Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1279–1332

TETRAHEDRON: *ASYMMETRY*

TETRAHEDRON: ASYMMETRY REPORT NUMBER 35

Asymmetric synthesis of organophosphorus compounds

Oleg I. Kolodiazhnyi *

Institute of Bioorganic Chemistry, National Academy of Sciences of Ukraine, Murmanskaya Street, 1, Kiev, 253094, Ukraine

Received 3 February 1998; accepted 27 February 1998

Contents

1	Introduction	1279
2	Asymmetric induction at the phosphorus atom	1280
2.1	Low-coordinate organophosphorus compounds	1280
2.2	Tricoordinate trivalent phosphorus compounds	1282
2.3	Tetracoordinate phosphorus compounds	1295
2.4	Hypervalent phosphorus compounds	1309
3	Transfer of chirality from phosphorus to other centers	1312
3.1	The Abramov reaction	1312
3.2	The Pudovik reaction	1313
3.3	Enantioselective cycloaddition	1314
3.4	Chiral phosphorus-stabilized anions	1315
4	Conclusion	1326

1. Introduction

The asymmetric synthesis of organophosphorus compounds is a relatively new field, which has developed mostly during the past two decades.[1–11] The major factor stimulating the rapid development of the asymmetric synthesis of P-chiral organophosphorus compounds is their great practical value as ligands in catalysts for asymmetric organic synthesis,[1–5] They are efficient reagents in the asymmetric synthesis of organic and organophosphorus compounds, important in the study of biochemical mechanisms[3] and in the study of the stereochemical course of reactions at stereogenic phosphorus.[1,2,4]

Many previous reviews and literature compilations have dealt with phosphorus stereochemistry.[1,6–10] The most interesting of them is certainly the review of Valentine Jr.,[11] describing the chemistry of compounds containing stereogenic phosphorus centers. The lack of a review dedicated to the modern asymmetric synthesis of organophosphorus compounds induced us to write this report to provide a survey with emphasis on the most recent findings.

* E-mail: biophacs@biophacs.kiev.ua

PII: S0957-4166(98)00089-5

The review consists of two main parts treating the asymmetric synthesis of chiral organophosphorus compounds. The first part describes asymmetric induction at the phosphorus atom. This part analyses the synthesis of optically active compounds with different coordination numbers at the phosphorus atom. Asymmetric induction in the transfer of chirality from phosphorus to other centers (Abramov reaction, Pudovik reaction, Michael addition, Claisen rearrangements, 2,3-Wittig rearrangement), reactions of enantioselective cycloaddition, chiral phosphorus-stabilized anions and enantioselective olefination are discussed in the second part. This part of the review emphasizes the practical aspects of organic synthesis using chiral organophosphorus compounds. The present division of the review focuses on those compounds having demonstrated or potential uses as reagents in asymmetric synthesis.

2. Asymmetric induction at the phosphorus atom

For the preparation of enantiomerically homogenous molecules, chemists have basically two options. The molecules can either be synthesized in racemic form and resolved, or the synthesis can be performed in an enantioselective fashion so as to produce enantiomerically enriched products. Stereoselectivity in the synthesis of chiral molecules can be realized by asymmetric induction of chirality (asymmetric synthesis)[3,12] or via kinetic resolution.[13]

The term ‘asymmetric synthesis’ was first used in 1894 by Emil Fisher and defined in 1904 by W. Markwald[12] as a reaction which produces optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of analytical processes. Morrison and Mosher[3] consider the asymmetric synthesis as a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are formed in unequal amounts. Kagan and Fiaud[13] suggested that, “kinetic resolution can be defined as a process in which one of the enantiomer constituents of a racemic mixture is more readily transformed into a product than the other (enantioselective reaction)”. If the reaction is stopped before completion, unequal amounts of the diastereomerically substituted organophosphorus compounds should thus be obtained. The remaining unreacted starting material will also exhibit optical activity. Different examples of kinetic resolution were described.[13–18] Enzymatic kinetic resolutions of P-chiral phosphine derivatives in many cases give excellent results.[5,17]

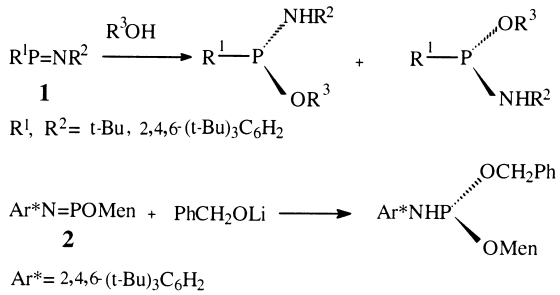
Asymmetric synthesis and kinetic resolution can be interrelated when a chiral reagent or catalyst is first used to perform an asymmetric synthesis and then is reused to carry out a kinetic resolution on the partially resolved product obtained in the asymmetric synthesis.[13,18]

Tervalent tricoordinate and pentavalent tetracoordinate organophosphorus compounds can exist in optically active states and are configurationally stable. Phosphorus atoms in low-coordinate valent states (mono- and dicoordinate trivalent phosphorus, tricoordinate pentavalent phosphorus) possess axial or planar symmetry and cannot be optically active. Pentacoordinate and hexacoordinate phosphorus compounds are conformationally unstable, though some of them were obtained in optically active form. Chiral pentacoordinate and hexacoordinate phosphorus compounds are important intermediates in asymmetric syntheses, therefore their stereochemistry has been studied in detail.

2.1. Low-coordinate organophosphorus compounds

Examples of the asymmetric synthesis at low-coordinate phosphorus compounds are limited. Many prochiral structures of low-coordinate phosphorus, interesting for asymmetric synthesis, have not been studied up to now. Attempts at the diastereoselective addition of optically active alcohols and amines

[(−)-menthol, (−)-menthylamine, (−)-α-phenylethylamine] to λ^3-iminophosphines **1**, possessing trigonal configurations were performed by Romanenko, Markovsky and Mikolajczyk (Scheme 1).[19]



Scheme 1.

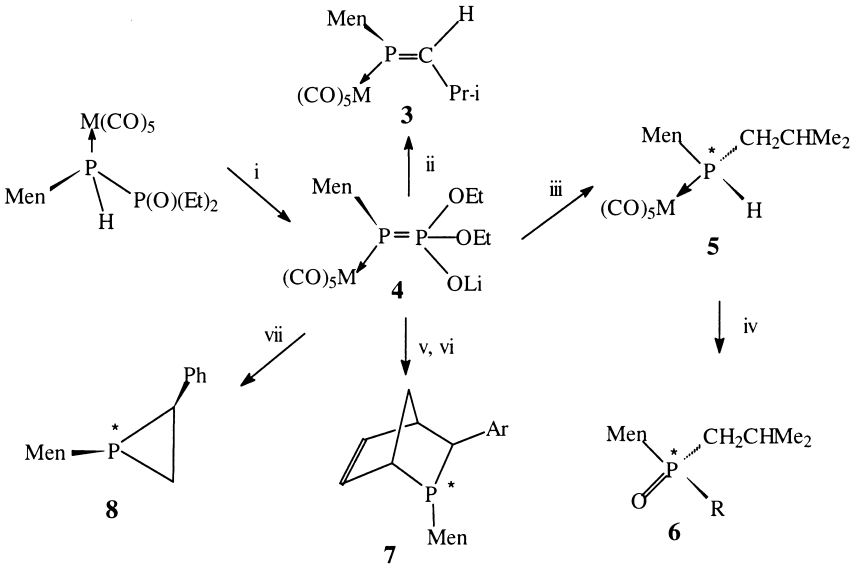
The stereoselectivity of this reaction was low: the highest level of stereoselectivity (34% *de*) was observed in the case of the reaction of λ^3-iminophosphine **1** with (−)-menthol. However, in the presence of chiral tertiary amines [(−)-*N*-dimethylmenthylamine or (−)-*N*-dimethyl-1-methylbenzylamine] the reaction of λ^3-iminophosphines **1** with methanol afforded methoxyaminophosphine of 55% enantiomeric excess.[20] Good stereoselectivity (*de* 80%) was obtained upon the addition of benzyl alcoholate to *P*-menthoxy-λ^3-iminophosphine **2**.[21]

Phospha-alkenes in the form of their tungsten and molybdenum complexes were used by Mathey and co-workers for asymmetric syntheses (Scheme 2).[22–26] Prochiral L-menthyl phospha-alkene complexes **3** were prepared from phospha-Wittig reagents **4** and aldehydes.[24] Catalytic hydrogenation of **4** using RhL^+_2 catalysts proceeds with high stereoselectivity. With L_2=diphos the diastereomeric excess of **4**, R=H, was better than 90%, and with L_2=(−)-CHIRAPHOS only one diastereomer of **5** was obtained. At −80°C, alkylation of **5,** proceeded with complete stereoselectivity to give the corresponding oxides **6**, after oxidation with Me_3NO. Mathey also introduced the phospha-Wittig reagent **4** into the reaction with aromatic aldehydes and cyclopentadiene to obtain phosphanorbornene derivatives **7** as single stereomers (Scheme 2).[23]

Reaction of the anion of pentacarbonyl(diethoxyphosphoryl)phosphine tungsten complex **4** with enantiomerically pure (*S*)-styrene oxide led to the formation of the optically active (phosphirane)$W(CO)_5$ complexes **8** (24:76 *dr*),[25,26] decomplexation of which has been performed by heating with diphos [bis(diphenylphosphino)ethane] to lead to the formation of the phosphiranes **7** (Scheme 2).

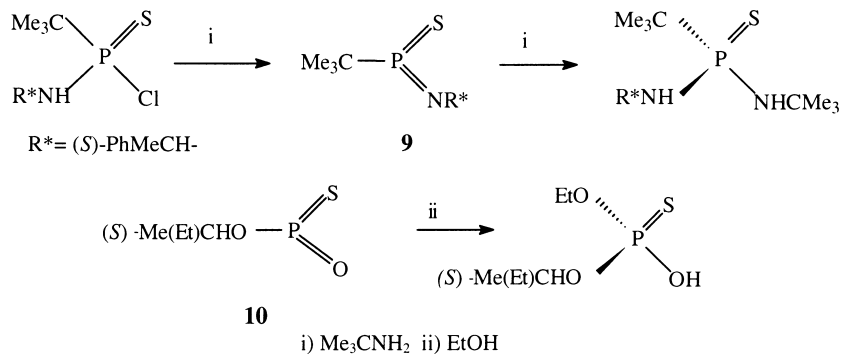
The stereochemistry of the reaction at the prochiral pentavalent tricoordinate phosphorus atom, possessing planar structure, has been studied by very few (Scheme 3). Thus the addition of *tert*-butylamine to the metathioiminophosphate **9,** generated by dehydrochlorination of N-substituted amide chlorophosphate, proceeded stereoselectively with the formation of a diastereomer mixture, the ratio of which increased with the decrease of the solvent polarity from 57:43 (MeCN) up to 80:20 (cyclohexane).[27,28] In other cases, addition of an alcohol to prochiral (*S*)-*sec*-butoxy metathiophosphonate **10** possessing a planar–trigonal configuration led to the formation of an equimolar mixture of diastereomers (Scheme 3).[29]

Hence, low-coordinate organophosphorus compounds are interesting starting compounds for asymmetric synthesis. However, their stereochemistry has been studied insufficiently. Looking into the future one can expect a wide application of low-coordinate organophosphorus compounds as starting reagents in asymmetric synthesis.



i) BuLi; ii)-PrCHO; iii) H_2, CH_2Cl_2/L_2Ph^+; iv) t BuOK/RX, Me_3NO; v) c-C_5H_6, ArCHO; vi) *diphos;* vii) *(S)*-phenyloxirane, *diphos*; M=Mo, W;

Scheme 2.



i) Me_3CNH_2 ii) EtOH

Scheme 3.

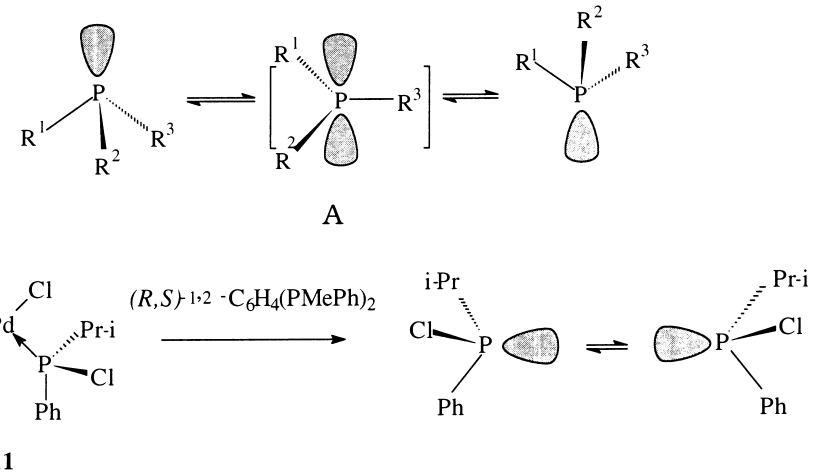
2.2. Tricoordinate trivalent phosphorus compounds

Chiral trivalent organophosphorus compounds play a key role in the stereochemistry of phosphorus. A principal application of the tertiary phosphines is their use as chiral ligands in catalysts for asymmetric synthesis. Therefore much effort has been devoted to elaboration of convenient methods for their synthesis.[1,4,5,11]

2.2.1. Configurational stability and epimerization

A trivalent phosphorus atom bonded to three substituents in a pyramidal geometry and possessing one unshared electron pair may spontaneously undergo inversion of configuration. Such a process of pyramidal atom inversion must involve passage through a transition state **A** in which the lone pair possesses pure *p* character and the bonds from the central atom to the substituents are sp^2 (Scheme 4).

Trivalent phosphorus compounds are more configurationally stable, than nitrogen compounds. Racemization of trivalent phosphorus compounds depends strongly on their structure, first of all on electron-



Scheme 4.

accepting substituents at the phosphorus atom, which decrease the configurational stability. The barrier of inversion in acyclic phosphines is about 150 kJ/mol, whereas the barrier of inversion for acyclic amines is about 30 kJ/mol.[30] Mislow showed that the barrier of inversion in phosphines depends on the electronegativities of substituents bonded to the phosphorus atom.[24] However in many cases compounds bearing electron-accepting groups at the phosphorus atom are racemized. For instance, electron-accepting groups in the *para*-position of phenyl rings in arylphosphines reduce the barrier of inversion.[31] Moreover, chiral chlorophosphines are conformationally labile compounds existing as an equilibrium racemic mixture of (*R*)- and (*S*)-enantiomers. Although calculations indicate substantial pyramidal stability at phosphorus in halophosphines of the type R^1R^2PX, attempts to isolate enantiomerically pure chlorophosphines have been unsuccessful.[32–34]

Thus *tert*-butylphenylchlorophosphine of 49.4% enantiomeric excess, prepared by Omelanczuk, lost its optical activity over 20 h in the polarimeter cell.[33] Recently, Wild and co-workers showed that the isopropylphenylchlorophosphine in palladium(II) complex **11** can be resolved, however, liberation of epimeric chlorophosphines from complexes led to complete racemization of the free phosphines within 5 min (Scheme 4).[34]

The esters of chiral trivalent phosphorus acid R_2POR are more stable than chlorophosphines and can be isolated enantiomerically pure.[34] However racemizations of P-chiral phosphorus esters R_2POR occur with measurable rates at room temperature. Acids catalyze racemization of chiral phosphonic esters and may involve not only the pyramidal inversion but also exchange of the ester group.[2,11,36]

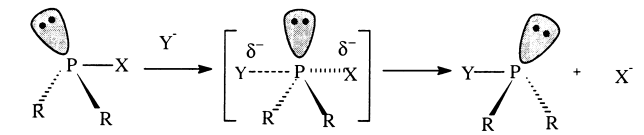
Tertiary alkylaryl- and diarylphosphines are more or less configurationally stable. They have a barrier of pyramidal inversion of 30–35 kcal/mol and may be obtained as individual enantiomers at or near ambient temperature. They can be isolated and, in some cases, purified by distillation under vacuum. However at high temperatures they can racemize. Syntheses of P-chiral tertiary phosphines must take into account the moderate epimeric stability of these substances.

Mechanisms other than pyramidal inversion, such as ligand exchange have been also observed in the stereomutation of trivalent phosphorus, for example, a rapid phosphorus inversion, accelerated by $(p–p)_p$ and $(p–d)_p$ conjugation.[37] The reduction in barrier height can be explained by the presence of *d* orbitals on an adjacent substituent, as in the diphosphine and the silylphosphines. The extreme rate acceleration in the phospholes must be due to aromatic character in the transition state to inversion.[37]

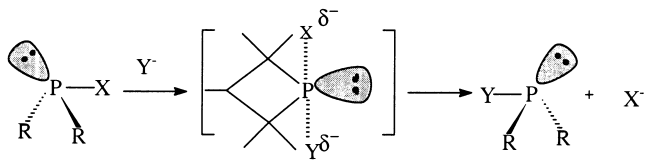
2.2.2. Synthesis

Until now, non-racemic chiral trivalent organophosphorus compounds have been obtained in the following ways: asymmetric synthesis, kinetic resolution and stereospecific synthesis. Asymmetric synthesis is an attractive route to chiral trivalent phosphorus compounds. The successful development of the asymmetric version of many transition metal catalyzed reactions is dependent upon the design and synthesis of new chiral ligands and inter alia of new chiral phosphines. The important route to chiral tertiary phosphines is by nucleophilic substitution at the trivalent phosphorus atom in the presence of tertiary bases.

2.2.2.1. *Nucleophilic substitution* The most frequently encountered reactions in organic phosphorus chemistry are nucleophilic substitution reactions. The mechanism and steric course of S_NP reactions have been intensively studied. In the overwhelming majority of cases S_N2 nucleophilic substitution at chiral tricoordinate trivalent phosphorus results in inversion of configuration that assumes the formation of pentacoordinate anions of type **12**, containing attacking and leaving groups in apical positions, in spite of the extension of the steric strain due to arrangement of the four-membered cycle in a diequatorial position.[35,38] Stereochemical consequences of nucleophilic substitution at chiral phosphorus may be different in cyclic systems. Ring size in particular can affect considerably stereochemical results (Scheme 5).[42–46]



12



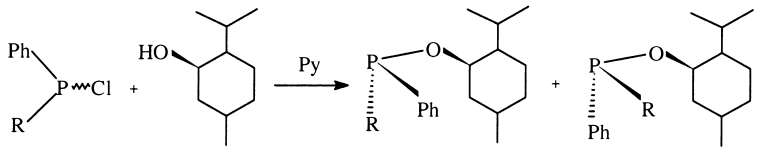
13

Scheme 5.

The transition state supposes the inversion of configuration at the phosphorus atom in accordance with the replacement in chlorophosphetane, which is always accompanied with inversion of the configurations at the phosphorus atom. In this case the reaction proceeds via a transition state or intermediate of the S_N2 type, **13**, containing the attacking and leaving groups in apical positions, in spite of the extension of the steric strain due to arrangement of the four-membered cycle in a diequatorial position.[38]

The simplest potential asymmetric synthesis is the reaction of mixed phosphinic acid chlorides with chiral substrates. In the literature one can find different examples of such syntheses, though the stereoselectivity of these syntheses is, as a rule, not very high. In many cases trivalent phosphorus products were not isolated from the reaction mixture, and often diastereomeric ratios were not determined. The pioneering work in this area is due to Mislow, who obtained menthyl esters of phosphinic acids **14** in low stereochemical yield (Scheme 6).[39–44a]

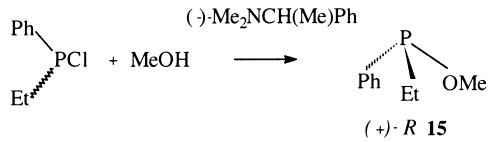
Mikolajczyk and co-workers[44b] have prepared several partially P-resolved alkylphosphinites and thiophosphinites by the reaction of asymmetric chlorophosphines with simple alcohols in the presence of chiral (−)-*N*,*N*-dimethyl-(1-phenylethyl)amine (Scheme 7). Enantiomeric yields of this reaction were



14

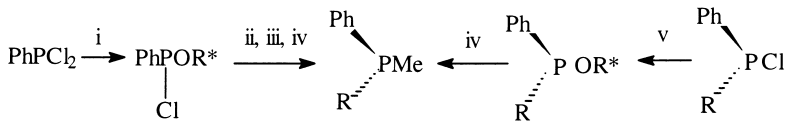
Scheme 6.

not high and up to now this theoretically interesting reaction has not been developed. The enantiomeric excess of the obtained compound **15** was only 10%. However, it is possible that the choice of reaction conditions and of a chiral tertiary base could give higher stereoselectivity.



Scheme 7.

Chodkiewicz has completed a synthesis of a homochiral phosphine **16** using (+)-cinchonine as a chiral auxiliary. Consecutive substitutions of chlorine in dichlorophenylphosphine by lithium cinchoninate and arylcyanocuprates led stereoselectively to the corresponding P(III) esters. The reaction of phenylalkylchlorophosphines with (+)-cinchonine proceeds analogously (Scheme 8).[45,46] The P-resolved phosphinites were then converted by reaction with alkyllithiums into chiral tertiary phosphines. However details of this methodology have not been published.

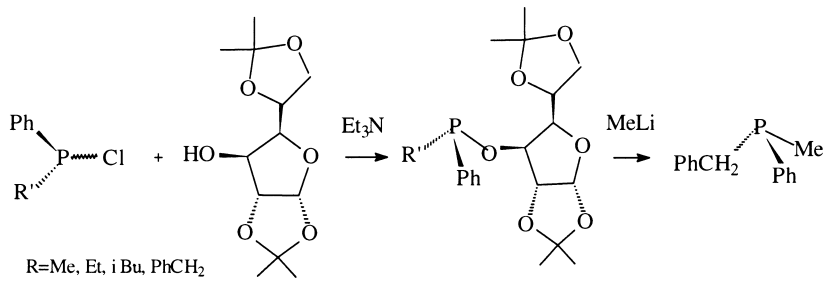


16

i) R*OLi ii) RCuCN, Li iii) KCN iv) MeLi v) R*OH/B [R*OH = (+)-cinchonine]

Scheme 8.

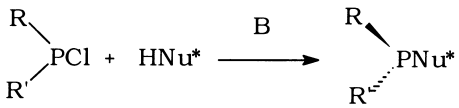
The best results were achieved in the author's laboratory with 1:2;5:6-disubstituted derivatives of glucofuranose as a very effective inducer of chirality at the phosphorus atom (Scheme 9).[47–49] It was shown that the reaction between 1,2:5,6-substituted derivatives of α-D-glucofuranose and non-symmetrical racemic chlorides of trivalent phosphorus acids in the presence of tertiary bases proceeds, depending on reaction conditions, with high stereoselectivity to give enantiomerically pure phosphinic acid esters **19**.



17

Scheme 9.

Table 1
Reaction of chlorophosphines with chiral nucleophiles in the presence of organic bases



R(R')	HNu*	Base	Solvent/Temp.	*de*	[ref.]
Bz(Ph)	GF	DABCO	Toluene/-20-+20 °C	~98	[52]
Bz(Ph)	GF	Et_3N	Toluene/-20-+20°	~96	[52]
i-Pr(Ph)	GF	Et_3N	Toluene/-20-+20°	~98	[52]
i-Bu(Ph)	GF	Et_3N	Toluene/-20-+20°	~98	[52]
i-Bu(Ph)	GF	$PhNMe_2$	Ether/+20°	65	[52]
i-Bu(Ph)	GF	Py	Ether/+20°	-20	[52]
i-Bu(Ph)	GF	NaH	DME/-20°		[52]
i-Bu(t-Bu)	(-)-HO(Me)$CH_2CH_2NEt_2$	Et_3N	Ether/20°	83	[52]
i-Bu(Ph)	(-)-Menthole	Et_3N	Toluene/+20°	20	[52]
i-Bu(Ph)	(-)-HOCH(Me)CH_2CO_2Et	Et_3N	Toluene/+20°	20	[52]
	NEA	NEA		35	[54]
t-Bu(Ph)	PEA	PEA	Benzene	60	[52]
t-Bu(Ph)	PEA	Et_3N	Benzene	80	[52]
t-Bu(Ph)	*(S)*-H_2NCH(Bu-i)CO_2Me	Et_3N	Benzene	15	[52,55]

Comments:

GF -=(-)-1,2:5,6-Diisopropylidene-D-glucofuranose; NEA= (-)-2-Naphthylethylamine;

PEA = (-)-2-Phenylethylamine.

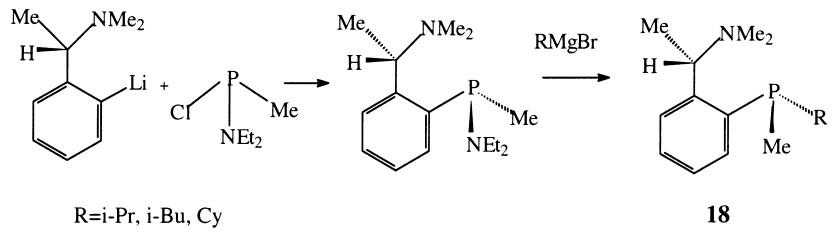
Careful observation of reaction conditions between alkylarylchlorophosphines and (−)-1,2:5,6-diisopropylidene- or (−)-1,2:5,6-dicyclohexylidene-α-D-glucofuranoses proceeds with very high stereoselectivity and can be an excellent method for preparation of enantiomerically pure phosphinites (Table 1).[48–52]

The substitution of alkoxyl groups in phosphinites by organolithium compounds occurs with inversion of configuration at the trivalent phosphorus atom to give tertiary phosphines **16** of the (*S*)-configuration.

The stereoselectivity of the reaction depends on the nature of the base and the solvent. Thus, the addition of racemic chlorophosphines to a solution of (−)-1,2:5,6-diisopropylidene-D-glucofuranose in toluene at 20°C in the presence of such strong tertiary bases as 1,4-diazabicyclo[2,2,2]octane (DABCO) or triethylamine furnishes, in good yield, the enantiomerically pure phosphinite having an (*S*)-configuration at the phosphorus atom. The highest *de* values were obtained in toluene as a solvent. The stereoselectivity of the reaction was also raised when an excess of chlorophosphine was used.[48] In the presence of weak bases, such as dimethylaniline in ether, a mixture of two diastereoisomers in the ratio 50:50 was obtained. Surprisingly, in the presence of pyridine instead of DABCO as the base the minor (*R*)-diastereomer becomes the major one. The reaction proceeds under kinetic control, via the formation of a cyclic intermediate complex having the *threo*- or *erythro*-diastereomer structure.[48,53] The stereoselectivity of the reaction of chlorophosphines with other chiral secondary alcohols [(*R*)-2-diethylaminopropanol, L-menthol, optically active lactates] and chiral amines is not as high as with 1,2:5,6-disubstituted derivatives of D-glucofuranose. For example, the diastereomeric excess in the case of the reaction of *tert*-butylisobutylchlorophosphine with (−)-1-diethylamino-2-propanol is only 68%.[48]

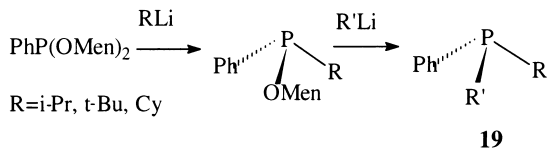
The reaction of chlorophosphines with chiral nucleophiles in the presence of tertiary bases depends strongly on the experimental conditions (Table 1).[39–43,52–57]

The reaction of aminochlorophosphines with chiral aryllithium reagents derived from enantiomeric α-phenylethylamine was used for the synthesis of C,P-chiral aryldialkyl- and alkyldiarylphosphines **18** (Scheme 10).[58,59]



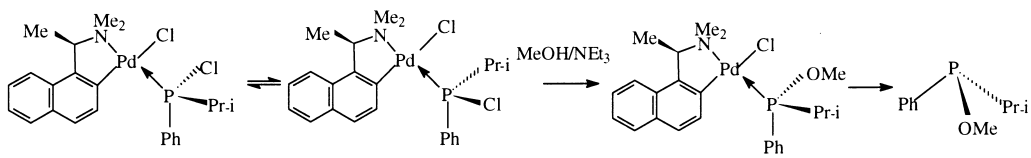
Scheme 10.

The reaction of prochiral dimenthyl phosphonite with alkyllithium at low temperature proceeds with formation of P-resolved menthyl alkylphenylphosphinites **19** of high diastereomeric purity (90–96% *de*), The second substitution gives enantiomerically enriched tertiary phosphines (73–79% *ee*; Scheme 11).[39,60]



Scheme 11.

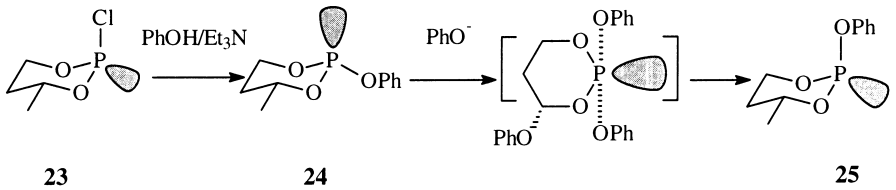
The reaction of racemic isopropylphenylchlorophosphines with *ortho*-metallated (*R*)-[1-(dimethylamino)ethyl]naphthalene palladium(II) complex in dichloromethane produces the pair of (*R,Rp*)- and (*R,Sp*)-diastereomeric complexes **20** in a 78:22 ratio (Scheme 12).[34] Crystallization of the single diastereomer from dichloromethane–diethyl ether proceeds by second-order asymmetric transformation, because of an equilibrium and interconversion between (*R,Rp*)- and (*R,Sp*)-isomers. Thus, the configurationally homogenous (*R,Rp*)-diastereomer **20** was separated in 82% overall yield. Addition of the (*R,Rp*)-diastereomer to an excess of triethylamine and methanol led to the quantitative and completely stereoselective formation of the (*R,Sp*)-phosphonite complex **21**. Substitution of the P-chloride in the (*R,Rp*)-diastereomer **20** by methoxide proceeds with complete inversion at phosphorus. Free configurationally stable (*R*)-**22** can be isolated from this complex in 93% *ee* by treatment of the complex with dppe.[61]



Scheme 12.

The stereochemical result of nucleophilic substitution at the trivalent phosphorus atom sometimes depends on reaction conditions. Thus the reaction of *trans*-**23** with an excess of phenol and triethylamine at room temperature led with retention of configuration to the *trans*-phenylphosphite **24** (84% *de*). At that time addition of phenol to the chlorophosphine to avoid an excess of phenoxide ion during the reaction

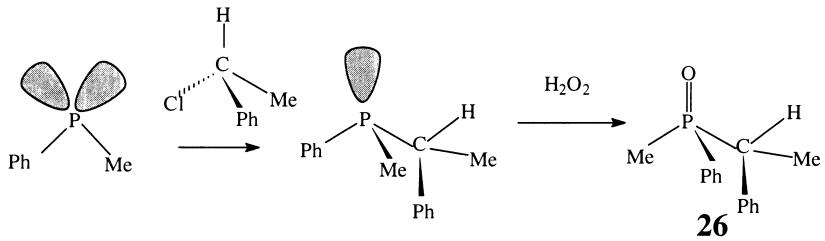
provides exclusively *cis*-phenylphosphite **25**. This result was explained by an S_N2P mechanism and a second attack, following an antiperiplanar pathway, which produces the thermodynamically more stable *trans*-diastereomer **25** (Scheme 13).[62]



Scheme 13.

2.2.2.2. *Electrophilic substitution* The number of known stereoselective electrophilic reactions at phosphorus proceeding with high asymmetric induction is not very high and practically limited to chiral tricoordinate phosphorus compounds that on reaction with electrophilic reagents produce more stable tricoordinate derivatives. It is generally assumed that the electrophilic attack is directed at the lone electron pair on phosphorus and that the reaction is accompanied by retention of configuration. The alkylation of P-prochiral phosphides was utilized by several groups, but in almost all cases asymmetric induction was low.[63–68]

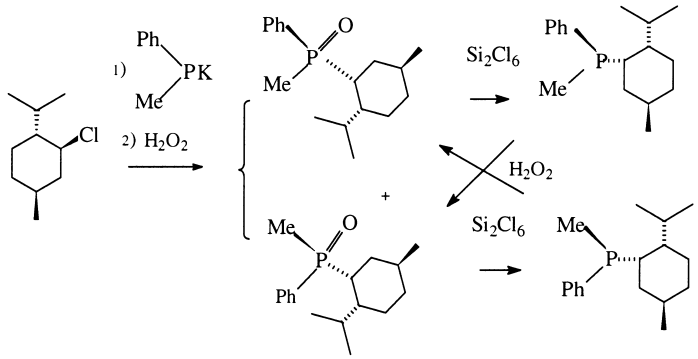
For example, the reaction of sodium methylphenylphosphide with (+)-(*R*)-1-chloroethylbenzene proceeding with 25% induction and resulting in the (−)-(*Sp*)-(*Sc*)-phosphine oxide **26** after oxidation was described by Naylor and Walker (Scheme 14).[67]



Scheme 14.

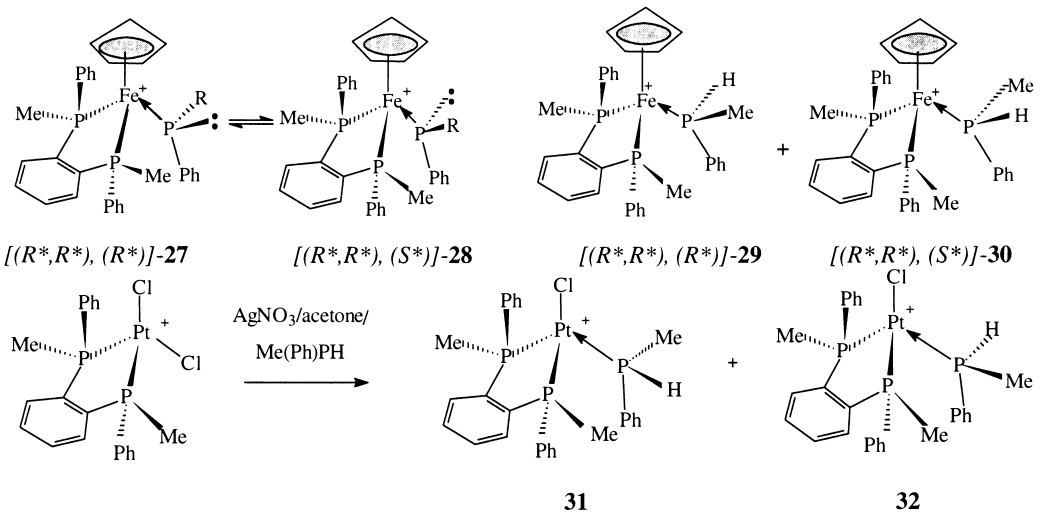
Both (*R*)- and (*S*)-phosphorus epimers of menthylmethylphenylphosphine and its phosphine oxide as well as epimers of neomenthylmethylphenylphosphine have been synthesized. The menthylmethylphenylphosphines were prepared from neomenthylmethylphenylphosphine by a method which is potentially general for the synthesis of phosphines and phosphine oxides having stereogenic groups at the chiral phosphorus.[68] Mosher and Fisher noted that diastereomers of menthylmethylphenylphosphine epimerized at 120°C to give a 70:30 equilibrium mixture of epimers (Scheme 15).[64,65]

Alkylation of phenylphosphine in cationic iron complexes has been studied by Wild and coworkers.[69,70] The reaction proceeded with 60% diastereoselectivity. At −95°C, deprotonation of the secondary phosphine complex [(*R**,*R**)(*R**)]-**27** (R=H) can be performed with complete stereoselectivity. Alkylation of the tertiary phosphidoiron complex, generated and maintained at −95°C, proceeds with retention of configuration and complete stereoselectivity. Reaction above this temperature gives a mixture of thermodynamic products **27** and **28** because of the relatively low barrier to inversion of the pyramidal phosphorus stereocenter in the intermediate tertiary phosphidoiron complex.[69,72] Reaction of (*R**,*R**)-$[(\eta^5\text{-}C_5H_5)\{1,2\text{-}C_6H_4P(MePh)_2\}FePH_2Ph]^+PF_6^-$ with iodomethane in the presence of triethylamine at 20°C produces a separable 4:1 mixture of **29** and **30**. In the case of platinum complexes, two



Scheme 15.

diastereomeric methylphenylphosphine diastereomers **31** and **32** have been obtained in a 1:3 ratio and the pure (*S*,*S*,*S*)-diastereomer was isolated by crystallization (Scheme 16).[72]



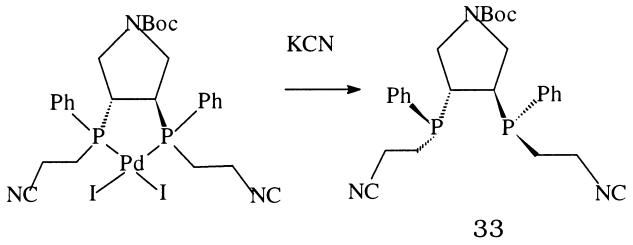
Scheme 16.

Soluble rhodium complexes containing enantiomers of (*R*,*R*)-1,2-phenylenebis(methylphenylphosphine) have been shown to be highly efficient catalysts for the asymmetric hydrogenation of a variety of prochiral Z-substituted enamide acids and esters.[70]

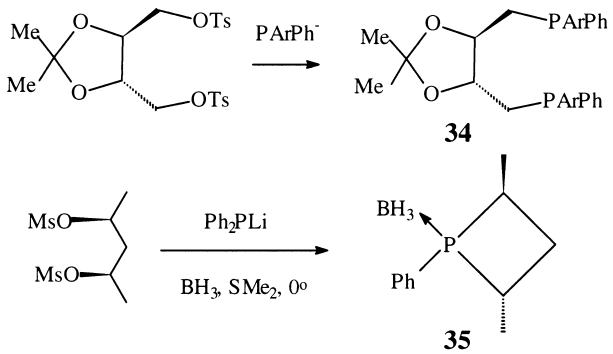
The reaction of C_2-symmetric bis(phosphides) with various electrophiles proceeds with the formation of only one (usually *S*,*R*,*R*,*S*) of the three possible products in high predominance of the total isomeric mixture. The isomerically pure [(*Rp*,3*R*,4*R*,*Rp*′)(*Sp*,3*R*,4*R*,*Sp*′)]-1-(*t*-butoxycarbonyl)-3,4-bis[(2-cyanoethyl)phenylphosphino] pyrrolidine **33** was prepared via the neutral di-iodopalladium complex and then split off from the palladium with cyanide ion (Scheme 17).[78,79]

Burgess and co-workers performed the synthesis of stereochemically matched biphosphine ligands, representing DIOP–DIPAMP hybrids. Absolute configurations of chiral phosphine ligands **34** were determined via single-crystal X-ray diffraction studies of molybdenum tetracarbonyl derivatives (Scheme 18).[63] Reaction of lithium phosphides with the mesylate or the cyclic sulfate, of (*R*,*R*)-2,4-pentanediol afford, as general access to new chiral ligands, **35** based on the phospholane moiety.

Mathey and co-workers reported that deprotonation and subsequent alkylation of (menthylphosphine)pentacarbonyltungsten with *i*-BuI gave two diastereomeric secondary phosphine complexes **36**

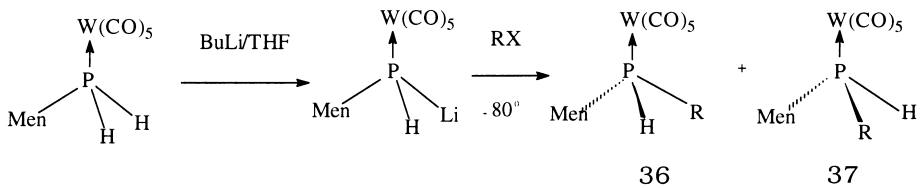


Scheme 17.



Scheme 18.

in the ratio 7:3 (Scheme 19). Further alkylation of these complexes led to the preferential formation of tertiary phosphines with a diastereomeric excess of 80%. Diastereomerically pure tertiary phosphines **37** have been isolated after crystallization and oxidative decomplexation.[23]

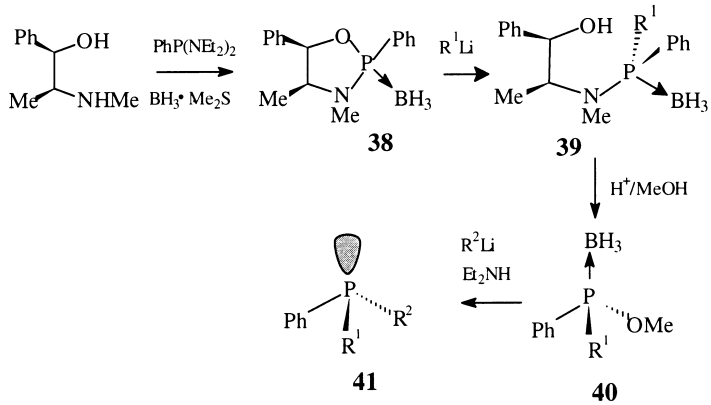


Scheme 19.

Different examples of alkylations and arylations of prochiral phosphides derived from the tartaric acid were also described by Nagel.[76–79]

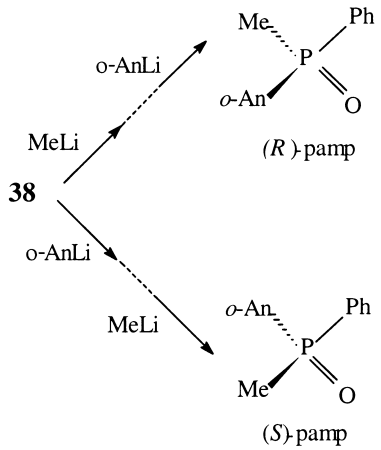
2.2.2.3. *Borate complex method* Juge and co-workers elaborated a general method for the asymmetric synthesis of enantiomerically pure tertiary mono- and diphosphine ligands based on the regio and stereoselectivity of the ring opening of the oxazaphospholidine–borane complex.[51,66] The diastereomerically pure borane complexes **38** were prepared in one step from bis(diethylamino)phenylphosphine, (−)-ephedrine and $BH_3 \cdot SMe_2$. The complexes **38** were isolated as crystalline products of (2*R*,4*S*,5*R*)-configuration and their structure was confirmed by X-ray analysis. Alkyl- and aryllithium compounds cleanly reacted with borane complexes **38** at low temperature in THF to give the corresponding aminophosphine boranes **39** by P–O bond cleavage, with a diastereomeric ratio of better than 92:8 (Scheme 20).

The X-ray crystal structure revealed that the ring cleavage of the borane complex proceeds with a retention of configuration at the phosphorus atom. The acid methanolysis of the aminophosphine boranes **39** gave quantitatively the corresponding phosphinites **40**. The reaction of the phosphinites **40** with alkyl- or aryllithiums in THF led to the optically active phosphine boranes which were easily isolated



Scheme 20.

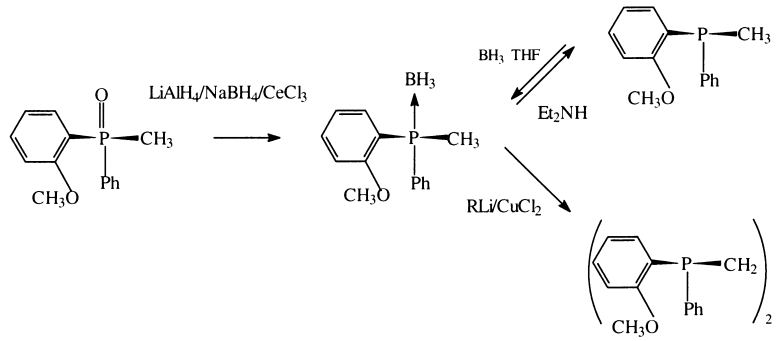
in good yield and stored without any special care. Enantiomeric excesses in this case were 85–100%. The transformaton of the phosphine boranes into the corresponding phosphines **41** was carried out quantitatively without loss of chirality by decomplexation under mild conditions using diethylamine (Scheme 21).[80,81]



Scheme 21.

Phosphine borane complexes **38** are versatile compounds generally crystalline and easily purified, which have proved useful in the asymmetric synthesis of phosphine ligands.[82] Phosphine boranes **38** could be utilized as electrophiles in a stereospecific sequence through which one aryl and one alkyl group can be introduced sequentially. The phosphine boranes could be converted into 1,2-diphosphinoethane complexes by oxidative coupling and afterwards into diphosphines, following the procedure described by Imamoto and co-workers.[83,84] This route provides the best practical source of the P-chiral diphosphine DIPAMP.[83] Antipodal phosphines can be obtained from ephedrine derivatives via the phosphinite boranes and aminophosphine boranes respectively prepared from the same starting complex (Scheme 21).

An interesting one-pot synthesis of phosphine boranes from phosphine oxides and a reagent system, $LiAlH_4$–$NaBH_4$–$CeCl_3$, was proposed by Imamoto. On the basis of this methodology a route to enantiomerically pure ligands for asymmetric hydrogenation has been developed (Scheme 22).[83] Optically active cyclic phosphines were synthesized by Marinetty and Ricard.[85,86]

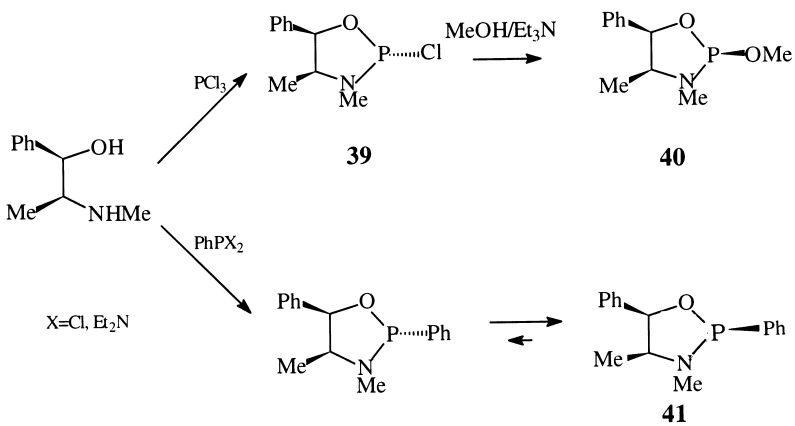


Scheme 22.

2.2.3. Ephedrine derivatives

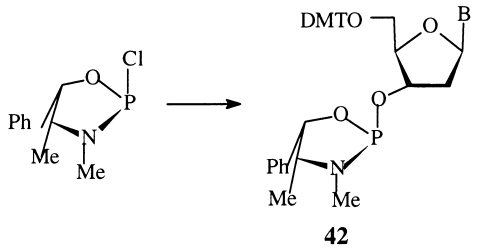
During the last few years, the stereochemistry of organophosphorus heterocyclic derivatives of ephedrine has been intensively studied. A variety of studies have been dedicated to the use of (1*R*,2*S*)-ephedrine as a chiral auxiliary, following on from the early pioneering observations of Inch and co-workers in this field.[87,88] Inch and co-workers reported the isolation of compounds in an isomerically pure form as distillable liquids and they assigned the structure as being monomeric and having a geometry in which the chlorine atom is *trans* to the CPh and CMe substituents.[89] The chlorophosphoramidate **39** was obtained by reaction of (1*R*,2*S*)-ephedrine with PCl_3 in the presence of *N*-methylmorpholine at −78°C (in 90% *de*). The chloridate **39** was distilled as a single diastereomer (although evidence for the presence of some *cis*-isomer in the crude reaction mixture was obtained), which with methanol in the presence of triethylamine afforded the methyl ester **40**.[89,90]

Brown and co-workers prepared oxazaphospholidine **41** by reaction of commercially available phenyldichlorophosphine with (−)-ephedrine in the presence of two equivalents of *N*-methylmorpholine in toluene at 0°C. Initially there was evidence for two diastereomeric compounds in the reaction mixture in ca 50:50 ratio, but after stirring for a day at ambient temperature only one diastereomer of **41** was obtained.[91] This compound was isolated as a low melting solid after distillation, again as a single isomer. Juge and Genet have also prepared pure oxazaphospholidines **41** from bis(diethylamino)phenylphosphine and (−)-ephedrine in toluene at 100°C, where one pure diastereomer was formed, presumably through thermodynamic control. The reaction provides the phosphines in the yields of up to 82% *de* (Scheme 23).[51]



Scheme 23.

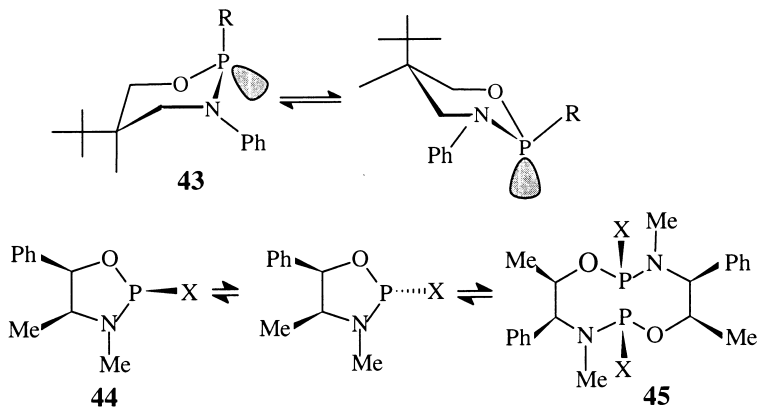
Reaction of the chlorophosphoramidate with 5′-O-DMT thymidine in the presence of triethylamine gave **42** as a single diastereomerically pure isomer in 84% isolated yield (Scheme 24).[91b]



42

Scheme 24.

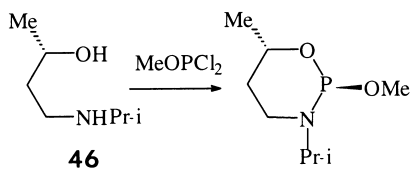
The conformations of the 2-*Z*-phenyl-1,3,2-oxazaphosphorinanes were investigated by ^{1}H and ^{31}P NMR spectroscopy and X-ray crystallography.[92] Conformational analysis of various phospholene derivatives was studied in terms of NMR data, NOE experiments and crystal structures.[94b] X-Ray and NMR studies of the 5,5-dimethyl-2,3-diphenyl-1,3,2-oxazaphosphorinane **43**, R=Ph, revealed a chair conformer with the phenyl group axially on the phosphorus atom. For the 1,3,2-oxazaphosphorinanes **43**, R=Me_2N, a chair–chair equilibrium was found in solution consisting of an 80–90% population with the Me_2N axial. The diastereomers of 1,3,2-oxazaphosphorinanes with *cis*- and *trans*-exocyclic *tert*-butyl groups exist in thermodynamic equilibrium at room temperature. Sum and Kee showed by mass spectroscopy that 1,3,2-oxazaphospholidines **44** (X=Cl, $OSiMe_3$) exist as dimers **45** (Scheme 25).[93,94]



43 **44** **45**

Scheme 25.

Condensation of (*S*)-aminol **46** with methyl dichlorophosphite in the presence of triethylamine as base in diethyl ether leads to the formation of a 92:8 ratio of diastereomers to give after purification by vacuum distillation *trans*- and *cis*-2-methyl-3-isopropyl-6-methyl-1,3,2-oxazaphosphorinanes. The major product was assigned the*trans*-configuration on the basis of its higher field NMR resonance (Scheme 26).[95] Denmark and co-workers performed the reaction of the aminoalcohol with ethyl dichlorophosphite and triethylamine in refluxing dichloromethane: the ratio of diastereomers in this case was 28:1.[74]



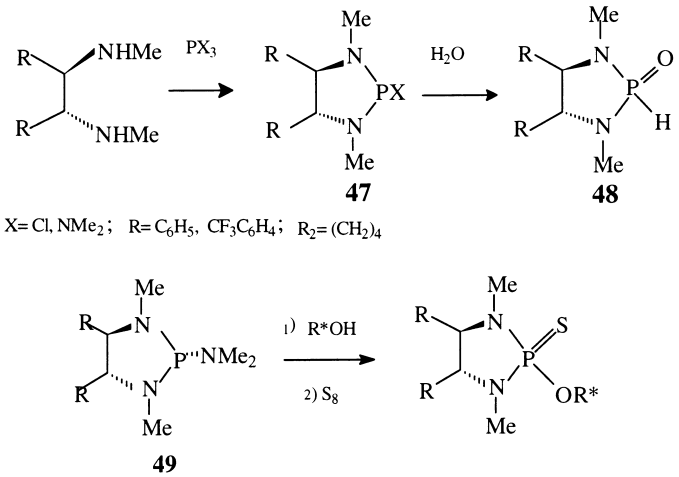
46

Scheme 26.

2.2.4. C_2-Symmetric compounds

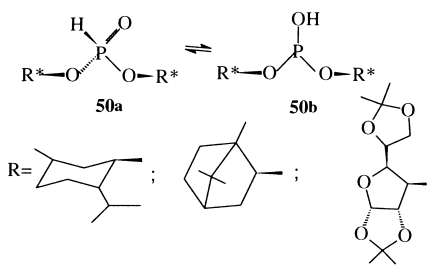
A large collection of molecules with C_2-symmetry has been introduced in organophosphorus chemistry as chiral auxiliaries: DIOP, CHIRAPHOS, DIPAMP, DPCP, PYRAPHOS, BINAP, BDPP and others.[1,2,22,96–110]

Some of the most interesting C_2-symmetric auxiliaries are chiral cyclic phosphonamides **47** and **48**.[98] The phosphorus atom of these compounds is not stereogenic due to the C_2-symmetry. Therefore either retention or inversion at phosphorous during derivatization of an enantiomerically pure alcohol yields a single diastereomer. In the majority of scenarios for absolute stereochemical control the presence of a C_2-symmetric axis within the chiral auxiliary reduces the number of possible diastereomers.[96] C_2-Symmetric reagents **49** (R=C_6H_5, 3-$CF_3C_6H_4$) have been proposed for a very simple and efficient determination of enantiomeric purity of alcohols by ^{31}P NMR by Alexakis and co-workers.[98b,99a,b] A large array of primary, secondary and tertiary alcohols, functionalized or not, was successfully tested. Sulfuration or selenation of the trivalent phosphorus derivatives **49**, carried out in the NMR tube, allows for a second ^{31}P NMR determination, in addition to the ^{1}H, ^{13}C and ^{19}F NMR spectra (Scheme 27).



Scheme 27.

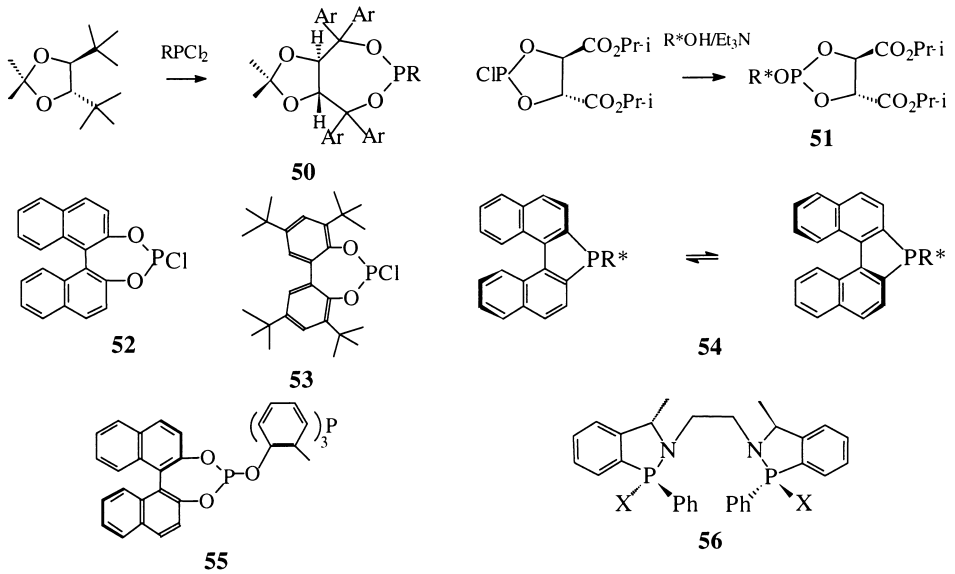
Reagents for the determination of the enantiomeric excess of diols and diamines with C_2-symmetry have been proposed on the basis of optically active C_2-symmetric dialkylphosphites **50**[111a] (Scheme 28) and chlorophosphites.[111b]



Scheme 28.

Bicyclic phosphates and phosphonites **50**, Ar=Ph, 2-Naphth; R=Me, Ph, MeO, PhO, Ph, are useful ligands and auxiliaries for enantioselective synthesis.[99b] (4*R*,5*R*)-δ-Carboalkoxy-2-chloro-1,3,2-dioxaphospholanes **51** were prepared by reaction of PCl_3 with dialkyltartrates. Only a single isomer of these compounds was registered by NMR.[104,105] These cheap and efficient chiral derivatizing agents were

used for the determination of the enantiomeric excesses of chiral alcohols by ^{31}P NMR.[106] Phospholes **52** are atropoisomerically chiral molecules, which may experience two different dynamic processes: rapid ring inversion (atropoisomerisation) of the binaphthalene backbone and pyramidal inversion at phosphorus.[109] Diastereomers **54** [R*=$CH_2CH(Me)Et$, neomenthyl] showed in the ^{31}P NMR spectrum at low temperature two separate resonances, which coalesced at ca 10°C into a single unresolved peak.[101,102] C_2-Symmetric ligands **55** have been prepared using an intramolecular cyclisation of a diazaphosphole borane complex, which can be applied to the asymmetric catalysis in hydrogenation, hydrosilylation and allylic substitution reactions. Baker and Pringle[110] described the optically active tetraphos ligand **56** having C_3-symmetry and its platinum(0) coordination chemistry. Optically active ligands of C_3-symmetry have attracted much interest because of their great potential in asymmetric catalysis (Scheme 29).



Scheme 29.

Reagents for the determination of the enantiomeric excess of diols and diamines with C_2-symmetry has also been proposed on the basis of menthyl dichlorophosphite.[111a]

2.3. Tetracoordinate phosphorus compounds

Compounds of tetracoordinate pentavalent phosphorus are the most important in the area of organophosphorus stereochemistry. These compounds are widely used as biologically active compounds and enantioselective reagents. Tetracoordinate organophosphorus compounds are required in optically active form to be effective synthetic tools for asymmetric carbon–carbon bond formation.

2.3.1. Configurational stability

Tetracoordinate organophosphorus compounds exhibit, in general, high configurational stability, although this depends on the structure of compounds. Thus, tertiary phosphine oxides are the most stable. Esters of chiral phosphorus acids are configurationally stable, but racemize slowly upon heating. For instance, diastereomers of menthyl benzylphosphonic acid at 120°C smoothly epimerize at phosphorus to give 1:1 mixtures of diastereomers.[111c] Chlorides of phosphorus acids are less stable and can be racemized at room temperature in the presence of nucleophilic agents. This is related to the formation

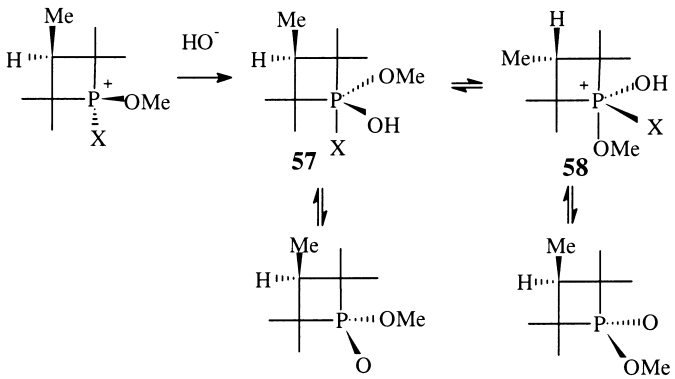
of bipyramidal pentacoordinated phosphorus species that invert their configuration. Mechanisms other than bipyramidal inversion, such as ligand exchange have been observed in the stereomutation of tetracoordinated phosphorus. A rapid phosphorus inversion, accelerated by $(p–d)_p$ bonding has been implicated in the stereomutation of allylmethylphenylphosphine sulfide.[37]

2.3.2. Nucleophilic substitution

The most frequently encountered reaction in organic phosphorus chemistry is nucleophilic displacement.

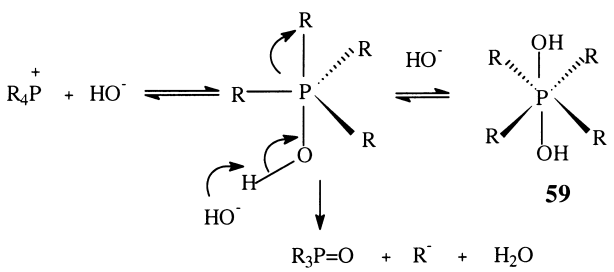
2.3.2.1. *Mechanism* The mechanism and steric course of nucleophilic substitution at the tetracoordinate phosphorus atom have been the main points of interest of many research groups: McEwen,[112,113] Mislow,[42,114] DeBruin and Johnson,[114–118] Trippett,[119,120] etc. The results of these studies have been discussed in many reviews on organophosphorus chemistry. Therefore only the most representative examples of nucleophilic substitution at chiral phosphorus concerning stereochemistry are discussed here.

The importance of pentacoordinate phosphorus intermediates in nucleophilic substitutions at tetracoordinate phosphorus has been recognized. De Bruin in his elegant studies of the mechanism of hydrolysis of cyclic phosphetanium salts has proposed phosphorane intermediates **57** and **58** (Scheme 30).[114–118]



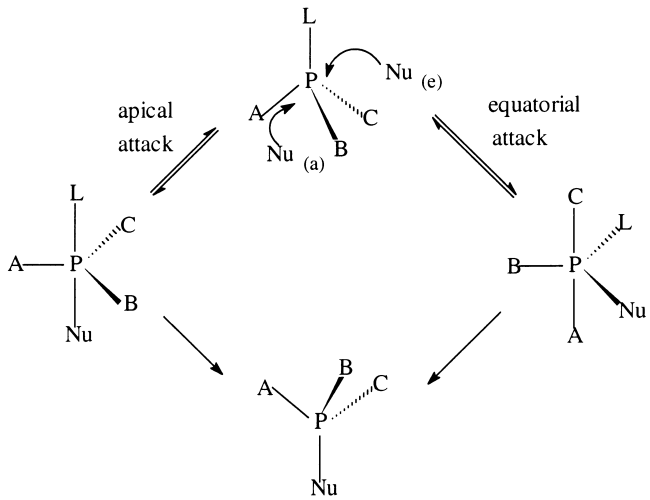
Scheme 30.

Stereochemical data proposed by McEwen include synchronous attack with elimination of the anion by a second hydroxide ion or with formation of the unstable hexacoordinated intermediate **59** bearing two hydroxides on the phosphorus. The reaction scheme includes two intermediates: one is pentacoordinate and the other is hexacoordinate. Stereochemical results are determined by structure, by time of life and by reorganisation of the ligands of these intermediate products (Scheme 31).[10]



Scheme 31.

The compounds of pentacoordinate phosphorus have trigonal bipyramidal geometry, which can be formed via equatorial attack or via apical attack (Scheme 32). It is customary to consider that such reactions occur synchronously by an S_N2P mechanism involving a trigonal bipyramidal phosphorane intermediate that is formed by addition of the nucleophile (Nu) opposite the leaving group (L) occupying the apical position and decomposes before any ligand pseudorotations have taken place.

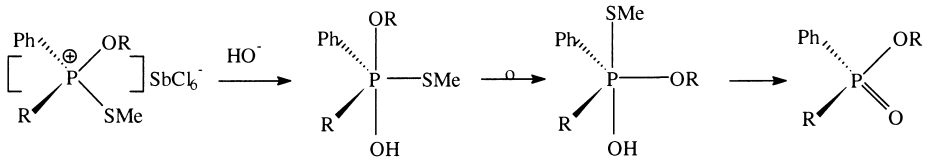


Scheme 32.

Apical attack on tetrahedral phosphorus can proceed in one of four ways to result in four different phosphoranes. These first formed phosphoranes can undergo a reorganization of ligands with formation of 10 enantiomeric pairs of phosphoranes, when the molecule contains five different substituents, each of which can convert into the reaction product. The result of group displacement (with retention or inversion) is dependent on the relative stability of phosphoranes and their rate of transformation.[114,121]

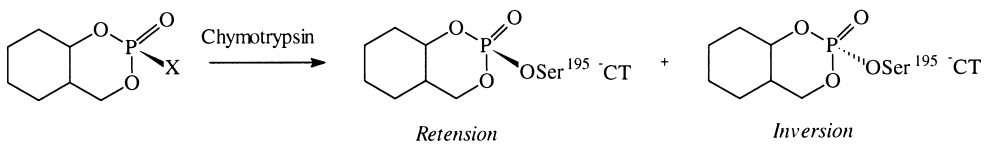
As a rule, nucleophilic substitution at stereogenic tetracoordinate phosphorus results in inversion of configuration, however in some cases retention takes place. For example, the alkaline hydrolysis of acyclic *t*-butylphosphonium salts results in inversion of configuration.[43] In general the stereochemical result (retention or inversion) of nucleophilic displacements at tetracoordinate phosphorus depends on the nature of the leaving group.[114,119] For example, Trippett found that alkaline hydrolysis of alkoxy(alkylthio)phosphonium salts proceeding with displacement of the methylthio group results in retention of configuration at phosphorus.[120] De Bruin and Johnson[116] came to the conclusion that alkaline hydrolysis of alkoxy(alkylthio)phosphonium salts **60** proceeds with inversion when the alkoxy group cleaves and with retention of configuration at phosphorus when the alkylthio group cleaves. A mechanism was proposed involving axial attack by the hydroxide ion on the face of the tetrahedral phosphonium salt opposite the alkoxy ligand, followed by competition between direct loss of the axial alkoxy ligand and an isomerization with subsequent loss of the alkylthio ligand from an axial position. The course of a displacement reaction at phosphorus which involves the formation of a phosphorane intermediate **61** is determined entirely by the energetics of the intermediate (Scheme 33).

Stereochemical and mechanistic aspects of nucleophilic substitution at the phosphorus in a six-membered ring, reported recently by Cremer and co-workers,[121b] strongly suggest an S_N2 reaction mechanism. Westheimer showed that all enzymatic reactions at phosphorus proceed with inversion and, therefore, occur without pseudorotation. In fact, there is no unambiguous evidence that pseudorotation or adjacent attack at the P-atom is a process of significance in any biological system, and formal retention is rationalized by a multistereo process with an even number of inversions.[122–125] Ruedl and co-workers



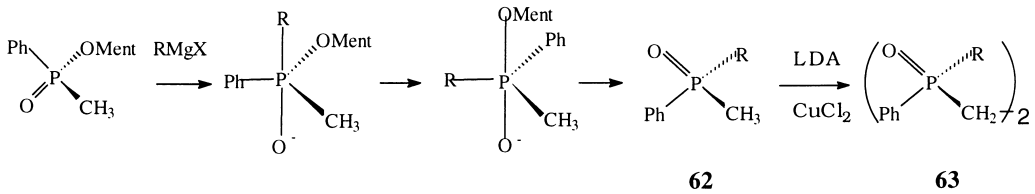
Scheme 33.

found recently that inhibition of δ-chymotrypsin by axial compounds proceeds via complete inversion of configuration at the P-atom, whereas the equatorial epimers with a higher conformational flexibility seem to follow a different stereochemical pathway which results in both inversion and retention. The results of the investigation showed that an adjacent attack does not need to be followed by pseudorotation, because the leaving group can move directly into the favorable apical position (Scheme 34).[126]



Scheme 34.

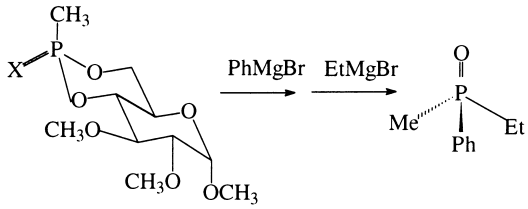
2.3.2.2. *Reaction with organometallic compounds* Enantioselective transformations of tetracoordinate phosphorus compounds are an important and versatile tool in the formation of new optically active organophosphorus compounds. The most popular means of preparing optically active phosphine oxides **62** is the method developed by Mislow,[39,42] based on the reaction between the diastereomerically pure (or strongly enriched in one diastereomer) menthyl phosphinate ester and Grignard reagents. The nucleophilic displacement of α-menthyl phosphinate ester with Grignard reagents proceeds with clean inversion of stereochemistry at phosphorus to afford the homochiral phosphine oxides. Organolithium reagents are more reactive but epimerization at phosphorus may occur.[39–42,56,114,127] The synthesis of enantiomerically pure phosphines and phosphine oxides with a stereogenic centre at phosphorus has attracted much attention. For example, the reaction of *o*-anisylmagnesium bromide with the phosphinite gives optically active (+)-(*R*)-*o*-anisylphenylmethylphosphine oxide **62** (95% *ee*), R=C_6H_4OMe-2 which was used for the synthesis of chiral organophosphorus ligands **63** [(+)-PAMP, (±)-DIPAMPO, DIPAMP and others] (Scheme 35).[45,51,89,90,96,128]



Scheme 35.

In the last few years, several attempts have been made to improve this route and to develop alternative approaches to homochiral phosphines and related compounds. The basic chemistry of Mislow was developed by Horner and co-workers who synthesized by this method a variety of monophosphine oxides with different aryl groups in optically active form.[32,36] Inch proposed a synthesis of chiral phosphinates from 1,3,2-dioxaphospholanes **64** prepared from carbohydrates (Scheme 36).[88,89]

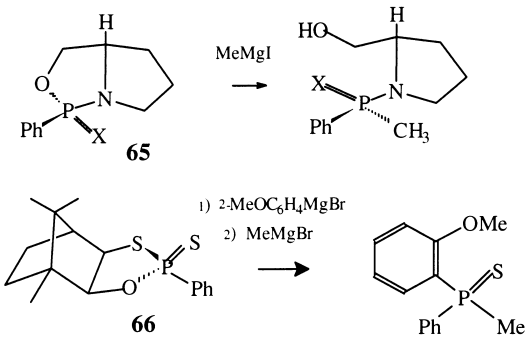
Koizumi and co-workers have studied the diastereomerically pure oxazaphospholidine oxide and sulfide **65** (X=O,S) and demonstrated that they react with Grignard reagents. The enantiomeric excess



64

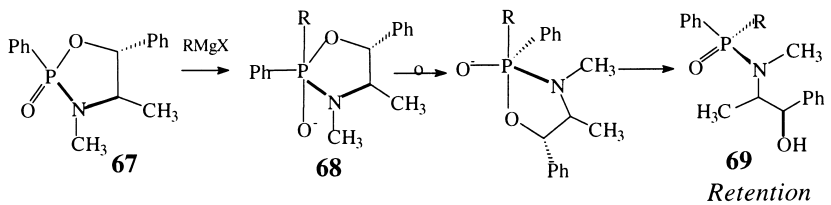
Scheme 36.

of the products was 73–99%.[131] Syntheses of enantiomerically pure tertiary phosphines using camphor derivatives **66** has been developed by Corey (Scheme 37).[132]



Scheme 37.

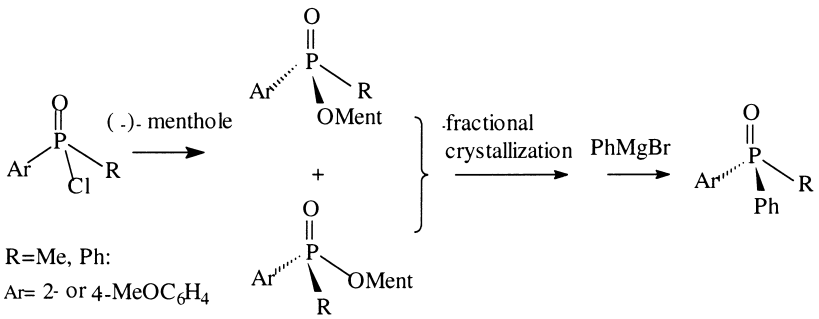
The synthesis of enantiomerically pure triaryl- and diarylvinylphosphine oxides from PCl_3 by three sequential nucleophilic displacements at phosphorus has been demonstrated (Scheme 38). The major diastereoisomer is formed with retention of configuration. Three nucleophilic displacements provide the three new P–C bonds of a chiral triarylphosphine, following on from the earlier discovery of the stereospecific P–O cleavage of oxazaphospholidines with arylmagnesium chloride.[91] The cyclic ephedrine derivatives **67** reacted with organomagnesium reagents in the opposite stereochemical sense to the open-chain examples of Mislow. This stereochemical divergence must require five-coordinate intemediates **68** in an associative pathway with the opportunity for pseudorotation.[51,129] The stereoisomerically pure oxazaphospholidine P-oxide **67** having (R_p)-configuration has been also obtained by oxidation of **44** with the *tert*-butylhydroperoxide. This product reacted stereospecifically with *o*-anisylmagnesium bromide to give the acyclic phosphonite **69** formed by P–O fission with retention of configuration. The ephedrine residue can be replaced by O-methyl under acid catalysis with inversion of configuration.[80,81,129,130]



Scheme 38.

Since the pioneering work of Mislow,[39] the synthesis of enantiomerically pure phosphines and phosphine oxides with a stereogenic centre at phosphorus has attracted much attention. Methods based on the fractional crystallization of the diastereomers of O-menthylphenyl phosphinate with stereospecific displacement and reduction have been developed. Nudelmann and Cram,[133,134] and then Mislow and

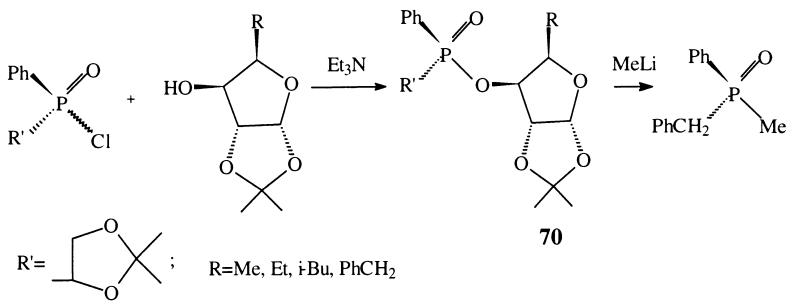
co-workers[40,41] demonstrated that unsymmetrically substituted menthyl phosphinates could be separated readily into their diastereoisomers. The reaction of phenylmethylphosphinothiochloride with (−)-menthol gives a mixture of diastereomers which was separated by crystallization from hexane.[68,135,136] Knowles found that the reaction of phenyl(4-methoxyphenyl)phosphinic chloride with (−)-menthol proceeds with the formation of a 4:1 mixture of diastereomers, which was then separated by crystallization (Scheme 39).[135,136]



Scheme 39.

While stereochemically reliable, this approach has several limitations. The diastereomeric menthyl phosphinate esters are prepared with low kinetic selectivity (2 or 3:1) and require separation before the next step. This becomes very tedious for liquid phosphinates, which include most alkane phosphinate esters. Therefore, some important classes of phosphinoxides are effectively inaccessible by this method.

2.3.2.3. *Reaction of phosphorus chlorides with chiral substrates* We have disclosed a promising and potentially inexpensive route to homochiral phosphine oxides, using diisopropylideneglucofuranose as the source of chirality.[47,49,50,137,138] Either phosphinate diastereomer can be prepared in excellent yield and with high diastereoselectivity by the appropriate choice of base. The reaction of the tetracoordinate phosphorus chlorides with D-glucofuranose in the presence of tertiary amines provides stereochemically pure (*S*)-phosphinates **70** (Scheme 40).



Scheme 40.

The reaction of phosphinic acid chlorides with D-glucofuranose was performed using an equimolecular ratio of reagents with an excess of triethylamine in toluene at room temperature for 12–24 h. The yields of phosphinates were 70–75%, and the diastereomeric excesses were 80–100%. The products were purified by crystallization from hexane. The ratio of diastereomers was not dependent on the excess of chloro phosphinate corresponding to thermodynamic control, unlike the reaction of trivalent phosphorus chlorides with glucofuranose (II) proceeding under kinetic control. The stereoselectivity of the reaction was influenced by the nature of the base and the solvent. The highest stereoselectivity was achieved in toluene with triethylamine as base (Table 2).

Table 2
The reaction of racemic chlorophosphinates with chiral secondary alcohols B

$$RR'P(O)Cl + R^*OH \rightarrow RR'P(O)OR^*$$

R	R'	R*OH	B	ratio	ref.
Ph	Me	GF	Et_3N	90:10	[138]
Ph0	Me	GF	Et_3N	97:3	[139]
Ph	Et	GF	Et_3N	96:4	[138]
Ph	i-Bu	GF	Et_3N	95:5	[138]
Ph	$PhCH_2$	GF	Et_3N	~100:0	[53]
Ph	Me	(*1S*)-borneol	DMAP	4:1	[140]
Ph	Me	(-)-menthol	DMAP	1:1	[140]
				2:1	[141]
Ph	Me	(-)-isopinocampheol	DMAP	1:1	[140]
Ph	Me	(+)-isoborneol	DMAP	74:26	[140]
4-$MeOC_6H_4$	Ph	(-)-menthol	Et_3N	4:1	[135,136]

Reaction of phosphinates with alkyllithiums proceeds with inversion of configuration at the phosphorus atom to provide optically active homochiral tertiary phosphine oxides. This methodology was later continued by Alcudia and co-workers[139] who performed the reaction with a tenfold excess of triethylamine and a threefold excess of chloro phosphinate to imitate the kinetic control of stereoselectivity. The phosphinites prepared by reaction with Grignard reagents were converted into tertiary phosphines. Phosphorylated derivatives of 1,2:5,6-disubstituted D-glucofuranose, including asymmetric phosphorus derivatives, where also prepared by E. Nifant'ev,[142] however with low stereochemical selectivity, because optimal experimental conditions were not found.

(1*S*)-Borneol was used as a chiral auxiliary.[140] Reaction of the racemic methyl(phenyl)phosphinic chloride with (1*S*)-borneol gave a 1:4 diastereomeric mixture of (1*S*)-bornyl (*Sp*)- and (*Rp*)-phosphinates, which were separated by column chromatography and reacted with (*o*-bromomethoxyphenyl)magnesium bromide to result in (*R*)-(*o*-methoxyphenyl)methyl(phenyl)phosphine oxide. Diastereomeric phosphinate esters were also formed from racemic methyl(phenyl)phosphinic chloride with the terpene alcohols (−)-menthol, (−)-isopinocampheol and (+)-isoborneol in the ratios 50:50, 50:50 and 74:26, respectively.[140] Michalski and co-workers[143] described the synthesis of menthyl amidophosphonates.

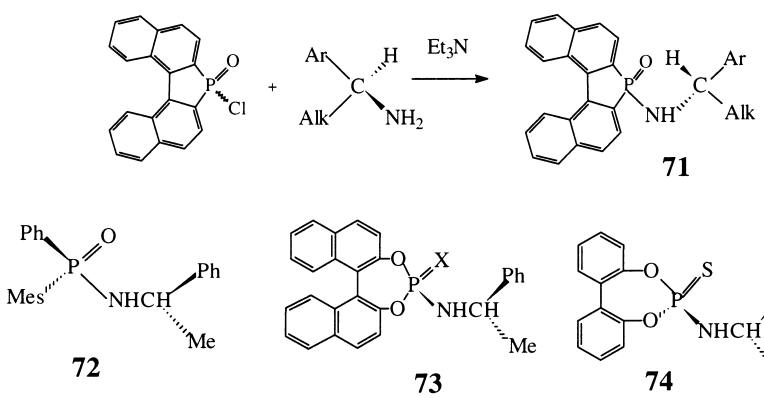
The reaction of phosphorus(V) chlorides with 2-arylethylamines proceeds analogously, but with less stereoselectivity.[144–147] Thus, the diastereoselectivity of the reaction of a twofold excess of 1,1′-binaphthyl-2,2′-diylphosphonyl chloride with chiral amines depends on the reaction temperature, on the increased steric hindrance by the substituent on the carbon atom α to the nitrogen atom and on the *ortho*-substitution of the benzene ring of the chiral amine (Table 3). The rate of formation of one enantiomer of (*S,R*)-1,1′-binaphthyl-2,2′-diyl-*N*-(*S*)-(α-alkylbenzyl)phosphoramidate **71** is greater than that of the other. The reaction is kinetically resolved, therefore half of the phosphoryl chloride remains unreacted (Scheme 41).[144]

Phenyl(2,4,6-trimethylphenyl)phosphinic chloride with (+)-(*R*)-1- methylbenzylamine in the presence of triethylamine provides in low stereoselectivity a mixture of (*RR*)- and (*RS*)-diastereomers of **72** in a 2.2:6.5 ratio (Scheme 42).[146]

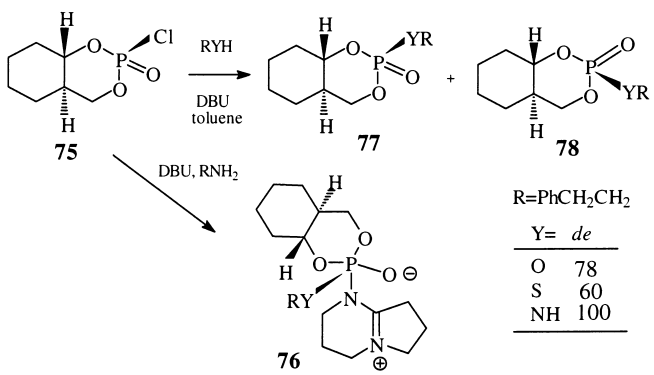
Meanwhile, the reaction of the biphenylthiophosphoryl chloride with (*S*)-methylbenzylamine in pyridine gives, in virtually quantitative yield, enantiopure phosphorothioamidate **73**.[147] A practical method for the preparation of enantiomerically pure 1,1′-binaphthalene-2,2′-diol and dithiol was proposed by De Lucchi.[147] These molecules may be considered as prototypes of the larger class of atropoisomeric chiral molecules with C_2-symmetry.[100]

Table 3
1,1′-Binaphthyl-2,2′-diylphosphonyl chloride with chiral amines (Scheme 41)

Alk	Ar	t °C	de of **71**, %
Me	Ph	0	27
		10	24
		20	20
i-Pr	4-ClC_6H_4	0	38
		10	31
		20	24
i-Pr	2-MeO-5-MeC_6H_3	0	82
		10	68
		20	33



Scheme 41.

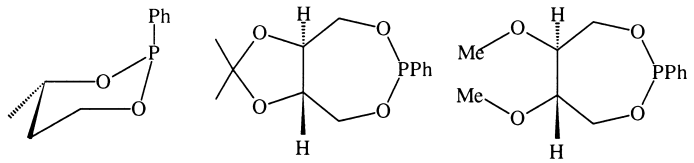


Scheme 42.

Reaction of the axially substituted (±)-chlorides **76** with O- and S-nucleophiles in the presence of DBN preferentially proceeds with retention of configuration at phosphorus, whereas the epimer ratio **77**:**78** is reversed with DBU as a base. N-Nucleophiles react exclusively with inversion. In the presence of DBU, a pentacoordinate intermediate **76** was isolated as the main product (Scheme 42).[122]

2.3.2.4. *Asymmetric Michaelis–Arbuzov reaction* The Arbuzov approach has been adopted by many authors, using a range of chiral auxiliaries.[148–157] Suga and co-workers reacted the cyclic phenylphosphonite **79**, prepared from (*S*)-1,3-butanediol with alkylhalides and demonstrated a regioselective ring opening by cleavage of the primary P–O bond.[148,149] The same group has utilized cyclic phosphonites **80**

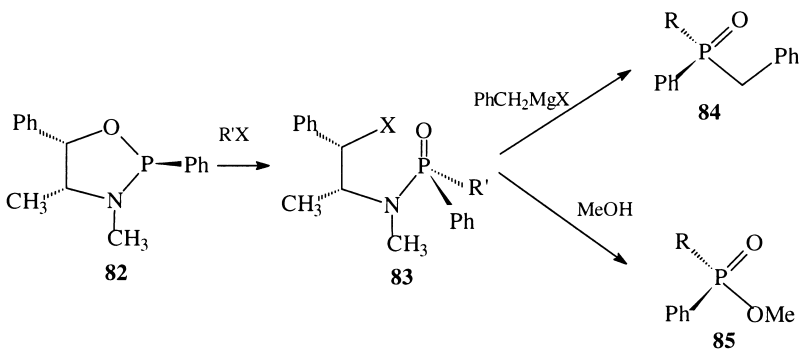
and **81** in a similar sequence, but here the enantiomeric purity of the resulting phosphine oxides was low (Scheme 43).



79 **80** **81**

Scheme 43.

In this area the most successful development is due to Juge, who has developed an approach based on the previously observed diastereoselectivity in the formation of the oxazaphospholidine from ephedrine.[66,148–150] Thus, oxazaphospholidines **82** undergo an efficient reaction with RX=MeI, EtI or PrI to give an average 9:1 ratio of phosphinic amide **83** to its diastereomer which were separable by fractional crystallisation. The product can be converted into diarylalkylphosphine oxides **84** by succesive acid-catalyzed methanolysis and Grignard displacement. In this way tertiary phosphine oxides were prepared in 95 and 92% *ee* respectively. Acid methanolysis of phosphinamides gives (*R*)-(+)-methylphenylphosphinate **85** with an *ee* of more than 96% (Scheme 44).[157] On the basis of this methodology, enantiomerically pure derivatives of thio- and selenophosphonium acids have been obtained.[90,89]



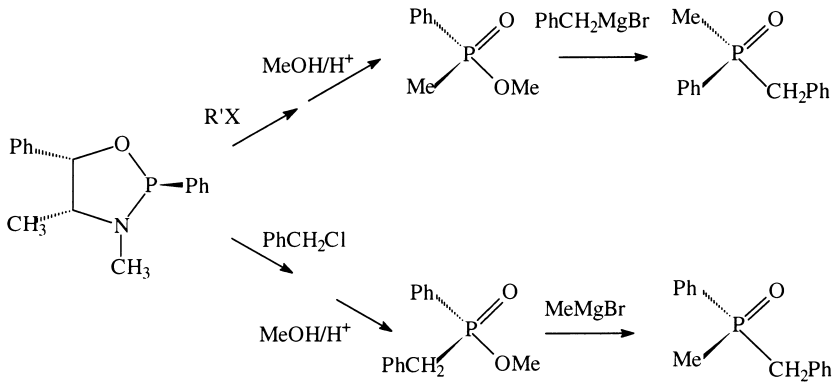
82 **83** **84** **85**

Scheme 44.

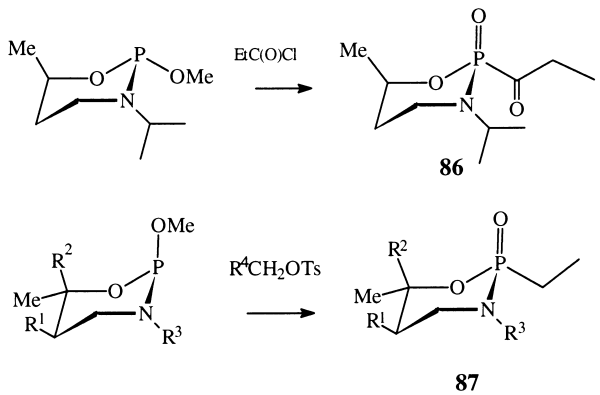
A general method for the asymmetric synthesis of phosphinates and phosphine oxides using the Michaelis–Arbuzov rearrangement of chiral diheterophosphacycloalkanes was proposed by Juge and Genet. (Scheme 45).[51,157] They showed that it is possible to prepare various organophosphorus compounds of known absolute configuration from only one heterocyclic compound. The reaction proceeds with retention of configuration at the phosphorus atom, however its stereoselectivity depends on the steric hindrance of the R′ group and experimental conditions. The reaction was monitored by NMR and clearly showed the formation of quasiphosphonium intermediates with the same diastereomeric ratio as that of the final products. No NMR signals in the P(V) phosphorane region were observed.

The Michaelis–Arbuzov reaction of propionyl chloride with the diastereoisomeric mixture of a 1,3,2-oxazaphosphorinane led stereoselectively to the formation of a cyclic acylphosphonate **86** as a 92:8 ratio of diastereomers (81% yield; Scheme 46).[95] An alternative synthesis leading predominantly to the *cis*-P-alkyloxazaphosphorinanes (ratio 5:1–11:1) involved conversion of the amino alcohols to the cyclic ethyl phosphite followed by subsequent Arbuzov reaction with an appropriate alkyltosylate (Scheme 46).[158]

Methoxycarbonylalkylmethyl side chains have been utilized for homochiral phosphine oxide synthesis. Pietrusiewicz and co-workers found that the vinylphosphine reacted with (−)-menthyl homoacetate to afford a diastereomeric mixture of the Arbuzov products. Diastereomer **88** crystallized from the crude



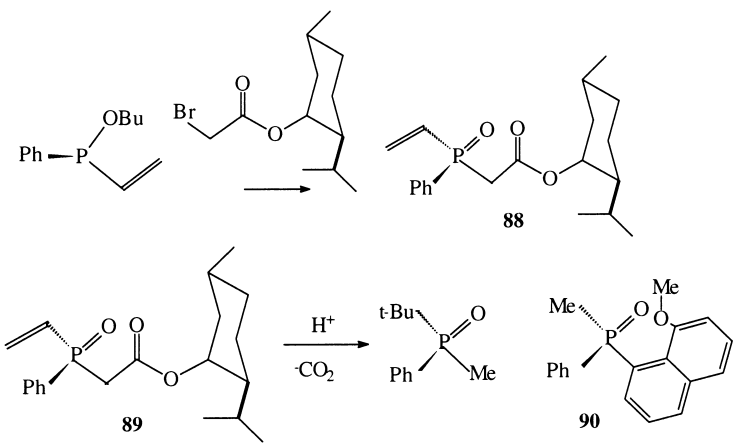
Scheme 45.



R^3 = t-Bu, R^4=Ph (8:1); R^3=t-Bu, R^4=Me (5:1); R^3= CEt_3, R^4=Ph (11:1)

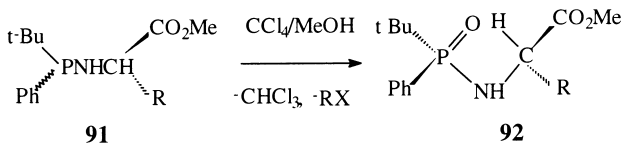
Scheme 46.

reaction mixture (Scheme 47).[151–154] Johnson and Imamoto, demonstrated that, prepared in the above manner, menthyl ester **89** could be readily separated into its diastereomers, which were separately subjected to hydrolysis and decarboxylation to give a tertiary phosphine oxide. This approach was successfully used to prepare a variety of phosphine oxides such as **90** (Scheme 47).[38,156]



Scheme 47.

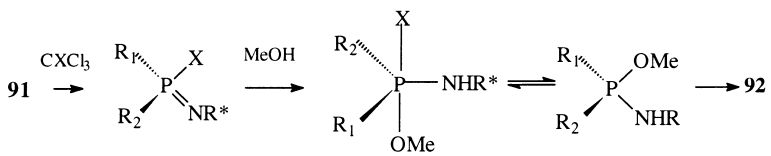
2.3.2.5. *Enantioselective oxidation and sulfurization of phosphines* Usually oxidation or sulfurization of tervalent phosphorus compounds proceeds stereospecifically, with a high degree of retention or inversion of configuration at phosphorus.[5,159] However, in the last few years an interesting methodology for the enantioselective oxidation and sulfurization of tervalent phosphorus compounds has been developed.[160–162] Thus, the oxidation of *N*-phosphinoamino acids in tetrachloromethane–alcohol or water proceeds stereoselectively to furnish mainly one of two possible diastereomers. In some cases the stereoselectivity achieved was 100%. This reaction is of special interest for the preparation of stereochemically pure derivatives of N-phosphorylated amino acids **92** having important practical significance, because existing methods for their synthesis are not stereoselective (Scheme 48).[48–50]



91 **92**

Scheme 48.

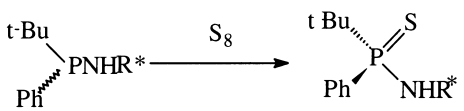
NMR spectroscopic studies showed that the reaction proceeds via the formation of alkoxyhalogenophosphorane **93** which undergoes pseudorotation to give the most thermodynamically stable diastereomer. Alkoxyhalogenophosphoranes exist in equilibrium with alkoxyphosphonium salts to convert into the amidophosphates **92**. The 94:6 ratio of **93** (δ_P −56 and −58 ppm) shows a high thermodynamic preference for one of the diastereomers. Alkoxyhalogenophosphoranes have been observed to prefer one of the diastereomers. Alkoxyhalogenophosphoranes have been observed, in the case of the compounds bearing the five-membered 1,3,2-oxazophospholane cycle, stabilizing the pentacoordinate state of diastereomers (Scheme 49).[162]



93

Scheme 49.

The reaction of trivalent phosphorus compounds with elemental sulfur is stereospecific and proceeds with inversion of configuration at phosphorus and with complete retention of the enantiomeric ratio of isomers.[159] However, certain aminophosphines react stereoselectively with elemental sulfur. In this case the reaction proceeds with a high degree of asymmetric induction at phosphorus to give predominantly one of the two possible diastereomers of **94** (Scheme 50).[155]



94

R*=*(S)*-CH(Me)Ph; *(S)*-CH(Bu-i)CO_2Me

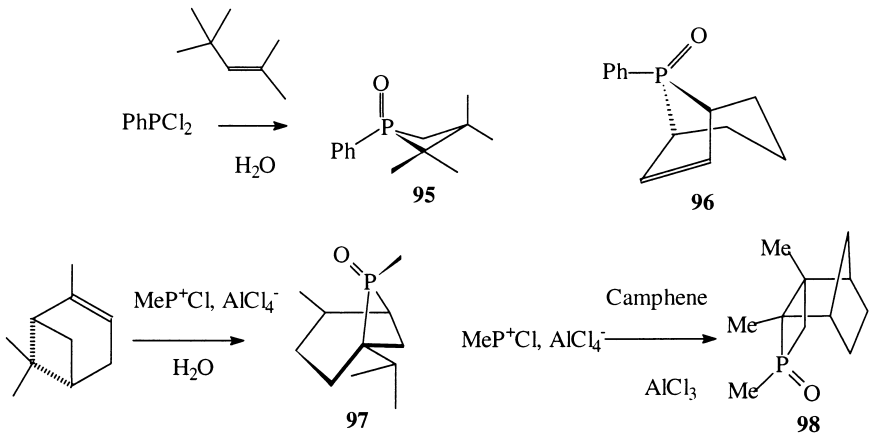
Scheme 50.

2.3.3. Addition of trivalent phosphorus compounds to multiple bonds

Addition of trivalent phosphorus compounds to C–C and C–heteroatom multiple bonds is an important and versatile tool in the formation of new compounds containing P–C bonds.[163–173] These reactions are

very well studied and generalized in reviews. Recently, stereochemical studies of these reaction have been also performed.

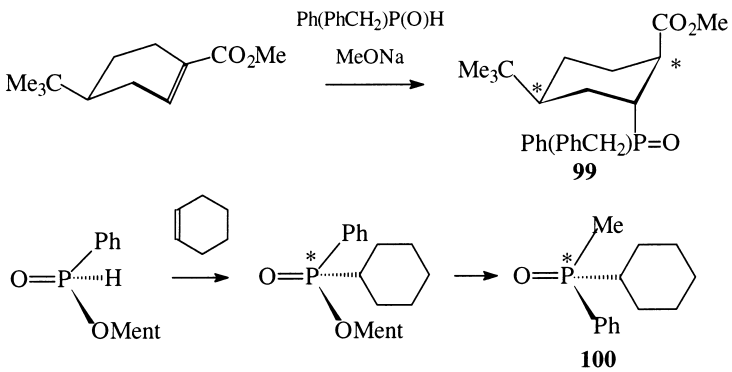
Dichlorophenylphosphine on treatment with 2,4,4-trimethyl-2-pentane forms a cyclic phosphonium salt, which on hydrolysis gives a mixture of diastereomeric phosphetane 1-oxides **95**. The ratio of diastereomers depends on the method used to quench the intermediate salt.[164] In many cases addition of chlorophosphines to dienes proceeds stereoselectively. For example, the addition of phenyldichlorophosphines to cycloheptadiene provides stereochemically pure *cis*-product **96** (Scheme 51).[165]



Scheme 51.

Substituted phosphetanes can be easily made from a branched olefin and phosphenium cation $MePCl^+$, $AlCl_4^-$, in a reaction which involves a 1,2-Me shift. Asymmetric reaction of α-pinene with $MePCl^+$, $AlCl_4^-$ gives a bridged bicyclic phosphetane **97** whose structure has been unequivocally assigned on the basis of chemical, spectral and X-ray analysis.[166,167] The formation of this compound can be rationalized by the opening of the cyclobutane ring in the primary adduct allowed by a 1,2-H migration and phosphetane ring closure. An analogous reaction was realized with the camphene: compound **98** (Scheme 51).[167]

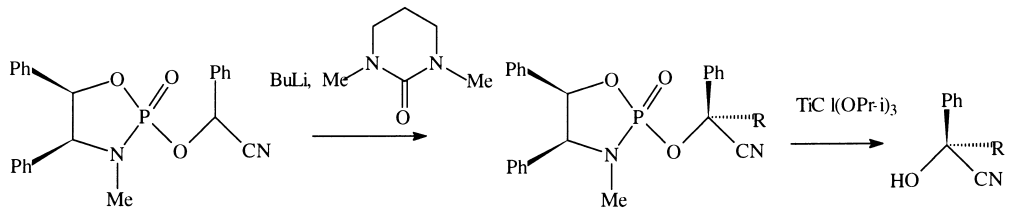
The Michael addition of secondary phosphine oxides to cyclohexane-1-carboxylates (both flexible and biased) gives exclusively the axially substituted products **99** (Scheme 52).[168,169] Another possibility is the stereospecific alkylation of menthylphenyl phosphinate. Alkylation of menthylphenyl phosphinate proceeds with retention of configuration at phosphorus. Many chiral phosphinates **100** are potentially available via this method.[114–118,170–173]



Scheme 52.

2.3.4. Miscellaneous

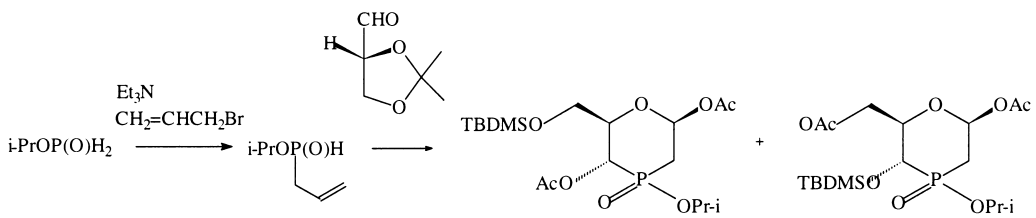
High asymmetric induction (96%) was achieved in the diastereoselective alkylation of cyanohydrin carbanion generated from the chiral phosphate **101**. The synthesis of the optically active (*R*)-*tert*-cyanohydrins **102** demonstrated how P-chiral auxiliaries temporarily linked to the substrate through heteroatoms can be used in asymmetric synthesis (Scheme 53).[174]



101 **102**

Scheme 53.

A stereoselective method to insert a heteroatom into a sugar framework was developed by Gallagher.[176] Alkylation of isopropyl phosphoric acid with allyl bromide in the presence of the triethylamine affords isopropyl allylphosphonite **103** (65%), which reacts smoothly with (*R*)-2,3-O-isopropylideneglyceraldehyde to give the dialkyl phosphinates **104** as a mixture of diastereomers (81%), readily separable by chromatography (*de* of >95%; Scheme 54). Derivatives of ephedrine and chiral glycoles have been used as reagents for a determination of enantiomeric purity of alcohols by NMR analysis.[22,175]

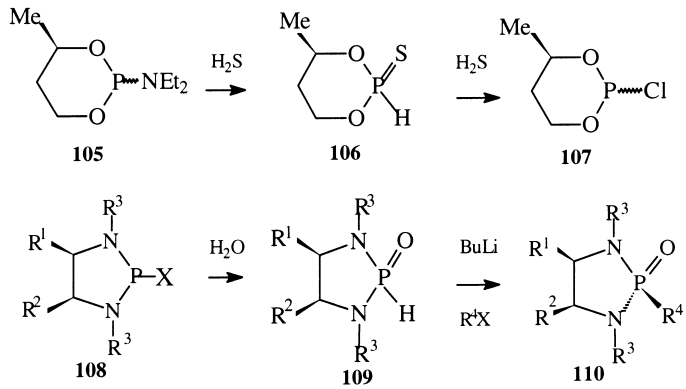


103 **104**

Scheme 54.

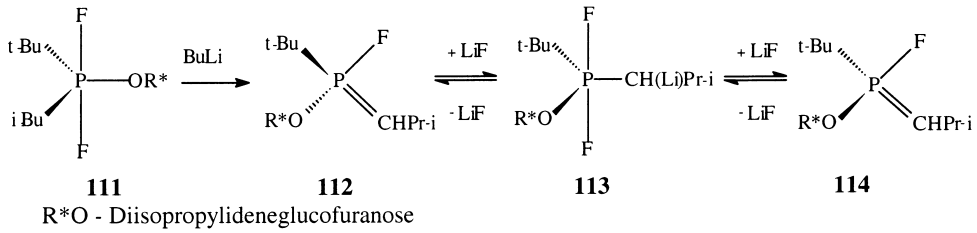
Thermal and acid-catalyzed rearrangements of the 3-thio- and 3-seleno-1,3,2-dioxaphosphorinanes,[177] to the isomeric esters with complete retention of configuration at phosphorus have been discussed.[178–180] Hydrothiolysis of the stereoisomeric mixture of amines **105** provides a single phosphorothioate, whereas the reaction of the corresponding chlorides **107** gives both isomers of **106** (Scheme 55).[181]

Chiral phosphoric acid diamides **109** were prepared by hydrolysis of **108** with one equivalent of water. Deprotonation of these acids with *n*-butyllithium or LDA gives the lithium salt which reacted smoothly with alkylhalides to give substituted phosphonamides **110** in good yield.[130] Chiral phosphonium ylides and chiral P-stabilized carbanions are configurationally stable at phosphorus. This configurational stability persisted through different electrophilic reactions.[98a,109,112,113,159,182,183] On the basis of chiral phosphonium ylides, syntheses of different chiral organic compounds were developed, in which asymmetric induction in the transfer of chirality from phosphorus to another center was observed (see Section 3.4). An interesting example of thermodynamically controlled asymmetric synthesis is the dehydrofluorination of alkoxyfluorophosphoranes **111** bearing chiral ligands, resulting in a mixture of diastereomers of P-fluoroylids **112** and **113** in a 1:1 ratio. The P-fluoroylids reversibly add the lithium salt to form a fluorophosphorane intermediate **114** and undergoes pseudorotation to provide the most thermodynamically stable diastereomer. Determination of the heats of formation for ylides bearing an



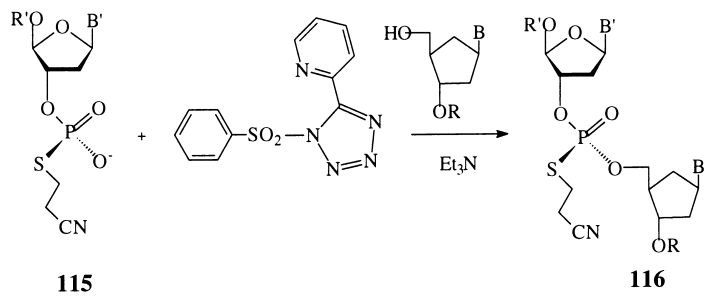
Scheme 55.

(*S*)-diethylamino-2-propanol group by means of CNDO calculations revealed that the (*S*,*R*)-diastereomer is more energetically advantageous (Scheme 56).[183]



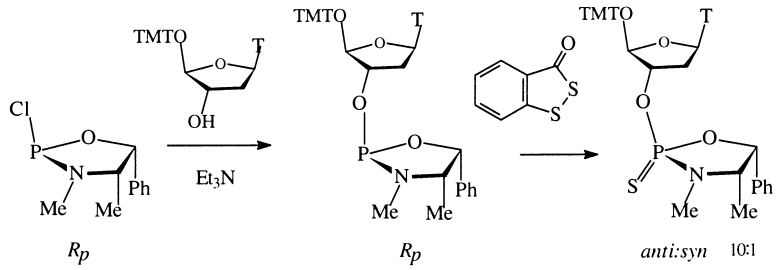
Scheme 56.

Since the discovery that oligonucleoside phosphorothioates (oligo-S) can protect cells effectively from the lethal action of the HIV-1 virus, a number of reports have appeared concerning improvements in their synthesis.[91b,184–189] A variety of examples of stereoselective/stereospecific syntheses of oligo-S were reviewed by Stec and Wilk.[184] For instance, Costick and Williams demonstrated that reaction of P-prochiral substrates **115** with 3′-O-acetylthymidine leads to the formation of the corresponding dinucleoside **116**, which contains the diastereomers in a 79:21 ratio (Scheme 57).[186]



Scheme 57.

Iyer and co-workers proposed a stereoselective synthesis of the nucleoside by reaction of the chiral oxazaphospholidine with 5′-DMT-T. The phosphoramidite synthon was stereoselectively converted by oxidative sulfurization into new (*Rp*)-nucleoside synthons for the synthesis of oligonucleotides (Scheme 58).[91b,189]



Scheme 58.

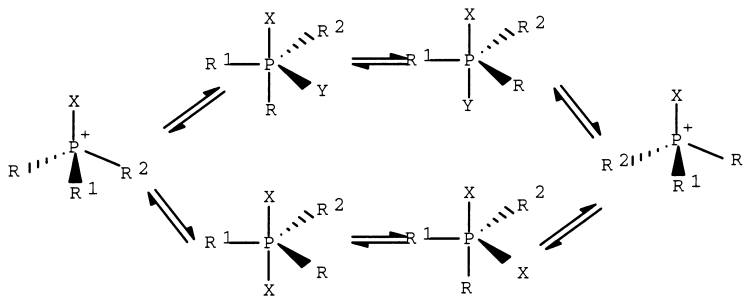
2.4. Hypervalent phosphorus compounds

The ability of the phosphorus atom to increase its coordination number was recognized many years ago. Penta- and hexacoordinate species have been isolated. However it was more or less accepted that this expansion of coordination can be implicated only when the phosphorus atom is surrounded by electronegative groups and all attempts to access hypervalent phosphorus species have been designed accordingly.

In the past few years, numerous experimental results have illustrated the fundamental importance of penta- and hexacoordinate phosphorus species in the stereochemistry of reactions at phosphorus. The importance of pentacoordinate intermediates in substitution reactions at phosphorus is now well accepted. In this context the existence of stable penta- and hexacoordinate phosphorus derivatives and their structure have elicited considerable interest.

2.4.1. Pentacoordinate phosphorus compounds

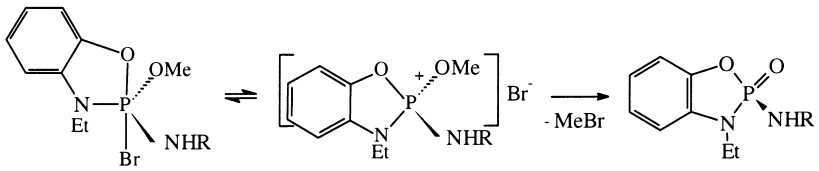
Pentacoordinated phosphorus compounds have attracted attention as models of the transition state in non-enzymatic and enzymatic phosphoryl transfer reactions.[125,190,191] Phosphorus compounds exhibit a marked tendency to expand their coordination, leading to five- or six-coordinate species. Very often the compounds of tetracoordinate phosphorus are found in equilibrium with compounds of pentacoordinate phosphorus, for which pseudorotation with fluctuations of axial and apical bonds are characteristic (Scheme 59).



Scheme 59.

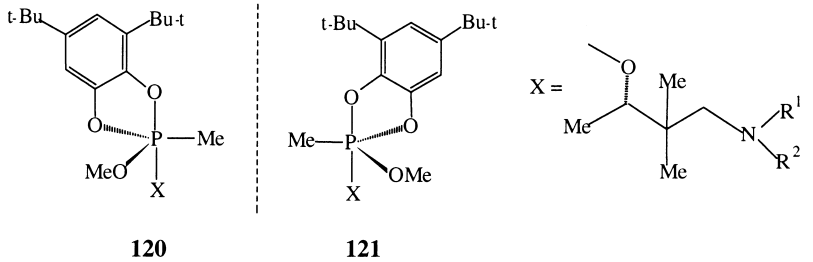
Thus, as shown in Section 2.3.2.5, enantioselective oxidation of racemic aminophosphines **91** by ROH/$CXCl_3$ proceeds via the formation of an alkoxyhalogenophosphorane **93**, which exists in equilibrium with alkoxyphosphonium salt which is ultimately converted into the amidophosphate **92** (Scheme 49). The equilibrium position depends on substituents at the phosphorus atom. Alkoxyhalogenophosphoranes have been obtained for compounds **118**, bearing the five-membered 1,3,2-oxazophospholane ring, which stabilizes the pentacoordinate state of the diastereomers. Bicyclic alkoxy-

halogenophosphoranes **118** were obtained as a 94:6 diastereomer mixture. Phosphoranes convert gradually at room temperature into the amidophosphate **119** (Scheme 60).[162]



Scheme 60.

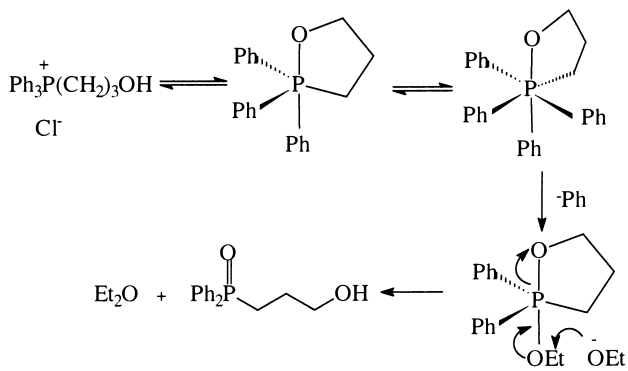
Moriarty and co-workers[192] isolated and characterized stable pseudorotamers of chiral monocyclic oxyphosphoranes **120** and **121** having five different substituents bound to phosphorus. Pentacoordinate diastereomers show two spots by TLC, two signals of approximately equal intensity in the ^{31}P NMR and two sets of signals for ^{1}H and ^{13}C NMR, indicating that the compounds were composed of two diastereomerically related isomers with different configuration at phosphorus. These diastereomers have been separated by column chromatography or fractional crystallization. Stereoisomers have been studied by NMR spectra, and X-ray analysis (Scheme 61).



Scheme 61.

2.4.2. Hexacoordinate phosphorus compounds

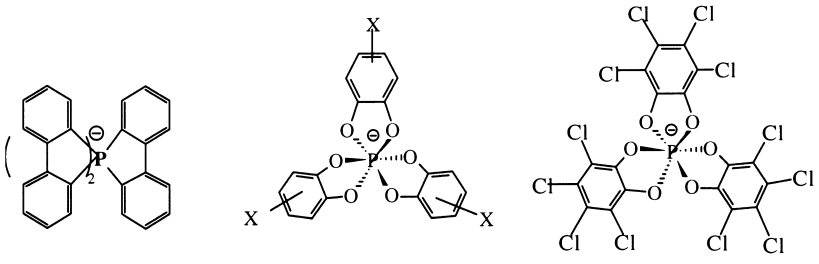
At the present time, many organic compounds of hexacoordinate phosphorus are known and in some cases such compounds mimic intermediate products or transition states in nucleophilic displacements at the tetrahedral phosphorus. Kinetic studies of the decomposition of 3-hydroxypropyltriphenylphosphonium chloride catalyzed by ethoxide ions showed the presence of a hexacoordinate intermediate or transition state formed in the case of the attack of the ethoxide ion on a pentacoordinate intermediate (Scheme 62).[193]



Scheme 62.

The octahedral geometry of pentavalent hexacoordinate phosphorus allows the formation of chiral phosphate anions by complexation with three identical, symmetrical, bidentate ligands.[191,261] Enantiopure anions of D_3-symmetry can be used in several fields of chemistry that involve chiral or prostereogenic cationic species. Resolution of enantiomeric cations, determination of their enantiomeric purity, and asymmetric synthesis of cationic species have several applications.

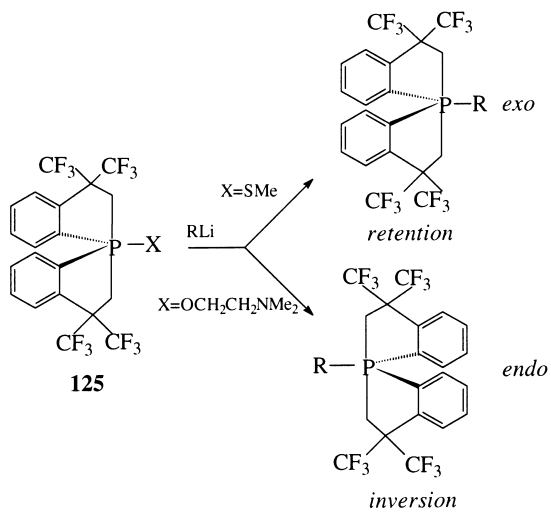
The synthesis of optically active penta-arylphosphorane **122** have been performed by Hellwinkel who succeeded in synthesizing propeller-shaped anion spirophosphoranes, constituting a mixture of two rapidly equilibrating pseudorotational isomers.[204] Optically active phosphate(V) ions **123** with a hexacoordinated phosphorus center were described, however they are configurationally unstable. Koenig and Klaebe showed that racemization of phosphate(V) ions **123** is acid catalyzed and follows a rate law that is first-order in substrate.[9,194a,194b] Determination of the kinetic parameters led to the suggestion of pseudorotation as the rate-determining step.[194a,204b] Lacour and co-workers[204b] prepared the configurationally stable, enantiomerically pure tris(tetrachlorobenzenediolato)phosphate(V) anion **124** from electron-poor tetrachlorocatechol (Scheme 63).



122 **123** **124**

Scheme 63.

The stereochemistry of the substitution reaction of fluxional phosphorane **125** has been reported to depend upon the incoming nucleophile, thus implying the presence of hexacoordinate intermediates. The stereochemical studies of nucleophilic substitution of sterically rigid phosphoranes, performed by Akiba and co-workers[195a] showed the presence of equatorial chalcogen substituents and that the stereochemistry can be altered by changing the coordination ability of the leaving group to a lithium cation (Scheme 64).



125

Scheme 64.

The nucleophilic substitution reaction of SMe compounds with alkyllithium reagents resulted in inversion of configuration, whereas that of OMe compounds gave various ratios of inversion and retention products depending on the stereochemistry of the diastereomeric reactant, phosphoranes and solvent. In the case of $OCH_2CH_2NMe_2$ as the substituent, the reaction proceeds only with the formation of retention products. Retention of configuration indicates clearly that attack on pentacoordinate phosphorus had occurred from the rear side of a carbon atom to furnish hexacoordinate species from which extrusion of X had followed from the same face (Scheme 64).

3. Transfer of chirality from phosphorus to other centers

Over the last few years, optically active organophosphorus compounds have found wide application in asymmetric synthesis. This is mainly because organophosphorus compounds are quite readily available in optically active form. Moreover, the chiral phosphorus moiety that induces optical activity can be easily removed from the molecule, thus presenting an additional advantage in the asymmetric synthesis of chiral organic compounds. On the basis of optically active organophosphorus compounds, syntheses of different chiral organic compounds have been developed in which asymmetric induction involves the transfer of chirality from phosphorus to another center. All these reactions, which can be defined as processes of transfer of chirality from a stereogenic phosphorus atom to a newly formed steereogenic carbon or heteroatomic center, can be divided into two groups.

(i) Reactions resulting in the formation of diastereomeric organophosphorus compounds containing the induced new stereogenic center as well as the optically active phosphorus atom. Here it is necessary to take into consideration the number of newly formed stereogenic centers, i.e. to consider reactions proceeding with 1,2- or with 1,4-asymmetric induction.

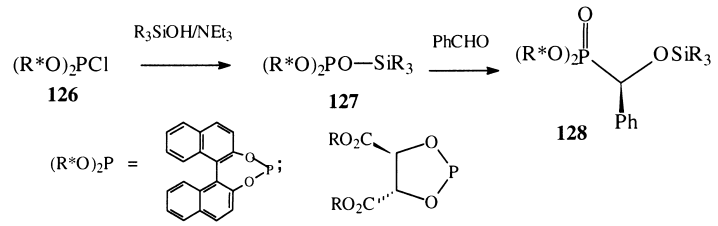
(ii) Reactions in the course of which the formation of a new stereogenic center is accompanied by elimination of the phosphorus moiety.

3.1. The Abramov reaction

Silyl phosphite esters $(RO)_2POSiR'_3$ have been shown to be remarkably versatile phosphorylating reagents.[96b] Chiral silylated organophosphorus reagents can be used in the asymmetric phosphorylation of prochiral unsaturated organic substrates such as aldehydes. One is the asymmetric variant of the Abramov reaction. This was applied to compounds possessing C_2-symmetry where only a single stereoisomeric form exists for the silylated organophosphorus(III) reagent and hence only two possible isomers can be produced in the reaction with benzaldehyde.[165–168]

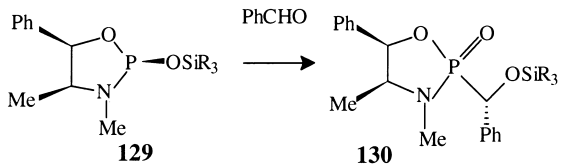
The silylphosphite compounds **126** have been synthesized by the reaction of binaphthalatochlorophosphites with R_3SiOH.[195b] These chiral compounds are active asymmetric phosphonylating reagents. They undergo the Abramov reaction with benzaldehyde at room temperature to afford new silyloxy esters **127** in high yield and with good stereoselectivity. Silylphosphites derived from chiral (+)-dimethyl L-tartaric esters **128** as auxiliaries have been obtained, however, they are not sufficiently useful because they do not react very cleanly with benzaldehyde (Scheme 65).[105]

The 2-triorganosiloxy-1,3,2-oxazaphospholidines **129** undergo the Abramov reaction with benzaldehyde at room temperature to afford new esters in high yield and with good stereoselectivity. Recrystallization of diastereomeric mixtures from pentane affords α-siloxyphosphonate esters **130** as white crystalline solids in up to 88% isolated yield and 95% isomeric purity.[93,196] The reaction is kinetically controlled



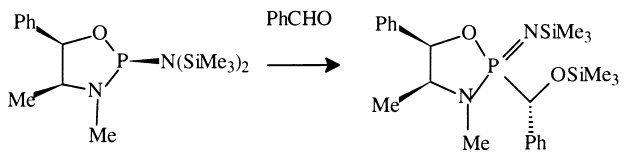
Scheme 65.

and the transfer of the silyl group to the oxygen is intramolecular, which results in retention of relative configuration at the phosphorus atom (Scheme 66).[197]



Scheme 66.

Very good stereoselectivity of the reaction was obtained with the cyclic silylated diamide derived from ephedrine, which provides mostly one enantiomer (>98%; Scheme 67).[198]



Scheme 67.

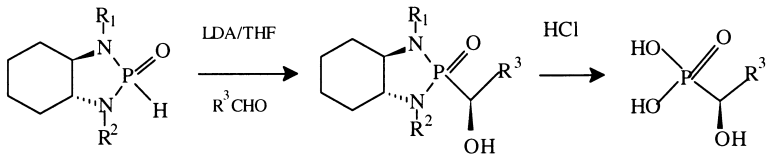
Addition of trimethylsilylphosphites to (*S*)-triisopropylsilyloxy lactaldehyde leads to the formation of β-silyloxy-α-aminophosphoric esters in good yields and >98:2 diastereomeric ratio.[163]

3.2. The Pudovik reaction

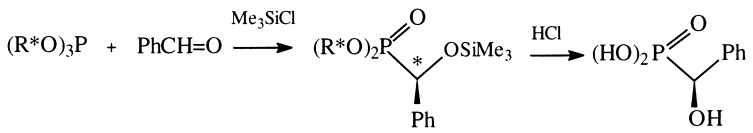
The reaction of dialkylphosphite anions with aldehydes (the Pudovik reaction) is a method for the synthesis of α-hydroxy phosphonamides, many of which are biologically active and have been shown to inhibit different enzymes. The absolute configuration at the α-position in substituted phosphonic acids is very important for biological activity.

Spilling and co-workers investigated the use of chiral phosphorus compounds as reagents for asymmetric synthesis, and have developed a method for the asymmetric synthesis of α-hydroxyacid derivatives formed by addition of a chiral phosphoric acid diamide to aldehydes. Addition of aldehydes to chiral phosphoric acid anions in THF solution proceeds stereoselectively to α-hydroxyphosphonamides **131** in good yield and good stereoselectivity (54–93% *de*). The diastereoselectivity was strongly dependent upon the diamide used and ranged from poor to good.[121,199] It was found that the reaction proceeds irreversibly and under kinetic control. The phosphonamides were hydrolyzed with aqueous HCl in dioxane to provide α-hydroxyphosphonic acids **132** (Scheme 68).[121,199a,b,200,201]

Good stereoselectivity was obtained in the case of the reaction of C_3-symmetric tris(glucofuranosyl) phosphonite with arylaldehydes in the presence of Me_3SiCl, which provides mainly one enantiomer **133** (Scheme 69).[55]



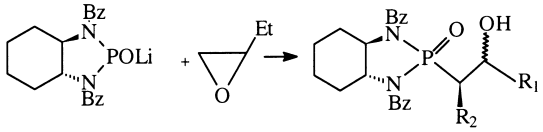
Scheme 68.



R*O=(-)-1:2;5:6-diisopropylidene-*D*-glucofuranosyl

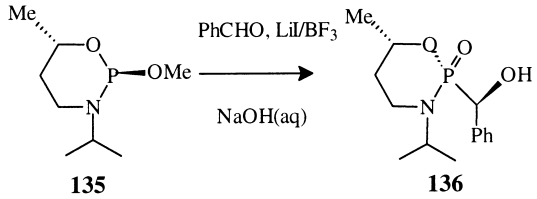
Scheme 69.

Reaction of a lithiated optically active bis(dialkylamido)phosphite with 1,2-epoxybutane gives the 2-hydroxyalkylphosphonic diamide **134** with poor stereoselectivity (*de* 33%), but opened a potential route to the optically active alkylphosphonic acids (Scheme 70).[202]



Scheme 70.

Gordon and Evans described the condensation of diastereoisomeric 2-methoxy-1,3,2-oxazophosphites with a variety of aldehyde–boron trifluoride etherate complexes resulting in diastereoisomerically enriched mixtures of α-hydroxy-2-oxo-1,3,2-oxazaphosphorinanes **135** (75:25 diastereomeric ratio; Scheme 71).[197]



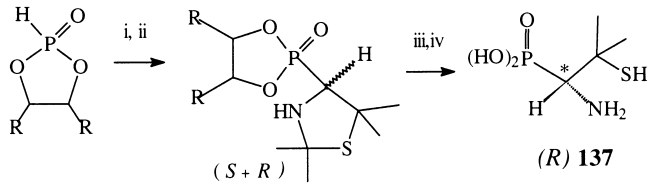
Scheme 71.

Enantiomerically pure dioxaphospholane oxides add to 2,5-dihydro-2,2,5,5-tetramethylthiazole in the presence of boron trifluoride as a catalyst to give a 2:1 diastereomeric mixture, which was separated by column chromatography (Scheme 72).[168]

3.3. Enantioselective cycloaddition

Brandi and Pietrusiewicz were able to demonstrate that 1,3-dipolar cycloaddition of prochiral divinylphosphine derivatives to a five-membered ring nitrone led to highly diastereomerically enriched (up to 92%) cycloadducts **138** with predictable stereochemistry at phosphorus.[71,203–206]

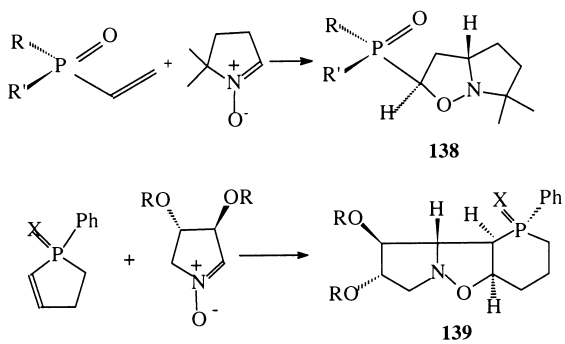
Enantiomerically pure five-membered ring nitrones derived from L-tartaric acid via C_2-symmetric O,O′-protected 3,4-dihydroxypyrrolidines undergo highly regio- and stereoselective cycloaddition



i=2,5-dihydro-2,2,5,5-tetramethylthiazole, ii= BF_3 Et_2O; iii-separation of diastereomers, iv=hydrolysis

Scheme 72.

reactions with racemic 2,3-dihydro-1-phenyl-1*H*-phosphole 1-oxide and 1-sulfide. In all cases formation of only two diastereomeric cycloadducts is observed and their ratio (up to 10:1) is dependent on the size of the protecting group at the nitrone and on the extent of conversion (Scheme 73).



Scheme 73.

The 1,3-dipolar cycloaddition of nitrones to diphenylvinylphosphine oxides, sulfides, and selenides proceeds stereoselectively to form cycloadducts **138** under conditions that avoid cycloreversion. The selectivity decreases with an increase in the electron-withdrawing ability of the substituent according to the sequence:

$$Ph_2P > PhMeP(O) > Ph_2P(S) \geq Ph_2P(O) > (EtO)_2P(O)$$

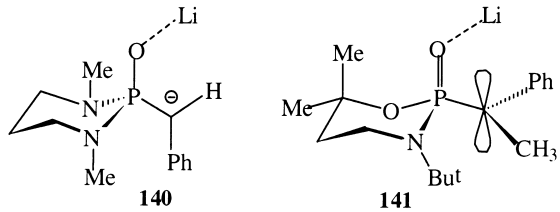
The stereoselectivity indicates that for both regiochemical orientations the cycloadditions prefer *exo* transition states for *E*-dipoles and *endo* transition states for *Z*-dipoles. The predominant formation of the 5-*exo* products in cycloadditions involving *E*-dipolarophiles suggests additionally that this preference is considerably stronger for large substituents destined for position 5 (isoxazolidine numbering) in the product than for those directed to position 4.[207]

3.4. Chiral phosphorus-stabilized anions

The chemistry of phosphorus-stabilized anions in the areas of structure and reaction stereoselectivity attracts the attention of many chemists.[74,163,208–220] Theoretical investigations of chiral phosphorus(V)-stabilized carbanions have been performed by Cramer and co-workers.[213a,b] The rotational coordinates about the P–C bond have been studied at the HF/3–21G* level, with stationary points characterized at levels equivalent to MP3/6–31+G*//HF/6–31+G*. The locations of localized minima on the rotational coordinate were found to be dependent on opportunities for hyperconjugative stabilization.

Cramer[213] and Denmark[215,217,218,220,221] studied NMR spectra and performed X-ray analyses of phosphorus-stabilized carbanions **140** and **141**. X-Ray crystallography showed that the Li–C distance (3.88 Å) is greater then the sum of the van der Waals radii. The carbanion is planar and at nearly a 0° angle to the P=O to maximize P-type interaction and the preferred conformation of the anion is parallel.

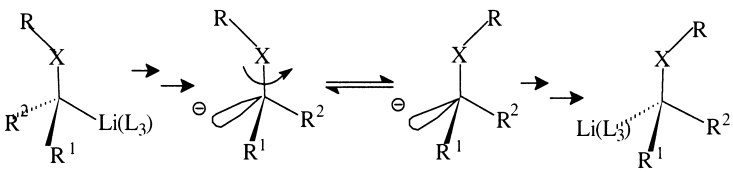
The barrier to rotation about the P(1)–C(b) bond is very low (<8 kcal/mol).[217,221] The lithium salts exist in general as dimers in THF solution, and in the solid state there is no metal–carbon contact.[217] The most remarkable feature of the anion **140** is the pyramidality of the nitrogen, clearly disposing the methyl groups to axial and equatorial positions. The downfield shift of the ^{31}P NMR resonance is indicative of the polarization of the phosphoryl group to stabilize the anion (Scheme 74).[215]



140 **141**

Scheme 74.

The preferred conformation for P-carbanion **140** is that which maximizes opportunities for hyperconjugative stabilization.[213] The rate of racemization of phosphonate carbanions **141** slows down in the presence of HMPA, because the HMPA increases the barrier of rotation around the P–C bond: $\Delta G^{\ddagger}$=9.8 kcal/mol (THF), $\Delta G^{\ddagger}$=11.4 kcal/mol (THF–HMPA solution).[158,222] Aggarval analyzed the mechanism of racemization of heteroatom-substituted organolithium compounds **142**, X=heteroatom, including phosphorus, and came to the conclusion that rotation of the C–P bond plays a dominant role in racemization, which is reduced with increasing concentration of P-stabilized carbanions **143** (Scheme 75).[223]



142 **143**

Scheme 75.

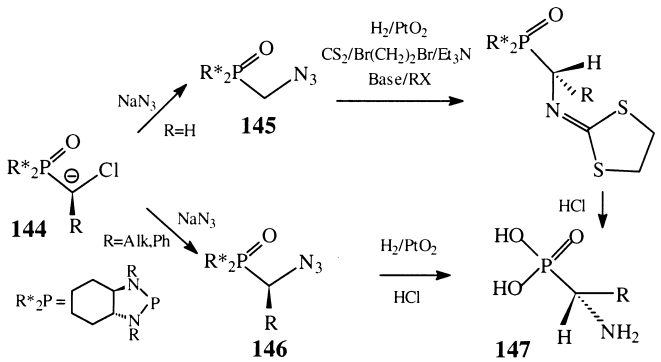
Reactions of chiral P-stabilized carbanions with electrophiles can proceed with the formation of diastereomeric organophosphorus compounds, with the newly induced stereogenic center formed as a consequence of 1,2- or 1,4-asymmetric induction. Chiral phosphonium ylides and chiral P-stabilized carbanions are configurationally stable at phosphorus. This configurational stability at phosphorus persisted through alkylation, hydrolysis, reduction and Wittig reactions as well as reactions with epoxides.[109,112,113,159,182,183] Reactions of chiral P-stabilized carbanions with carbonyl compounds possessing axial asymmetry (enantioselective Wittig and Horner–Wittig reactions) result in the formation of chiral alkenes with the elimination of the phosphorus moiety.

3.4.1. 1,2-Asymmetric induction

This section is concerned with the reactions of chiral phosphorus-stabilized carbanions that involve 1,2-asymmetric induction and embraces alkylation, amination, carboxylation and acylation reactions. Aminoalkylphosphonic acids have been extensively studied because of their bio-active properties.[73,225–230]

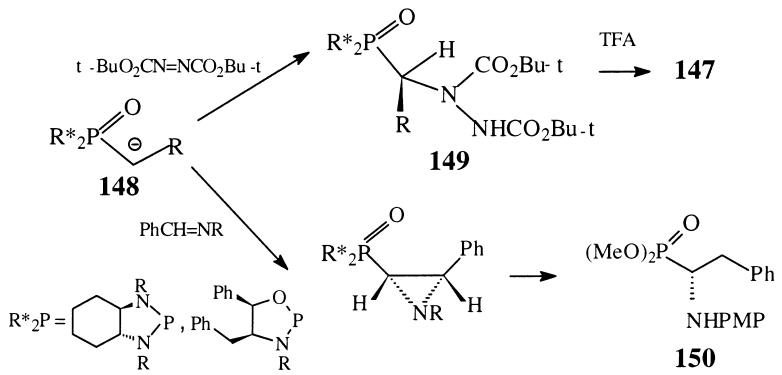
It has been shown that the biological activity of α-aminophosphonic acids is dependent upon their absolute configuration, which makes the asymmetric synthesis of this class of compounds both interesting and of practical significance.[75] A general method for the asymmetric synthesis of enantiomerically pure

or enriched α-amino-α-alkylphosphonic acids **147**[98b,231] in either enantiomeric form has been described based on the amination and alkylation of chiral bicyclic chloromethylphosphonamides **144**, R=H, derived from (*R*,*R*)- and (*S*,*S*)-1,2-diaminocyclohexanes — a readily available C_2-symmetrical template, via the azides **145** (Scheme 76).[158,231a] The enantiomeric purity of α-amino-α-alkylphosphonic acids **147** was 84–98%. Another route to α-aminophosphonic acids **147** is possible from the α-chloro-α-alkylamides **144**, R=Alk, Ph. Nucleophilic displacement with the azide ion gives the corresponding α-azido derivatives **146**. Mild acid hydrolysis followed by hydrogenation of the azido group led in almost quantitative yield to the corresponding α-aminophosphonic acids **147**. The enantiomeric purity of these α-amino-α-alkylphosphonic acids **147** was 78–98% (Scheme 76).[98,209,231a]



Scheme 76.

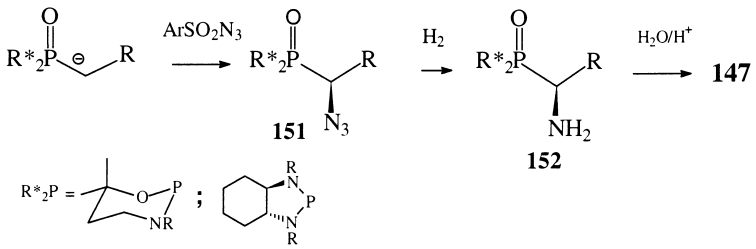
Stereoselective electrophilic aminations of anions of chiral non-racemic α-alkylphosphonamides **148**, derived from *N*,*N*-dimethyl (*R*,*R*)-1,2-diaminocyclohexane with azo-compounds proceed with moderate to excellent enantioselectivities. The products **149** were hydrolyzed and reduced to the corresponding α-alkyl-α-aminophosphonic acids **147**, which are being extensively studied in view of their relations to amino acids and bioactive peptides.[233] Sisti and co-workers reported recently that electrophilic amination of 1,3,2-oxazaphospholanes with azo-compounds proceeds with 52–83% diastereoselectivity in good agreement with theoretical calculations.[224] Hanessian and co-workers[232] described also the synthesis of α- and β-aminophosphonic acids **150** based on the stereoselective addition of carbanions of chiral α-chloromethylphosphonamides **144** to imines. The α-aminophosphonamide derivatives **150** were obtained with greater than 95:5 diastereoselectivity (Scheme 77).



Scheme 77.

Hanessian[163] studied aminations of carbanions derived from (*R*,*R*)-diaminocyclohexane also using

trisyl azide for stereoselective electrophilic amination. The enantiomeric purity of **151** was 68–80% (Scheme 78).

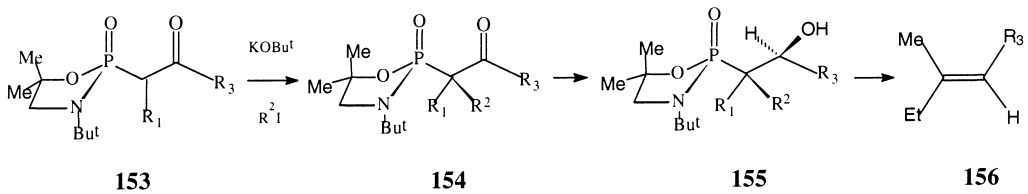


Scheme 78.

Consecutive hydrolysis of **151** and hydrogenation afforded aminoacids **147** with 63–99% *ee*. Hanessian[163] and Denmark[76] proposed asymmetric electrophilic amination by trisyl azide of phosphorus-stabilized anions derived from (*R,R*)-diaminocyclohexane, chiral oxazaphosphorinanes and diazaphospholidines. This method affords the α-azidophosphonoamidate **151** with excellent diastereoselectivity. The minor diastereomer could not be detected by NMR spectroscopy or HPLC. In the best cases (*S*)-α-aminophosphonic acids **147** with 92% *ee* have been obtained. In another method, Denmark[158] suggested deprotonation of oxazaphosphorinanes with BuLi and treatment of the carbanion with trisyl azide. The intermediate lithiosulfonyltriazine was captured with acetic anhydride to afford, after decomposition, a single isomer **151** in excellent yield. Again the minor diastereomer could not be detected by NMR or HPLC. Reduction of compound **151** was accomplished by hydrogenation (1 atm, Pd/C) to give the α-aminophosphonamidate **152**. The selectivity in azide transfer was at least 50:1. The free α-aminophosphonic acids **147** could be obtained in good yield by acetic hydrolysis (Scheme 78).[239]

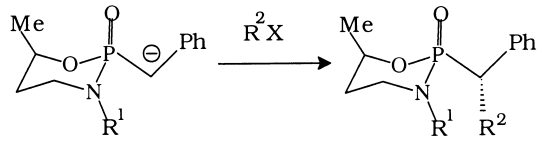
The reaction is shown to be dependent on the structure of the P-alkyl-substituent and the choice of amination procedure. Using the oxaphosphorinanes, a high level of asymmetric induction can be achieved. *cis*-Oxazaphosphorinanes provide the α-aminophosphinic acids **147** with 92% *ee* as the (*S*)-antipodes.

Denmark and Amburgey studied enantioselective alkylations of P-carbanions. The quaternary stereocenter was created by alkylation of the various β-ketophosphonamidates as their potassium or sodium enolates. Alkylated β-ketophosphonamidates **154** could be prepared with excellent diastereoselectivities by complementary alkylation of phosphonates **153** with EtI or MeI. Stereoselective reduction gave diastereomers of β-hydroxy phosphonamidates **155** in the ratio 1:14–1:150. Thermal cycloelimination afforded the olefins **156** in very good yields and stereospecificity (Scheme 79).[74]



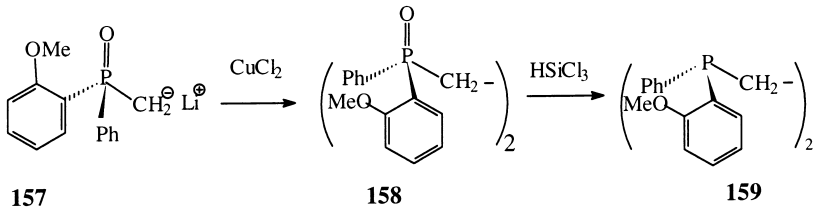
Scheme 79.

The alkylation of a series of enantiomerically pure *cis*- and *trans*-3-substituted 2-benzyl-6-methyl-1,3,2-oxazaphosphorinane 2-oxides was found to be sensitive to the bulk of the N-substituents R.[234] The original design of the auxiliary was made on the basis of the strongly dissymmetric environment around the anionic center due to the sterically disparate groups, i.e., *N-tert*-butyl and O-electron pair and a strong rotator bias in the anion (Scheme 80).



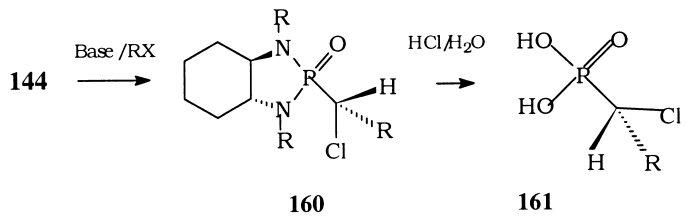
Scheme 80.

Vineyard and co-workers generated carbanions **157** by action of R_2NLi. This carbanion was then oxidatively coupled with copper salts. The biphosphine oxide **158** was converted into biphosphine **159** with inversion at the phosphorus center using a mixture of trichlorosilane and triethylamine in acetonitrile solution. This biphosphine **159** was used as a ligand in rhodium complexes (Scheme 81).[136]



Scheme 81.

The enantiomerically pure or enriched α-chloro-α-alkylphosphonic acids **160** in both enantiomeric forms have been obtained by asymmetric alkylation of bicyclic C_2-symmetric phosphondiamides **144**.[235] The methodology consisted of the treatment of the chloromethyl or ethyl phosphonamides with a base such as BuLi or LDA in THF followed by addition of an appropriate alkylhalide at −100°C. The resulting products **160** were obtained in high yield and in good enantiomeric excess. The high stereoselectivity of the reaction was explained by attack of the initially formed anion **144** on the electrophile preferentially from the side facing the lone pair of one of the nitrogen atoms than the side facing the *N*-methyl group (*de* 90:10–99:1; Scheme 82).[231]



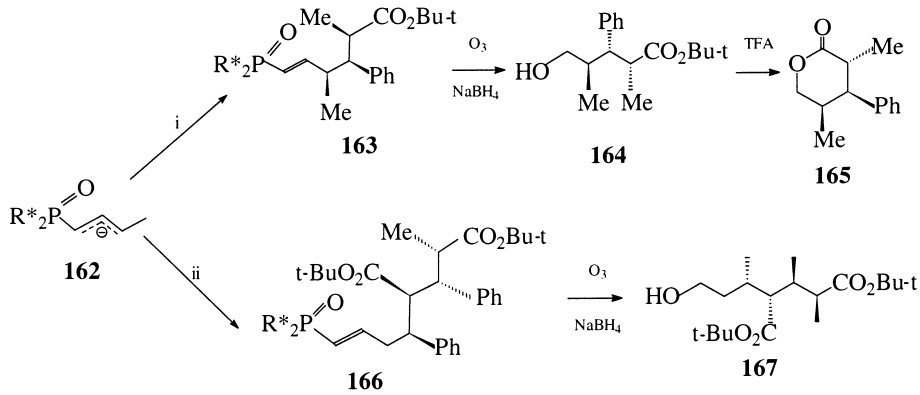
Scheme 82.

3.4.2. 1,4-Asymmetric induction

One of the most fundamental questions surrounding the use of stabilized allyl anions in their reaction with electrophiles is the α/γ-regioselectivity. This reactivity has been found to be highly dependent on the steric and electronic nature of stabilizing groups as well as the nature of the electrophile. The most useful synthetic application of the allyl anions is the Michael addition reaction.[236–241]

3.4.2.1. *Michael addition* Highly stereocontrolled sequential asymmetric Michael addition reactions with cinnamate esters, which lead to the generation of three and four contiguous stereogenic centers has been described by Hanessian. An asymmetric Michael reaction of the anion **162**, generated by BuLi from the crotyl phosphonamide, with the *tert*-butyl cinnamate followed by addition of methyl iodide led to formation of adducts **163** in a ratio of 92:8. Ozonolysis and sodium borohydride reduction gave the hydroxy ester derivative **164** as a single isomer. Treatment with TFA in dichloromethane led to the

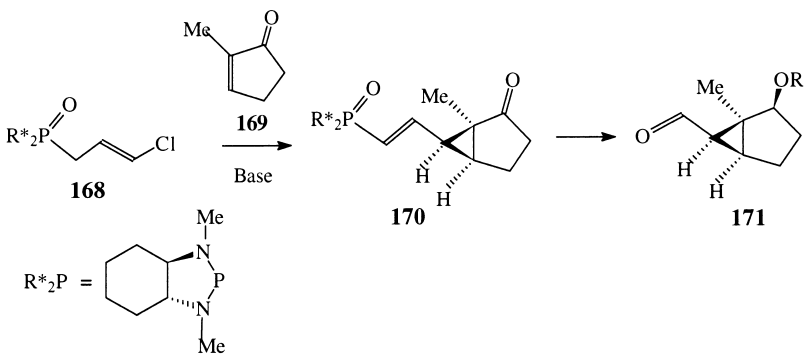
lactone **165** containing three contiguous carbon substituents (Scheme 83).[236] Following the same protocol as above and quenching the enolate with methyl triflate the same authors obtained a 90:10 mixture of diastereomers **166**. Ozonolysis, reduction and chromatographic separation gave the hydroxy ester **167** as a single isomer, harboring four contiguous stereogenic centers (Scheme 83).[85,238]



i= PhCH=CHCO$_2$Bu-t, MeI; ii= PhCH=CHCO$_2$Bu-t, MeOSO$_2$CF$_3$, Py;

Scheme 83.

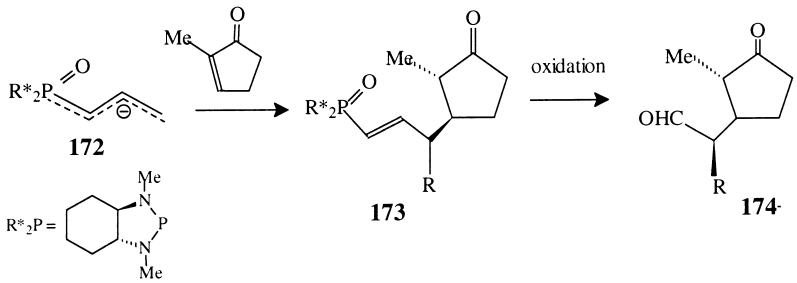
Reactions of anions derived from chiral non-racemic allyl and crotyl bicyclic phosphonoamides with α,β-unsaturated cyclic ketones, esters, lactones and lactams take place at the γ-position of the reagents and lead to diastereomerically pure or highly enriched products of conjugate addition. High diastereoselectivity was observed for the asymmetric Michael addition reaction of racemic 2-allyl-1,3,2-oxazaphosphorinane 2-oxide with cyclic enones (88–90% *de*).[218,237] The highly stereocontrolled conjugate 1,4-addition of the carbanion of the *trans*-chloroallyl phosphonamide **168** to α,β-unsaturated carbonyl compounds **169** provides diastereomerically pure or highly enriched cyclopropane derivatives. The reaction proceeds with the concomitant formation of the corresponding cyclopropanes **171** as a result of an intramolecular attack of the enolate upon the intermediate allylic chloride **170** (Scheme 84). The reaction gives the crystalline *endo,endo* isomer of cyclopropane **170** in 90% yield.[240,241]



Scheme 84.

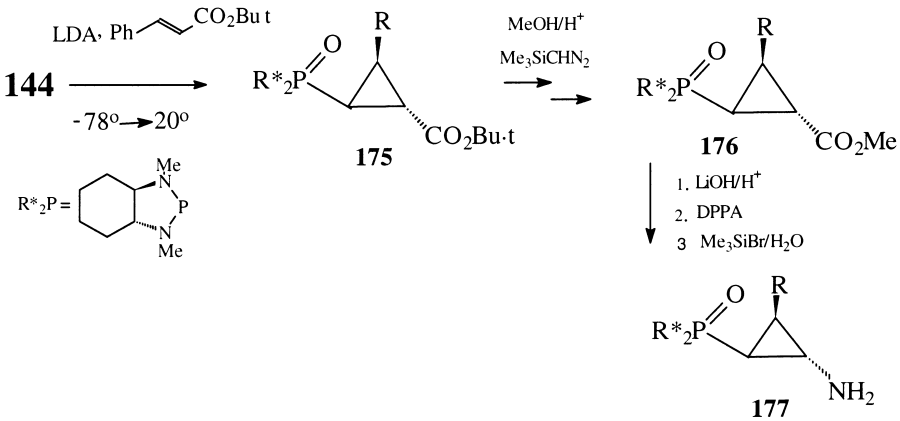
Stereoselective reduction of the carbonyl group (NaBH$_4$/MeOH), protection and oxidative cleavage by ozonolysis affords the aldehyde **171**. Alternatively, utilization of the *cis*-chloroallyl phosphonamide reagent with the same enone **169** leads to the isomeric *exo,endo* product **173** as the major isomer (>90:10; Scheme 85).[236,238,241] Reaction of anions **172** derived from chiral non-racemic allyl and crotyl bicyclic phosphonamides with α,β-unsaturated cyclic ketones take place at the γ-position of the reagents and leads to diastereomerically pure or highly enriched products of conjugate addition product **173**.

Oxidative cleavage led to products corresponding to the formal conjugative addition of an acetaldehyde or a propionaldehyde anion equivalent to α,β-unsaturated carbonyl compounds **174**. The inclusion of HMPA was found to enhance the ratio of γ-1,4-addition and to improve the stereoselectivity in the case of 3-methylcyclopentanone. Mono-, di- and trisubstituted cyclopentanones are obtained as single diastereomers.[236]



Scheme 85.

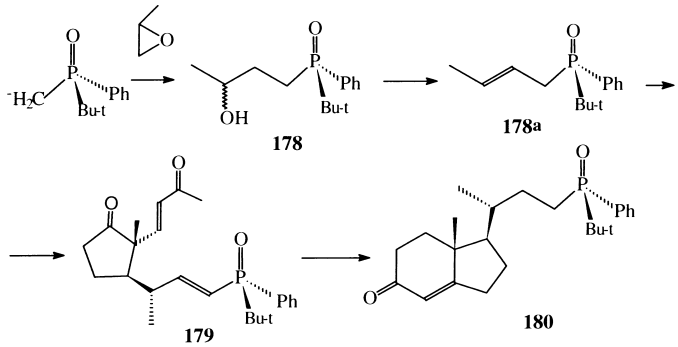
The stereocontrolled conjugate addition of anions derived from the chiral α-chlorophosphonoamides **144** to α,β-unsaturated esters leads to the corresponding 3-chloroester adducts which undergo intramolecular expulsion of chloride to give the corresponding cyclopropanes **175** (*dr* 5:1–100:0). The thus-obtained cyclopropanes **175** were then converted into 3-substituted cyclopropane 2-aminophosphonic acids **177** (Scheme 86).[242]



Scheme 86.

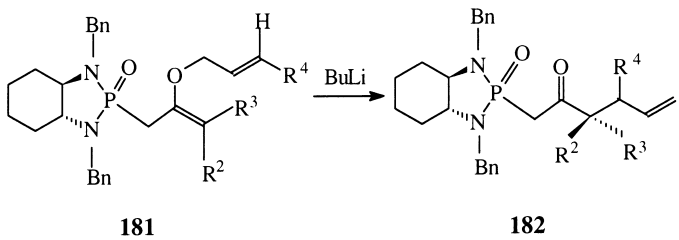
Haynes has since described the enantioselective γ-1,4-addition of individual enantiomers of (*E*)-2-butenyl-*tert*-butylphenylphosphine oxide to 2-methyl-2-cyclopentenone and formulated a model for the asymmetric induction. *t*-Butyl(methyl)phenylphosphine oxide was lithiated with butyllithium and then treated with propylene oxide and then with BF_3–ether to provide a 1:2 mixture of diastereomers of the γ-hydroxyphosphine oxide **178**, which was converted into (*S*)- and (*R*)-allyl-*tert*-butylphenylphosphine oxides **178a**. The lithiated **178a** was treated with 2-methylcyclopent-2-enone to give unsaturated diketone **179** which was converted into the corresponding enantiomers of hydrindenones **180**, suitable for conversion into vitamin D analogs and their enantiomers (Scheme 87).[243,244]

3.4.2.2. *Claisen rearrangement* The carbanion-accelerated Claisen rearrangement (CACR) of allyl vinyl ethers has proven to be a reaction of synthetic potential. The utility of various phosphonamide



Scheme 87.

groups has been examined in the context of the carbanion-accelerated Claisen rearrangement. The *N,N′*-dibenzyl-1,3,2-diazaphospholidine group is the most optimal for the construction of the CACR precursor and the stereoselectivity of its rearrangement. Using butyllithium as the base the phosphonamides **181** rearranged readily at −20°C into **182** with complete regioselectivity, in good yield and a high level of diastereoselectivity (>95% *de*). However in a simple Claisen rearrangement of the chiral *N,N′*-dibenzyl-1,3,2-diazaphospholidine **181** derived from *trans*-1,2-cyclohexandiamide, the relative asymmetric induction was poor (~20% *de*; Scheme 88).[216,218]



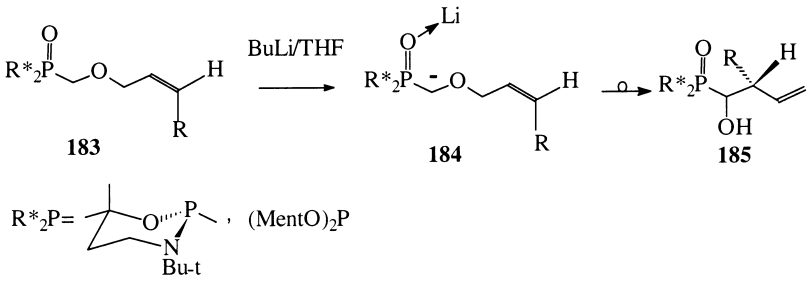
Scheme 88.

The carbanion-accelerated Claisen rearrangement of phosphorus-stabilized anions was faster than in the case of sulfone-stabilized carbanions.[216]

3.4.2.3. *[2,3]-Wittig rearrangement* The [2,3]-Wittig rearrangement is a special class of [2,3]-sigmatropic rearrangements which involves α-oxy carbanions as the migrating terminus to afford various types of homoallylic alcohols. The most significant feature of the [2,3]-Wittig rearrangement is its ability of efficient diastereocontrol over the newly created stereogenic centers through the proper choice of the combination of substituents and substrate geometry.[245]

The [2,3]-Wittig rearrangement of a chirally modified phosphorus-stabilized anion proceeds with excellent diastereo- and enantioselectivity for allyloxymethyl and *Z*-2-butenyloxymethyl derivatives. Deprotonation of 1,3,2-oxazaphosphorinate with butyllithium in THF at −70°C generated the phosphorus-stabilized anion **183**, which underwent the [2,3]-Wittig rearrangement to afford a single diastereomer of hydroxy 3-butenyl-1,3,2-oxazaphosphorinanes **184** in good yield. The configuration of the hydroxy-bearing stereocenters of compounds (*S*)-(+)- and (*R*)-(−)-**185** was determined by comparison of the sign of the specific rotation with compounds prepared by independent syntheses (Scheme 89).[246]

Another interesting example of the [2,3]-Wittig rearrangement was described by Collignon. A diastereoselectivity of up to 90% was achieved in the rearrangement of the lithiated derivative of the allyloxymethylphosphonate **192**, by using the chiral dimenthylphosphinyl ester group as the stereodirecting

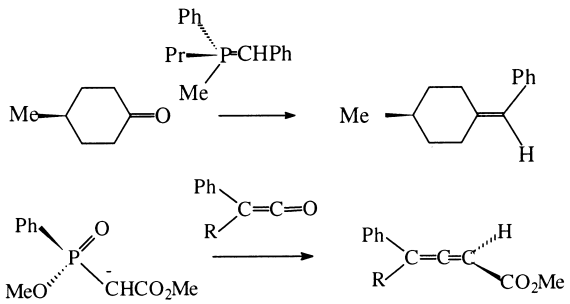


Scheme 89.

auxiliary. After treatment with an excess of butyllithium in THF at −78°C, dimethyl allyloxymethylphosphonate **192** underwent complete [2,3]-Wittig rearrangement giving, after low temperature acid hydrolysis of the reaction mixture and subsequent work up, (1-hydroxy-3-buten)-1-yl phosphonate **193**, isolated in 95% yield as a mixture of two diastereomers in a 96:4 ratio.[247] Chiral non-racemic 1-hydroxyphosphonates are interesting precursors for other α-functional phosphonates.

3.4.3. Enantioselective olefination

The Horner–Wittig, as well as Wittig reactions between P-ylides or P-stabilized carbanions and aldehydes or ketones is an important and practical method for the construction of carbon–carbon double bonds. Many attempts to develop an asymmetric version of the Wittig and Horner–Wittig reactions have been reported over the past three decades.[214,248,249] Different chirally modified phosphinates, phosphonates, phosphonamides, phosphinothionic amides, phosphine oxides, oxazaphosphorinanes, oxathiaphosphorinanes and phosphoranes have been employed for asymmetric olefination with variable success.[250–274] The first of these was performed by Bestmann, who employed chiral P-ylides for the synthesis of optically active allenes and cycloalkylidenes (Scheme 90).[182,250] Bestmann also described asymmetric catalysis in the Wittig reaction.[251]



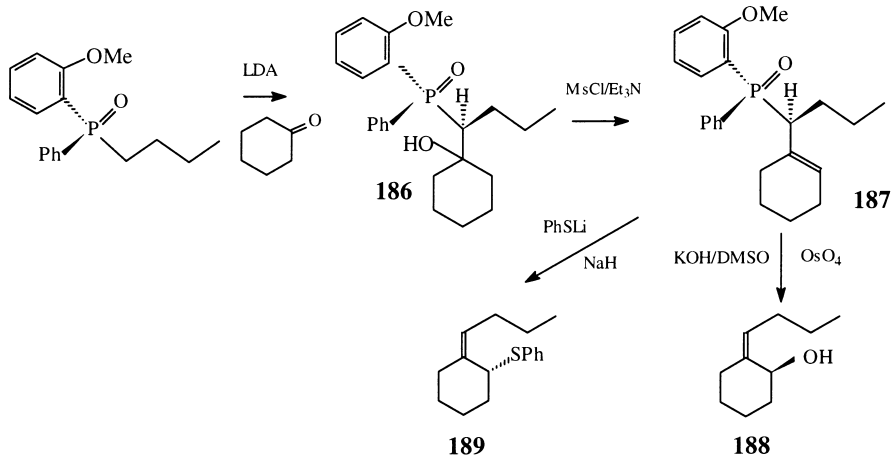
Scheme 90.

It was shown that the reaction between chiral ylides and chiral acyl halides resulted in partial kinetic resolution and the production of optically active allenes.[8,259] The reaction of the carbanion obtained from optically active O-methylphenylphosphinyl acetate with unsymmetric ketenes and with racemic 2-substituted cycloalkanones was reported by Musierowicz and co-workers (Scheme 90).[254] The ketenes reacted smoothly with (*Sp*)-phosphorylated carbanion in a benzene–ether solution to induce the formation of the allenes of (*R*)-configuration. The *ee* was approximately 12–17%.[253,254,262]

Since the Wittig reaction does not create a new sp^3 carbon center, efforts to develop an asymmetric version of the Wittig reaction have been focused mainly on alkylidenecycloalkanes with axial chirality.[263,264]

Optically active (*ortho*-methoxyphenyl)phenylphosphine oxide was used to create the three new stereogenic carbon atoms of the carbon framework **186**, which was built up by stereoselective electro-

philic attack on a cyclic allylic phosphine oxide. Elimination of the chiral auxiliary in a Horner–Wittig reaction gives compounds **187**. Optically active phosphine oxide was converted into the optically active (*S*)-(+)- alcohol **188** and into the optically active sulfide **189** (Scheme 91).[161]



Scheme 91.

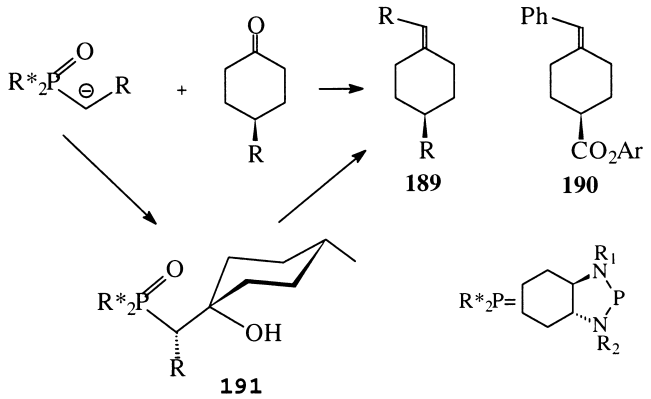
Highly selective syntheses of dissymmetric olefins (86–100% *ee*) that employ a novel electrophilic activation of the Horner–Wittig process have been described. Axially dissymmetric (alkylcyclohexylidene)ethanes were produced with up to 90% enantiomeric excess from cyclohexanones derivatives and chiral P-stabilized carbanions.[98,266,267] The reaction of 4-*tert*-butylcyclohexanone with the anion of **190** generated with potassium diethylamide gives a 82% yield of (*R*)-4-*tert*-butylcyclohexylideneethane with an enantiomeric excess of 90±2%.[98,210]

Treatment of alkylcyclohexanones with carbanions derived from the C_2-symmetric (*R,R*)- and (*S,S*)-*N,N′*-dimethyl 1,2-*trans*-cyclohexanephosphondiamides leads to enantiomerically pure allylidene, benzylidene and propylidene alkylcyclohexanes.[234] A series of chiral (arylmethylene)cycloalkanes was synthesized in optically active form for incorporation in a liquid crystal based optical switch.[270a]

The methodology developed by Hanessian[235] includes isolation of β-hydroxyl intermediates **191**, purification and transformation into 4-substituted cyclohexanones. The treatment of alkylcyclohexanones with anions of chiral (*R,R′*)- and (*S,R*)-bicyclic allyl or benzylphosphondiamides led to the corresponding β-hydroxyphosphonamide intermediates **191** in excellent yield and very good enantioselectivity (Scheme 92).

The isolation of an intermediate of β-hydroxyphosphonamides **191** allowed the clarification of the mechanism of reaction. The disposition of the phosphoryl appendage probably reflects a preferential 'equatorial' attack on the carbonyl group and the orientation of the α-phenyl group evidently corresponds to the attack on the pro-*S* face of the anion by the electrophile.

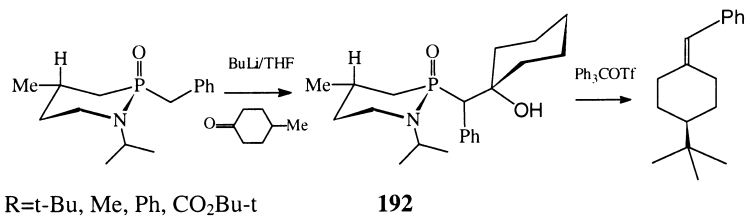
Wittig–Horner reactions in the solid state of the inclusion compound of 4-methyl- or 3,5-dimethylcyclohexanone and an optically active host compound with (carbethoxymethylene)triphenylphosphorane gave optically active 4-methyl- and 3,5-dimethyl-1-carbethoxymethylene cyclohexane.[124,256] An 82% *de* of 4-substituted cyclohexanones was obtained with carbanions derived from menthol phosphonates.[229] Chiral phosphonamidate anions derived from 1,3,2-oxazaphosphorinane 2-oxides were successfully applied to enantioselective olefination of 4-substituted cyclohexanes. In all cases the adducts **192** were obtained by Denmark in high yields and excellent diastereoselectivity (88–100%). The triflate-induced olefination also proceeded smoothly to afford dissymmetric olefins with complete stereo-



R= Alk, Ar, Allyl

Scheme 92.

specificity. Optimization (brief warming at 60°C in acetonitrile) led to the highest enantiomeric excesses (Scheme 93).[214,270b]

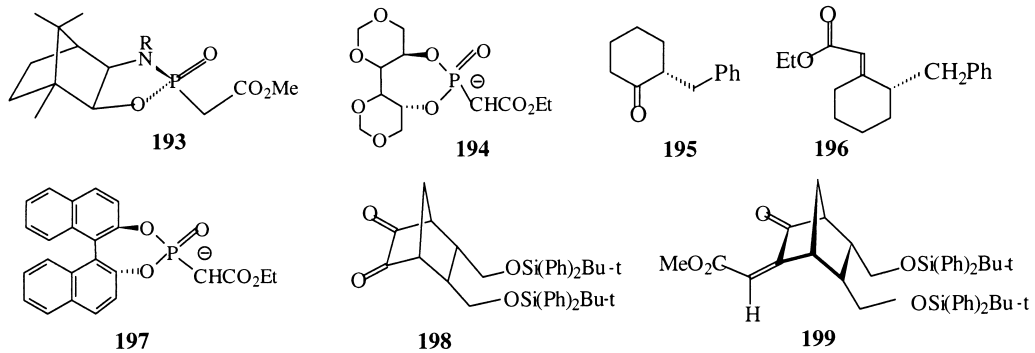


R=t-Bu, Me, Ph, CO_2Bu-t **192**

Scheme 93.

Readily available camphor-derived amino alcohol auxiliaries were used for the preparation of oxazaphospholidine-2-oxides **193**, which were then converted into phosphorus-stabilized carbanions by action of lithium bis(trimethylsilyl)amide.[107] The asymmetric carboalkoxyalkylidenation of 4-substituted cyclohexanones was effected by these chirally modified Horner–Wittig reagents in good yields and respectable levels of enantioselectivity (78–86%). The selectivity of the reaction depends on the anion, temperature, solvent and substituent at the nitrogen atom. Electron withdrawing N-substituents R of **193** led to a slower reaction but higher selectivities, while increasing solvent polarity (Et_2O<DMF) decreases the rate and increases stereoselectivity (Scheme 94). Asymmetric carboalkoxyalkylidenation with chiral Horner–Wittig reagents was also conducted by Japanese authors.[108] Natural mannitol was converted into a C_2-symmetric dimethylene acetal and then into chiral tricyclic phosphonate **194**. Kinetic resolution of racemic α-substituted carbonyl compounds by the Horner–Wittig reaction with this chiral tricyclic phosphonate **194** led to the formation of carboalkoxyalkylidene **195** in high yield and good stereoselectivity.[108] The absolute configuration of **195** was determined as (*S*) (Scheme 94).[108] The reaction between racemic α-benzylcyclohexanone and the chiral dinaphthylphosphonate **197** led to chiral olefins **196** with good stereoselectivity.[108]

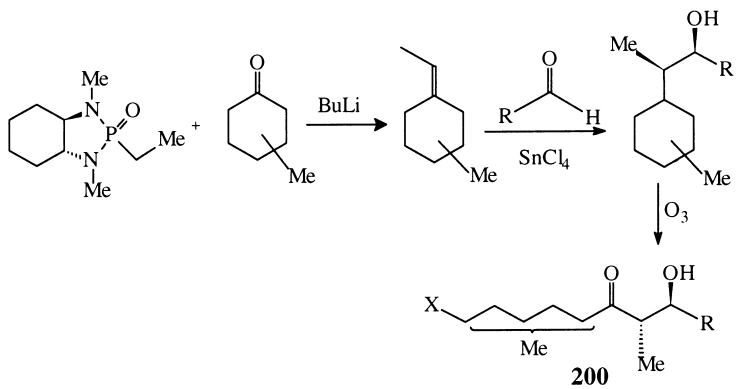
Fugi and co-workers[273] studied asymmetrization of a *meso*-dicarbonyl compound **198** by the Horner–Wittig reaction utilizing the chiral phosphonoacetate reagent **197**, bearing binaphthol as the chiral auxiliary. Treatment of *meso*-α-dicarbonyl compound **198** with the anion **197** gave β-alkoxycarbonyl-α,β-unsaturated ketone **199** in nearly 98% enantiomeric excess. The chiral cyclic phosphonoacetate **199** was very effective for enantiogroup differentiation in *meso*-α-diketone **198** to



Scheme 94.

give the *Z*-olefin **199**, in which complete transfer of chirality from the binaphthol moiety to product was realized. The absolute stereochemistry was determined by X-ray analysis.[273]

Hanessian and Beaudoin elaborated an elegant chemical method based on the construction of chiral alicyclic cyclohexenes and involving the application of sequential asymmetric olefination and ene reaction. Oxidative cleavage led to their acyclic counterparts **200**, containing stereochemically defined *C*-methyl groups (Scheme 95).[235,236]



Scheme 95.

4. Conclusion

I hope that this review of chiral organophosphorus compounds will be useful to chemists interested in various aspects of chemistry and stereochemistry. The facts and problems discussed provide numerous possibilities for the study of additional stereochemical phenomena at phosphorus.

Looking to the future it may be said that the asymmetric synthesis of organophosphorus compounds will be and should be the subject of further studies. Opportunities lie in the development of the application of prochiral low-coordinate phosphorus compounds, the study of the stereochemistry of reactions as synthetic starting compounds and intermediates and studies dedicated to the stereochemistry of phosphorus in living processes.

Further development will involve studies of the stereochemistry of hypervalent organophosphorus compounds. In spite of the successes in the area of basic research of hypervalent phosphorus compounds, their synthetic applicationss in asymmetric synthesis is obviously deficient at present. Finally, wider applications of optically active organophosphorus reagents in asymmetric organic synthesis will appear.

References

1. Morrison J. D., Mosher H. S. *Asymmetric Organic Reactions*; Englewood Cliffs, New Jersey, 1971.
2. (a) Kagan H. B. In *Asymmetric Synthesis*, ed. J. D. Morrison; Academic Press, Orlando, 1985, Vol. 5, pp. 1–39. (b) Kagan H. B. In *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson; Pergamon Press, Oxford, 1982, Vol. 8, p. 463.
3. (a) Frey P. A. *Tetrahedron* **1982**, *38*, 1541. (b) Bruzik K., Tsay M. D. *J. Am. Chem. Soc*. **1984**, *106*, 747.
4. (a) Apsimon J. W., Lee Cotier T. *Tetrahedron* **1986**, *42*, 5254. (b) Noyori R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons, New York, 1994.
5. Pietrusiewicz K. M., Zablocka M. *Chem. Rev*. **1994**, *94*, 1375.
6. Emsley J., Hall C. D. *The Chemistry of Phosphorus*; Harper and Row, New York, 1976, Chapter 8.
7. Holmes R. *Pentacoordinated Phosphorus*, *ACS Monograph 176*, 1980, Vol. II.
8. Johnson A. W. *Ylides and Imines of Phosphorus*; John Wiley & Sons, New York, 1993, p. 147.
9. Klaebe A., Koenig M., Wolf R., Ahlberg P. *J. Chem. Soc., Dalton Trans* **1977**, 570.
10. McEwen W. E., Berlin K. D. *Organophosphorus Stereochemistry*; John Wiley & Sons, Strassbourg, 1975, Parts I and II.
11. Valentine Jr. D. In *Asymmetric Synthesis*, ed. J. D. Morrison, J. W. Scott; Academic Press, Orlando, 1984, Vol. 4, Chapter 3, p. 263.
12. Markwald W. *Ber*. **1904**, *37*, 1368.
13. Kagan H. B., Fiaud J. C. *Topics in Stereochemistry* **1988**, *18*, 249.
14. Wittig G., Cristau H. J., Braun H. *Angew. Chem., Int. Ed. Engl*. **1967**, *6*, 700.
15. Cernia E., Giongo G. M., Marcati F., Marconi W., Palladino N. *Inorg. Chim. Acta*. **1974**, *11*, 195.
16. Macpherson A. J., Smith D. J. H. *J. Chem. Res*. S. **1984**, 32.
17. (a) Li Y.-F., Hammerschmidt F. *Tetrahedron: Asymmetry* **1993**, *4*, 109. (b). Dresher M., Hammerschmidt F. *Tetrahedron* **1997**, *53*, 4627.
18. Kielbasinski P., Zurawinski R., Pietrusiewich M. K., Zastocka M., Mikolajczyk M. *Tetrahedron Lett.* **1994**, *35*, 7081.
19. Markovski L. I., Romanenko V. D., Ruban A. V., Drapailo A. B., Mikolajczyk M., Omelanczuk J., Perlikovska V. *Zh. Obshch. Khim*. **1988**, *58*, 2627.
20. Mikolajczyk M., Omelanczuk J., Perlikovska W., Markovski L. I., Romanenko V. D., Ruban A. V., Drapailo A. B. *Phosph., Sulf. and Silicon* **1988**, *36*, 267.
21. Romanenko V. D., Reitel G. V., Kachkovskaya L. S., Mikolajczyk M., Omelanczuk J., Perlikovska V. *Zh. Obshch. Khim*. **1993**, *63*, 1182.
22. Anderson R. C., Shapiro M. J. *J. Org. Chem*. **1984**, *49*, 1304.
23. de Vaumas R., Marinetti A., Ricard L., Mathey F. *J. Am. Chem. Soc*. **1992**, *114*, 261.
24. Baechler R. D., Mislow K. *J. Am. Chem. Soc.* **1971**, *93*, 773.
25. Marinetti A., Mathey F., Ricard L. *Synthesis* **1992**, 157.
26. Marinetti A., Ricard L. Mathey F. *Organometallics* **1993**, *12*, 1207.
27. Harger M. J. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1256.
28. Freeman S., Harger M. J. P. *J. Chem. Soc., Chem. Commun.* **1985**, 1394.
29. Quin L. D., Sadani N. D., Wu X.-P. *J. Am. Chem. Soc* **1989**, *111*, 6853.
30. Rauk A., Allen L. C., Mislow K. *Angew. Chem., Int. Ed. Engl*. **1970**, *9*, 400.
31. Baechler R. D., Mislow K. *J. Am. Chem. Soc.* **1970**, *92*, 3090.
32. Horner L. *Pure Appl. Chem.* **1964,** *9*, 225.
33. Omelanchuk J. *J. Chem. Soc., Chem. Commun.* **1992**, 1718.
34. Pabel M., Willis A. C., Wild S. B. *Tetrahedron: Asymmetry* **1995**, *6*, 2369.
35. De Bruin K. E., Zon G., Naumann K., Mislow K. *J. Am. Chem. Soc*. **1969**, *91*, 7027.
36. Horner L. *Pure Appl. Chem.* **1980**, *52*, 843.
37. Lambert J. B. In *Topics in Stereochemistry*, ed. N. L. Allinger, E. L. Eliel; Wiley, New York, 1971, Vol. 6, p. 19.
38. Johnson C. R., Imamoto T. *J. Org. Chem*. **1987**, *52*, 210.
39. Korpiun O., Lewis R. A., Chickos J., Mislow K. *J. Am. Chem. Soc*. **1968**, *90*, 4842.
40. Korpiun O., Lewis R. A., Chickos J., Mislow K. *J. Am. Chem. Soc*. **1968**, *90*, 4847.
41. Korpiun O., Mislow K. *J. Am. Chem. Soc*. **1967**, *89*, 4784.
42. Lewis R. A., Mislow K. *J. Am. Chem. Soc*. **1969**, *91*, 7009.
43. Lewis R. A., Naumann K., De Bruin K. E., Mislow K. *J. Chem. Soc., Chem. Commun.* **1969**, 1010.
44. (a) Mikolajczyk M., Omelanczuk J., Perlikovska V. *Tetrahedron* **1979**, *35*, 1531. (b) Mikolajczyk M., Drabowicz J., Omelanczuk J., Fluck E. *J. Chem. Soc., Chem. Commun.* **1975**, 382.

45. (a) Chodkiewicz W., Guilerm D. *Tetrahedron Lett*. **1979**, 3573. (b) Chodkiewicz W., Jore D., Wodski W. *Tetrahedron Lett*. **1979**, 1069.
46. Chodkiewicz W. *J. Organomet. Chem*. **1984**, *173*, C55.
47. (a) Kolodiazhnyi O. I., Grishkun E. V. *Tetrahedron: Asymmetry* **1996**, *7*, 967. (b) Kolodiazhnyi O. I., Ustenko S. N., Grishkun E. V., Golovatyi O. R. Abstract of Lectures of XIII Int. Conf. on Phosphorus Chem., Jerusalem, 1995, p. 34. (c) Kolodiazhnyi O. I., Grishkun E. V., Golovatyi I. R. *Zh. Obshch. Khim*. **1995**, *65*, 1214.
48. Kolodiazhnyi O. I., Grishkun E. V. *Phosph., Sulf. and Silicon* **1996**, *115*, 115.
49. Kolodiazhnyi O. I. Theses of Symp. on Organic Chemistry, St Petersbourg, May 16–20, 1995, p. 137.
50. Kolodiazhnyi O. I. *Zh. Obshch. Khim*. **1995**, *65*, 1926.
51. Juge S., Genet J. P. *Tetrahedron Lett*. **1989**, *30*, 2783.
52. Kolodiazhnyi O. I., Grishkun E. V., Golovatyi O. R., Ustenko S. N. *Phosph., Sulf. and Silicon* **1995**, *103*, 183.
53. Kolodiazhnyi O. I., Grishkun E. V., Golovatyi O. R., Ustenko S. N. *Phosph., Sulf. and Silicon* **1996**, *109/110*, 485.
54. Uznanski B., Grazkowski A., Krzyzanovska B. *J. Am. Chem. Soc.* **1992**, *114*, 10197.
55. Kolodiazhnyi O. I., Sheiko S., Grishkun E. V. *Zh. Obshch. Khim*., in press.
56. Jacobus J., Mislow K. *J. Chem. Soc., Chem. Commun.* **1968**, 253.
57. Seiferth D., Welch D. E., Heeren J. K. *J. Am. Chem. Soc*. **1964**, *86*, 1100.
58. Horner L., Jordan M. *Phosphorus and Sulfur* **1980**, *8*, 225.
59. Yamamoto K., Tomita A., Tsui J. *Chem. Lett*. **1978**, 3.
60. Neuffer J., Richter W. J. *J. Organomet. Chem*. **1986**, *301*, 289.
61. Pabel M., Willis A. C., Wild S. B. *Tetrahedron: Asymmetry* **1995**, *6*, 2369.
62. Cordillo B., Garduno C., Guadarrama G., Hernandez J. *J. Org. Chem*. **1995**, *60*, 5180.
63. Burgess K., Ohlmeyer M. J., Whitmire K. H. *Organometallics* **1992**, *11*, 3588.
64. Fisher C., Mosher H. *Tetrahedron. Lett*. **1977**, 2487.
65. King R. B., Bakos J., Hoff C. D., Marco L. *J. Org. Chem*. **1979**, *44*, 3095.
66. Juge S., Stephan M., Achii S., Genet J. P. *Phosphorus and Sulfur* **1990**, *50*, 267.
67. Naylor R. A., Walker B. *J. Chem. Soc., Chem. Commun.* **1975**, 45.
68. Valentine Jr. D., Blount J. F., Toth K. *J. Org. Chem*. **1980**, *45*, 3691.
69. Crisp G. T., Salem G., Stephens F. E., Wild S. B. *J. Chem. Soc., Chem. Commun.* **1987**, 600.
70. Crisp G. T., Salem G., Wild S. B., Stephens F. S. *Organometallics* **1989**, *8*, 2360.
71. Pietrushiewicz K. M., Wieczorek W., Cichi S., Brandi A. *Heteroat. Chem.* **1991**, *2*, 661.
72. Bader A., Salem G., Willis A. C., Wild S. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1227.
73. Atherton F. R., Hassal C. H., Lambert R. W. *J. Med Chem*. **1986**, *29*, 29.
74. Denmark S. E., Amburgey J. *J. Am. Chem. Soc.* **1993**, *115*, 10386.
75. Atherton F. R., Hall M. J., Hassal C. H., Lambert R. W., Lloid Ringrose W. J. P. S. *Antimicrob. Agents Chemother*. **1979**, *15*, 696.
76. Nagel U., Krink T. *Chem. Ber*. **1993**, *126*, 1091.
77. Nagel U., Rieger B. *Chem. Ber*. **1988**, *121*, 1123.
78. Nagel U., Bublewitz A. *Chem. Ber*. **1992**, *126*, 1061.
79. Nagel U., Rieger B., Bublewitz A. *J. Organomet. Chem*. **1989**, *370*, 223.
80. Juge S., Stephan M., Merdes R., Genet J. P., Halut-Desportes S. *J. Chem. Soc., Chem. Commun.* **1993**, 531.
81. Juge S., Stephan M., Laffitte J. A., Genet J. P. *Tetrahedron Lett*. **1990**, *31*, 6357.
82. Juge S., Uziel J., Riegel N., Aka B. *Tetrahedron Lett*. **1997**, *38*, 3405.
83. (a) Imamoto T., Kusumoto Y., Suzuki N., Sato K. *J. Am. Chem. Soc*. **1985**, *107*, 5301. (b) Imamoto, T., Oshiki T. *Bull. Chem. Soc. Jpn* **1990**, *63*, 3719.
84. Imamoto T., Oshiki, T., Onazawa T., Kusumoto Y., Sato K. *J. Am. Chem. Soc*. **1990**, *112*, 5244.
85. (a) Marinetti A., Ricard L. *Tetrahedron* **1993**, *49*, 10291. (b) Marinetti A., Buzin F.-X., Ricard L. *Tetrahedron* **1997**, *53*, 4627.
86. Marinetti A., Ricard L *Organometallics* **1994**, *13*, 3956.
87. Hall C. R., Inch T. D. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2368.
88. (a) Hall C. R., Inch T. D. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1104. (b) Hall C. R., Inch T. D. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1646.
89. Hall C. R., Inch T. D. *Tetrahedron Lett*. **1976**, 3645.
90. Cooper D. B., Hall C. R., Inch T. D. *Tetrahedron Lett*. **1974**, 2697.
91. (a) Brown J. M., Carey J. V., Russell M. J. H. *Tetrahedron* **1990**, *46*, 4877. (b) Iyer R. P., Regan J. B., Egan, W., Beaucage S. L. *J. Am. Chem. Soc*. **1990**, *112*, 1253.

92. Huong Y., Arif A. M., Bentrude W. G. *J. Org. Chem.* **1993**, *58*, 6235.
93. Sum V., Kee T. P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1778.
94. (a) Sum V., Kee T. P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2701. (b) Polniazek R. P., Foster A. L. *J. Org. Chem*. **1991**, *56*, 3137.
95. Gordon N. J., Evans Jr. S. A. *J. Org. Chem*. **1993**, 58, 5295.
96. (a) Whitsell J. K. *Chem. Rev*. **1989**, *89*, 1581. (b) Wozniak L., Choinowski J. *Tetrahedron* **1989**, *45*, 2465.
97. Brunner H. In *Topics in Stereochemistry*, ed. E. L. Eliel, S. H. Wilen; John Wiley, New York, 1988, Vol. 18, pp. 129–248.
98. (a) Hanessian S., Delorme D., Beaudoin S., Leblanc Y. *J. Am. Chem. Soc*. **1984**, *106*, 5754. (b) Alexakis A., Mutti S., Mangeney P. *J. Org. Chem.* **1992**, *57*, 1224.
99. (a) Alexakis A., Frutos J. C., Mutti S., Mangeney P. *J. Org. Chem.* **1994**, *59*, 3326. (b) Seebach D., Hayakawa M., Sakaki J., Schweizer W. B. *Tetrahedron* **1993**, *49*, 1711. (c) Alexakis A., Mutti S., Normand J. F., Mangeney P. *Tetrahedron: Asymmetry* **1990**, *1*, 437.
100. Gladiali, S., Fabbri, D. *Chem. Ber*. **1997**, *130*, 543.
101. Dore A., Fabbri S., Gladiali S., De Lucchi O. *J. Chem. Soc., Chem. Commun*. **1993**, 1124.
102. Pastor S. D., Shum S. P., Rodebaugh R. K., Debellis A. D., Clarke F. H. *Helv. Chim. Acta*. **1993**, *76*, 900.
103. Buisman G. J. H., Martin M. E., Vos E. J., Klootwijk A., Kamer P. C. J., van Legwen P. W. N. M. *Tetrahedron: Asymmetry* **1995**, *6*, 719.
104. Cooper D. B., Inch T. D., Lewis G. J. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1043.
105. Pickersgill F., Devitt P. G., Kee T. P. *Synth. Commun*. **1993**, *23*, 1643.
106. Brunel J.-M., Pardigon O., Maffei M., Buono G. *Tetrahedron: Asymmetry* **1992**, *3*, 1243.
107. Denmark S. E., Rivera J. *J. Org. Chem*. **1994**, *59*, 6887.
108. Narasaka K., Hidai E., Hayashi Y., Gras J. L. *J. Chem. Soc., Chem. Commun*. **1993**, 102.
109. Fabbri D., Gladiali S., De Lucchi O. *Synth. Commun*. **1994**, *24*, 1271.
110. Baker M. J., Pringle P. G. *J. Chem. Soc., Chem. Commun.* **1993**, 314.
111. (a) Kolodiazhnyi O. I., Grishkun E. V. *Zh. Obshch. Khim.*, in press. (b) Brunel J.-M, Faure B. *Tetrahedron: Asymmetry* **1995**, *6*, 2353. (c) Bodalsky R., Koszuk J. *Phosph., Sulf. and Silicon* **1989**, *44*, 87.
112. McEwen W. E., Kumli K. F., Blade-Font A., Zanger M., Vanderwerf C. A. *J. Am. Chem. Soc*. **1964**, *86*, 2378.
113. McEwen W. E., Blade-Font A., Vanderwerf C. A. *J. Am. Chem. Soc*. **1962**, *84*, 677
114. (a) De Bruin K. E., Mislow K. *J. Am. Chem. Soc*. **1969**, *91*, 7393. (b) Zon G., De Bruin, K. E., Naumann K., Mislow K. *J. Am. Chem. Soc.* **1969**, *91*, 7023.
115. De Bruin K. E., Petersen D. M. *J. Org. Chem*. **1972**, *37*, 2772.
116. De Bruin K. E., Johnson D. M. *J. Am. Chem. Soc*. **1973**, *95*, 4675.
117. De Bruin K. E., Perrin E. D. *J. Org. Chem*. **1975**, *40*, 1523.
118. De Bruin K. E., Padilla A. G., Campbell M. I. *J. Am. Chem. Soc*. **1973**, *95*, 4681.
119. De'ath N. J., Ellis K., Smith D. J. H., Trippett S. *J. Chem. Soc., Chem. Commun*. **1971**, 714.
120. Tripett S. *Pure Appl. Chem.* **1974**, *40*, 595.
121. (a) Blazis V. J., Koeller K. J., Spilling S. D. *J. Org. Chem*. **1995**, *60*, 931. (b) Tasz M. K., Gamliel A., Rodriguez O. P., Lane T. M., Cremer S. E., Bennett D. W. *J. Org. Chem*. **1995**, *60*, 6281.
122. Merckling F. A., Ruedl, P. *Tetrahedron Lett*. **1996**, *37*, 2217
123. Thatcher C. R. J., Kluger R. *Adv. Phys. Org. Chem*. **1989**, *25*, 99.
124. Toda F. *Top. Cur. Chem.* **1988**, *149*, 211.
125. Westheimer F. H. *Acc. Chem. Res*. **1968**, *1*, 70.
126. Ganci W., Meier E. J. M., Mercling F. A., Przibille G., Ringeisen U., Ruedl P. *Helv. Chim. Acta* **1997**, *80*, 421.
127. Zon G., Mislow K. *Fortschr. Chem. Forsch*. **1971**, *19*, 61.
128. Benson S. C., Snyder J. K. *Tetrahedron Lett*. **1991**, *32*, 5885.
129. Carey J. V., Barker M. D., Brown J. M., Russell M. J. H. *J. Chem. Soc., Perkin Trans. 1*. **1993**, 831.
130. Koenig M., Klaebe A., Munoz A., Wolf R. *J. Chem. Soc., Dalton Trans*, **1976**, 955.
131. Koizumi T., Yanada R., Takagi H., Hirai H., Yoshii E. *Tetrahedron Lett*. **1981**, *22*, 477; **1981**, *22*, 571.
132. Corey E. J., Chen Z., Tanoury G. J. *J. Am. Chem. Soc*. **1993**, *115*, 1101.
133. Nudelmann A., Cram D. J. *J. Am. Chem. Soc*. **1968**, *90*, 3869.
134. Nudelmann A., Cram D. J. *J. Org. Chem.* **1971**, *36*, 335.
135. Knowles W. S., Sabacky M. J., Vineyard B. D., Weinkauff D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.
136. Vineyard B. D., Knowles W. S., Bachman G. L., Weinkauff D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.
137. Kolodiazhnyi O. I. *Zh. Obshch. Khim*. **1995**, *65*, 1926.

138. Kolodiazhnyi O. I., Grishkun E. V., Otzaluk V. M. *Zh. Obshch. Khim*. **1997**, *67*, 1210.
139. Benabra A., Alcudia A., Khiar N., Fernandez I., Alcudia F. *Tetrahedron: Asymmetry* **1996**, *7*, 3353.
140. Schmidt U., Riedl B., Griesser H., Fitz C. *Synthesis* **1991**, 655.
141. Valentine Jr. D., Scott J. W. *Synthesis* **1978**, 329.
142. Nifant'ev E., Gratshev M. K., Vasianin L. K. *Zh. Obshch. Khim*. **1995**, *65*, 1926.
143. Lopusinski A., Luczak L., Michalski J. *J. Heteroat. Chem*. **1995**, *6*, 365.
144. Wangi M., Liu S. Z., Hu B. F. *J. Org. Chem*. **1995**, *60*, 7364.
145. Hulst R., Zijlstra R. W. J., Feringa R. L., Koen de Vries N., ten Hoeve W., Wynberg H. *Tetrahedron Lett*. **1993**, *34*, 1339.
146. Hamor T. A., Jennings W. B., Lovely C. J., Reeves K. A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 843.
147. (a) Delogu G., Fabbri D., Dettori M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 413. (b) Fabbri D., Delogu G., De Lucchi O. *J. Org. Chem*. **1993**, *58* ,1748.
148. Segi M., Nakamura Y., Nakajima T., Suga S. *Chem. Lett*. **1983**, 913.
149. Kato T., Kobayashi K., Masuda S., Segi M., Nakajima T., Suga S. *Chem. Lett*. **1987**, 1915.
150. Richter W. J. *Chem. Ber*. **1984**, *117*, 2328.
151. Bodalski R., Rutkowska-Olm E., Pietrusiewicz K. M. *Tetrahedron* **1980**, *36*, 2353.
152. Pietrusiewicz K. M., Zablocka M., Monkiewicz J. *J. Org. Chem*. **1984**, *49*, 1522.
153. Pietrusiewicz K. M., Zablocka M. *Tetrahedron Lett*. **1989**, *30*, 477.
154. (a) Pietrusiewicz K. M., Zablocka M. *Tetrahedron Lett*. **1988**, *29*, 937. (b) Pietrusiewicz K. M., Zablocka M. *Tetrahedron Lett*. **1988**, *29*, 1987.
155. Kolodiazhnyi O. I., Grishkun E. V., Neda I., Schmutzler R. *Zh. Obshch. Khim*., in press.
156. Imamoto T., Sato K., Johnson C. R. *Tetrahedron Lett*. **1985**, *26*, 783.
157. Juge S., Wakselman M., Stephan M., Genet J. P. *Tetrahedron Lett*. **1990**, *31*, 4443.
158. Denmark S. E., Chatani N., Pansare S. V. T., *Tetrahedron* **1992**, *48*, 2191.
159. Horner L., Winkler H. *Liebigs Ann. Chem*. **1965**, *685*, 1.
160. Kafarski P., Lejczak B. *Phosph., Sulf. And Silicon* **1991**, *63*, 193.
161. Warren S., Harmat N. J. S. *Tetrahedron Lett*. **1990**, *31*, 2743.
162. Kolodiazhnyi O. I. *Tetrahedron Lett*. **1995**, *36*, 3921.
163. le Bec C., Wickstrom E. *Tetrahedron Lett*. **1994**, *35*, 9525.
164. (a) Cremer S. E., Chorvat R. J., Trivedi B. C. *J. Chem. Soc., Chem. Commun.* **1969**, 769. (b) Cremer S. E., Chorvat R. J. *J. Org. Chem*. **1967**, *32*, 4066.
165. Awerbuch O., Koshman Y. *Tetrahedron* **1975**, *31*, 33.
166. Vilkas E., Vilcas M., Joniaux D., Pascard-Billy C. *J. Chem. Soc., Chem. Commun.* **1978**, 125.
167. Vilkas E., Vilcas M., Sainton J., Meunier B., Pascard C. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2136.
168. Mikolajczyk M., Drabowicz J., Kielbasinski P. *Houben-Weil*, Vol. E21, S. 5701.
169. Kolodiazhnyi O. I., Zemlianoy A. I., Kukhar V. P. *Zh. Obshch. Khim*. **1989**, *59*, 1451.
170. Farnham W. B., Murray Jr. R. K., Mislow K. *J. Chem. Soc., Chem. Commun*. **1971**, 146.
171. Farnham W. B., Murray Jr. R. K., Mislow K. *J. Am. Chem. Soc*. **1970**, *92*, 5809.
172. (a) Herriot A. *J. Am. Chem. Soc*. **1971**, *93*, 3304. (b) Kabachnik M. I., Zakharov L. S., Kudryavtsev I. Yu., Petrovskii P. V., Scherbina T. M., Laretina A. P. *Izv. AN* **1994**, *10*, 1840.
173. Wasiak J., Michalski J. *Tetrahedron Lett*. **1994**, *35*, 9473.
174. Schrader T. *Angew. Chem*. **1995,** *107*, 1001.
175. Johnson C. R., Elliot R. C., Penning T. D. *J. Am. Chem. Soc*. **1984**, *106*, 5019.
176. Gallagher M. J., Ranasinghe M. G., *J. Org. Chem*. **1996**, *61*, 436.
177. Stec W. J., Uznanski B., Bruzik K., Michalski J. *J. Org. Chem*. **1976**, *41*, 1291.
178. Maryanoff B. E., Hutchins R. O., Maryanoff C. A., *Topics in Stereochemistry*; John Wiley & Sons, New York, Vol. 11, p. 187.
179. Mikolajczyk M. *J. Chem. Soc., Chem. Commun*. **1969**, 1221.
180. Mikolajczyk M. *Angew. Chem., Int. Ed. Engl*. **1969**. *8*, 511.
181. Predvotitelev D. A., Afanas'eva D. N., Fillipovich Y. B., Nifant'ev E. E. *Zh. Obshch. Khim*. **1974**, *44*, 1697.
182. Bestmann H. J., Tomoskozi I. *Tetrahedron* **1968**, *24*, 3299.
183. (a) Kolodiazhnyi O. I. *Rus. Chem. Rev. Uspekhi Khimii*. **1997**, *66*, 246. (b) Kolodiazhnyi O. I. *Tetrahedron* **1996**, *52*, 1855. (c) Kolodiazhnyi O. I., Ustenko S. N., Golovatyi O. R. *Tetrahedron Letters* **1994**, *35*, 1755. (d) Kolodiazhnyi O. I., Ustenko S. N. *Zh. Obshch. Khim*. **1993**, *63*, 2149.
184. Stec W. J., Wilk A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 709.

185. Moriguchi T., Wada T., Sekine M. *J. Org. Chem.* **1966**, *61*, 9223.
186. Costick R., Williams D. M. *Nucleic Acids Res*. **1987**, *15*, 9921.
187. Endo M., Komiyama M. *J. Org. Chem*. **1996**, *61*, 1994.
188. le Bec C., Wickstrom E. *J. Org. Chem*. **1996**, *61*, 510.
189. Iyer R. P., Yu D., Ho N.-H., Tan W., Agraval S. *Tetrahedron: Asymmetry* **1995**, *6*, 51.
190. Holmes R. *Chem. Rev*. **1996**, *96*, 927.
191. (a) Carrelhas A. C., Brazier J.-F., Houalla D., Wolf R. *Phosphorus* **1977**, *8*, 61. (b) Klaebe A., Brazier J. F., Carrelas A. C., Garrigues B., Marre M. R. *Tetrahedron* **1982**, *38*, 2111.
192. Moriarty R. M., Hiratake J., Liu K., Wendler A., Awasthi A. K., Gilardi R. *J. Am. Chem. Soc.* **1991**, *113*, 9374.
193. Horner L., Simons G. *Phosphorus and Sulfur* **1984**, *19*, 65.
194. (a) Cavezzan J., Etemad-Moghadam G., Koenig M., Klaebe A. *Tetrahedron Lett*. **1979**, 795. (b) Koenig M., Klaebe A., Munoz A., Wolf R. *J. Chem. Soc., Perkin Trans. 2* **1979**, 40.
195. (a) Kojima S., Nakamoto M., Yamazaki K., Akiba K. *Tetrahedron Lett*. **1997**, *38*, 4107. (b) Greene N., Kee T. P. *Synth. Commun*. **1993**, *23*, 1651.
196. Sum V., Davies A. J., Kee T. P. *J. Chem. Soc., Chem. Commun*. **1992**, 1771.
197. Gordon N. J., Evans Jr. S. A. *J. Org. Chem*. **1993**, *58*, 5293.
198. (a) Sum V., Kee. P., Thornton-Pett M. *J. Chem. Soc., Chem. Commun*. **1994**, 743. (b) Sum V., Patel M. T., Kee T. P., Thornton-Pett M. *Polyhedron* **1992**, *11*, 1743.
199. (a) Blazis V. J., De la Cruz A., Koeller K. J., Spilling C. D. *Phosph., Sulf. and Silicon* **1993**, *75*, 159. (b) Blazis V. J., Koeller K. J., Spilling S. D. *Tetrahedron: Asymmetry* **1994**, *5*, 499.
200. Koeller K. J., Spilling C. D. *Tetrahedron Lett*. **1991**, *32*, 6297.
201. (a) Rath P., Spilling C. D. *Tetrahedron Lett*. **1994**, *35*, 227. (b) Kolodiazhnyi O. I., Grishkun E. V., Sheiko S. *Zh. Obshch. Khim*., in press.
202. de Jonch C. P., Modro T. A. *Phosphorus and Sulfur* **1993**, *79*, 161.
203. Brandi A., Cichi S., Goti A., Pietrusiewicz K. M., Zablocka M., Wisniewski W. *J. Org. Chem*. **1991**, *56*, 4383.
204. (a) Hellwinkel D. *Chem. Ber.*, **1966**, *99*, 3642. (b) Lacour J., Ginglinger C., Grivet C., Bernardinelli G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 608.
205. Brandi A., Cichi S., Goti A., Pietrusiewicz K. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1063.
206. (a) Goti A., Cichi S., Brandi A., Pietruchiewicz K. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1371. (b) Brandi A., Cichi S., Goti A., Koprowski M., Pietrusiewicz K. M. *J. Org. Chem*. **1994**, *59*, 1315.
207. Brandi A., Cichi S., Goti A., Pietrusiewicz K. M., Wisniewski W. *Tetrahedron* **1990**, *46*, 7093.
208. Ahlbrecht H. *Chem. Ber*. **1986**, *117*, 1239.
209. Bennani Y. L., Hanessian S. *Tetrahedron Lett*. **1990**, *31*, 6465.
210. (a) Hanessian S., Bennani Y. L., Delorme D. *Tetrahedron Lett*. **1990**, *31*, 6461. (b) Hanessian S., Delorme D., Beaudoin S., Leblanc Y. *Chem. Scr*. **1985**, *88*, 1419.
211. Schollkopf U. *Lieb. Ann. Chem*. **1987**, 45.
212. Togni A., Pastor A. *Tetrahedron Lett.* **1989**, *30*, 1071.
213. (a) Cramer C. J., Denmark S. E., Miller P. C., Dorow R. L., Swiss K. A., Wilson S. R. *J. Am. Chem. Soc*. **1994**, *116*, 2437. (b) Denmark S. E., Cramer C. J. *J. Org. Chem*. **1990**, *55*, 1806. (c) Denmark S. E., Marlin J. E. *J. Org. Chem.* **1987**, *52*, 5742.
214. Denmark S. E., Chen C. T. *J. Am. Chem. Soc.* **1992**, *114*, 10674.
215. Denmark S. E., Dorow R. C. *J. Org. Chem.* **1990**, *55*, 5926.
216. Denmark S. E., Marlin J. E. *J. Org. Chem.* **1991**, *56*, 1003.
217. Denmark S. E., Miller P. C., Wilson S. R. *J. Am. Chem. Soc*. **1991**, *113*, 1468.
218. Denmark S. E., Stadler H., Dorow R. L., Kim J. H. *J. Org. Chem*. **1991**, *56*, 5063.
219. Denmark S. E., Rajendra G., Marlin J. E. *Tetrahedron Lett*. **1989**, *30*, 2469.
220. Denmark S. E., Dorow L. R. *J. Org. Chem*. **1990**, *55*, 1806.
221. Denmark S. E., Dorow R. L. *J. Am. Chem. Soc*. **1990**, *112*, 864.
222. Denmark E. S., Swiss K. A., Wilson S. R. *J. Am. Chem. Soc*, **1993**, *115*, 3826.
223. Aggarval V. K. *Angew. Chem*. **1994**, *33*, 175.
224. Pagliarin R., Papeo G., Sello G., Sisti M., Paleari I. *Tetrahedron* **1996**, *52*, 13783.
225. Barlett P. A., Jacobsen N. E. *J. Am. Chem. Soc*. **1981**, *103*, 654.
226. Barlett P. A., Kezer W. B. *J. Am. Chem. Soc*. **1984**, *106*, 4282.
227. Barlett P. A., Giannousis P. P. *J. Med. Chem*. **1987**, *32*, 119.

228. Boutin J. A., Cudennec C. A., Hautefaye P., Lavielle G., Pierre A., Schaeffer C. *J. Med. Chem*. **1991**, *34*, 1998.
229. Cassaigne A., Neuzel E. *Exp. Ann. Biochim. Med*. **1980**, *34*, 165.
230. Hilderbrand R. L. *The Role of Phosphonates in Living Systems*; CRC Press, Boca Raton, FL, 1984.
231. (a) Bennani Y. L., Delorme D., Hanessian S. *Tetrahedron Lett*. **1990**, *31*, 6461. (b) Bongini A., Camerini R., Pamenzio H. *Tetrahedron: Asymmetry* **1996**, *37*, 1467.
232. Hanessian S., Bennani Y. L., Herve Y. *Synlett* **1993**, *1*, 35.
233. Maffre D., Dumi P., Vidal J.-P., Escale P., Girard J.-P. *J. Chem. Res., Synop*. **1994**, 30.
234. Denmark S. E., Chen C. T. *J. Org. Chem*. **1994**, *59*, 2922.
235. Hanessian S., Beaudoin S. *Tetrahedron Lett*. **1992**, *33*, 7655.
236. Hanessian S., Gomtsyan A., Payne A., Herve Y., Beaudoin S. *J. Org. Chem*. **1993**, *58*, 5032.
237. Denmark S. E., Kim J. H. *J. Org. Chem*. **1995**, *60*, 7535.
238. Hanessian S., Gomstyan A. *Tetrahedron Lett*. **1994**, *35*, 7509.
239. Abel A. D., Hoult D. H., Morris R. M. *J. Org. Chem.* **1993**, *58*, 1531.
240. Reissig H.-U. *Angew. Chem., Int. Ed. Engl*. **1996,** *35*, 971.
241. Hanessian S., Andreotti D., Gomstyan A. *J. Am. Chem. Soc*. **1995**, *117*, 10393.
242. Hanessian S., Cantin L. D., Roy S., Andreotti D., Gomstyan A. *Tetrahedron Lett*. **1997**, *38*, 1103.
243. Haynes R. K., Stokes J. P., Hambley T. W. *J. Chem. Soc., Chem. Commun.* **1991**, 58.
244. Haynes R. K., Freeman R. N., Mitchell C. R., Vonwiller S. C. *J. Org. Chem*. **1994**, *59*, 2919.
245. Nakai T., Tomooka K. *Pure Appl. Chem*. **1997**, *68*, 595.
246. Denmark S. E., Miller P. R. *Tetrahedron. Lett*. **1995**, *6*, 6631.
247. Gulea-Purcarescu M., About-Jaudet E., Collignon N. *Tetrahedron Lett*. **1995**, *36*, 6635.
248. Gais H. E., Schmidl G., Ball W. A., Bund J., Hellmann G., Erdelmeier J. *Tetrahedron Lett*. **1988**, *29*, 1773.
249. Rehwinkel H., Skupsch J., Vorbruggen H. *Tetrahedron Lett*. **1988**, *29*, 1775.
250. Bestmann H. J., Heid E., Ryschka W., Lienert J. *Lieb. Ann. Chem.* **1974**, *1684*.
251. Bestmann H. J., Lienert J. *Chem. Ztg*. **1970**, *94*, 487.
252. Koizumi T., Takahashi T., Matsui M., Maeno N. *Heterocycles* **1990**, *30*, 353.
253. Mussierowicz S., Wroblewsli A. E. *Tetrahedron* **1980**, *96*, 1373.
254. Mussierowicz S., Wroblewsli A. E., Krawczyk K. K. *Tetrahedron Lett*. **1975**, 437.
255. (a) Rein T., Reiser O. *Acta Chem. Scand.* **1996**, *50*, 369. (b) Rein T., Anvelt J., Soone A., Kreuder R., Wulff C., Reiser O. *Tetrahedron Lett.* **1995**, *33*, 7655.
256. Toda F., Akai H. *J. Org. Chem*. **1990**, *55*, 3446.
257. Trost B. M., Curran D. P. *J. Am. Chem. Soc*. **1980**, *102*, 5699.
258. Trost B. M., Curran D. P. *Tetrahedron Lett*. **1981**, *22*, 4929.
259. Kolodiazhnyi O. I. *Phosphorus Ylides Chemistry*; Naukova Dumka, Kiev, 1994, pp. 1–560.
260. Bestmann H. J., Lienert J. *Angew. Chem., Int. Ed. Engl*. **1969**, *8*, 763.
261. Hellwinkel D. In *Organic Phosphorus Compounds*, Vol. 3, ed. Kosolapoff G. M., Maier L.; Wiley, New York, 1973, p. 185.
262. Tomoskozi I., Bestmann H. J. *Tetrahedron Lett*. **1964**, 1293.
263. Gais H.-J., Bulow G. *Tetrahedron Lett*. **1992**, *33*, 461.
264. Gais H.-J., Bulow G. *Tetrahedron Lett*. **1992**, *33*, 465.
265. Bestmann H. J. *Pure Appl. Chem.* **1980**, *52*, 771.
266. Hanessian S., Beaudoin S. *Tetrahedron Lett*. **1992**, *33*, 7659.
267. Hanessian S., Bennani Y. L. *Tetrahedron Lett*. **1990**, *31*, 6465.
268. Johnson C. R., Elliot R. C., Meanwell N. A. *Tetrahedron Lett*. **1982**, *23*, 5005.
269. Koshiwabara K., Hanaki K, Fujita J. *Bull. Chem. Soc. Jpn* **1980**, *53*, 2275.
270. (a) Lemieux R. P., Schuster G. B. *J. Org. Chem*. **1993**, *58*, 100. (b) Bartoli G., Marcantoni E., Sambri L., Tamburini M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2046.
271. Hayasi T., Konishi H., Ito H., Kumada M. *J. Org. Chem*. **1987**, *51*, 3772.
272. Noyori R., Ikeda T., Ohkuma T. *J. Am. Chem. Soc*. **1989**, *111*, 9134.
273. Tanaka K., Ohta Y., Fuji K., Taga T. *Tetrahedron Lett*. **1993**, *34*, 4071.
274. Harmat N. J. S., Warren S. *Tetrahedron Lett*. **1990**, *31*, 2743.