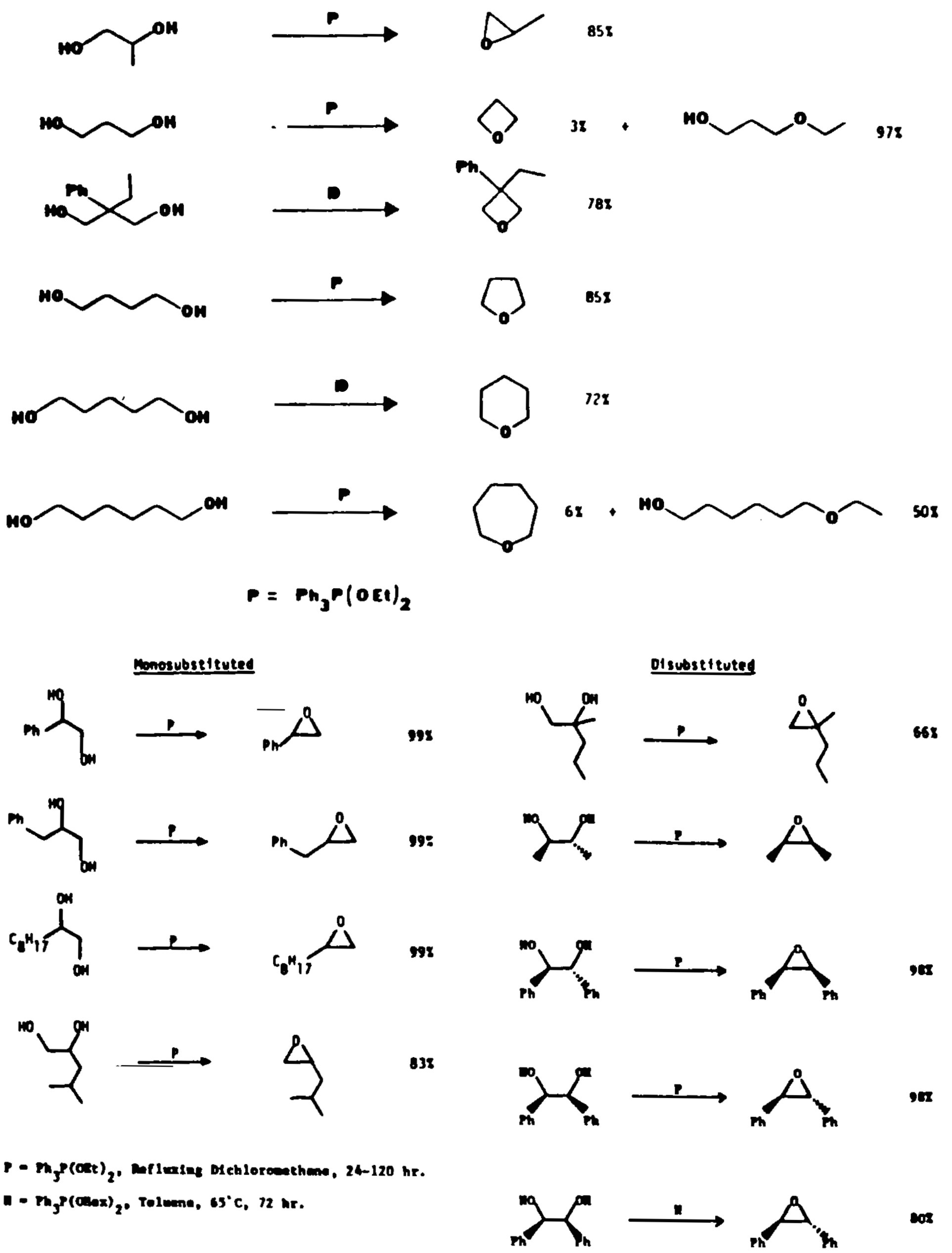
1,4-Butanediol and 1,5-pentanediol are smoothly converted to tetrahydrofuran (85%) and tetrahydropyran (72%), respectively, with DTPP; however, reaction of DTPP with 1,6-hexanediol affords essentially no oxepane ($< 6\%$) but mainly 6-ethoxy-1-hexanol (50%) and starting diol (44%) by GLC and ^{13}C NMR analysis.

These and other results summarized in Table I, reveal the potential usefulness of DTPP-promoted cyclodehydrations of 1,2-, 1,4-, and 1,5-diols to the corresponding cyclic ethers. In general, the rate of ring closure decreases in the following order of chain → ring formation: $3 > 5 > 6 > 4 > 7$. This trend, resulting from the relative enthalphy differences due to ring strain and entropic differences associated with ring closure, is also found in the cyclodehydration of diols employing the TPP—CCl_4—K_2CO_3 reagent [6c] and the dialkoxydiarylsulfurane reagent reported by Martin *et al.*[13]

Despite their immense biological significance, only a few synthetic routes to arene oxides (from diols) are currently available. As a straightforward demonstration of the utility of DTPP, 9,10-epoxy-9,10-dihydrophenanthrene (**6**) can be prepared in

TABLE I

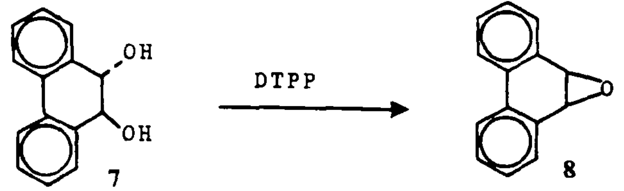
Efficiency of Ring Closure in the $Ph_3P(OEt)_2$ Promoted Cyclodehydration of 3, 4, 5, 6, and 7-Membered Rings.



P = $Ph_3P(OEt)_2$, Refluxing Dichloromethane, 24–120 hr.

H = $Ph_3P(OHex)_2$, Toluene, 65°C, 72 hr.

> 99% by cyclodehydration of 9,10-dihydro-*trans*-9,10-phenanthrenediol (7) with DTPP in $CH_3CN : CH_2Cl_2$ solvent.



Interestingly, reactions of tri- and tetra-substituted 1,2-diols with DTPP afford *stable* 1,3,2-dioxaphospholanes which are selectively decomposed to epoxides, ketones, or allylic alcohols depending on the reaction conditions. For example, 1,3,2-dioxaphospholane **8** (^{31}P δ-48.3), obtained from reaction of DTPP with 2-methylpentane-2,3-diol (**9**), reacts with LiBr (60°C, 3 days in C_6D_6) to give only 2-methyl-3-pentanone (**10**; > 95% by ^{13}C NMR). In $CDCl_3$ solvent (60°C), 2-methyl-2,3-epoxypentane (**11**; 60% in 72 h) is the only product and in toluene solvent (100°C) both 3-hydroxy-2-methyl-l-pentene (**12**; 31%) and ketone **10** (26%) are obtained after 24 h. Amberlyst-15, a beaded polystyrene sulfonic acid resin, may promote rearrangement of phosphorane **8** or epoxide **11** to ketone **10**. The allylic alcohol **12** probably forms from intramolecular proton abstraction within the appropriate betaine followed by elimination of TPPO. An independent experiment has shown that LiBr does not promote rearrangement of an authentic sample of epoxide **11** to ketone **10** under these reaction conditions; therefore, it seems reasonable to suggest that hydride migration occurs directly from *within* phosphorane **8** or its betaine. (Chart 4)

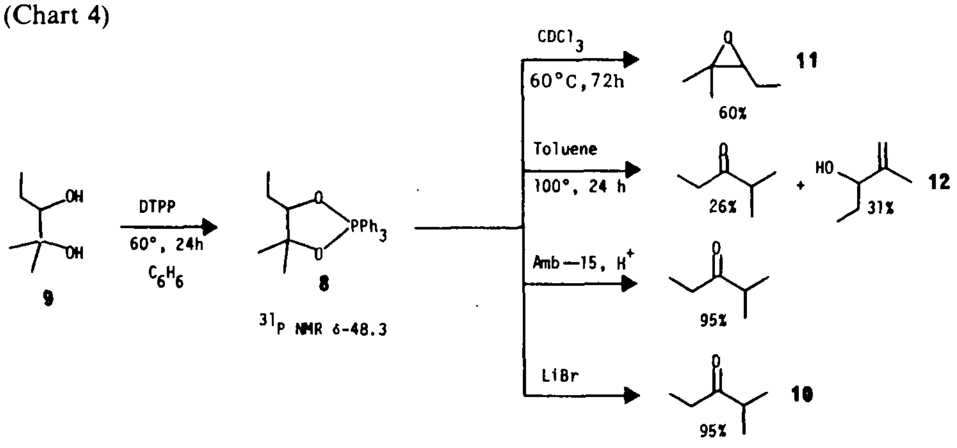
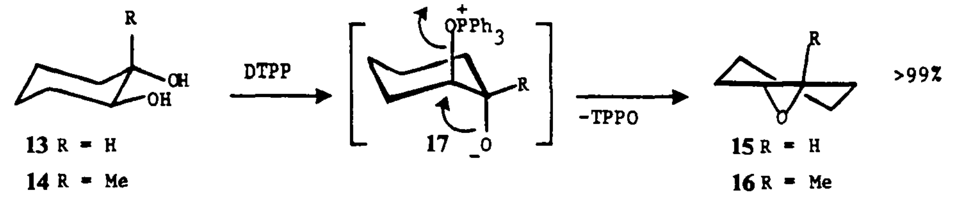
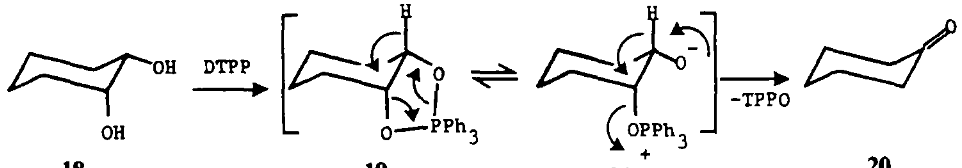


CHART 4 Reactions of Phosphorane 8.

trans-1,2-Cyclohexanediol (**13**) and 1-methyl-*trans*-1,2-cyclohexanediol (**14**) are quantitatively converted to the corresponding epoxides (**15**, **16**) when treated with



DTPP. Epoxide formation is consistent with the "3-exo-tet" cyclization from the transient betaine intermediate **17**. By contrast, *cis*-1,2-cyclohexanediol (**18**) reacts with DTPP in refluxing dichloromethane (48 h) to afford > 95% 1,3,2-dioxaphospholane **19** (^{31}P δ-37.7) which readily distills at 150°C (0.05 torr) with only minor decomposition. Vacuum thermolysis of dioxaphospholane **19** (220°C, 15–23 torr) gives cyclohexanone (**20**; > 90%). A synchronous 1,2-hydride shift within phosphorane **19** or the corresponding betaine **21** satisfactorily accounts for formation of ketone **20**.



18 **19** **21** **20**

It is also noteworthy that the ^{13}C NMR spectrum of **19** exhibits phosphorus-carbon couplings within the cyclohexyl ring where the geminal coupling ($^2J_{\mathrm{PO\underline{C}}}$ = 2.5 Hz) is smaller than the vicinal coupling constant ($^3J_{\mathrm{POC\underline{C}}}$ = 5.0 Hz). This is in contrast to the couplings observed for the *acyclic* dioxyphosphorane, Ph$_3$P(OEt)$_2$ (vide supra) (See Chart 5).

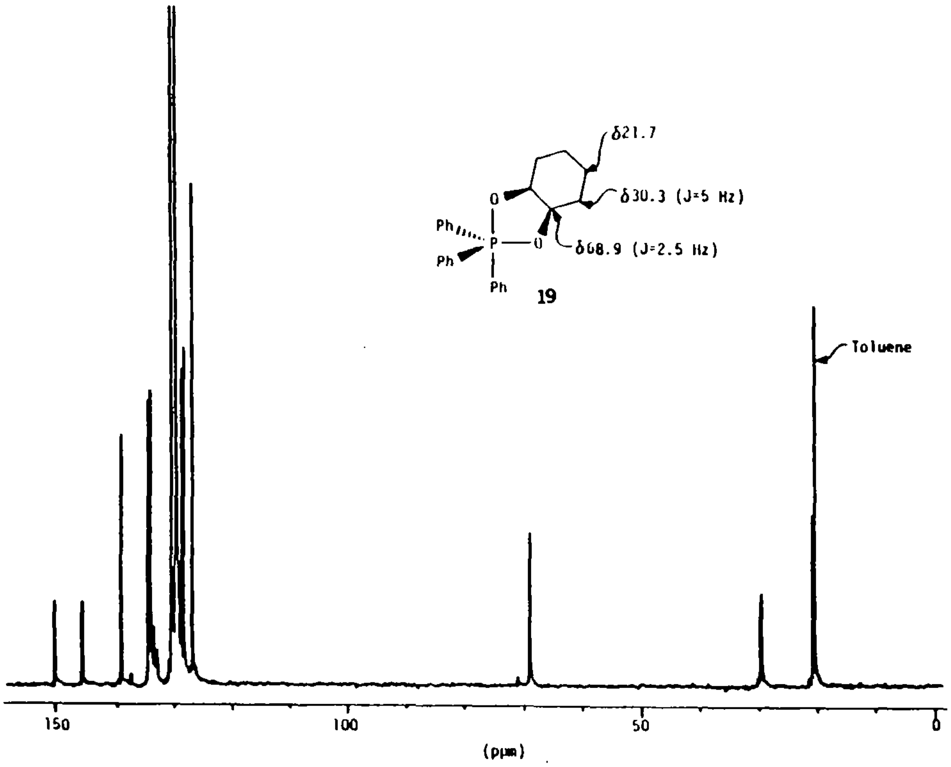
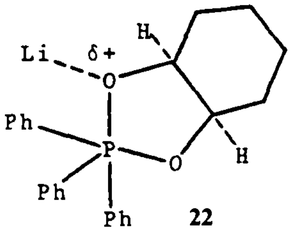


CHART 5 ^{13}C NMR spectrum of dioxyphosphorane **19**.

Interestingly, lithium bromide catalyzes the decomposition of dioxaphospholane **19** *at 60°C* to afford ketone **20** in 95%. It seems reasonable to suggest that here lithium cation coordinates with the apical oxygen (i.e., **22**) and this interaction serves to further weaken the P—O bond and promote formation of betaine **21** and the subsequent 1,2-hydride shift. In the presence of wet chloroform, dioxyphosphorane **19** is expectedly hydrolyzed to TPPO and diol **18** (Chart 6).



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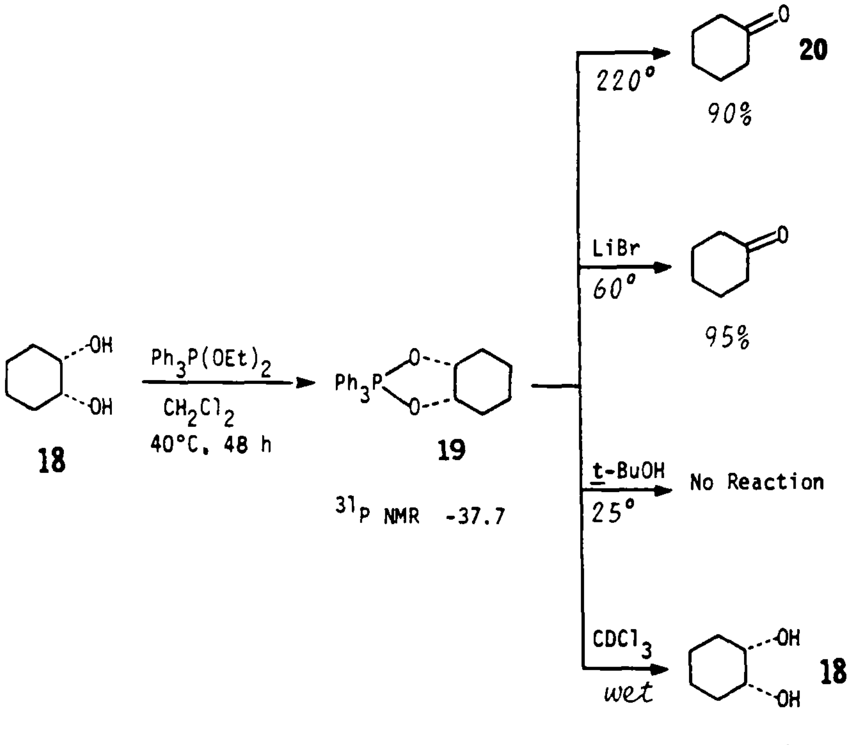

CHART 6 Reactions of dioxyphosphorane **19**.

In summary, DTPP is isolable, easy to prepare and stable in nonprotic anhydrous solvents. The cyclodehydration reaction conditions are mild (40–100°C) and effectively neutral. Finally, the isolation of the product(s) from triphenylphosphine oxide is conveniently accomplished by distillation or "rapid" column chromatography.

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