Synthesis and Properties of Phosphetanes

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Angela Marinetti was born in San Damiano d'Asti, Italy, in 1956. In 1979 she completed graduate studies at the University of Torino and she received her Ph.D. degree in 1984 at the University of Paris VI under the supervision of Professor F. Mathey. She worked as a postdoctoral fellow at the University of Rennes (Professor G. Jaouen) and at the University of Wisconsin in Madison (Professor R. West). In 1981, she became a permanent member of CNRS, where she is currently Directeur de Recherche. From 1981 to 1998 she was member of the research group directed by Professor F. Mathey at the Ecole Polytechnique (Palaiseau, France). In 1998, she joined the "Laboratoire de Synthèse Sélective Organique" directed by Professor J−P. Genêt, at the Ecole Nationale Supérieure de Chimie de Paris. Her research interests include the organic and organometallic chemistry of phosphorus and their implications in asymmetric catalysis.

Duncan Carmichael was born in Liverpool, England in 1960. After BSc (King's College, London), MSc and Ph.D. degrees (University of Sussex, with Alan Pidcock and John F. Nixon), he joined the phosphorus chemistry department at Ecole Polytechnique, headed by Francois Mathey, in 1989 and became a permanent member of CNRS in 1994. Having recently returned from sabbatical leave, studying enantioselectivity with John Brown in Oxford, he is currently interested in the synthesis of electroactive phosphametallocenes, their potential, and applications.

I. Introduction

The first synthesis of a phosphetane ring was reported by Kosolapoff and Struck in 1957:[1] a very small amount of phosphetanic acid (<1% yield) was

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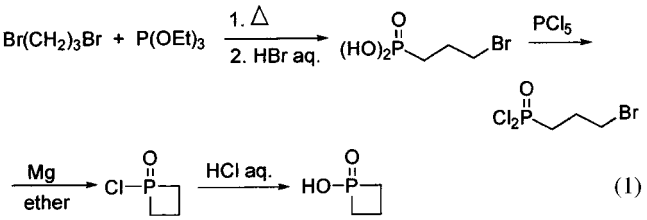
prepared from 1,3-dibromopropane and triethyl phosphite in a three-step sequence based upon Arbuzov and Grignard reactions (eq 1). The very low yield probably discouraged research in the field.



(1)

The next significant development was made in 1962 by McBride,[2] who discovered an apparent electrophilic addition of phosphenium ions to suitably substituted olefins that provided a very convenient access to phosphetanes (see section II.1). The McBride method remained the only viable phosphetane synthesis for about 20 years, when many of the studies in the field were performed. Consequently, most of the physical and chemical studies of phosphetanes have been made upon a single series of highly alkylated derivatives that are devoid of functional groups.

Many of these early studies on phosphetanes dealt with aspects of stereochemistry: the limited conformational freedom within the four-membered ring imposes constraints that allow phosphorus stereochemistry to be analyzed easily by spectroscopic methods. Thus, at this time, phosphetanes offered a uniquely valuable system for understanding the fluxionality and pseudorotations of pentacovalent intermediates in the reactions of tetracovalent phosphorus compounds.

For many years throughout the 1980s and early 1990s, almost no significant advances were made and only a few theoretical studies were reported. Interest in phosphetanes has recently been revived by the realization that phosphorus-containing heterocycles are excellent ligands for asymmetric catalysis and that there is some potential for phosphetanes as precursors for preparing phosphines *via* ring-opening reactions. Especially, new synthetic methods have been developed that allow the preparation of a wide range of optically active species and the use of chiral phosphetanes in asymmetric catalysis.

Thus, it seems that the chemistry of phosphetanes is ripe for development.

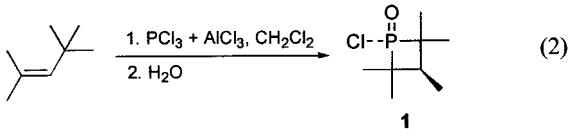
Phosphetane chemistry has not been specifically surveyed in recent years. The most recent review appeared in chapter 1.27 of *Comprehensive Heterocyclic Chemistry*, 2nd ed. (1996), by Kawashima and Okazaki,[3] which summarized the entire field of four-membered rings containing a group V element, thus including phosphetanes. The present article summarizes phosphetane chemistry and places particular emphasis upon the properties, syntheses, and applications that are likely to encourage new studies in this field.

II. Synthetic Approaches to the Four-Membered Rings

Two fairly general synthetic methods are available for building phosphetane rings. The first is the McBride method involving the apparent electrophilic addition of phosphenium cations to suitable olefins. Recently, this approach has been complemented and, to a degree, superseded by routes involving the addition of 1,3-bis-electrophiles to phosphide reagents or their synthetic equivalents. A small number of cycloaddition and rearrangement reactions have also been shown to afford specific classes, or even single compounds, of the phosphetane family.

1. The McBride Synthesis and Related Methods

In the early sixties, McBride et al. developed a new olefin phosphorylation procedure based on the reaction of electron-rich olefinic double bonds with PCl_3 in the presence of $AlCl_3$. In these reactions, the apparent addition of phosphenium ions to olefins generates carbocationic intermediates that are prone to rearrangement, with the nature of the final product depending mainly on the substitution pattern in the olefin. Use of 2,4,4-trimethyl-2-pentene as the phosphorylation substrate provided the first high-yield synthesis of any phosphetane derivative, the phosphetanic chloride **1** (eq 2).[2]

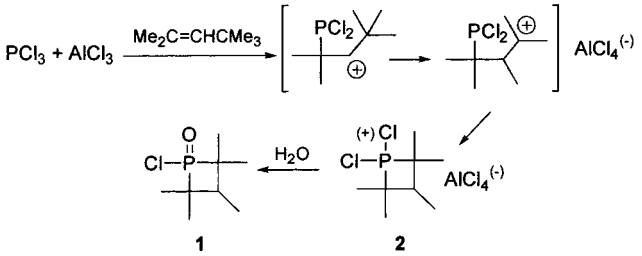


(2)

The *trans* isomer was obtained selectively.[4,20] Its stereochemistry was established by X-ray crystallography.[5]

The generally accepted mechanism (Scheme 1) involves addition of a phosphenium ion at the 2-position of the olefin. This is followed by [1,2]-shift of a methyl group to convert the first-formed intermediate into the more stable tertiary carbocation. The rearranged ion undergoes electrophilic addition to phosphorus to afford the phosphetanium salt **2**. Hydrolysis then gives **1**.[6]

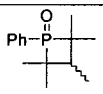
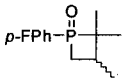
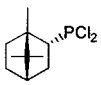
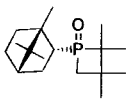
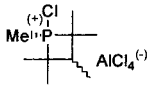
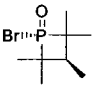
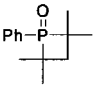
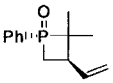
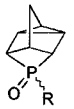
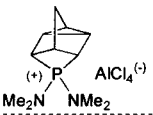
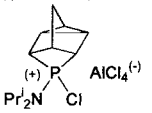
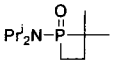
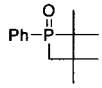
Scheme 1. Mechanism of the McBride Phosphetane Synthesis



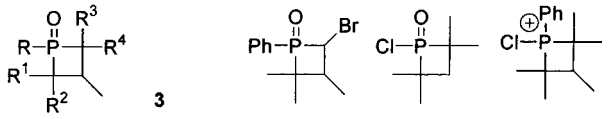
For practical reasons, the McBride synthesis is usually adapted to the preparation of phosphetane oxides. Nonetheless, trivalent phosphetanes are also available by triphenyl- and tri-*n*-butylphosphine reduction of the intermediate phosphetanium salts.[7,8]

Following the synthetic approach of eq 2, a range of olefins has been involved in the reactions with PCl_3, PBr_3, $ArPCl_2$, $MePCl_2$, etc. to give phosphetane oxides of the general formula **3**[9−14] (see Table 1).

Table 1. Examples of Phosphetane Synthesis *via* Electrophilic Additions to Olefins, Dienes and Cyclopropanes

RPX_2	Olefin, diene or cyclopropane	Reagents and conditions	Product	Yield	Ref.
$PhPCl_2$		1.$AlCl_3$, CH_2Cl_2, 5°C 2.H_2O	 *Cis*+*trans*	48%	9
$PhPCl_2$	 or 	1.$AlCl_3$, CH_2Cl_2, 5°C 2.H_2O	 *Cis*+*trans*	44% 69%	9 9
$PhPCl_2$		1.$AlCl_3$, CH_2Cl_2, 5°C 2.H_2O		58%	9
(p-FPh)PCl_2.$AlCl_3$ prepared *in situ* from FC_6H_5+PCl_3+$AlCl_3$		1.CH_2Cl_2, rt., 20h 2.H_2O, 0°C	 >90% *trans*	65%	12
$MePCl_2$		1.$AlCl_3$, CH_2Cl_2, 5°C 2.H_2O	 *Cis*+*trans*	23% 90% 78%	9 10 19
$PhPCl_2$		1.$AlCl_3$, CH_2Cl_2, 0°C 2.Bu_3P, 0°C	 *Gis*+*trans*	56%	8
		1.$AlCl_3$, CH_2Cl_2, 0°C 2.H_2O		50%	21
$MePCl_2$		$AlCl_3$, CH_2Cl_2, 5°C	 4:1 mixture	85%	19
PCl_3		1.$AlCl_3$, CH_2Cl_2, 0°C 2.H_2O	 84% *trans*	92%	20
PBr_3		1.$AlBr_3$, 0°C, CH_2Br_2 2.H_2O		62%	11
$PhPCl_2$		1.$AlCl_3$, CH_2Cl_2, 5°C 2.H_2O		46%	17
$PhPCl_2$		1.$AlCl_3$, CH_2Cl_2, rt 2.$NaHCO_3$		20%	16
$MePCl_2$		1.60-80°C, 2 weeks 2.H_2O.		R=Me 73%	28, 29, 30
$(EtO)_2PCl$		$FeCl_3$, CH_2Cl_2, 0°C to rt.		R = OH 84%	27
$(Me_2N)_2P^{(+)}AlCl_4^{(-)}$		CH_2Cl_2, 0°C to rt., 1h		95%	26
$Pr^i_2NPCl^{(+)}AlCl_4^{(-)}$		CH_2Cl_2, 0°C to rt.			26
$Pr^i_2NPCl^{(+)}AlCl_4^{(-)}$		1.CH_2Cl_2, rt., 2h 2. H_2O		80%	31
$PhPCl_2$		1.$AlCl_3$, CH_2Cl_2 2. H_2O			31

The major limitation of the McBride method is that the necessary rearrangement of the intermediate carbocation through a methyl group shift imposes the use of branched olefins such as 2,3,3-trimethyl-1-butene, 3,4,4-trimethyl-2-pentene, or 3,3-dimethyl-1-butene. Thus, the final phosphetanes are highly substituted species having at least three methyl groups on the ring carbons. The only example of C-functionalized species obtained by this method is the 2-bromophosphetane **4**, prepared from 1-bromo-3,3-dimethyl-1-butene.[15]



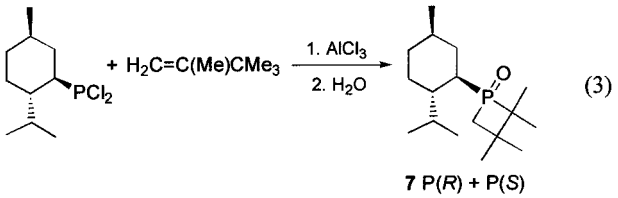
3 **4** **5** **6**

R^1-R^4 = H or Me

In a few cases, carbocations generated through phosphenium ion addition to the olefin may rearrange through migration of hydrogen,[9] vinyl, or phenyl substituents.[16] For example, [1,2]-hydrogen shift was observed in the synthesis of phosphetane **5** and analogues from 2,4-dimethyl-2-pentene.[17,18]

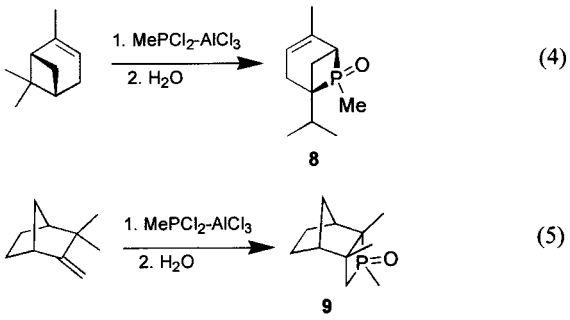
For unsymmetrically substituted species, the ratio of geometrical isomers (mainly *cis*−*trans* isomers with respect to the phosphorus substituent) depends not only on the nature of the reagents but also on the experimental conditions employed during the hydrolysis step.[9,19,20] Hence, the addition of water to the phosphetanium salt **6** gives the corresponding *cis*,*trans*-oxides in a 1:3 ratio, while the reverse addition of the phosphetanium salt to water furnishes the *cis*-oxide as the main product (2:1 ratio).[19]

More recently, the McBride synthesis has been used to prepare chiral phosphetane oxides through the reaction of optically active dichlorophosphines with 2,3,3-trimethyl-1-butene. Thus, menthyl-, myrtanyl-, bornyl- and isopinocampheyldichlorophosphines afford phosphetane oxides having chirality localized on both the phosphorus substituent and the phosphorus center. In all cases, epimeric mixtures were obtained with moderate to low selectivity.[7,21] As a representative example, the synthesis of the *P*-menthylphosphetane oxide **7**, is given in eq 3.



7 P(*R*) + P(*S*) (3)

Pure *P*(*R*)- and *P*(*S*)-epimers of *P*-menthylphosphetane oxides **7** can be separated in good yields by fractional crystallization. Reaction 3 allowed the first large-scale synthesis of optically pure phosphetanes. Previously, small samples of the optically active phosphetane oxides **8**[22] and **9**[23] had been isolated from the reactions of $MePCl_2$ with α-pinene and camphene, respectively (eqs 4 and 5).

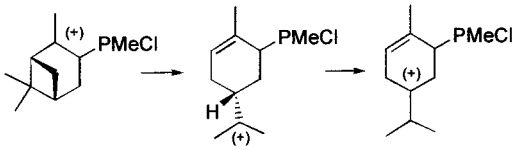


8 (4)

9 (5)

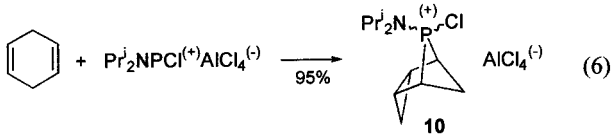
Again, they were formed through the apparent electrophilic addition of phosphenium ions to the double bonds in the terpene starting materials and rearrangement of the intermediate carbocations (Schemes 2 and 3).

Scheme 2. Carbocationic Intermediates in the Synthesis of 8

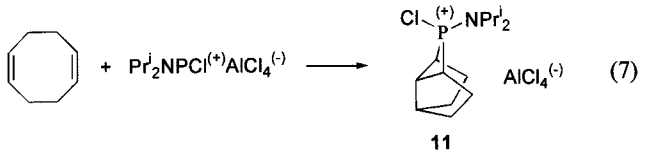


Scheme 3. Carbocationic Intermediates in the Synthesis of 9

In addition to the simple olefins above, a few other unsaturated substrates serve as starting materials for building phosphetane rings. Thus, Cowley developed the electrophilic addition of stabilized phosphenium ions to cyclic dienes as an approach to polycyclic phosphetanium salts. 1,4-Cyclohexadiene[24] and 1,5-cyclooctadiene[25] were used as starting materials for phosphetanes **10** and **11**, respectively (eqs 6 and 7).



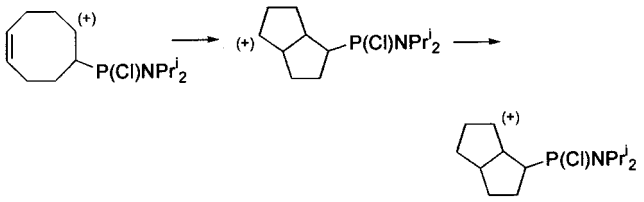
10 (6)



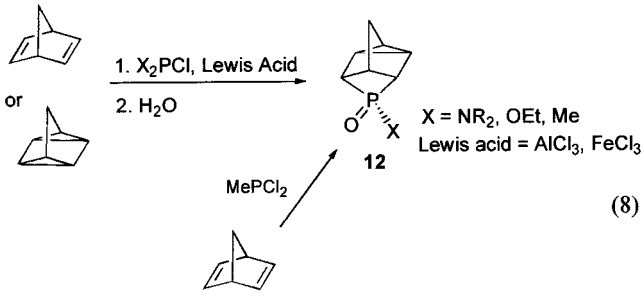
11 (7)

The stereochemistry of **11** was established by an X-ray crystal structure. The geometry of the molecule is controlled by the preference of the bulky diisopropylamino substituent to occupy a pseudoequatorial position. No experimental evidence for the reaction mechanism is available but, again, carbocations generated by the addition of the phosphenium ions to a double bond are likely intermediates (Scheme 4).

Scheme 4. Carbocationic Intermediates in the Synthesis of 11



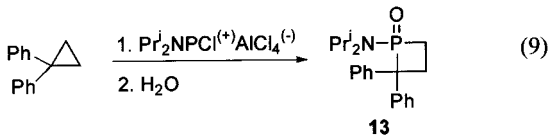
In similar reactions, norbornadiene reacts readily with stabilized phosphenium ions to afford tetracyclic phosphetanium salts and, after hydrolysis, the corresponding oxides **12**.[26,27]



(8)

Phosphetanes of the general formula **12** may also be obtained through both insertion of phosphenium ions into quadricyclanes (X = NR_2)[26] and McCormack-like cycloaddition of norbornadiene with methyldichlorophosphine (X = Me).[28] Unlike the phosphenium ion additions described previously, this last reaction does not require activation by Lewis acids. It affords either the pure *exo* isomer or a 4:1 isomer ratio in favor of the *exo* product as a function of the workup procedure.[29,30] The scope of this last approach to phosphetanes seems to be very restricted.

The synthesis of phosphetane **12** from quadricyclane suggests that other derivatives may be accessible through insertion of phosphenium ions into cyclopropanes. To date, only one report deals with such a phosphenium ion insertion which gave among other, the first C-aryl-substituted phosphetane, **13**.[31]

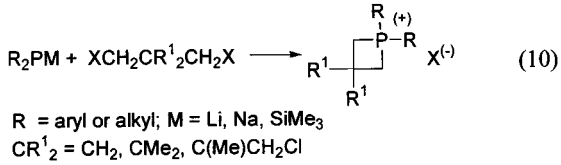


(9)

Additional representative examples of phosphetane syntheses through electrophilic additions of phosphorus derivatives to olefins, dienes, and cyclopropanes are given in Table 1.

2. Electrophilic Alkylation–Cyclizations on Phosphorus Derivatives

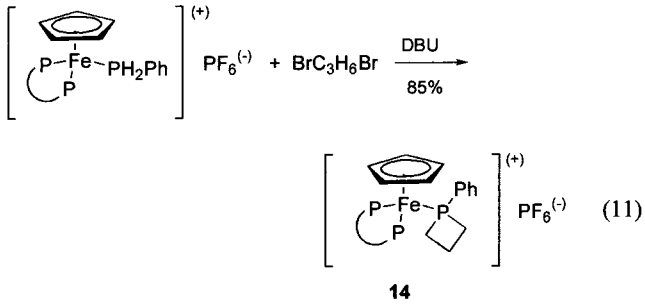
Although the combination of unfavorable entropy and ring strain mean that four-membered rings are usually more difficult to synthesize by cyclization reactions than their three- or five-membered homologues, it has long been established that phosphetanium salts can be prepared from monolithium phosphides and 1,3-dihaloalkanes (eq 10 and Table 2).[32,33]



(10)

More recently, this approach has been extended to the preparation of C-unsubstituted phosphetanium salts through the use of secondary phosphines or silylphosphines in the first alkylation step.[34]

Concerning trivalent phosphetanes, the most obvious synthetic approach involves the related reaction of primary phosphines with 1,3-difunctional electrophiles. This reaction has only been mastered recently. In an early investigation of the interaction of dilithium phenylphosphide with 1,3-dichloropropane, 1-phenylphosphetane was obtained in only 13% yield, because of chain-forming side reactions and an instability of the final product in the reaction mixture.[35,36] However, yields improved to 84% in an analogous reaction where the phenylphosphide nucleophile was complexed to an iron center (eq 11),[37,38]

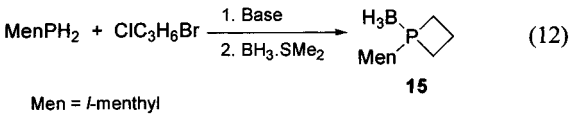


(11)

probably because of the stabilization conferred to the final phosphetane by complexation at phosphorus.

Subsequently, analogous cyclization reactions on phosphides, followed by coordination of the final phosphetanes to borane or sulfur prior to workup, have been shown to give satisfactory yields of C-unsubstituted aryl- and alkylphosphetane derivatives.[39−41] Representative examples are given in Table 2.

The drive to prepare phosphetanes from phosphides and 1,3-dielectrophiles has come mainly from the potential uses of chiral phosphetanes in catalysis. Two different approaches allowing access to chiral phosphetanes from phosphines and 1,3-dielectrophiles have been examined. In the first (eq 12) the

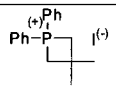
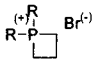
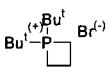
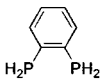
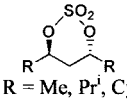
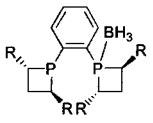
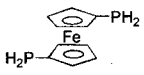
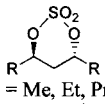
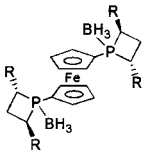
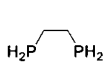
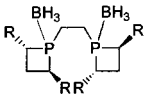
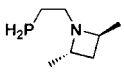
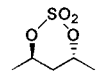
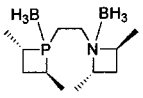
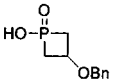
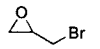
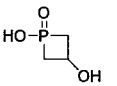
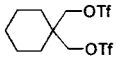
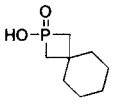


(12)

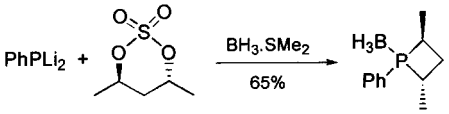
chirality is localized in the menthyl group attached to the phosphorus atom of a primary phosphine. Reaction between an achiral electrophile and the chiral phosphide gives a moderate 30% yield of 1-menthylphosphetane, isolated as its borane complex **15**.[39]

In the second method, optically pure difunctional electrophiles are made to undergo stereospecific substitution reactions with achiral phosphines to give

Table 2. Examples of Phosphetane Syntheses through Alkylation−Cyclization Reactions on Phosphorus Compounds

Phosphorus derivatives	Electrophiles	Reagents and conditions	Product	Yield (%)	Ref.
Ph_2PLi	$ClCH_2CMe_2CH_2Cl$	1.THF, rt 2.NaI, benzonitrile, reflux		49%	33
R_2PSiMe_3 R = Bu^t R = Mesityl	$I(CH_2)_3I$	 Neat, rt., 10 min. Neat, rt. 0.5 h		 84% 75%	 34
R_2PSiMe_3 R = Bu^t R = Pr^i	$Br(CH_2)_3Br$	 rt., 24 h rt. 24h		 76% 23%	 34
Bu^t_2PH	$Br(CH_2)_3Br$	1.Neat, rt., 1h 2.K_2CO_3, THF/CH_2Cl_2 reflux, 15 d		40%	34
$PhPH_2$	$MsO(CH_2)_3OMs$	1. 2 nBuLi, THF, -40°C 2. S_8		58%	41
	$TsO(CH_2)_3OTs$			60%	40
(Mesityl)PH_2 (1-Adamantyl)PH_2 (Ferrocenyl)PH_2 (Cyclohexyl)PH_2 (Ferrocenyl)CH_2PH_2		1.BuLi (2 equiv), THF, -78 to rt. 2. $BH_3.SMe_2$		62% 63% 50% 73% 72%	41 44 182
	 R = Me, Pr^i, Cy R = CH_2Ph	1.BuLi (4 equiv), THF, -78 to rt. 2. $BH_3.SMe_2$		40-46% 45%	41, 47 48
	 R = Me, Et, Pr^i, Pr, Bu^t	1.BuLi or LDA, THF, -78 to rt. 2. $BH_3.SMe_2$		45-55%	50,51
	 R = Me, Pr^i, Cy	1.BuLi (4 equiv), THF, -78 to rt. 2. $BH_3.SMe_2$		32-65%	49
		1.BuLi (2 equiv), THF, -78 to rt. 2. $BH_3.SMe_2$		25%	182
$H_2PO_2NH_4$	$(BrCH_2)_2CH(OBn)$	$HN(TMS)_2$, mesitylene, reflux, 20h		30%	52
$H_2PO_2NH_4$		$HN(TMS)_2$, mesitylene, reflux, 20h		27%	52
$H_2PO_2NH_4$		$HN(TMS)_2$, mesitylene, reflux, 20h		75%	52

C-chiral phosphetanes. This approach is typified in eq 13.[41] Notably, the same strategy has been applied

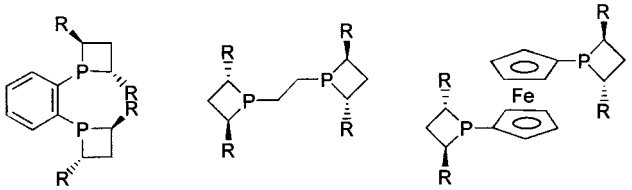


(13)

to the synthesis of other chiral phosphorus heterocycles, namely phospholanes[42] and phosphiranes.[43] The phosphetane synthesis of eq 13 is compatible with both aryl and alkylphosphines.[44,45] Mesylates or cyclic sulfates derived from optically pure 1,3-diols are the preferred starting materials, because the corresponding chiral diols are easily available on a

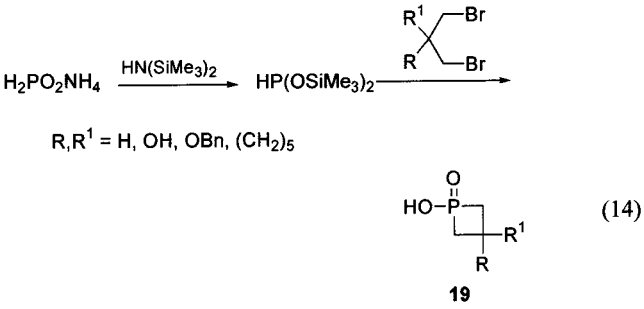
large scale through the enantioselective ruthenium-promoted hydrogenation of β-diketones.[46]

The complexation to borane confers a degree of stability and simplifies the purification step (particularly in small-scale experiments). The phosphetane can be readily recovered from the borane adduct by heating with excess 1,8-diazabicyclo[2.2.2]octane. The borane complexation step may be omitted when the final product can be distilled or crystallized under oxygen-free conditions. The most notable application of this method has been in the synthesis of the C_2-symmetric bisphosphetane derivatives **16**,[41,47,48] **17**,[49] and **18**,[50,51] whose rhodium and ruthenium complexes



display interesting catalytic properties (see section VI below).

A further approach to phosphetane rings makes a number of phosphetanic acids **19** available in a single

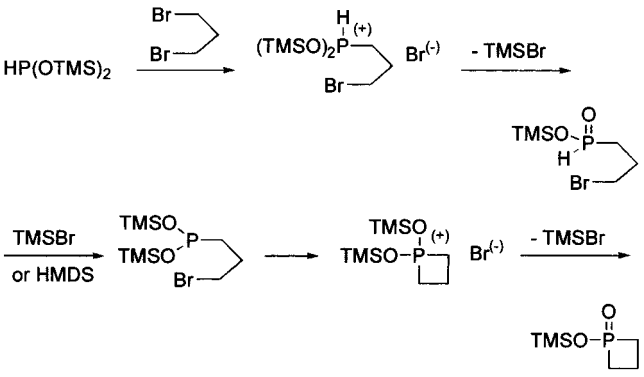


(14)

step through the double Arbuzov reaction of bis(trimethylsilyloxy)phosphine (BTSP) with dielectrophiles.[52] BTSP is conveniently generated in situ from hexamethyldisilazane and ammonium hypophosphite.

The proposed mechanism for the reaction with 1,3-dibromopropane is shown in Scheme 5.

Scheme 5. Assumed Mechanism for Reaction 14

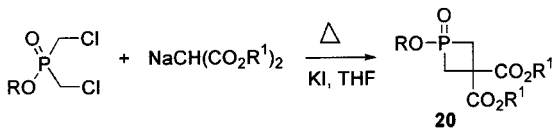


This reaction gives yields of 30−75% and is the best current routes to phosphetanic acids. It improves considerably upon two previous methods, an Arbuzov reaction at triethyl phosphite[1] and the addition of di-Grignard reagents to $Cl_2P(O)OEt$,[53] which give phosphetanic acid in yields below 10%.

Phosphetane syntheses *via* electrophilic cyclization reactions are exemplified in Table 2

3. Nucleophilic Cyclizations on Phosphorus Derivatives

Up to date, a single report describes the large-scale synthesis of phosphetanes by cyclization between bifunctional phosphorus derivatives and carbon nucleophiles.[54] The four-membered ring is formed from CPC and C fragments, by reacting bis(chloromethyl)-phosphonates with sodium malonates (eq 15).

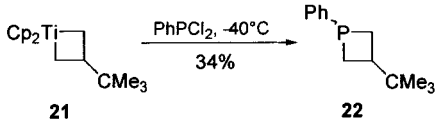


(15)

The phosphetanic esters **20** are obtained in good yields (60%). Subsequent acid hydrolysis in forced conditions affords the corresponding phosphetanic acids together with decarboxylated derivatives.

4. Heteroatom Transfer Reactions

Metallacycles involving early transition metals (Ti, Zr) undergo easy phosphorus-metal exchange reactions and are often useful starting materials for the synthesis of phosphorus-containing heterocycles.[55] This approach seems likely to provide a very useful access to phosphetane derivatives in the future, but only a single example of its use has appeared to date. Titanacyclobutane **21** reacts with phenyldichlorophosphine to afford a 1:1 *cis*−*trans* mixture of phosphetanes **22**.[56]



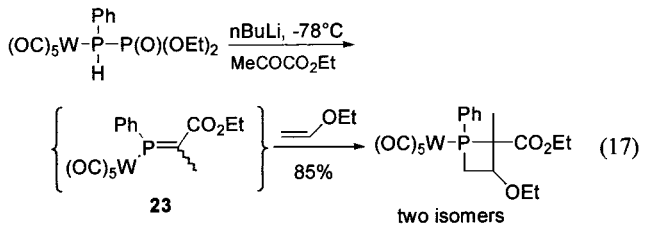
(16)

Separation of the *cis*- and *trans*-isomers was not attempted, and the products were used directly to investigate the behavior of phosphetanes as substrates in ring-opening polymerization reactions.

5. Cycloadditions and Rearrangements

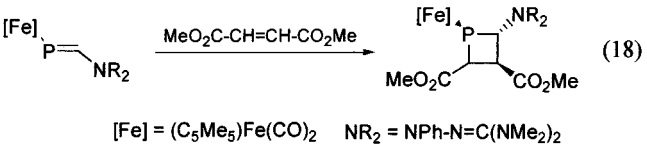
Phosphetanes have been formed through both intra- and intermolecular [2 + 2] cycloaddition reactions between phosphaalkenes and activated olefins. These reactions have usually been performed to determine the reactivity of low-coordinated phosphorus derivatives rather than as phosphetane syntheses per se. At present their synthetic usefulness is limited by the restricted availability of the phosphaalkene starting materials.

Cycloadditions usually take place between unsaturated reaction partners having complementary electronic characteristics. Thus, the first synthesis of phosphetanes through [2 + 2]-cycloadditions involved electron-poor phosphaalkene complexes and electron-rich olefins. An example is given in eq 17. The highly

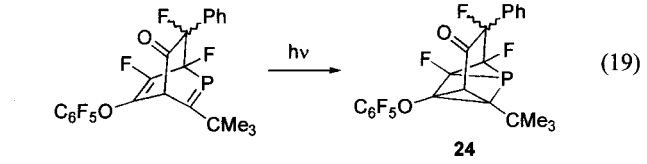


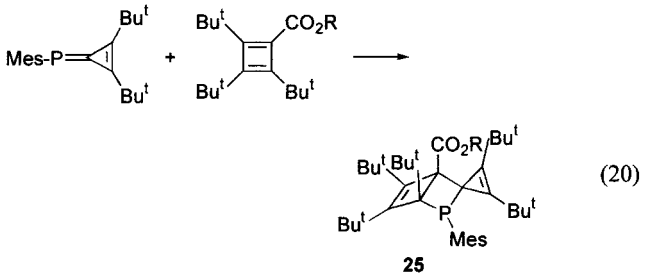
reactive phosphaalkene intermediates **23** are generated in a "phospha-Wittig" reaction from phosphorylphosphine complexes and ethyl pyruvate and are reacted in situ with enamines or enol ethers.[57]

The reverse case of a cycloaddition between a phosphaalkene derivative and an electron-deficient olefin is shown in eq 18.[58]



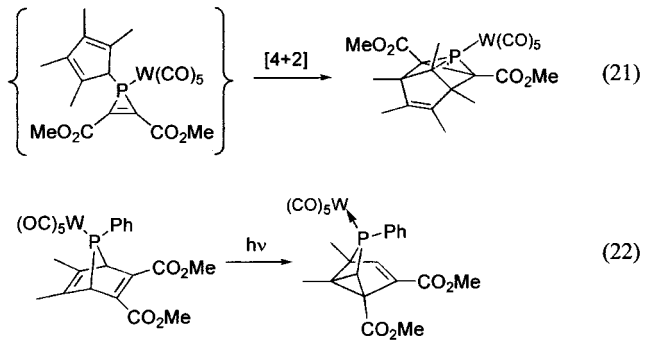
Two additional examples of [2 + 2] cycloaddition reactions with phosphaalkenes led to unstable polycyclic phosphetanes whose structures have been assigned as in eqs 19[59] and 20.[60] Compound **24**





results from an intramolecular cycloaddition reaction, while the spiro-linked phosphabicyclo[2.2.2]hexene **25** is formed in the reaction between phosphatriafulvene and a kinetically stabilized cyclobutadiene.

Finally, eqs 21 and 22 show two examples of polycyclic phosphetane derivatives that are produced through specific intramolecular reactions. They involve a [4 + 2]-cycloaddition of a cyclopentadienylphosphirene[61] and the photoinitiated rearrangement of a 7-phosphanorbornadiene,[62,63] respectively.



These interesting transformations have little synthetic utility at present.

6. Summary of Synthetic Methods

The main synthetic methods used to build the four-membered rings are summarized in Table 3.

III. Structural, Spectroscopic, and Theoretical Data

1. X-ray Diffraction Studies

Tri- and Tetracoordinate Phosphetanes

A number of X-ray crystal studies have been performed on tetracoordinated phosphetanes, while only one structure of a tricoordinated monocyclic phosphetane[48] has been reported. The majority of structural data on phosphetane oxides,[64−67] sulfides,[68,39,40] borane complexes,[44,48] and phosphetanium salts[69−71] establish basic trends that appear to be valid for most phosphetane types. First, phosphetanes have been found to have folded geometries, with steric repulsions between the substituents at C3 and phosphorus generally dictating the direction of the fold. Hence, for *cis*-configured phosphetanes, the phosphorus and C3 substituents generally lie diequatorially to minimize nonbonded interactions;[72] in the more ambiguous case of *trans*-configured compounds, the conformation is usually dominated by a preference for orienting the C3 substituent equatorially.[73] A selected example is illustrated in Figure 1.

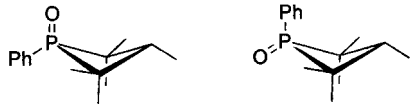


Figure 1. Solid-state geometry for *cis*- and *trans*-phosphetane oxides **26**.[64,65]

The fold angles made by the CCC and CPC planes for monocyclic phosphetanes vary from 0° to 30°. Nearly planar rings are observed in compounds with very bulky substituents at phosphorus or in the 3-position.[34,56] However, early attempts to rationalize the phosphetane fold angle as a function of the extent of ring substitution[74] must be viewed with some caution, as dihedral angles seem to be relatively sensitive to small changes in overall geometry.[75] This hypothesis receives support from several X-ray studies[34,36] that, in giving high thermal factors for the unique ring carbon atom, imply a folding disorder between energetically similar conformers lying on a soft potential surface. Recent data suggest that crystal packing forces may also play an important role.

In monocyclic phosphetanes, the P−C intracyclic bond lengths lie between 1.96 and 1.79 Å (cf. typical values for P−C bond length in classical phosphines at 1.84 Å), with sterically hindered, C_α-substituted phosphetanes showing P−C distances lying toward

Table 3. Summary of Synthetic Methods

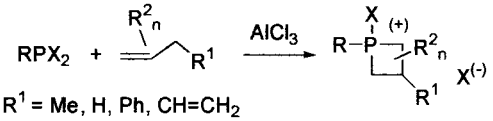
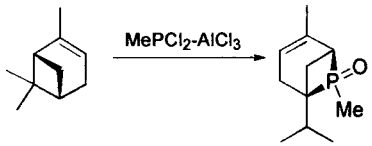
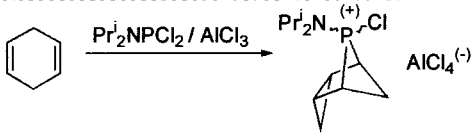
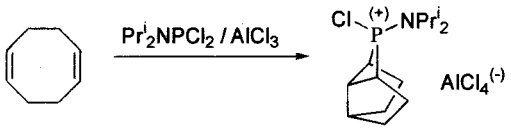
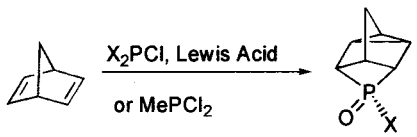
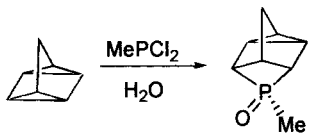
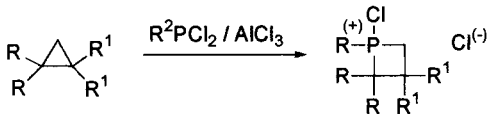
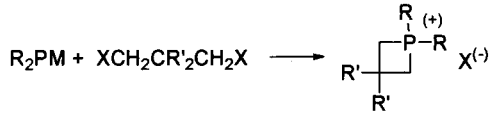
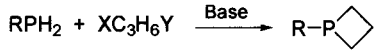
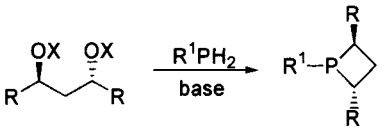
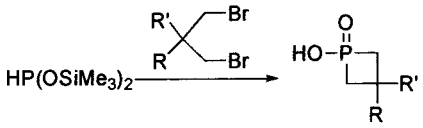
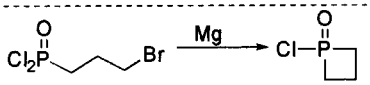
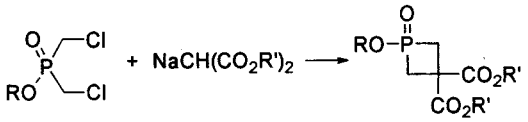
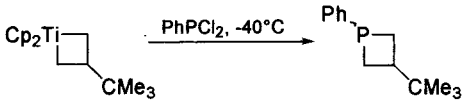
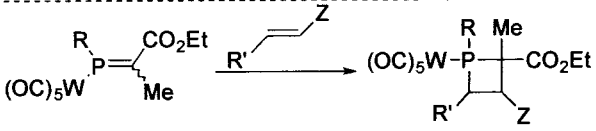
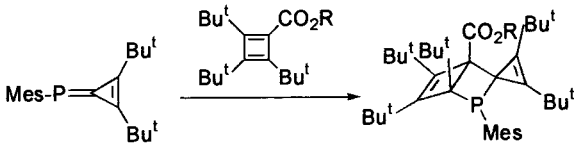
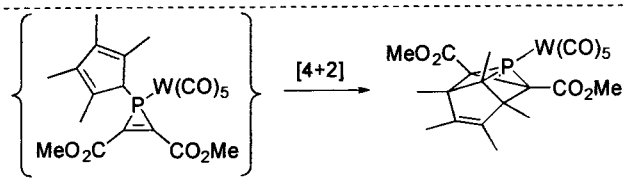
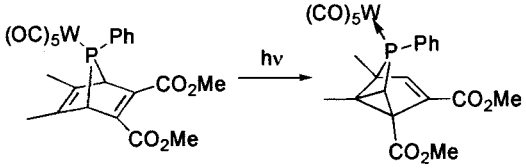
Methods	Examples	References
Electrophilic additions to olefins followed by rearrangements	 R^1 = Me, H, Ph, $CH=CH_2$ RPX_2= PCl_3, PBr_3, $PhPCl_2$, $MePCl_2$, $EtPCl_2$, $PhCH_2PCl_2$, *p*-MeO-Ph, *p*-ClPh-PCl_2, *p*-FPh-PCl_2, (3,4-dichlorophenyl)PCl_2, MenthylPCl$_2$, BornylPCl$_2$, IsopinocampheylPCl$_2$ olefin = 2,4,4-trimethyl-2-pentene, 2,3,3-trimethyl-1-butene, 3-methyl-1-butene, 3,3-dimethyl-1-butene, 2,3-dimethyl-1-butene, 2,4-dimethyl-2-pentene, 3,3-dimethyl-1,4-pentadiene, 3-methyl-3-phenyl-1,4-pentadiene, camphene, 1-bromo-3,3-dimethyl-1-butene	6, 7, 9-12, 14-17, 19, 21, 23, 33
		22
Electrophilic additions to dienes		24
		25
	 X_2PCl = $(Me_2N)_2PCl$, $(Et_2N)_2PCl$, $(iPr_2N)_2PCl$, $(EtO)_2PCl$	26, 28-30, 173
From cyclopropanes		28-30
	 R^2PCl_2 = *i*-Pr_2NPCl_2, $PhPCl_2$ R = Me, Ph; R^1= H, Me	31
Alkylation-cyclisation on phosphorus derivatives	 R_2PM = Ph_2PNa(or Li), *i*-Pr_2P(TMS), *t*-Bu_2P(TMS), Mes_2P(TMS) X = Cl, Br, I CR'_2 = $CMe(CH_2Cl)$, CH_2, CMe_2	32-34
	 RPH_2 = $PhPH_2$, [Fe]PH_2Ph, $MesPH_2$, *l*-menthylPH_2, (2,6-diMeO-Ph)PH_2 X, Y = Cl, Br, OTs, OMs	35-40

Table 3 (Continued)

Methods	Examples	References
		41, 44, 45, 47, 48, 50, 51, 182, 183
	OX = mesylate, cyclic sulfate R = Me, Et, *i*-Pr, *t*-Bu, cyclohexyl, CH_2Ph R^1= Ph, adamantyl, mesityl, cyclohexyl, ferrocenyl, ferrocenylmethyl, *o*-phenylene, ferrocenediyl, ethanediyl	
		52
	R,R' = H, OH, OBn, $(CH_2)_5$	
Cyclisations with nucleophilic reagents		1, 53
		54
	R, R' = Me, Et	
Heteroatom transfer reactions		56
[2+2]-Cycloadditions		57
	R' = H, Et; Z = OEt, $N(CH_2)_5$	
		60
	Other examples	58, 59, 174
[4+2]-Cycloadditions		61
Rearrangements		62, 63

the high end of the range (see Table 4). The angles at the ring carbon atoms (PCC angles of 84−88°; CCC angles of 96−102°) are rather wider than in other saturated four-membered heterocycles, as they are compensated by small CPC angles that vary from 76° to 86°.

The crystal structures of polycyclic derivatives may present specific features due to special constraints.[76]

Selected values for intracyclic bond angles and distances for representative tri- and tetracoordinated phosphetane derivatives, including transition metal complexes, are given in Table 4.

Table 4. Selected Bond Lengths and Bond Angles in Phosphetane Derivatives

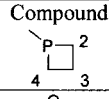
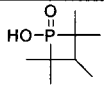
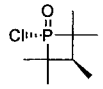
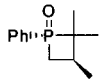
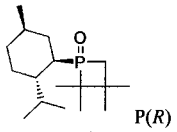
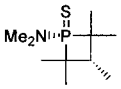
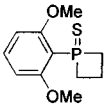
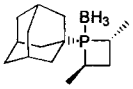
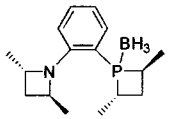
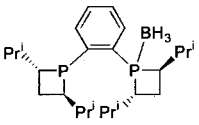
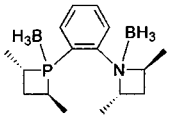
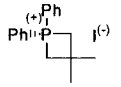
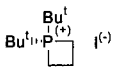
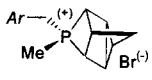
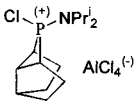
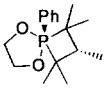
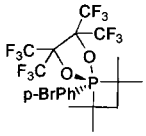
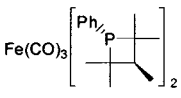
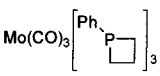
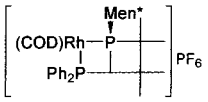
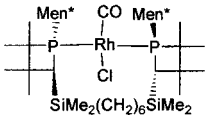
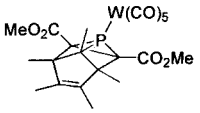
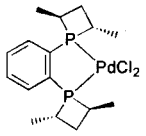
Compound	Bond Distances		Bond Angles		Dihedral Angle	Ref.
	P-C2	P-C4	C2-P-C4	C2-C3-C4	CPC/CCC	
	1.83(2)	1.83(1)	82.5(5)	101.0(9)	19.6	67
	1.83(3)	1.84(2)	85.9(11)	102.1(19)	26.4	5
	1.835(4)	1.788(5)	79.4(2)	97.3(3)	16.7	74
 P(*R*)	1.806(5)	1.852(6)	79.9(2)	96.3(4)		7
	1.854(1)	1.854(1)	81.20(4)	99.90(6)	28.7	68
	1.821(3)	1.813(3)	78.67(12)		28.5	40
	1.838(4)	1.851(5)	79.3(2)	99.4(3)		44
	1.855(2)	1.849(2)	78.33(7)	97.5(1)		182
	P(III) 1.863(3) P-BH$_3$ 1.851(2)	1.887(3) 1.849(3)	76.9(1) 80.1(4)			48
	1.855(2)	1.849(2)	78.33(7)	97.5(1)		182
	1.804(3)	1.802(3)	82.2(1)	97.9(2)	18.6	69
	1.80(1)	1.79(1)	81.7(7)	98.0(11)	0	34
	1.82(1)	1.82(1)	74.8(5)	90.3(6)	46.6	76
	1.820(15)	1.821(11)	85.2(6)	101.0(1)		25
	1.904(5)	1.894(5)	76.2(2)	98.5(4)		78
	1.96(2)	1.89(2)	78.1(9)			79
	1.895(7) 1.884(9)	1.896(7) 1.879(8)	78.2(3) 79.2(5)	101.1(6) 102.9(8)	20.3 (6.1)	176

Table 4 (Continued)

Compound	Bond Distances		Bond Angles		Dihedral Angle	Ref.
	P-C2	P-C4	C2-P-C4	C2-C3-C4	CPC/CCC	
	1.850(6)	1.861(6)	77.2(2)	100.6(6)	12.5(5)	35, 36
	1.898(7)	1.873(8)	78.3(3)	97.9(5)		117
	1.889(3)	1.882(3)	77.6(1)			113
	1.836(3)	1.924(3)	72.21(12)			61
	1.841(3)	1.859(4)	79.5(2)			48

Pentacoordinate Phosphetanes

In principle, there is little energy difference between a phosphorane with trigonal bipyramidal (*tbp*) and with square planar pyramidal (*spy*) geometries, but the square pyramidal geometry dominates X-ray determinations. Notable exceptions are the extremely strained species such as **27** (Figure 2), where the

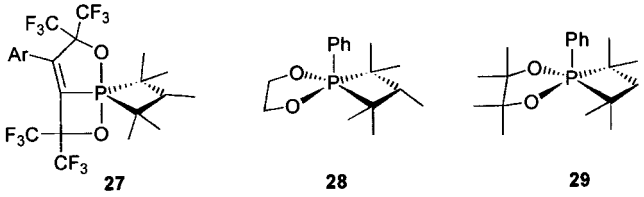


Figure 2. Solid-state structures for phosphetane-based phosphoranes.

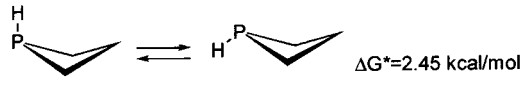
phosphorane adopts a *tbp* geometry with the phosphetane ring in the normally disfavored equatorial−equatorial configuration.[77]

Bicyclic compounds, such as **28**[78] and **29**,[79] show structures that are displaced by between 13% and 39% along the Berry coordinate leading from the *spy* geometry to the *tbp* structure.

These *spy* structures are probably retained in solution because very similar solution and solid-state ^{31}P NMR shifts are found for phosphoranes shown to have square-pyramidal geometries by X-ray diffraction.[80] However, these data may not be truly representative of the general class, because structural evidence for the form of simple (as opposed to bicyclic and spirocyclic) phosphetane-containing phosphoranes is lacking. A model[81] incorporating sterical and ring-strain parameters to define the ground and transition state energies linking *spy* and *tbp* structures for phosphoranes supports the assumption that the energy difference between the *tbp* and *spy* structures for simple phosphetane-containing phosphoranes is relatively small.

2. Theoretical Studies

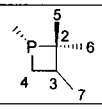
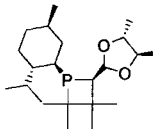
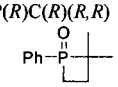
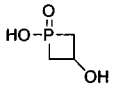
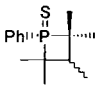
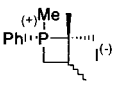
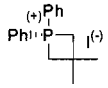
Two relatively recent theoretical studies treating trivalent phosphetanes give a detailed insight into the nature of the phosphetane ring. Bachrach,[82] employing HF/6-31G* and MP2/6-31G* calculations to investigate the parent phosphetane, found that the lowest energy conformer orients the PH substituent axially, shows P−C and C−C bond lengths of 1.88 and 1.54 Å, respectively, and has a ring fold of 24°.



lowest energy conformer

Its invertomer, having an equatorial P−H bond, P−C = 1.88 Å, C−C = 1.55 Å, and a fold of 28.2°, lies 1.08 kcal mol^{-1} higher in energy because of lone pair−C(3)H repulsions. The ring flip barrier linking these structures is small: 2.5 kcal mol^{-1} at the higher calculational level. Further analysis showed that the barrier for inversion at the phosphetane phosphorus atom is 42.6 kcal mol^{-1} at MP2/6-31G*//HF31G* +ZPE, which is only 3 kcal mol^{-1} higher than for dimethylphosphine using the same model. Hence, the phosphetane ring appears sufficiently flexible to accept the widening of the CPC angle required for inversion but confers some configurational stability upon the phosphorus atom. These data concur with an earlier CNDO/2 calculation that gave 44.3 kcal mol^{-1} as the inversion barrier for 1-methylphosphetane.[83] Finally, the ring strain in phosphetane was estimated at 17.9 kcal mol^{-1}. This rather low value,

Table 5. Selected ^{13}C NMR Data for Phosphetane Derivatives

	δ C(2) [J_{P-C}]	δ C(3) [J_{P-C}]	δ C(4) [J_{P-C}]	δ C(5) [J_{P-C}]	δ C(6) [J_{P-C}]	δ C(7) [J_{P-C}]	Ref.
	34.52 [2.6]	49.70 [5.9]		32.71 [27.8]	20.92 [4.9]	8.12 [13.5]	88
cis and *trans*	30.22 [5.9]	54.02 [2.7]		26.24 [31.8]	26.52 [2.5]	9.96 [0]	
	41.26 [1.5]	40.16 [3.9]	28.74 [0.6]	25.15 [25.5]	23.05 [4.5]	27.84 [8.4] 26.13 [5.5]	33
	40.52 [0]	47.36 [1.9]		17.9 [25.9]		36.01 [5.1]	30
exo and *endo*	40.47 [6.1]	40.17 [14.7]			21.34 [7.9]	34.64 [14.7]	
 P(*R*)C(*R*)(*R*,*R*)	43.4 [0]	41.7 [4.4]	36.8 [3.0]	104.5 [23.1]			114
	48.76 [62.5]	26.69 [15.8]	28.64 [52.2]	23.81 [3.7]	22.77 [3.7]		33
	44.05 [59.4]	46.89 [10.0]		24.66 [4.4]	19.83 [2.2]	9.71 [12.6]	10
cis and *trans*	45.41 [59.4]	42.61 [6.3]		17.28 [4.6]	24.71 [3.6]	7.31 [23.0]	
	48.6 [72]	57.9 [17]					52
	45.79 [47.3]	48.73 [6.9]		26.09 [2.2]	21.70 [2.5]	8.23 [21.5]	10
cis and *trans*	46.62 [47.9]	51.06 [5.4]		22.52 [1.7]	25.48 [4.2]	9.55 [20.9]	
	44.91 [48.5]	38.72 [15.9]	24.86 [46.1]	23.31 [3.9]	17.75 [1]	15.92 [23.7]	10
cis and *trans*	45.53 [48.6]	40.49 [17.1]	25.35 [47.7]	18.13 [1]	23.94 [3.7]	15.87 [21.2]	
	40.29 [53.2]	37.41 [19.1]				31.54 [12.1]	33

when compared to that of azetidine, cyclobutane, and siletane, was attributed to a combination of the small CPC angle and long PC bonds, which allow relatively open intracyclic angles at carbon.[82]

A second, more recent study, aimed at understanding the ^{31}P NMR properties of phosphorus heterocycles, has optimized the geometry of the parent phosphetane at the higher MP2/6-31G(*d*) level using energies calculated at MP2/6-311G(*d*,*p*).[84] It confirmed that the pseudoaxial PH orientation is favored over the equatorial (by 1.32 kcal mol^{-1}) but gave a rather large fold angle (38.8°) for the axial conformer. It indicates that the HOMO−LUMO gap in phosphetane is smaller than in phosphiranes, phospholanes, and phosphinanes and, in simple hybridization terms at the STO-3G level, characterizes the phosphetane lone pair as a nonbonding $sp^{2.12}$ orbital.

3. Theoretical Treatments of NMR Data

NMR data for five nuclei (phosphorus,[12,85−87] carbon,[10,33,88−91] hydrogen,[9,14,15,33,92,93] fluorine,[13,17,123,154,164] and oxygen[94]) have been used to probe the structure and stereochemistry of phosphetanes. Mainly, conventional rules (e.g., dependence of P−H couplings on dihedral angles, etc.) are applied to stereochemical assignments,[33,95] and only a few peculiarities have been noticed within the NMR data. For instance, ^{13}C NMR studies[33] suggest shielding of the intracyclic α-carbons as a result of ring contraction, but clear-cut trends could not be established

Table 6. ^{31}P NMR Data for Selected Phosphetane Derivatives

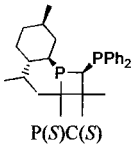
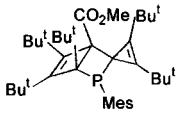
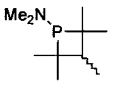
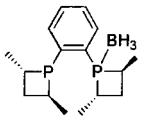
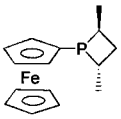
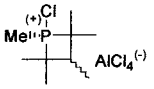
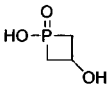
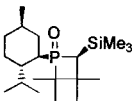
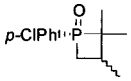
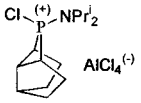
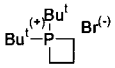
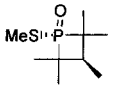
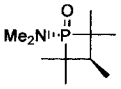
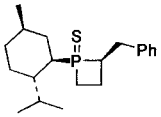
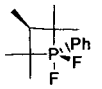
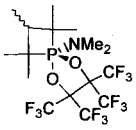
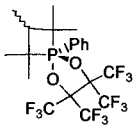
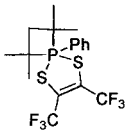
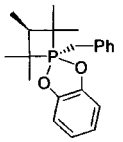
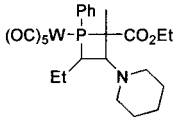
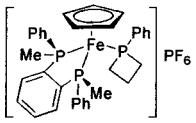
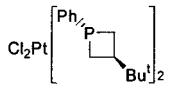
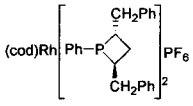
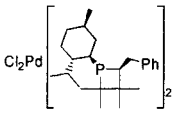
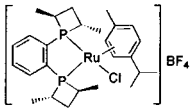
Compound	δ ^{31}P	Ref.	Compound	δ ^{31}P	Ref.
	44 (CH_2Cl_2)	17		13.9 (C_6D_6)	36
 P(*S*)C(*S*)	24.4 -18.6 [J_{PP}=87] (C_6D_6)	117		7.7 (C_6D_6)	60
 *cis* and *trans*	149.0 169.2 ($CDCl_3$)	87	 *cis* and *trans*	99.8 127.5 ($CDCl_3$)	87 85
	47.5 *(exo)* 39.7 *(endo)*	30		49.1 16.9 [J_{PP}=36]	41
	18.4 (C_6D_6)	182	 *cis* and *trans*	126 114 (CH_2Cl_2)	19
	40.0 (D_2O)	52		68.0 (C_6D_6)	113
 *cis* and *trans*	48.6 43.6 ($CDCl_3$)	12		79.4 (CH_2Cl_2)	25
	80.3 (CH_2Cl_2)	34		137	134
	75.4 ($CDCl_3$)	132		53.4 ($CDCl_3$)	131, 85
	77.3 (THF)	39		-3.0 and 30 [J_{P-F}=932 and 769] (at −100°C)	17
 *cis* and *trans*	11.2 (C_6H_6)	13	 *cis* and *trans*	7.7 3.4 (C_6H_6)	123 13
	-17.1 (CH_2Cl_2)	161		4.2 ($CDCl_3$)	165
	37.1 (C_6D_6)	57		99.47 [J_{PP}=50.7 and 49.2] ($CDCl_3$)	37

Table 6 (Continued)

Compound	δ ^{31}P	Ref.	Compound	δ ^{31}P	Ref.
	10.88 [J_{PtP}=3415] (CH_2Cl_2)	56		65.3 [J_{PRh}=147] (CD_2Cl_2)	182
	62.6 (C_6D_6)	114		101.8 115.2 [J_{PP}=30]	48

because of superimposed substituent effects. Trivalent phosphetanes display unusually small intracyclic $^1J_{P-C}$ couplings. They have been explained in terms of bond angle distortions that confer decreased *s*-character upon the intracyclic bonds. ^{13}C NMR data for selected phosphetane derivatives are summarized in Table 5.

In addition, a few theoretical analyses of NMR data have appeared that especially concern the most characteristic property shown by phosphetanes, their ^{31}P NMR shift. (^{31}P NMR data for selected phosphetane derivatives are given in Table 6.) The abnormally low-field ^{31}P NMR shift (compare 1-phenylphosphetane at 13.9 ppm with diethylphenylphosphine at −15.5 ppm) has been shown by MP2/6-311G(*d*,*p*) level GIAO calculations[84] to result from the combination of a moderately *p*-rich lone-pair hybrid orbital and a relatively small phosphetane HOMO−LUMO gap. These generate an abnormally negative paramagnetic shielding term along the C_s symmetry axis lying perpendicular to the mean carbon plane that effects the downfield shift. The same calculations found no significant influence of the four-membered ring upon the shifts of the intracyclic carbon atoms lying α to phosphorus.

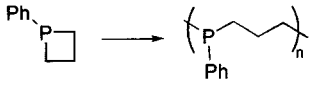
IV. Chemical Properties

The most obvious chemical properties of phosphetanes might be expected to arise from strain, with ring opening and ring enlargement reactions to be predominant. However, the geometrical constraints of the four-membered ring also play a more subtle role in controlling the stereochemistry of many reactions taking place at the phosphorus atom. The following section emphasizes those aspects of reactivity that are specific to phosphetanes and only briefly treats any behavior common to other phosphorus heterocycles.

1. Ring-Opening and Ring-Expansion Reactions

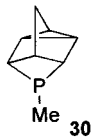
Ring-Opening Reactions

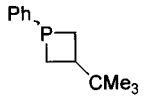
The possibility of preparing poly(propylphosphine) materials by ring-opening of weakly substituted phosphetanes has stimulated recent interest in this area. However, it seems that the structural integrity of most phosphetanes is only slightly diminished by ring strain. For example, ring-opening polymerization (eq 23) has only been unequivocally observed for C-unsubstituted trivalent phosphetanes and, even


(23)

then, only when isolated in the pure state. Dilute solutions appear to be stable.[36]

In other experiments, a sample of 2,3,3-trimethyl-1-phenylphosphetane gave an unspecified polymeric material upon prolonged standing at room temperature,[9] and a partial polymerization of the highly strained tetracyclic phosphetane **30** was observed upon distillation.[30]

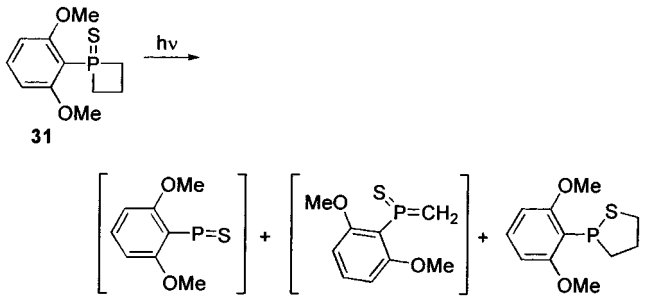

30


22

However, the attempted polymerization of the 1-phenyl-3-*tert*-butylphosphetane **22** required heating at 250 °C for 5 days.[56]

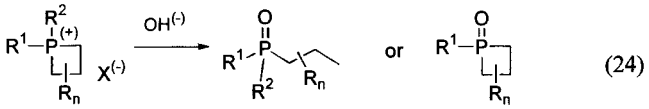
Phosphetane sulfides and borane complexes, even when devoid of carbon substituents, seem to be quite stable toward polymerization.[39,41] Cleavage of the four-membered ring of phosphetane sulfides has been observed under photochemical conditions (*hν*, 254 nm). Though the nature of the final products is not fully established, the assumed fragmentation pattern suggests formation of potentially interesting reactive intermediates such as phosphinidene and phosphaalkene sulfides (Scheme 6).[40]

Scheme 6. Assumed Fragmentation Pattern for Phosphetane Sulfide 31



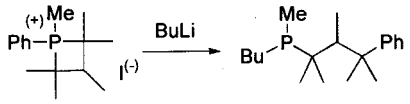
The most frequently observed examples of ring cleavage provoked by incoming reagents occur during nucleophilic additions to phosphetanium salts. In most cases, nucleophiles (e.g., OH^-, eq 24) attack phosphorus, and if no good leaving group is present at P, the pentacoordinated intermediate species may

rearrange to ring-opened products.[3,96−99] Nonetheless, functionalities ranging from halides to benzyl groups are lost in preference to ring opening at phosphorus.



(24)

Most phosphetane derivatives are stable toward organolithium nucleophiles, but a few examples of additions of organolithium derivatives to phosphetanium salts, sulfides, and oxides have been reported. These additions provoke ring openings[30] and, in certain cases, migration of a phenyl substituent from phosphorus to the γ-carbon atom,[96,100−102] as shown in eqs 25 and 26.



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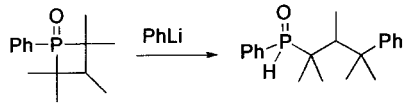
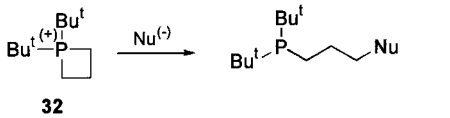


(26)

These ring openings have not found synthetic applications but are occasionally observed as side reactions.

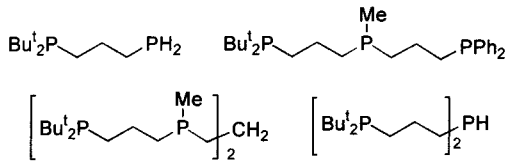
When the nucleophile enters at carbon rather than at phosphorus, ring opening reactions may have greater preparative potential. For instance, the phosphetanium salt **32** affords various γ-functionalized phosphines upon reaction with nucleophiles[34] (eq 27)



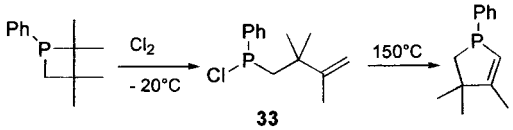
(27)

and bidentate and polydentate ligands have been synthesized in high yields by cleavage of **32** with lithium phosphides (Scheme 7). In these reactions the protection of the phosphorus center by the bulky substituents orients the nucleophile toward the α-carbon atom.

Scheme 7. Polyphosphines from Ring-Opening Reactions



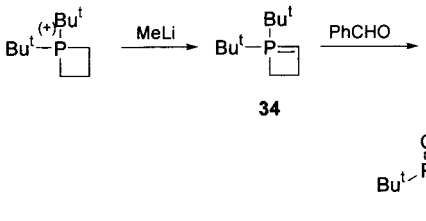
Some trivalent phosphetanes undergo ring opening, to γ-unsaturated chlorophosphines such as **33**, upon reaction with chlorine (eq 28).[28,103] Further treatment with chlorine at 150 °C induces quantitative cyclization to the corresponding phospholenes. However, it should be mentioned that, in other experiments, reaction of chlorine with various 2,2,



(28)

3,4,4-tetramethylphosphetanes afforded the expected P-chlorophosphetanium chlorides, with no ring-opening products.[19]

The Wittig reaction of phosphetane-derived ylides with carbonyl compounds constitutes another synthetically useful ring-opening reaction. The ylide **34**, formed classically by deprotonation of a phosphetanium salt with a strong base, reacts with aldehydes or ketones to afford γ-unsaturated phosphine oxides (eq 29).[34]

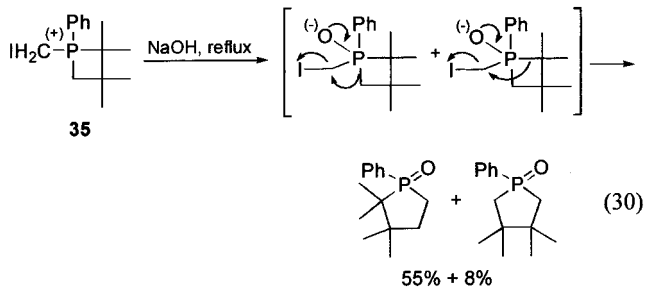


(29)

Ring Expansion Reactions

Two different methods are available for the ring expansion of phosphetanes to give phospholanes. They involve alkaline hydrolysis of certain phosphetanium salts or addition of acetylenic esters to trivalent phosphetanes. Examples are given in eqs 30−33.

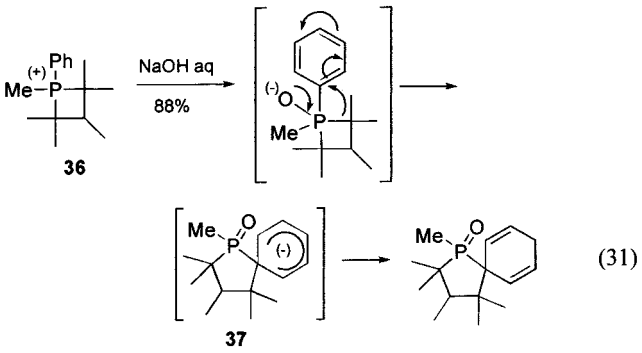
The quaternization of phosphetanes with methylene iodide, followed by alkaline hydrolysis, provides a route to phospholane oxides through insertion of the methylene unit into the four-membered ring.[104,105] The unsymmetrical *P*-iodomethyl salt **35** gives rise to two isomeric phospholanes, with ring extension occurring predominantly by migration of the unsubstituted methylene group (eq 30).[96]



(30)

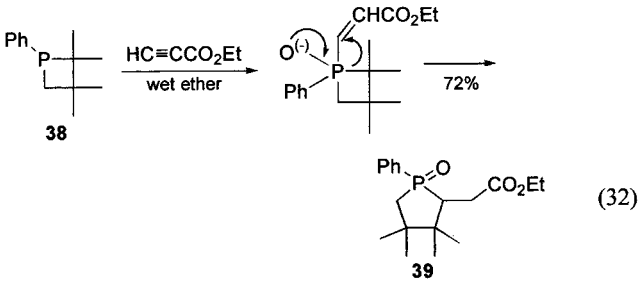
Alkaline hydrolysis of the aryl-substituted phosphetanium salt **36** also provokes an unusual ring expansion, which occurs with dearomatization of the phenyl substituent (eq 31). Deuterium-labeling experiments support a mechanism involving the intermediate cyclohexadienyl anion **37**.[101,104,106]

Reactions between trivalent phosphetanes and ethyl propiolate in wet ether also give phospholane oxides.[96,101] Here, the electrophilic addition of the acetylenic ester to the phosphorus atom and subsequent addition of water are followed by a rearrangement wherein a phosphetane carbon acts as a leaving group, as shown in eq 32. In unsymmetrically sub-



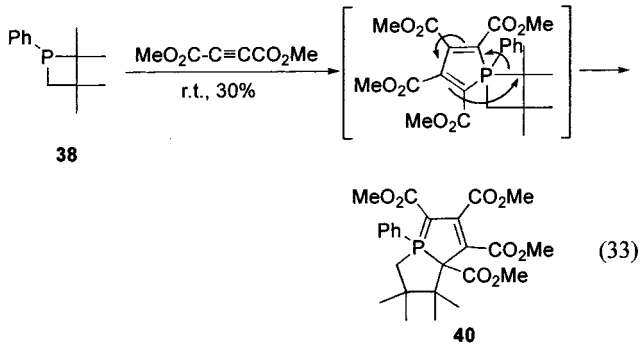
(31)

stituted phosphetanes **38**, migration of the CMe_2 group is preferred, giving **39**.



(32)

A last example of ring enlargement is provided by the reaction between phosphetane **38** and dimethyl acetylenedicarboxylate, which gives the stable ylide **40** (eq 33).[96] It also involves migration of a phosphetane CMe_2 group, in this case from an intermediate spirocyclic phosphorane.

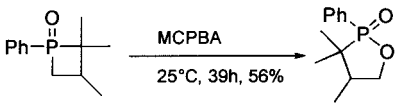


(33)

The above ring expansions have a common mechanistic point, inasmuch as pentacovalent phosphorane intermediates are always implicated in the key ring expansion step. Release of ring strain presumably drives the departure and migration of a phosphetane carbon moiety from the pentacoordinated phosphorus atom to the α-substituent, to give the tetracoordinated phospholane products.

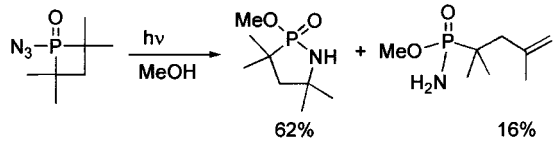
Several other ring-enlargement reactions involve heteroatom insertion into the phosphetane ring.

Oxygen insertions into a P−C bond are known for many strained phosphine oxides.[107] Similar reactions also occur for mono- and polycyclic phosphetane oxides upon room temperature oxidation with peracids over several hours (eq 34). Reactions are often regioselective, with insertion occurring predominantly at the least substituted carbons. Yields are generally high, so that phosphetanes serve as practical precursors for 1,2-oxaphospholanes.[108,109]



(34)

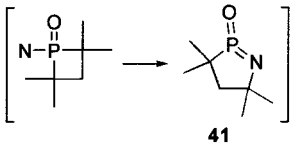
Insertion of nitrogen into various phosphetane rings has been performed through photolysis of the corresponding 1-azidophosphetane oxides in methanol (eq 35).[110−112] The main side products are ring-opened methyl phosphonamidates.



(35)

It has been proposed that these reactions proceed through the insertion of nitrenes into the phosphetane ring in a Curtius-like rearrangement (Scheme 8). However, the mechanism remains uncertain,

Scheme 8. Assumed Intermediates for Reaction 35



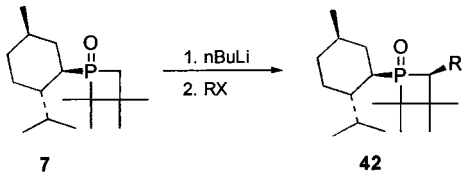
because the same metaphosphonimidate **41** could be obtained by a ring enlargement with concerted loss of nitrogen. The synthetic utility of these nitrogen insertions is somewhat reduced by their poor regio- and stereochemistry. So, mixtures of regioisomers (nitrogen insertion in both P−C bonds) are usually obtained when unsymmetrically substituted phosphetanes are employed, and mixtures of *cis* and *trans* stereoisomers are formed when the phosphetane ring bears a monosubstituted carbon (unselective methanol addition to **41**).

2. Reactivity of the Ring Carbons

Functionalizations of preformed phosphetanes, to confer specific structural characteristics, have been confined to optically pure phosphetanes. In these cases, the aim has been to match the structures of phosphetane ligands to the specific requirements of a given catalytic reaction. Substituents have been introduced at the α-carbon of chiral phosphetane oxides through metalation−substitution reactions and have been subjected then to further elaboration.

The phosphorus-stabilized carbanion obtained upon reaction of the P-menthylphosphetane oxide **7** with *n*-butyllithium reacts stereospecifically with activated alkyl halides,[7] chlorosilanes,[113] dimethylformamide,[114] and other electrophiles to afford the α-substituted phosphetane oxides **42** in optically pure form (eq 36).

Functionalization at the ring carbon has been performed on both pure epimers of the *P*-menthylphosphetane oxide **7**. The incoming R substituent occupies an equatorial position, *trans* to the menthyl group, probably as a consequence of sterical constraints and 1,3-diaxial interactions within the hindered four-membered ring. Analogous metalation−



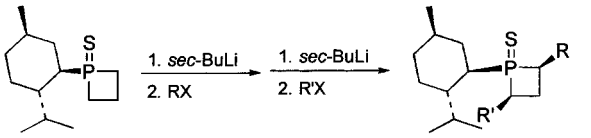
(36)

7 42

R	CH_2Ph[7]	Br[7]	CHO[114]	$P(O)Ph_2$[117]
Yield	78%	68%	45%	50%

R	$SiMe_2Ph$[113]	$(SiMe_2)_2O$[113]	Allyl[116]
Yield	83%	80%	73%

substitution reactions have been performed successively on both α-carbons of the *P*-menthylphosphetane sulfide **43** (eq 37).[39]



(37)

43 44 (major isomer)

R,R'	$PhCH_2$, H	$PhCH_2$, $SiMe_3$	$PhCH_2$, $PhCH_2$
Yield	77%	75%	45%

The stereochemical course of both alkylation steps is dominated by the *anti*-directing effect of the *P*-menthyl group, whose influence in the second step outweighs the effects of the R substituent introduced in the first. Overall, the selectivity is sufficiently high to allow a useful preparation of diastereomerically pure phosphetane sulfides **44**.

These α-substitution reactions provide the means to prepare a number of modified optically pure phosphetanes bearing either additional functional groups,[115] chiral centers,[114,116] or coordination sites.[115,117] Selected examples are compounds **45**−**47** (Figure 3) bearing respectively an hydroxyl, a di-

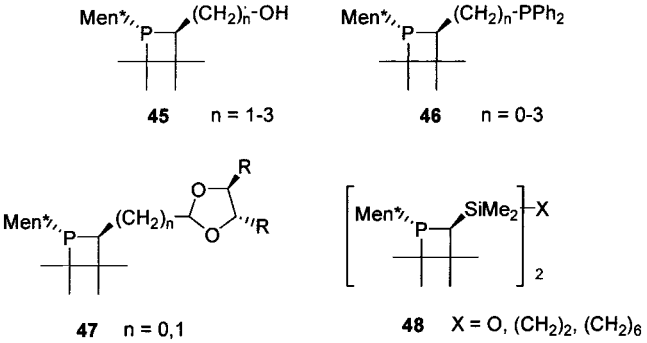


Figure 3. Examples of α-functionalized chiral phosphetanes.

phenylphosphino, and a chiral dioxolane group. Compounds **48** represent bis-phosphetanes, including a *trans*-spanning diphosphine (**48**, for X = $(CH_2)_6$), which are formed by connecting two phosphetane units through a silylated chain.[113]

3. Reactivity of the Phosphorus Atom

This section reviews reactions where the phosphetane moiety is retained and focuses on aspects of the reactivity at phosphorus that specifically reflect the presence of the phosphetane ring.

Many experimental data and much theoretical work indicate that the four-membered ring profoundly influences the stereochemical outcome of reactions at phosphorus. This is the case for almost all reactions of tetracoordinate phosphetanes that proceed through Berry's pseudorotation[118] of intermediate phosphorane derivatives. *Inter alia*, pseudorotation phenomena govern the stereochemistry of nucleophilic substitutions at phosphorus and the reductions of phosphetane oxides. Thus, pseudorotation phenomena will be treated in some detail hereafter.

Pseudorotation within trigonal-bipyramidal molecules induces pairwise exchange of apical and equatorial ligands by way of a square-pyramidal transition state or intermediate (Figure 4).

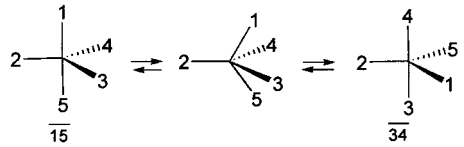


Figure 4. Pseudorotation processes in trigonal bipyramidal molecules.

A formal topological treatment, recalled hereafter, has been given by Mislow.[119,120] A pentacoordinated molecule having five different substituents has 20 stereoisomers (10 *dl* pairs). Any given stereoisomer has three different pseudorotations, which allow access to three other stereoisomers in a single step (connectivity = 3). Such interconversions may be presented as a hexasterane graph,[121] where the vertexes represent different isomers and the pseudorotations occur along the edges (Figure 5). Conventionally, the labels at each vertex denote the substituents found in the apical positions. Barred and unbarred labels are used to represent enantiomers, which are interconverted by a minimum of five consecutive pseudorotations.

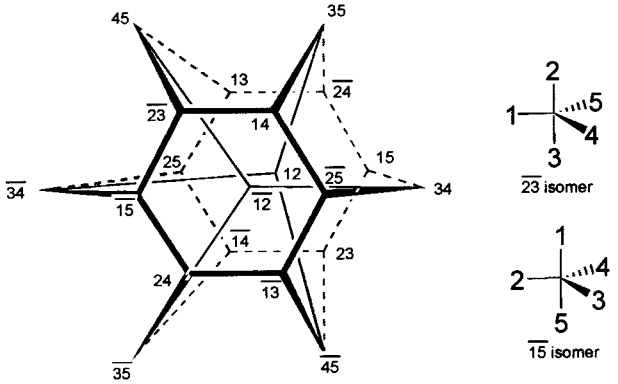


Figure 5. Hexasterane graph for pentacoordinate pseudorotating molecules.

The apicophilicity[122−124] of the phosphorus substituents constitutes one of the most important factors governing the relative stability of different isomers. Initially, the apicophilicity of a given substituent was seen as a function of its electronegativity, with more electronegative groups being more apicophilic (see ref

119 and references therein). A second approach postulated an inverse correlation between apicophilicity and the ability of a substituent to act as a π-donor, equatorial π-bonding to phosphorus being more efficient than axial π-bonding.[125,126,128] Steric requirements also affect to some extent the apicophilicity. Additional data on apicophilicity and implications in pseudorotation processes can be found for instance in ref 127−130 and references therein.

Incorporating a phosphetane ring into a pentacoordinate phosphorane imposes strict geometrical constraints, limiting the number of possible isomers. The phosphetane is incapable of spanning the two apical positions, which eliminates two vertexes, and the very small intracylic CPC angle confers a strong preference for the phosphetane ring to adopt an axial−equatorial (ax−eq) geometry, thus favoring those isomers with an ax−eq phosphetane ring (marked vertexes in Figure 6).

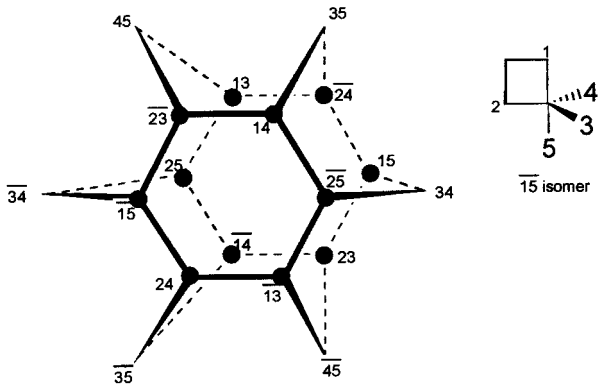
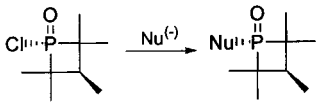


Figure 6. Hexasterane graph for pentacoordinate phosphetanes.

This explains, for instance, the high stability of phosphoranes containing small rings toward racemization: in Figure 6 it can be clearly seen that any pathway from one configuration to its enantiomer must pass through a high-energy intermediate (star point vertex), where the ring spans a disfavored eq−eq position. Other effects of geometrical constraints related to the presence of the four-membered ring will be discussed below.

Stereochemistry of the Nucleophilic Substitutions on Phosphetanic Acid Derivatives and Phosphetanium Salts

P-Chlorophosphetane oxides are very readily available from olefins and PCl_3 (eq 2) and are used as starting materials for the synthesis of other phosphetane derivatives, through reaction with alcohols,[4,10] amines,[11,131] thiols,[132] water,[11,133] organolithium,[19] and Grignard reagents[13,98,134] (eq 38). These



(38)

reactions usually proceed with excellent stereoselectivity, with mainly retention of phosphorus configuration.[4,11,134] Retention of stereochemistry is also observed in the acid cleavage of phosphetanic amides into phosphetanic chlorides.[11,135]

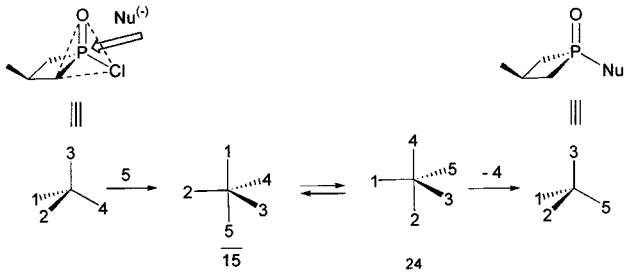


Figure 7. Stereochemistry of nucleophilic substitutions at phosphorus.

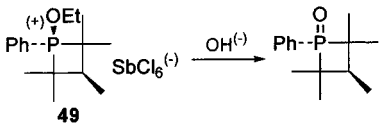
The stereochemical outcome can be explained as follows. The mechanism is associative, since *the release of ring strain in the pentacoordinate intermediate provides a considerable driving force for associative reactions*.[136,137] In the intermediate phosphorane, *the phosphetane is constrained to an apical−equatorial orientation*, because of the acute CPC bond angle (<90°). Figure 7[120] shows a facial (or apical) attack of a nucleophile at a tetrahedral phosphonic chloride and the shortest pathway for placing the leaving group in an apical position. (Apical attack and departure are assumed to be the preferential modes of bond making and breaking.[120]) This is a single-step pseudorotation process that implies retention of phosphorus configuration. When dismissing intermediates with the unfavorable diequatorial arrangement of the phosphetane ring, inversion requires two successive pseudorotation steps before leaving-group departure, so inversion is disfavored when elimination is fast relative to pseudorotation.

The few known exceptions[138] where retention is not observed may be rationalized in terms of the relative apicophilicity of the leaving group and the other substituents at phosphorus: the stereochemical outcome may be affected when other groups on phosphorus have higher apicophilicity than the leaving group.

Other reaction mechanisms are only barely noticed for substitution reactions on phosphetanic acid derivatives. Thus, a few examples of acid-induced solvolyses of phosphetanic chlorides and amides are known,[139−141] which follow an S_N2 displacement mechanism. Here, the presence of the four-membered ring slows the reaction rate with respect to acyclic analogues, because the phosphetane ring must occupy two equatorial positions in the transition state to allow the entering and leaving groups to be collinear.

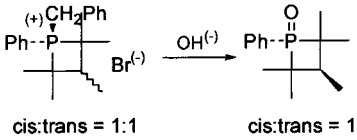
Phosphetanium salts also undergo well-documented nucleophilic substitutions. These reactions involve phosphorane intermediates and, consequently, respect the same stereochemical rules as substitutions at phosphetanic acid derivatives. Retention or inversion of phosphorus configuration after reaction is again governed by the relative apicophilicity of the phosphorus substituents[136] and the rate of pseudorotation relative to loss of the leaving group. Examples are given hereafter.

The alkaline hydrolysis of chloro-[19] and alkoxyphosphetanium salts,[142] such as **49**, proceed stereospecifically with retention of configuration at phosphorus. These contrast with the inversion of configuration observed with acyclic alkoxyphosphonium salts.[143]



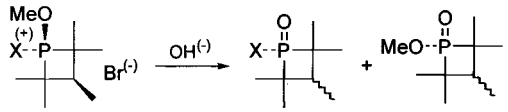
49 (39)

Lack of stereospecificity[144] or the preferential formation of one isomer, as in eq 40,[145] can be observed if pseudorotation is fast compared to the elimination step or if substituents with comparable apicophilicity are bound to phosphorus.



cis:trans = 1:1 cis:trans = 1:9 (40)

This means that studies on the product distribution and isomer ratios obtained in targeted substitution reactions made it possible to determine an order of kinetic apicophilicity for a number of common functionalities. The order Cl ~ SMe > ArO ~ *i*-PrO ~ EtO ~ MeO ≫ NMe_2 > alkyl > vinyl ~ aryl was derived from eq 41[122,146] in conjunction with results from other studies.[123,147−149]



X = OEt, O*i*-Pr, NMe_2, SMe, Cl (41)

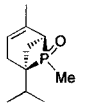
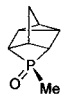
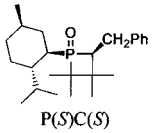
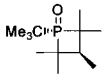
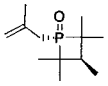
It is noteworthy that alkaline hydrolysis rates for cyclic phosphonium salts increase significantly upon moving from large ring or acyclic compounds to smaller ring compounds. Thus, for example, *P*-benzylphosphetanium bromides are hydrolyzed to the corresponding oxides 10^4 times faster than analogous phospholanium bromides.[150] This reflects relief of ring strain in the intermediate phosphorane. Ring strain also accelerates the alkaline hydrolysis of phosphinate esters (10^2 times faster than acyclic analogues).[151,152]

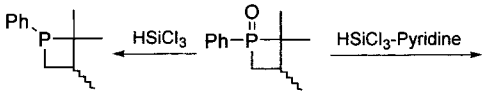
Note: unlike the nucleophilic substitutions on tetravalent derivatives above, substitutions on trivalent *P*-chlorophosphetanes with amines, alcohols, or organolithium reagents take place as expected, with inversion of the phosphorus configuration.[13,87,134,153] In a few cases only, when the entering group is rather mobile (alkoxy and amino groups), the first-formed product can be isomerized by subsequent substitution reactions.[153]

Reduction of Phosphetane Oxides

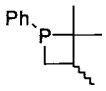
From stereochemical studies it is known that trichlorosilane and phenylsilane reduce classical acyclic phosphine oxides with retention of phosphorus configuration but that the trichlorosilane−triethylamine (or pyridine) adduct predominantly gives inversion. When the phosphine oxide is incorporated into a strained ring structure, this behavior is often reversed: inversion or racemization are found with trichlorosilane while retention occurs with pyridine−trichlorosilane.[86] This pattern also occurs during the reduction of phosphetane oxides (see for instance eq 42).[86]

Table 7. Representative Examples of Phosphetane Oxide Reductions

Starting Oxide	Reagents and Conditions	Stereochemistry	Ref.
	$HSiCl_3$-Et_3N	Retention	9
	$HSiCl_3$-Et_3N	Retention	19
	$HSiCl_3$-Pyridine	Retention	86
	$HSiCl_3$-Et_3N	Retention or partial inversion	9
trans-cis mixtures	$HSiCl_3$	Epimerisation to 95% *trans* isomer	86
	$HSiCl_3$- pyridine	Retention	108 86
	Si_2Cl_6	Retention	142
	$HSiCl_3$ $HSiCl_3$-pyridine	Predominant inversion Epimerization (67% retention)	30, 86 86
	$HSiCl_3$-Et_3N $PhSiH_3$	Retention Retention (from *exo*-isomer)	30 30
 P(*S*)C(*S*)	$HSiCl_3$-Et_3N	Retention	7 114
	$HSiCl_3$	Epimerization to the *trans*-isomer	15
	$PhSiH_3$	Partial inversion (isomers ratio = 3:2)	13
	$PhSiH_3$	Retention	13
	Polymethylsiloxane	Partial inversion (isomers ratio = 4:1)	134



cis:*trans* = 5:95 *cis*:*trans* = 42:58

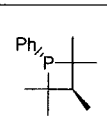
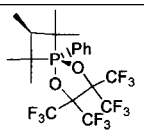
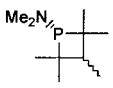
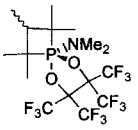
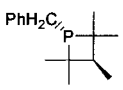
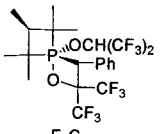
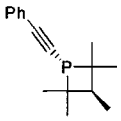
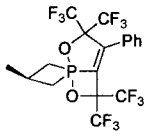
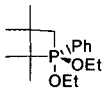
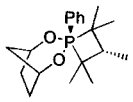
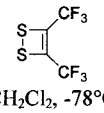
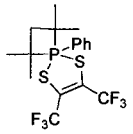
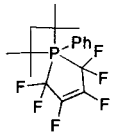
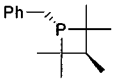
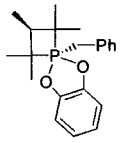
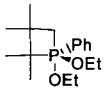
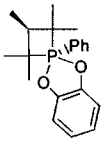


(42)

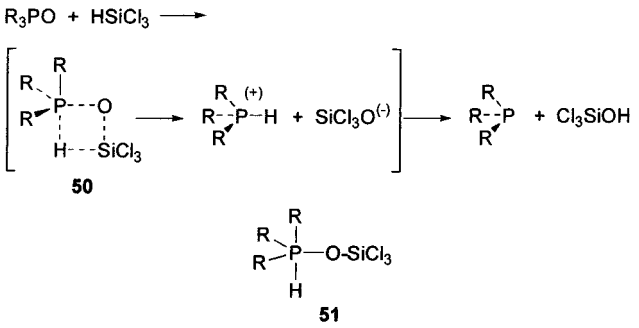
cis:*trans* = 42:58

Monocyclic phosphetanes are usually reduced with complete retention by the trichlorosilane−amine complex.[9,7,13,19,101,108] Trichlorosilane gives variable results,[15,85] apparently dependent on structural features of the phosphetane oxide. Sometimes stereoselective formation of a given isomer may occur. Representative examples are shown in Table 7.

Table 8. Synthesis of Phosphetane-Containing Phosphoranes

Starting Materials	Reagents and Conditions	Products	Yields	Ref.
	$(CF_3)_2CO$, toluene, -78° to 0°C		95%	13
	$(CF_3)_2CO$, toluene, -78° to 0°C	 *cis* and *trans*	74%	13
	$(CF_3)_2CO$, toluene, -78° to 0°C		68%	13
	$(CF_3)_2CO$, CH_2Cl_2, -78°C			77
	$(EtO)_2$, CH_2Cl_2, 5°C, 48h			158
	 benzene, -78°C to rt.			160
	$(CF_3O)_2$, CH_2Cl_2, - 78°C			17
	 CH_2Cl_2, -78°C		60%	161 162
	CF_2=CF-CF=CF_2	 + isomer		163
	Catechol, $ClNPr^i_2$ ether, -78°C		64%	165
	1.Et_3OBF_4, CH_2Cl_2 2.EtONa, EtOH			158
	1.Me_3OPF_6, CH_2Cl_2, rt. 2.Pyrocatechol, NPr^i_2		42%	167
	SF_4, -70 to 0°C		77%	78

The variable stereochemical outcome of the trichlorosilane-promoted reductions is tentatively assigned to the generation of a true pentacovalent intermediate **51**, which suffers isomerization through pseudorotation, while the usual reduction process goes through the four-center transition state **50**. The cyclic strain of the phosphine oxides promotes the development of the true pentacovalent intermedi-



ate.[86] Unlike trichlorosilane, the trichlorosilane−amine complex does not act as an hydride donor to phosphorus or, if it does, it does not create a P(V) intermediate.[86]

The trichlorosilane-mediated reductions may also be susceptible to trichlorosilane-promoted isomerization of the final trivalent phosphetane or scrambling by adventitious HCl.[15,86] Thus, the trichlorosilane−amine complex usually represents the best reagent for the stereospecific reduction of strained phosphine oxides.

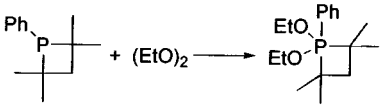
The stereochemical issue of the reductions of phosphetane oxides by phenylsilane depends on the ring substituents: both retention of configuration and epimerization at phosphorus have been observed.[13,154] Reductions with Si_2Cl_6 proceed with complete retention of configuration at phosphorus,[119,142] while $LiAlH_4$ induces epimerization of the phosphetane oxide.[155]

Finally, the stereochemical outcome of the reduction of fused polycycles becomes difficult to predict, given the importance of ring strain in these reactions.[30,86,108]

Synthesis of Phosphoranes

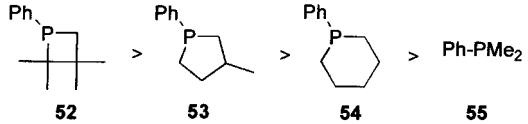
Phosphetane-containing phosphoranes are readily available from either trivalent phosphetanes, phosphetane oxides, or phosphetanium salts by conventional methods. Examples are given in eqs 43−46 and in Table 8.

Trivalent phosphetanes are converted directly to phosphoranes by electrophilic additions of various reagents such as hexafluoroacetone,[13,77,156,154] alkylperoxides (eq 43),[157−160] disulfides,[161,162] hexafluorobutadiene[163] or bis(trifluoromethyl)peroxide[17,164] (the last reaction giving difluorophosphoranes).



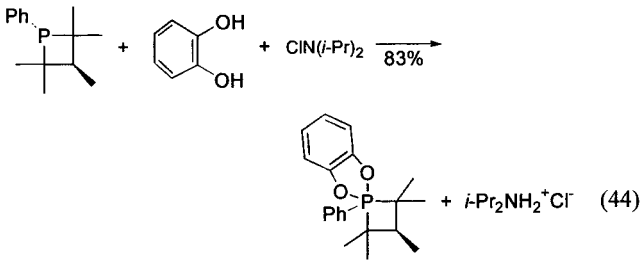
(43)

For reactions between phosphines **52**−**55** and diethyl peroxide,[158] rates seem to correlate with ring size in the following order:



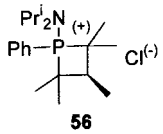
The corresponding phosphoranes may undergo partial ionization in solution. The degree of ionization appears to fall in the order six-membered > five-membered ≫ four-membered rings, with phosphetanes showing no evidence for ionization on the NMR time scale. These effects almost certainly reflect the increase in ring strain upon moving from a pentacoordinated structure to a tri- or tetracoordinated compound, which is especially marked for phosphetanes.[158]

Other phosphorane syntheses start from either trivalent phosphetanes or phosphetane oxides[158] and proceed through phosphetanium salt intermediates. These include the convenient synthesis of spirophosphoranes by means of catechol in the presence of *N*-chloroamines, shown in eq 44.[165]



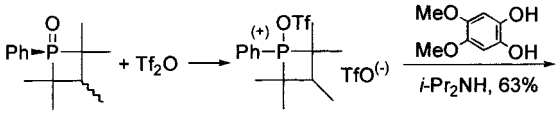
(44)

Intermediate formation of the phosphetanium salt **56** has been assumed, based on the known reaction of *N*-chloro amines with phosphines.[166]

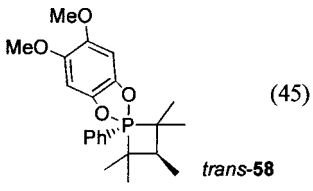


56

Similarly, phosphetane oxides and sulfides are converted to phosphoranes by reaction with catechols after O- or S-alkylation with triflic anhydride and oxonium salts, respectively. An example is given in eq 45.[167] The use of triflic anhydride induces isomer-



cis- or *trans*-**26** **57**

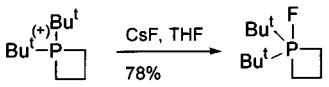


(45)

trans-**58**

ization at the phosphonium triflate stage, **57**, so that only the thermodynamically more favored isomer, *trans*,*trans*-**58**, is obtained. With oxonium hexafluoroantimonate salts the reaction is completely stereospecific, because of the configurational stability of the corresponding, intermediate phosphonium salts.

Other phosphorane syntheses include conversion of phosphetane oxides to difluorophosphoranes with sulfur tetrafluoride (Table 8)[78] and cesium fluoride addition to phosphetanium salts (eq 46).[34]



(46)

Phosphorus Stereochemistry in Pentacoordinate Phosphetanes

Most studies on phosphetane-based phosphoranes have been oriented toward an understanding of stereochemistry and the evaluation of activation barriers to pseudorotation.[13,81,123,154,156,157,149,160,164,170] These are expected to increase when the phosphorane incorporates a four-membered ring and NMR experiments suggest an activation energy of about 20 kcal/mol for placing the four-membered ring in an equatorial−equatorial configuration in a trigonal bipyramid. A few representative studies are summarized hereafter.

Phosphorane **59** has been obtained as a mixture of two noninterconverting diastereoisomers, as shown in Figure 8.

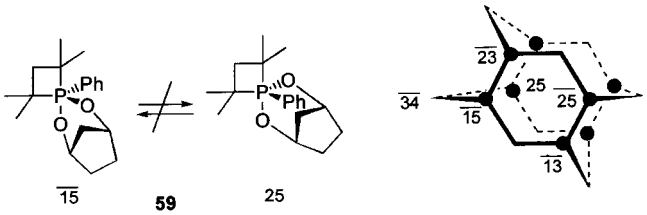
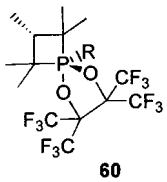


Figure 8. Distinct isomers of the spiro-phosphorane **59**.

In the hexasterane graph, 4 represents the phenyl substituent and 1,2 the phosphetane ring, and bold points indicate the most stable isomers. (Each hexagon contains three distinct isomers, identical pairwise to the other three isomers). The two noninterconverting isomers are represented by the vertexes of top and bottom hexagons, respectively. Interconversions should go through diastereoisomers where the phosphetane and/or the dioxaphospholane rings are in the eq−eq position. Given that heating of **59** to 145 °C resulted in decomposition, without any indication of interconversion, a lower limit for the activation barrier was therefore calculated at 19.5 kcal/mol.[160]

The ^{1}H and ^{19}F NMR studies of phosphorane **60** (R = Ph) at variable temperature led to similar conclusions.[13,156] While pseudorotation between allowed structures (both rings in ax−eq positions) is fast on the NMR time scale, even at −60 °C, interconversion between *cis*- and *trans*-phosphetane isomers, which requires the 1,2,3-dioxaphospholane ring to assume an eq−eq position, was not observed even at 160 °C. The free energy of activation for pseudorotations placing the phosphetane ring in eq−eq positions—without epimerization—has been evaluated at 19.6 kcal/mol for R = Ph (coalescence temperature of the ^{19}F NMR signals = 140 °C).



60

It has also been considered that all isomers of phosphorane **60** having the phosphetane ring in an eq−eq position have the R substituent in an axial position. Consequently, all other things being equal, the relative pseudorotation barriers for phosphoranes **60** bearing various R substituents should also measure the apicophilicity of the R substituent. The following apicophilicity order has been established: OPh > NR_2 > 2-furyl[154] >Me> *i*-Pr > Ph.[13,123]

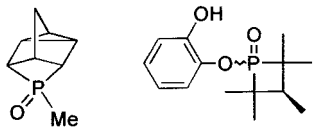
Related NMR studies confirming the above geometrical features and activation barriers for pseudorotation processes have been performed on other phosphetane-based monocyclic and spirophosphoranes.[164,168] It should be noted that the results of these stereochemical studies hold irrespective of the ground-state geometry of the phosphoranes—trigonal pipyramidal or square pyramidal. The exact solution structure of these compounds cannot be considered established.

Configurational Stability at Phosphorus

Trivalent Phosphetanes. Configurational stability at phosphorus is usually heightened when the inverting center is incorporated into a small ring and trivalent phosphetanes are configurationally stable over a wide temperature range. *trans*-1-*tert*-Butyl-2,2,3,4,4-pentamethylphosphetane was isomerized to a 1:1 mixture of *cis* and *trans* isomers by heating at 157 °C.[19] The analogous *P*-phenyl-substituted compound isomerizes slowly at 110 °C and gives an equilibrium 3:2 mixture of isomers after 2.5 h at 165 °C,[9] while the *P*-methyl-substituted phosphetane showed no inversion after 4 days at 162 °C.[169] *P*-Amino and *P*-methoxyphosphetanes are unchanged after several months at 25 °C.[153]

Phosphetanium Salts. When associated with nonnucleophilic counterions (e.g., $AlCl_4^-$, SbF_6^-), phosphetanium salts are configurationally stable. However, *P*-chlorophosphetanium chlorides exist as an equilibrium mixture of isomers at room temperature because of Cl^- association to give pentacoordinated intermediates and subsequent pseudorotation.[19,30] Even a triflate counterion is sufficiently nucleophilic to induce isomerization of phosphetanium salts.[167]

Phosphetane Oxides. Generally speaking, phosphetane oxides and phosphetanic acid derivatives are configurationally stable, although specific structural features may facilitate epimerization. Thus, the highly strained tetracyclic phosphetane oxide *endo*-**61** undergoes very rapid isomerization to the more stable *exo*-isomer, when crystals are exposed to the atmosphere, but also isomerizes in a sealed ampule, in the apparent absence of atmospheric moisture.[30] The *cis*-isomer of the *o*-hydroxyphenyl phosphetanic ester **62** is converted easily to the *trans*-isomer at room temperature.[168,170]



61 62

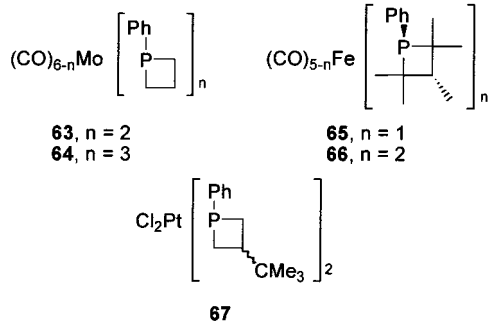
Phosphetane oxides can be epimerized in acidic medium[171,172] and by treatment with $LiAlH_4$ in THF[155] or $SiCl_4$ in acetonitrile.[142]

All the epimerization reactions above proceed *via* phosphorane intermediates.

V. Coordination Chemistry

Comparatively little is known about phosphetane coordination compounds, which first appeared in 1984[62] and are now accessible through two distinct synthetic pathways. In one, a preformed phosphetane is simply coordinated to the desired metal center. In the other, the phosphetane ring is built from its components within a metal coordination sphere[173−175] (see section II). The performance of this second method is often excellent, as demonstrated by the synthesis of the iron-coordinated phosphetane complex **14** (eq 11), which is equal in terms of yield (84%) to its phospholane and phosphorinane analogues.[38] Low oxidation state, strongly binding metal centers such as $[W(CO)_5]$[57,61,62] (eqs 17 and 21) and $[CpFe(PR_3)_2]^+$[38] (eq 11) fragments are used (Table 9). This approach is likely to be much less useful for redox-active and poorly coordinating metals. The method will be useful especially when the desired complex incorporates a phosphetane that is either very labile or not available by the usual preparations of free phosphetanes.

In the majority of cases, complexes are prepared by the simple addition of a phosphetane ligand to the required metal center. For monodentate phosphetanes, reactions of 1-phenylphosphetane with $Mo(CO)_4$(nbd) and $Mo(CO)_3$(mesitylene) provided *cis*-**63** and *fac*-**64** (Figure 9) in isolated yields of 58% and 81%, respectively.[35,36]



63, n = 2
64, n = 3

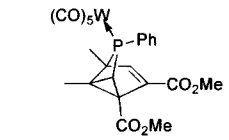
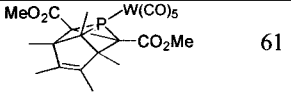
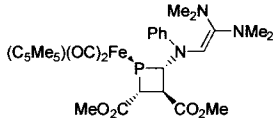
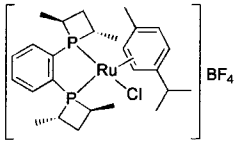
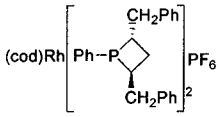
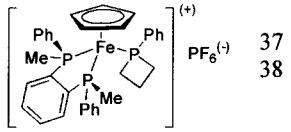
65, n = 1
66, n = 2

67

Figure 9. Transition-metal complexes of monodentate phosphetanes.

The more hindered 2,2,3,4,4-tetramethyl-1-phenylphosphetane reacts with $Fe_2(CO)_9$ at room temperature to give, according to ^{31}P NMR spectroscopy, a 3:2 mixture of **65** and air-sensitive *trans*-**66** in 95% combined yield after 3 days; crystals of **66** could be obtained subsequently from hexane.[176] The reaction of a mixture of *cis*- and *trans*-**22** with a dichloromethane solution of $PtCl_2$(cod) gave the anticipated *cis*-bis(phosphetane)$PtCl_2$ complexes, *cis*-**67**, as a mixture of isomers.[56]

Table 9. Additional Examples of Phosphetane−Transition Metal Complexes

Complex	Ref.	Complex	Ref.
	62		61
	58		48
	182		37 38

Platinum complexes are often used in attempts to evaluate ligand properties. Thus, comparisons of the structures of the relatively simple phosphetane complexes *cis*-**67** with classical platinum−bis(phosphine)-dichloride complexes show fairly short PtP and PtCl bonds and imply a relatively small thermodynamic *trans*-influence for phosphetanes. This might be anticipated for ligands having a relatively strong s-component in the phosphorus lone pair hybrid orbital. Nonetheless, this analysis sits uneasily with the relatively normal $^1J_{PtP}$ coupling constants (3378−3453 Hz) observed in *cis*-**67**, and the precise coordination properties of phosphetanes remain to be established.[56]

The coordination chemistry of optically pure, chiral phosphetanes has been studied in some depth, with special attention given to the preparation and characterization of complexes that are potential catalyst precursors. The optically active *P*-menthylphosphetanes afford stable palladium(II) and ruthenium complexes, under usual reaction conditions. Thus, the Pd−allyl complex **68**[116] and the *trans*-bis(phosphetane)$PdCl_2$ complex **69**[114] (Figure 10) have been prepared from $[(allyl)PdCl]_2$ and $Pd(PhCN)_2Cl_2$, respectively, and characterized by X-ray crystallography.

Reaction of the *P*(*R*),*C*(*S*)-2-benzyl-3,3,4,4-tetramethyl-1-menthylphosphetane **71** with $Ru_3(CO)_{12}$/HCO_2H proceeds normally to give the formato-bridged dimer **70**.[115]

The same phosphetanes display only moderate coordinating properties toward iridium and rhodium in *cis*-coordinated complexes: interaction between *P*(*R*),*C*(*S*)-**71** and $[Ir(cod)Cl]_2$ with subsequent treatment by NH_4PF_6 gave **72** (eq 47), where coordination is poor, as reflected in broad NMR signals in deuteriobenzene.[114]

Similarly, reaction of **71** with $Rh(cod)_2PF_6$ produced only a left-shifted equilibrium with the majority of the phosphetane remaining uncoordinated (eq 47).[144]

The sterical hindrance between the two *cis*-ligated phosphetanes could be responsible for the lability of

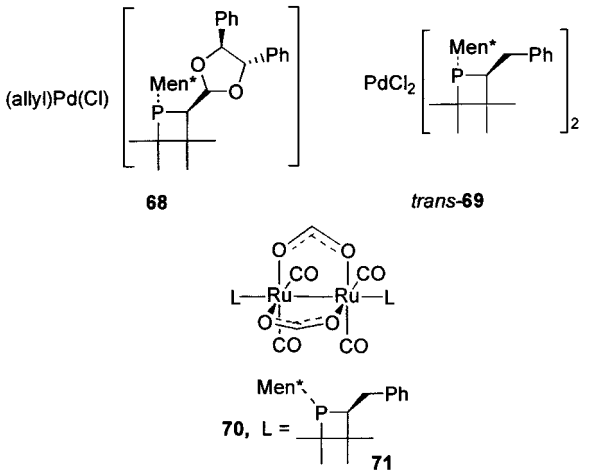
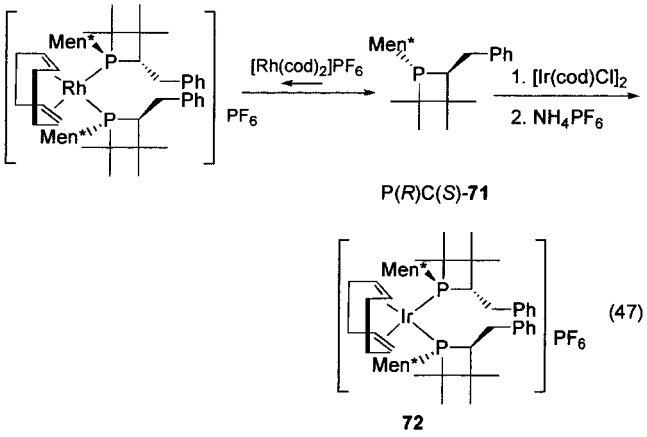


Figure 10. Organometallic complexes of chiral monodentate phosphetanes.



these complexes. This assumption is supported by the easy formation of stable bis(phosphetane)rhodium complexes, such as **73** (Figure 11), from less hindered

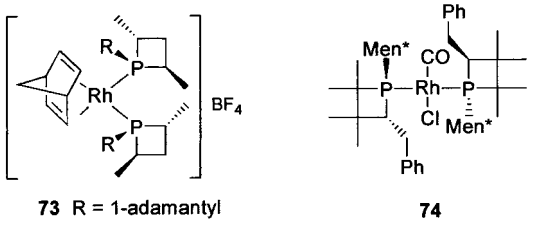
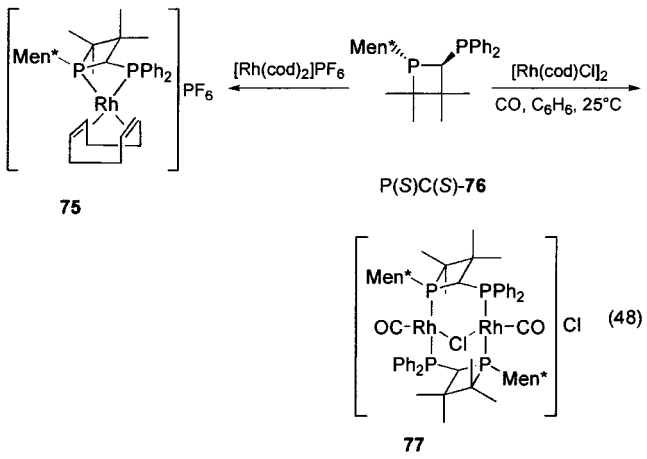


Figure 11. Rhodium complexes of chiral monodentate phosphetanes.

phosphetanes,[44,45,182] as well as by the observed stability of the *trans*-complex **74** obtained from phosphetane **71** and $[Rh(CO)_2Cl]_2$ by halide bridge cleavage and CO displacement.[115]

The relatively poor coordinating properties displayed by the *P*-menthyl-substituted monodentate ligands above toward some catalytically useful metals (mainly rhodium and iridium) have prompted efforts to develop the coordination chemistry of chelating phosphetanes. Early studies established that the chiral dppm analogue *P*(*S*),*C*(*S*)-**76** binds well to rhodium centers. It gives the chelating complex **75** with $[Rh(cod)_2]PF_6$ and the bimetallic A-frame compound **77** when reacted with $[Rh(cod)Cl]_2$ under an atmosphere of CO (eq 48).[117]



A *trans*-spanning bidentate phosphetane, **48**, was also found to coordinate firmly to the [RhClCO] fragment to afford **78** (Figure 12).[113]

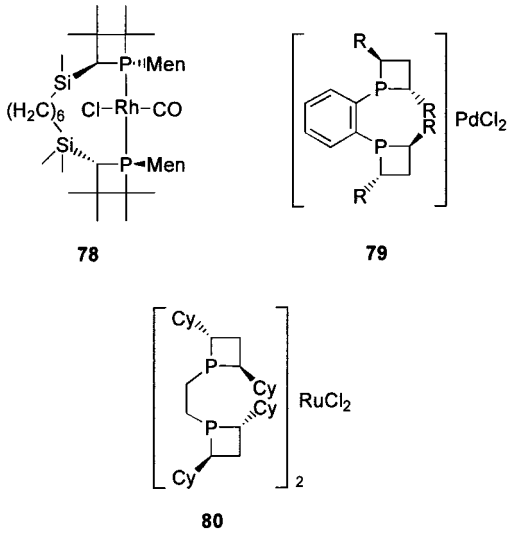


Figure 12. Organometallic complexes of chiral bidentate phosphetanes.

More recently, the similarities between the DuPHOS and BPE series of ligands and 1,2-bis(phosphetano)benzenes **16** and bis(phosphetano)ethanes **17**, respectively, have prompted the synthesis and isolation of a variety of potential catalyst precursors. Full details of the synthesis of the Ru(*p*-cymene)Cl(**16**)BF_4, $PdCl_2$(**16**), and $RuCl_2$(**17**)$_2$ complexes have appeared. The X-ray structure of **79**, for R = Me, and **80** have been determined.[48,49]

Clearly, the coordination chemistry of monodentate phosphetanes differs slightly from that of classical trialkylphosphine ligands. Hindered phosphetane derivatives may display labile bonding to the metals and should then have a role to play in processes where ligand dissociation is important. The stability of complexes containing chiral chelating phosphetane ligands suggests promise in asymmetric catalysis.

VI. Catalytic Applications of Chiral Phosphetanes

Chiral cyclic phosphines have useful properties as ligands in transition-metal-assisted asymmetric catalysis. The most impressive demonstration can be

seen in the development of processes employing the phospholane-based chiral ligands DuPHOS, BPE, and analogues.[177] However, apart from this noteworthy exception, chiral phosphines having a phosphorus atom incorporated into a monocyclic structure have not attracted particular attention.

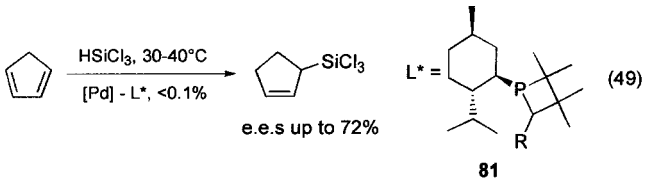
Concerning phosphetanes, it can be anticipated that many structural features make them well-adapted for use as chiral ligands. Especially noteworthy are the restricted conformational flexibility, which should enhance the efficiency of the chiral transfer during the catalytic process, and the slightly increased inversion barrier at phosphorus, which improves the configurational stability of P-chiral species. Consequently, in the past few years efforts have been devoted to developing phosphetane chemistry into a useful foundation for chiral ligand design.[178]

Two separate series of chiral phosphetanes have been employed as auxiliaries in asymmetric catalysis: the *P*-menthylphosphetanes **81** and the C_2 symmetric bis-phosphetanes **16**−**18**.

1. Monodentate Phosphetanes

The *P*-menthylphosphetanes **81** form a class of highly hindered, P-chiral, electron-rich, and, for the most part, monodentate phosphines. As such they should find specific applications in organometallic catalysis.[179] Thus, exploratory studies have been devoted to evaluating, first, their compatibility with various catalytic processes and, then, their efficiency and selectivity.

The monodentate phosphetanes **81** appear to be acceptable ligands for palladium-catalyzed hydrosilylation of olefins such as cyclopentadiene (eq 49) and styrene.[114,180]

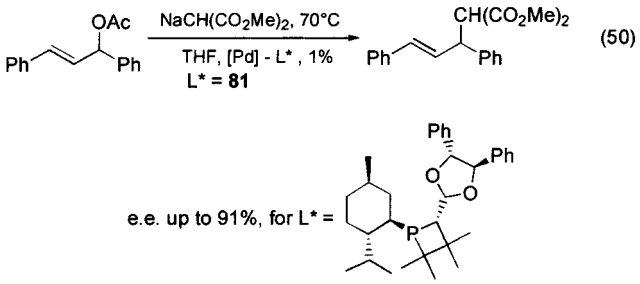


(49)

81

Especially high catalytic activity is observed with a 1:1 phosphetane-to-palladium molar ratio, with significant inhibition by excess phosphine ligand being observed. This confirms previous assumptions of the intermediacy of monophosphine−palladium complexes in hydrosilylations and is consistent with the widespread use of monodentate ligands in these reactions. The phosphetane-assisted hydrosilylation of styrene generally shows low enantiomeric excesses (<30%), but ee values rising to about 70% are obtained for cyclopentadiene hydrosilylation in systems containing phosphetanes **81** for R = 1,3-dioxolanes (65% ee for R = (*R*,*R*)-dimethyldioxolane and 72% ee for R = (*R*,*R*)-diphenyldioxolane). These values are competitive with those given by the most effective phosphines known at present.[116]

The *P*-menthylphosphetanes **81** have also been tested in the palladium-catalyzed allylic nucleophilic substitution of 1,3-diphenylpropenyl acetate with the sodium salt of dimethyl malonate (eq 50).[116]



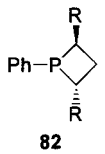
(50)

The electron-rich nature of these phosphines confers only moderate activation of the allyl−palladium complexes toward nucleophiles, with consequently low reaction rates. As with hydrosilylations, the enantiomeric excesses in this reaction are highly dependent upon the nature of the R substituent and the relative configurations of the various chiral centers, particularly phosphorus. For each pair of epimeric phosphetanes within the series of *l*-menthyl-derived phosphines **81**, the *R*-configuration at phosphorus invariably gives the higher enantioselectivity. Nonetheless, the configurations at other centers also tune the induction. Thus, the four epimers of phosphetane **81** for R = 4,5-diphenyl-1,3-dioxolane (see eq 50) gave ee values rising from 0% (for the *P*(*S*),*C*-(*S*),(*R*,*R*) epimer) to 82% (for the *P*(*R*),*C*(*R*),(*R*,*R*) epimer), under the same reaction conditions.

These catalytic tests show that *P*-menthylphosphetanes are efficient, moderately enantioselective ligands for palladium-promoted reactions. Chiral induction from these ligands can clearly be improved by an appropriate choice of the ring substituents, especially the easily modified R groups installed α to the phosphorus center.

A few experiments have been performed to evaluate the potential of the *P*-menthyl-substituted class of phosphetanes **81** in rhodium-mediated olefin hydrogenation reactions.[115] Within this series, monodentate ligands show low catalytic activity and poor enantioselectivity when employed in the hydrogenation of model dehydroamino acid derivatives. This observation is clearly consistent with the observed lability of their rhodium complexes, due to sterical hindrance.

The less hindered monodentate phosphetanes **82** give stable rhodium complexes and moderate-to-high enantioselectivities (up to 86% ee) in rhodium-catalyzed hydrogenations of functionalized olefins.[45,182]

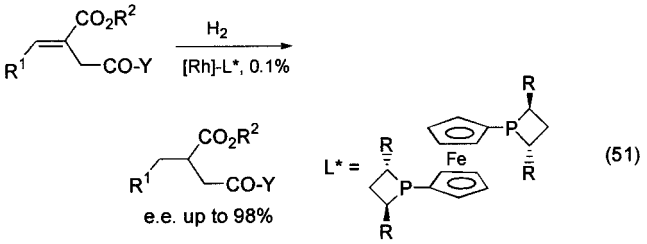


82

2. Bidentate C_2-Symmetric Phosphetanes

The C_2-symmetric, bidentate structure of phosphetanes **16**−**18** makes them especially suited for use in ruthenium- and rhodium-promoted hydrogenations of prochiral substrates. These ligands are easily available from optically pure *anti*-1,3-diols, and their catalytic properties can be modulated and optimized by variation of the R substituents.

All the ferrocenylphosphetanes **18**, as well as the bis(phosphetano)benzenes **16** and the bis(phosphetano)ethanes **17** bearing hindered substituents, are air-stable compounds in the solid state and oxidize slowly in solution. They have been tested in rhodium-catalyzed olefin hydrogenations. The bis(phosphetano)ferrocenes **18** show uniformly high efficiency and enantioselectivity, with unprecedentedly high enantioselectivities attained in the hydrogenations of itaconate derivatives (e.e. up to 99%, eq 51).[50,51,183]

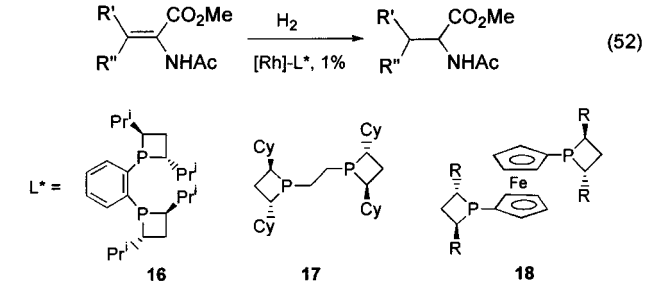


(51)

R^1	R^2	Y	Ligand / R	e.e.	Ref
H	Me	OMe	**18** / Me	91%	50
			18 / Et	98%	51
			18 / Pr^i	78%	
Ph	H	morpholino	**18** / Et	98%	
Pr^i	H	morpholino	**18** / Et	94%	
Bu^t	H	morpholino	**18** / Et	99%	

A key feature of these ligands seems to be the combination of the flexible ferrocene backbone (to increase the catalytic activity) with the rigid phosphetane moiety (to ensure stereochemical control). In this respect, it is noteworthy that simple monodentate phosphetanes such as **82** perform better than the corresponding phospholanes in various rhodium-catalyzed hydrogenations, as a result of their restricted flexibility.

In preliminary studies, some of the bis-phosphetanes **16**, **17**, and **18** have been tested in the hydrogenation of model dehydroamino acid derivatives. Selected results are given in eq 52.[184,50]



(52)

R"	R'	Ligand / R	e.e.	Ref
Ph	H	**16**	90%	184
		17	15% (10 bar)	
			70% (100 bar)	
		18 / Me	90%	50
H	H	**18** / Me	69%	
		18 / Pr^i	94%	
Ph	Me	**16**	80%	184

The rhodium complexes of **16** and **17** show high catalytic activities but only moderate enantioselectivities (e.e. up to 90%) by comparison with the very high optical yields given by the analogous, phospholane-based DuPHOS and BPE ligands.[185]

However, abnormal effects of H_2 pressure on the enantioselectivity, with increased enantiomeric excesses at higher pressures, are observed in these reactions. These experimental data contributed to point out the unusual behavior of electron-rich phosphines and the corresponding mechanistic implications. The most recent literature suggests that hydrogenations mediated by electron rich diphosphines (DuPHOS, BPE, BisP*, etc) follow an "hydride mechanism"[186] (alternative assumptions have also been made[187]), while most of the usual chiral ligands (DIOP, Chiraphos, BINAP, etc) follow a kinetically controlled "olefin mechanism". Phosphetanes seem to have intermediate behavior at low hydrogen pressure, but they resemble electron-rich ligands at higher hydrogen pressures (Figure 13).

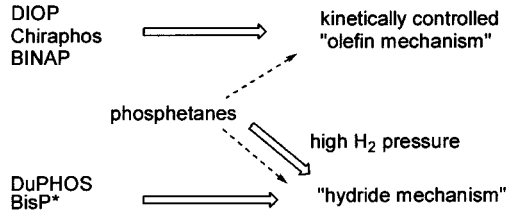
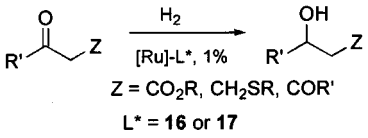


Figure 13. Assumed mechanisms for the [(COD)Rh-(P*P)]$^+$-catalyzed hydrogenations of dehydroamino acid derivatives.

These effects presumably result from the slightly lowered electron-donor capacity of the phosphetane ligands relative to phospholanes.

The bis(phosphetano)benzenes **16** and bis(phosphetano)ethanes **17** also show a significant potential in ruthenium-promoted hydrogenations of functionalized carbonyl derivatives (eq 53).[47−49] With ligands



(53)

R'	Z	Ligand / R	e.e.	Ref
Me	CO_2Me	**16** / Cy	84%	47
		16 / CH_2Ph	86%	48
		17 / Cy	92%	49
Ph	CO_2Et	**16** / Pr^i	94%	47
		17 / Cy	90%	49
Me	$(CH_2)_2SPh$	**16** / Pr^i	97%	
Me	COMe	**16** / Pr^i	98%	
		17 / Cy	98%	49

16, the catalytic activity is moderate, so rather severe reaction conditions must be employed (80 bar, 80 °C).

The level of enantioselectivity reflects the nature of the R substituents: hindered groups, such as *i*-Pr, CH_2Ph or cyclohexyl, usually give the best selectivity. Moreover, sterically hindered ligands display increased air stability and are thus preferred for practical reasons.

High enantiomeric excesses are obtained in the hydrogenations of β-keto esters, γ-keto sulfides, and, particularly, β-diketones. The last reaction affords *anti*-1,3-diols in high diastereomeric excesses and

good optical purity (ee > 95% for the crude hydrogenation product, increased to 100% after crystallization). The same diols can be used as starting materials for the synthesis of the phosphetane ligands in a crossed, self-breeding cycle.

Analogous catalytic properties, with slightly increased activity, have been noticed for the bis(phosphetano)ethanes−ruthenium complexes.[49]

The few catalytic studies above underline that bidentate chiral phosphetanes are interesting agents for both fundamental studies and more applied uses. Further catalytic developments are expected. Furthermore, the easily available monodentate phosphetanes, bearing either chiral or chirotopic phosphorus centers, are also promising ligands for specific applications in enantioselective catalysis.

VII. Concluding Remarks

A number of synthetic routes to both simple and optically active phosphetanes are now sufficiently developed to allow phosphetanes to be considered as basic "building blocks" for further chemistry. At present, the most interesting characteristics of these rings appear to be their moderate strain and conformational rigidity. Neither of these properties has been fully exploited to date.

When considering ring strain and the related reactivity, it seems likely that the potential of phosphetanes as precursors for ring-opened polymeric materials should be refined and developed in the future. Furthermore, the strain within phosphetanes suggests that they may find synthetic uses through the extrusion of reactive phosphorus-containing intermediates during ring fragmentation reactions. Thus, likely applications should involve the functionalization of phosphetanes prior to retrocycloaddition to give functionalized phosphaalkenes or, equally, uses as precursors for phosphinidenes and their derivatives.

Conformational rigidity is a key feature of phosphetanes as far as their use as chiral auxiliaries is targeted. The potential of chiral phosphetanes as efficient and rather inexpensive chiral ligands is already reasonably well established, and while this field is still young, the efficiency of the corresponding phospholane ligands suggests a potential for rapid advances in this area.

Finally, developments in calculational chemistry should hopefully allow an expansion in the theoretical understanding of phosphetanes and aid in their exploitation.

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