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## Polycyclic Carbon–Phosphorus Heterocycles

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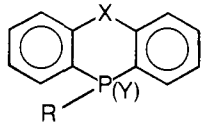
### I. Introduction

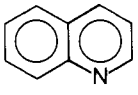
Carbon–phosphorus (C–P) heterocycles constitute a class of compounds the interest in which has developed rapidly within the past decade. This review focuses on the chemistry of fused polycyclic C–P systems with a minimum of two rings, one of which *must* contain *only* carbon and phosphorus. Thus, phosphorus heterocycles containing another heteroatom in the ring (with one exception) have not been included. The one exception we have permitted was that illustrated by the general structure **1**. This class was included for the sake of completeness and because of the close similarity to phosphaanthracenes.




**1** X = NR′, O, S
Y = lone pair, O, S

Coverage of *Chemical Abstracts* and the current literature was through August of 1975, although earlier reviews[140,232,322] had included the very meager data available through 1966 and may be examined by the reader for the early work. For compounds to be included in the tables (available on microfilm), a judgment was made of the structural data given in the experimental section of a publication. Because of the relative lack of systematic investigations in polycyclic C–P heterocycles, we have often included ancillary references on closely related simple systems along with the primary references.

Although sulfur analogs of many phosphorus compounds might be comparable from a geometric and electronic point of view, bicyclic C–P heterocycles have been frequently referred to in analogy with nitrogen-containing systems. Quinoline (**2**) and 1-phosphanaphthalene (**3**) fall in this category although general

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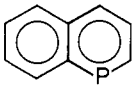



**3**

properties and utility of the parent bicyclic phosphorus compounds and relatives thereof have only been scarcely reported with a few exceptions.

This review has covered the synthesis, properties, and reactions of polycyclic C–P heterocycles. Rather than discuss properties under a separate heading, it was deemed more useful to the reader to include such data when a particular compound was first prepared. This should minimize multisearches. Some sections contain only a few references bearing on C–P heterocycles per se, and some introductory discussions have been provided on simple alicyclic and acyclic systems. It is our contention that these areas are almost certain to develop rapidly and therefore merit inclusion in this review in spite of the meager and unrelated data available.

A few scattered reviews have appeared on a variety of subjects in organophosphorus chemistry and reference has been made to them where such data were applicable for clarity and to provide sources for the reader to gain additional depth in a specific but less related area. For example, within the past 10 years, several series have appeared on various aspects of organophosphorus chemistry and include: "Topics in Phosphorus Chemistry" (Interscience),[126] "Organophosphorus Chemistry" (The Chemical Society),[334] and "Organic Phosphorus Compounds" (Wiley).[216] Special topics of considerable value have been published also, some of the more comprehensive being: "Structure and Mechanism in Organo-Phosphorus Chemistry",[177] "The Chemistry of Organo-Phosphorus Pesticides",[101] "Interpretation of Infrared Spectra of Organophosphorus Compounds",[331] "The Organic Chemistry of Phosphorus",[207] "Analytical Chemistry of Phosphorus Compounds",[134] "NMR

Studies of Phosphorus Compounds",[263] "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, and Bismuth",[227] "Phosphorus Compounds",[283] and "Organophosphorus Stereochemistry", Parts I and II.[265] Small portions of the information given in this review were found greatly scattered in these works, but the researcher or prospective researcher in the field will find these references very useful for related simple systems. We would be negligent not to mention the journal *Phosphorus* (Gordon and Breach) which has been published since 1971 and contains much data in this field (now *Phosphorus and Sulfur*).

The chemistry of bicyclic C–P heterocycles is in its infancy but is likely to develop rapidly if the well-known biological activity of nitrogen relatives holds true even for some of the phosphorus counterparts. Unfortunately, nomenclature in the area is tragically unsystematic and we have elected to use names graciously suggested in many instances by Dr. Kurt Loening, Director of Nomenclature of *Chemical Abstracts*.

Rather than divide the discussion into families of compounds, the paucity of data prompted use of reaction types for the synthesis and chemistry of bicyclic C–P heterocycles. It is hoped that this technique will create a systematized approach to the subject for a prospective reader and stimulate cross fertilization of ideas by chemists working in other disciplines than the organic chemistry of phosphorus.

The following abbreviations have been used in the manuscript:

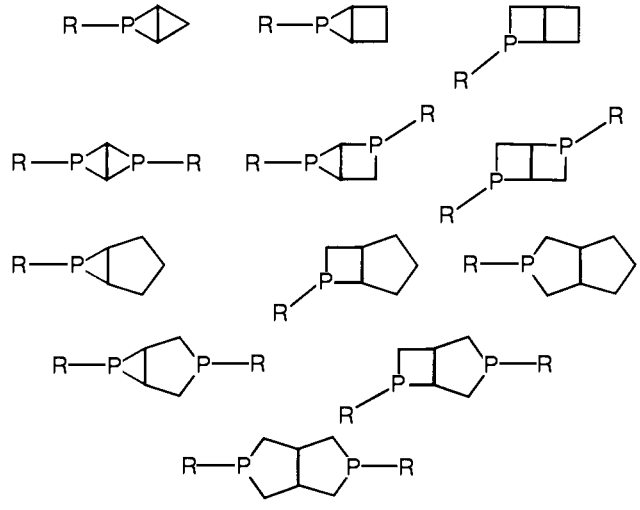
| | |
|---|---|
| Bu | Butyl |
| Bz | Benzyl |
| *t*-BuOH | *tert*-Butyl alcohol |
| *t*-BuOK | Potassium *tert*-butoxide |
| Diglyme | Di(ethylene glycol) dimethyl ether or bis(2-methoxyethyl) ether |
| DBN | 1,5-Diazabicyclo[3.4.0]non-5-ene |
| DBU | 1,5-Diazabicyclo[5.4.0]undec-5-ene |
| DME | 1,2-Dimethoxyethane or glyme |
| DMF | N,N-Dimethylformamide |
| Et | Ethyl |
| $Et_2O$ | Diethyl ether |
| $Eu(dpm)_3$ | Tris(dipivalomethano)europium(III) |
| HMPA | Hexamethylphosphoramide |
| $HSiCl_3$ | Trichlorosilane |
| MCPA | *m*-Chloroperbenzoic acid |
| Me | Methyl |
| Ms | Mesyl |
| NBS | *N*-Bromosuccinimide |
| Ph | Phenyl |
| PPA | Polyphosphoric acid |
| Pr | Propyl |
| $Pr(fod)_3$ | Tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)praseodymium(III) |
| RT | Room temperature |
| $Si_2Cl_6$ | Hexachlorodisilane |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| THMP | Tris(hydroxymethyl)phosphine |
| Ts | Tosyl |
| Vitride | $NaAlH_2(OCH_2CH_2OCH_3)_2$ or sodium bis(2-methoxyethoxy)aluminum hydride |

## II. Methods of Synthesis

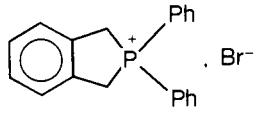
### A. Cyclic Quaternization

Cyclic quaternization has been the most commonly employed method for the synthesis of C–P heterocyclic systems. It involves the inter- or intramolecular attack of a suitably oriented phosphine on an atom holding the leaving group (usually a halide or a tosylate) with the simultaneous quaternization of the phosphorus atom. The vast majority of the compounds reported in the early literature on C–P heterocycles have been prepared by this method.[140] Although several excellent methods have been developed in recent years for the synthesis of C–P heterocycles, the process of cyclic quaternization has continued to be used because of several advantages, the chief of which being procedural simplicity.

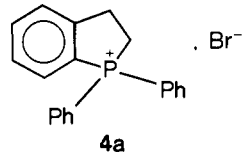
One can envision a number of simple polycyclic C–P systems such as shown below (or isomers thereof), none of which have been reported. The majority of data published has most often



included a C–P heterocycle fused to an aromatic ring. To anyone familiar with the field of organophosphorus chemistry, cyclic quaternization might well be a method of choice to initiate the synthesis of any of the above unknown compounds. As a starting point the simple member **4** of the isophosphinodolinium family



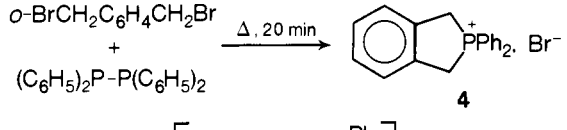
**4**



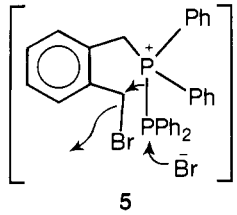
**4a**

or the phosphindolinium family **4a** comes to mind, since these polycyclic C–P heterocycles are the P analogs of dihydroisoindoles and dihydroindoles, respectively.

A facile synthetic entry to an isophosphindolinium system was reported recently via treatment of *o*-xylyl dibromide with tetraphenyldiphosphine (from diphenylphosphonous chloride and calcium carbide) in *o*-dichlorobenzene to yield the bromide **4**, characterized via picrate and perchlorate salts.[231,320] Although



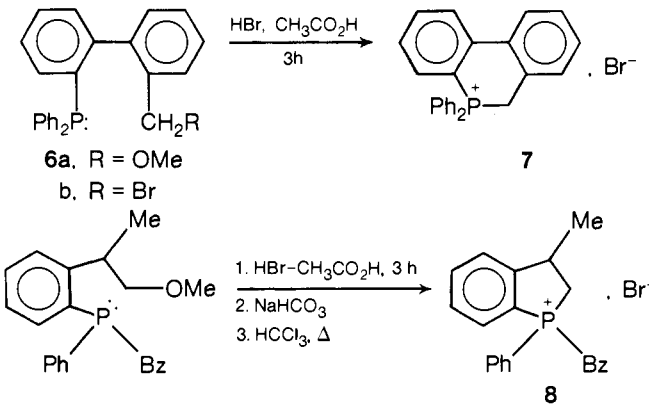
**4**



**5**

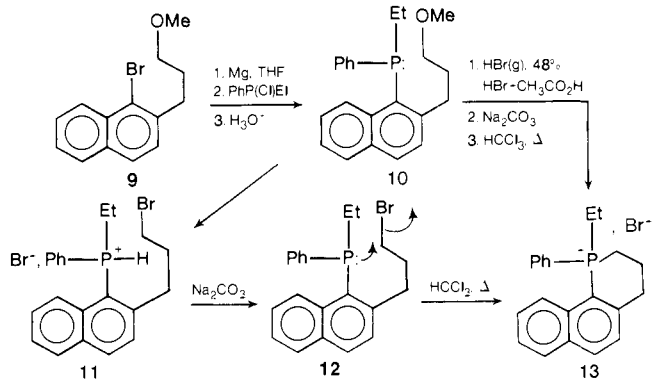
the yield of **4** was modest (31%), the method was attractive from ease of experimentation.[320] The reaction presumably occurred via cyclization of the intermediate **5**.

Cookson and Crofts[68] treated a boiling solution of phosphine **6a** in acetic acid with hydrogen bromide and prepared 9,10-dihydro-9,9-diphenyl-9-phosphoniaphenanthrene bromide (**7**), mp 335–337 °C, in quantitative yield. In this reaction, the



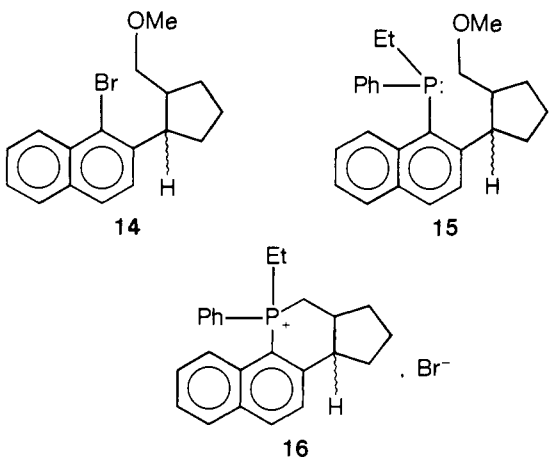

cleavage of the ether **6a** occurred to form initially the bromomethyl phosphine **6b** which underwent an intramolecular cyclization providing salt **7**. The approach was based on a general technique developed by Mann.[229] Mislow and coworkers[97] also utilized this technique to prepare the phosphindolinium system **8** as a mixture of diastereoisomers (32%) in almost equal amounts as revealed by $^1H$ NMR spectroscopy.

A general synthetic pathway has been developed for the synthesis of phosphaphenanthrene as indicated.[58] A useful



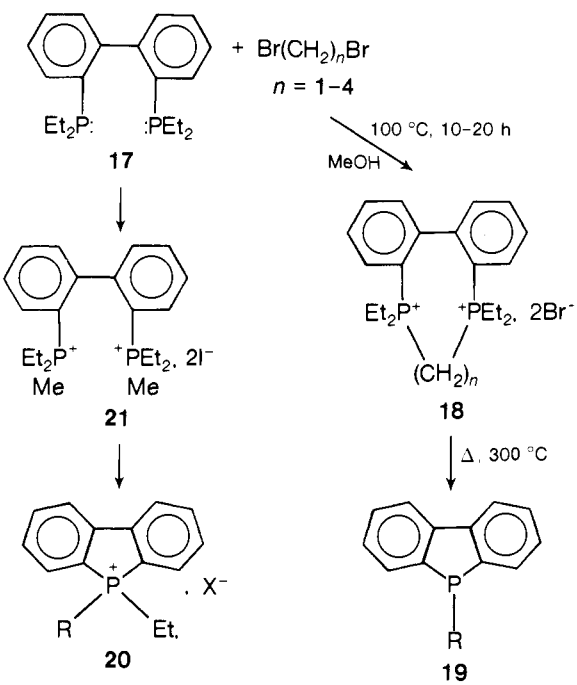

feature of this method was the introduction of a dissymmetric phosphorus moiety at the C-1 position of a naphthalene ring via the Grignard reaction of **9** to afford **10**, followed by intramolecular quaternization. The key step, in this case, presumably involved the intermediate **11**, which resulted from the cleavage of the methoxy ether function in **10** with the simultaneous protonation of the basic phosphine by HBr. Phosphine **12**, generated in situ by neutralization of **11** with base, then cyclized intramolecularly to 1-ethyl-1,2,3,4-tetrahydro-1-phenylbenzo[*h*]phosphinolinium bromide (**13**), mp 227.5–228.5 °C (50%). The $^1H$ NMR spectrum of salt **13** had signals at $\delta$ 1.5–4.7 (8 H, m, ring methylenes and $PCH_2CH_3$), 1.0–1.32 (3 H, tt, $J_{HCCH}$ = 7.5 Hz, $J_{PCCH}$ = 20.5 Hz, $PCH_2CH_3$), and 7.35–8.45 (11 H, multiplet, aromatic) and agreed with the proposed structure. However, satisfactory elemental analysis on the salt **13** was not obtained as a nonstoichiometric quantity of the solvent of crystallization was entrained, but the perchlorate and the picrate derivatives made by anion metathesis gave correct elemental analyses. The structure of the bromide **13** was recently certified by x-ray crystallographic analysis which showed that the conformation of the phosphorinane ring was a near-perfect half-chair.[167] Interestingly, the cyclic salt **13** exhibited activity against P-388 lymphocytic leukemia.[58,167] In view of this finding, other C–P heterocyclic quaternary salts should be scanned for possible biological activity. Partial resolution of the phosphonium bromide **13** via silver hydrogen D-(−)- and L-(+)-dibenzoyltartrates was realized and represented the first instance of successful resolution of a C–P heterocycle with a truly asymmetric phosphorus atom of the type [abcdP$^+$], $X^-$. By this general approach, dissymmetric cyclic phosphonium salts, which could be resolved into optically active antipodes, could be easily prepared.

The same group also accomplished the first total synthesis of a phosphasteroid system.[59] The converging synthesis utilized 2-bromonaphthalene and 2-(hydroxymethyl)cyclopentanone as starting synthons, and the tricyclic intermediate **14** was eventually constructed by a multistep reaction sequence. Transfor-



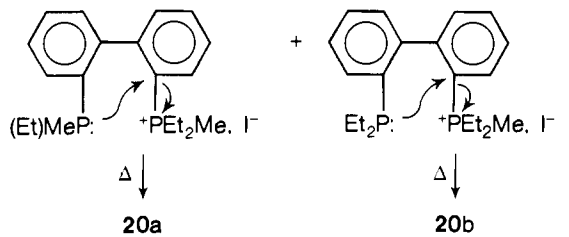

mation of the bromo ether **14** to the phosphine **15** was accomplished by an extension of the earlier procedure[58] for incorporating the dissymmetric phosphorus moiety via a Grignard reaction. The crucial step, the intramolecular quaternization, was effected by the same procedure adopted previously[58] to provide the first tetracyclic phosphonium bromide **16** (43%). The corresponding perchlorate, mp 183.5–187 °C, gave correct elemental analysis and had the expected infrared and $^1H$ NMR spectrum. The stereochemistry of the C/D ring junction in **16**, however, was not delineated.[59] The method should be applicable, with slight modifications, to the synthesis of phosphorus analogs of medicinally important sex hormones. A summary of phosphasteroid systems prepared to date was released recently.[90]

Intermolecular quaternization of diphosphines with alkyl or aryl dihalides, in certain cases, has provided quite novel cyclic phosphonium salts. By the simple interaction of 2,2-biphen-



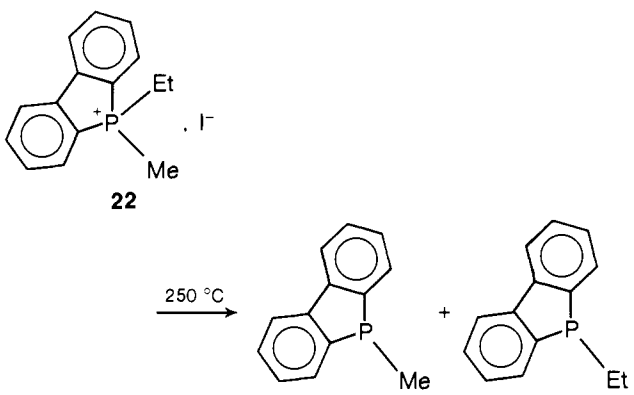

a, R = Me
b, R = Et

ylenebis(diethylphosphine) (**17**) with $\alpha,\omega$-dibromoalkanes containing a trace of methanol in a sealed tube at 100 °C (10–20 h). Mann and co-workers[9,11] obtained a number of such salts **18** ($n$ = 1, mp 228–230 °C). Characterization of these hygroscopic salts **18** was effected through the preparation of dipicrates which incidently was added proof that these salts, indeed, were cyclic.[11] Examination of molecular models of the salts suggested that the heterocyclic rings were buckled but almost strainless. Also, the absence of characteristic absorption of the biphenyl system in the electronic spectrum (250-nm region) suggested a lack of coplanarity of the aromatic rings of the biphenyl system.[11] Thermal decomposition of the bridged salts **18** proceeded in high yield to afford a mixture of 9-alkyl-9-phosphafluorenes (**19a** and **19b**) and their hydrobromides **20a** and **20b** in varying proportions. Likewise, thermal decomposition of the dimethiodide **21** (lacking the bridge unit) gave also a mixture of the phosphines **19a** and **19b** (1:4.8) and their hydriodides (**20a,b**).




**20a** **20b**

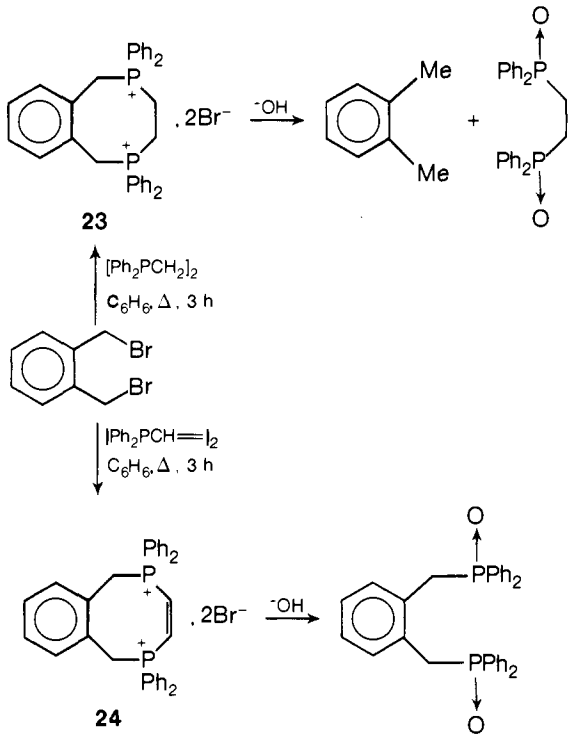
These observations were accommodated in a mechanism indicated. A similar $S_Ni$ displacement mechanism was suggested for the ring-contraction reaction observed in the thermal decomposition of the cyclic diphosphonium salts **18.** Comparable ring contraction reactions were earlier noted by the same workers with diarsonium salts.[9,11] It is worthy of note that the thermal decomposition of phosphonium salts **22** has also been observed in these phosphafluorene systems.[11]




**22**

Similarly, *o*-xylyl dibromide reacted with ethylenebis(diphenylphosphine) and *cis*-vinylenebis(diphenylphosphine) in boiling benzene (3 h) to afford a 1:1 adduct in both cases in almost quantitative yield.[3] The cyclic structures **23** and **24** were assigned to these adducts based on combustion analysis of the respective dipicrates. $^1$H NMR spectral data favored a cyclic structure for the salts. Molecular weight (osmometry) and conductivity at different concentrations were measured on **24.** At concentrations above 0.01 M (in $CH_3OH$), the cyclic salt **24** was associated and behaved as a 1:1 electrolyte. Conductance measurements, however, showed it to be a 2:1 electrolyte. Such behavior was observed earlier with monocyclic diphosphonium salts.[2] No explanation has been proposed in either case. Hydrolysis of **23** and **24** gave dramatically differing results as shown.[3]

Treatment of the salt **24** with base (collidine or *n*-butyllithium) gave a red solution, but attempts to isolate 1,4-diphosphoniacyclooctene in the form of a stable salt failed.[3] The failure was attributed to the opening of the eight-membered ring either by the attack of the base on the quaternary phosphorus or by base

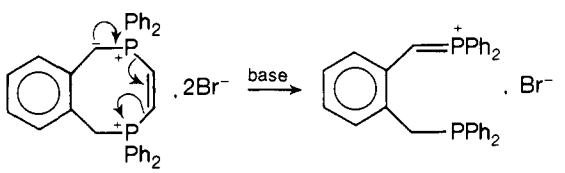



**23**



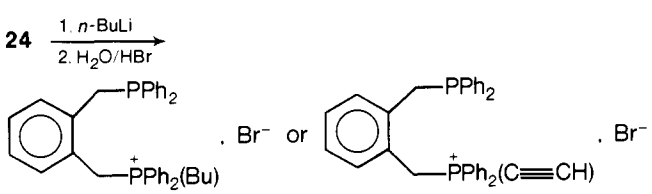

**24**

abstraction of the vinyl hydrogen. In view of the development of red color, it is conceivable that the initially formed ylide caused the expulsion of the two-carbon fragment to give **25** as indicated.




**24** **25**

Attack on **24** by *n*-BuLi in pentane led to a new salt suggested to be either salt **26** or **27.** A summary of syntheses and $^1$H NMR data for salts related to **23** and **24** has been released.[75]

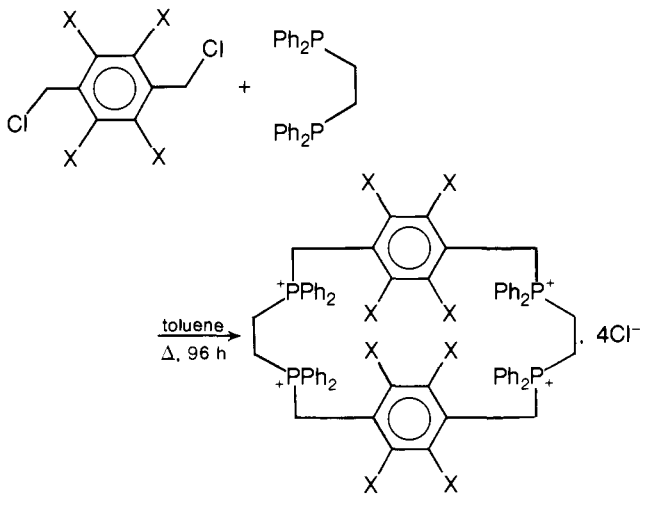



**26** **27**

Reaction of *p*-xylyl dichloride and substituted *p*-xylyl dichlorides with ethylenebis(diphenylphosphine) in boiling toluene (96 h) also produced adducts in excellent yields, which have been finally assigned the cyclic structure **28.**[341] Quaternary salts **28** showed only one strong signal around −27 ppm (rel to 85% $H_3PO_4$) in the $^{31}$P NMR spectrum ($F_3CCO_2H$), which ruled out all logical acyclic structures. $^1$H NMR spectral data also supported the cyclic structure **28.**

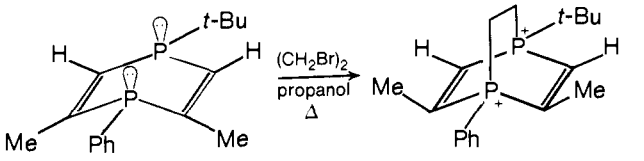
Märkl[244] employed the method of cyclic quaternization to differentiate the cis and trans isomers of 1,4-dihydro-1,4-diphosphabenzene (**29**). The cis isomer in which the phosphorus electron pairs are oriented in the same direction quaternized with 1,2-dibromoethane to yield the bridged salt **30,** mp 211–213 °C, in near-quantitative yield while the trans isomer did not react.[244]

Cyclic quaternization remains a standard procedure for preparing C–P heterocycles. No doubt other polycyclic systems will be obtained via this approach in the future.



28

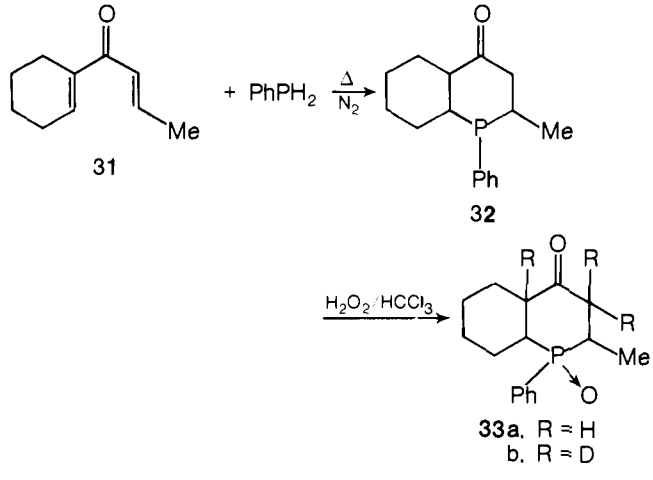
a, X = H; b, X = Cl; c, X = Me



29 30 , $2Br^-$

## B. Nucleophilic Additions

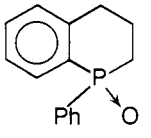
The double Michael addition of a primary phosphine to substituted divinyl ketones has been employed with success to prepare certain bicyclic C–P heterocycles. The method originally developed by Welcher and co-workers[348] for monocyclic C–P heterocycles has been recently expanded by Kashman and co-workers[192,193,199,200] to synthesize phosphadecalone, phosphabicyclo[3.2.1]octane, phosphabicyclo[3.3.1]nonane, and phosphaadamantane systems. For example, addition of phenylphosphine to propenyl cyclohexenyl ketone (**31**) gave a phosphadecalone **32** as an inseparable mixture of isomers.[200] Upon oxidation of the mixture with hydrogen peroxide, 2-phenyl-2-oxo-3-methylphosphabicyclo[4.4.0]decan-5-one (**33a**) was obtained as a crystalline solid, mp 178–180 °C. The



31 32

33a, R = H
b, R = D

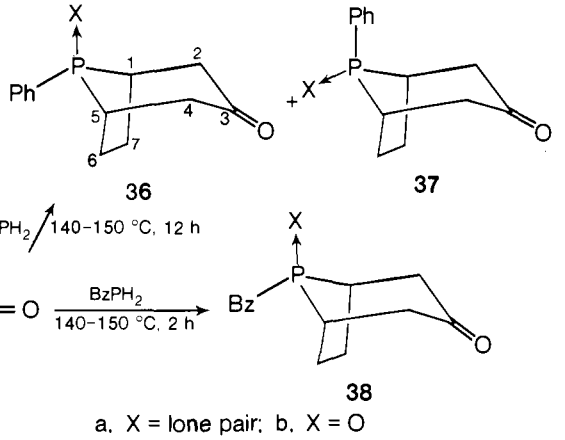
structural assignment was based on the $^1H$ NMR spectrum of the trideuterio compound **33b**, prepared by treating the oxide **33a** with NaOD in $CH_3OD$, coupled with mass spectral analysis of **33b**. The ring fusion in **33a** was assumed to be trans as no epimerization occurred on treatment of **33a** with $CH_3ONa$. For the same reason, the methyl group at C-3 in **33a** was presumed to be in an equatorial position. Normal couplings [$\delta$ 1.07, dd, 3 H, ($J_{PCCH_3}$ = 15 Hz, $J_{CHCH_3}$ = 7 Hz) in $DCCl_3$] for the oxide **33a** as well as a normal $\nu_{C=O}^{KBr}$ of 1705 $cm^{-1}$ and $\nu_{P=O}^{KBr}$ of 1175 $cm^{-1}$ in the infrared spectrum probably were suggestive of a relatively strain-free, fused system. A closely related phosphine oxide **34**



34

had a $\nu_{P=O}^{Nujol}$ of 1180 $cm^{-1}$, seemingly indicative that such fused systems may not alter the P=O force constant very much regardless of the presence of a conjugative effect.[299] Interestingly, the phosphine **32** had a $\nu_{C=O}^{KBr}$ of 1700 $cm^{-1}$ and did not hint at much, if any, P:- - -C=O interaction. X-ray data of **33a** would be helpful in establishing unequivocally the ring junction.

Likewise, addition of phenylphosphine to 2,6-cycloheptadien-1-one (**35**) for 12 h at 140–150 °C ($N_2$) gave a mixture (40% conversion) of 8-phenyl-8-phosphabicyclo[3.2.1]octan-3-ones (**36a** and **37a**), epimeric at the P atom.[193] The major product **36a** was obtained as a crystalline solid, mp 144–146 °C. Oxidation of the mixture of **36a** and **37a** with hydrogen peroxide in chloroform furnished the oxides **36b** and **37b** in a ratio of 9:1. Addi-

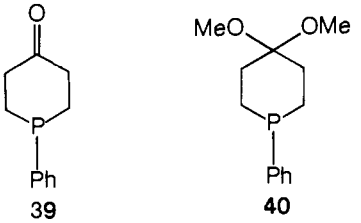


36 37

35 38

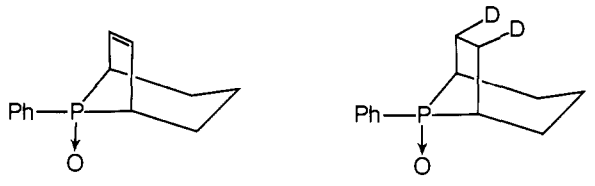
a, X = lone pair; b, X = O

tion of the more nucleophilic benzylphosphine to the ketone **35** produced a mixture of products from which 8-benzyl-8-phosphabicyclo[3.2.1]octan-3-one (**38a**) and its oxide **38b** were obtained as crystalline products after careful chromatography. Structural assignments here again were based on spectral data (IR, MS, and $^1H$ NMR). The $\nu_{C=O}^{KBr}$ was 1700 $cm^{-1}$ in both the phosphines **36a** and **38a** as well as the oxides **36b**, **37b**, and **38b**.[193] Thus, a chair form for the phosphorinanone ring (or perhaps a flattened chair form in view of the recent x-ray data on 1-phenyl-4-phosphorinanone (**39**) and its dimethyl ketal **40** which gave such a result)[268,288] may not be unreasonable.

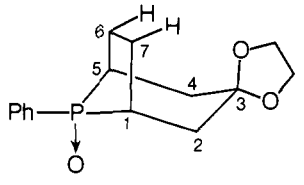


39 40

The $^1H$ NMR spectrum of **36a** was complex owing to the overlap of the ring proton signals, but the tetradeuterio derivative, obtained by treating **36a** with DCl and $D_3PO_4$ in dioxane, gave an interpretable spectrum. However, comparatively simple spectra resulted by the addition of $Eu(dpm)_3$ to solutions of the oxides **36b** and **37b**. A separate study of the oxides **41**, **42**, and **43**, which were derivatives of the related phosphabicyclic system, revealed only a partial clarification of the $^1H$ NMR spectra



41 42

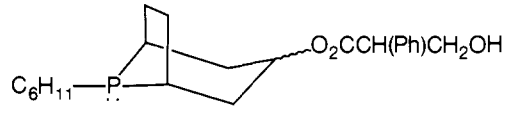


43

with $Eu(dpm)_3$, although protons $\alpha$ to the P=O were shifted *more* than protons $\alpha$ to C=O group in **36b** and **37b.**[194] This and other data supported the P=O group as the principal coordination site rather than the C=O group, however.

An interesting observation was made in the conversion of oxide **36b** to ketal **43.** Protons at C-2 and C-4 [$\delta$ 2.40–3.00 and 3.30–3.60] in **36b** were shifted to higher fields [$\delta$ 1.80–2.2 and 2.64–3.00, respectively] than in ketal **43.** In contrast, protons at C-6 and C-7 experienced a marked deshielding in ketal **43** (from $\delta$ 1.60–2.10 in oxide **36b** to $\delta$ 2.20–2.60 in ketal **43**). This was apparently the result of deshielding caused on H-6 and H-7 by the nonbonding electron pairs on an oxygen atom of the ketal. It strongly suggested the absence of a boat form for the phosphorinanone–ketal ring system. The configuration around the phosphorus atom in **36a** was claimed to have been established by x-ray analysis of its methiodide salt.[199,367] However, an x-ray analysis of a nickel chloride complex somewhat related to **36a** has been the only related system released.[315]

Synthesis of the related P-containing atropine analog **44** has

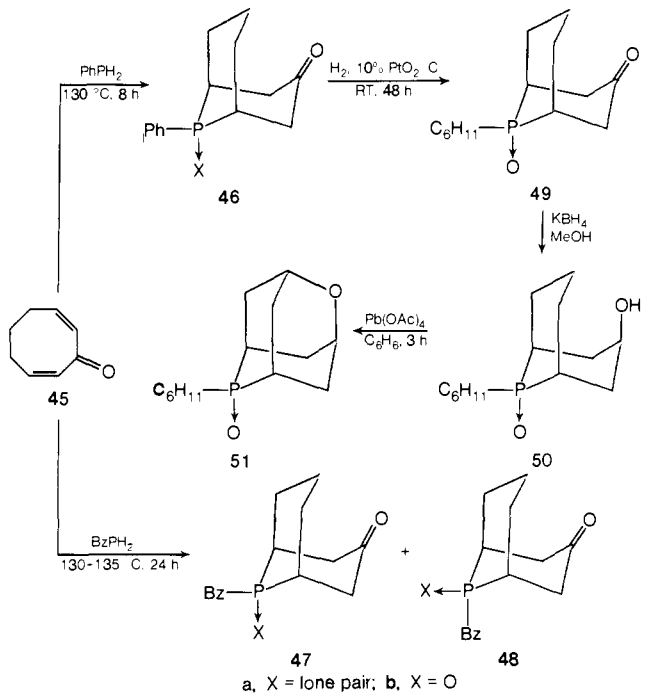


44

been achieved by the same group[192] via similar reactions previously discussed.[193,199] No biological activity has yet been reported for **44.** Although **44** has the electron pair on the P atom in an anti arrangement to the two carbon bridge, as in the illustration, the disposition of groups has not been unequivocally proven.

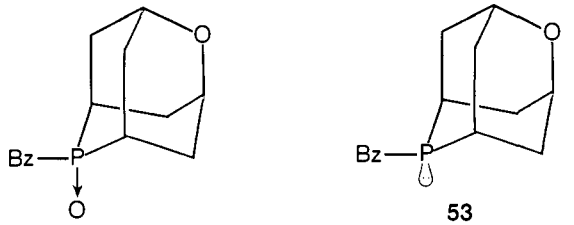
Similarly, addition of phenylphosphine to 2,7-cyclooctadien-1-one (**45**) gave 9-phenyl-9-phosphabicyclo[3.3.1.]-nonan-3-one (**46a**) as the only isolable crystalline product (50%), mp 133–135 °C.[199] However, addition of benzylphosphine provided a mixture of the P epimers **47a** and **48a** and their corresponding P-oxides **47b** and **48b.** The structures of the phosphines were supported by spectral data and by conversion to the corresponding oxides and quaternary salts. Unfortunately, the use of $Eu(dpm)_3$ did not clarify the spectra of the phosphine **46a** or the oxide **46b.**

Curiously, the phenyl group in the oxide **46b** was easily reduced to **49** on catalytic hydrogenation even at atmospheric pressure and room temperature in preference to the carbonyl group. However, the latter was reduced with potassium borohydride in methanol to the endo alcohol **50** which underwent transannular oxidation with lead tetraacetate to produce 2-phospha-6-oxaadamantane (**51**) in low yield.[199] Similarly the benzyl compounds **47b** and **48b** gave two epimeric alcohols when treated with $KBH_4$ in $CH_3OH$. Lead tetraacetate oxidation of the mixture of alcohols led to **52** as the main product which gave the phosphine **53** when reduced with trichlorosilane in benzene.



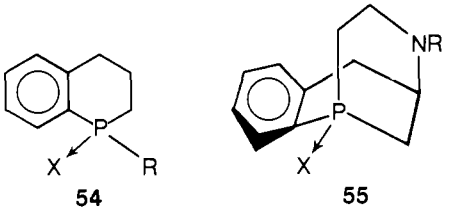
45 46 47 48 49 50 51

a, X = lone pair; b, X = O



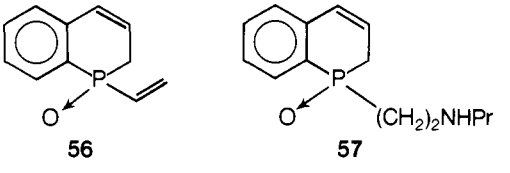
52 53

A series of experiments to prepare P analogs of benzomorphan analgetics resulted in improved procedures for members of **54**[64,299] and **55.**[299] The key precursor for the tricyclic system



54 55

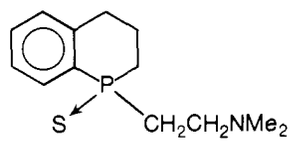
**55** was the vinyl-substituted oxide **54** (R = $CH_2$=CH, X = O). Thus, addition of propylamine to the vinylphosphine oxide **56** at room temperature (18 h) yielded the aminophosphine oxide **57.**



56 57

Upon heating **57** at 140 °C for 60 h in a sealed tube, cyclization occurred to afford 4-propyl-1,2,3,4,5,6-hexahydro-1,5-methano-4,1-benzaphosphocine 1-oxide (**55**) (R = *n*-Pr). The cyclization also proceeded with methylamine but failed with ammonia or 2-phenethylamine. $^1H$ NMR, infrared and mass spectral data supported all of the structures.

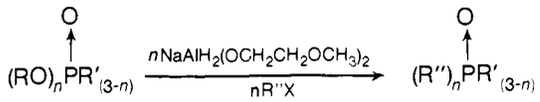
Deoxygenation of the methylamine analog **55** (X = O, R = Me) with trichlorosilane gave the corresponding phosphine (89%) which was easily converted to the sulfide by $S_8$.[64] Although this sulfide was apparently devoid of any analgesic activity in mice, as were the other benzomorphan analogs, a related, open system **58** showed weakened activity.



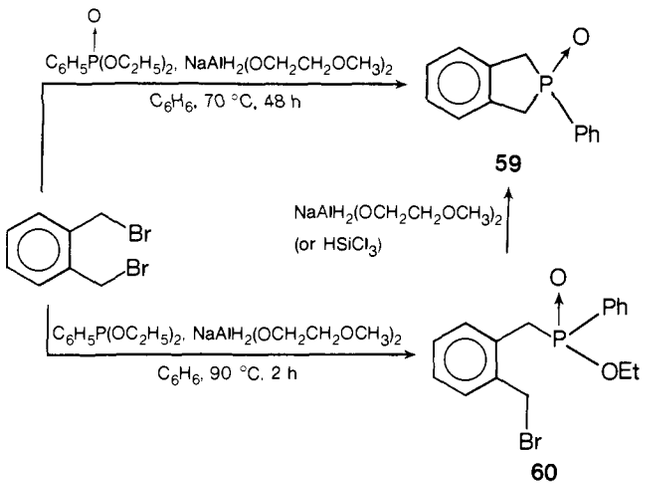
58

## C. Cycloalkylations

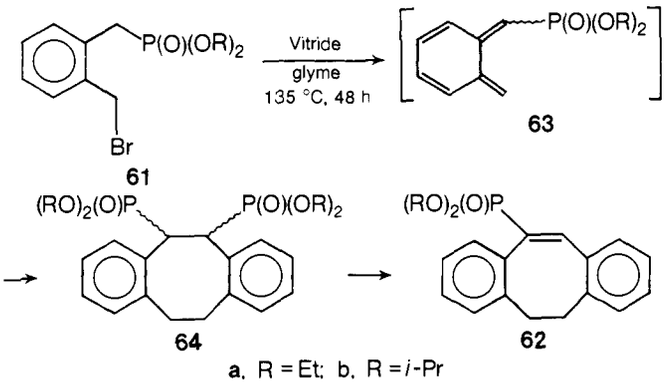
Cycloalkylations of either phosphorus anions with alkyl halides or carbanions with phosphorus halides have been utilized recently for the synthesis of a few novel polycyclic, C–P heterocycles. A general method for forming carbon–phosphorus bonds was discovered by Wetzel and Kenyon[353] in the reaction of a phosphorus ester (phosphate, phosphonate, or phosphinate) with an alkyl or aryl halide in the presence of sodium bis(2-methoxyethoxy)aluminum hydride (commercially available as Vitride). The reaction indicated was believed to proceed via the alkylation



of a phosphorus anion. The reagent was successfully utilized by Chan and co-workers for the synthesis of isophosphindolines[53-55] and macrocyclic bis(phosphine oxides).[56] For instance, *o*-xylyl dibromide reacted with diethyl phenylphosphonate in the presence of Vitride to afford, in a single step, 2-phenylisophosphindoline 2-oxide (**59**) as white crystals (mp 89–91 °C) in



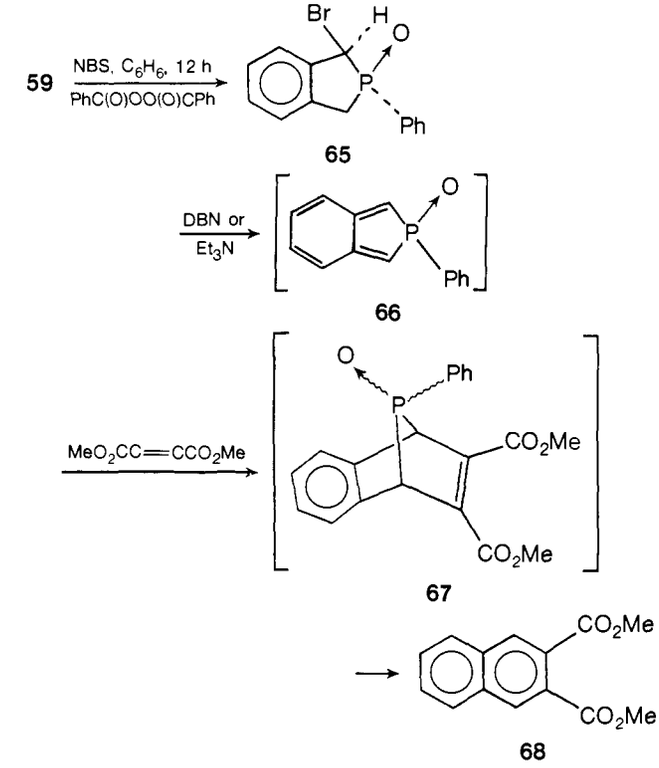
moderate yield.[54] On the other hand, diethyl phenylphosphonite condensed with *o*-xylyl dibromide at controlled temperature to furnish the crystalline ethyl (2′-bromomethylbenzyl)phenylphosphinate (**60**), which underwent further cyclization with either Vitride reagent or with a limited amount of trichlorosilane to oxide **59**. Surprisingly, this type of internal cyclization to give an isophosphindoline system failed with the dialkyl phosphonates **61a** and **61b** in presence of Vitride reagent when diglyme was used as the solvent at an elevated temperature (135 °C).[55] The major products isolated in these cases were **62a** and **62b**, confirmed by spectral data (IR, $^1$H NMR, MS). A mechanism was invoked involving the dimerization of an unstable *o*-xylyl intermediate **63**, formed from **61** by proton abstraction via the hydride reagent to furnish **64** followed by $\beta$-elimination of a phosphoryl group. The intermediacy of **63** was supported by the isolation and characterization of **64** when the reaction was conducted under milder conditions (125 °C for 30 h). Attempts, however, to trap the suggested diene intermediate **63** with a variety of dienophiles (dimethyl maleate, dimethyl acetylenedicarboxylate, or anthracene) failed.[55] Although the potentialities of the Vitride reagent are yet to be fully uncovered, the examples discussed imply that it may have limited utility at least with substrates in



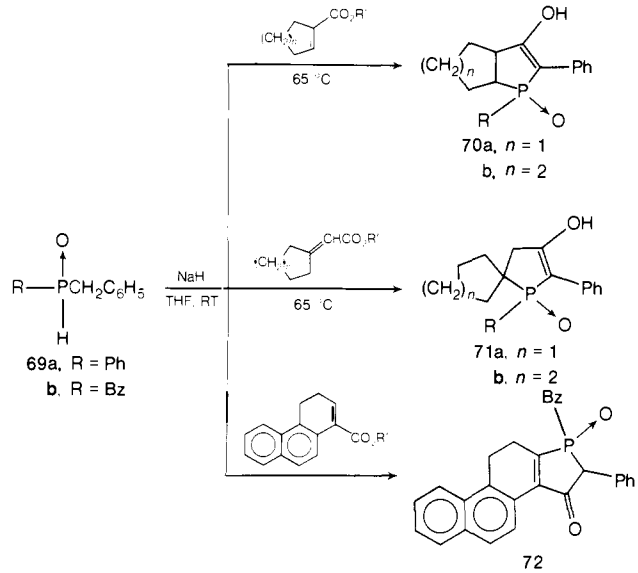
a, R = Et; b, R = *i*-Pr

which proton abstraction is a competing reaction with hydride substitution at phosphorus.

An elegant attempt was also made to convert oxide **59** to an isophosphindole system.[53] Radical-catalyzed bromination of oxide **59** with NBS in benzene (12 h) gave the monobrominated product **65** (50%), which was subsequently dehydrobrominated with either DBN or triethylamine in boiling benzene. Oxide **66** formed but rapidly dimerized since only a dimeric product, mp 216–220 °C, could be isolated (65%). However, formation of the oxide **66** was strongly implied from a study of the dehydrobromination of **65** in the presence of a powerful dienophile (dimethyl acetylenedicarboxylate) and could have led to unstable **67**[53] which decomposed to 2,3-naphthalenedicarboxylate **68**.

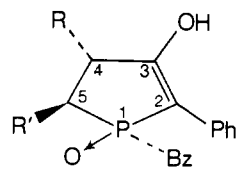


Very recently, certain phosphorus anions, prepared via treatment of secondary phosphine oxides containing at least one benzyl group with sodium hydride in THF at room temperature, were added to $\alpha,\beta$-unsaturated esters which underwent cyclization in situ to afford unusual polycyclic, C–P heterocycles in good yields (38–72%).[35,279] A notable feature of this technique was the synthesis from **69** of simple cyclic, bicyclic, and spiro systems (**70** and **71**) which contained the phospholan-3-one moiety. The 17-phosphasteroid **72** was also prepared from this general procedure (20%). Infrared spectra of **70a**, **71a**, and **71b**, both in the solid state and in solution (methanol and pyridine),




exhibited bands at 2700–2330 (broad, OH) and 1610 $cm^{-1}$ (strong, C=C), indicative of a highly enolized compound. Exceptions were **70b** and **72** which existed mainly in the keto form (1725 $cm^{-1}$, strong, C=O). The orientation of the P=O group in these systems and the stereochemistry of the ring junction in **70** and **72**, however, were not delineated.[35]

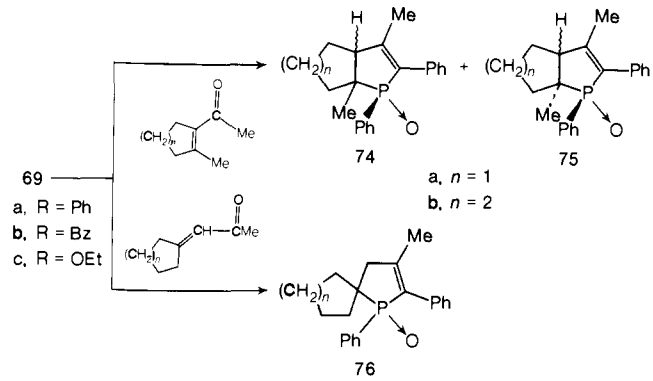
Other work[279] indicated that the yields of the phospholan-3-one 1-oxides could be increased when 2 equiv of sodium hydride in THF was employed. By this modification, it was possible to prepare a number of substituted phospholan-3-one 1-oxides **73** in good yields (49–89%). Examination of molecular models



**73**a, R = H; R′ = H
b, R = Me; R′ = H
c, R = H; R′ = Me
**d**, R = Me; R′ = Me
**e**, R = H; R′ = Ph
f, R = R′ = $(CH_2)_3$
**g**, R = H; R′ = Ph

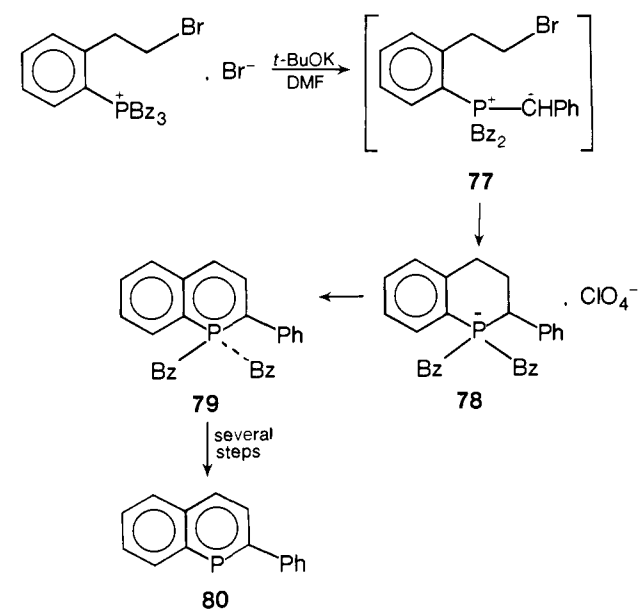
and an extensive analysis of the $^1H$ NMR spectra of **73** strongly suggested a cis arrangement for P=O and R′ (at C-5) and a trans arrangement for R′ and R (at C-5 vs. C-4). This also implied a high degree of stereospecificity in the intramolecular cyclization step. Confirmation was gained by the x-ray analysis of the simple monocyclic system **73d**, mp 181–183 °C, prepared under identical conditions.[279] The x-ray data also revealed that the enol form was present in the solid state, supporting spectral data. It was noted that **73d** had two signals in $^{31}P$ NMR at +70.4 and +57.7 ppm, due to the enol and keto forms, respectively.

Several substituted 2-phospholene 1-oxides **74** and **75** have also been prepared employing secondary benzylphosphine oxides with $\alpha,\beta$-unsaturated ketones utilizing similar reaction conditions.[36] The yields varied considerably among the compounds obtained (25–67%) with a maximum for the spiro system **76b**. Spectral data (IR, $^1H$ NMR, $^{31}P$ NMR) were included for the structures. An important observation made in the $^1H$ NMR spectrum of the stereoisomers **74** and **75** was the shielding effect of the phenyl on a vicinal substituent located on the same side of the ring. For example, the methyl group at C-5 in the cis isomer **74a** appeared at $\delta$ 0.9 and in the trans isomer **75a** at $\delta$

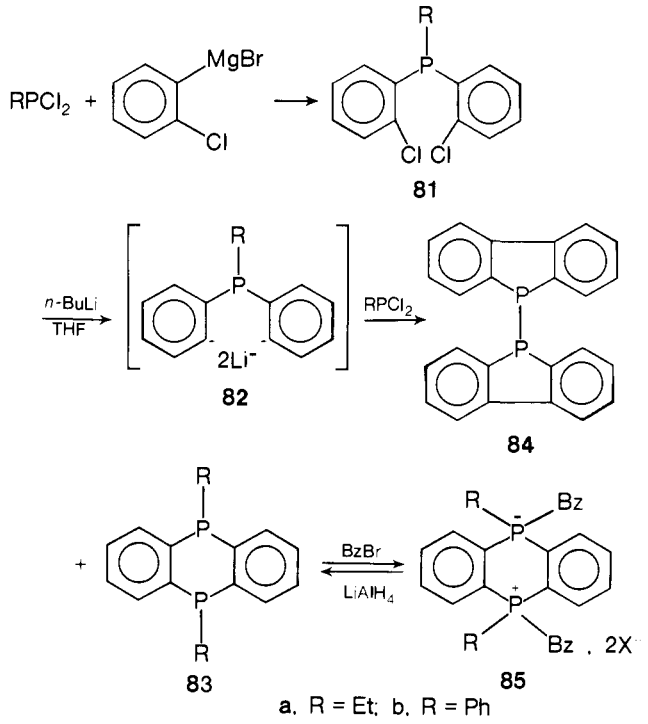



1.49. Similarly, the C-5 methyl group in the cis isomer **74b** was shielded ($\delta$ 0.9) compared to the counterpart in the trans isomer **75b** which was deshielded ($\delta$ 1.35). The $^{31}P$ signals in the cis isomers **74a** and **74b** occurred at −66.4 and −62.0 ppm, respectively. In contrast, the trans isomers **75a** and **75b** had signals at −64.0 and −59.0 ppm, respectively. There are virtually no $^{31}P$ NMR chemical shift data recorded on geometric isomers with which these values could be compared.[105] Differences in the $^{31}P$ chemical shift noted with geometric isomers of different ring size may aid isomer identification.

An intramolecular C-alkylation of an intermediate alkylidenephosphorane **77** was utilized to prepare a salt of 1,1-dibenzyltetrahydro-2-phenyl-1-phosphonianaphthalene (**78**) [isolated as the perchlorate salt (80%)], mp 160–161 °C.[238] This phosphonium salt **78** was a necessary precursor in the eventual synthesis of 1,1-dibenzyl-2-phenyl-1-phosphanaphthalene (**79**) (mp 123 °C and $M^+$ at *m/e* 404, rel int 65%)[238] and also the heretofore unreported 2-phenyl-1-phosphanaphthalene ($^{31}P$ NMR −197 ppm) (**80**).[239] A novel migration of one benzyl group from P to C-4 occurred upon heating **79** at 230–250 °C to give 1,4-dibenzyl-2-phenyl-1,4-dihydro-1-phosphanaphthalene (mp 126–128 °C).[238]

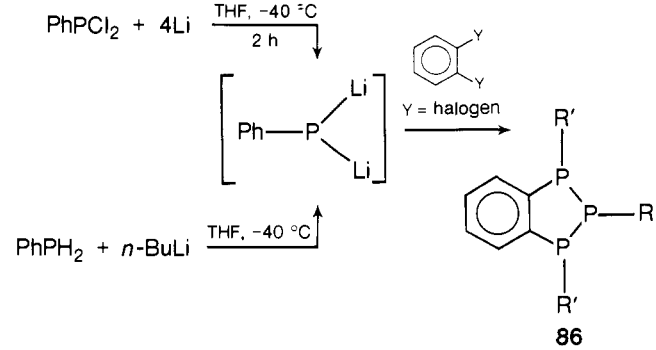



Even with the rapid developments in the last two decades in multiple anion chemistry, the utilization of these multiple anions in the synthesis of polycyclic C–P heterocycles has not kept pace. Only few reports have appeared in the recent literature. Early pioneering work in this area was recorded by Davies and Mann[79] who developed a convenient two-step procedure for the phosphanthrene system. The method consisted of treatment of *o*-chlorophenylmagnesium bromide with ethylphosphonous dichloride to give di(*o*-chlorophenyl)ethylphosphine (**81**a) and



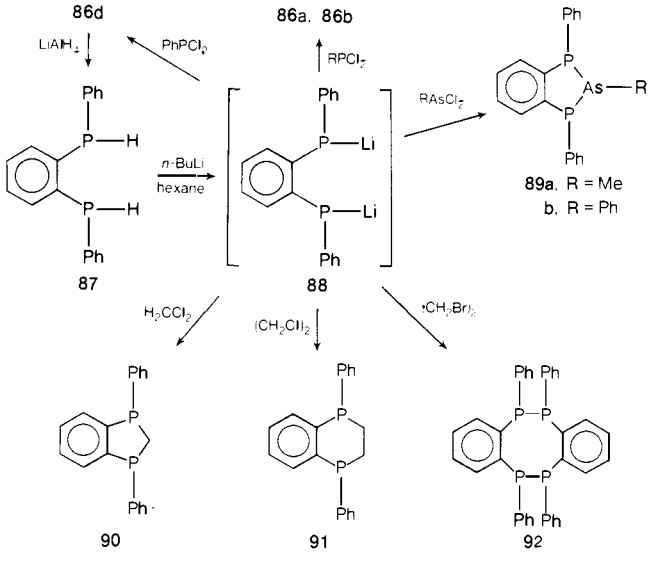

a, R = Et; b, R = Ph

subsequent reaction of **81a**, via the dilithio derivative **82a**, with ethylphosphonous dichloride to afford the phosphanthrene **83a**. With a view to obtain the desired material free of the by-product 9,9′-bi(9-phosphafluorenyl) (**84**), the crude reaction product was directly quaternized with benzyl bromide to give the bisquaternary salt **85a**. Subsequent reduction of this salt with lithium aluminum hydride furnished diethyldiphosphanthrene (**83a**), isolated in two isomeric forms, mp 52–53 and 96–97 °C. Two diiodides, mp 326 and 320–321 °C, were prepared as well as two dioxides, mp 235 and 257 °C, the latter via basic hydrolysis of the isomeric diiodides. In contrast, the diphenyldiphosphanthrene **83b**, prepared by a similar procedure, occurred in a single form only. These results were interpreted in terms of a "butterfly conformation" folded about the axis of the two phosphorus atoms. Most aspects of the stereochemistry of these systems have already been treated.[112,227] Later, a more rapid method for the preparation of diphenyldiphosphanthrene (**83b**) was devised[230] which involved the interaction of phenyldilithiophosphine (prepared from lithium and diphenylphosphonous dichloride or *n*-butyllithium and phenylphosphine in THF) with *o*-dihalobenzenes at low temperature. The diphosphanthrene **83b** (isolated as the dibenzyl salt **85b**) was, however, obtained in a much lower yield compared to the earlier method, but the reaction afforded additionally the novel 1,2,3-triphenyl-1,2,3-triphosphaindane (**86d**), mp 184–186 °C, as the principal product. The yields of



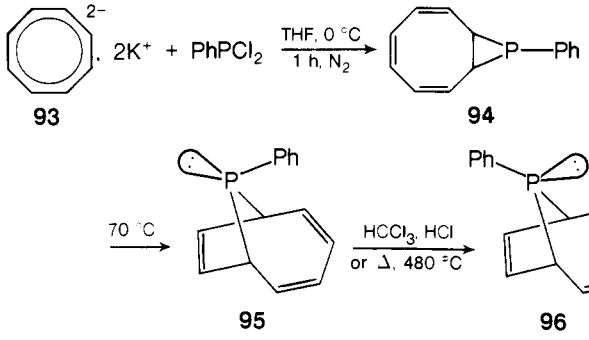

a, R = Me; R′ = Ph
b, R = Et; R′ = Ph
c, R = R′ = Et
d, R = R′ = Ph

diphosphanthrene and phosphaindane formed were particularly dependent upon the reaction conditions. Also, the reaction was discovered to be more general for the preparation of P-substituted phosphaindanes rather than diphosphanthrene systems. A mechanism involving the interaction of a benzyne intermediate with polyphosphine units $(RP)_n$ was suggested to account for the formation of both the products. A large body of chemical and spectral data established the structure of phosphaindane **86d**. An x-ray crystallographic analysis of this compound was also carried out which revealed the fused bicyclic system as planar with the 1- and 3-phenyl groups cis to each other and trans to the 2-phenyl group.[78] A P–C bond length average of 1.825 Å was found. An important reaction of phosphaindane **86d** was the facile reduction by lithium aluminum hydride to afford *o*-phenylenebis(phenylphosphine) (**87**) in high yield (86–95%).[228] This bisphosphine formed the key starting material for the synthesis of a number of benzo-fused, C–P heterocycles with two or more phosphorus atoms in the ring. For example, the dilithio derivative **88** reacted with alkylphosphonous dichlorides to give phosphaindanes **86a** and **86b** and with methyl- and phenylarsonous dichlorides to furnish phosphaarsoles **89a** and **89b**, respectively.




Additionally, the dilithiodiphosphine **88** reacted with dichloromethane to afford **90** as a mixture of stereoisomers and with 1,2-dichloroethane to furnish the 1,4-benzodiphosphorin **91**. However, reaction with 1,2-dibromoethane provided not the expected 1,4-benzodiphosphorin but the novel tetraphosphocin **92**, albeit in a very low yield (0.3%). Transformation of these products to quaternary salts and sulfides, as well as extensive $^{31}P$ NMR and mass spectral analyses of the derivatives, established the structure of these polyphosphines.[228] An x-ray analysis of the crystalline 1,4-benzodiphosphorin **91** showed the heterocyclic ring in a half-chair form with the two phenyl groups cis to one another with respect to the plane of the benzo ring.[300]

A unique process was discovered by Katz and co-workers[202] for the synthesis of novel bridged C–P heterocycles. The reaction involved treatment of potassium cyclooctatetraenide (**93**) with dichlorophenylphosphine at low temperature to afford the bicyclic phosphine **94**. On warming to 70 °C (or more slowly at room temperature), the phosphine rearranged providing the bicyclic phosphine **95** (45.9%) as a crystalline solid, mp 85.5–86.5 °C. Interestingly, phosphine **95** was found to undergo epimerization to **96** either on heating in acidified chloroform solution or on pyrolysis at 480 °C in the gas phase. Detailed $^1H$ NMR spectral analyses of these unusual bicyclic phosphines and transformations to P-oxides, quaternary salts, and palladium chloride complexes rigorously supported parent structures. Novel phosphine **94** exhibited the phorphorus signal at a very

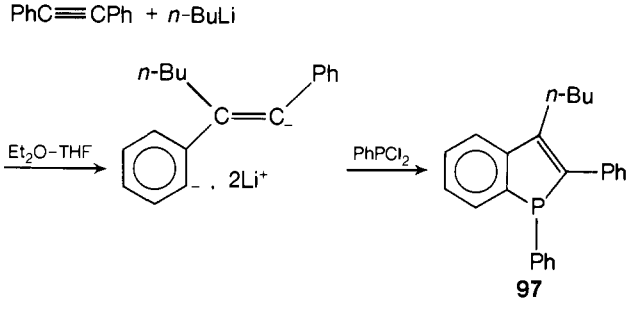



93 94 95 96

high field (+181 ppm) in its $^{31}P$ NMR spectrum (rel to 85% $H_3PO_4$).

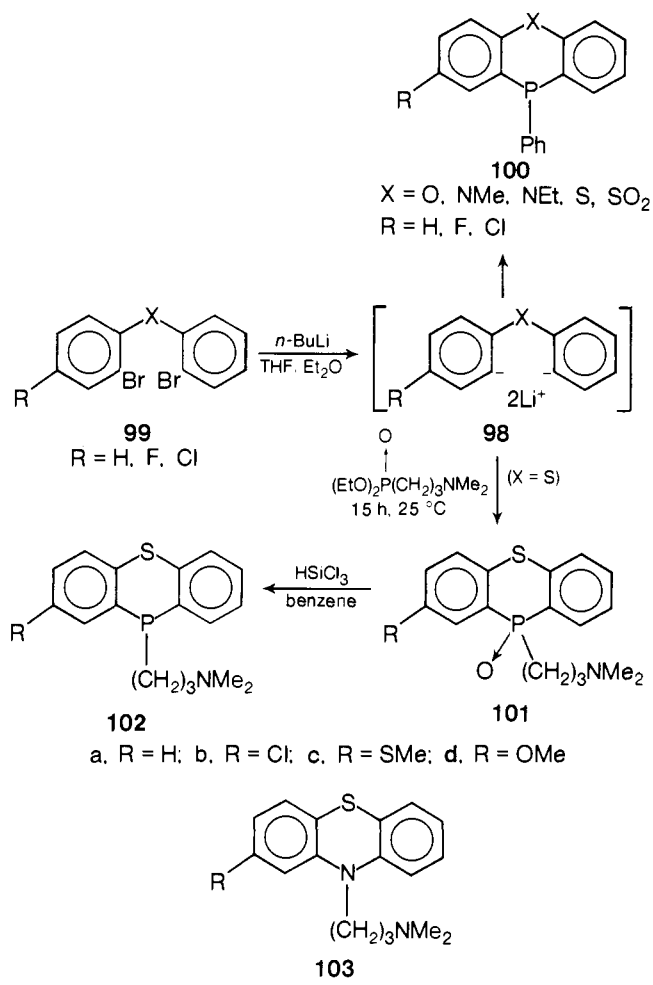
In contrast, the bridged phosphines **95** and **96** exhibited $^{31}P$ signals at +79 and +14 ppm, respectively (rel to 85% $H_3PO_4$). Thus a vast difference in the $^{31}P$ chemical shifts for an epimeric pair of phosphines, not encountered hitherto in phosphorus chemistry, was indicated to be the result of phosphorus 3d orbital overlap with the $\pi$-molecular orbitals of the carbon skeleton.[202] Such a large $\Delta\nu_{^{31}P}$ value must be viewed with caution for diagnosis of epimeric phosphines, even bicyclic, unsaturated systems, since few analogous cases are known.

Reaction of a dilithio intermediate, formed from diphenylacetylene with *n*-butyllithium in 1:1 diethyl ether:THF (or better in hexane:tetramethylenediamine), with phenylphosphonous dichloride afforded 3-*n*-butyl-1,2-diphenylphosphindole (**97**), as colorless plates, mp 90–91.2 °C, in moderate yield (40–45%).[97,291] Oxidation with peroxide gave the corresponding phosphine oxide (90%).[291]




97

In the last decade, a very large number of tricyclic systems with an additional heteroatom in the ring have been prepared by the multiple anion generation procedure. Although, by our definition in the Introduction, these compounds did not fit the C–P heterocyclic class to be discussed, the family has been included because of close structure relationships to carbon analogs and for the sake of completeness. For example, the dilithio derivative **98** of diphenyl ether,[125] *N*-alkyldiphenylamine,[329] diphenyl sulfide, and diphenyl sulfone[38,358] (prepared via treatment of the corresponding dibromide **99** with *n*-butyllithium) reacted readily with phenylphosphonous dichloride to afford the respective phosphines **100** (R = H) in a single step in moderate yields. A few derivatives of **100** having meta substituents (R = F, Cl) have also been recorded.[38,125,358] Phosphine **100** (X = $NMe_2$, $NEt_2$; R = H) has been claimed to possess antioxidant and antiwear properties in high-temperature lubricants while certain other members of **100** (X = S, $SO_2$; R = H) were useful as fungicides.[38] The dilithio derivative **98** was also condensed with diethyl (3-dimethylaminopropyl)phosphonate to obtain a series of dimethylaminopropylphosphine oxide derivatives **101** and were evaluated for antidepressant activity.[358] Oxides **101** exhibited tranquilizer properties in mice in the 30–50 mg/kg dosage range. In one instance, phosphine **102** was obtained by the reduction of the phosphine oxide **101a** with trichlorosilane. Phosphine **102** (R = H) showed ultraviolet maximum at 263 nm ($\epsilon$ 4,750) and closely resembled its nitrogen analog **103** [254 nm ($\epsilon$ 30,000)], possibly suggestive of delocalization of the 3p electrons of phosphorus into the ring system.[358]




99 R = H, F, Cl

98

100

101

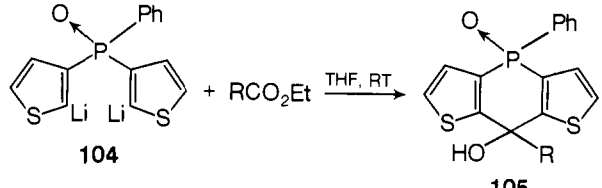
102

a, R = H; b, R = Cl; c, R = SMe; d, R = OMe



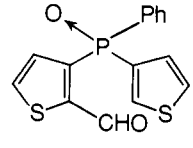

103

The dianion employed may also contain the phosphorus moiety and involve only a condensation at carbon to prepare new polycyclic derivatives. For instance, dianion **104**, formed from



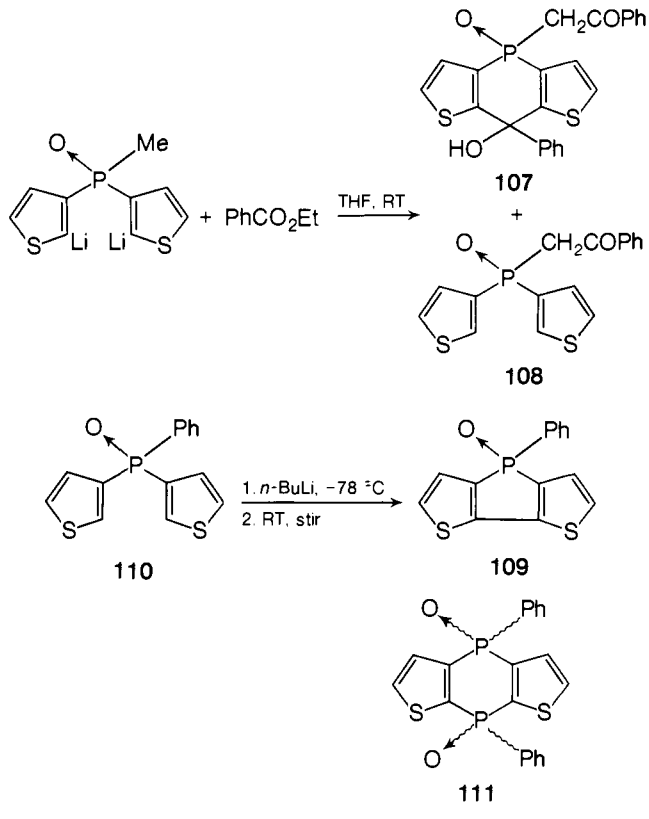

104 105

R = Ph, Me, 3-pyridyl



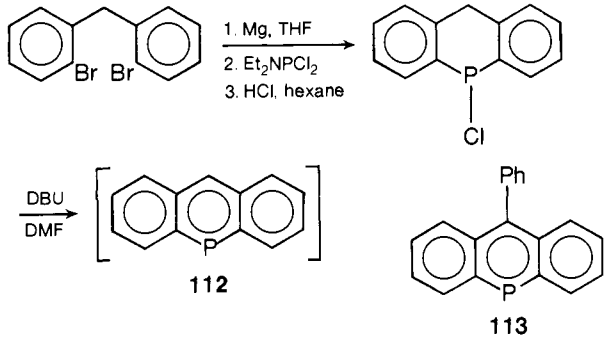

106

phenyldi(3-thienyl)phosphine oxide, upon treatment with *n*-butyllithium, condensed with a variety of esters to afford novel cyclic oxides **105**.[218] However, condensation of this dianion **104** with ethyl formate did not yield a cyclic carbinol, but rather the acyclic aldehyde **106**, the formation of which was attributed to the difference in reactivity of ethyl formate compared to the other esters.[218] With the multiple anions available from reaction of methyldi(3-thienyl)phosphine oxide and *n*-butyllithium, the condensation with ethyl benzoate afforded both the cyclic oxide **107** as well as the acyclic product **108**.[218] Without any added esters, the phenyldi(3-thienyl)phosphine oxide (**110**), upon treatment with *n*-butyllithium and warming to room temperature, underwent an intramolecular ring closure to novel **109**.[218] Condensation of related dianion **104** with phenylphosphonous



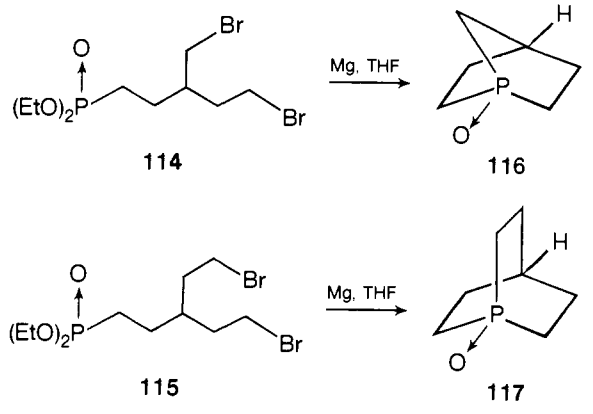

dichloride gave a separable mixture of the cis and trans isomers **111**.

An initial reaction in one of the synthetic sequences for the preparation of the still rather elusive dibenzo[*b*,*e*]phosphorin (**112**) [or 9-phosphaanthracene] involved the condensation of the di-Grignard reagent from bis(*o*-bromophenyl)methane with diethylaminophosphorodichlorodite.[211] The intermediate



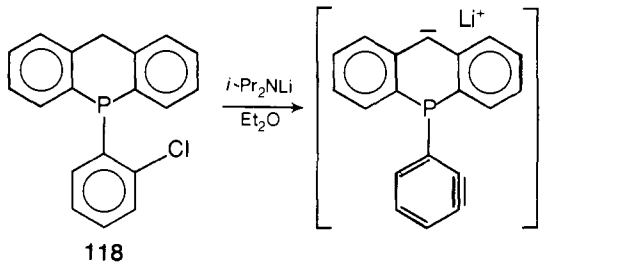

phosphinous chloride was dehydrohalogenated with DBU in DMF. Since **112** could not be isolated, characterization was achieved on solutions thereof.[211] Surprisingly, analysis of the UV spectrum of **112** (in toluene) revealed a similar pattern to that of anthracene rather than of acridine. Atmospheric oxygen or the addition of sodium hydroxide or anhydrous HCl to the toluene solution of **112** destroyed the UV spectrum immediately. A Friedel–Crafts-type phosphorylation has yielded the related 10-phenyldibenzo[*b*,*e*]phosphorin [or 10-phenyl-9-phosphaanthracene] (**113**) and will be discussed under section II.F.

Recent advances in the synthesis of heterocyclic bridge compounds with a P atom at the bridgehead position have confirmed earlier predictions that chemical reactivities and spectral properties were dependent on molecular geometry at phosphorus.[140] Unfortunately, most of these compounds contained either two phosphorus atoms or a phosphorus atom and a different heteroatom (usually a nitrogen atom) at the bridgehead positions.[140] Simple phosphabicyclo systems with only a phosphorus atom at the bridgehead position defied many attempts for synthesis despite several elegant approaches.[354] For the first time, Wetzel and Kenyon[354,355] utilized an internal Grignard cyclization of **114** and **115** employing high-dilution




techniques for the syntheses of 1-phosphabicyclo[2.2.1]heptane 1-oxide (**116**) and its higher homolog 1-phosphabicyclo[2.2.2]-octane 1-oxide (**117**). Both oxides **116** and **117** were obtained as crystalline solids, mp 207–210 and 291–293 °C, in very modest yields (11 and 6%).[354,355] Exhaustive spectral analysis ($^{13}C$ NMR, IR, MS, $^{1}H$ NMR) coupled with elemental analysis and molecular weight determinations by the osmometric method rigorously supported the structures of the oxides. Oxides **116** and **117** showed P=O stretch at 1235 and 1169 $cm^{-1}$, respectively, in the infrared spectrum ($CCl_4$), and an examination of the P=O stretching frequencies in a few other strained phosphine oxides permitted a correlation to be made between ring strain and P=O bond energy.[355] In addition, oxide **116** exhibited multiple bands in the P=O region and a detailed examination of an isoelectronic series of acyclic and monocyclic phosphine oxides with various percentages of $^{18}O$ enrichment suggested that the origin of these bands was presumably via Fermi resonance. $^{1}H$ NMR spectra ($DCCl_3$) of oxides **116** and **117** at 60 MHz showed a complex pattern in the methylene region which was separated to a certain degree through the use of Eu(dpm)$_3$.[354,355] However, a 220-MHz $^{1}H$ NMR spectrum of the oxide **116** exhibited three sets of distinct peaks at $\delta$ 1.74–1.87 (6 H, complex multiplet), 1.96 (4 H, symmetric multiplet), and 2.23 (1 H, doublet of multiplets, $J_{^{31}PCCH}$ = 28 Hz).[355] The unusually large $J_{^{31}PCCH}$ of 28 Hz between phosphorus and the proton on the bridgehead carbon (C-4) was accounted for by the P–C–C–H dihedral angle of approximately 180°. A similar trend was noted in the proton-decoupled $^{13}C$ NMR spectra of the oxides **116** and **117**. A large value of 35 and 47 Hz for the coupling constant between the phosphorus and the bridgehead carbon was observed in the oxides **116** and **117**, respectively. In a number of organophosphorus compounds, an angular dependence of the coupling constant $J_{^{31}PC-^{13}C}$ similar to the Karplus relationship for $J_{HCCH}$, has been suggested as valid.[6,129] A similar relationship has now been suggested to be equally valid for $J_{^{31}P-^{13}C}$.[40,41,206,226,352,355] Mass spectral fragmentations also supported the structures of **116** and **117**. Unfortunately the $^{31}P$ NMR signals for the oxides were not reported.[355]

Recently the synthesis of another bicyclic strained system was recorded with phosphorus at the bridgehead position.[190] Cyclization of 9-(*o*-chlorophenyl)-9,10-dihydrophosphaanthracene (**118**) with an excess of lithium diisopropylamide in ether afforded crystalline **119**, mp 242–243 °C, in fair yield (35%). The reaction occurred via anion attack on a presumed benzyne precursor. Earlier, Hellwinkel and Schenk[154] reported the preparation of azaphosphatriptycene **120**, mp 255–255.5 °C, by treatment of tris(*o*-lithiophenyl)amine (from the corresponding bromo derivative **121**a and *n*-butyllithium in ether), with triphenyl phosphite. The infrared spectrum of phosphatriptycene (**119**) closely resembled that of triptycene itself. Such a similarity with

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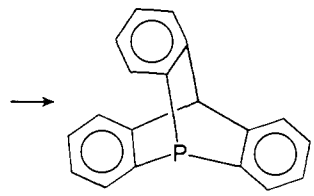

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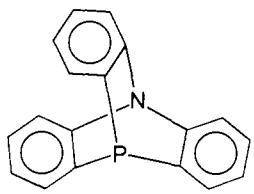

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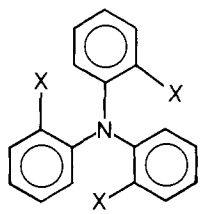
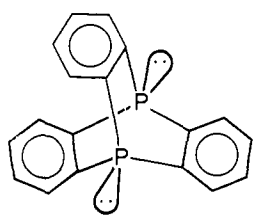


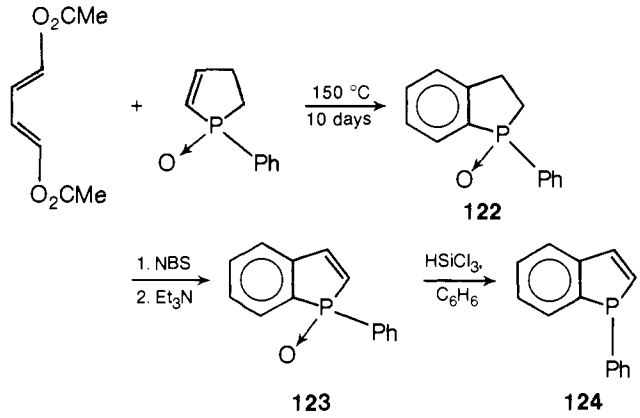
121a, X = Br
b, X = Li

triptycene and arsatriptycene was also evident in the UV spectrum of phosphatriptycene **119.** This appeared to rule out appreciable electronic interaction between the heteroatom and the aromatic rings. In contrast, azaphosphatriptycene had little resemblance to that of azatriptycene in the UV spectrum. Both the phosphorus analogs of triptycene formed quaternary salts and P-oxides. Curiously, the mass spectra of **119** and **120,** similar to triptycene itself, were abundant with doubly and triply charged ions.[154,190] The $^{31}P$ signals for phosphines **119** and **120** occurred at +64.8 and +80 ppm, respectively, (rel to 85% $H_3PO_4$) which may be due to high s character in the free electron pair on phosphorus.[154,190] A value of +43.0 ppm was found for diphosphatriptycene (see section II.G).[347]

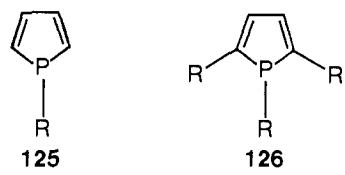


## D. Cycloadditions

The cycloaddition reaction involving a phosphorus atom as part of a dienophile or diene has received considerable attention in the last decade as a useful synthetic pathway for previously unknown C–P heterocycles (ref 18, 82, 140, 216, 236, 259, 283, 286). The following sequence involved the initial cycloaddition of *trans-trans*-1,4-diacetoxybutadiene with 1-phenyl-2-phospholene 1-oxide[57] and gave key intermediates 1-phenyl-2,3-dihydrobenzo[*b*]phosphole 1-oxide (**122**) and 1-phenylbenzo[*b*]phosphole 1-oxide (**123**) which were characterized. Oxide **123** was hygroscopic (mp 84–88 °C) and showed protons for ArH and =CH in the $^1H$ NMR spectrum. 1-Phenylbenzo[*b*]phosphole (**124**) (mp 66–68 °C) had a UV spectrum consisting of $\lambda_{max}$ (log $\epsilon$) at 233 (4.39), 260 (4.05), 306 (3.56), and 316 nm (3.56) and resembled that of 1-phenylindole. $^1H$ NMR analysis of **124** showed an AMX pattern for the vinyl protons ($J_{AM}$ = 7.2 Hz, $J_{AX}$ = 16 Hz, $J_{MX}$ = 38 Hz; $\delta_M$ 6.80 and $\delta_A$ 7.49).

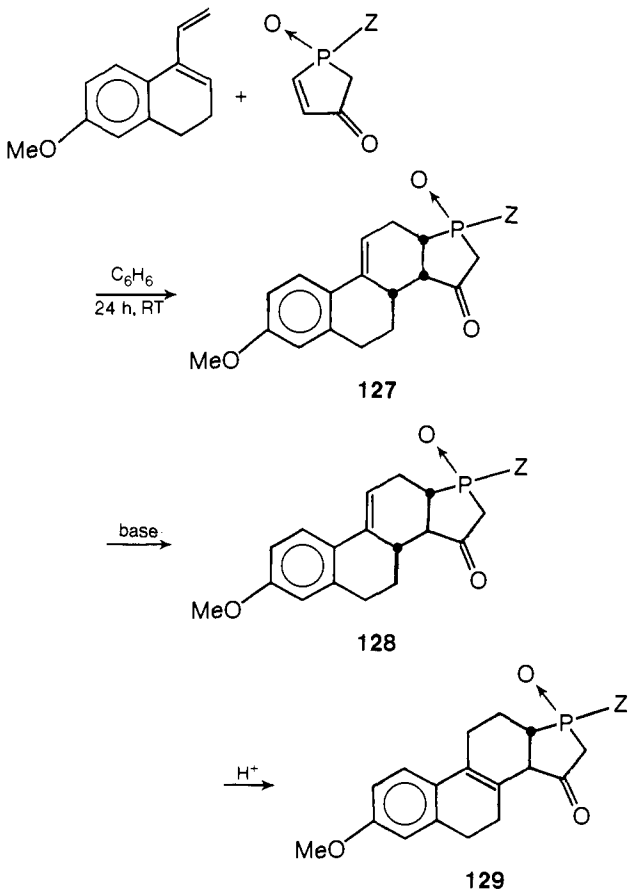



Phosphine **124** oxidized in air without subsequent dimerization. Such behavior differed from certain oxides of phospholes **125** (R = Me, Ph). The latter dimerized, a process which will be discussed later in this chapter.[261,262] Indeed **124** behaved more like 2,5-substituted phospholes **126.**[182,383,384]



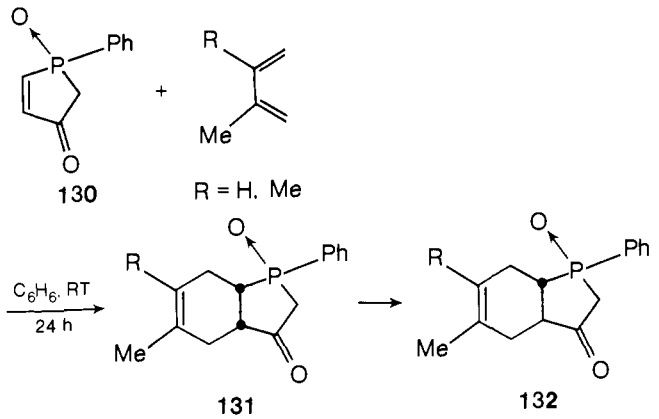
125 126

A similar approach was used by Kashman[198] in the preparation of derivatives of a 15-keto-17-phosphaestrone **127.** The C/D cis product **127** could be epimerized easily with a trace of base to the more stable C/D trans isomer **128.** Compound **128** was further characterized by acid isomerization of the double bond




Z = Ph, Me, OMe

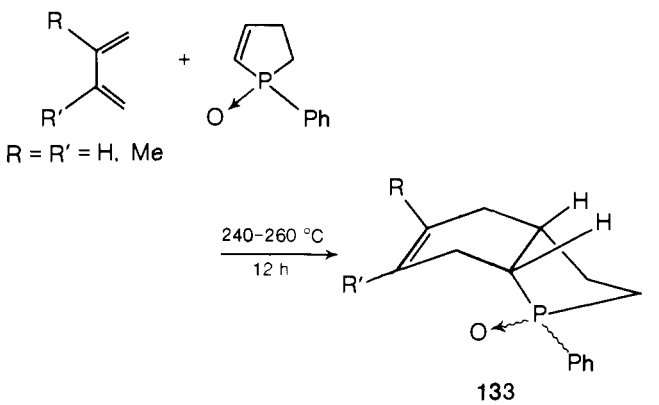
from the 9(11) to 8(9) position to form **129** as well as by IR, MS, and NMR analysis. This propensity for cis–trans isomerization at the bridge was attributed to the presence of the keto function. In order to test this hypothesis, the reactions of 1-phenyl-1-oxo-2-phospholen-4-one (**130**) with 2,3-dimethyl-1,3-butadiene




**130** **131** **132**

and isoprene were examined.[198] The initial adducts **131** in both cases were observed to isomerize rapidly to the more stable trans ring-fused products **132.** In the discussion of the previous phosphasteroid preparations, the inertness of several unspecified 2- and 3-phospholenes with respect to cycloaddition with 2,3-dimethyl-1,3-butadiene and 1-vinyl-6-methoxy-3,4-dihydronaphthalene was cited as the reason for the need to add a keto group to increase reactivity as was found in **130.**[198]

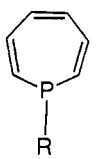
This second functionality, perhaps, may not be necessary since 1-phenyl-2-phospholene 1-oxide has been shown to condense with 2,3-dimethyl-1,3-butadiene to yield 2,3,3a,4,7,7a-hexahydro-5,6-dimethyl-1-phenylphosphindoline 1-oxide (**133**). The reaction, however, required more drastic




**133**

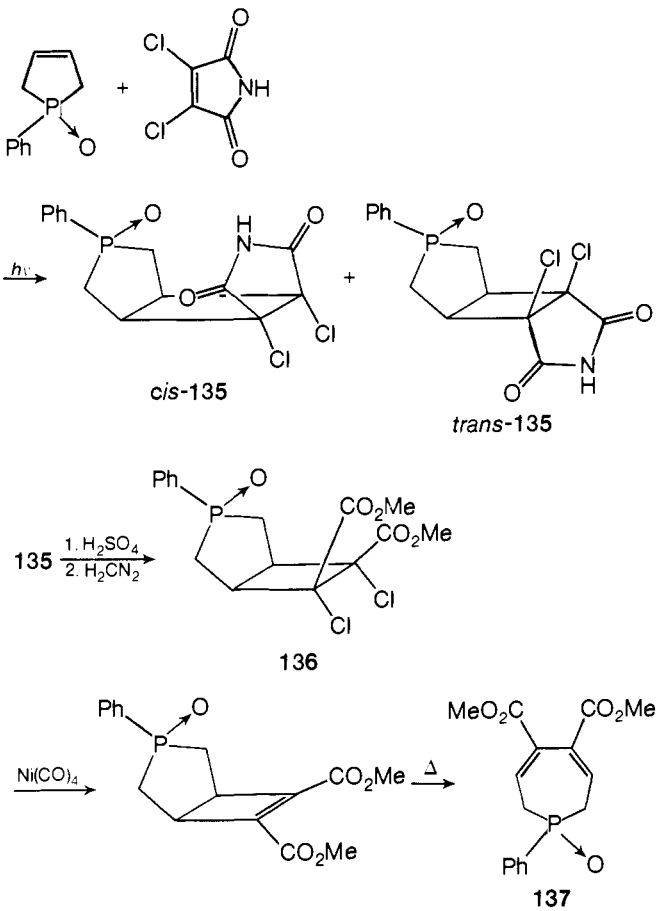
conditions (240–260 °C, 12 h) than those cited above.[271] Butadiene and isoprene were reported to react in a similar fashion as 2,3-dimethyl-1,3-butadiene.[271]

The initial step in one of the early preparative schemes to obtain the phosphepin ring system **134** involved the photo-



**134**

chemical cycloaddition of 1-phenyl-3-phospholene 1-oxide with dichloromaleimide to yield both *cis*-**135** and *trans*-**135** adducts.[247] However, no isomer distribution was mentioned and the cis isomer was utilized in subsequent reactions. Treatment of *cis*-**135** with sulfuric acid followed by diazomethane led to the methyl ester **136.**[247] The ester was dechlorinated to the al-

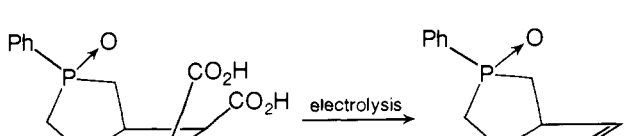



*cis*-**135** *trans*-**135** **136**



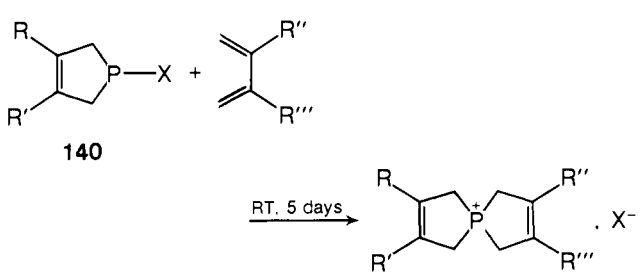

**137**

kene which underwent thermal-catalyzed valence isomerization to the seven-membered ring **137.** Related acid **138** was decarboxylated in pyridine/$H_2O$ at 100 V (0.2 A) at a platinum electrode to the bicyclic, C–P heterocycle **139.**




**138** **139**

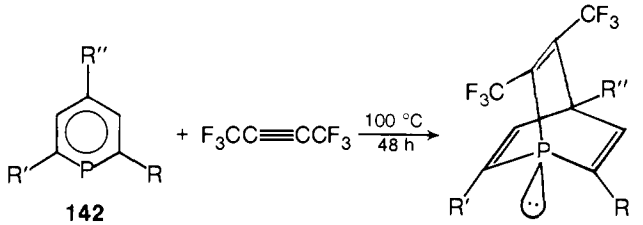
The choice of phosphorus-containing alkenes for cycloaddition reactions appear to depend somewhat on the reactivity of the substituents bonded to phosphorus. In the previous examples, phospholene oxides were used and afforded the expected Diels–Alder adducts. In contrast, when 1-halophospholenes were treated with conjugated dienes, spirophosphonium salts containing two phospholene rings were produced rather than the bicyclic, C–P heterocycles. For example, condensation of 1-halo-3-phospholenes **140** with either isoprene or 2,3-dimethyl-1,3-butadiene afforded the phosphaspiranes **141.**[344] The exact position of the double bonds in **141** is unproven.




**140** **141**

R = Me; R′ = H, Me; R″ = Me; R‴ = H, Me
X = Br or Cl

Cycloaddition reactions have also been observed with phosphorus as a part of a diene. For example, 2,4,6-trisubstituted phosphorins **142** have served as starting materials for the syn-

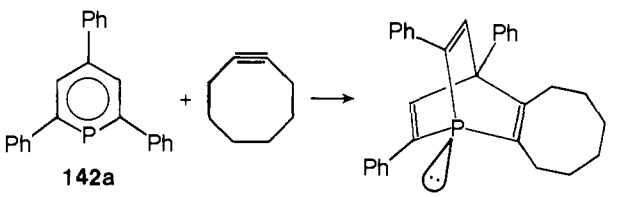


**142** **143**

| R = R′ | R″ |
|---|---|
| a, Ph | Ph |
| b, *t*-Bu | Me |
| c, Me | Ph |

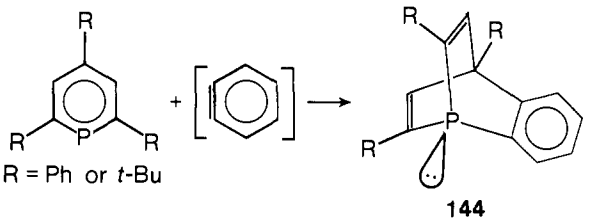
thesis of substituted phosphabarrelenes (1-phospha[2.2.2]-octa-2,5,5-trienes) (**143**).[242] Cycloaddition of the highly reactive dienophile hexafluorobutyne even under mild conditions gave phosphabarrelenes **143**.[242] It is of note that the $^{31}P$ signal (benzene) of **143**a occurred at +65 ppm (rel to 85% $H_3PO_4$) and supported the identity of the tertiary phosphine.

A similar result was observed with cyclooctyne and 2,4,6-triphenylphosphorin.[234] Interestingly, the $J_{PCCH}$ coupling in **143a**



**142a**

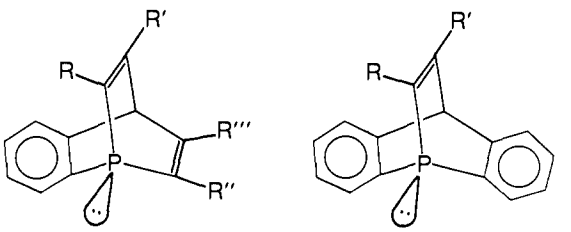
was 7 Hz and was 6 Hz in the product of the reaction of **142**a with cyclooctyne.[234] Benzyne has also been treated with 2,4,6-trisubstituted phosphorins to afford the corresponding benzophosphabarrelenes **144**.[243] Couplings for $J_{PCCH}$ in **144** were 6



R = Ph or *t*-Bu

**144**

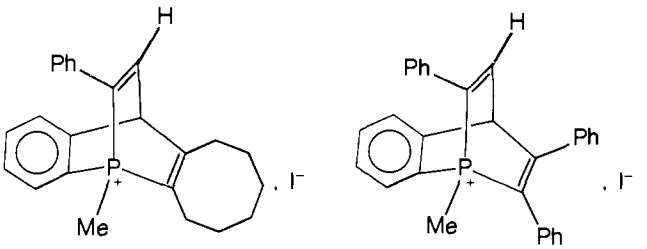
Hz (R = Ph) and 7 Hz (R = *t*-Bu) in $DCCl_3$. Thus the nature of R may not be especially critical in influencing P–H magnetic coupling. This work has been extended to a few benzo- (**145a**) and dibenzophosphabarrelenes (**145b**) starting from 2-phenyl-



**145a** **145b**

R = R′ = $CF_3$; R″ = Ph; R‴ = H

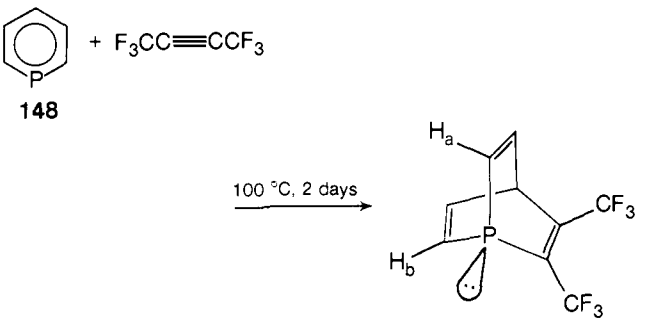
1-phosphanaphthalene.[240] Ir, MS, $^1H$ NMR and UV spectral data appeared to support these novel structures. The $^{31}P$ NMR of **145a** had a signal at +68 ppm (rel to 85% $H_3PO_4$) suggesting high s character in the lone pair of electrons on phosphorus. However, this compound was reportedly not alkylated with methyl iodide nor was it oxidized.[240] In contrast, both derivatives **146** and **147** formed easily in boiling benzene from the appropriate phosphines. The inertness of the bis(trifluoromethyl)-substituted derivative toward quaternization with methyl iodide



**146** **147**

is reminiscent of that property of hexakis(trifluoromethyl)diphosphabarrelene.[217]

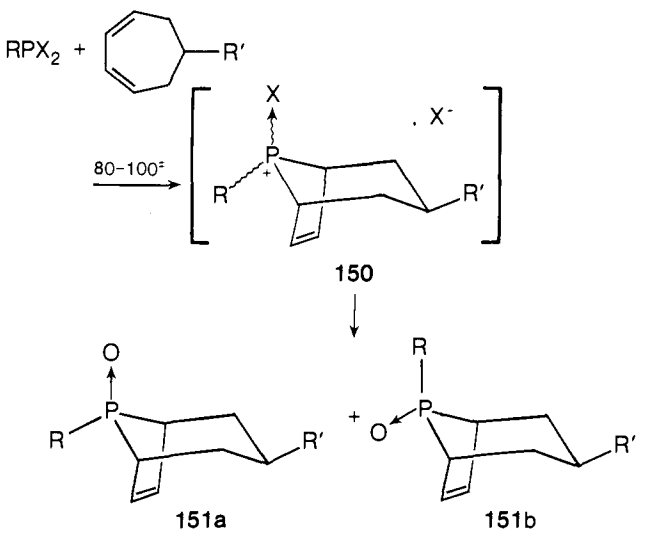
Phosphabenzene[21] (**148**) and hexafluorobutyne were reported to give a phosphabarrelene **149**.[23] The bridgehead proton in the



**148** **149**

$^1H$ NMR spectrum ($CCl_4$) appeared as a triplet at $\delta$ 5.43 ($J$ = 7 Hz). Protons $H_a$ and $H_b$ appeared as doublet of doublets centered at $\delta$ 6.95 ($J_{P-H}$ = 5 Hz and $J_{H-H}$ = 7 Hz).

With respect to the recent interest in the tropanic systems from both a conformational as well as configurational standpoint,[110] the synthesis and stereochemical investigations of the heretofore unknown 8-phosphabicyclo[3.2.1]octane system have been reported by three different cycloaddition-type reactions.[25,193,196] Cycloaddition of a series of dihalophosphines with



**150**



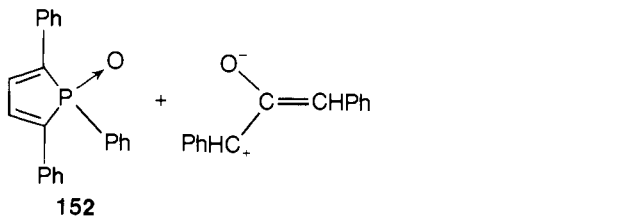
**151a** **151b**

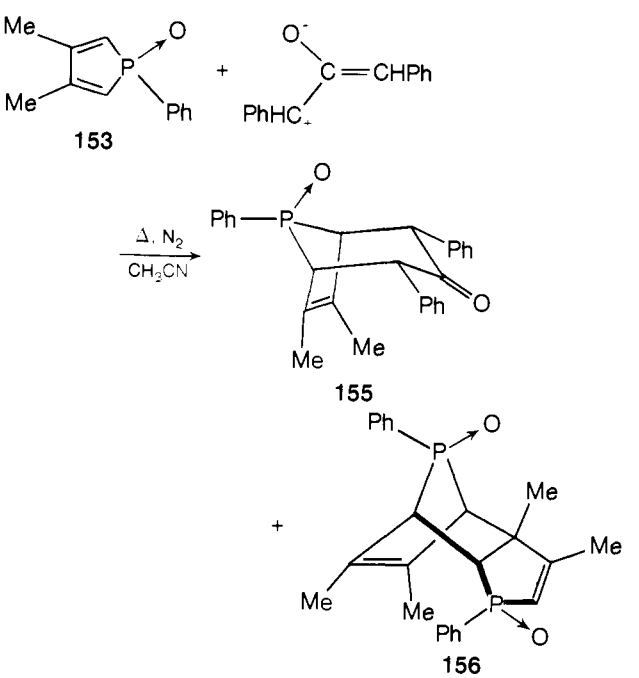
R = Ph; X = Cl or Br; R′ = H
R = Et; X = Cl; R′ = H
R = Me; X = Cl or Br; R′ = H
R = Me; X = Cl; R′ = $O_2CMe$
R = Ph; X = Cl; R′ = $O_2CMe$

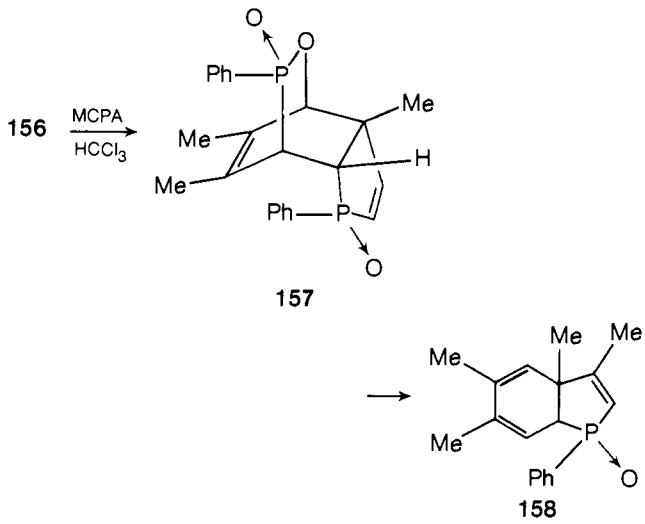
either cyclohepta-1,3-diene or 1-acetoxycyclohepta-3,5-diene afforded the 8-alkyl- or 8-aryl-8-phosphabicyclo[3.2.1]oct-6-enes **150** and -6-en-3-yl acetates. Considerable difference in reactivity of the phosphorus halide was noted to be dependent upon the presence of an alkyl or aryl substituent.[25] It was observed that with $MePX_2$ both of the P epimers **151a** and **151b**

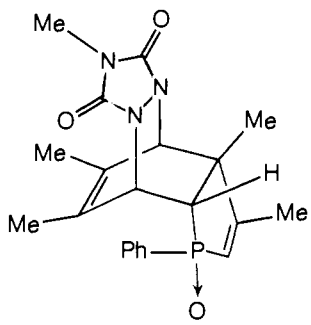
could be isolated, but with $EtPX_2$ or $PhPX_2$ only a single stereoisomer was obtained.[25] $^1H$ NMR analysis of the crude initial adduct **150** in the $MePX_2$ case indicated only one isomer. Consequently, it was tentatively concluded that the formation of the two P epimers in the $MePX_2$ case occurred during the hydrolysis. No reason was given for the failure of this process in the cases with the ethyl and phenyl derivatives. Apparently, the preferred P epimer had the alkyl or aryl P substituent in an equatorial position on the phosphorinane ring of **151a**.[25,193] Complexation studies with $Eu(dpm)_3$ were also used to elucidate the stereochemistry of these bicyclic systems along with an x-ray analysis of the reduced isomers of **151a** (R = Ph, R′ = H).[25]

Another approach to the 8-phosphabicyclo[3.2.1]octane adducts involved the cycloaddition of selected oxyallylic cations to phosphole sulfides or oxides.[196] Reaction of 1,2,5-triphenylphosphole 1-oxide (**152**) and 1-phenyl-3,4-dimethylphosphole 1-oxide (**153**) with the dibenzyloxyallyl cation (generated from di(α-bromobenzyl) ketone with NaI in boiling acetonitrile) afforded the desired 1,2,4,5,8-pentaphenyl-8-oxo-8-phosphabicyclo-[3.2.1]oct-6-en-3-one (**154**) and 2,4,8-triphenyl-6,7-dimethyl-8-oxo-8-phosphabicyclo[3.2.1]oct-6-en-3-one (**155**), respectively.[196] In the latter case, the major product was the phosphole dimer **156**.[196] An unusual oxygen insertion into the C–P bond of **156** was observed when the latter and *m*-chloroperbenzoic acid were allowed to react in $HCCl_3$ at room temperature.[196] The phosphinate **157** rearranged upon standing to the bicyclic phospholene 1-oxide **158** which could be trapped with 4-methyl-1,2,4-triazoline-3,5-dione to give a new adduct **159** (mp 252–253 °C). Spectral data appeared to confirm the structure.

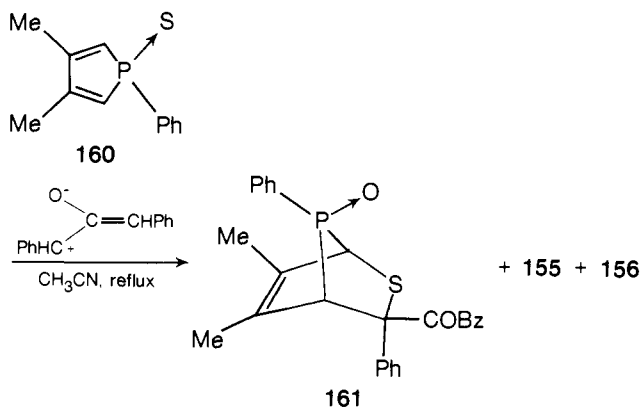


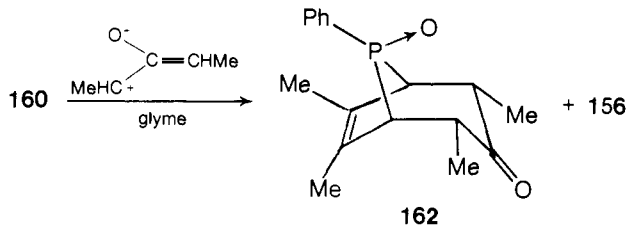



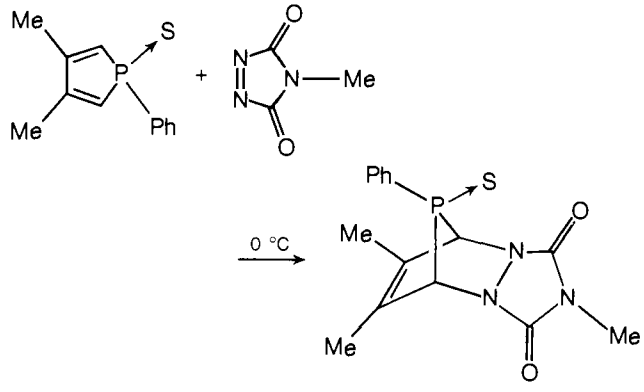




With 1-phenyl-1-thio-3,4-dimethylphosphole (**160**) a somewhat surprising result was noted. Treatment of **160** with the dibenzyloxyallyl ion gave the oxy derivatives **155** and **156** plus a new bicyclic system **161** [mp 202–204 °C, $\nu^{KBr}$ 1715 (C═O), 1195 (P═O) $cm^{-1}$].[196] No thio analogs of **155** or **156** were isolated. The reaction of this phosphole sulfide with the oxyallyl cation (generated from 2,4-dibromo-3-pentanone with a Zn/Cu couple) also afforded the oxides **156** and **162** but none of the new sulfur-containing heterocycle **161**.[196] A plausible rationale for these observations was accommodated by invoking participation



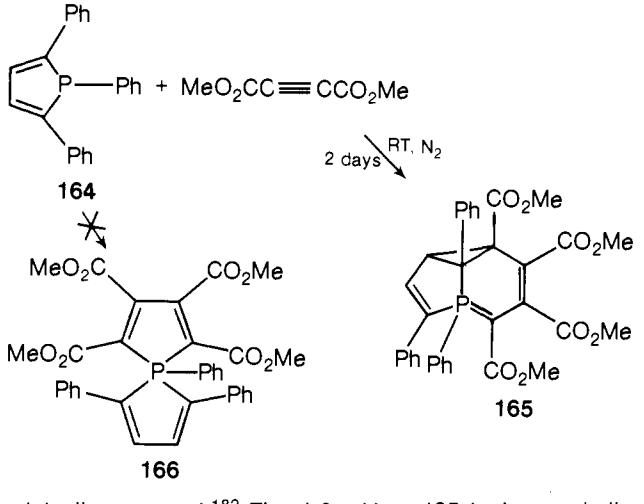



of the halide ion ($I^-$ from NaI) in the transformation of P=S to P=O. The mechanism must be considered tentative since free halogen is not an expected reactant in the medium.[196] It was also observed that the phosphole sulfide reacted in a [2 + 4] cycloaddition with the dienophile 4-methyl-1,2,4-triazoline-3,5-dione to give a new polycyclic system **163**.[196]

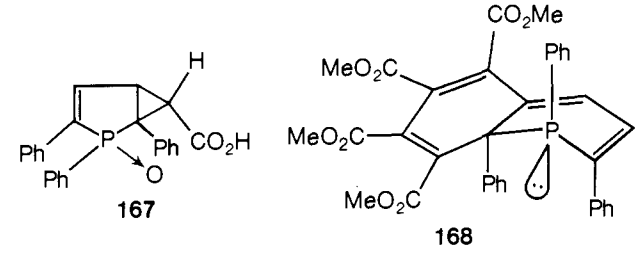


**163**

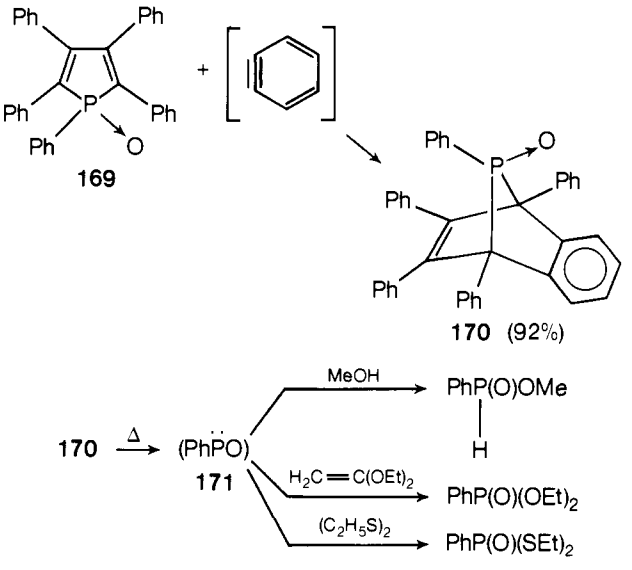
1,2,5-Triphenylphosphole (**164**) has also been observed to react with the powerful dienophile dimethyl acetylenedicarboxylate.[182,346] However, there was some disagreement as to the nature of the 1:2 adduct (phosphole:dienophile). Extensive spectral and chemical analysis has supported the tricyclo allylidenephosphole **165** and not the 1,1′-spirophosphole **166** as



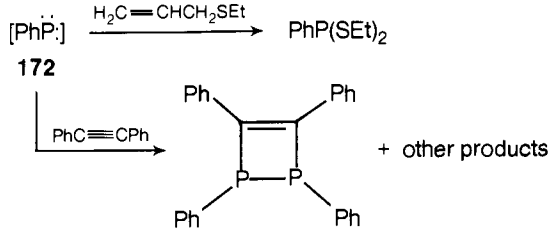
originally proposed.[182] The 1:2 adduct **165** had very similar spectral properties to those of known **167**[48] and also underwent a rearrangement in boiling chloroform to give phosphine **168**.[346] The structure assignment for the latter was based on extensive spectral analysis.



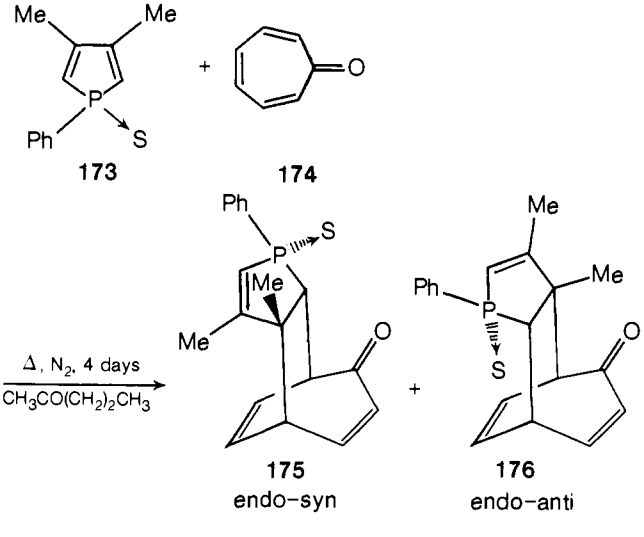
1,2,3,4,5-Pentaphenylphosphole 1-oxide (**169**) condensed with benzyne, generated at 40 °C, to yield 2,3-benzo-1,4,5,6,7-pentaphenyl-7-phosphabicyclo[2.2.1]hept-5-ene 7-oxide (**170**).[327] At 155 °C, **170** decomposed to tetraphenylnaphthalene in near-quantitative yield along with a polymer of $(C_6H_5PO)_n$. A series of thermal decompositions of **170** in the presence of a variety of reactants led the authors to postulate formation of phenylphosphinidene oxide (**171**). Although the



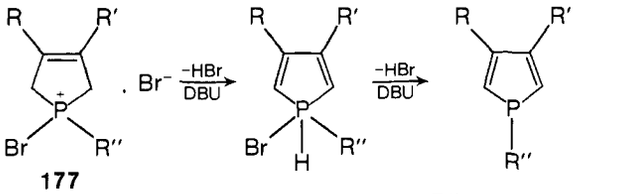
mechanistic rationale was speculative,[327] the data were reminiscent of the postulated intermediacy of phenylphosphinidene (**172**) when pentaphenylcyclopentaphosphine was thermolyzed.[93]



3,4-Dimethyl-1-phenylphosphole 1-sulfide (**173**) reacted with tropone (**174**) at 100 °C to yield the two [4 + 2] adducts **175** and **176**.[197] The endo-exo, syn-anti relationship in **175** and **176** was elucidated by extensive $^1H$ NMR analysis.[197] Sulfide **175** had a $\nu_{C=O}$ at 1650 $cm^{-1}$ while **176** had a band at 1655 $cm^{-1}$.



The formation of crystalline dimers when phospholes were allowed to stand has been known for some time.[140] In this regard, a novel method for the preparation of phospholes involving treatment of aryldihalophosphine cycloadducts **177** with DBU has afforded, in certain cases, the dimeric oxide **178a** or sulfide dimer **178b** during workup of the reaction mixtures containing crude phospholes.[261] Interestingly enough, the sulfide derivatives (R′ = R″ = Me; R = R‴ = H) with a phenyl group attached to phosphorus display two $^{31}P$ NMR signals at −3 and −50 ppm.[261] In this report, it was also noted that the phenylphospholes **179**,



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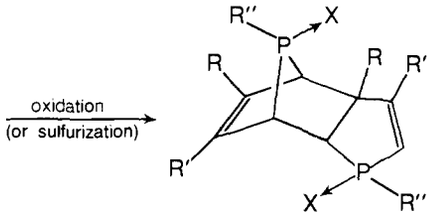
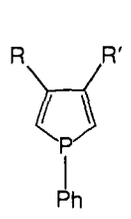


178

R = R′ = H or alkyl  a, X = O
R″ = alkyl or aryl  b, X = S

upon treatment with alkyllithium reagents in the presence of *N,N,N′,N′*-tetramethylethylenediamine, were converted to the corresponding alkylphospholes.[260,261] Subsequent oxidative workup of the cleavage reaction of **179** also yielded dimer **178** in selected examples.[260]



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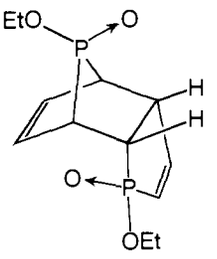

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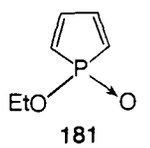
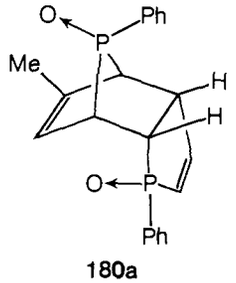
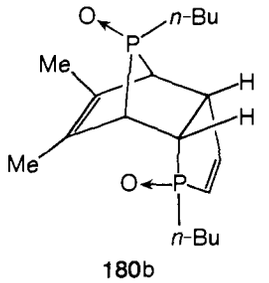


181

Tentative structural configurations of these dimers were based to a large extent on $^{1}H$ NMR and $^{31}P$ NMR studies.[260,262] A problem has existed regarding the orientation of the P=X group with respect to the two other bridging groups. An x-ray analysis of **180** (from **181**) has revealed the endo isomer with the stereochemistry as shown and with a C-P-C angle of a strained 87°.[61,203,210] Two $^{31}P$ NMR signals were observed for **180** at −70 ppm and −83 ppm in $HCCl_3$.[210] The saturated compound gave similar shifts. This arrangement of the P=O group is likely correct for most dimers of phospholes. However, this was not the view expressed in the $^{1}H$ NMR analysis of related phosphole dimers (**180a** and **180b**) of 1-phenyl-3-methylphosphole 1-oxide

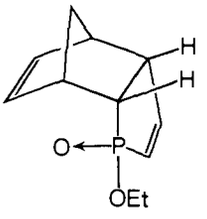


180a



180b

and 1-*butyl*-3,4-*dimethylphosphole* 1-oxide.[262] Thus, precursor of **180,** the phosphinate **181** also behaved like a phosphole with respect to dimerization. Ester **181** condensed with excess cyclopentadiene in ethanol at 25 °C to give the adduct **182** but was inert toward maleic anhydride.[339] Increased C substitution as in **183**[209] and **184**[63] retarded autodimerization, although the former and maleic anhydride yielded **185** (after hydrolysis),[209] while **184** condensed with dimethyl acetylenedicarboxylate to give **186**,[63,327] presumably through a bicyclic C-P heterocyclic intermediate. A similar situation was reported when phosphole **164** and maleic anhydride were heated at 120–130 °C.[48] In a



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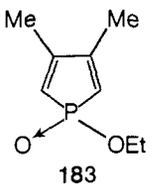

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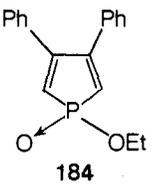

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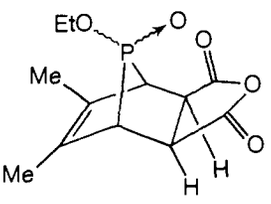

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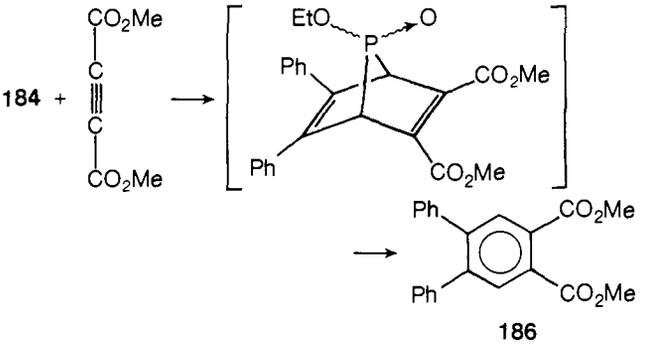
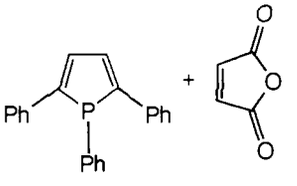
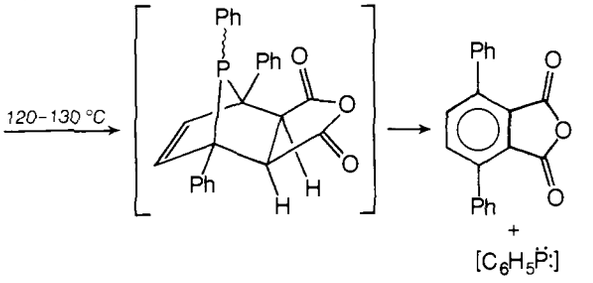


186

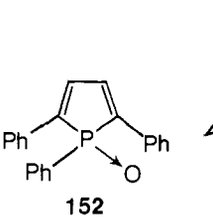
corresponding reaction, phosphole 1-oxide **152** gave a stable



164



adduct **187** (78%) and, with acrylonitrile, gave **188** (40%) of unknown stereochemistry at P. Diels–Alder reaction of 1,2,5-



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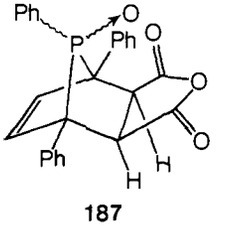

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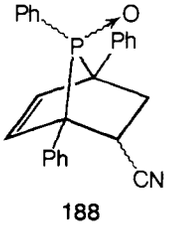
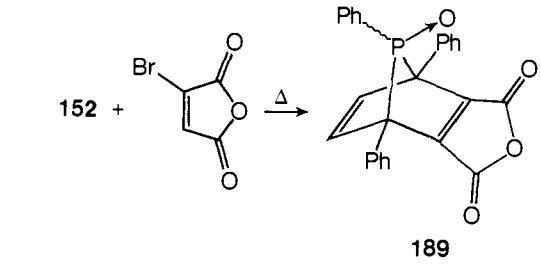


188

triphenylphosphole 1-oxide (**152**) with α-bromomaleic anhydride afforded the novel polycyclic derivative **189.**[309]

In the dehydrobromination of **190** with *t*-BuOK in DMF, 1-phenylphosphole 1-oxide (**191**) probably formed, but only the Diels–Alder adduct **192** was isolated (66%).[246] The corresponding phosphole sulfide behaved similarly.[246]



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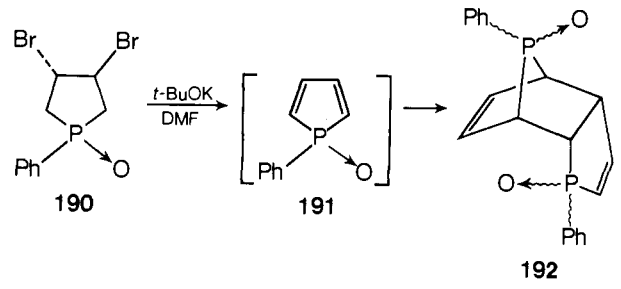
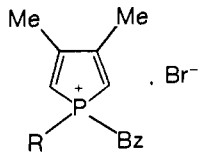


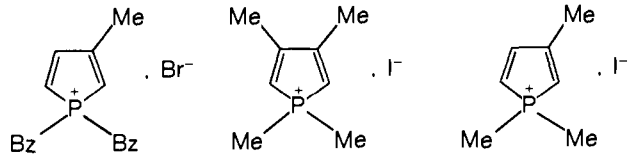
190 191 192

Phospholium salts **193** (R = Bz, Me) did not form dimers.[285]



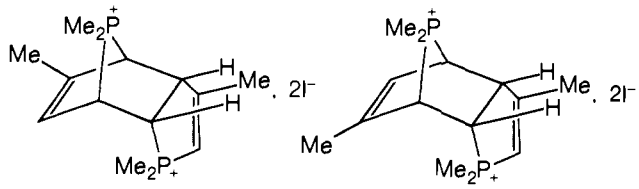
193

However, ease of formation of dimers in this family was attributed, in part, to the number of C substituents on the parent phospholium ring as well as the nature of the P substituents.[285] For example, salts **194** and **195** were stable as monomers while



194 195 196

**196** dimerized and gave two $^{31}P$ NMR signals at −55.3 and −56.4 ppm ($D_2O$) suggesting two possible isomers **197** and **198.**[285] The two signals may be due to different shielding of P

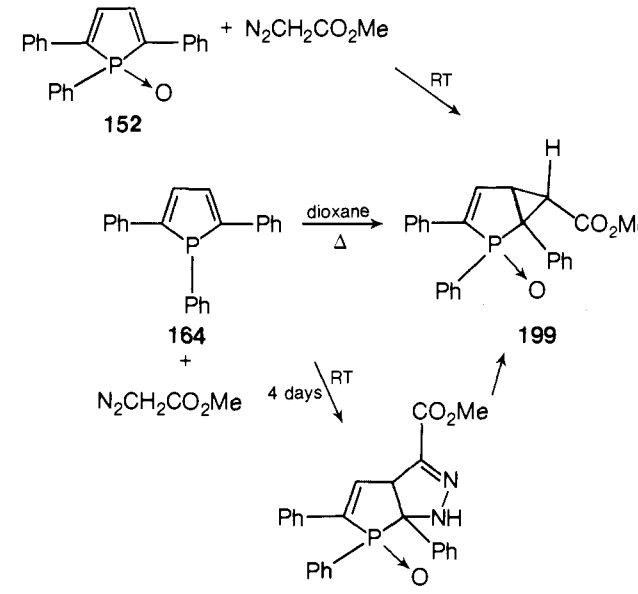


197 198

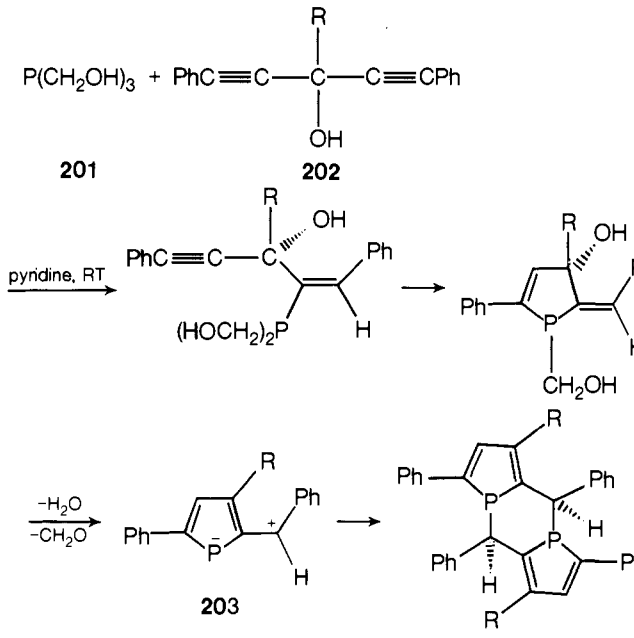
as a result of positional isomerism of the methyl group on $sp^2$ carbon as shown. Several other examples were reported by these workers.[285]

It was recorded that if phosphole **164** had little aromatic character, reaction with methyl diazoacetate should yield a cyclic adduct.[48] The oxidized product **199** (tentatively assigned) was isolated from reaction in dioxane while more mild conditions gave **200.** Treatment of **152** with methyl diazoacetate in dioxane reportedly gave **199** although the structure of the latter was somewhat in doubt. Diazomethane attacked **152** (20 days, −20 °C), but the intermediate lost $N_2$ to give the same product **199.**

A rather unusual dimeric product was reported to result from the cycloaddition of tris(hydroxymethyl)phosphine (THMP, **201**) with 1,5-diaryl-3-alkyl-3*H*-penta-1,4-diyn-3-ols **202.**[237] Self-condensation of the 1,3-dipolar intermediate **203** formed from



152 164 199 200



201 202 203 204

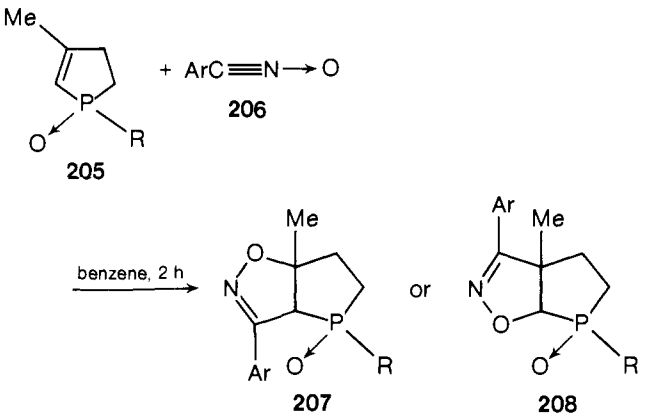
R = H, Me, Et, Ph

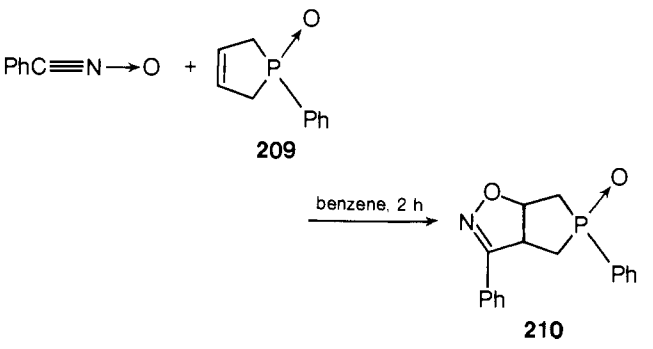
the initial primary adduct shown and subsequent cyclization followed by the loss of water and formaldehyde gave the dimer **204.**[237] The proposed structure of this dimer **204** was based on the extensive spectral data (MS, $^1H$ NMR and UV) along with elemental analysis.[237]

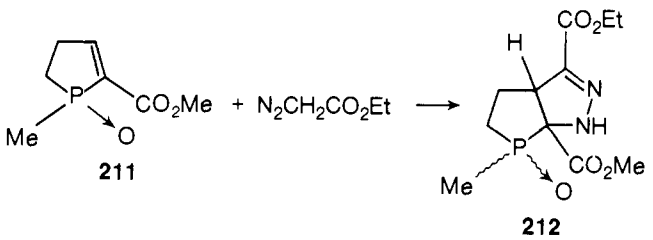
A 1,3-dipolar cycloaddition product has also been uncovered in the reaction of 2-phospholene oxides **205** with aromatic nitrile oxides **206.**[19] However, no evidence was presented in favor of either **207** or **208** for the structure of the 1:1 adduct. It was observed that the reaction of 1-phenoxy-1-oxo-3-phospholene (**209**) with benzonitrile oxide apparently gave the adduct **210** (37%).[19] Several other examples were reported by these workers,[19] but supporting structural data were lacking.

Similarly, phospholene oxide **211** also underwent reactions with 1,3-dipoles such as ethyl diazoacetate to yield the bicyclic system **212** with the rings fused at the 2,3 positions of the phospholane.[284] The high reactivity of **211** was exemplified by its ease of polymerization in benzene solution at room temperature.

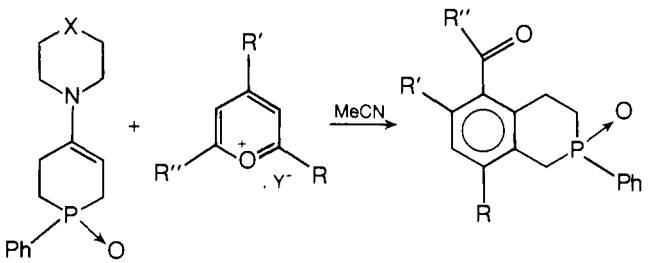
Enamine derivatives of 4-phosphorinanones were observed to undergo cycloaddition reactions. For example, the morpholino



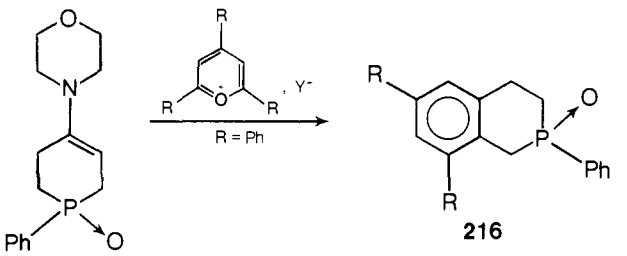

enamine of 1-phenyl-4-phosphorinanone 1-oxide (**213**) reacted in acetonitrile with the pyrylium salts **214** to give the corresponding acyl-substituted isophosphinoline oxides **215.**[235]

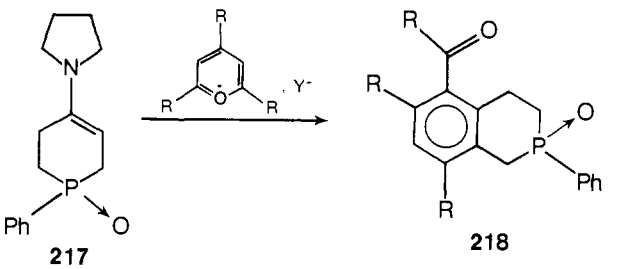


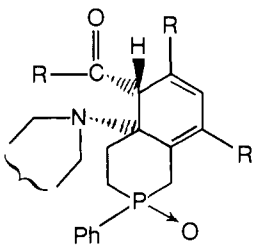

X = − or O
R = R′ = R″ = Ph
R = R″ = *p*-MePh; R′ = Ph

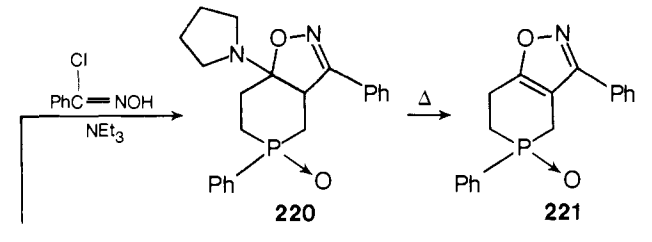
An interesting observation in this report was reaction of the morpholino enamine **213** with the 2,4,6-triphenylpyrylium salt **214** (R = Ph) which afforded only the acyl free derivative **216.**[235] In contrast, the corresponding pyrrolidino enamine **217** gave the acyl product **218.** This anomaly was attributed to the difference in the reactivity of the amine moieties in the elimination step from the dihydro intermediate **219** to give products.[235]

These enamines were also found to condense with 1,3-dipoles, such as benzonitrile *N*-oxide and diphenylnitrile imine (both generated in situ) to give the novel heterocycles **220, 221,** and **222.**[235] Reaction of the pyrrolidine derivative **217** with dimethyl acetylenedicarboxylate afforded the bicyclic **223.**[235]

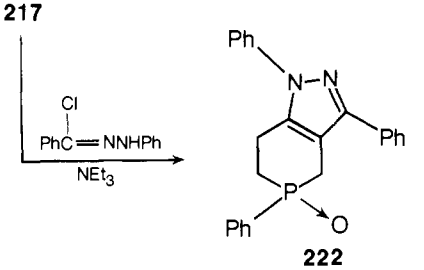


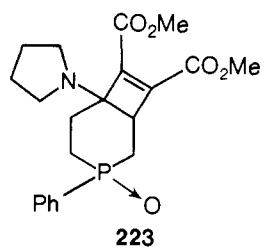



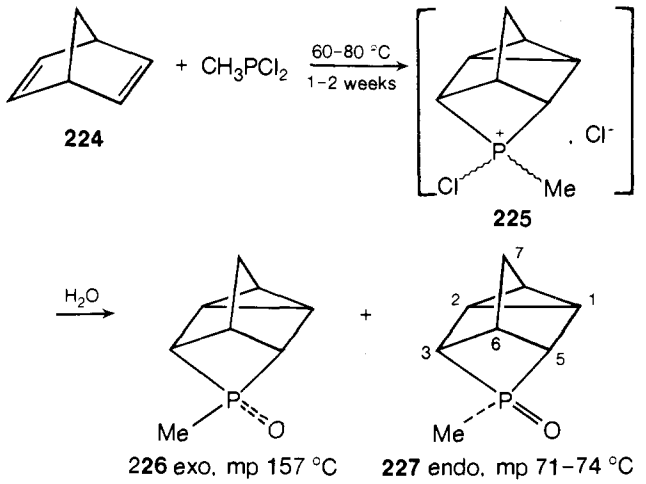




217



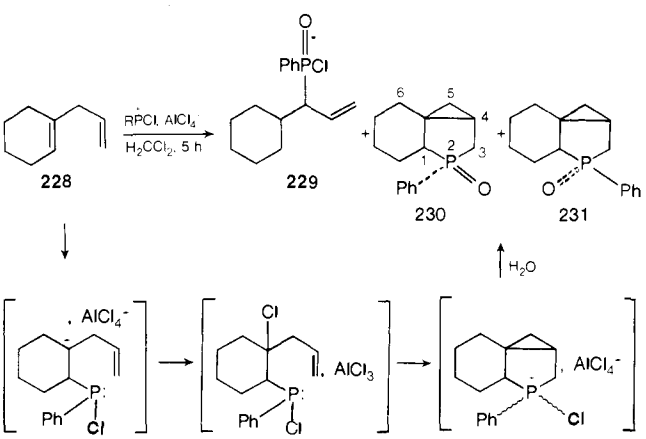




The reaction of methylphosphonous dichloride and bicyclo[2.2.1.]heptadiene (**224**) at room temperature (24 h) was reported by Green[127] to furnish a 1:1 adduct. Hydrolysis of the adduct **225** yielded a crystalline multicyclic phosphine oxide, mp 157 °C. Recently, Cremer and co-workers[73] reinvestigated the above reaction at 60–80 °C (1–2 weeks) and, after careful workup, isolated two phosphine oxides [mp 157 and 71–74 °C] in a ratio of 4:1, respectively. The *exo*-**226** and *endo*-**227** isomers were assigned to the higher and lower melting oxides,



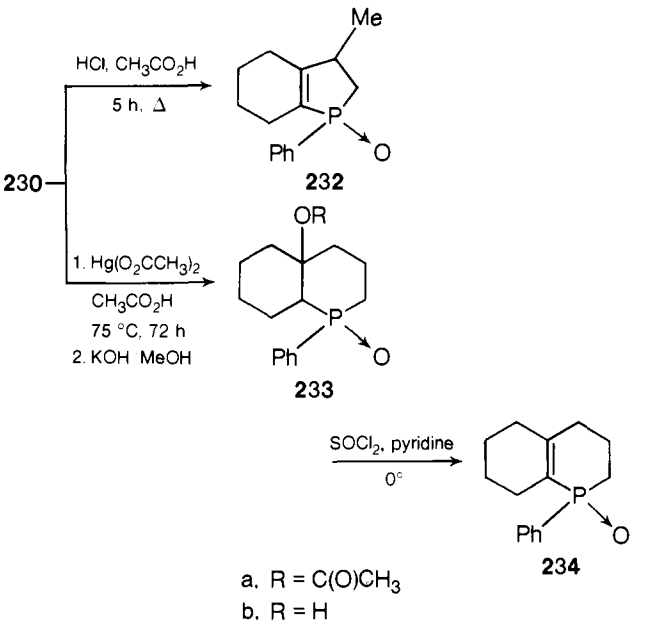

respectively. The proton at C-6 in **227** appeared at $\delta$ 3.3 and was shifted downfield owing to the close proximity of the P=O group in contrast to **226** in which H-6 resonated at $\delta$ 1.90. In the $Eu(dpm)_3$ shifted spectrum, the downfield shift was stated as increased but no position was specified. The $^{13}C$ NMR spectrum ($DCCl_3$) confirmed the exo and endo assignments: C-6 for **226**, $\delta$ 31.03 ($J_{CCP}$ = 7.1 Hz) and 39.49 ($J_{CCP}$ = 20.1 Hz) for **227**. The $^1H$ NMR of the adduct **225** at 25–30 °C showed only a doublet for P–$CH_3$. Upon cooling to −20 °C, a pair of doublets was observed due to both the exo and endo isomers. Addition of $AlCl_3$ to a solution of **225** in $H_2CCl_2$ gave a 2:1 ratio of the isomers and inhibited a rapid equilibration. This was probably a result of preventing formation of a pentasubstituted phosphorane intermediate required for isomer equilibration.[73]

An electrophilic cycloaddition reaction between $RPX_2 \cdot AlX_3$ complexes and 1,4-dienic systems has been employed by Kashman and co-workers[200] to synthesize novel C–P heterocycles. Thus, 1-allylcyclohex-1-ene (**228**) condensed with the




phenylphosphonous dichloride and aluminum chloride complex at 0 °C to furnish, after hydrolysis, three phosphorus-containing compounds, viz., **229, 230,** and **231,** after separation by column chromatography. The structure of the major compound **229,** an oil, followed from elemental analysis and spectroscopic data (IR, MS, $^1H$ NMR). Oxides **230** and **231** were obtained as crystalline solids, (mp 153–155 and 94–95 °C) and their relative amounts depended on the nature of X in $PhPX_2$ (X = Cl or Br). Spectroscopy (IR, $^1H$ NMR, UV) coupled with combustion analysis again helped to establish the structures. An interesting feature in the $^{31}P$-irradiated $^1H$ NMR spectrum of **231** was the appearance of protons at C-5 at $\delta$ 0.1–0.3 in comparison to **230** in which the corresponding protons resonated at $\delta$ 0.9–1.2 due to the anisotropic effect of the cis-oriented P=O group.

Confirming proof for the presence of the cyclopropane ring in the oxide **230** was obtained by chemical transformation which, incidently, provided new unusual bicyclic C–P heterocycles. For

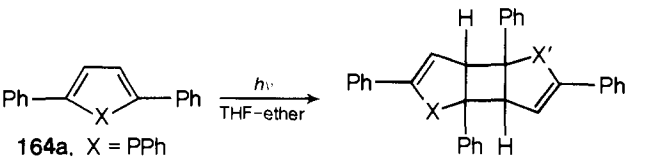



example, treatment of **230** with acid gave **232,** whereas mercuric acetate in acetic acid furnished **233**a, which upon hydrolysis and dehydration with $SOCl_2$, yielded **234.** The $^1H$ NMR spectrum of **233**a was devoid of cyclopropane ring protons, implying ready opening of the cyclopropane ring in **230.** Oxide **230** was also reduced by $HSiCl_3$, and the phosphine was characterized as its methiodide (mp 192–193 °C). These reactions firmly established the structure of oxide **230** except for the configuration of the hydrogen at C-1. A very tentative mechanism for the formation of **230** was also proposed. Complexes of $MePCl_2 \cdot AlCl_3$ and $PCl_3 \cdot AlCl_3$ were also tried in the reaction with **228** and the corresponding P-oxides were isolated in moderate yields.[200] This general reaction was, of course, a spin off of the pioneering work of Jungerman and co-workers with dienes and $RPX_2 \cdot AlX_3$.[189]

## E. Photochemical and Thermal Reactions

Until recently, photochemical and thermal reactions to procure polycyclic C–P heterocycles had not been extensively explored. However, a number of reports have appeared in the current literature demonstrating the utility of these techniques to the synthesis of several most unusual phosphorus-containing systems. Applications of many common methods of syntheses to the preparation of these systems have often proved unfruitful.

A photochemical [2 + 2] dimerization of 1,2,5-triphenylphosphole (**164**a) with a medium-pressure mercury arc lamp and Pyrex filter has been explored.[30] Irradiation of **164**a in 50%



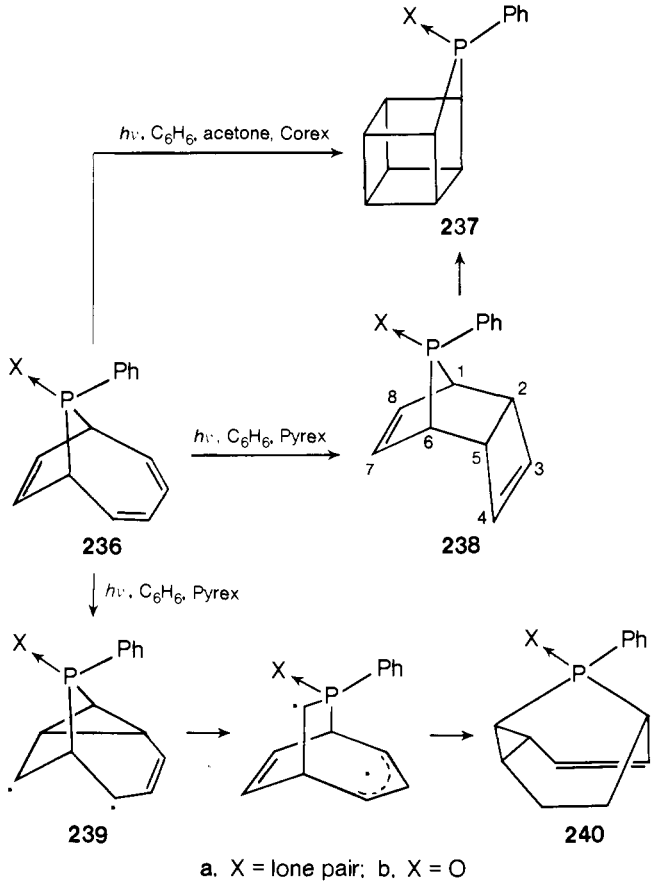

**164**a, X = PPh
b, X = $SiMe_2$

**235**a, X, X' = PPh
b, X = PPh; X' = $SiMe_2$

THF–ether for 7 h provided dimer **235**a as a white solid, mp 229–230 °C, in good yield. Elemental, mass spectral, and $^1H$ NMR spectral analysis identified **235a;** the latter showed olefinic and aromatic protons at $\delta$ 7.03 and a multiplet (2 H) at $\delta$ 4.88 which collapsed to a doublet with the decoupling of the phosphorus spin. No rationale for the "head-to-tail" arrangement in dimer **235**a was proposed. Proof of the stereochemistry of the cyclobutane ring was also not furnished. Dimerization was found

to be reversible when light of a higher energy (no filter) was employed. Attempts to trap the excited intermediate in presence of a tenfold excess of an alkene or an acetylene were unsuccessful. When a 1:1 mixture of **164a** and **164b** was irradiated, the mixed dimer **235b,** mp 248–249 °C, formed. As pointed out in this report,[30] the ease with which this dimerization occurred would tend to cast doubt upon the degree of aromaticity in this phosphole ring.

Unique, multicyclic C–P ring systems have been obtained from separate photochemical reactions of the bridged phosphine 9-phenyl-9-phosphabicyclo[4.2.1]nonatriene (**236a**) and its oxide (**236b**).[201,338] For example, photolysis of phosphine oxide

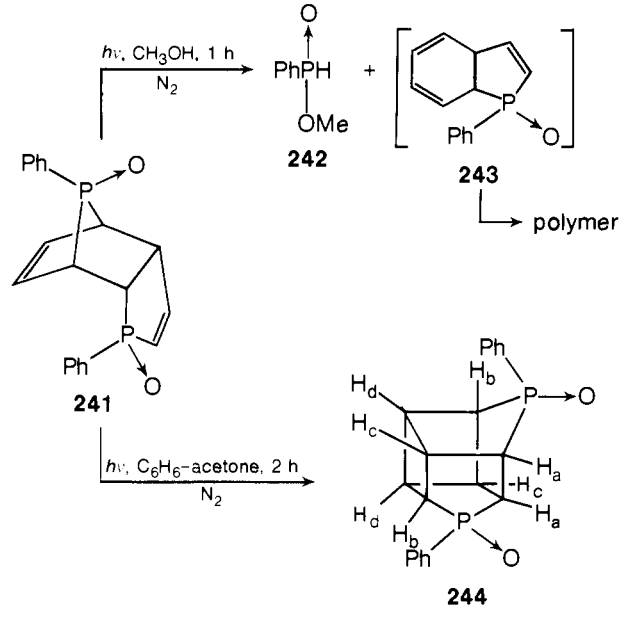



a, X = lone pair; b, X = O

**236b** through Corex (λ ≥ 280 nm) in benzene–acetone gave oxide **237b,** mp 122–123 °C (25–40%). The structure of **237b** followed from $^1$H NMR spectral data which contained multiplets at δ 3.39 (6 H), 3.88 (2 H), and 7.43 (5 H). Oxide **237b** was further characterized via trichlorosilane reduction in triethylamine–benzene to phosphine **237a,** mp 58–59 °C (76%). Formation of homocubane derivative **237b** was postulated to involve the tricycle endo intermediate **238b,** since this material could be isolated when **236b** was photolyzed through Pyrex (λ ≥ 300 nm) in benzene without acetone (28% yield) or in acetone solution for a short period (45% yield). Oxide **238b** (mp 175–177 °C) showed in the $^1$H NMR spectrum, besides the aromatic protons, a symmetrical pattern [H-2, δ 2.90 (2 H), doublet $J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz; H-1, 3.33 (2 H); H-3, 5.50 (2 H, singlet); H-7, 6.27 (2 H, doublet $J_{PH}$ = 11 Hz, triplet $J_{H\text{-}6,H\text{-}7}$ = 3.2 Hz)]. Double irradiation at the resonance frequency of phosphorus and H-1 gave two singlets for the olefinic protons confirming the above assignments. The endo stereochemistry for **238b** followed from the normal coupling of $J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz. Elemental and mass spectral data also supported the structure **238b.**[201,338]

Subsequent photolysis of **238b** afforded **237b.** On the other hand, photolysis of the bridged phosphine **236a** through Pyrex in benzene gave presumably diradical **239a** which led to phosphabarrelene **240a,** mp 43–45 °C (25%), characterized easily as the oxide **240b** (mp 101–102 °C). The $^1$H NMR spectrum of both **240a** and **240b** were temperature dependent and at room temperature resembled that of the parent hydrocarbon. The overall difference between the conversion of **236b** → **237b** and the conversion of **236a** → **240a** was suggested to result from a difference in reactivity of a singlet vs. a triplet excited state. The P epimer of **236** behaved similarly on photolysis providing the P epimer of **237** and **240,** respectively.[201,338]

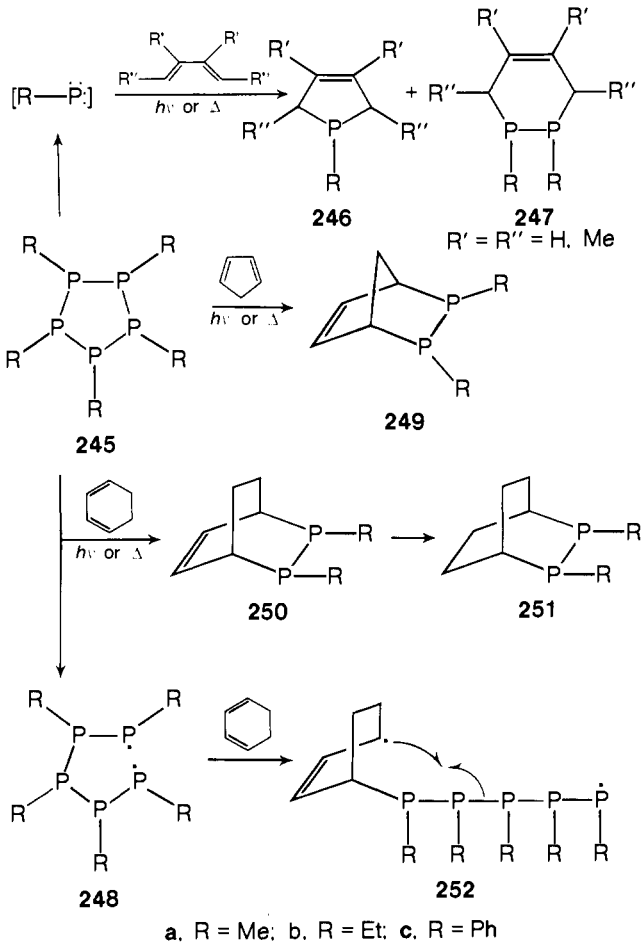
Quite recently, yet another multicyclic system related to **237** was recorded via photolysis (300 W, high-pressure mercury lamp) of the endo dimer **241** of 1-phenylphosphole oxide (see




section II.D for its preparation).[333] In this example, such differences in the reactivity of a singlet and triplet excited state were more clearly reflected. Direct irradiation of the endo dimer **241** in methanol for 1 h apparently caused extrusion of phosphinidene oxide, since methyl phenylphosphinate (**242**) was isolated (60%) as the only product. However, attempts to isolate and/or trap the other suspected part, the dihydrophosphindole (**243**), failed presumably due to rapid polymerization.[333] In contrast, sensitized irradiation of dimer **241** in benzene–acetone solution stimulated an intramolecular [2 + 2] cycloaddition to provide the multicyclic system **244** in virtually quantitative yield. This was analogous to the photochemical cycloaddition of cyclopentadienone dimer.[27] The structure of the adduct **244** (mp 249–250 °C) was unequivocally established. Infrared analysis showed peaks at 1440 (P–$C_6H_5$) and 1182 cm$^{-1}$ (P=O). The $^1$H NMR spectrum ($DCCl_3$) revealed four pairs of methine protons at δ 3.72 ($H_a$), 3.34 ($H_b$), 3.10 ($H_c$), and 2.83 ($H_d$), respectively, besides the aromatic protons at δ 7.38–7.88. Addition of Eu(dpm)$_3$ in varying amounts to a solution ($DCCl_3$) of **244** gave related shifts for $H_a$, $H_b$, $H_c$, and $H_d$ of δ 1.00, 0.61, 0.46, and 0.38, respectively.[333] A similar extrusion of phenylphosphinidene oxide from a bridged phosphine oxide and its insertion into the O–H bond of alcohols was reported earlier by Stille and co-workers.[327] It was suggested that such an insertion mechanism was unlikely in view of the large dissociation energy of the O–H bond[308] (cf. section II.D).

A number of workers have attempted to generate the deoxygenated species phenylphosphinidene ($C_6H_5\ddot{P}$:) or the phosphinidenes (R$\ddot{P}$:) by photochemical as well as thermal decompositions of various phosphorus-containing compounds.[308,309] These neutral, electron-deficient species, by analogy with carbenes, were expected to undergo insertion reactions with C–H bonds and addition reactions with unsaturated compounds (alkenes, dienes, alkynes). The ultimate goal, however, was to develop a more general method of synthesizing C–P heterocy-

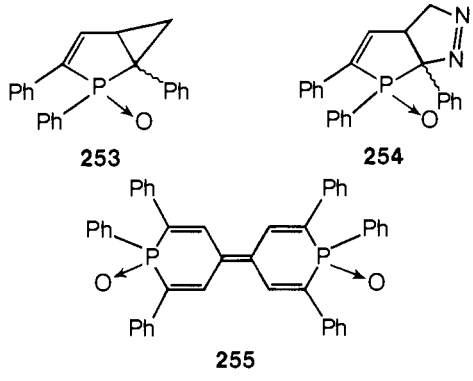
cles. Although at the moment this objective has not been completely realized, nevertheless these species have either been postulated as reactive intermediates or as ions in the mass spectrum of compounds containing a P-phenyl group.[67,93,159,308,309,366] Early work in this area was carried out by Schmidt and co-workers[308,309] who appeared to have demonstrated the formation of phenylphosphinidene ions by the decomposition of pentaphenylcyclopentaphosphane[317] (**245c**) via a pyrolysis-mass spectrometric analytical technique. Also,



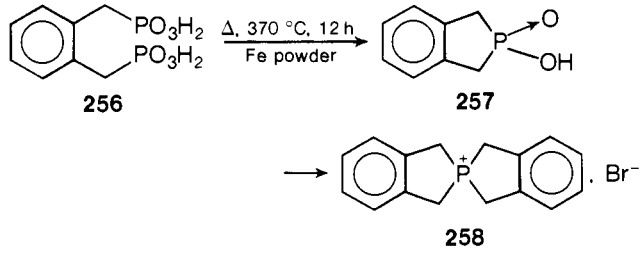

**a**, R = Me; **b**, R = Et; **c**, R = Ph

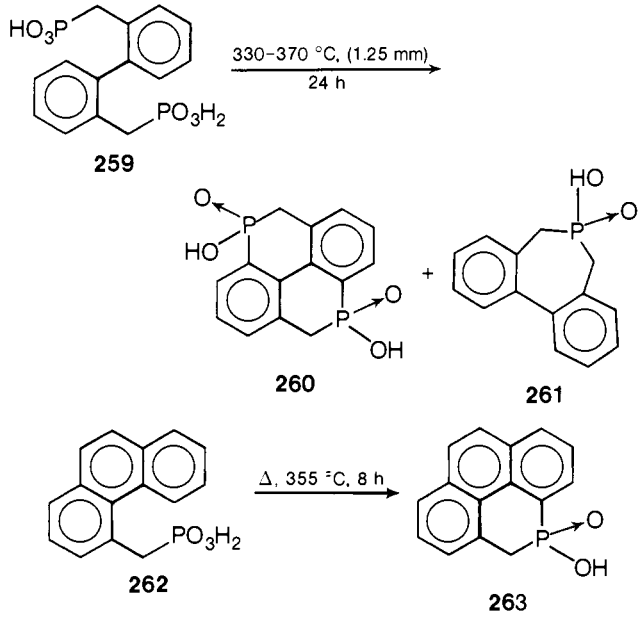
thermal decomposition of cyclophosphanes **245a**, **245b**, and **245c** in the presence of 1,3-dienes gave a mixture of phospholenes **246** and tetrahydrodiphosphorins **247** in overall yields of 30–65% depending presumably upon whether the phosphinidene R–P̈: or the diradical **248** was the attacking species. In contrast, photochemical fragmentation of cyclophosphanes **245a**, **245b**, and **245c** in the presence of diene acceptors afforded only tetrahydrodiphosphorins **247** in a maximum yield of 50%. When the photolysis of pentaethylcyclopentaphosphane (**245b**) was performed in the presence of cyclopentadiene or cyclohexadiene, the bicyclic diphosphine **249b** or **250b** resulted. With cyclohexadiene, the initial product **250b** underwent reduction in situ with excess diene to give hexahydro derivative **251b**. A mechanism was postulated involving the addition of diradical **248** to the diene (shown with cyclohexadiene). At low temperatures, photolysis of the cyclophosphane **245c** gave an ESR signal presumed to be due to the diradical **248c** (or **252c**). Whether or not a phosphinidene intermediate was involved in the reaction was not confirmed.[309] It seems worthy of mention that phenylphosphinidene ($C_6H_5P$̈:) has been suggested as the intermediate which inserted into the C–S bond of allyl ethyl sulfide at 100 °C[93] and into a C–C bond of biphenylene at 400 °C[94,130] to give 9-phenylphosphafluorene.

An interesting fragmentation of the bicyclic system **253** (prepared from **254**)[179] via photolysis in THF gave the unusual conjugated dimeric oxide **255**. Photolysis of **254** also gave **255** which melted at 436–438 °C and had UV maxima at 325 (log ε 4.53) and 438 nm (4.91).

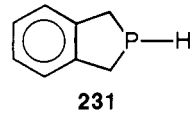



Thermal cyclization of arenephosphonic acids in vacuo at elevated temperatures (350–370 °C) has afforded, in limited cases, polycyclic C–P compounds in low yields (20–30%).[295–297] *o*-Xylyldiphosphonic acid (**256**), for example, cyclized at 370 °C (12 h) to 1,3-dihydro-2-hydroxyisophos-



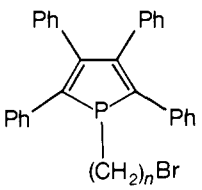




phindole 2-oxide (**257**) (28%), when only an equimolar quantity of iron powder was included in the reaction.[295] Isophosphindoline prepared from the methyl ester of acid **257** via reduction of its

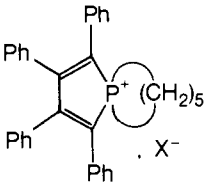



ester with diphenylsilane quaternized with *o*-xylyl dibromide in THF to afford the novel spiro salt **258** as a high-melting solid (mp 338–345 °C, 14%).[295] Similarly, the diphosphonic acid **259** underwent thermal cyclization to provide 4,9-diphosphapyrene derivative **260** in 10% yield and 6,7-dihydro-6-hydroxy-5*H*-

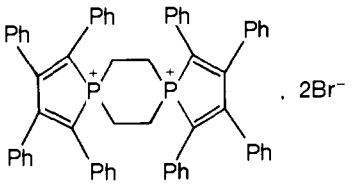
dibenzo[c,e]phosphepin (**261**) as the major product (30%) resulting from a rather unusual cyclodephosphonation process.[296] The diphosphinic acid **260** (mp 392–395 °C) itself was not characterized but was converted with diazomethane to an equimolar mixture of the corresponding cis and trans dimethyl esters which were identified by infrared, $^1$H NMR, and elemental analysis data. On the other hand, the phosphepin derivative **261**, which melted at 246–248 °C, analyzed correctly and showed the expected ratio of methylene to aromatic protons in the $^1$H NMR spectrum.[296] Likewise, the phosphonic acid **262** cyclized to the 4-phosphapyrene derivative **263** (mp 255–257 °C) in a low yield (22%).[297] However, attempts to extend the procedure to the cyclization of 1-naphthylmethylphosphonic acid and 2-(1-naphthyl)ethylphosphonic acid were unsuccessful.[297] This general technique for thermal cyclizations had been discovered earlier by Lynch[224] who successfully synthesized several derivatives of the 9-phosphaphenanthrene ring system, a process reported previously.[140] Thermal cyclization of highly substituted phospholes such as **264** has led to a variety of products such as **265** and **266.** For instance, by heating **264** ($n$ = 5) at 200 °C



**264**



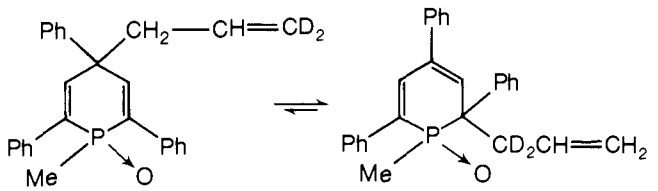
**265**



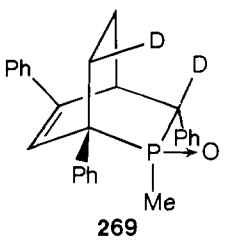
**266**

for 10 min, yellow **265** was obtained in modest yield (31%).[39] In a similar manner from phosphole **264** ($n$ = 2) at 175 °C with benzonitrile in an evacuated sealed tube there was obtained **266** (61%, mp 320–325 °C).

An interesting rearrangement was observed by heating **267** in toluene which gave **268** via [3,3]sigmatropic rearrangement.[301] Upon extended heating of **267,** a crystalline product was obtained for which the tentative structure **269** was suggested. The latter was indicated as being examined by x-ray analysis, and the structure must therefore be considered tentative.



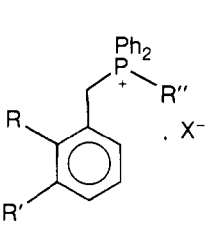
**267** **268**



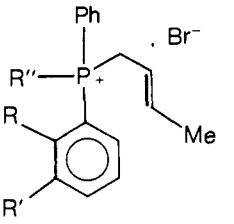
**269**

## F. Electrophilic Additions and Cyclizations

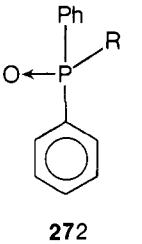
Friedel–Crafts-type cyclizations have been most widely used in the synthesis of polycyclic C–P heterocycles via two different routes. The first example involved an alkenyl chain attached to a phosphorus atom as the center of attack with the formation of a C–C bond, and the second route, wherein a C–P bond was formed, involved electrophilic attack by phosphorus.[345] The former method was a comparatively new approach to the synthesis of polycyclic C–P heterocycles and recently has been successfully utilized to synthesize the rare tetrahydroisophosphinolinium, tetrahydrophosphinolinium, and dihydrophosphindoline systems from readily available starting materials.[90,98,225,282] For example, open-chain phosphonium salts and phosphine oxides, as exemplified by structures **270, 271,** and **272,** possessed the correct structural and functional features



**270**



**271**



**272**

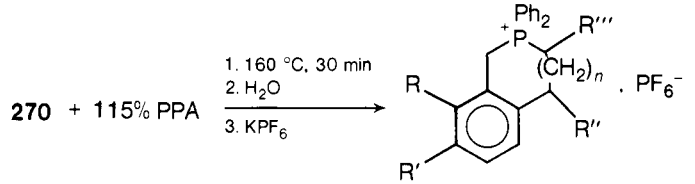
for cyclization at carbon to give the desired cyclic C–P heterocycles **273, 274,** and **275,** respectively (see Chart I). The required cyclization was carried out with 115% polyphosphoric acid (PPA) at an elevated temperature (160–200 °C) for a short time to produce the C–P heterocyclic systems in modest to good yields (40–70%). $^1$H NMR, $^{31}$P NMR, infrared, mass spectral, and elemental analyses of the above cyclized products were in agreement with the proposed structures.[90,98]

The reaction was believed to proceed through a mechanism reminiscent of a cation-alkylation process.[282] Stereochemical analysis of the products and $^{31}$P NMR monitoring of the cyclization process at variable temperatures supported a mechanism of marked similarity to a cation alkylation of an arene in an electrophilic substitution process. An intermediate with a strong $^{31}$P NMR signal was observed in the reaction of **271**a to give **274a** but was absent when **270**a was converted to **273a.** (Scheme I). The latter observation was rationalized on the basis of a rapidly formed intermediate of a classic type in electrophilic substitution.[282]

Recently, the above procedure has been extended to include C–P heterocyclic systems with a carbonyl group in the molecule.[225] For example, phosphonium salts represented by **276** cyclized smoothly with 115% PPA to afford benzophosphenium salts **277** in modest yields (40–50%). In these cyclic compounds, the functionalization of the C–P system by the presence of the C=O group provides a base for constructing additional rings.

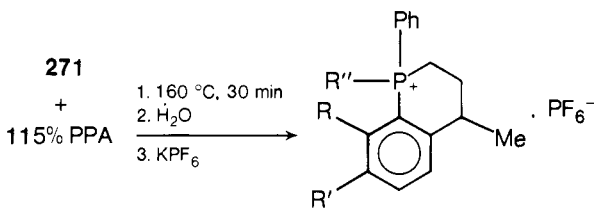
Few other workers have employed PPA to effect cyclization of carboxylic acids to obtain C–P heterocycles. Henning[161] cyclized acid **278a** to isophosphinoline **279a** (38%) with PPA at 130 °C. Very recently, Bickelhaupt and co-workers[117] obtained **279b** (mp 204–205 °C) starting from **278b** following Henning's procedure.[161] Utilizing the ketophosphinic acids **279b,** phosphine **280b** was isolated and purified in route to **281b** as shown.[117] An astonishing feature in the $^1$H NMR spectrum of **280b** was the appearance of the phosphine proton as a broad singlet at $\delta$ 4.26 while infrared analysis showed the normal P–H vibration at 2250 cm$^{-1}$. Reaction of **280b** with phosgene and subsequent treatment with DBU furnished 3-methyl-2-phosphanaphthalene (**281b**) as a white crystalline solid, mp 64.5–69 °C (approximately 10% yield). The electronic spectrum of **281b** in ether had absorptions at 252 ($\epsilon$ 28 850), 304 (6630), 343 (450), and 360 (270) nm with features similar to naphthalene and isoquinoline. The spectrum disappeared rapidly on admission of air. The $^1$H NMR spectrum[117] had resonances at $\delta$ 9.84 (d, $^3J_{PH}$

CHART I



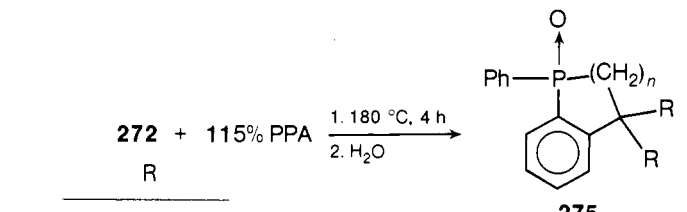

273

| Compd | R | R' | R'' | Compd | R | R' | R'' | R''' | n |
|---|---|---|---|---|---|---|---|---|---|
| 270a | H | H | $-CH_2CH=CH_2$ | 273a | H | H | Me | H | 1 |
| 270b | H | Me | $-CH_2CH=CH_2$ | 273b[a] | H | Me | Me | H | 1 |
| 270c | H | H | $-CH_2CH=CHMe$ | 273c | H | H | Me | H | 2 |
| 270d | H | Me | $-CH_2CH=CHMe$ | 273d | H | Me | Me | H | 2 |
| 270e | H | H | $-CH=CH_2$ | 273e[b] | H | H | H | H | 1 |
| 270f | H | H | | 273f | H | H | $-(CH_2)_3-$ | | 1 |
| 270g | Benzo | | $-CH_2CH=CH_2$ | 273g | Benzo | | Me | H | 1 |
| 270h | Benzo | | | 273h | Benzo | | $-(CH_2)_3-$ | | 1 |




274

| | R = R' | R'' |
|---|---|---|
| a | H | Ph |
| b | H | Me |
| c | H | Et |
| d | Benzo | Ph |



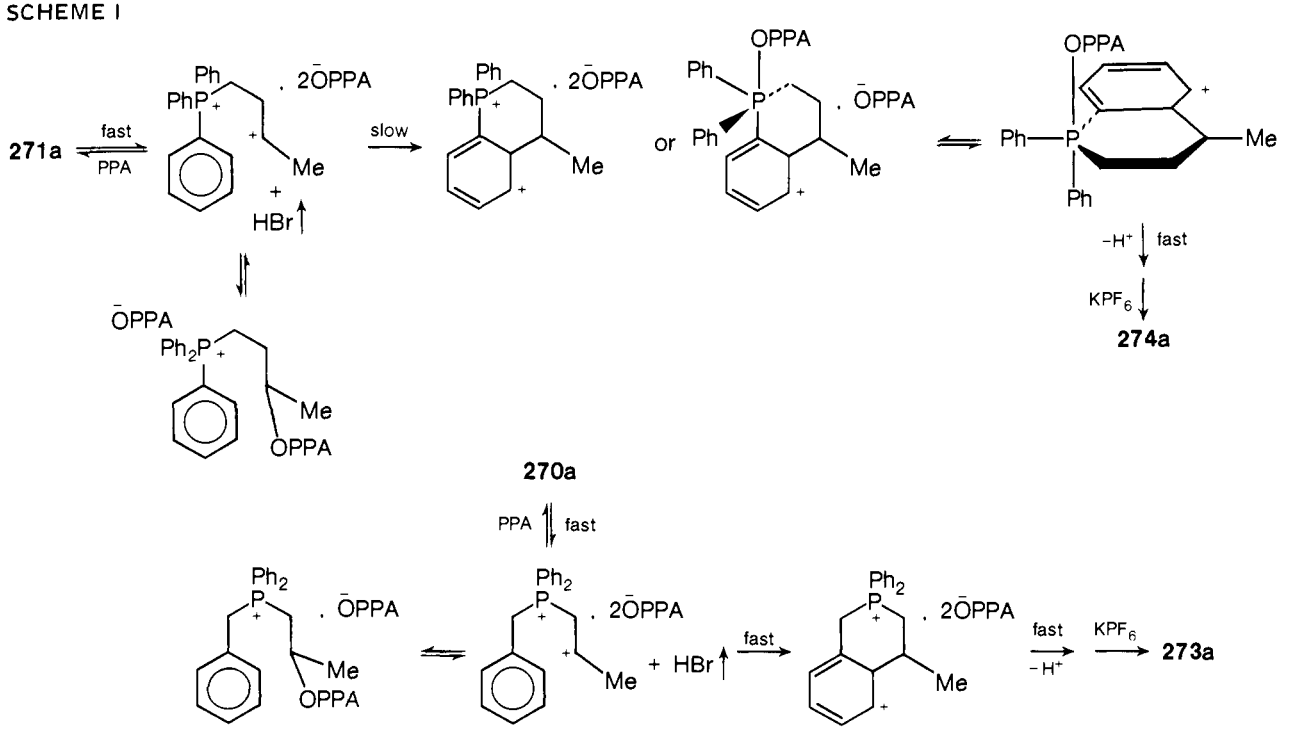

| | R |
|---|---|
| a | $CH_2CH=CH_2$ |
| b | $CH_2CH=CHMe$ |
| c | $CH_2CMe=CH_2$ |
| d | $CH_2CH=CMe_2$ |

275

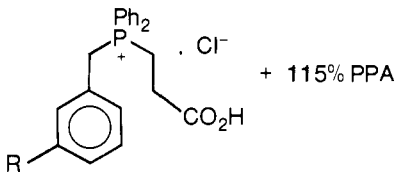
| | R | R | n |
|---|---|---|---|
| a | H | Me | 1 |
| b | H | Me | 2 |
| c | Me | Me | 1 |
| d | Me | Me | 1 |

[a] Isolated as the bromide salt and was converted to the $PF_6^-$ derivative. [b] The reaction was carried out at 300 °C for 1.25 h.

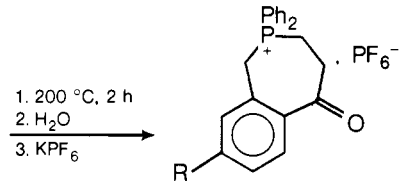
SCHEME I




= 35 Hz, 1 H, H-1), 8.57 (d, $^3J_{PH}$ = 7.5 Hz, 1 H, H-4), and 7.85–8.35 (m, 4 H, benzo-$C_6H_4$). 3.30 (d, $^3J_{PH}$ = 13.5 Hz, 3 H, Me) with a marked resemblance to phosphabenzene.[21] The electronic spectrum and $^1H$ NMR data were seemingly in accord with the molecule being an aromatic system. The mass spectrum exhibited the base peak at *m/e* 160 and an intense peak at *m/e*

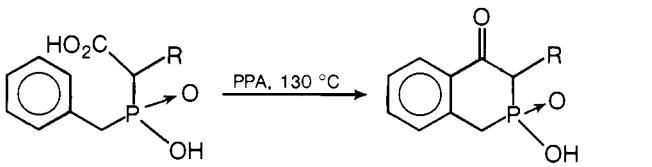



276

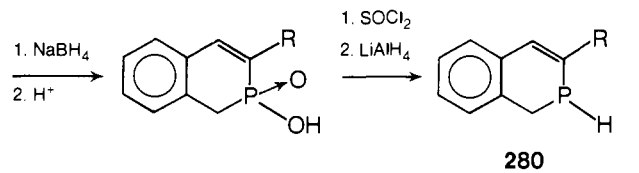



277

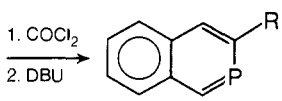
a, R = H; b, R = Cl; **c**, R = Me




278 279




280

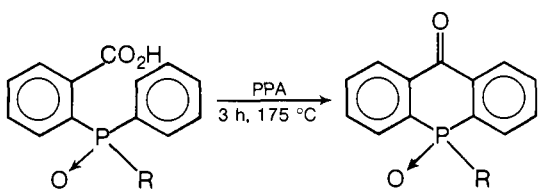



281

a, R = H; b, R = Me

128 (96%). Phosphanaphthalene (**281a**) was also prepared in similar fashion but was characterized only in solution by UV spectroscopy.

Freshly prepared PPA has also been employed to effect cyclization of the acid **282a** to the oxide **283a** (50%).[311] Phosphine

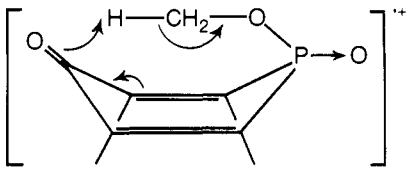



**282** **283** (50%)

a, R = Ph; b, R = OH; **c**, R = OMe

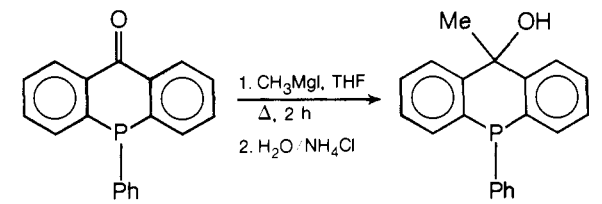
oxide **283a** (mp 222–223 °C) showed absorptions in the UV spectrum (ethanol) at 240 (shoulder, log ε 5.26), 261 (4.93), and 284 (4.96) nm and a parent peak at *m/e* 304 in the mass spectrum.[311] The mass spectrum of the related systems **283b** and **283c** have also been studied in some detail.[132] A notable feature in the mass spectrum of **283b** was the loss of $PO_2H$ and C=O from the molecular ion (*m/e* 244) to give intense ions at *m/e* 180 (100%) and *m/e* 216 (64%). In contrast, the methyl ester **283c**, *m/e* 258, lost $CH_2O$ moiety giving the base peak at *m/e* **228**. It is conceivable that a direct hydrogen transfer from the ester methyl to the carbonyl oxygen took place in this particular case if a butterfly conformation existed which would permit the two groups to be in close proximity as shown in **284**.[131,132] The long P–C bonds might permit this [P–C ≈ 1.75–1.84 Å vs. C–C 1.54 Å].[160,166,167]

With a view to study the conformational preferences of the substituents and the P-inversion barriers on phosphorus in

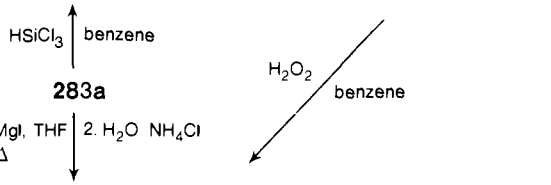


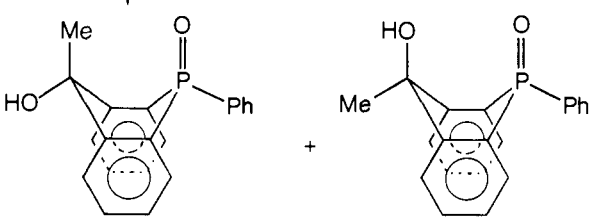

**284**

molecules which could possibly exist in a butterfly conformation, the hydroxy phosphine **286** has been prepared from phosphine **285**.[60] The known ketophosphine oxide **283a**[190,311] was ob-

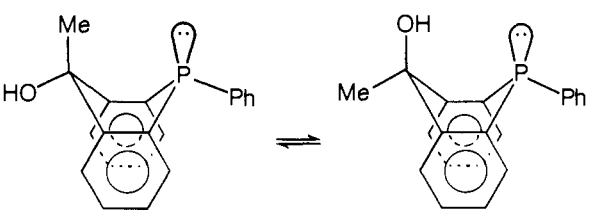



**285** **286**

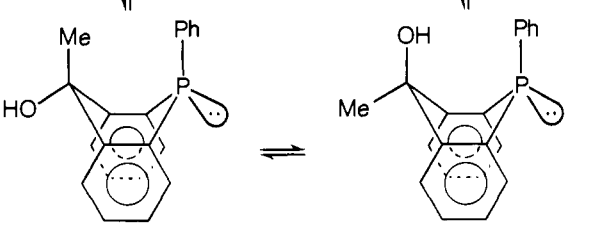



**287** **288**

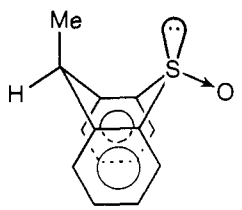



**286a**

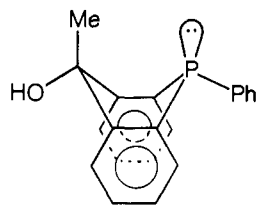



tained in an improved yield (65%) by the ring closure of the acid **282a** with 115% PPA at 175 °C (2 h). Deoxygenation with trichlorosilane in benzene gave the reported ketophosphine **285**. Addition of methylmagnesium iodide to **285** furnished a single hydroxy phosphine **286**, mp 156–157 °C, isolated in excellent yield (80%). Phosphine **286** had the normal $\nu_{O-H}$ band at 3250 $cm^{-1}$ (broad) in the infrared spectrum and the expected ratio of aromatic to methyl protons in the $^1H$ NMR spectrum. An interesting feature in the $^1H$ NMR spectrum ($DCCl_3$), however, was the appearance of the methyl protons at $\delta$ 1.59 as a doublet, which could arise due to the fluttering of the aromatic rings. At −18 °C, the doublet coalesced to a singlet which now resonated at $\delta$ 1.57. These findings were seemingly suggestive of a rapidly equilibrating system in solution due to the fluttering of the wings. It could not be eliminated from consideration that a "flattened"

**286** was formed as the "fluttering" rate was sharply reduced at −18 °C. Thus, a smaller $^5J_{PH}$ could result in a single broad peak being formed and the equilibria with **286a** may not exist. In the solid state, the hydroxy phosphine **286** was expected to be configurationally stable. Oxidation of the hydroxy phosphine **286** at room temperature by hydrogen peroxide furnished a single phosphine oxide (mp 261–262 °C) which displayed in the $^1$H NMR spectrum ($(CH_3)_2SO$-$d_6$) a sharp singlet for the methyl group protons at $\delta$ 1.74. In comparison, attack of methylmagnesium iodide on **283a** yielded an isomeric mixture of phosphine oxides **287** and **288** (mp 261–262 and 329–330 °C) in approximately equal amounts, readily separable by fractional crystallization. The lower melting oxide was identical with the compound obtained by hydrogen peroxide oxidation of **286.** The methyl protons in the higher melting oxide resonated at $\delta$ 1.12 as a sharp singlet in the $^1$H NMR spectrum ($(CH_3)_2SOd_6$) as contrasted to the lower value in the lower melting oxide. Very recently, Ternay and Evans[330] reported the conformational preferences of the methyl group in related sulfur systems having a butterfly conformation. It was concluded that a methyl substituent in the pseudo-axial position in **289** was deshielded ($\delta$ 1.36) whereas

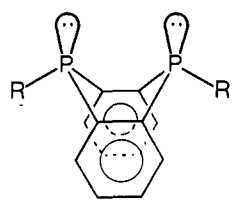


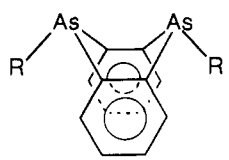

**289**




**286a**

it was more shielded ($\delta$ 1.90) in the pseudo-equatorial position owing to the diamagnetic anisotropy of the aryl rings. On the basis of the chemical shifts, we have tentatively assigned the structures **287** and **288** to the lower and the higher melting hydroxyphosphine oxides, respectively. An x-ray crystallographic analysis has substantiated that phosphine **286** isolated as a solid has the structure **286a.**[60] This work is related to the studies of Mann and co-workers[79,80] on 5,10-dihydrophosphanthrene derivatives and arsenic analogs[204] of the type shown. The phos-

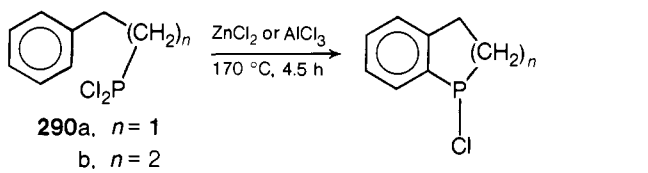


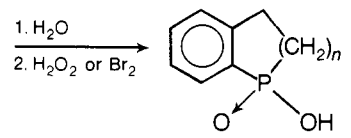

phanthrene system was discussed under the section on cycloalkylation (II.C).

A second route employing Friedel–Crafts cyclizations involved the reaction of phosphonous dichlorides with Lewis acids, usually zinc chloride or aluminum chloride. For example, phosphonous dichlorides **290a** and **290b** cyclized at 170 °C with zinc chloride, to afford, after hydrolysis–oxidation, crystalline phosphinic acids **291a** (72%) and **291b** (91%).[65,299] With aluminum chloride to effect cyclization of **290b** under similar conditions, **291b** was realized but in a much lower yield (75%).[65,299] Curiously, compounds **292** and **293** did not cyclize with a variety of Lewis acids ($ZnCl_2$, $SnCl_4$, $AlCl_3$, $PCl_5$). It has been suggested by others[65] that cyclization of **292** did occur but the relatively stable complex with the Lewis acid was not easily hydrolyzed. An interesting study of the relationship of proton chemical shifts promoted by addition of increasing amounts of $Eu(fod)_3$ to a solution of the methyl ester **294** (prepared from **291**; $n$ = 1) attests to the powerful coordinating ability of the P=O group.[65]

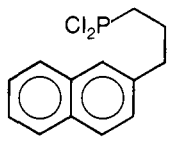
Whereas intramolecular cyclizations of alkenes and carboxylic acids at the carbon center often proceeded readily in good yields to produce cyclic products, similar cyclizations of



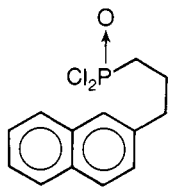

**290a**, $n$ = 1
b, $n$ = 2



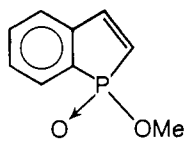

**291**




**292**

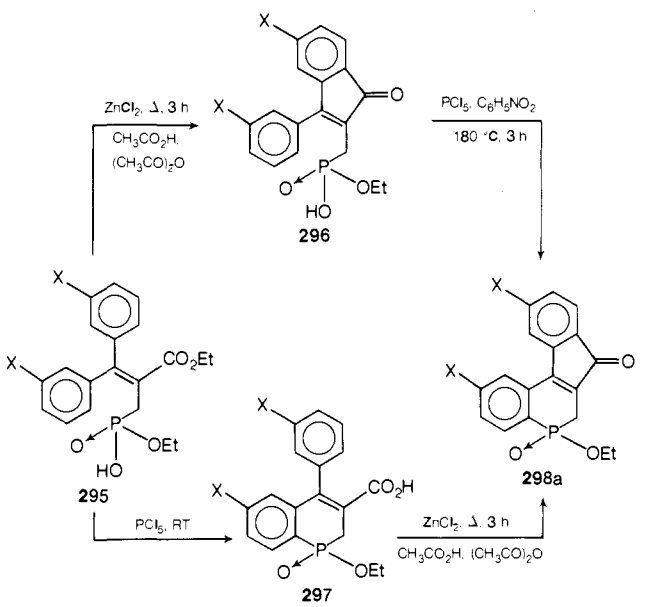



**293**




**294**

phosphonic and phosphinic acids at the phosphorus atom occurred with great difficulty and more often in low yields.[128] A rare example in which this contrast in reactivities was reflected has been reported by Griffin and Bryant.[128] The phosphonate **295a,**

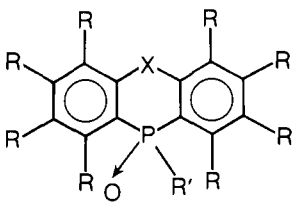



a, X = H; b, X = OMe

obtained by the Stobbe condensation of benzophenone with ethyl β-carbethoxyphosphonate, cyclized at carbon with zinc chloride in boiling acetic acid–acetic anhydride mixture to produce **296** in excellent yield (91%).[128,257] Cyclization of **295a** at the phosphorus atom with a variety of Friedel–Crafts reagents ($SnCl_4$, $P_2O_5$, $AlCl_3$) was less effective. However, $PCl_5$ at room temperature gave the cyclic product **297a** in a low yield (7%) and much of an unspecified dephosphonated compound. A methoxy substituent in the aromatic ring, which would activate the para position as in **295b,** did not significantly improve the yield (only 11% of **297b** was obtained). With these cyclizing agents, which would promote side reactions, extensive deal-

kylation of carbethoxy and/or phosphonate groups was observed. Ester **296a** and acid **297a** were separately cyclized with $PCl_5$ in nitrobenzene (180 °C) and zinc chloride in acetic acid–acetic anhydride mixture to yield the novel tetracyclic C–P heterocycle **298a** in 35 and 78% yields, respectively. Likewise, **296b** and **297b** were cyclized to **298b.** Ester **298a** (mp 207–208 °C) had absorptions in the infrared at 1710 (C=O) and 1260 $cm^{-1}$ (P=O) and the expected $^1H$ NMR spectrum. The methylenes adjacent to the phosphorus atom in **298a** were easily exchanged when treated with sodium ethoxide in deuterioethanol and with sodium hydride in $(CH_3)_2SO$-$d_6$. However, the rate of exchange for **298a** was only 1.5–1.7 times faster than that for **296a.** Moreover, UV spectral analysis of $(CH_3)_2SO$ solutions of **298a** did not reveal aromatic features since the spectrum of **296a** was essentially identical.

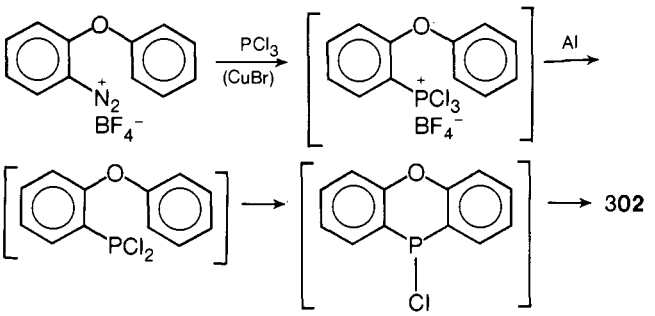
The versatility of the Friedel–Crafts method could be gauged by its application to the synthesis of a wide variety of phosphinic acids of the general formula **299,** differing in the heteroatom and



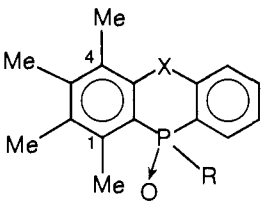
**299**

X = O, NH, S, $SO_2$, CO, $CH_2$, $CH_2CH_2$
R′ = H, OH, Me, Ph, Bz, $(CH_2)_3NMe_2$
R = H, Me, Et, F, Cl

substituents in the aromatic rings, formed in low to moderate yields (ref 13, 47, 118–123, 125, 135, 186–188, 221–223, 328). Also known in this class were a few phosphines, phosphine oxides, and phosphonium salts. No other group of C–P heterocyclic compounds has received so much attention and the growing interest in these types of C–P systems could be due to potential practical applications. For the sake of completeness, the members of **299** were included as stated in the Introduction. For example, condensation of phosphorus trichloride with di-*p*-tolyl ether (**300b**) in the presence of aluminum chloride followed by aqueous alkali treatment yielded the secondary phosphine oxide **301b** (82%) which autooxidized at its melting point (160 °C) or on heating with dilute alkali to acid **302b,**[120,123] best identified as its dicyclohexylammonium salt.[120,222,223] Replacement of phosphorus trichloride in the above reaction with methyl- or arylphosphonous dichloride gave the corresponding phosphine oxide.[222] The yields of the phenoxaphosphinic acids and the phosphine oxides in these series were higher (40–60%) by this procedure if the positions para to the oxygen were blocked by substituents (**300,** R = R′ = Me, Et, F, Cl). Note that **300a** yielded **302a** in a very low yield (2%). However, the yield of **302a** could be improved to 25% by employing the diazo method,[92,223] which consisted of treatment of the diazonium tetrafluoroborate with $PCl_3$ in the presence of cuprous bromide followed by reduction with aluminum. This technique was also of value to prepare substituted phenoxaphosphinic acids.[221–223] When bromine was the substituent in the para

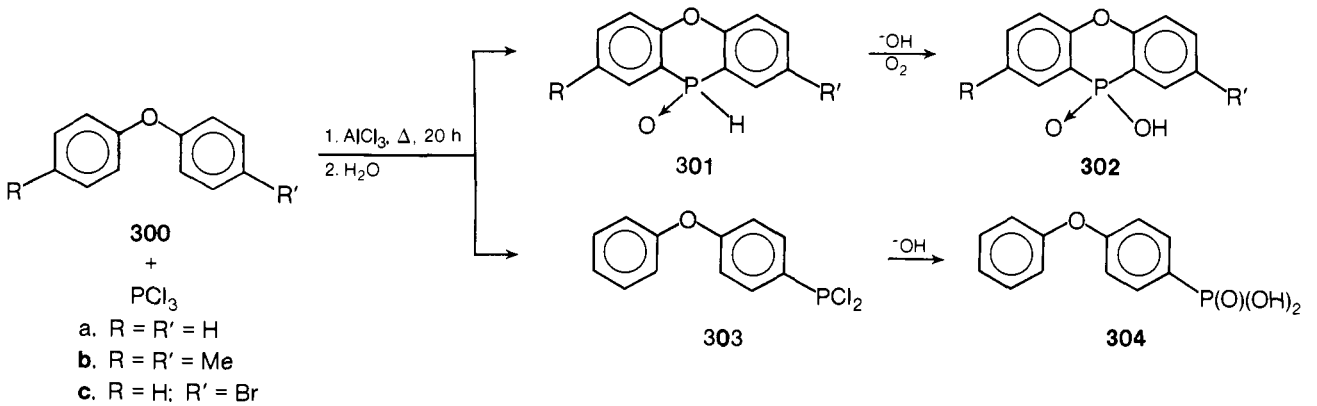


position, as in **300c,** it was displaced by $PCl_3$ to yield initially **303,** which on hydrolysis gave *p*-phenoxyphenylphosphonic acid (**304**).[119] The IR spectra of the phenoxaphosphinic acids exhibited prominent bands at 2600, 2250, 1650 (broad, P–OH), 1490–1440 (P–Ph stretch), 1280–1260 (C–O stretch), 1190–1140 (P=O stretch), and 978–974 $cm^{-1}$ (P–O stretch).[222,223] In the UV spectrum, main absorptions occurred at 210–220 (log ε 4.50–4.60), 240–250 (log ε 4.20–4.30) and 298–304 nm (log ε 3.65–3.75) and substituents in the aromatic rings (alkyl, halogen) had little effect.[223] The $^1H$ NMR spectra ($F_3CCO_2H$) of a number of these acids possessing alkyl substituents at various positions have been scrutinized,[221,223] and an unusually large, long-range coupling of 8 Hz was observed between the phosphorus and the hydrogens at C-4 and C-6 positions. Shift values of δ 2.70, 2.45, 2.50, and 2.50 were calculated for the methyl group at 1, 2, 3, and 4 positions, respectively (in **305**), from an analysis of the $^1H$ NMR spectra of methyl-



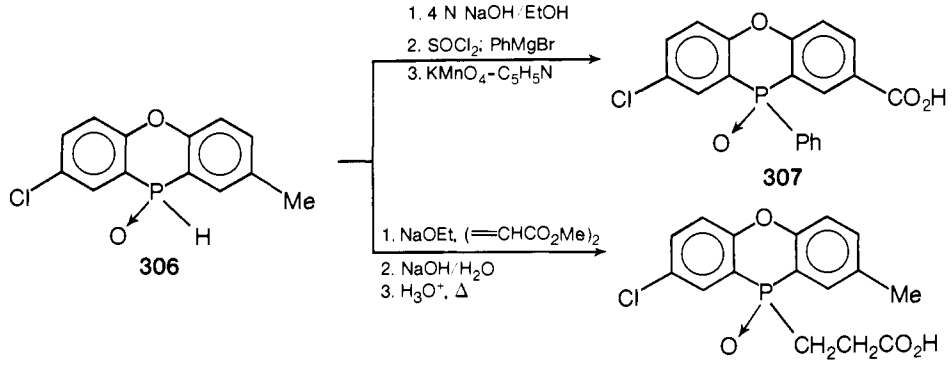
**305**

substituted phenoxaphosphinic acids. These values were unaffected by substituents (i.e., Me, F, Cl) in the other ring but an *o*-methyl group in the same ring caused an upfield shift by 0.10 ppm.[221,223] A good fit between the observed and the calculated chemical shift was apparent. The mass spectra showed the molecular ion as an intense peak and was usually the base peak. All the acids examined showed loss of the ($PO_2H$) moiety and elimination of OH and PO groups and further fragmentation de-



**300**
+
$PCl_3$
a. R = R′ = H
**b.** R = R′ = Me
**c.** R = H; R′ = Br

**301** **302** **303** **304**



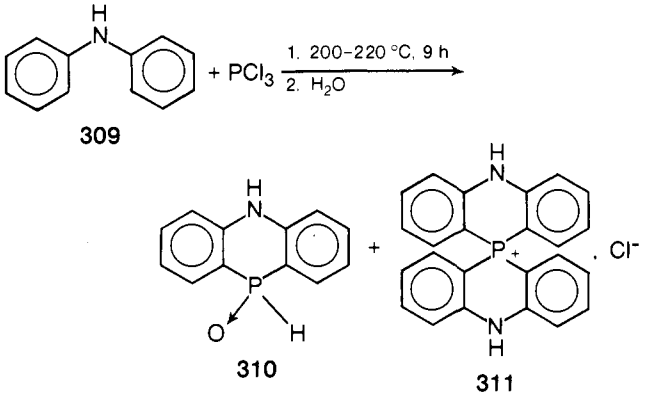

306 307 308

pended upon the nature of the substituents in the aromatic rings.[120,121,124,223]

In passing, it might be mentioned that several polymeric chelates of the acid **302b** with metals (copper, zinc, cobalt, nickel, and chromium) have been prepared and their thermomechanical properties studied.[214,215] This area of chelation is relatively new with this family.

In a study directed toward optical resolution, Campbell[47] prepared 2-chloro-8-methylphenoxaphosphine 10-oxide (**306**) (mp 149–150 °C) by a Friedel–Crafts method. Conversion of **306** to acids **307** and **308** was by the reactions shown. Attempts to resolve both the acids **307** and **308** by forming diastereoisomeric salts with amines, however, were unsuccessful. A plausible explanation could be that hydration of the P=O bond occurred on salt formation and gave a trigonal-bipyramidal intermediate which led to the formation of a racemic mixture.[47]

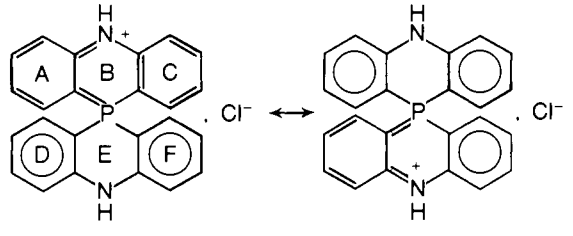
The condensation of diphenylamine (**309**) with phosphorus trichloride at 200–220 °C followed by quenching of the reaction mixture with water was reported earlier by Haring[135] to yield the




309 310 311

secondary phosphine oxide **310.** Freedman and co-workers[186–188] repeated the reaction and obtained, in addition to the oxide **310,** a novel spirophosphonium salt **311** (mp 400 °C) in about 8% yield. Salt **311** gave correct elemental analysis and displayed a base peak at *m/e* 364 (M − HCl) in its mass spectrum. Support for the spiro structure **311** was obtained by x-ray diffraction studies which showed unusual bond orders.[187,188] In particular, the data revealed short bond distances for C–N (1.37–1.38 Å) and C–P (1.77 Å) which implied extensive electron delocalization in the central rings. Supplementary evidence for aromatic character in the central rings was found in $^{31}P$ NMR analysis which revealed a phosphorus signal at +21 ppm (TFA or $(CH_3)_2SO$) as compared with expected values −20 to −30 ppm shown by simple phosphonium salts.[216]

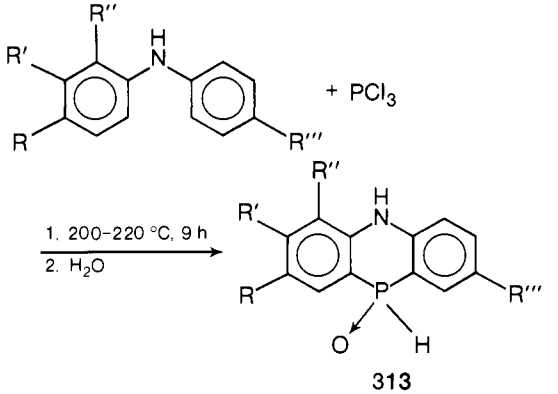
The $^{31}P$ NMR chemical shift of a number of phosphonium salts are available.[216] A good correlation between the $^{31}P$ NMR chemical shift and the electron density around the phorphorus is evident. The high positive $^{31}P$ NMR chemical shift observed for salt **311** suggested resonance stabilization in the central rings through hybrids such as **312.** X-Ray data also revealed that the molecule was distorted and that the tricycle D–E–F was planar whereas the tricycle A–B–C was distorted, benzene rings A and C making an angle relative to one another of 14.5°.[188] If **312** is



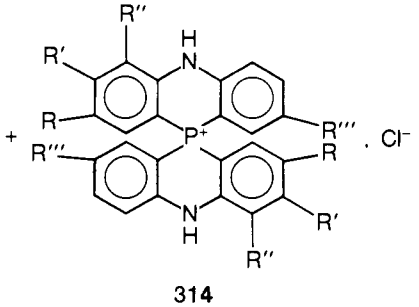

312

a reasonable approximation of the hybrid, the x-ray data are confusing. Spirophosphonium salt **311** represented a rare example having both phosphorus and the nitrogen atoms in the spiro system.

In a recent article,[186] the same group of workers synthesized several ring-substituted phosphine 10-oxides **313** and the high-melting spirophosphonium salts **314.** A mechanism was



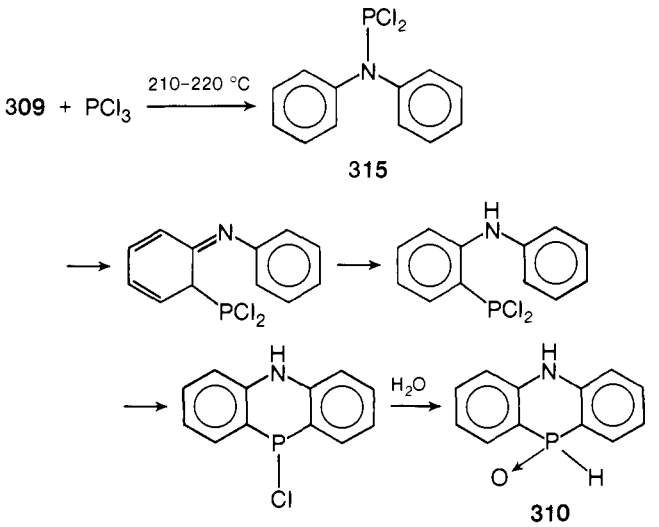

313



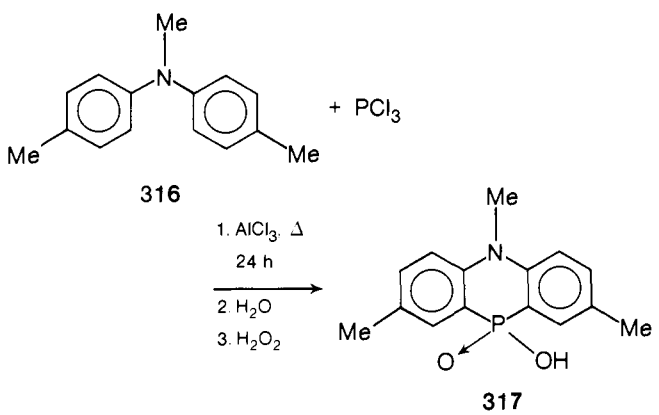

314

| | R | R' | R'' | R''' |
|---|---|---|---|---|
| a | Me | H | H | H |
| b | Me | H | H | Me |
| c | H | Benzo | | H |

proposed for the interaction of diarylamines like **309** with phosphorus trichloride involving the initial formation of a diarylphosphoramidous dichloride **315** followed by migration of the

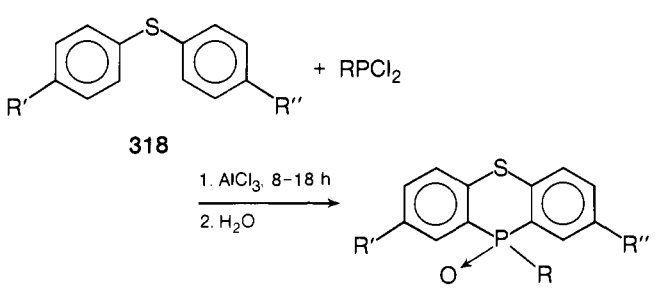



$PCl_2$ moiety to the ortho position and subsequent ring closure usually encountered in electrophilic cyclizations. Extension of the above procedure to obtain N-substituted phosphazine 10-oxides failed; presumably the phosphoramidous dichloride was not formed in this case. However, in the presence of aluminum chloride, the reaction of *N*-methyldi-*p*-tolylamine (**316**) with




phosphorus trichloride did occur to furnish the desired oxide, which was directly oxidized to the acid **317**, albeit in low yield (12%).[186]

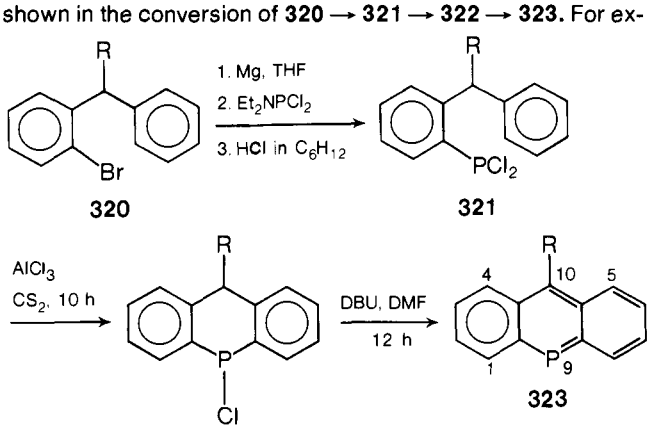
In an analogous manner, condensation of para-disubstituted diaryl sulfides **318** with phosphorus trichloride in the presence



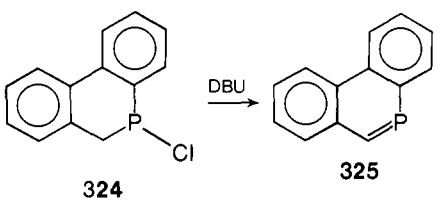

R′ = R″ = Me; R′ = Me, R″ = Cl; R′ = F, R″ = Cl

of aluminum chloride (followed by basic workup (15–40%)[122]) has afforded several derivatives of phenothiaphosphinic acids **319**. A few phosphine oxides **319** (R = Me, Ph), phosphines, and salts were also obtained in this class.

Friedel–Crafts conditions have proved applicable in the preparation of certain valuable intermediates, which were subsequently transformed to unusual C–P heterocyclic systems shown in the conversion of **320** → **321** → **322** → **323**. For example, the tricyclic chlorophosphine **322a** and **322b** served as precursor for 10-phenyldibenzo[*b*,*e*]phosphorin (or 10-phenyl-9-phosphaanthracene) (**323a**).[212,302] Compounds **322a** and **322b** were obtained by the Friedel–Crafts cyclization of *o*-(diphenylmethyl)phenylphosphonous dichloride (**321**) in the presence of aluminum chloride in $CS_2$ (41%). Dehydrochlorination of **322b** with DBU led to the formation of the stable 10-phenyldibenzo[*b*,*e*]phosphorin (**323b**) as yellow crystals (mp 173–176 °C) in an unspecified yield. It may be recalled (section II.C) that an earlier attempt by the same workers to prepare the unsubstituted dibenzo[*b*,*e*]phosphorins in a stable form was unsuccessful, and only spectroscopic data on solutions were obtained.[211] Nevertheless, the electronic spectrum recorded for the parent compound was useful in identifying **323** as an aromatic substance, since similarities between the two were apparent. The $^1H$ NMR spectrum of compound **323b** ($CS_2$) had resonances in the region $\delta$ 7.7–8.5 (11 H) and 8.72–9.25 (2 H, presumably those on C-4 and C-6) which amply testified to its aromatic character.[212] No $^{31}P$ NMR data were included. Chlorophosphine **324** and DBU gave dibenzo[*b*,*d*]phosphorin (or




**a**, R = Me; **b**, R = Ph




9-phosphaphenanthrene) (**325**).[213] Since compound **325** was unstable, its identity was established by the UV spectrum [$\lambda_{max}$ 372 (log $\epsilon$ 0.45)] which resembled more closely phenanthridine than phenanthrene. The mass spectrum of **325** showed a molecular ion (*m/e* 232) and consisted also of singly and doubly charged ions.[213]

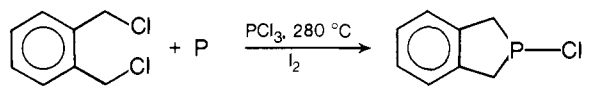
Many efforts have been expended to obtain polycyclic phosphorus-containing aromatic systems. With the availability of substituted phosphorins, it is anticipated that many interesting reactions are yet undiscovered. In fact, a few pertinent observations with the simple phosphorins[245,269] have already been discussed under cycloaddition reactions (section II.D).

## G. Miscellaneous Methods

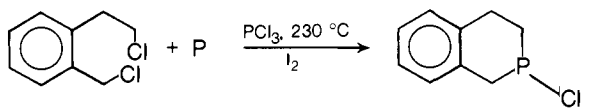
A few polycyclic C–P systems have been synthesized by rather uncommon but elegant techniques. Unfortunately, the reactions utilized in these diversified methods precluded their inclusion in the previous sections discussed. Although the approaches would appear at the moment to be of limited appli-

cability, brief accounts have been described in this section in view of some of the novel systems prepared.

Direct alkylation of elemental phosphorus (white or red) with organic halides was perhaps one of the earliest techniques developed for the synthesis of organophosphorus compounds.[289,326] A variety of products, namely halophosphines, tertiary phosphines, tertiary phosphine oxides, and quaternary phosphonium salts, have been shown to be formed in this reaction depending on the starting material and reaction conditions.[289] Isolation of pure products was an anticipated difficulty in this procedure. Nevertheless, a few polycyclic, C–P heterocycles have been prepared by this procedure by some investigators,[347] notably by the Russian workers.[28,29] In patented processes,[28,29] the alkylation of *o*-xylyl dichloride and *o*-(β-chloroethyl)benzyl chloride with white phosphorus at high temperatures in the presence of phosphorus trichloride and catalytic amounts of iodine or iodides were described to afford the phosphinous chlorides **326** and **327**, respectively. Likewise,

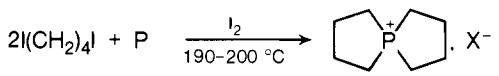



**326**




**327**

alkylation of red phosphorus with 1,4-diiodobutane furnished the novel 5-phosphoniaspiro[4.4]nonane triiodide (**328**a) (40%).



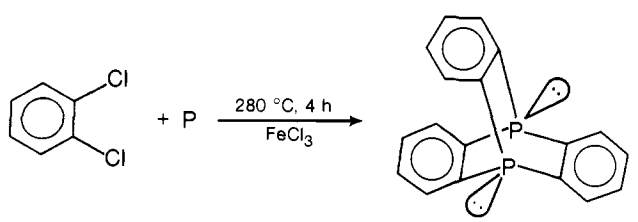

**328**

a, X = $I_3$

b, X = I

which lost iodine on steam distillation and gave spirophosphonium salt **328b** as colorless needles (mp 204–205 °C).[88] Metathesis of **328b** in an anion-exchange process provided a number of new spiro salts. Identification of these salts was mainly via elemental analysis since no spectral data were provided. Walker and co-workers[76] found a value of −72 ppm (rel to 85% $H_3PO_4$) for the phosphorus signal of **328b.** The value was astonishingly large compared to the value of −39.9 ppm obtained for tetraethylphosphonium iodide, a fact which probably reflected considerable distortion of bond angles at the phosphorus atom due to the ring constraints.[76] Unfortunately, not many spiro systems have been investigated from the standpoint of a molecular orbital pattern. The closest relative is the bisbiphenylylphosphorane system which will be discussed in section V.A.

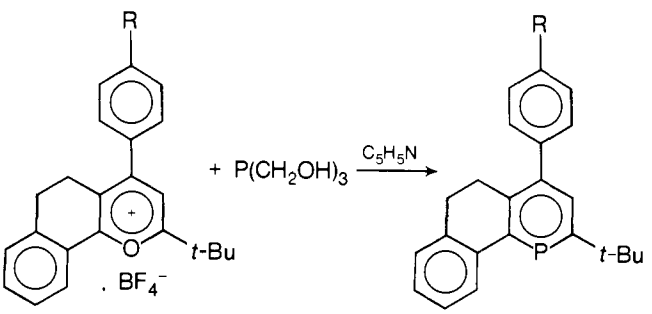
Another strained system with two phosphorus atoms at the bridgehead positions was reported via reaction of *o*-dichlorobenzene with white phosphorus in the presence of catalytic amounts of ferric chloride in a sealed glass tube at 280 °C (4 h).[347] Thus, novel 1,6-diphosphatriptycene (**329**) (20%) was obtained as a white solid (mp 323–325 °C) in a single step. Di-




**329**

phosphine **329** with excess benzyl bromide formed only a monoquaternary salt; presumably the monosalt formed was insoluble in the reaction medium and did not react further. Oxidation of **329** with peracetic acid in ethyl acetate, however, furnished the corresponding *dioxide*. Absorption bands in the UV spectrum of **329** occurred at 218 (ε 1.03 × $10^5$), 267 (ε 1.86 × $10^3$), 275 (ε 2.16 × $10^3$), and 283 nm (ε 2.28 × $10^3$) while the infrared spectrum (KBr) showed strong bands at 1431, 1258, 1230, 1160, 1105, 750, 725, 545, and 473 $cm^{-1}$. A $^{31}P$ NMR decoupled $^1H$ NMR spectrum showed an AA′XX′ pattern, usually noted with symmetrically ortho-disubstituted benzene derivatives, with normal coupling constants.[347] The $^{31}P$ NMR signal of phosphorus was detected at +43 ppm (rel to 85% $H_3PO_4$) and, by comparison with the reported value of +8 ppm for triphenylphosphine,[340] implied considerable distortion of the C–P–C bond angle.[126e] A recent x-ray crystallographic analysis confirmed the caged structures for 1,6-diphosphatriptycene **329** and its dioxide.[310] A C–P bond length of 1.845 Å with a C–P–C bond angle of 97° for compound **329** was recorded. In contrast, the dioxide showed a C–P bond length of 1.827 Å and a C–P–C bond angle of 100.5°. Interestingly, the mass spectrum of phosphatriptycene **329** consisted of doubly and triply charged parent ions in addition to a strong parent peak at *m/e* 290 and fragment peaks at *m/e* 257, 183, and 107.[347]

Reaction of pyrylium fluoroborates with tris(hydroxymethyl)-phosphine in pyridine to afford polycyclic phosphorins was a new approach to polycyclic, C–P heterocycles although it had been applied to phosphorins.[91,233,277,345] Application of this procedure

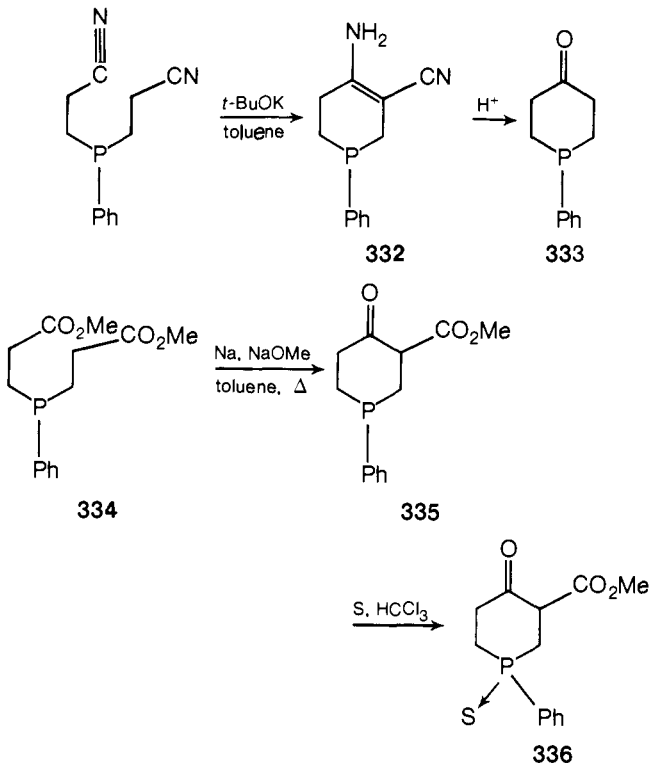



**330** **331**

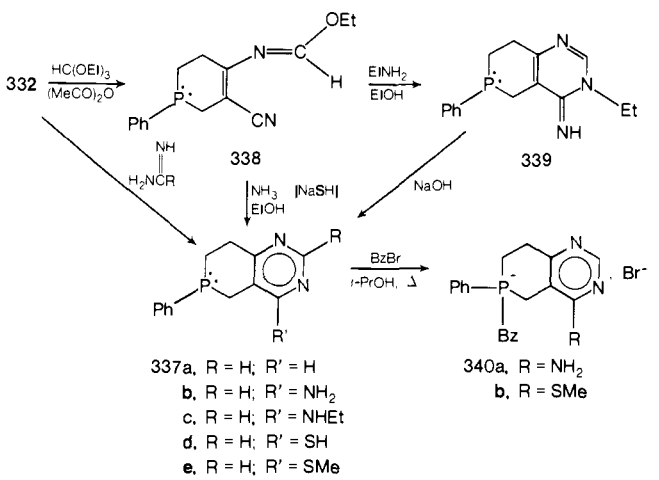
**a**, R = H; b, R = OMe; c, R = Cl; **d**, R = Me

by Dimroth and co-workers[91] to the tetrafluoroborates **330** gave the tricyclic phosphorins **331** with different electronegative substituents in high yields (66–81%). Crystallographic analysis of a representative member, namely that of **331b,** revealed the phosphorin ring as planar with a C–P–C angle of 103° and C–P bond distance of 1.75 Å.[102]

It was possible to utilize *o*-enaminonitrile **332** for the synthesis of a very large number of a new family of fused carbon–phosphorus heterocycles, namely phosphorino[4,3-*d*]pyrimidines and phosphorinoindoles.[318,319,321,325] The reported procedure[349] for the Thorpe condensation of bis(2-cyanoethyl)phenylphosphine to the enaminonitrile **332** and its subsequent hydrolysis with acid to give phosphorinanone **333** was perfected[324] for large-scale preparation of the key starting materials required in these investigations. A procedure was also developed which involved a Dieckmann cyclization of bis(2-carbomethoxyethyl)-phenylphosphine (**334**) with sodium methoxide in boiling toluene to provide unstable β-keto ester **335.** Subsequent conversion of **335** to the crystalline phosphine sulfide **336** was accomplished (overall yield, 45–60%). Initial condensation of the enaminonitrile **332** with formamidine acetate in acetic acid furnished the phosphorino[4,3-*d*]pyrimidine **337a** in a low yield (7%).[321] In contrast, guanidine hydrochloride reacted with **332** only under basic conditions (*t*-BuOK) providing the pyrimidine **337b** in modest yield (34%). This general procedure was also extended to the preparation of several carbocyclic pyrimi-



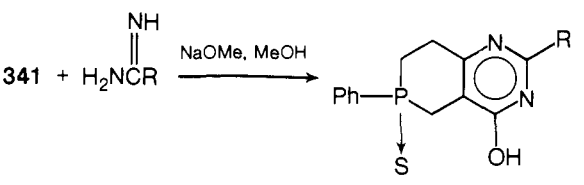

dines.[321] Much of the starting enaminonitrile, however, was recovered (50–80%) in these reactions. Subsequently, it was discovered[318] that crude ethoxymethylene derivative **338,** derived from enaminonitrile **332** by boiling with triethyl orthoformate and acetic anhydride, reacted directly with ammonia providing pyrimidine **337a** in a much higher yield (66%).[318] Additionally, compound **338** condensed with anhydrous ethanolic ethylamine and sodium hydrosulfide to afford new pyrimidines **339** and **337d,** respectively, in essentially the same yield. All the phosphorinopyrimidine structures were rigorously proved via elemental as well as spectral data (IR, MS, $^1$H NMR, $^{31}$P NMR). Dimroth rearrangement of **339** to **337c** by boiling with 0.1 M sodium hydroxide was an added proof in favor of structure **339.**



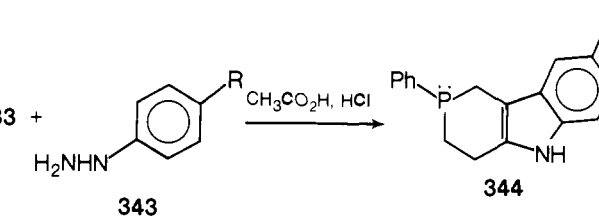

The well-known biological activity and chemotherapeutic usefulness of the general family of 5,6.7,8-tetrahydroquinazolines,[20] and the expectation that phosphonium salts might possess similar activity due in part perhaps to increased solubility in water, provided incentive to prepare a few representative salts **340** in the phosphorinopyrimidine series.[318] Specific methylation of the mercapto group of **337d** with 10% sodium hydroxide and methyl iodide to furnish **337e** was successfully accomplished without either carbon–phosphorus bond formation or cleavage.

Quaternization of **337a** and **337e** with benzyl bromide in 2-propanol proceeded smoothly at the phosphorus center, rather than at the amino or methylthio groups, to furnish salts **340**a and **340b,** respectively, in high yields (74 and 79%). A large change of the $^{31}$P NMR signal in the phosphine precursors from ca. +44 to ca. −18 ppm (rel to 85% $H_3PO_4$) proved the site of quaternization was at P. One of these salts, namely **340b,** was resolved via an anion-exchange method through the use of hydrogen silver L-(+)- and D-(−)-dibenzoyltartrates.[318] Both the enantiomers exhibited respiration related cytotoxicity in *Bacillus subtilis* but not in *Pseudomonas fluorescens* or sarcoma 180. However, there was no inhibition of growth of KB cells.[166] Crystallographic analysis of **340b** showed the phosphorinane ring was a distorted half-chair with phosphorus 0.6 Å out of the plane.[166]

Condensation of the β-keto ester **341** with guanidine hydrochloride, acetamidine hydrochloride, and thiourea under anhydrous basic conditions gave, after neutralization, the corresponding phosphorino[4,3-*d*]pyrimidinols **342a, 342b,** and **342c** as solids in good yields (67, 52, and 80%).[319] A notable feature in the $^1$H NMR spectrum of these pyrimidinol sulfides was the downfield shift of the ortho protons from the rest of the phenyl protons. The $^{31}$P NMR chemical shifts for **342a, 342b,** and **342c** were observed at −31.41, −39.02, and −39.0 ppm, respectively (rel to 85% $H_3PO_4$).[319]




Condensation of 1-phenyl-4-phosphorinanone (**333**) with various substituted phenylhydrazines **343** or phenylhydrazine hydrochlorides presumably produced phenylhydrazones which underwent cyclization in situ with glacial acetic acid and concentrated hydrochloric acid. The corresponding phosphorinoindoles **344** formed as high-melting crystalline solids.[325] With phenylhydrazine **343c,** cleavage of the ether occurred during the condensation owing to acidic conditions. Also, compounds **344e–g** were isolated only as their P-oxides owing to rapid oxidation of the corresponding phosphines. It was found that indolization resulted when the original arylhydrazine had an electron-releasing substituent in the 4 position. Interestingly, quaternization of phosphorinoindole **344**a with 1-(chloromethyl)naphthalene in dry toluene occurred at phosphorus rather than nitrogen. Shift of the $^{31}$P NMR signal at +25.8 ppm in phosphine **344a** to −13.8 ppm in the salt (rel to 85% $H_3PO_4$) established the quaternary nature of the P atom. Additionally, the mass spectrum of this salt showed strong peaks at *m/e* 406 (M − Cl) and *m/e* 405 (M − HCl).[325]

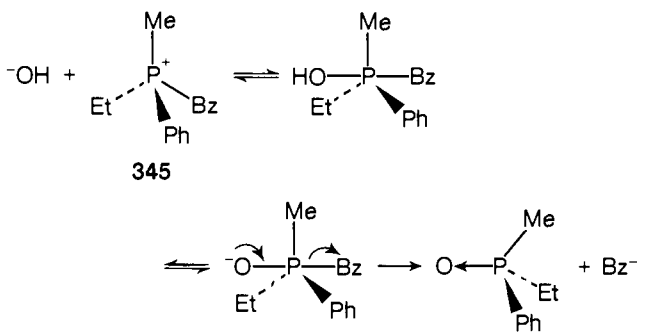


## III. Reactions at Phosphorus

### A. Hydrolysis

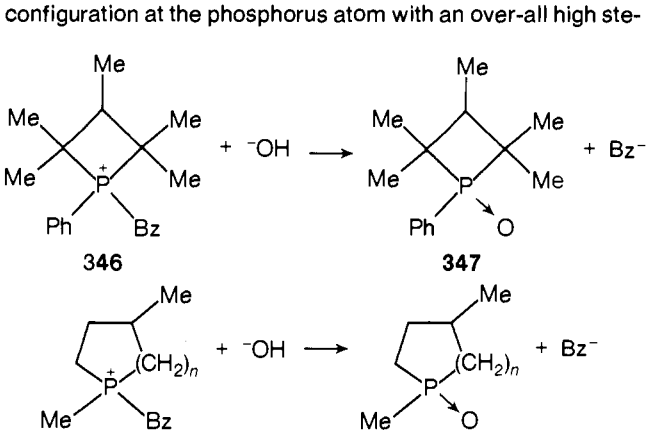
Phosphonium salts, upon treatment with aqueous alkali, undergo cleavage in general to afford a phosphine oxide and a hydrocarbon, whereas phosphates, phosphonates, and phosphinates were hydrolyzed by both base and acid to give the corresponding acid salts.[75,264] Although, mechanisms for these reactions might appear quite simple, they were rather complex and only in the last few years has some insight been gained as a result of some brilliant efforts, notably by Marsi, McEwen, Mislow, Ramirez, Trippett, and Westheimer. Several reviews and miscellaneous reports on the subject have appeared on simple systems (ref 70, 73, 84, 113, 114, 116, 168, 178, 250, 252, 254–256, 265, 270, 351, and 362). A majority of the phosphonium salts in the polycyclic family have been subjected to alkali treatment with the objective to obtain the corresponding phosphines, via the precursor oxides, as a method for proof of structure without a rigorous kinetic study. Only a few systems have been examined thoroughly. Nevertheless, they have been included and compared with the more widely studied acyclic and monocyclic compounds in the discussion to follow.

Alkaline hydrolysis of acyclic phosphonium salts has a number of interesting features.[264,265] Briefly stated, the hydrolysis in general (a) follows third-order kinetics i.e., rate $\approx [^-OH]^2$ [salt]; (b) occurs with *inversion* of configuration at P; and (c) proceeds with the expulsion of a group capable of departing as the most stable anion, the order of preference of leaving groups being benzyl > phenyl > methyl > ethyl. Consistent with these data, a mechanism indicated with the acyclic salt **345** was proposed



**345**

by McEwen.[264] In contrast to this behavior, Trippett and coworkers[69,104,137,138] discovered that the alkaline hydrolysis of the cis and trans isomers of phosphetanium salts **346** to produce the corresponding oxides **347** occurred with net *retention* of configuration. It was later found that either isomer of salt **346** gave the same mixture of isomeric oxides, possibly via pseudorotating hydroxyphosphoranes.[17] However, a retention of configuration at the phosphorus atom with an over-all high stereospecificity was noted by Marsi[248,249,255] in the alkaline decomposition of both geometric isomers of phospholanium salts **348**a to afford the respective oxides **349**a. Subsequent to these findings, a few other workers[74,95] observed complete retention of configuration and stereospecificity in the hydrolytic cleavage of diastereomeric phosphetanium and phospholanium salts. Such difference in the stereochemical behavior of acyclic and cyclic phosphonium salts in the cleavage by hydroxide ion was recognized as probably due to fundamental structural differences in the initially formed intermediates. A large body of data[264,351] inferred that alkaline hydrolysis of acyclic phosphonium salts proceeded most often via a trigonal-bypyramidal phosphorane intermediate **350** and that the most electronegative group (R)

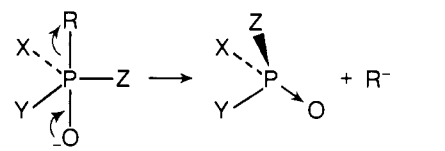


**346** **347**

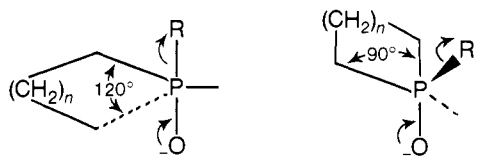


**348** **349**

a, $n = 1$; b, $n = 2$; c, $n = 3$



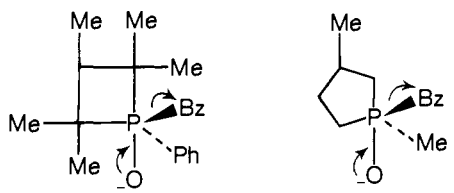
**350**



**351** **352**

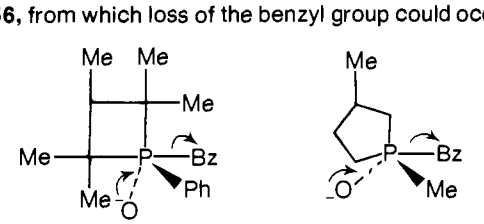
a, $n = 1$; b, $n = 2$; c, $n = 3$

was expelled as an anion from the apical position. Inversion of configuration noted with acyclic salts was accounted for on the basis that in the phosphorane intermediate **350**, the hydroxide ion, the phosphorus atom, and the electronegative group (R) were collinear and that the electronegative group (R) departed from a side opposite to the hydroxide ion.[264,351] Such an arrangement of groups with small-membered cyclic salts, depicted in **351**, would place the heterocyclic ring in a diequatorial arrangement displaying a C–P–C ring angle close to 120° and would result in a strained system. Instead, the ring would occupy apical-equatorial positions with an internal C–P–C angle of 90° (illustrated in **352**), and the loss of a group (R) could occur from an equatorial position. Retention of configuration observed with the salts **346**[69,104,115,137,138] and **348a**[248,249] was rationalized via invoking the phosphorane intermediates **353** and **354**. Apical



**353** **354**

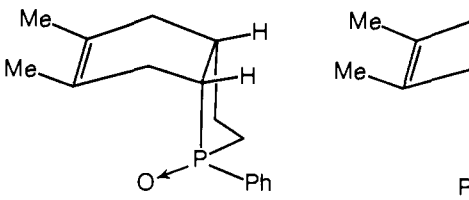
introduction of a nucleophile and apical departure of a group has generally been favored over apical introduction and equatorial departure.[351] Another possibility, namely apical introduction, pseudorotation, and apical departure, could also account for the observed retention of configuration. Phosphoranes **353** and **354** might undergo pseudorotation to the new trigonal bipyramids **355** and **356**, from which loss of the benzyl group could occur from



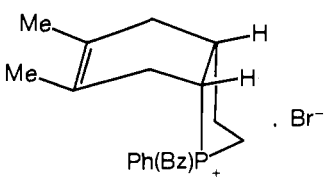
**355** **356**

an apical position. The high stereospecificity with which both the geometric isomers of the salts **346** and **348a** were cleaved to give the respective oxides **347** and **349a** in particular, negated a pseudorotation process from consideration. Moreover, spectral evidence suggested inhibition of a pseudorotation process in certain small-membered rings.[249,351] A novel ring expansion[69,104,138] with certain phosphetanium salts during hydrolysis has been discussed elsewhere (section III.B) and has been an unusual phenomenon to be considered in these hydrolytic processes.

Interestingly, condensation of 1-phenyl-2-phospholene 1-oxide with 2,3-dimethyl-1,3-butadiene in a sealed tube at 260° C for 12 h gave a mixture of isomeric oxides **357** and **358** (one isomer was isolated, purified, and identified).[271] Although the salt **359**



**357** **358**

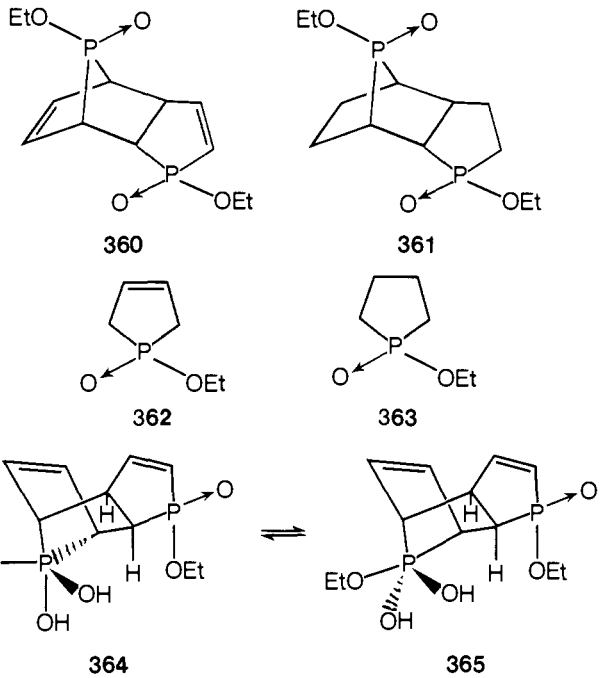


**359**

was of unknown configuration at phosphorus, hydrolysis with aq 10% NaOH gave one of the oxides. In spite of the lack of data on the configurations at P for both oxides **357** and **358,** preservation of the five-membered ring in the bicyclic system suggested an equatorial departure for the benzyl anion. Of course, this assumed the five-membered ring was bonded in an apical-equatorial manner to P. Obviously, knowledge of the absolute configuration at P in these systems will be required to determine the overall stereochemistry of the hydrolysis.

A logical extension of the hydrolysis studies to six-eight-membered cyclic salts by Marsi[250,251] yielded most instructive results. On subjecting each of the pure *cis*- and *trans*-phosphorinanium salts **348b** to hydrolysis, mixtures of stereomeric oxides **349b** of different compositions were obtained which indicated the absence of a common intermediate for the isomeric salts and the oxides formed.[250] In this case only, both the "McEwen mechanism" leading to the inverted product and the mechanism suggested for the small-membered cyclic salts **346** and **348a** were postulated to be operating.[251] In contrast, both the *cis*- and *trans*-phosphepanium salts **348c** were cleaved to their respective *cis*- and *trans*-oxides **349c** with complete inversion of configuration at phosphorus and may have formed via the "McEwen mechanism" proposed for the acyclic salt **345.** This would suggest that the pentacovalent intermediate **351c** tolerated diequatorial placement of the seven-membered heterocyclic ring, apparently due to its flexibillty.[251]

Although the ability of the pentacovalent compounds to undergo pseudorotation was discovered in 1960 by Berry[34] (sometimes referred to as "Berry pseudorotation"), it was Westheimer who developed the theory with successful application to account for the rapid rate of hydrolysis of certain cyclic phosphates which were discussed in his review.[351] Pertinent to our present discussion was the hydrolysis of the bicyclic phosphinates **360** and **361** in acid and base media.[85,86,208,351] Curiously, one of the two ester groups in **360** and **361** was hydrolyzed at a much faster rate compared with either the second ester group in the same molecule or to their simple cyclic ana-



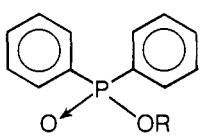
**360** **361**

**362** **363**

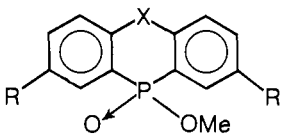
**364** **365**

logs **362** and **363** or acyclic analogs. The increased rate was attributed to the relief of strain at the bridge position in forming the corresponding trigonal-bipyramidal intermediates, of which **364** is an example from **360.** In intermediate **364,** the ring occupied one apical and one equatorial position. Pseudorotation **364** → **365** followed by the loss of the alkoxy function from the apical position accounted for the overall hydrolysis.[85,86,351]

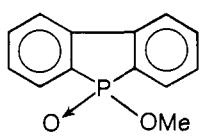
Electronic interaction involving 3d orbitals of phosphorus in several simple and heterocyclic phosphinates has been investigated by Haake and others[66,131,133,266] in several kinetic studies of alkaline hydrolysis. Use of oxygen-18 enriched water in the hydrolysis of the simple diaryl phosphinates **366** implied direct



**366a**, R = Me
**b**, R = Et
**c**, R = *n*-Pr
**d**, R = *i*-Bu
**e**, R = *i*-Pr
**f**, R = neopentyl



**367a**, X = $CH_2$; R = H
**b**, X = CO; R = H
**c**, X = S; R = Me
**d**, X = SO; R = Me
**e**, X = $SO_2$; R = Me



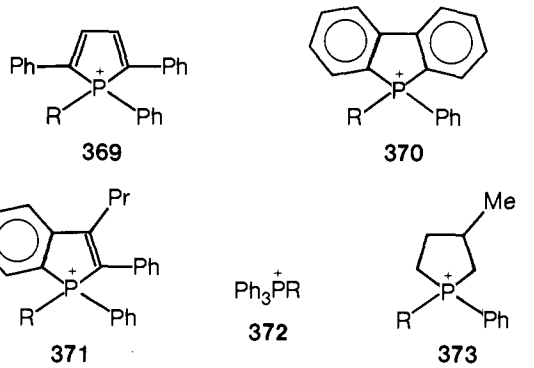
**368**

attack of hydroxide ion on phorphorus and no exchange into the phosphinyl oxygen. A second-order rate law was noted. The hydrolysis was also sensitive to both polar and steric effects.

Comparison of the data of **366a** with the heterocyclic phosphinates **367** and **368** revealed no substantial differences in the rates and activation parameters ($\Delta G^*$, $\Delta H^*$, $\Delta S^*$). One would have anticipated an acceleration in the rates for the heterocyclic phosphinates **367** which have varying degrees of planarity (possibly a "butterfly conformation"). A still higher rate for the planar phosphinate **368** was conceivable, compared to the diaryl phosphinate **366a** as a result of increased $\pi$ interactions. It was

concluded that the large size of d orbitals on phosphorus permitted overlap with the p orbitals of the phenyl rings despite nonplanarity of the heterocyclic system **367**.[66,131] However, no generalization was made regarding the rate of hydrolysis of these phosphinates with the geometry of the transition state. A substantially higher rate observed with **367b** was explained on the hypothesis that hydroxide ion attacked the carbonyl carbon atom forming a ketal anion which in turn attacked the phosphorus atom in a transannular reaction.[66]

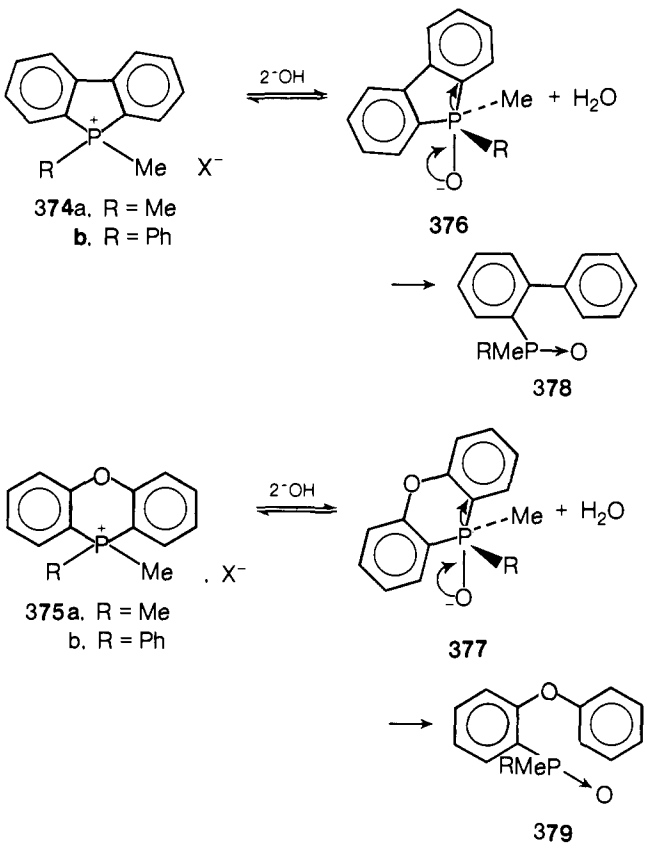
Additional evidence for the aromatic character of certain phospholes was provided by Mislow[100] from a study of the rate of retro-cyanoethylation (induced by sodium methoxide) of phospholium salt **369** and phosphonium salts **370, 371, 372,** and **373** via UV analysis of the reaction. The process exhibited

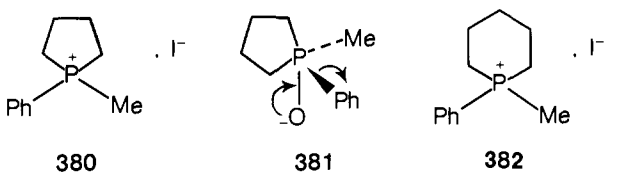



R = $CH_2CH_2CN$; anion = $SbF_6^-$

second-order kinetics. Comparison of the rate data at 41.6 °C strongly suggested an accelerating effect for **369** relative to other phosphonium salts **370–372.** The enormous rate increase depended on the assumption that the rate-determining step involved heterolysis of the P–C bond with concurrent delocalization of the lone pair on phosphorus in the resulting phosphole.[100]

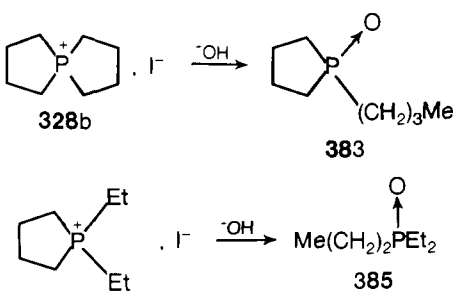
Allen and Millar[11-13] examined the kinetics of alkaline hydrolysis of a few phosphonium salts in which the heterocyclic ring was cleaved and compared the data with the reported hydrolysis of simple salts in which the ring was preserved with an interesting result. The systems employed were 9-phosphoniafluorene **374** and phenoxaphosphonium salts **375,** which underwent cleavage with hydroxide ion. Both phosphonium salts followed a third-order rate law which implied that the rate-determining step involved the collapse of the phosphorane intermediates **376** and **377** respectively to give oxides **378** and **379.** The relative rates of hydrolyses of the two salts **374** and **375** were not significantly higher; the phosphoniafluorene salt **374** hydrolyzed only twice as fast as phenoxaphosphonium salt **375.** Aksnes[4,5] had earlier reported that the phospholanium salt **380** hydrolyzed 1300 times more rapidly than the phosphorinanium salt **382** and interpreted this vast difference of the rates in terms of relief of eclipsing strain present in **380** or a result of interaction of the ring $\alpha$-hydrogens with the methyl and phenyl rings attached to phosphorus on forming the trigonal-bipyramidal intermediate **381.** Furthermore, the phosphorus atom in the almost planar five-membered ring was more accessible for attack by hydroxide due to restricted rotation of the exocyclic substituents. The activation parameters for the salts **374**a and **375a** (for the process in which the ring was cleaved) were found to be 18.9 and 21.8 kcal/mol, respectively. Comparison of activation energies with the reported values of 37.6 and 38 kcal/mol for the cyclic salts **380** and **382,** respectively (in which the ring was preserved), led to the inevitable conclusion that ring cleavage was associated with lower activation energy than those in which the ring was preserved. Moreover, apical attack and apical departure observed with the heterocyclic salts **374** and **375** were energetically more favorable than apical attack and equatorial cleavage



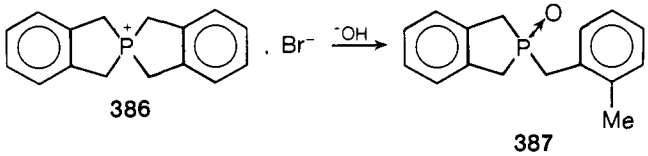




suggested for the simple salts **380** and **382.**[4,5,12,13] Basic hydrolysis of phosphonium salts and esters of phosphorus acids has been specifically dependent upon the electronic environment around the phosphorus atom. Since $^{31}P$ NMR shifts in simple systems have been related to the electron density around the phosphorus atom,[126e] surprisingly a systematic investigation by the same workers did not reveal a correlation between rates of hydrolysis of **374a** and **375a** with their $^{31}P$ NMR chemical shifts.[16]

Hydrolysis of the spirophosphonium salt **328b** to afford the corresponding phosphine oxide **383** has been reported by several groups.[76,77,88,152] For purposes of comparison, the monocyclic salt **384** cleaved to furnish the major acyclic oxide **385.** Preliminary rate measurements indicated the spiro salt **328b** hydrolyzed at a considerably higher rate than the representative five-membered, cyclic salt **384.** The enhanced rate was considered as a consequence of relief of steric strain present in the spiro salt **328b** in forming the pentavalent intermediate. Although the preferred geometry of the pentavalent intermediate was a

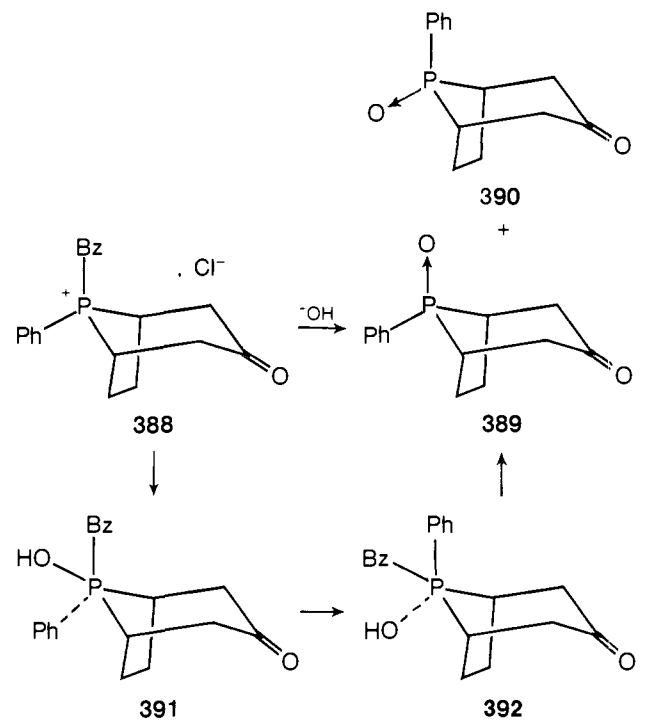


trigonal bipyramid in most cases, this need not be the case with spiro systems lacking fused rings since such an intermediate would require diequatorial bonding of one of the heterocyclic rings. Unfortunately, kinetic data on many spiro systems have not been available although the cleavage of the salt **386** to the oxide **387**, somewhat related to **328b**, has been effected.[295]



386 387

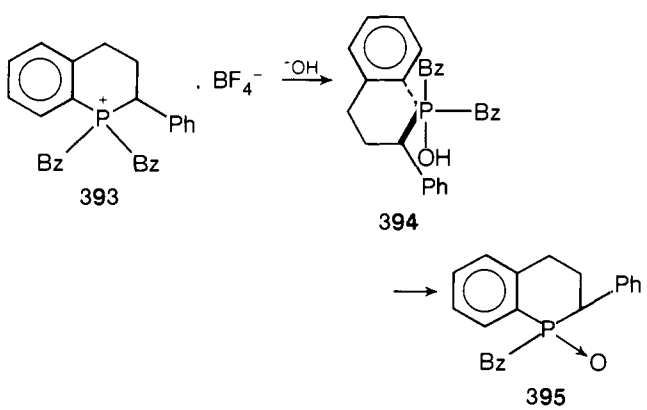
An unusual example of hydrolysis of a rigid system **388** was reported by Kashman,[193] who noted retention of configuration in the major oxide **389** [(90%) formed along with isomeric **390**]. Rigidity of the ring system **388** would have expectedly inhibited



390 + 388 389 391 392

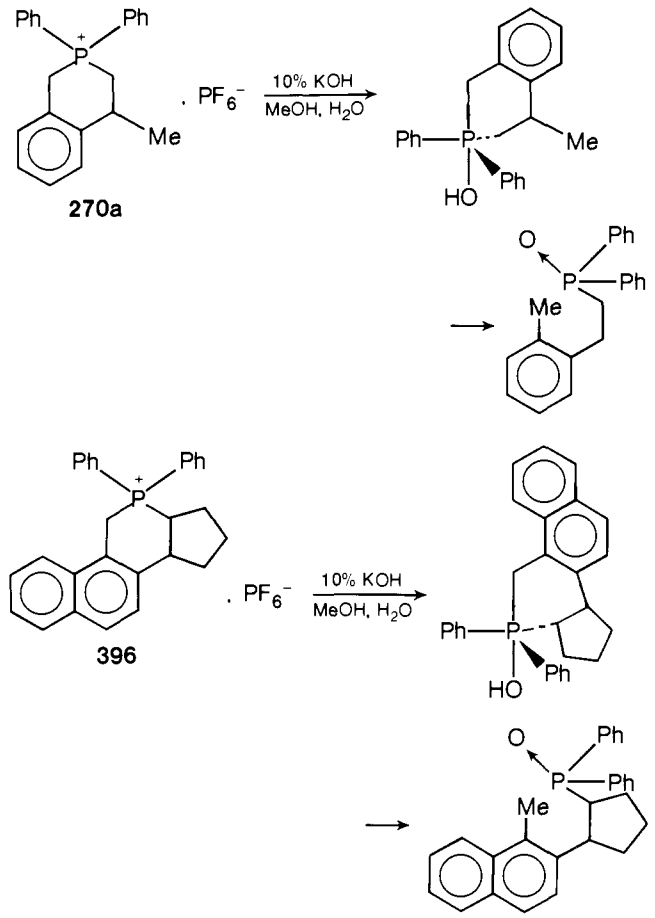
a linear arrangement of the hydroxide and the departing benzyl group in the trigonal-bipyramidal intermediate. Apical introduction, pseudorotation **391** → **392**, and apical departure of the benzyl anion were suggested to account for the formation of the major oxide **389**.

For the hydrolysis of 1,1-dibenzyltetrahydro-2-phenylphosphonianaphthalene tetrafluoroborate (**393**), a diequatorial placement of a six-membered ring in a trigonal bipyramid **394** was favored by Märkl.[239] The product was oxide **395** (100%). The preservation of the benzylic carbon–P bond in the ring was rather striking.



393 394 395

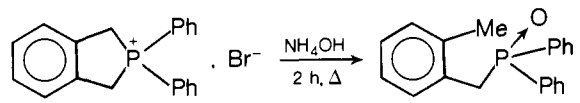
Polycyclic carbon–phosphorus heterocycles **270a** and **396** gave benzylic–P cleavage.[90] Since only one $ArCH_2$–P bond was present in both cases (compared to **393**), apical departure of the



270a 396

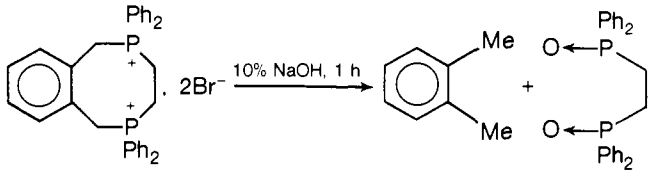
benzylic type group would require an apical-equatorial bonding of the six-membered ring to P. Thus, it would appear that apical–equatorial or diequatorial bonding to P in a trigonal bypyramid involving a C–P heterocycle may be accommodated in a six-membered system.

A vast majority of the phosphonium salts have been cleaved with either aqueous alkali or alcoholic alkali. A cleaner conversion of an isophosphindolinium salt **397** to the oxide **398** (82%) was reported with 10% ammonium hydroxide.[320]



397 398

An elegant attempt has been made to rationalize all data pertaining to base decomposition of certain biphosphonium salts from the standpoint of mechanisms, rates, intermediates involved, and the nature of products formed.[44,75] Bisphosphonium salts were found to follow the same kinetic pattern encountered with acyclic salts, i.e., rate ≈ $[^-OH]^2[salt]$.[44] When the salt was employed in excess, the expected second-order rate law was realized, indicating clearly that the pathways were different. For example, the different products in the hydrolysis of the bis salts **399** and **400** with excess alkali were discussed in terms of nonbonded interactions in the trigonal bipyramids resulting from the attack of hydroxide on both the phosphorus atoms.[3] Because of the considerable flexibility presumed in the eight-membered ring in **399**, a linear arrangement of the hydroxyl group with a benzyl carbon atom or a bridge carbon atom at both the phosphorus centers in the bipyramids was probably permitted. Examination of the molecular models indicated no severe nonbonded interactions between the ortho hydrogens of the phenyl



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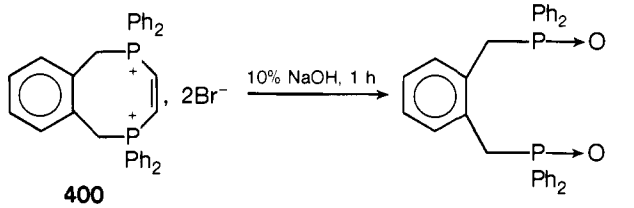
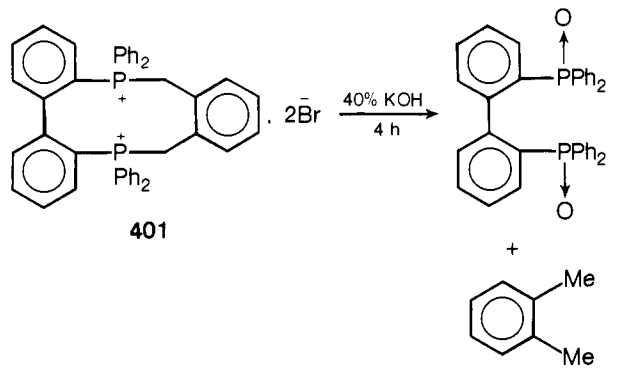


400

ring on phosphorus and the methylene hydrogens when the hydroxyl group and benzyl carbon atom occupied apical positions. The interactions were less severe when the bridge carbons were apical. Subsequent decomposition of **399** took place at each center with the loss of the more electronegative benzyl groups. The situation, however, appeared different with the unsaturated bis salt **400.** In the trigonal bipyramids, loss of either both bridge carbons or both benzyl groups from the sterically crowded molecule would relieve strain and was suggested to be the overriding factor for the exclusive expulsion of the bridge fragment.[44]

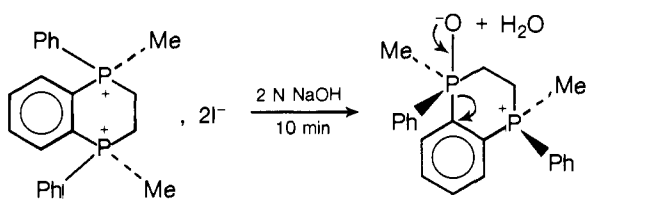
A similar argument was put forth for the large salt **401.** The



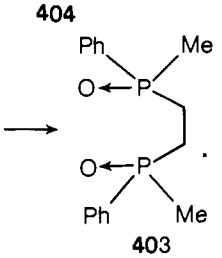
401

latter has been reported[11] to undergo smooth cleavage with alkali.

Hydrolysis of 1,4-benzodiphosphorin **402** with aqueous sodium hydroxide has been shown to yield ethylenebis(methylphenylphosphine oxide) (**403**) as the sole product (82%).[228] Exami-

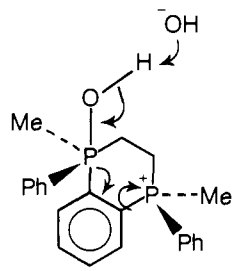


402 404



403

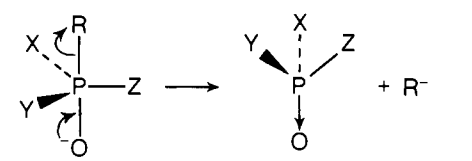
nation of molecular models suggested that the preferred direction of attack by the hydroxide ion was collinear with the P–phenylene bond. Consequently, a trigonal bipyramid **404** in which the hydroxyl group and the P–phenylene bond occupied apical positions was favored. Subsequent decomposition of **404** proceeded with the elimination of the phenylene group as an anion followed by conversion of an unknown intermediate to **403.** The bis(phosphine oxide) **403** system has two dissymmetric phosphorus atoms and was in reality a mixture of (±) and meso isomers. Which of the two isomers was the meso form and which was the racemate could not be distinguished. However, isolation of this mixture enabled the authors to discard an alternative concerted mechanism for the hydrolytic cleavage which would be expected to provide only the meso bis(phosphine oxide)[228] as might arise from intermediate **404a.**



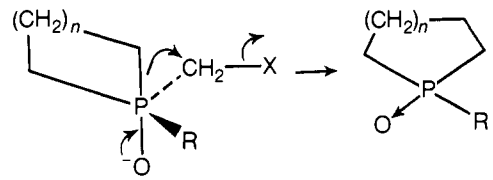
404a

## B. Ring Expansion and Ring Opening

Evidence has been accumulated to indicate that the alkaline hydrolysis of a phosphonium salt proceeds through a trigonal-bipyramidal phosphorane intermediate **350** in many in-



350

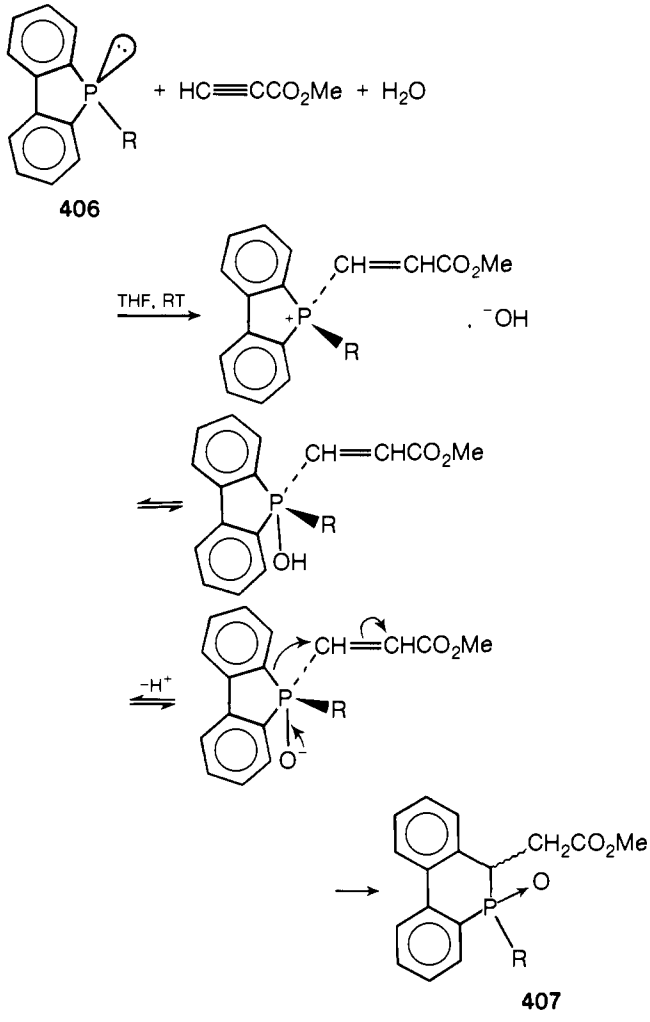


405

$n = 1, 2$

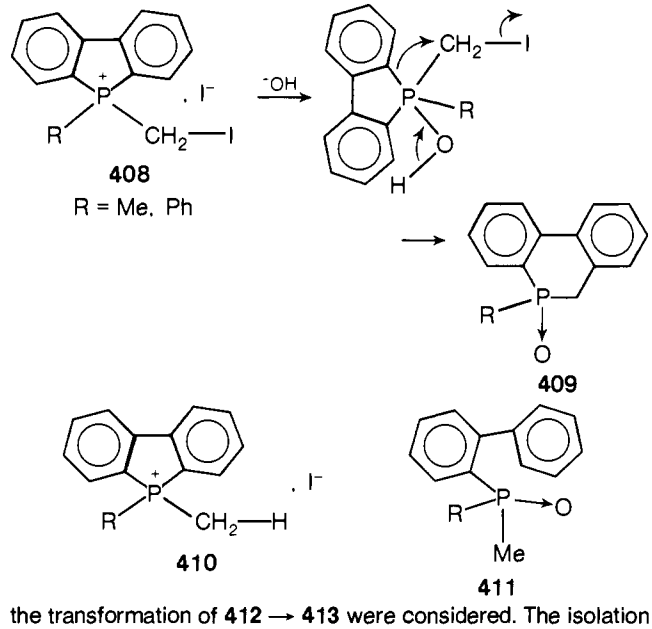
stances.[113,114,178,351] The more electronegative substituents attached to phosphorus tend to exhibit a preference for apical positions. Phosphorane **350** may pseudorotate and the most electronegative group (R) may be expelled as the anion from the apical position.[104,249] However, when the phosphorus atom was present in a small strained ring such as **405** ($n$ = 1 or 2), the pseudorotation process was relatively slow. Thus, the ring system was constrained to occupy an apical-equatorial arrangement,[99,249] and, in such cases, ring expansion usually occurred owing to relief of steric strain with migration of a pair of electrons in the ring to form a bond with the $\alpha$-carbon atom with concomitant expulsion of a group X.

Tebby[15,292] reported the reaction of 9-methyl-9-phosphafluorene (**406,** R = Me) with methyl propiolate and water in THF at 20 °C to 9-methyl-10-(methoxycarbonylmethyl)-9,10-dihydro-9-phosphaphenanthrene 9-oxide (**407,** R = Me). This gave the first example of the ring expansion of 9-phosphafluorene to 9-phosphaphenanthrene. In subsequent papers,[294] it was demonstrated that the ring expansion occurred (under reflux conditions) even when the substituent on the phosphorus was expected to compete in the 1,2-migration (**406,** R = Ph, Bz). The following mechanism was suggested.[294]




Subsequent to this discovery, several groups of workers[10,13,14,137,249] reported similar ring expansions in the alkaline hydrolysis of a number of suitably substituted phosphoniafluorene quaternary salts **408** (R = Me, Ph) to give **409.** This phenyl-to-carbon migration had been first observed in an open-chain system, i.e., with $(C_6H_5)_3P^+CH_2Br,Br^-$ when subjected to alkaline hydrolysis.[305] That the need of a good leaving group on the $\alpha$-methylene carbon was mandatory was noted in the alkaline hydrolysis of **410** (R = Me, Bz). Only the oxide **411** was identified.[10] A study of $J_{PCH}$ couplings of relatives of **408** and **410** was reported along with open-chain analogs.[14]

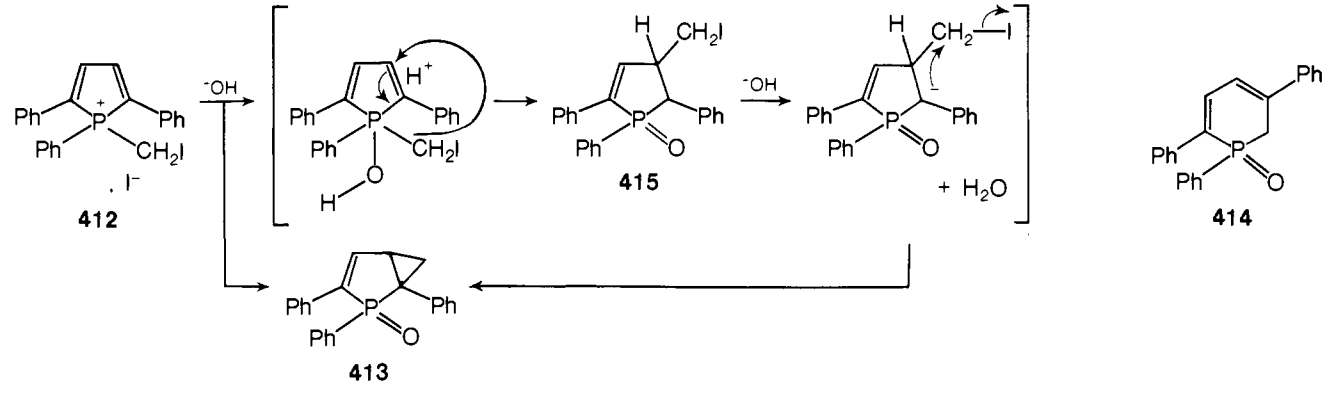
An unusual ring expansion was recorded by Hughes and Srivanavit[179,180] when the phosphonium salt **412** was boiled with aqueous methanolic sodium hydroxide for 24 h. A good yield (74%) of phosphabicyclo[3.1.0] oxide **413** was realized instead of the expected phosphine oxide **414.** Several mechanisms for

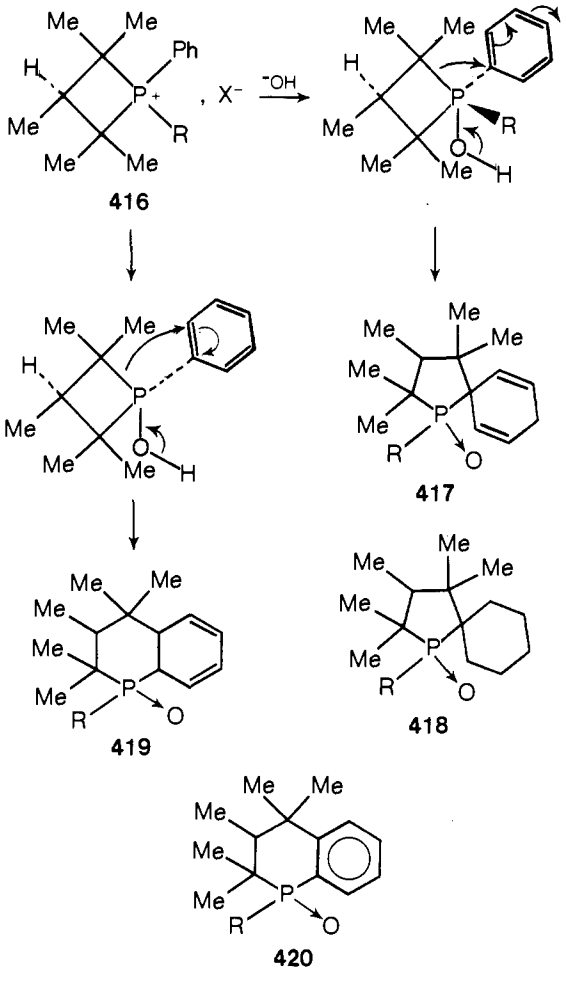



the transformation of **412** → **413** were considered. The isolation of intermediate **415** when the reaction was performed under milder conditions, and the subsequent conversion **415** → **413,** suggested the mechanism in Scheme II.

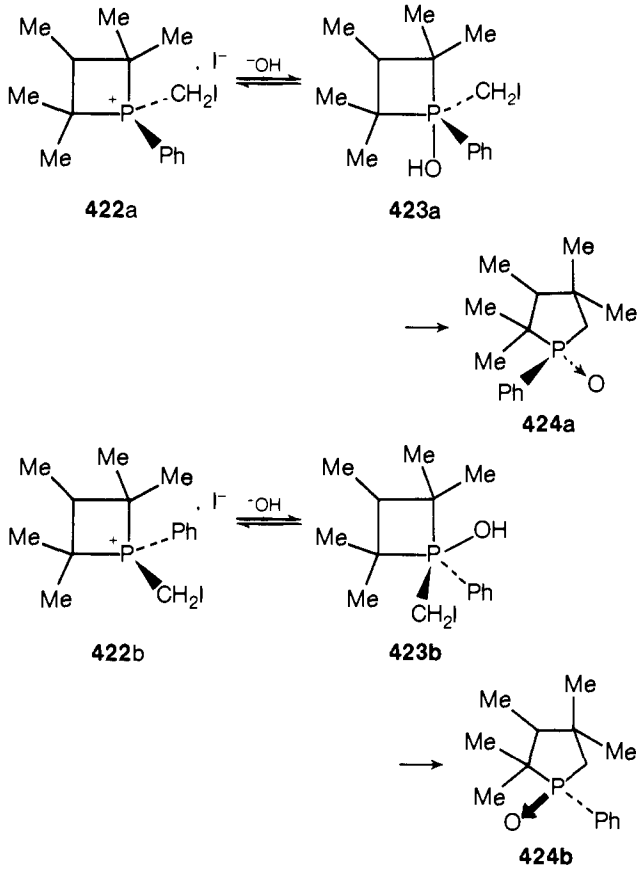
Trippett and co-workers recorded in a series of papers[17,69,104,137,138] the facile ring expansion of certain phosphetanium salts when the latter were subjected to alkaline hydrolysis. For example, the phosphetanium salt **416** (X = I) gave a high yield (88%) of a phosphine oxide upon alkaline hydrolysis.[104] The spiro structure **417** was assigned to the phosphine oxide on the basis of spectral data. The IR spectrum lacked the features expected of phenyl attached to phosphorus (1440 $cm^{-1}$)[331] and of monosubstituted phenyl. Moreover, the UV spectrum was devoid of aromatic absorption or that absorption expected for a cyclohexa-1,3-dienyl system. The $^1H$ NMR spectrum indicated the absence of aromatic protons. The phosphine oxide absorbed 2 mol of hydrogen on catalytic hydrogenation and gave a saturated oxide **418.** A mechanism consistent with all of the data was proposed. Shortly after this work was published, Cremer and Chorvat[72] repeated the experiment with the salt **416** (X = Br) and proposed an alternative structure **419** for the phosphine oxide since tetrahydrophosphinoline **420** was obtained on dehydrogenation. Deuterium-labeling experiments by Cremer[71,74] and subsequently by Hawes and Trippett[138] helped to discard the conjugated diene structure **419** in favor of the spiro structure **417** for the ring-expanded product. The spiro-fused structure **417** for the rearranged product has now been anchored by x-ray analysis.[45] It may be mentioned that the structure of the product of dehydrogenation of **414,** namely **420,** has also been proved by x-ray data.[139] It was considered likely that the oxide **417** rearranged to **420** under the conditions of dehydrogenation.

SCHEME III



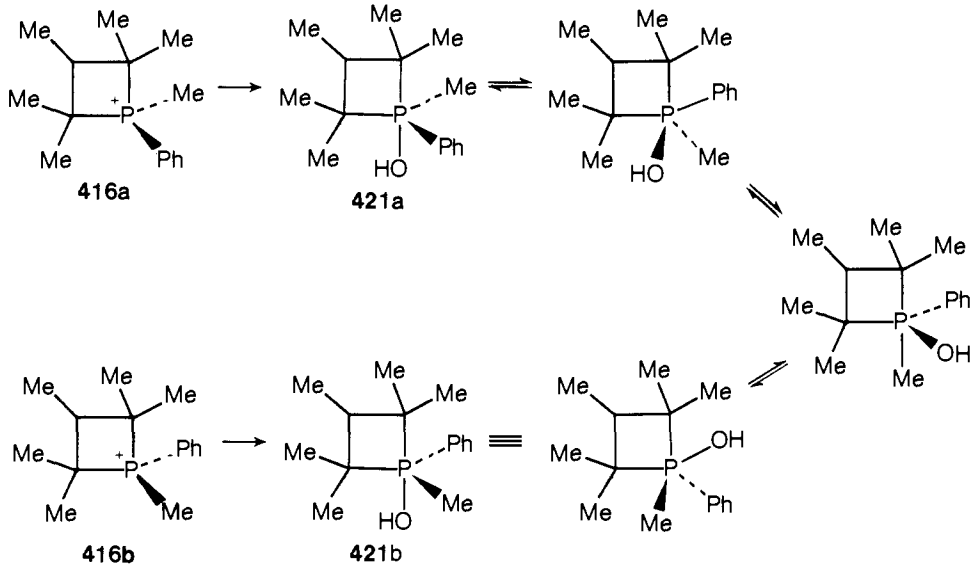


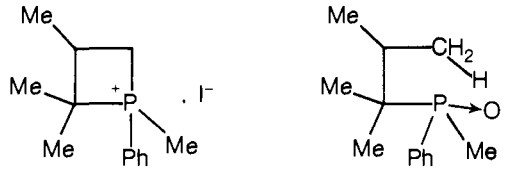

The phosphetanium salt **416** can exist as geometrical isomers **416a** and **416b** and both the cis and trans isomers gave the same oxide **417** upon alkali treatment. Trippett[17,137] proposed that the probable pentavalent phosphorane intermediates **421a** and **421b** were sufficiently long-lived to pseudorotate, thereby equilibrating the geometric isomers which resulted in a loss of stereospecificity in the overall reaction. In contrast, hydrolysis of the *cis*- and *trans*-iodomethylphosphetanium salts **422a** and **422b** proceeded with retention of configuration in the oxides expected from ring expansion.[17] That migration of the apical $-C(CH_3)_2$ was faster than the equilibration of the phosphoranes **423a** and **423b** by a pseudorotation process was indicated by the isolation of



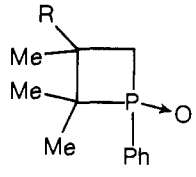

cis, trans isomers **424a** and **424b.** Few other well-defined examples of ring expansion and ring opening in the phosphetane family can be found in the literature.[69,103] However, when *gem*-dimethyl groups were absent at the **4** position of a phosphetane, as in **425**, the C–P ring opened to give the oxide **426.**[103] An identical process occurred with the corresponding oxides **427** (R = H, Me) at 100 °C in 10 N sodium hydroxide to yield open-chain oxides **428** (R = H, Me).[69] Surprisingly, both isomers of **429** were inert to these severe conditions.[69] To be sure, many acyclic phosphine oxides require fusion with sodium hydroxide before reaction can proceed with concomitant loss of the group which has the most stable anion precursor.[171]

Ring expansions for the moment have appeared to be unique to small-ring phosphorus compounds. Attempts[12,13] to effect similar ring expansions in six-membered ring system (**430** and **431**) resulted either in the cleavage of the ring or expulsion of




425


426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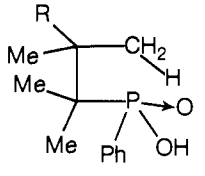
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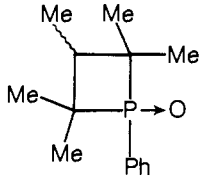
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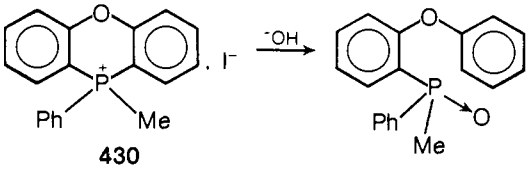
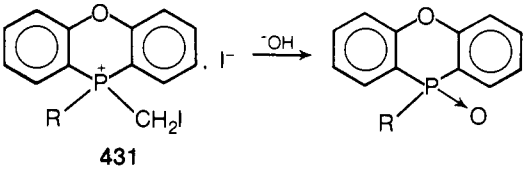

430 379b

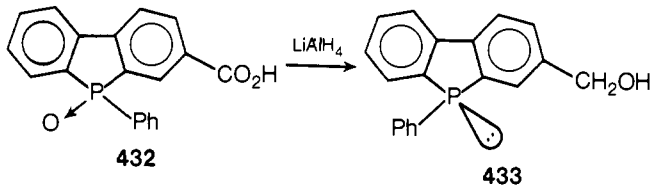

431

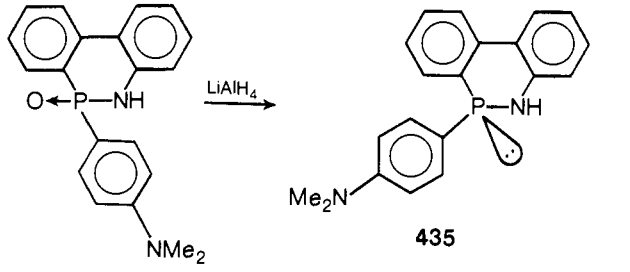
a group. Other related examples of hydrolytic cleavage have been discussed in section III.A. To date, ring expansions with six-membered systems containing only carbon and phosphorus have not been found although an examination for this type of trial experiment with negative results may have escaped our search.

## C. Reduction

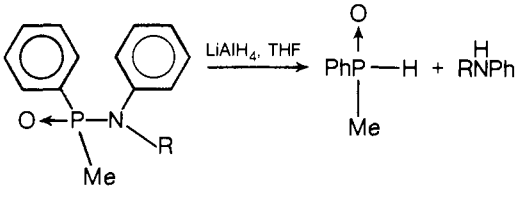
Reduction of phosphine oxides can provide an easy route to the corresponding phosphines, otherwise difficultly accessible. Reductive methods[109,216] that have been employed include the metal hydride reduction, the cathodic reduction, and the use of silicon compounds, particularly in simple alicyclic and acyclic systems.

Among the hydride reagents, $LiAlH_4$[50,51,104,162,267] and calcium hydride[108,109] were used to deoxygenate phosphine oxides in the early developments but have now been heavily supplanted by the superior members of the silane family.[32,109,216] A major drawback with $LiAlH_4$ was in the reduction of optically active phosphine oxides which afforded phosphines of low optical purity due to rapid stereomutation.[162] For instance, Campbell and Way[51] employed $LiAlH_4$ to reduce optically active **432** but obtained racemic **433.** In contrast, the optically active phosphine oxide **434** was reduced to the optically active phosphine **435** with retention of configuration at phosphorus.[50] which, incidently, was the first example of a compound whose optical activity could be attributed to a pyramidally stable trivalent phosphorus.[50,162] This incredulity led Mislow and co-workers to examine the factors responsible for the racemization in the case of oxide **432** and absence of racemization in the case of **434.**[162] The data


432 433

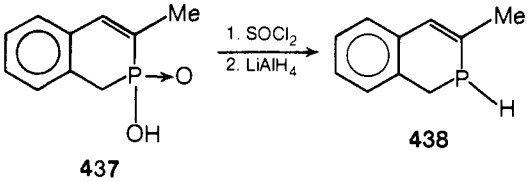

434 435

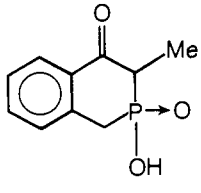
obtained by the reduction of an optically active acyclic phosphine oxide (+)-methylphenyl-*n*-propylphosphine oxide with $LiAlH_4$ clearly indicated that racemization of the phosphine oxide was virtually complete before more than 10% had been reduced to the phosphine. It was suggested that reversible addition of $LiAlH_4$ to the phosphine oxide, followed by pseudorotation of the phosphorane intermediate and subsequent dissociation to phosphine oxide and $LiAlH_4$, could account for the observed stereomutation of **432.** The absence of racemization in the case of **434** was attributed to the influence of the electron pair on the neighboring NH group.[162] Very recently, $LiAlH_4$ reduction of the two phosphinanilides **436a** and **436b** at room temperature for


436a, R = H
b, R = Me

varying periods of time were recorded and revealed that **436a** and **436b** were stereochemically stable under the above-mentioned conditions.[163] However, at higher temperatures, P–N bond cleavage occurred rather than the deoxygenation of the P=O group. The observed stability and stereochemistry in the reduction of **434** with $LiAlH_4$ was suggested to be the probable result of restraints imposed by the azaphosphorus ring system as well by the neighboring NH group.[163]

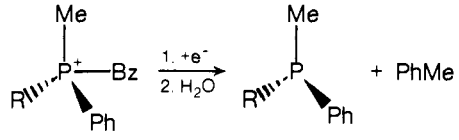
In limited cases only, $LiAlH_4$ has been employed in the reduction of certain phosphinic acids to the corresponding secondary phosphines (**437** → **438**) via the corresponding acid chloride. However, yields were only modest (21%).[117,224] $NaBH_4$


437 438


439

in $H_2O$ reduced the C=O and *not* the P=O group in acid **439**, the precursor of **437**.[117]

Cathodic reduction of phosphonium salts of the type **440** was reported to give tertiary phosphines **441** in high yields.[175] Horner[172,173,175] pioneered the technique to obtain optically active tertiary phosphines from optically active phosphonium salts with net *retention* of configuration and high optical purity. For example, the salts **440** were resolved with acidic silver D-dibenzoyltartrate into the antipodes, and the benzyl group was eliminated as the anion by cathodic reduction to afford the corresponding optically active phosphine **441**. Difficulties in constructing an electrochemical cell to prepare the less accessible optically active phosphonium salts have rendered this method somewhat impractical.[253] Furthermore, the reduction itself was complicated by the anodic oxidation of the bromide or iodide ion to the corresponding halogen, which, in turn, may cause chemical oxidation of the phosphine.[253] No specific applications in the reduction of polycyclic phosphine oxides of the type covered in this review were uncovered in the literature search.



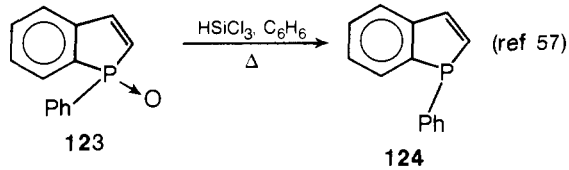

**440** **441**

a, R = Et; b, R = Pr; c, R = $CH_2CH{=}CH_2$

The marked facility of reduction of phosphonium salts by $LiAlH_4$ has been studied primarily in acyclic systems.[267] Optically active, benzyl-substituted salts gave racemic phosphines under conditions where such phosphines were reported optically stable.[162,267] In view of the recovery of optically pure (+)-benzylmethylphenyl-*n*-propylphosphonium bromide from the reducing mixture of $LiAlH_4$ in THF at room temperature, a pseudorotation process involving a presumed phosphorane intermediate has been suggested.[162] No such studies have been conducted with polycyclic C–P heterocycles that we could find.

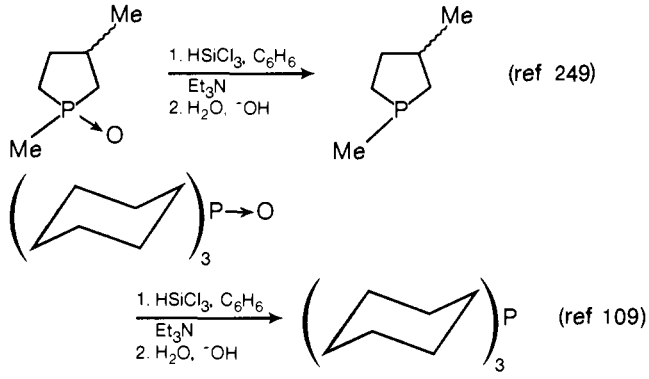
The use of organic and inorganic silicon compounds has been recognized as the simplest and most direct approach to reduce phosphine oxides to the corresponding phosphines.[109,216] Among the silicon compounds tried, trichlorosilane, hexachlorodisilane, perchloropolysilane, phenylsilane, and diphenylsilane have been extensively employed by numerous investigators (ref 32, 73, 84, 108, 109, 170, 213, 216, 273, 274) in simple alicyclic and acyclic systems. The literature abounds with plenty of examples, and the reductive procedure adopted has been described in section II. In this section, only the relative merits of the commonly used silicon members together with any unusual behavior will be briefly discussed. It is worthy of note that trialkylsilanes in trifluoroacetic acid have been employed to reduce the carbonyl group of aryl compounds to methylenes.[350]

Trichlorosilane has been the most widely employed reagent among the silanes to effect reduction of phosphine oxides to the corresponding phosphines. The reaction can usually be carried out by heating the phosphine oxide and excess trichlorosilane in an inert solvent (commonly benzene) for varying periods (2–3 h) followed by an aqueous alkali treatment. The phosphines, produced generally in good yields (70–90%), may be isolated in pure state or, if air sensitive, can be directly transformed into a stable salt. Some examples were given in section II dealing with the reduction of oxides to phosphines such as **123** to **124**.

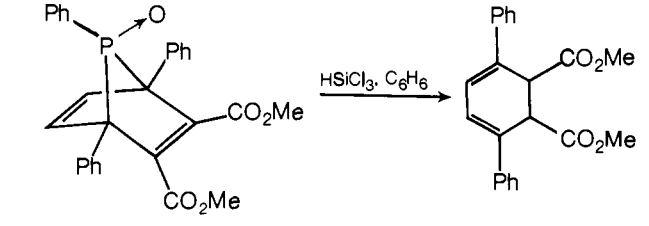



**123** **124**

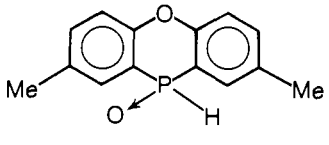
A few other examples from simple systems illustrate only a small fraction of available cases. The subject, including the mechanism, has been discussed.[270,274]



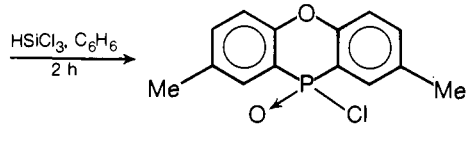

Only with a few polycyclic systems has a novel reducing role of trichlorosilane been encountered.[54,123,197,309] Although the mechanisms operating in **442** → **443** and **444** → **445** were not clear, it was assumed that the reduction of the phosphinate in **446** → **447** followed the standard mechanism for reduction of phosphine oxides.[274]



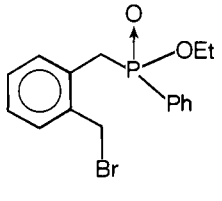

**442** **443**



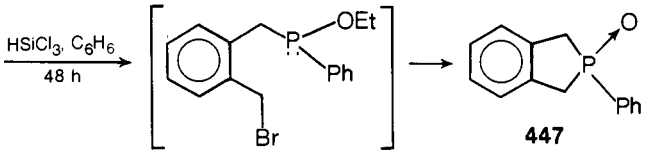

**444**




**445**



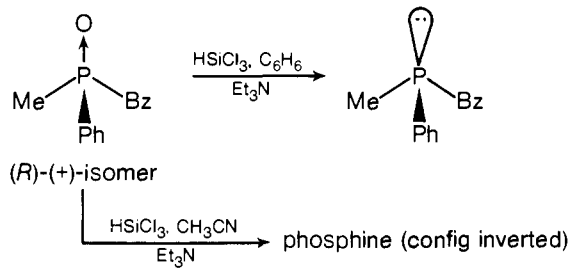

**446**



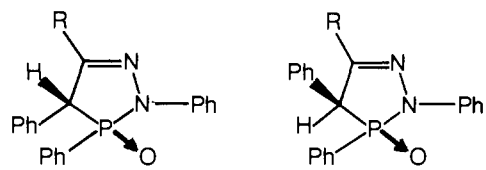

**447**

The stereochemistry of the reduction of phosphine oxides with trichlorosilane was investigated by Horner and Balzer[170] and later by Mislow and co-workers[274] which culminated in useful generalizations.[270] Optically active phosphine oxides could be reduced by trichlorosilane to phosphines with net *retention* of configuration and in high optical yield. In the presence of weak bases ($pK_b$ > ca. 7) like $C_5H_5N$, $Et_2NPh$, etc., phosphine oxides gave phosphines with predominant retention of configuration. In the presence of strong bases ($pK_b$ < ca. 5) like $Me_3N$, $Et_3N$, etc., the stereochemical outcome was inversion.[274] Also, the

optical purity of the phosphine formed was solvent dependent. By appropriate choice of the conditions, enantiomeric phosphines can be prepared in high optical yield.[274] An example in a simple system is illustrative.[274] A comprehensive and critical evaluation of the pyrimidal inversion process on phosphorus in phosphines has been reviewed.[270] The use of DNMR to study the inversion barriers for many simple systems was summarized.[290]



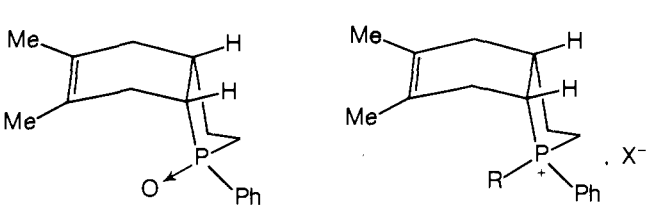

The lack of stereospecificity in trichlorosilane reductions has been recently noted with the pure diazaphospholene oxides **448** and **449.**[26] Stereomutation of the initial phosphine oxides by the




a, R = Ph; b, R = Bz

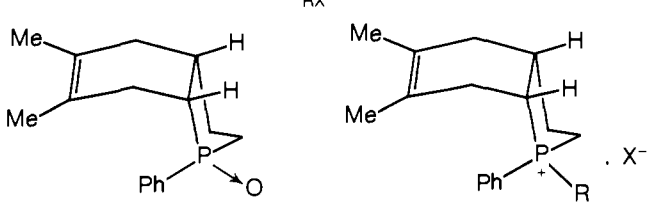
reductant by-products ($SiCl_4$, $Si_2OCl_6$, $(OSiCl_2)_n$) was suggested to occur. A pentacoordinate intermediate, as was considered with $LiAlH_4$, was invoked to explain stereomutation.[26,274]

Mislow and co-workers[273,274] introduced $Si_2Cl_6$ and octachlorotrisilane as effective reagents for the reduction of phosphine oxides to phosphines. The reaction, usually carried out in boiling benzene or in chloroform at room temperature, gave high yields (70–90%) of phosphines. Acyclic phosphine oxides were reduced with predominant inversion of configuration, whereas small-membered cyclic oxides were reduced with retention of configuration. The optical purity of the phosphine, however, depended on the time of contact with hexachlorodisilane.[273,274] Also, the amount of stereomutation of products in the reduction process was dependent upon the contact time with $Si_2Cl_6$.[271] For example, the bicyclic phosphine oxides **357** and **358** were reduced with $Si_2Cl_6$ in benzene, and the resulting phosphines were directly quaternized with methyl iodide and/or benzyl bromide to furnish a mixture of isomeric phosphonium salts **450a,b** and **359a,b,** possibly in the same ratio as **357:358.** The ratios of **450a:450b** and **359a:359b** were estimated for each isomer from the areas of protons in the P-$CH_3$ and P-$CH_2$ groups in the $^1H$ NMR spectra. The results clearly indicated the dependency of the stereomutation of the products with contact time of reagents.[271]




**357** **450a**, R = Me; X = I
**359a**, R = Bz; X = Br

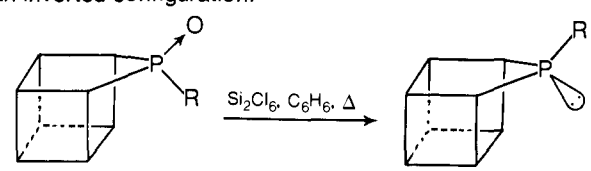
or $Si_2Cl_6$, $C_6H_6$, RX +



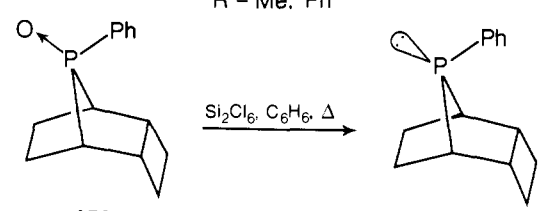

**358** **450b**, R = Me; X = I
**359b**, R = Bz; X = Br

| Time $Si_2Cl_6$ | Ratio 450a:450b | Ratio 359a:359b |
|---|---|---|
| 12 min | 10:1 | — |
| 15 min | 7:4 | 2:1 |
| 120 min | 3:2 | 3:2 |

The effectiveness of $Si_2Cl_6$ in reduction of a few angle-strained phosphine oxides **451** and **452** has been reported.[201,336,338] The simple system (*R*)-(+)-benzylmethylphenylphosphine oxide also gave the corresponding phosphine with inverted configuration.[274]

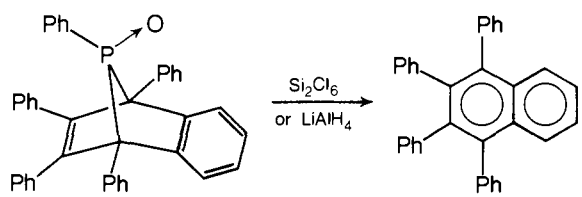



**451** **453.**




**452**

A rare example of an elimination of the P=O group from the oxide **454** during an attempted reduction with $Si_2Cl_6$ (or $LiAlH_4$) has been recorded.[327] The exact mechanism has not been clarified.

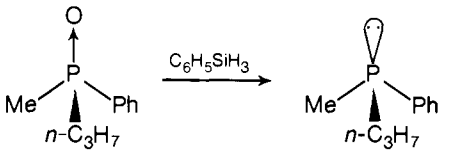



**454**

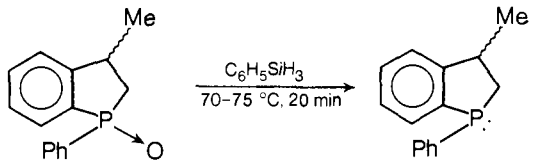
Perchloropolysilanes of the general formula $Si_nCl_{2n+2}$ may also be employed in the deoxygenation of phosphine oxides with predominant inversion of configuration. Again, Mislow and coworkers[274] have shown that such species were probably involved even in the reduction of phosphine oxides with $HSiCl_3$ in the presence of a strong base. In view of the ready availability of the lower members of the perchloropolysilane series, no work describing the deoxygenation of cyclic phosphine oxides with these reagents has been uncovered.[274]

Quite recently, Marsi[253] investigated the advantages of employing phenylsilane for the deoxygenation of phosphine oxides over the other silanes. Although the reducing property of phenylsilane was discovered by Fritzsche a decade earlier,[108] Marsi[253] carried out a systematic study of the stereochemical outcome of the reductions. Several acyclic and monocyclic phosphine oxides were successfully reduced in yields varying from 85 to 96%, and in all cases the reduction took place with net retention of configuration.[256] The reduction was usually performed by mixing the phosphine oxide and phenylsilane without a solvent under $N_2$ in a ratio of 3:2. Excess phenylsilane (bp 120 °C) was removed under reduced pressure, and the pure

phosphine was vacuum distilled. Siloxane polymers were nonvolatile and formed the pot residue. Phenylsilane has been available commercially or can be easily prepared from phenyltrichlorosilane by $LiAlH_4$ reduction.[33] An example has been illustrated for clarity.[253] Reduction of diastereomers of 3-

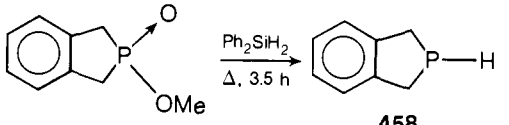



methyl-1-phenylphosphindoline oxide (**455**) with phenylsilane has been reported to give a near-quantitative yield of the diastereomeric phosphines **456.**[97]

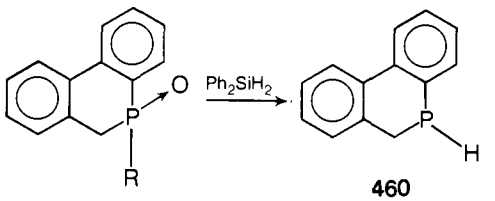



**455** **456**

Diphenylsilane has been used to reduce phosphinic acids or phosphinates to phosphines.[213,295,297] For example, reduction of **457** with neat diphenylsilane gave isophosphindoline **458** in a yield of 98%.[295] Similar reductions of the tricyclic phosphinic acid **459a** yielded the phosphine **460** (92%).[224,297] It should be mentioned here that Lynch[224] was unsuccessful in reducing the acid chloride **459b** with $LiAlH_4$ to **460,** whereas the methyl ester **459c** was reduced in low yield and was then converted to the dimethiodide.[297] Interestingly, the chloride **459b** could be reduced to the secondary phosphine oxide of **460.**[224]




**457** **458**



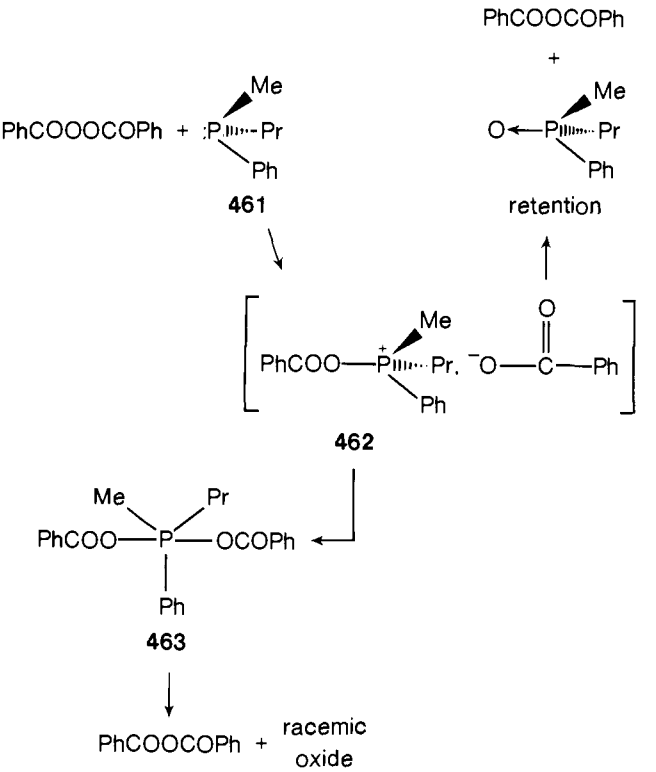

**460**

**459a**, R = H
**b**, R = Cl
**c**, R = OMe

## D. Oxidation

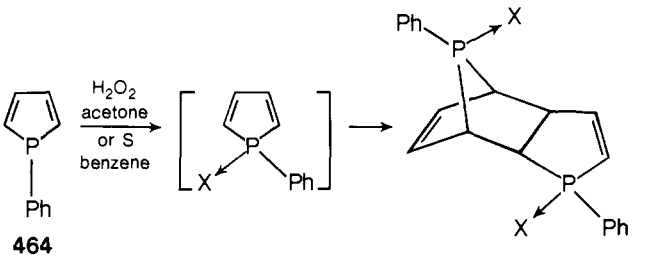
Oxidation has been a most common technique employed in organophosphorus chemistry for identifying phosphines as the corresponding phosphine oxides. Almost all the well-known oxidants, both organic and inorganic, have been used for this purpose.[216] Hydrogen peroxide has remained the most widely used reagent and in various strengths (1–30%) both in homogeneous and heterogeneous media. The yields were often near quantitative. Some phosphines were so readily oxidized in air that isolation in a pure state was precluded. The relative ease of oxidation depended on the electronic as well as steric factors around the phosphorus atom.[216] In general, phosphines bearing alkyl substituents have a greater propensity to undergo oxidation than those carrying aryl substituents.[216]

That the oxidation of simple tertiary phosphines with hydrogen peroxide, *tert*-butyl hydroperoxide, and atmospheric oxygen proceed, in general, with retention of configuration at phosphorus has ample precedent in the literature.[26,52,87,169,200,216] In an impressive study, Horner and Winkler[174] demonstrated that extensive racemization of the phosphine oxide occurred in the oxidation of (+)-methylpropylphenylphosphine (**461**) with benzoyl peroxide in different solvents and increased with the polarity of the solvent. To accommodate these findings, a mechanism involving initial formation of the ion pair **462** was suggested. While dissociation of the ion pair **462** accounted for the retention, combination of the anion with the P atom in the ion pair **462** resulted in a symmetrical trigonal-bipyramidal intermediate **463.** Its subsequent dissociation had to be invoked to explain racemization.[174] One would expect polycyclic phosphines to behave similarly although no examples were found.



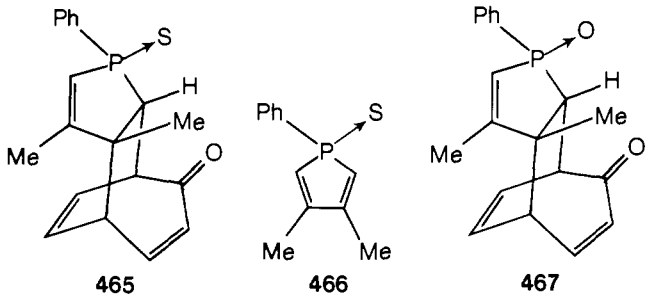

Conversion of tertiary phosphines with sulfur to phosphine sulfides (usually solids) has been yet another simple method available for the characterization of phosphines and has been assumed to proceed with retention of configuration.[64,65,69,216,299] Sulfurization of the optically active phosphine **461** with diphenyl sulfide at room temperature in toluene and/or acetonitrile proceeded with 46 and 94% racemization, respectively, and, here again, was explained in terms of a pentavalent intermediate.[174]

A case of dimerization during oxidation of phosphole **464** with hydrogen peroxide in acetone or on treatment with sulfur in boiling benzene was reported by Märkl.[246]




**a**, X = O; **b**, X = S

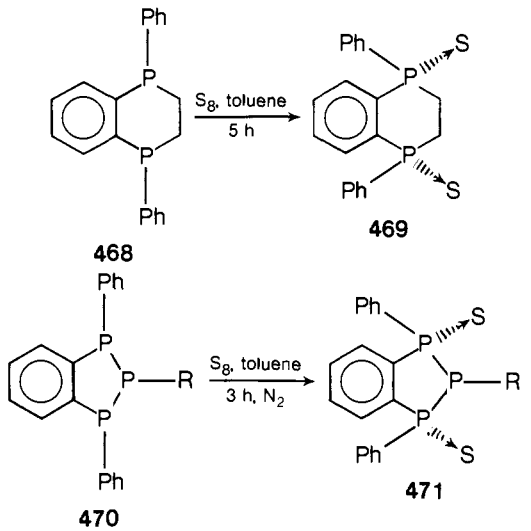
The conversion of phosphine sulfides to phosphine oxides probably can proceed with retention of configuration as has been observed with the corresponding phosphinates.[83] With Diels–Alder adduct **465,** obtained from reaction of equimolar quantities of 3,4-dimethyl-1-thio-1-phenylphosphole (**466**) and tropone in



465 466 467

2-pentanone at 100 °C for 4–6 days, the conversion to oxide **467** with 30% hydrogen peroxide in acetone was 85%. It was assumed that sulfide **465** and oxide **467** had the same relative configurations.[197]

Treatment of 1,4-benzodiphosphorin (**468**) with an excess of sulfur in toluene afforded the disulfide **469** (88%), presumably with retention of configuration.[228] In contrast, 2-methylbenzo-



468 469

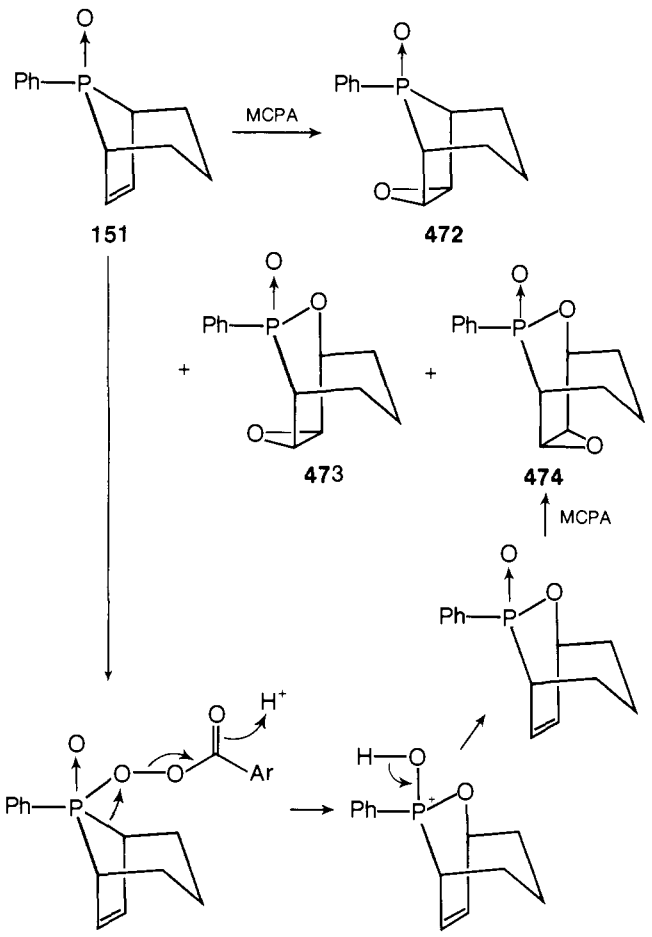


470 471

a, R = Me; b, R = Et; c, R = Ph

triphosphole (**470a**) reacted with sulfur (3 equiv) to afford a single crystalline disulfide **471a**, mp 154–155 °C, in a modest yield (48%).[228] Two distinct signals in the $^{31}P$ NMR spectrum (in $HCCl_3$) with a doublet at −60.6 ppm ($J_{PP}$ = 252 Hz) and a triplet at +77.5 ppm in a ratio of 2:1 coupled with mass spectral data permitted assignment of the product as symmetrical 1,3-disulfide **471a**. One would expect the central phosphorus atom to be more reactive toward sulfur because of electron-donating methyl group. Perhaps steric factors dictated the course of the reaction. However, the sulfurization with a large excess (more than 3 equiv) of sulfur was not investigated. Likewise, benzotriphospholes **470b** and **470c** reacted with sulfur.[228,230] In all these phospholes, sulfurization was assumed to proceed with retention of configuration.

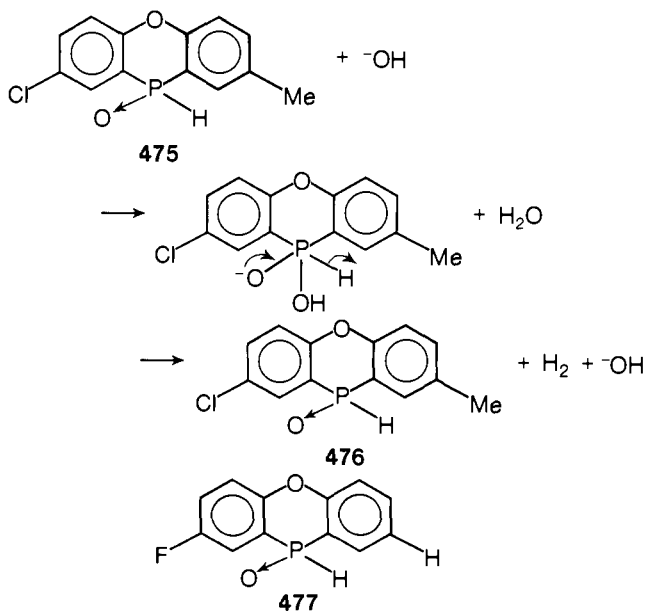
An unusual Baeyer–Villiger oxidation of a P=O group with peracid was noted by Kashman and Awerbouch[25,195] during the epoxidation of the double bond of phosphabicyclic phosphine oxide **151**. Use of a large excess of *m*-chloroperbenzoic acid (heating for several days) in polar solvents resulted in three compounds in low yields, i.e., the expected epoxide **472** and the phosphinates **473** and **474**. A mechanism involving the migration of an allylic carbon to the electron-deficient oxygen (very similar to Baeyer–Villiger oxidation of ketones) was suggested for the formation of the phosphinates **473** and **474**. The rearrangement was observed even when a methyl group (instead of a phenyl group) was present in an equatorial position of the phosphorinanone ring. It seemed that for such a migration to occur readily, a sterically hindered double bond was needed as in the oxide **151**. It was noted that the P epimer of **151** (which had a P=O



151 472 473 474

group in an equatorial position) underwent epoxidation even at room temperature.[25,195] Simple systems are known too.[316]

An unusual oxidation process was observed by Campbell and Stevens[49] when the secondary phosphine oxide **475** was treated with ethanolic sodium hydroxide or sodium ethoxide at room temperature and gave **476**. Hydrogen was evolved and the so-



475 476 477

dium salt of diphenylphosphinic acid **476** resulted. A mechanism involving attack of hydroxide on the P=O group followed by explusion of hydride ion (supported by labeling experiments) was put forward. Secondary phosphine oxides in the presence of base normally form phosphorus anions and behave as nucleo-

philes (either at phosphorus or oxygen).[35,279] The ability of **475** to act as an electrophile toward bases was remarkable. The conversion of the related oxide **477** with a secondary amine (dicyclohexylamine) to the dialkylammonium salt of an acid related to **476** (detected by other workers too[123]) also vouched for the dual character of these secondary phosphine oxides.

## E. Metalation Reactions

Alkali metal cleavage of a carbon–phosphorus bond in organophosphorus compounds has been another synthetically useful reaction occurring at the phosphorus atom. Usually, the cleavage was effected with Li, K, or Na in inert solvents such as THF, dioxane, toluene. The classic example involved cleavage of triphenylphosphine by lithium metal in THF. Although this cleavage had been known for many years, only Britt and Kaiser[42,43] examined this reaction critically via ESR spectroscopy and concluded that there were two distinct steps. The first step was a phenyl cleavage with the formation of metal diphenyl-

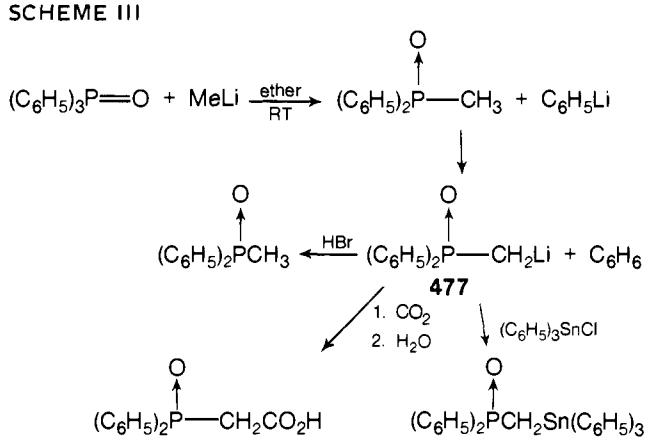
$$(C_6H_5)_3P + 2M \longrightarrow (C_6H_5)_2P\text{-}M + C_6H_5\text{-}M$$
$$(C_6H_5)_2P\text{-}M + M \longrightarrow (C_6H_5)_2P\text{-}M^{\cdot-} + M^+$$

phosphine and metal phenide. Radical anion formation could then occur in the subsequent step by the reduction of metallodiphenylphosphine with excess of metal. Only a few C–P heterocycles have participated in this type of study.

Metal phosphides formed by this procedure could be hydrolyzed, oxidized, or alkylated in situ to obtain a variety of useful organofunctional phosphorus compounds, otherwise obtainable by multistep sequences. Metal phenide, a coproduct in the alkali metal cleavage reaction, sometimes interfered in subsequent reactions, decreasing the over-all yield of the product. However, this by-product could be selectively destroyed, if desired, by the addition of an equimolar amount of *tert*-butyl chloride without appreciable reduction in yields.[1] Strangely, this very useful reaction has not been fully explored in polycyclic C–P heterocycles despite extensive demonstrations by Issleib[184,185] and Gilman[361] as to the importance of such metal phosphides in organophosphorus chemistry. Some reactions of simple alkali metal phosphides were covered in an earlier review.[183]

A closely related reaction was the action of organometallic reagents on triphenylphosphine oxide or sulfide in inert solvents.[313,314] For example, treatment of triphenylphosphine oxide with methyllithium in ether at room temperature resulted in diphenylphosphinylmethyllithium (**477**) and benzene. Subsequent

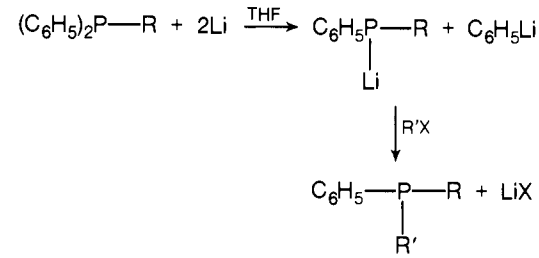
SCHEME III



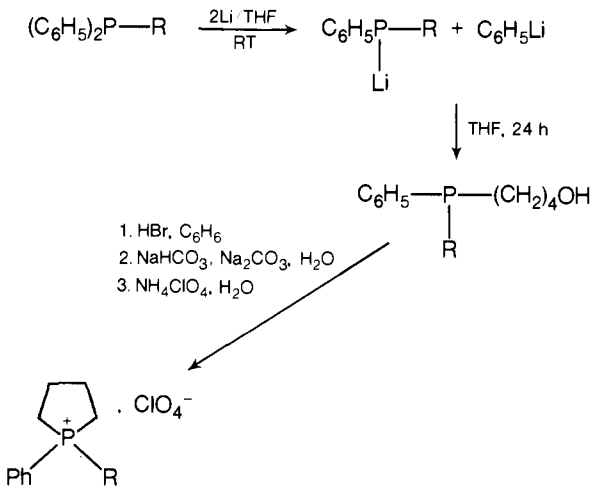

quenching of the reaction mixture with aqueous HBr afforded methyldiphenylphosphine oxide (84%); carbonation gave carboxymethyldiphenylphosphine oxide (47%) while triphenyltin chloride afforded triphenyltinmethyldiphenylphosphine oxide (76%) (Scheme III). The mechanism of this process was shown to involve a very rapid exchange step followed by a slower metalation reaction.[314] With the Grignard reagents, both the steps were relatively slower.

In unsymmetrical phosphines, usually the most electronegative group attached to phosphorus has been found to cleave, and the order of cleavage of C–P bonds was $\alpha$-naphthyl, phenyl, *p*-tolyl, 2,5-dimethylphenyl, ethyl, and cyclohexyl.[183] Based on this, a method has been developed recently for the preparation of dissymmetric tertiary phosphines in high yields (70–80%) via cleavage of diarylalkylphosphines by lithium metal in THF followed by in situ alkylation (Scheme IV).[323] Advantageously, one could utilize this method to prepare dissymmetric phosphine oxides, sulfides, and phosphonium salts of polycyclic C–P heterocyclic systems by appropriate reactions.

SCHEME IV



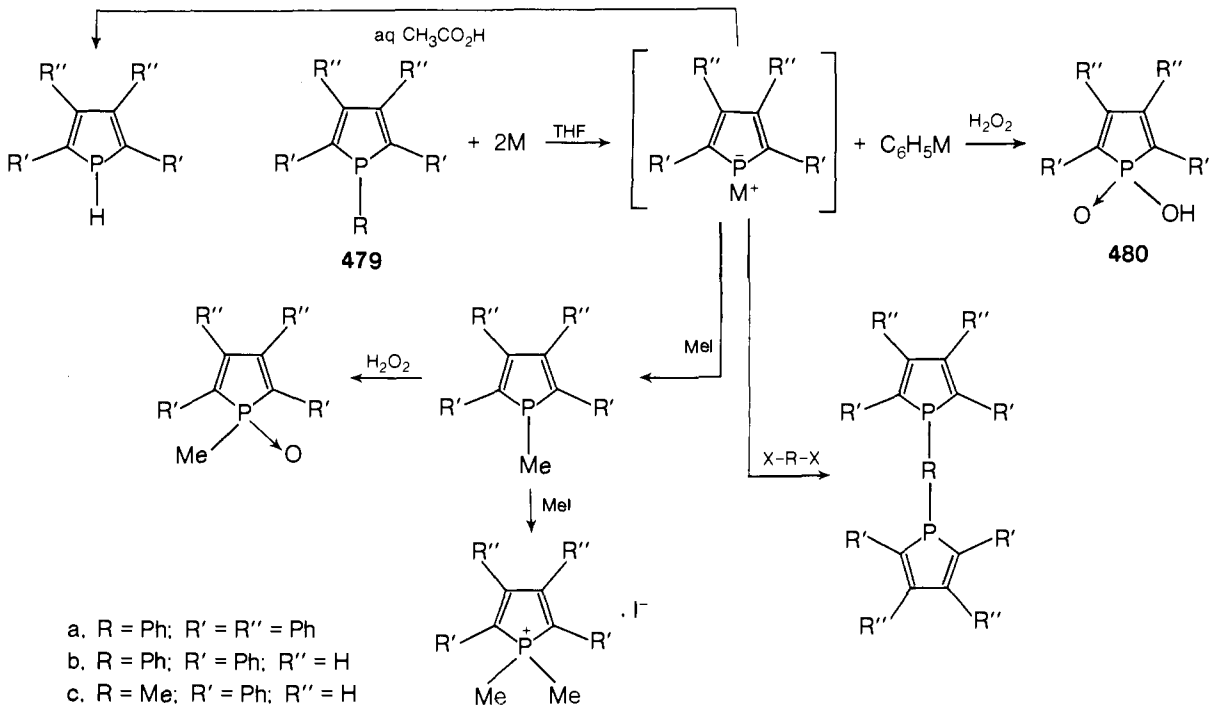

Alkali organophosphides have been known to cleave cyclic ethers.[183] A recent method utilized the cleavage of tetrahydrofuran by lithium organophosphides to afford initially 4-hydroxybutylorganophosphines which were cyclized intramolecularly via the bromide in a basic medium to afford phospholanium salts **478** in high yields (73–86%).[280,281] Extension of this synthetic procedure to tetrahydropyran afforded the desired phosphorinanium salt (50.4%). In this case, an extended reflux period (196 h) was essential. The use in polycyclic C–P heterocycles remains to be investigated.




**478**

R = Me, Et, Pr, Bu, Ph

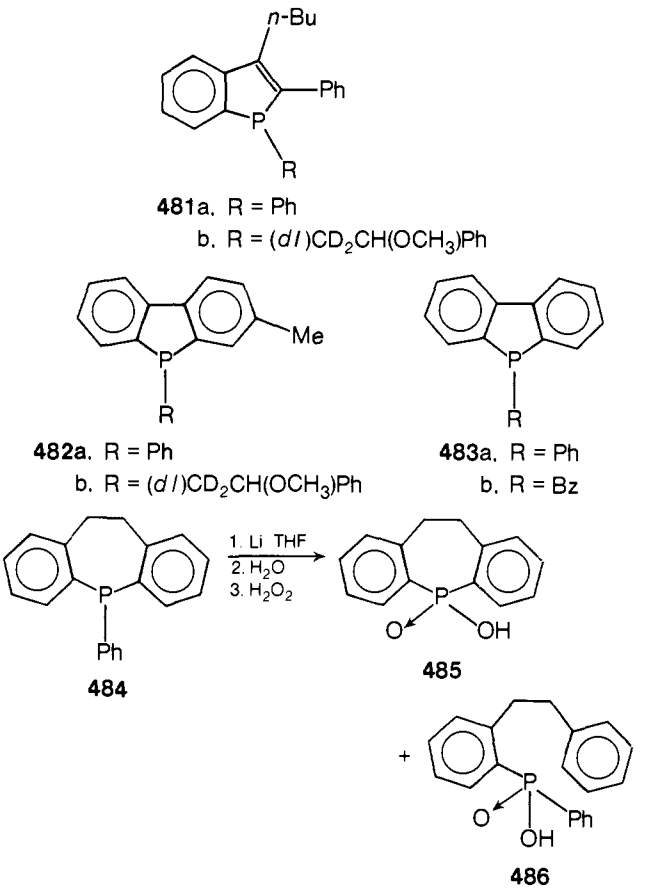
With cyclic phosphines, cleavage with alkali metals could occur either by the fission of ring or exocyclic carbon–phosphorus bond. Numerous investigators[39,97,107,260-262] have examined the cleavage of several substituted phospholes with various alkali metals (Li, K, and Na) and organometallic reagents in different solvents. While the objective was to prepare phosphole derivatives by this procedure, there was some interest in evaluating the aromatic properties of phospholes.[205] In all cases investigated, cleavage of the exocyclic carbon–phosphorus bond occurred. A probable reason for this could be aromatic stabilization of the derived anion.[39,205,332] Interestingly, phosphole anions were resistant to one-electron addition compared to triphenylphosphine, and this was considered as evidence for aromatic character in the phosphole system.[96,265]



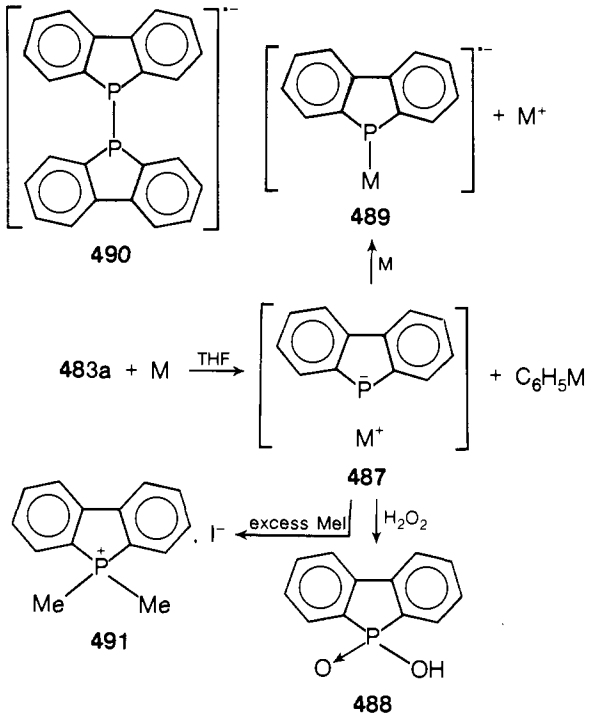

Phospholes **479a** and **479b** with a P-phenyl group were found to react readily with Li and K in THF, dioxane, and toluene.[39] Subsequent reactions of the respective metal phospholides led to a wide variety of compounds shown. However, reaction of phospholes **479** with Na in THF was reported to be sluggish. Freedman and co-workers[107] reinvestigated this reaction in THF and dioxane with freshly cut sodium pellets (diameter about 1/16 to 1/4 in.) and obtained phosphinic acid **480a** after hydrolysis and oxidation of the reaction mixture in good yield (74%). It was opined that the surface condition of the alkali metal was an important factor in this reaction. Several P-phenyl phospholes were converted by this procedure to P-*t*-Bu phospholes with *tert*-butyllithium in hexane–tetramethylethylenediamine and were later transformed to derivatives.[260,261] Interestingly, the signals noticed in the ESR spectrum of reaction products of phospholes **479a–c** with alkali metals (Li, Na, and K) in ether solvents (THF, DME) at room temperature and at −80 °C were ascribed to radical polymerization of the cleaved phenyl group and *not* to the anions of the phospholes.[205,332] A case in point was the cleavage of 1,2,5-triphenylphosphole **479b** and pentaphenylphosphole **479a** with potassium in THF and DME.[332] In the presence of sodium or lithium, no radicals were detected by ESR.[205,332] Moreover, when the group attached to phosphorus was alkyl, no similar signal was observed as when the group was phenyl.

Alkali metal cleavage of the P–C bond external to the heterocyclic ring was observed in the conversion of polycyclic compounds **481a** → **481b**, **482a** → **482b**, and **483a** → **483b**.[97,99] Only Freedman and co-workers[328] reported cleavage of the heterocyclic ring in the conversion of **484** → **485**. In addition to the desired product (52%), phosphinic acid **486** was reported formed. The wide range in the melting point (38–65 °C) reported for acid **486** and low C,H analysis made the assignment questionable in spite of some supporting $^1H$ NMR and MS data.

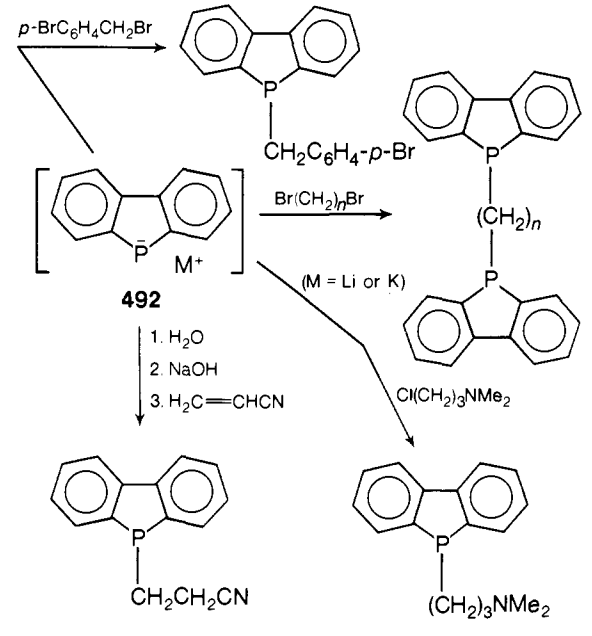
Britt and Kaiser[43] investigated the reaction of dibenzophosphole **483a** with alkali metals under identical conditions employed with triphenylphosphine and reported similarities between the two except that the reaction proceeded much slower and in lower yields. The identity of metal dibenzophospholide **487** was established by oxidation with hydrogen peroxide to the corresponding phosphinic acid **488**. Further reaction of the metal phospholide with alkali metals changed the color of the solution




from yellow to red-brown. Analysis of the reaction products via ESR spectroscopy at −65 °C indicated one phosphorus atom per radical. Based on analogy with the reaction of triphenylphosphine, the radical was formulated as **489**. In addition, ESR spectral analysis revealed the presence of another radical to which structure **490** was assigned. Anion radical **489** was reported to be thermally unstable at room temperature due to decomposition to black material. Contrary to this observation, Braye and co-workers[39] found that treatment of dibenzophosphole **483a** with a 4 M ration of potassium in boiling dioxane followed by alkylation with excess methyl iodide afforded the

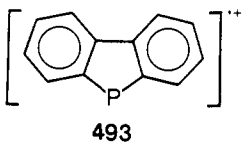


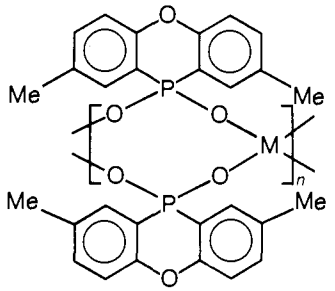

phosphonium salt **491** in high yield (76.5%). This indirectly implied a high thermal stability for anion radical **489.** It was suggested that ESR signals detected earlier by Britt and Kaiser[43] could be a result of radical polymerization of the cleaved phenyl group since structure **489** was not compatible with the signals observed.[39] Several reactions of the metal phospholide **492** led to functionalization of dibenzophosphole, a situation not easily provided by other routes.[39]




Phosphafluorene systems like **482, 483,** and **487–491** were reported in the early review of C–P heterocycles which should be consulted for the variety of preparative approaches for synthesis thereof.[51,140] Interestingly, the mass spectra of several diarylphosphinates[132] and certain alkylidene triphenylphosphoranes have an ion which has been tentatively assigned the structure **493.** Thus, the system's stability would seem to lend credence to the supposition that related radicals could be stable in solution.

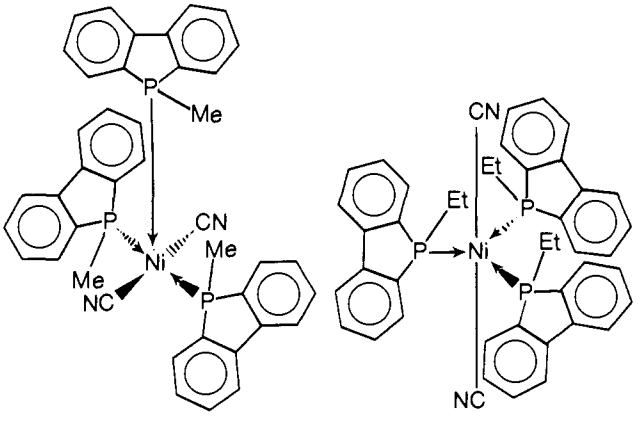
Some novel chemistry of organophosphorus–metal complexes has been recently investigated (ref **7**, 8, **62**, 106, 165, 214, 215, 258, 315, 360). Some phosphinic acid–metal complexes, of the type **494,** have been prepared and studies involving thermochemical properties discussed.[214] A subse-



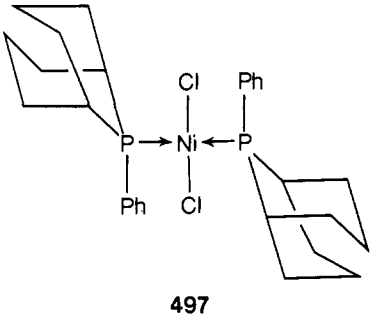




M = Cu, Zn, Co, Ni

quent report by the same authors[275] presented related complexes of **494** involving chromium as the chelating metal. An x-ray study by Mann and co-workers[8] revealed a tetragonal-pyramidal conformation for dicyanotris(9-methyl-9-phosphafluorene)nickel(II) (**495**) and a trigonal-bipyramidal conformation for dicyanotris(9-ethyl-9-phosphafluorene)nickel(II) (**496**). Ul-



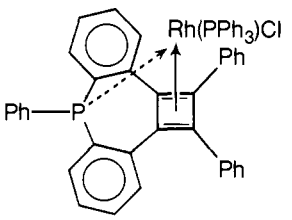

traviolet spectroscopy, however, did not reflect any structural restraints inherent in the complexes **495** and **496.**[8] The synthesis of a 9-phenyl-9-phosphabicyclononane–metal complex **497** and x-ray crystallographic analysis confirmed the absolute configuration of this complex.[375]




A series of rhodium–9-phenyl-9-phosphafluorene complexes, as well as rhodium–phosphole complexes, have been prepared, and the rate of hydrogenation of 1-hexene utilizing these complexes was reported.[165] Remarkably, the reduction could be effected at 20 °C.

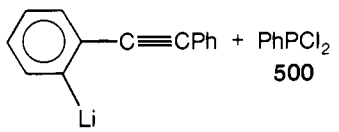
Evidence for a cyclobutadiene unit has been proposed by

Winter[360] in the structure of [1,2,7-triphenyl-7*H*-dibenzo[*b*,*f*]-*n*-cyclobuta[*d*]phosphepin] [triphenylphosphane]rhodium(I) chloride (**498**) from the lithium derivative **499** and phenylphos-



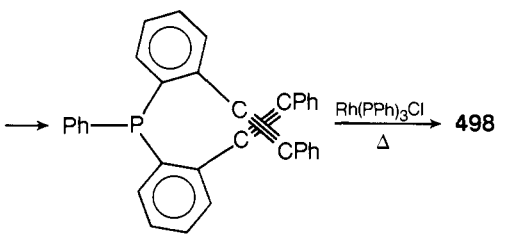

**498**

phonous dichloride (**500**). The key intermediate **501** [mp 150–151 °C, 42%] exhibited a $^{31}P$ NMR signal at +11.9 ppm ($FCCl_3$) as well as a band for the alkynyl function ($\nu_{C\equiv C}$ 2210 $cm^{-1}$) in the infrared. The lack of a free $^{31}P$ NMR signal for the




**500**

**499**




**501**

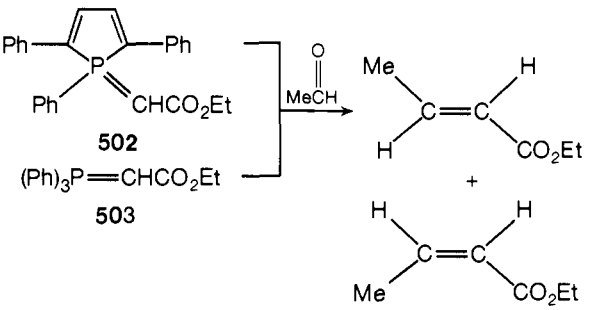
phosphepin phosphorus in complex **498** indicated that bonding to rhodium was also operative with the P atom in the C–P heterocycle.[360] Undoubtedly, the lack of easy preparations for polycyclic C–P heterocycles has retarded development of metal complexation studies, in spite of the obvious that stereochemical control of certain reactions could be very significant.

## *IV. Reactions at Carbon*

Reactions at carbon in polycyclic, C–P heterocycles have not been extensively studied. A lack of information could be associated with the fact that most of these heterocycles were previously unknown, and the reactions at phosphorus were usually explored first. Many reports have been confined to reactions associated with a carbanion generated at the carbon attached to phosphorus, namely in ylide formation, alkylation, deuteration, enolization, and carbonation. These reactions have been collectively discussed with few novel examples from the monocyclic C–P heterocycles.

The well-known Wittig reaction[81,181,278] for the elaboration of carbon chains constitutes an important method in organic chemistry and applications in the synthesis of valuable intermediates and natural products have been countless. Since the discovery of the reaction, several investigators attempted to modify the procedure in an effort to improve the yield of alkene, to reduce reaction times, and particularly to obtain the alkene free of phosphine oxide. Corey's modification of the Wittig reaction through the use of sodium hydride and dimethyl sulfoxide satisfied these requirements and has been outstanding from simplicity of experimental procedure.[81b] Few C–P heterocyclic systems have been investigated toward this end.

Hocking[48,164] noted that 1,2,5-triphenyl-1-carbethoxymethylenephosphole (**502**) underwent Wittig reaction with aldehydes and ketones under a variety of conditions. The reagent, however, was less reactive and less stereoselective compared to a conventional Wittig reagent such as triphenylcarbethoxymethylenephosphorane (**503**). For example, with acetaldehyde Wittig reagent **503** gave ethyl crotonate (82% total yield with 11% being the cis isomer) whereas under identical conditions the heterocyclic reagent **502** produced the crotonate mixture in lower yield (39% total yield with 24% being the cis isomer). With most of the substrates studied where geometrical isomerism was possible, the cis isomer predominated from heterocyclic reagent **502** in contrast to the conventional Wittig reagent **503.** Furthermore, changes in the polarity of the solvent and temperature of the reaction had little effect on the cis:trans isomer ratio.[164] The difference in the ratio of the geometrical isomers was attributed to a relatively more strained configuration at the phosphorus atom in the heterocyclic Wittig reagent **502** compared to the usual Wittig reagent **503.** It was originally thought that **502** was unreactive toward cyclohexanone,[48] but this was later shown to be only a very slow process.[164] In view of the reduced reactivity of the heterocyclic reagent **502** toward ketones, it was pointed out that the reagent could be employed in placing different ligands on an aldehydic carbonyl group and a ketonic carbonyl group in the same molecule through successive Wittig reactions with the new reagent and the conventional reagent. Unfortunately, the reagent was quite sensitive to atmospheric conditions.[164] Thus, reagent **502** has not found wide applicability because of the lack of special advantages. More recently, the behavior of heterocyclic ylides **504** and **505** in Wittig olefin synthesis have been examined.[359] Even with these ylides, there

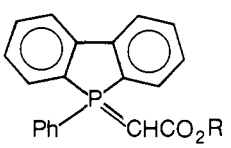



**502**

$(Ph)_3P{=}CHCO_2Et$

**503**

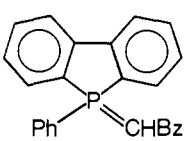
(plus the corresponding phosphine oxide)




**504**

$(Ph)_3P{=}CHCO_2R$

**506**



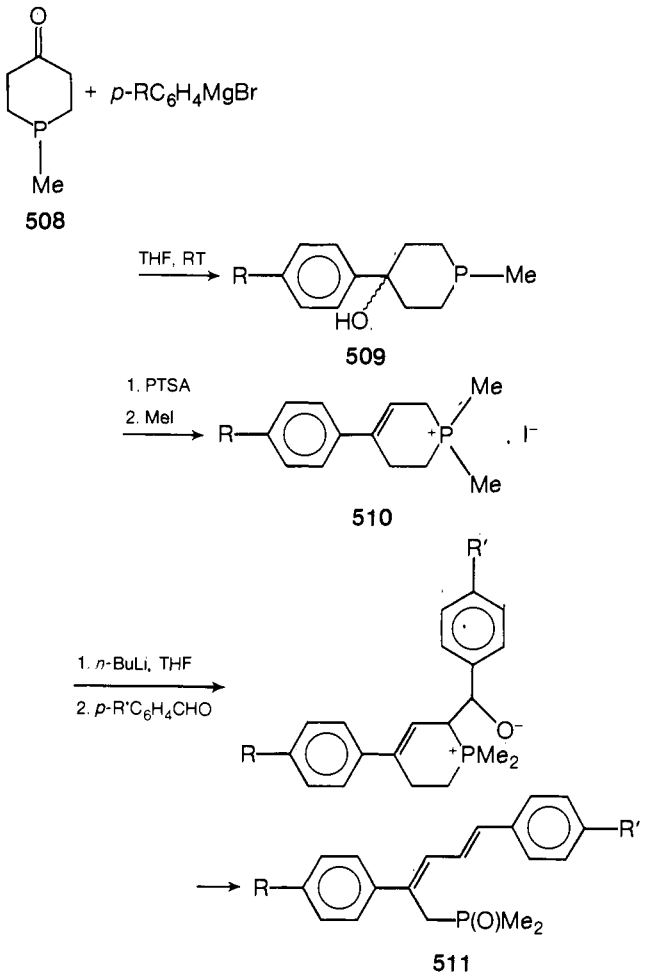

**505**

$(Ph)_3P{=}CHBz$

**507**

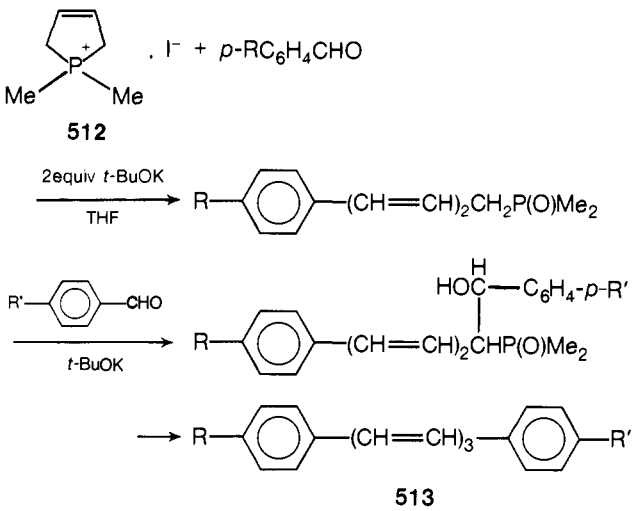
was greater preponderance of the cis alkene over the trans isomer compared to the acyclic ylides **506** and **507.** For instance, the Wittig reaction of **505** with acetaldehyde and benzaldehyde both in benzene and in ethanol afforded predominantly the cis alkene. Interestingly, the rates of reactions with the heterocyclic ylides **504** and **505** with benzaldehyde followed the same kinetic pattern noted with the acyclic analogs **506** and **507;** presumably the reactions followed similar pathways. However, the reactivities of **504** and **505** toward representative ketones were not reported.[359]

An entirely different approach utilized cyclic phosphonium salts in the Wittig reaction with carbonyl compounds.[219] Condensation of 1-methyl-4-phosphorinanone (**508**) with arylmagnesium bromides gave a carbinol mixture **509** which was dehydrated with *p*-toluenesulfonic acid followed by quaternization with methyl iodide to yield phosphonium salts **510.** Cyclic ylides formed by treatment of the salts **510** with a base were treated with a variety of aromatic aldehydes to give 3,6-diaryl-3,5-hex-



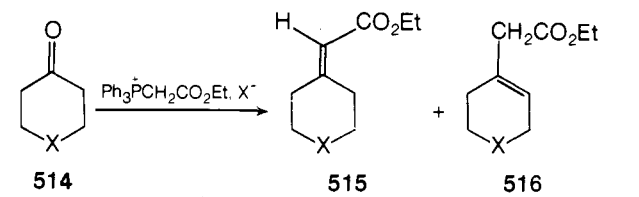

| | a, | b, | c, | d, | e, | f, | g, | h, |
|---|---|---|---|---|---|---|---|---|
| R = | OMe, | OMe, | F, | F, | F, | F, | Me, | Me |
| R' = | H, | OMe, | OMe, | F, | Me, | $NO_2$, | H, | F |

adienyldimethylphosphine oxides **511** in fair yields (13–50%). In a typical run, a suspension of the salt **510** (R = OMe) was treated with *n*-butyllithium in THF followed by the addition of benzaldehyde. After workup and chromatography, the crystalline diene **511a** (mp 135–137 °C) was realized in modest yield (50%). Oxide **511a** had the expected features in the $^1$H NMR spectrum. The trans–trans configuration was suggested for **511a** from the characteristic ultraviolet absorption at 330 nm ($\epsilon$ 33 000). In similar fashion, the cyclic ylides reacted with ketones to produce the phosphorus-containing dienes in respectable yields.[219] An extension of the study to a five-membered cyclic phosphonium salt, namely, 1,1-dimethyl-3-phospholenium iodide (**512**), yielded still a more surprising result. Treatment of the mixture of the salt **512** and aryl aldehydes with 3 equiv of potassium *tert*-butoxide in THF afforded 1,6-diphenylhexatriene (**513**) as a crystalline solid, mp 194–197 °C (26%). The initial Wittig product, in this case, contained an active methylene group and therefore participated in an aldol condensation with a second equivalent of the aldehyde to produce the triene **513**. Support for the initial oxide intermediate shown was gained via a study of the reaction of **512** with equimolar quantities of the base and aldehyde which produced a mixture isolated as a gum. The generality of the procedure was demonstrated by carrying out the reaction with several other aldehydes to obtain the triene **513**, albeit in low yields (10–26%).[220] Although only phosphonium salts **510** and **512** have so far been investigated,[219,220] the novelty of the products realized should be incentive to prepare related polycyclic quaternary salts.



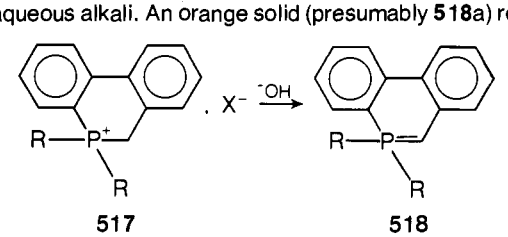

a, R = R' = H; b, R = R' = Me; c, R = R' = OMe

It seems worthy of mention that Quin and co-workers[287] followed the Wittig reaction of 1-methyl-4-phosphorinanone (**514a**) with carbethoxymethylenephosphorane, prepared in situ from carbethoxymethyltriphenylphosphonium bromide and sodium ethoxide. A 1:1 mixture of the isomers **515a** and **516a** was obtained. In contrast, reaction of ketone **514a** with the carbanion of triethyl phosphonoacetate gave exclusively **515a** (55%). Likewise, *N*-methyl-4-piperidone (**514b**) with the carbanion of triethyl phosphonoacetate gave only the isomer **515b** (68%). In a separate study, it was noted that pure $\alpha,\beta$-unsaturated esters **515a, 515b,** and **515c** underwent isomerization both under basic and thermal conditions to afford, in each case, isomers of **515** and **516.** This indirectly accounted for the formation of the isomeric mixture in the Wittig reaction of **514a** and **514b.** The greater propensity of the phosphine **514a** and the amine **514b** to isomerize was attributed to the influence of the electron pair on the heteroatom in the enolization process.[287]



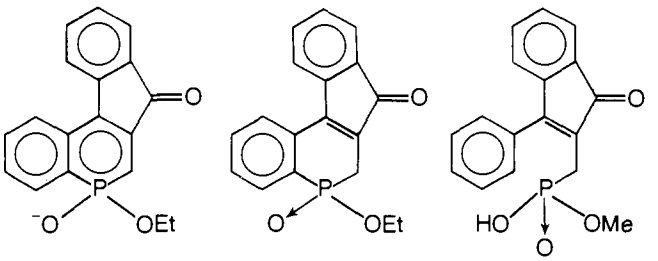

a, X = PMe; b, X = NMe; c, X = $CH_2$

An elegant attempt was made by Cookson and Crofts[68] to prepare the ylide from the phosphonium salt **517a** by treatment with aqueous alkali. An orange solid (presumably **518a**) resulted which showed intense aromatic absorptions in the UV spectrum and by comparison with the phosphonium salt **517a** revealed a bathochromic shift. The data were compatible with the formulation of the phosphorane **518a** which would be expected to be stabilized by forming the aromatic ring. Phosphorane **518a** failed to participate in Wittig reactions with benzaldehyde and *p*-nitrobenzaldehyde. Surprisingly, the phosphonium salt **517a** was not cleaved; only when the phosphonium salt **517a** was added to aqueous sodium hydroxide at 100 °C was the expected




a, R = Ph; b, R = Me

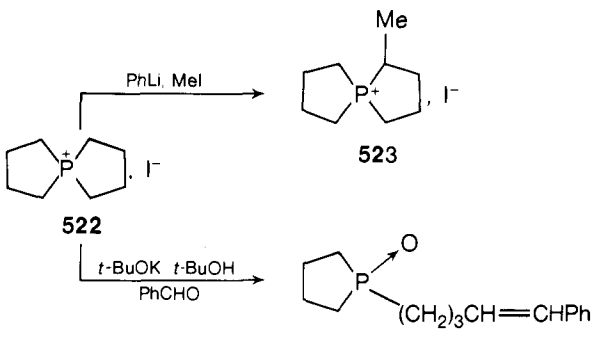
phosphine oxide realized.[68] It is of note that the corresponding methiodide **517b** with phenyllithium also gave an orange solid, presumably phosphorane **517b** which was not characterized thoroughly.[297] A similar attempt was made to prepare the potentially aromatic anion **519** from dihydrophosphinoline **520** by



519 520 521

treatment with sodium ethoxide in deuterioethanol and with sodium hydride in $(CH_3)_2SO$-$d_6$.[128] Although the protons of **520** were exchanged, the rates of exchange were only 1.5–1.7 times higher than the rates observed for the methyl ester **521** for which no aromatic stabilization was possible with the same reagents. Furthermore, UV spectra of solutions of **520** and **521** in $(CH_3)_2SO$ (containing 1 equiv of sodium hydride) were nearly alike. Both exchange and spectral studies revealed no aromaticity in the anion; presumably the electronegative substituents on phosphorus destabilized the ylide.[128]

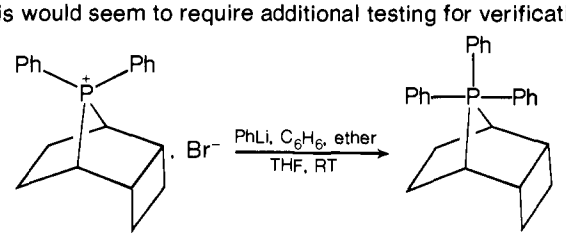
Relatively few strained systems to date have been tested for capability to form an ylide. Walker and co-workers[76] investigated the behavior of spiro phosphonium salt **522** on treatment with base. The $\alpha$ protons of **522** exchanged for deuterium in sodium



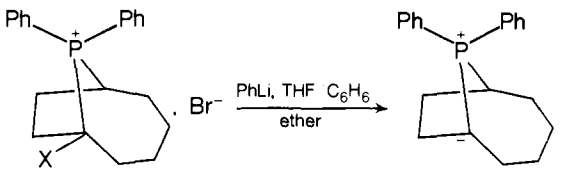
522 523 524

ethoxide and deuterioethanol (to the extent of 74%) during 1 week at room temperature. Alkylation of **522** with methyl iodide in the presence of phenyllithium at room temperature afforded the alkylated product **523** (30%). However, salt **522** also condensed in a Wittig reaction with benzaldehyde over 2 days in *tert*-butyl alcohol containing potassium *tert*-butoxide to afford the oxide **524.**

An even more striking result was obtained by Turnblom and Katz[336] when the phosphonium salts **525** and **526** were treated with phenyllithium. Salt **525** formed pentavalent phosphorane **527,** whereas **526** formed the ylide **528.** It was not unequivocally determined whether a critical angle at phosphorus existed below which phosphonium salts and phenyllithium formed pentavalent phosphoranes and above which ylides formed.[336] This hypothesis would seem to require additional testing for verification.



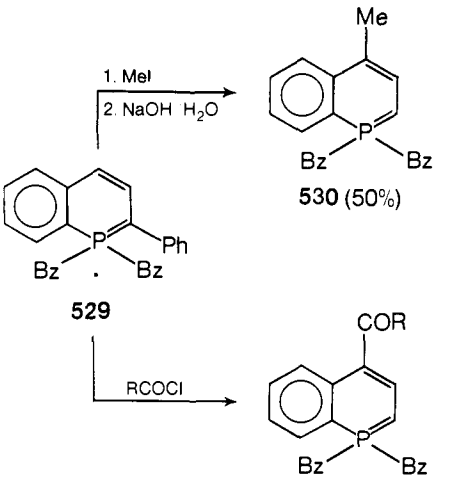
525 527



526a, X = H
b, X = D

528

In a report concerned primarily with the synthesis of 1,1-dibenzyl-2-phenyl-1-phosphanaphthalene (**529**) a few novel reactions at carbon were reported.[238] Alkylation of **529** with



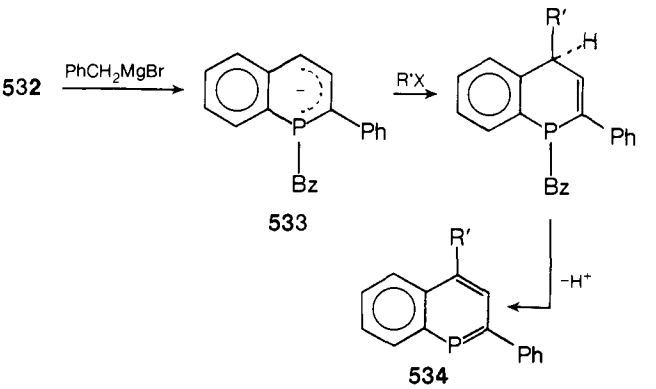
530 (50%)

529

531, R = Ph (68%), OEt

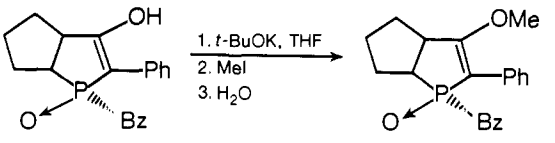
methyl iodide and deprotonation with sodium hydroxide gave 1,1-dibenzyl-4-methyl-2-phenyl-1-phosphanaphthalene (**530**). Acylation of **529** with either benzoyl chloride or ethyl chloroformate also afforded the carbonyl derivatives **531** ($\nu_{C=O}$ 1500 $cm^{-1}$; R = Ph) with spontaneous deprotonation. This unusual alkylation may be unique to these phosphoranes.[176,238]

Reaction of 2-phenylphosphanaphthalene (**532**) with benzylmagnesium bromide (or *tert*-butylmagnesium chloride) in glyme gave a deep purple anion **533,**[241] which could be alkylated to give the dihydro compounds shown, which in turn underwent aromatization to **534** [R′ = $CO_2Et$, $\nu_{C=O}$ 1720 $cm^{-1}$; $^{31}P$ NMR ($HCCl_3$) −227 ppm].[241] Application of the technique to larger C–P heterocyclic systems remains to be explored.



532 533 534

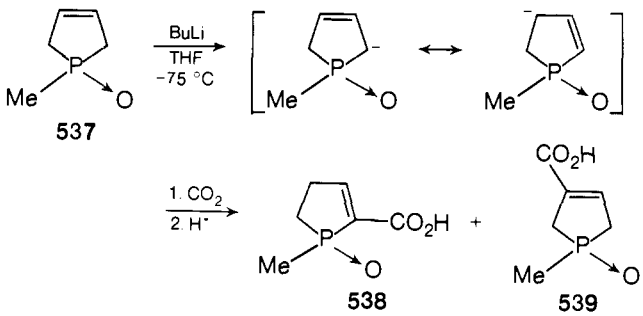
The attempted alkylation of 4-oxo-2-benzyl-2-phosphabicyclo[3.3.0]octane 2-oxide (**535**) (in enol form) with methyl iodide in the presence of potassium *tert*-butoxide gave the O-methyl



535 536

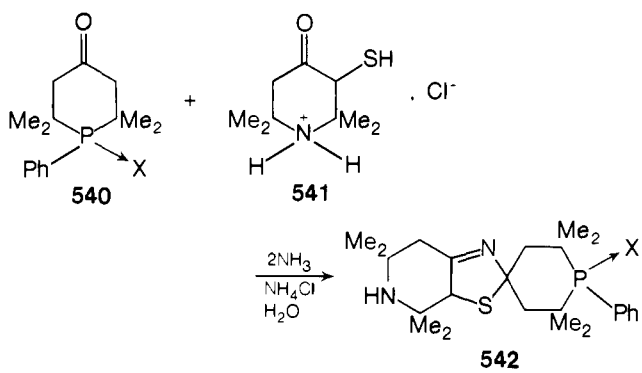
enol ether **536** rather than the expected C-alkylated product.[279] This result was added evidence for the predominance of the enolic form in the starting material.[279]

A rare example of C-carbonation of a simple C-P heterocycle was reported by Quin.[284] The anion derived from 1-methyl-3-phospholene oxide (**537**) by treatment with *n*-butyllithium at −75 °C underwent carbonation to afford a mixture of acids **538** and **539** in the ratio 2:1 (50%). Although structurally similar poly-

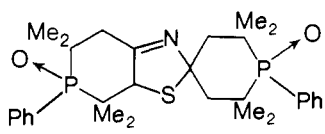


cyclic systems have not been subjected to such a reaction, one would expect similar behavior. Of particular interest in this reaction was the carboxyl function which should serve as a handle for elaboration of a carbon chain.[284] In this regard, acid **538**, which has the correct functionalities and ring size, should draw attention as a possible starting material for the synthesis of phosphorus analogs of prostaglandins.

1-Phenyl-2,2,6,6-tetramethylphosphorinan-4-one 1-oxide (**540a**) reacted with 3-mercapto-2,2,6,6-tetramethyl-4-piperidone hydrochloride (**541**) and ammonia to give the novel spiro com-



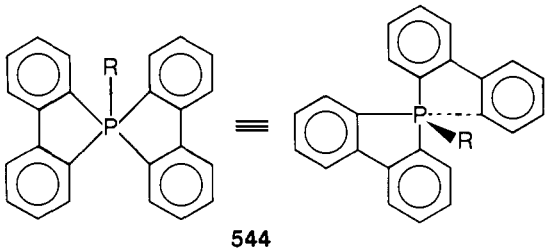
pound 5,5,7,7-tetramethylpiperidino[5,4-c]-$\Delta^3$-thiazoline-2-spiro-4′-(1′-phenyl-2′,2′,6′,6′-tetramethylphosphorinane) 1-oxide (**542a**) or 1-sulfide (**542b**).[24] Those condensations occurred at carbon rather than phosphorus. The dimeric derivative **543** was also reported by a somewhat related procedure.[24]



## V. Pentasubstituted Phosphorus Systems

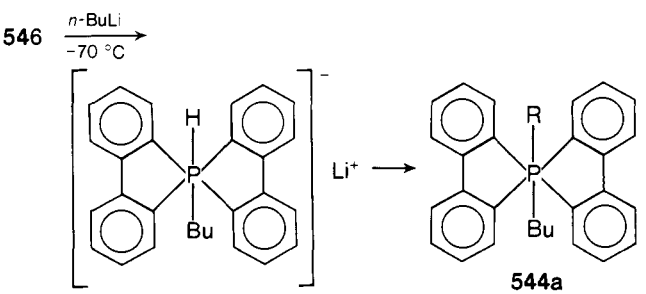
### A. Bis(2,2′-biphenylylene)phosphoranes

Pentasubstituted phosphoranes have been of considerable interest both from the standpoint of syntheses as well as stereochemical analyses.[113,114,140,181,362] With respect to polycyclic C-P heterocycles, this area of organophosphorus chemistry has been associated predominantly with derivatives of bisbiphenylylenephosphorane systems **544**. The early synthetic work has been discussed in detail elsewhere.[140] The

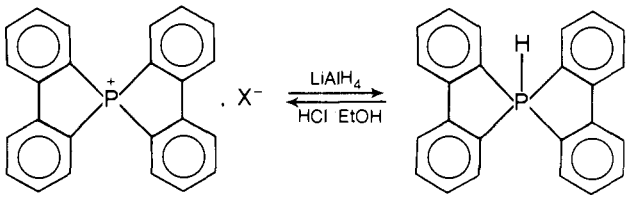


paucity of reports concerned with other related C-P phosphoranes can be related to the strong propensity of each of the two five-membered rings to readily accommodate, with minimum strain, apical-equatorial positions of the trigonal-bipyramid structure usually assigned to pentasubstituted phosphorus. Thus, many conformers or rotamers exist in solution to make conformational analysis difficult.

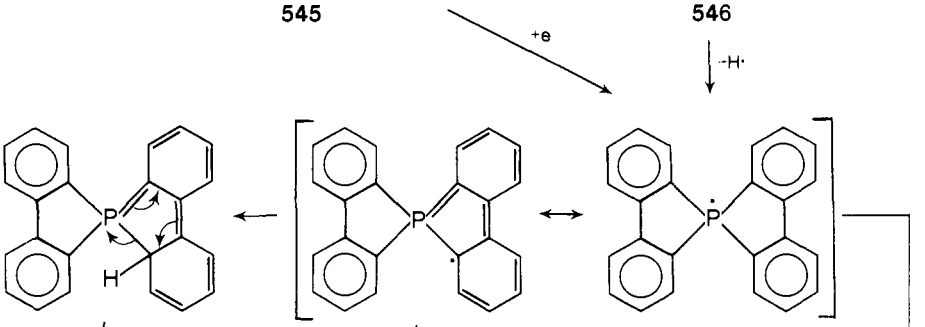
A major approach to simple pentasubstituted phosphoranes developed by Wittig involved the reaction of tosylimines with selected organolithium reagents. The technique has been previously reviewed.[140,216,362,363] Recent developments have revolved around the interaction of suitable organometallic reagents with tetraarylphosphonium salts.[142] For example, treatment of bis(2,2′-biphenylylene)phosphonium iodide (**545**) with lithium aluminum hydride in ether or sodium borohydride in ethanol afforded the first stable derivative **546** related to the hypothetical phosphorane, $PH_5$.[142] Although the phosphorane **546** was quite stable in the dark (under $N_2$), considerable decomposition occurred on heating (95–100 °C). Normal P-H stretch at 2097 $cm^{-1}$ in the infrared spectrum, a doublet centered at $\delta$ 9.33 ($J_{P-H}$ = 482 Hz) in the $^1H$ NMR spectrum (benzene), and a distinct signal due to phosphorus at −9.33 ppm in the $^{31}P$ NMR spectrum (rel to 85% $H_3PO_4$) supported structure **546** as a phosphorane.[142,148] Furthermore, treatment with ethanolic HCl or ethanolic iodine solution regenerated bis(2,2′-bisphenylylene)-phosphonium cation in good yield. Exposure of phosphorane **546** in benzene solution to diffuse daylight resulted in quantitative conversion to bis(2,2′-biphenylylene)phosphoranyl radical (**547**) also formed when **545** was treated with Na/K alloy in benzene.[143] A well-defined doublet in the ESR spectrum with a coupling constant of 18 G supported the identity of the phosphoranyl radical **547**. The radical decayed mostly to the phosphines **548** and **549** with minor amounts of **550** and **551**.[148] Free-radical phosphorus chemistry is in its infancy especially in polycyclic C-P heterocycles. Phosphorane **546** underwent nucleophilic exchange at low temperature (−70 °C) with *n*-butyllithium to afford exclusively *n*-butylbis(2,2′-biphenylylene)phosphorane **544a**.[148,306,307] At room temperature,



however, the reaction provided a mixture of the phosphorane **544a** and the phosphine **548**, which could result from the initially formed anion by P-C bond cleavage followed by protonation.[148] Such a nucleophilic ligand exchange reaction was also extended to the preparation of other phosphoranes. For example, the methyl- (**544b**) or phenylbis(2,2′-biphenylylene)phosphorane (**544c**), when treated with selected organolithium reagents in ether, underwent ligand exchange to provide new phosphoranes, which were characterized thoroughly by spectral data (IR, $^1H$




545 546

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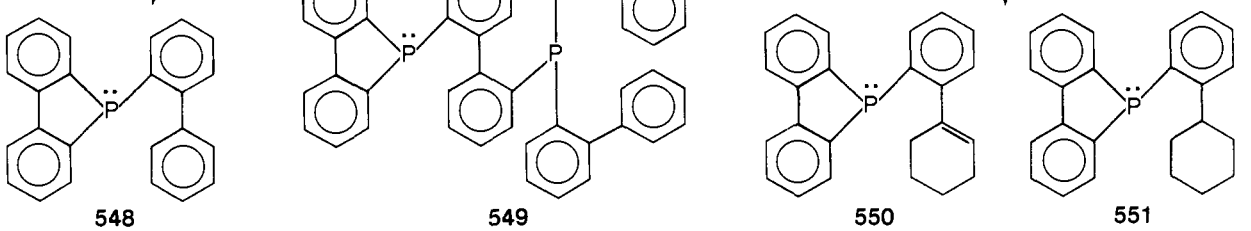
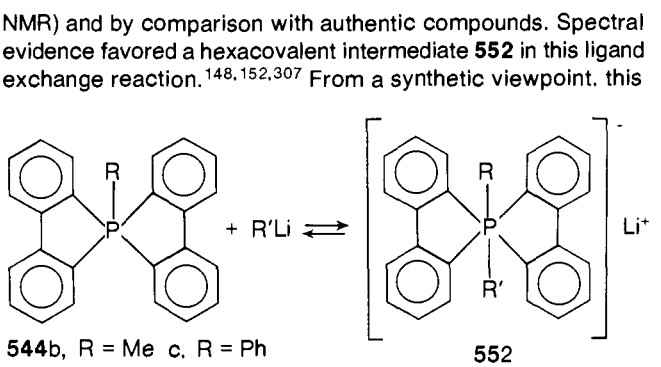


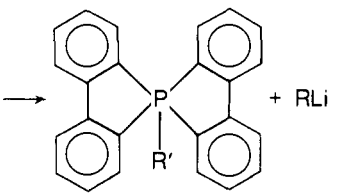
548 549 550 551

NMR) and by comparison with authentic compounds. Spectral evidence favored a hexacovalent intermediate **552** in this ligand exchange reaction.[148,152,307] From a synthetic viewpoint, this ligand exchange process has many advantages. Specifically, phosphoranes differing in the nature of R′ group can be readily prepared from a single common intermediate. Curiously, the phenyl compound **544c** decomposed thermally to the phosphine **553**[362] (degraded in several steps to **554**).

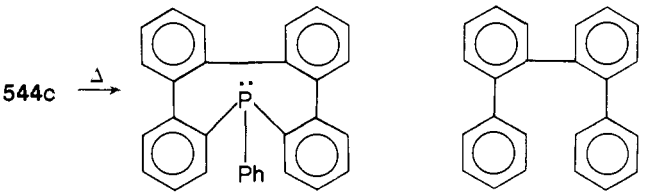


**544**b, R = Me c, R = Ph

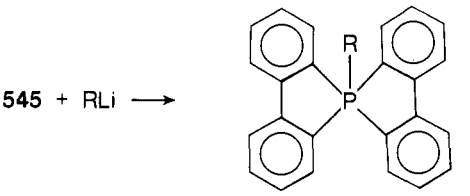
552



**544**a, R′ = *n*-Bu
c, R′ = Ph
d, R′ = *p*-MePh
e, R′ = *p*-MeOPh

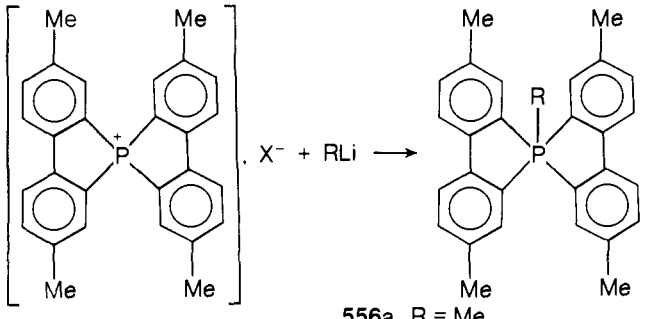


553 554



**544**f, R = HC═CMe$_2$
g, R = 2-furanyl
h, R = 2-thienyl
i, R = 2-benzo[*b*]thienyl
j, R = 2-biphenylyl
k, R = 8-methoxy-1-naphthyl
l, R = 8-dimethylamino-1-naphthyl
m, R = 1-naphthyl

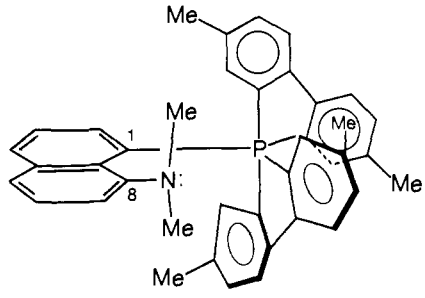
Richards and Tebby,[293] despite their earlier failure to obtain an acetylenic phosphorane by the interaction of a phosphonium salt with lithium phenylacetylide, applied the method and succeeded in obtaining the butenylphosphorane **544f** and heteroaromatic phosphoranes **544g–l** by the interaction of phosphonium salt **545** with the appropriate lithium reagents. Phosphoranes possessing 2-biphenylyl and substituted 1-naphthyl moieties were prepared by Hellwinkel and co-workers[152] who demonstrated the versatility of this synthetic procedure with phosphonium salt **555** and lithioorganics providing several substituted phosphoranes **556a–g**. Earlier, some of these



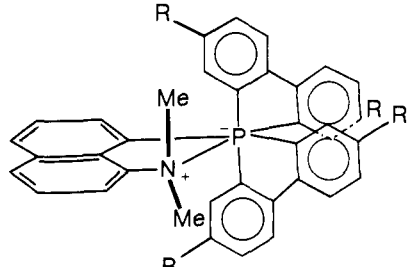

555

556a, R = Me
b, R = Et
c, R = 2-naphthyl
d, R = Bz
e, R = 2-biphenylyl
f, R = 8-Y-1-naphthyl (Y = H, F, Cl, Br, Me, OMe, $NMe_2$).
g, R = 8-quinolinyl

phosphoranes were prepared by the tosylimine method.[141,357] Spectral analyses of a few of these phosphoranes afforded valuable information concerning phosphorus(V) species. For example, the magnitude of the geminal coupling constant in the isobutenylphosphorane **544f** was larger ($J_{P-H}$ = 24.3 Hz) than usually encountered in phosphines and phosphonium salts, presumably due to phosphorus in a pentavalent state.[293] Many intense bands in the UV spectrum of the phosphoranes **544f–i** in the region 250–300 nm were observed in addition to the usual band at 238 nm (biphenyl conjugation). These bands were thought to originate from two types of phosphorus(V)–aryl interaction arising from apical and equatorial orientation of groups. Resonance signals due to phosphorus in phosphoranes **544f–i** were detected at +94.2, +98.5, +94.2, and +89.4 ppm, respectively (rel to 85% $H_3PO_4$). In comparison, a value of +85.0 ppm was reported for phenylphosphorane **544c**; the upfield shifts in **544f–i** were suggested to be related to increased electron density around the phosphorus atom.[293] Extensive $^1H$ NMR analysis of bis(4,4′-dimethyl-2,2′-biphenylylene) (8-dimethylamino-1-naphthyl)phosphorane (**556f**) strongly implied a trigonal bipyramid as the ground-state configuration with the dimethylamino group favored in a rigid position and nearly parallel to the equatorial plane as indicated.[150–152] The free rotation of the dimethylamino group in phosphoranes **544l** and **556f** [Y = $N(CH_3)_2$] was apparently restricted. Both $^1H$ NMR and $^{31}P$ NMR



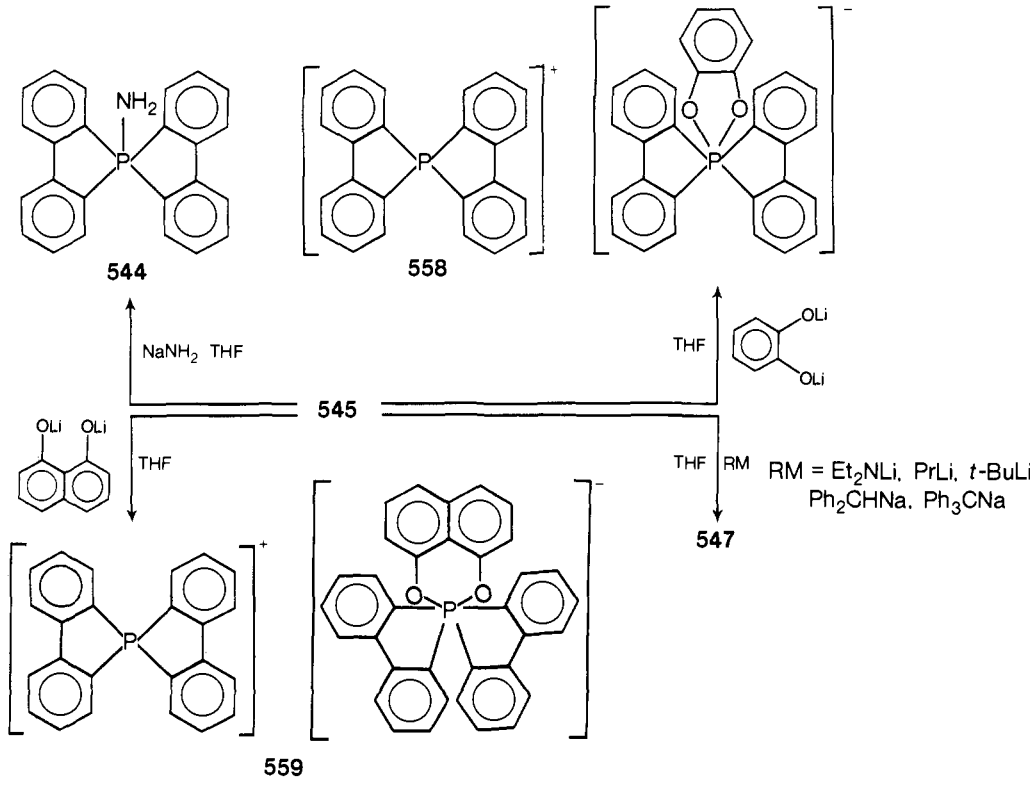

556f




557 R = H, Me

spectral data discounted an inner onium-ate structure as depicted in **557** for the phosphoranes **544l** and **556f** [Y = $N(CH_3)_2$].[151,152] In $CS_2$, **556f** had a $^{31}P$ NMR signal at +84.3 ppm (previously reported at +85 ppm)[151] while **544l** had a signal at +85 ppm.[152] Mass spectral fragmentation for these phosphoranes was also recorded.[159,160]

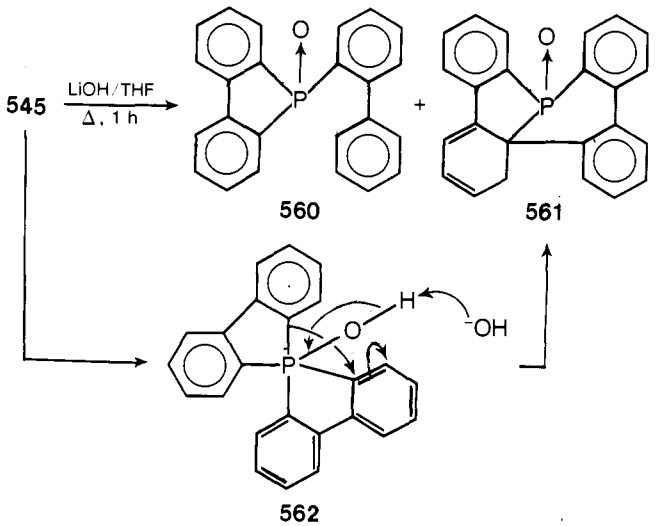
Hellwinkel[157] also prepared the aminophosphorane **544** (R′ = $NH_2$) by treating the phosphonium salt **545** with sodamide in THF. Formation of the aminophosphorane **544** (R′ = $NH_2$) was



rather unusual since the normal product from treatment of an acyclic tetraarylphosphonium salt with sodamide was known to be the triarylphosphimine.[272] In addition, it was found that

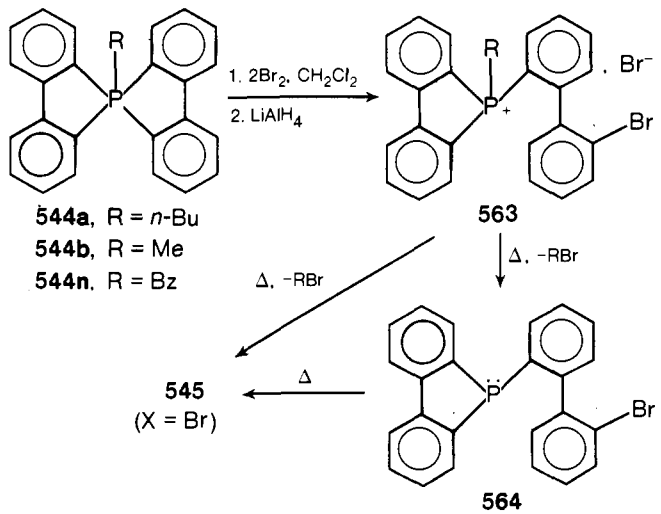
$$Ph_4P^+ \cdot I^- \xrightarrow{NaNH_2} Ph_3P{=}NH$$

treatment of the phosphonium salt **545** with a series of bases, which were all known to be good electron transfer reagents, gave only the phosphoranyl radical **547** and not the expected phosphoranes.[157] The phosphonium salt **545** also reacted with arylenediolates to form onium-ate complexes containing a hexasubstituted phosphorus as in **558** and **559.**[155] Unusual behavior of bisphenylylene systems in some reactions was also noted by Hellwinkel.[156] Treatment of the phosphonium salt **545**

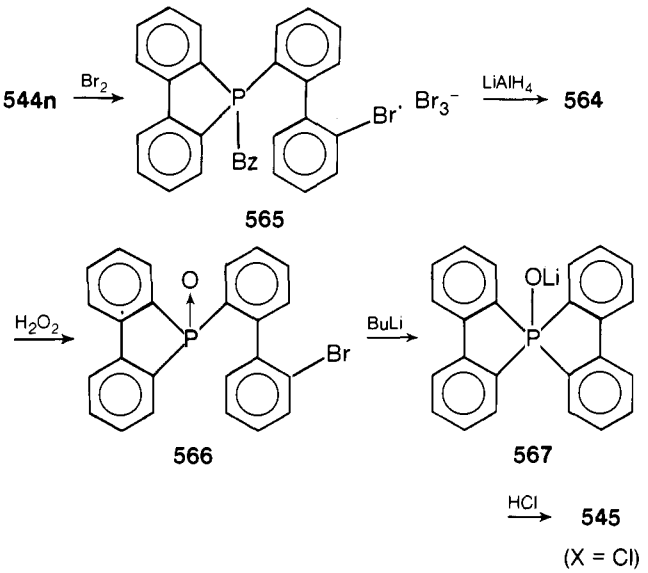



with lithium hydroxide afforded the expected phosphine oxide **560** only as a minor product, and the major product was the oxide **561** formed from a skeletal rearrangement.[156] The substituted phosphonium salt **555** behaved in a similar fashion.[156] The favored formation of the rearranged oxide **561** was attributed to a synchronous deprotonation of the intermediate hydroxyphosphorane **562.**[156]

A reverse procedure was also developed to convert alkylbis(2,2′-biphenylylene)phosphoranes to bis(2,2′-biphenylylene)phosphonium salts.[149] The phosphoranes **544a, 544b,** and **544n** were treated with bromine and then reduced to the corresponding phosphonium salt **563.**[149] Thermolysis of this salt




produced phosphine **564** or the phosphonium salt **545** depending upon the temperature of reaction. Cyclization of the phosphine **564** to the phosphonium salt **545** could be effected separately. The amount of the phosphine **564** vs. the salt **545** produced depended upon the halogen utilized either as the anion or in the aryl halide in **563** and **564.**[149] In the case of benzylphosphorane **544n,** another synthetic procedure leading to phosphonium salt



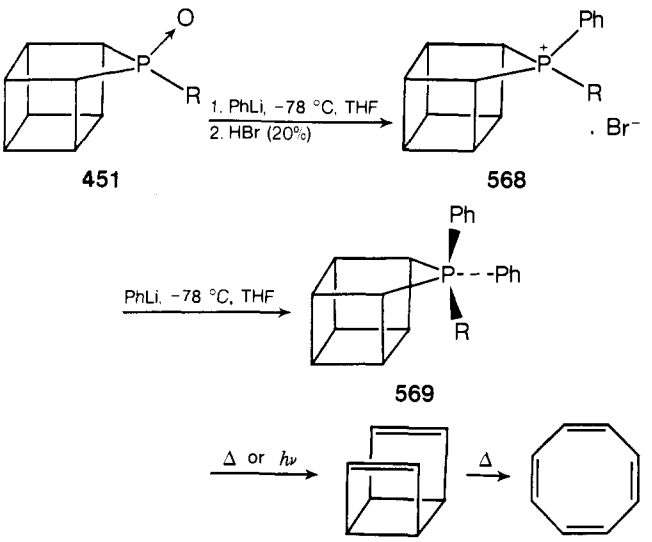

was developed. Initial treatment of phosphorane **544n** with bromine afforded the phosphonium tribromide **565,** which was reduced with lithium aluminum hydride to phosphine **564.** Oxidation of **564** gave the expected phosphine oxide **566,** which upon treatment with *n*-butyllithium, underwent an intramolecular cyclization to **567** and subsequent hydrolysis gave the phosphonium salt **545.**[149]

Besides the synthetic aspects involved with pentasubstituted phosphorus, the bis(2,2′-biphenylylene)phosphorane derivatives have also been studied with respect to the polytopal rearrangements of phosphorus species. The specific utilization of the biphenylylene derivatives simplified the analyses considerably due to the preference of each of the five-membered rings to accommodate apical–equatorial positions in the trigonal bipyramid of the ground state. Thus, a fifth substituent should reside in an equatorial position. The introduction of functionalities either in the 4,4′ positions of the biphenylylene rings or the fifth substituent has afforded spectral analyses not completely compatible with "Berry pseudorotation".[141,151,356,357,362] For example, in those cases with a variety of groups for the fifth substituent of bis(4,4′-dimethyl-2,2′-biphenylylene)phosphorus compounds **556a–566g,** analyses of the temperature-dependent NMR spectra indicated the possible intermediacy of a tetragonal pyramid.[141,150,151,356,357] However, in the case of 2,4,6-triisopropylphenylbis(4,4′-dimethyl-2,2′-biphenylylene)phosphorane, the somewhat less reliable variable-temperature $^1H$ NMR analyses suggested that pseudorotation involved only a trigonal-bipyramidal intermediate.[356,357] Thus, the presence of a tetragonal-pyramidal structure in other cases of spectrally inferred pseudorotation processes should be viewed with great caution and only then with detailed spectral analyses of the specific system.

## B. Homocubylphosphoranes

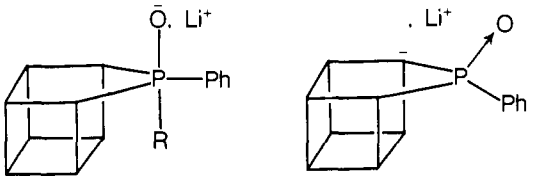
Although most of the polycyclic C–P systems containing a pentavalent phosphorus have been derivatives of the 2,2′-biphenylyl moiety,[140,362] (cf. section V.A) a few reports, mainly by Katz and Turnblom,[203,337,338] have appeared concerning the preparation, isolation, and characterization of some stable cycloalkyl pentavalent homocubylphosphoranes. For example, in the conversion of **451** (R = Ph) → **568** → **569** the rather unusual homocubyltriphenylphosphorane **569** was obtained (Scheme V).[203] This synthetic sequence included a number of interesting

SCHEME V




451 568 569

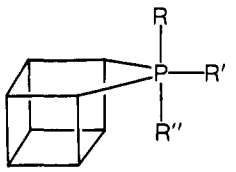
reactions, the directions of which were related, in part, to the relief of angle strain around the phosphorus atom (C–P–C angle of the ring was suggested to be less than 90 °).[203] In this respect, the conversion of the phosphine oxide **451** (R = Ph) to the phosphonium salt **568** at −78 °C probably involved the pentavalent intermediate **570**, which upon acidification with aqueous hydrogen bromide, was deoxygenated to the stable phosphonium




570 571

salt **568** (mp 310–311 °C).[203,338] The formation of intermediate **570** would be favored owing to relief of ring strain upon formation of the trigonal-bipyramid configuration. This assumption was based on the configuration cited as preferred for pentavalent phosphorus compounds rather than the ylide **571**.[203,338] However, the reaction was very temperature dependent. Interestingly, tetraphenylphosphonium bromide and phenyllithium yielded pentaphenylphosphorane.[365] In contrast, tetramethylphosphonium iodide and methyllithium gave the ylide $(CH_3)_3P{=}CH_2$.[364] Methyltriphenylphosphonium bromide and phenyllithium appeared to produce reversibly methyltetraphenylphosphorane immediately before ylide formation.[312]

Treatment of the phosphine oxide **451** (R = Ph) with phenyllithium at *room temperature* afforded only the ylide **571**.[338] In the same series of reports, the synthesis of the first stable pentaalkylphosphorane **572a** (R = R′ = R″ = Me) was accomplished by procedures similar to those for **569**.[337,338] The $^1H$

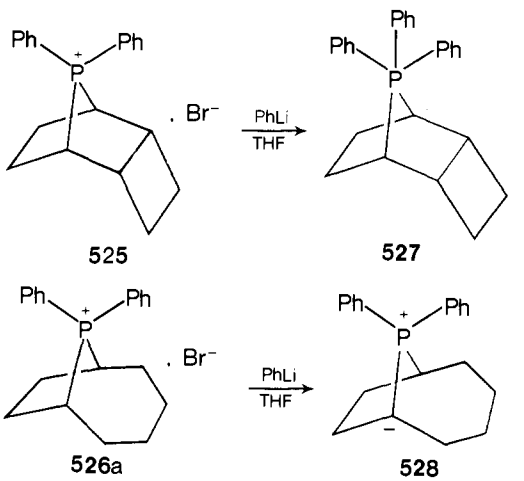


**572a**, R = R′ = R″ = Me
b, R = R′ = Ph; R″ = Me
c, R = R′ = Me; R″ = Ph

NMR spectrum at room temperature of **572a** showed all the methyl protons to be equivalent. The simplicity of the spectra was suggestive of positional exchange of groups by rapid pseudorotation. A $^{31}P$ NMR signal occurred at +90 ppm (rel to 85% $H_3PO_4$) in $C_6D_6$. Also, depending upon the choice of the initial phosphonium salt and the organolithium reagent, the mixed phosphoranes **572b** and **572c** were obtained.[337,338] Curiously, the UV spectrum of **572a** showed strong absorption up to 300 nm with a shoulder at 230 nm (log ε 3.45). Treatment of the homocubylphenylmethylphosphonium iodide (**573**) with methyllithium at room temperature afforded a mixture of **572a**, **572b**, and **572c** (17:20:63).[337,338]


573

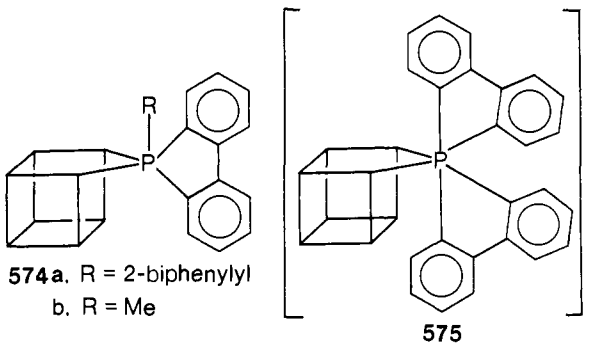
The limits of the C–P–C angular dependence of phosphorane vs. ylide formation in these cycloalkyl phosphorus derivatives was also determined. Reaction of the bicyclo[2.2.1]heptane derivative **525** with phenyllithium gave the pentavalent phosphorane **527** mp 118–119 °C,[336,338] whereas the bi-




525 527 526a 528

cyclo[4.2.1]nonane derivative **526a** (differing from the former by only one bond) gave the ylide **528**.[336,338] Additional support that **525** and **526a** bracketed this angular dependence region for phosphorane versus ylide formation was garnered from the observation that the phosphonium salt **525** could be prepared from the corresponding phosphine oxide and phenyllithium as shown in **451** (R = Ph) → **569**.[336,338] The salt **526a** could *not* be prepared in this manner.

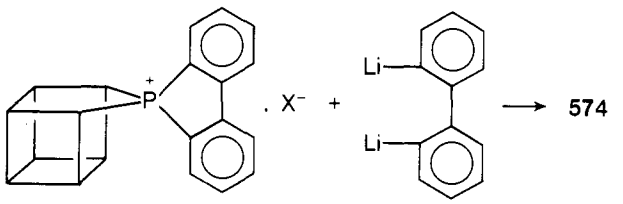
The 2,2′-biphenylyl derivative **574** (R = biphenyl-2-yl) has also



**574a**, R = 2-biphenylyl
b, R = Me

575

been synthesized, rather than the hexacoordinated phosphate **575**, in a manner analogus to **451** (R = Ph) → **569** when the phosphonium salt **576** was treated with 2,2′-dilithiobiphenyl.[335] The methyl derivative **574b** was obtained in a similar fashion.[335]

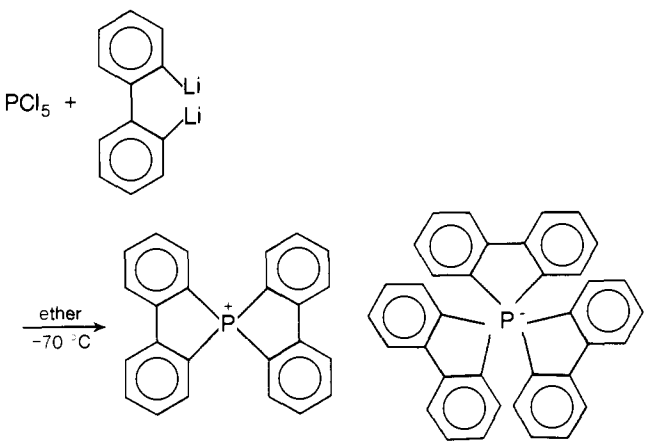


576

The barriers to the processes of pseudorotation in the homocubyltrimethylphosphorane **572a** and the homocubylphenyldimethylphosphorane **572c** have also been determined by analyses of the low-temperature $^1$H NMR spectra.[46] The $\Delta G^*$ values of the barriers for pseudorotation at −167 °C were calculated to be between 5.1 and 4.9 kcal/mol, respectively.[46] This range should be compared with values of 11.9[150] and 20.8[356] kcal/mol for the biphenylylene phosphorane **544** depending upon the substituent R.

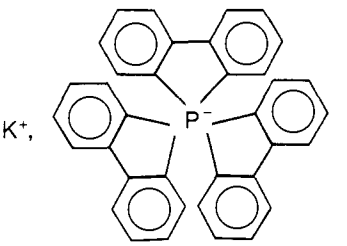
## VI. Hexacoordinate Phosphorus Systems

Paralleling the recent advances in the chemistry of pentavalent bis(2,2′-biphenylylene)phosphoranes (section V.A) has been that of hexacoordinated phosphorus(V) species. Hellwinkel isolated the first trischelated complex, [bis-2,2′-biphenylylenephosphonium][tris-2,2′-biphenylylenephosphate] (**577**), via reaction of 2,2′-dilithiobiphenyl (DLB) with phosphorus pentachloride at −70 °C (variable yields of 2–20%).[144–147] It was interesting to note that the hexasubstituted phosphate moiety gave a $^{31}$P NMR signal at +186.5 ppm (DMF) which was comparable to that of $PF_6^-$ (+118 ppm) and $PCl_6^-$ (+305 ppm).[140] A superior method for the preparation of **577** was recently discovered to involve the addition of an ethereal solution of phosphorus trichloride to DLB at room temperature (in considerably higher yield, 50%).[298] Surprisingly, little has been recorded in the area of hexacoordinated phosphorus(V) complexes, but the meager chemistry was examined several years ago.[140,181,216] The discussion here will focus on results obtained within the past few years.

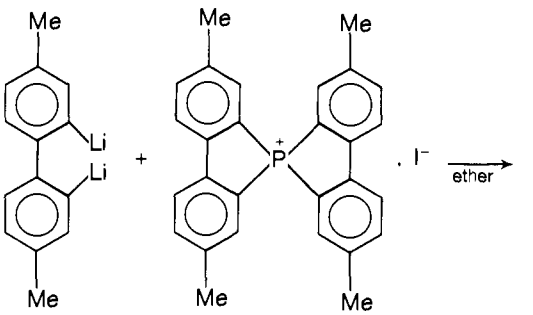


577

Hellwinkel has continued his pioneering efforts and has been able to resolve the enantiomers of potassium tris-2,2′-biphenylylenephosphate (**578**) via the methylbrucinium salts.[144] Extremely high rotations were recorded for both enantiomers $[\alpha]^{24}_{578}$ −1250 ± 15° for the +/ isomer and $[\alpha]^{24}_{578}$ +900 ± 50 for the *d* form.[144] In addition, condensation of salt **555** with 2,2′-dilithio-4,4′-dimethylbiphenyl gave the large complex system **579.** Again resolution of the hexasubstituted phosphate portion of **579** was obtained by preparation of the methylbrucinium salt.[145]



578



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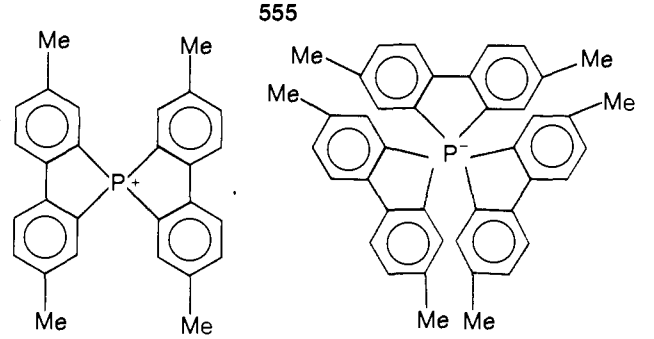
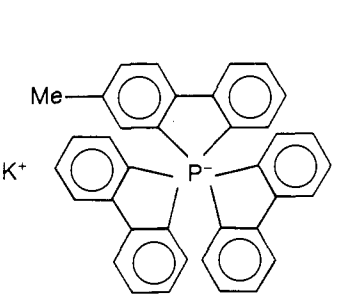


579

In studies of the stereochemical reactivity of these complexes, Hellwinkel cleaved **580** with methanolic HCl to yield three phosphoranes **581, 582,** and **583** in a ratio of 5:1:1 (via $^1$H NMR). $^1$H NMR analysis revealed the methyl groups at $\delta$ 2.0–2.4 (**581**), 2.06 (**582**), and 2.10 (**583**).[146] However, in subsequent experiments with the separate enantiomers of **580,** only one product.



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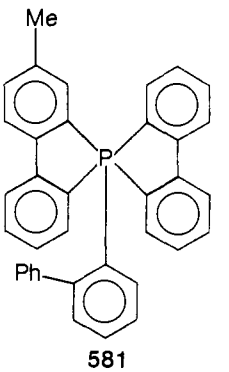
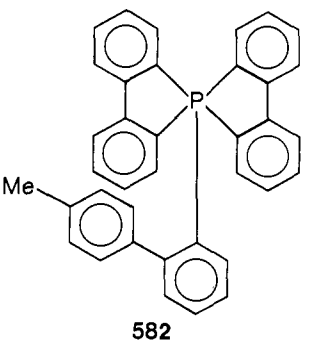


581



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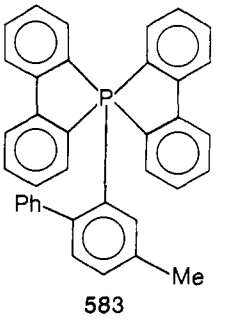
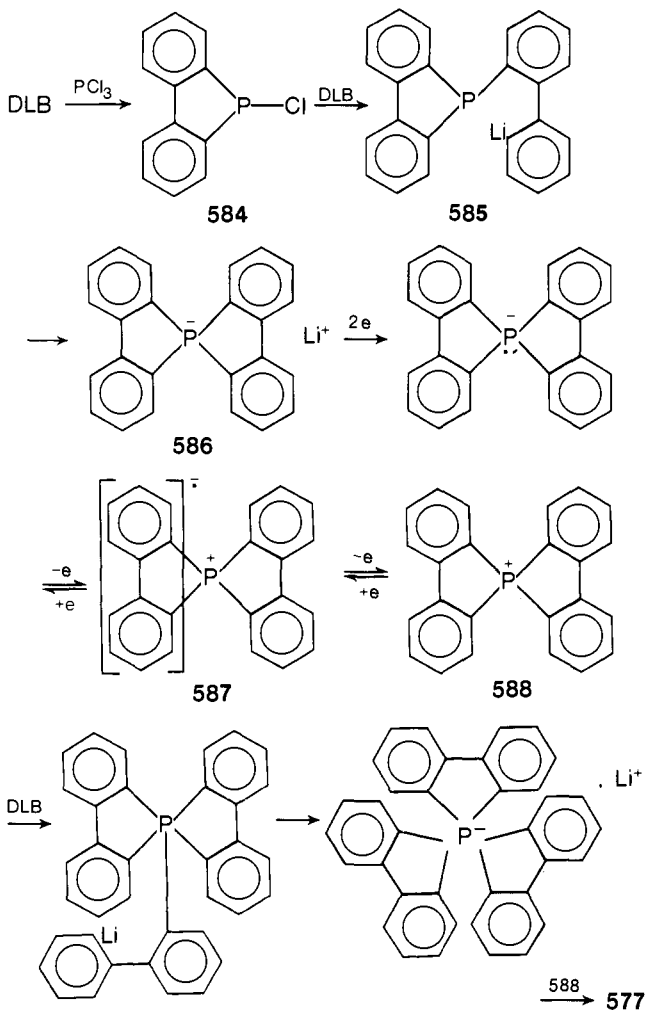


583

optically active **581,** was isolated. Undoubtedly the methyl group exerted pronounced influence on the direction of cleavage in salt **580.**[146] The bulk of all early work has been covered in the earlier summary.[140]

Recently, Hellwinkel and Mason[153] have shown that the (−) isomer of **578** possessed an octahedral arrangement of the biphenyl ligands about phosphorus with M($C_3$) (left-handed helix) absolute configuration. Circular dichroism and UV spectroscopic studies also revealed extensive π-electron delocalization between the biphenyl groups.

An electron spin resonance (ESR) study suggested a possible mechanism for the formation of **577** from phosphorus trichloride and DLB.[298] Thus, the first intermediate in the sequence was probably the phosphinous chloride **584.** Addition of another molecule of DLB would give the phosphine **585,** which could cyclize to the anionic phosphine **586.** The nature of intermediate **587** (delocalization of the charge into the biphenyl group) was suggested by the large value (148 G) of the phosphorus splitting constant. The isolation of **577** was also suggested to arise from its high insolubility in absolute ether employed.[298]



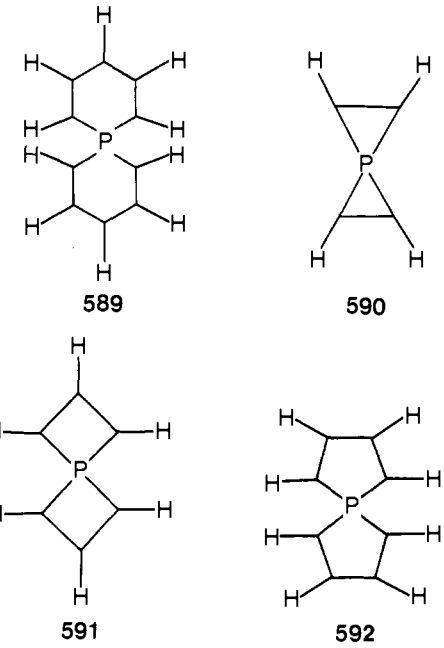

Because of the successful resolution of several hexaorganyl phosphorus(V) species,[145,146] these compounds were employed in attempted asymmetric induction reactions.[158] Upon treating optically active phosphate **577** ([α] ±1257.5°, average value for both enantiomers) with DLB, only racemic **577** ([α] ±556°, average) was obtained, however.

Very little information concerning these novel and intriguing hexacoordinated complexes has been published since 1972. Undoubtedly, this field will expand although solubility problems would appear to be severe.

## VII. Quantum Mechanical Calculations

Quantum mechanical calculations as applied to polycyclic carbon–phosphorus systems have been rare and have generally involved the interaction of the phosphorus d orbitals in a π-bonding situation with the carbon p orbitals. However, MO calculations in simple phospholes[276] and phosphabenzenes[136,275] have been investigated. A review of P–C bonding characteristics of a few C–P heterocycles has been released.[191]

One major consideration for these calculations has been the symmetry requirements of the d orbitals as compared to those of the p orbitals.[22] If the orbitals possessed a common nodal plane, considerable d–pπ interaction would be feasible. A brief report by Ashe has considered this type of interaction as applied to a series of (*n* + 1)phosphonia[*n*,*n*]spirarenes in which two parts of the system are mutually perpendicular to each other.[22] The "spirarenes" considered were **589, 590, 591,** and **592,** depicted as general structures. The problem with these calculations rested in defining the resonance integral parameter of phosphorus in terms of that of carbon. The following values for



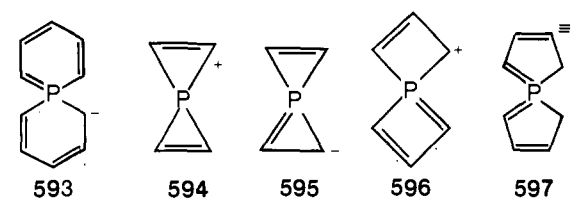

a coulomb integral of a phorphorus 3d orbital were taken as:

$$\alpha_{pp} = \alpha_{cc} + a\beta_{cc}$$

and that of an integral for a carbon 2p with a phosphorus 3d orbital as:

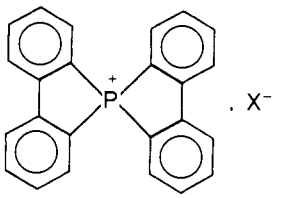
$$\beta_{pc} = b\beta_{cc}$$

Starting with **589,** parameter *b* was increased from zero. As the resonance integral increased, the nonbonding orbitals of **589** were lowered in energy and became bonding. As a result, the anion **593** would be predicted to be a stable species. For **590,**




if the interaction with phosphorus were weak, **594** would be expected to approximate to two isolated ethylene molecules. With strong phosphorus interaction in **590,** the anionic form **595** would be favored. System **591** with increased phosphorus interaction should give the cation **596.** In the case of the [4.4]

spirarene **592**, weak phosphorus interaction would approximate to two butadiene fragments, whereas strong interaction would afford the predicted highly unstable trianion **597**. The cation of salt **545** of the [4,4] system has been well recognized.[143] The

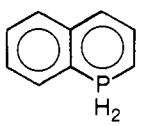


**545**

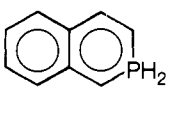
conclusions resulting from these calculations were: (a) the interaction of the phosphorus atom always reduced the energy content affording a stabilizing effect and (b) the strongest stabilization may occur for cations such as **596** since the positive charge would increase the parameters of coulomb and resonance integrals.

In recent years, a number of phosphorus heterocycles with the P atom in a delocalized $\pi$-electron system have been synthesized and the degree of aromaticity was evaluated mainly from spectral data (IR, $^1$H NMR, $^{31}$P NMR, and UV) in conjunction with chemical reactivities. Vilceanu and co-workers[342] have carried out HMO calculations on a few systems in an attempt to correlate certain parameters with both physical and chemical properties. The behavior of these systems indicate participation of phosphorus 3d orbitals in the delocalized system. Several models[37,89] have been proposed for heteroatoms with 3d orbitals, namely: (a) Fukui model,[111] with one $\pi$-electron and one d$\pi$-orbital; (b) anti-Hückel model, with a $3d_{xy}$ orbital with $\beta$ integrals of different signs for the two bonds with the neighboring atoms; (c) Dewar model with two orthogonal 3d$\pi$ orbitals at the heteroatom; and (d) different models with weak interaction between the $\pi$-orbital of the heteroatom and those of the neighboring atoms. The main difficulty with the pentavalent tetracoordinated phosphorus atom, however, has been in estimating the values of the coulomb and resonance integrals $\alpha$ and $\beta$ for the C–P bond. The Hückel parameters which were determined by these various methods were the resonance energies, the energy levels of the highest occupied orbital, and the lowest empty orbital, electronic bond orders, and electronic charge distribution.

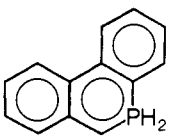
HMO calculations for phosphabenzene utilizing the above models and assuming either a strong or weak P–C interaction gave best results with Fukui and Dewar models.[342] Predictions for 1,1-diphenylphosphabenzene made from HMO calculations were in agreement with those suggested from experimental data. An extension of the calculations to the polycyclic C–P heterocycles **598, 599, 600,** and **601** by the same workers[343] has



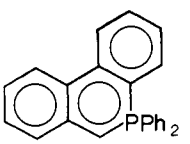
**598**



**599**



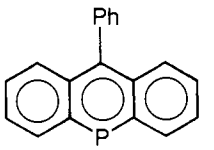
**600**



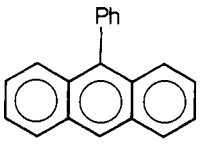
**601**

yielded some valuable information. With the Fukui and Dewar models, there was a fair degree of correlation between the difference in energies of the highest occupied and lowest empty orbitals and the wavenumber for the first maximum of the electronic absorption spectrum. However, agreement of these calculations with the spectral data of some acyclic phosphorus derivatives were not considered satisfactory. Although the comparison of these calculations on the C–P heterocycles with the limited experimental, spectral, and chemical data were encouraging, an exhaustive comparison with Hückel calculations was still not possible owing to the insufficiency of experimental data.[343] With those correlations possible, the Fukui model with the specific parameters (discussed previously) was considered the most promising.[343]

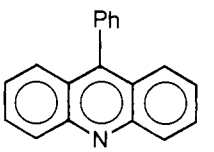
A partial confirmation of an approximate quantum mechanical calculation for a phosphorin (that the two highest occupied $\pi$-molecular orbitals were reversed in energy level sequence) was reported in the analyses of the photoelectron spectrum of 10-phenyldibenzo[*b*,e]phosphorin (**113**).[302,304] This analysis



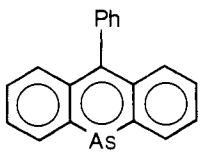
**113**



**602**



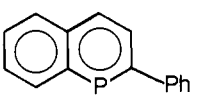
**603**



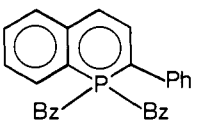
**604**

was compared with the spectra of 9-phenylanthracene (**602**), 9-phenylacridine (**603**), and 10-phenyldibenzo[*b*,*e*]arsenin (**604**).[302] There was very good correlation of the first ionization potentials of these heterocycles with the quantum mechanical calculation in that the $\pi$ MO with a nonzero coefficient on the heteroatom was higher in energy than the $\pi$ MO with its node on the heteroatom.[302] Other systems have been compared.[31]

Ionization potentials have been estimated for C–P heterocycles **605** and **606**.[303] A comparison was made of the ionization potentials of these systems with corresponding nitrogen heterocycles and showed very similar values. As more of these polycyclic C–P heterocycles become available, a better detailed comparison of spectroscopic properties with quantum mechanical calculations should afford a refinement of these approximate calculations with a more accurate estimate of the parameters utilized.



**605**



**606**

## *VIII. Appendix*

A survey of the literature from August 1975, through September 1976, has resulted in more than 40 additional publications on polycyclic C–P heterocycles. The work will be cited briefly in order of the sections given in the Contents.

Wiseman and Krabbenhoft[409] have found that syn and anti isomers of 9-phenyl-9-phosphabicyclo[3.3.1]nonan-3-one 9-oxide can be obtained by a Michael addition process employed by Kashman[193,199] previously (section II.B). Both chemical and $^{13}$C NMR analyses were employed.

Under cycloalkylations (section II.C), single C–P ring formation via reduction of $\omega$-haloalkyl-substituted phosphonates has appeared in a full paper.[405] Preliminary papers were recorded earlier.[55,353] Undoubtedly, the utility of the procedure can find application in polycyclic C–P heterocycles. A few special cycloalkylations involving tricyclic C–P heterocycles have also been published.[377,388]

Novel acylphosphines[376,387] have been reported in a cycloalkylation procedure using dilithium reagents (see also section II.C). A few physical properties are given also. An unusual P–P-containing compound was made in similar fashion.[401]

Chan and Nwe[371] have continued their work in cycloadditions for the preparation of isophosphindoline systems (see section II.C).[53,54,57] Several unique bicyclic C–P heterocycles have also appeared from the laboratories of Kashman[389] (see section II.D)[194,200] and Quin[402] (see also section II.D for similar condensations) with ample $^{13}C$ NMR data for stereochemical analysis.

Photocatalyzed cyclization of *o,o'*-bis(phenylethynyl)triphenylphosphine afforded a highly substituted phosphindoline.[408] Other photolysis reactions occur in section II.E.

A series of β-hydroxyalkylphosphine oxides undergo dehydration to alkyl- or vinyl-substituted phosphine oxides. The latter cyclized to five- or six-membered C–P heterocycles[380] (cf. section II.F).[90,282] A key step in the synthesis of a substituted 2-phosphanaphthalene was a PPA-catalyzed acylation.[378] UV, $^{13}C$ NMR, and $^{1}H$ NMR spectra are included for the 2-phosphanaphthalene derivatives.

A more detailed paper on the preparation of 1,6-diphosphatriptycene from *o*-dichlorobenzene and white phosphorus[404] has appeared (cf. section II.G).[347] The related monophosphorus–carbon analog has undergone $^{1}H$ NMR and IR analyses[410] in an effort to evaluate bonding properties and bond angle size in the tricyclic system (cf. section II.C, compound **119**).[190]

A number of papers have appeared on the theory of pseudorotation[369,372,379,391] and especially as applied to hydrolysis[379] and reduction[379] in a variety of phosphorus compounds (cf sections III.A and III.C). Data are critically evaluated.

A series of polycyclic C–P heterocyclic P-oxides containing an epoxide ring have been reduced to the corresponding phosphines without rupture of the oxirane ring.[403] $^{1}H$ NMR and $^{13}C$ NMR data are included in the stereochemical analysis.

A variety of phosphine–metal complexes of C–P heterocyclic systems have been investigated recently (ref 373, **375**, 385, 386, 396, 399, 406) (cf. section III.E). Two tribenzo[*b,d,f*]phosphepin oxides have been obtained by this type of complexation.[407]

Improved procedures for several pentasubstituted, hexacoordinated, and related P-containing systems were released.[381,382,392] Considerable spectral data have been included (cf. sections V and VI).

Photoelectron spectra[368,388,393–395,397] on phospharenes and phospholes have shed light on the aromatic qualities of these heterocycles. Theoretical studies on the aromaticity of phospholes[374] as well as a review[383] are now available.

Several other polycyclic C–P heterocycles have been reported.[370,384,398,400] X-Ray analysis of 6-methyl-6-oxo-3,5,7-triphenyl-6λ$^5$-phosphatricyclo[3.3.1.0$^{2,7}$]non-3-ene has confirmed[398] the predicted unusual structure (cf. section II.E).[301] Mass spectral analysis of 1-phosphabicyclo[2.2.1]heptane 1-oxide (**116**) and 1-phosphabicyclo[2.2.2]octane 1-oxide (**117**) (section II.C) was recorded recently.[390]

A few new entries are added to the appendized tables.

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**Supplementary Material Available.** Tables of compounds will appear following these pages in the microfilm edition of this volume of the journal. The tables (236 pp) contain structural formulas, molecular formulas, melting points, boiling points, spectral data, physical data, and reference numbers which correspond to the references provided at the end of this review. The classes of compounds covered are: phosphines, phosphonium salts, phosphine oxides, phosphine sulfides, phosphinic acids, salts of phosphinic acids, phosphinates, organophosphorus–metal complexes, pentavalent phosphorus compounds, and compounds with more than one phosphorus atom. Microfiche (4 × 6 in., 24×, negative, silver halide) of the supplementary material may be ordered directly from Business Operations, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Full bibliographic citation (journal, title of article, author) and prepayment ($2.50, U.S.; $3.00, PUAS, Canada; $3.50, other foreign countries) are required.

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