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Stereochemistry, mechanisms and applications of electrophilic reactions of organophosphorus compounds

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The review summarizes and systimatizes data on the stereochemistry, mechanisms and applications of electrophilic reactions of organophosphorus compounds. Asymmetric versions of the Michaelis – Arbuzov, Michaelis – Becker, Hirao, Staudinger, Pudovik and other reactions are considered. Key issues of asymmetric electrophilic catalysis are discussed. The reaction conditions, catalytic systems and structures of the reaction products are presented. Asymmetric electrophilic reactions are used in organic synthesis and in studies of the mechanisms of chemical processes involving organophosphorus compounds. The bibliography includes 209 references.

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1. Introduction

Electrophilic reactions play an important role in the chemistry of trivalent phosphorus compounds.[1–3] For example, the Michaelis – Arbuzov, Staudinger, Atherton – Todd, Appel, Pudovik, phospha-Mannich reactions and phospha-aldol condensation begin with the electrophilic attack on the phosphorus atom, which is the site of the highest electron density.[3–5] Electrophilic reactions are used to synthesize products of practical value, such as phosphine ligands and pharmaceutical agents, and substances for agricultural purposes.[4–6]

Of special interest are asymmetric reactions involving chiral reagents, in particular, asymmetric electrophilic catalysis, which provide a route to chiral compounds that are difficult to synthesize by other methods. In this regard, asymmetric electrophilic reactions have attracted increasing attention of synthetic chemists. According to the guidelines of the US Food and Drug Administration (FDA), all pharmaceuticals, agrochemicals, food additives, *etc.* should

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be applied and patented in enantiopure form. Many commercial chiral ligands, trivalent phosphorus derivatives (DIOP, DuPhos, PAMP, DIPAMP) and catalysts based on these compounds were synthesized by electrophilic alkylation, arylation, *etc*. reactions. The Staudinger ligation, which can occur directly in living cells, is of paramount importance for biological chemistry. Of great interest are electrophilic reactions of phosphorus compounds with a positively charged halogen atom (Appel, Atherton – Todd, Corey – Fuchs, *etc*. reactions), which are commonly used in the synthesis of natural compounds and their analogues.

Electrophilic reactions are characterized by high stereospecificity and proceed with retention of the absolute configuration at the chiral phosphorus. This is the difference from nucleophilic $S_N2(P)$ reactions, which generally occur with inversion of configuration. This distinguishing feature of electrophilic $S_E2(P)$ reactions provides a powerful tool for studying the mechanisms of organophosphorus processes. The stereospecificity of electrophilic reaction is essential for highly complicated syntheses of natural compounds, in which chiral organophosphorus reagents are being increasingly used. Hence, an analysis and systematic review of stereospecific electrophilic reactions are of great theoretical and applied importance.

Despite a large body of publications on classical examples of electrophilic transformations involving the phosphorus atom, a systematic review of the stereochemistry of electrophilic reactions is still lacking. In 1968, Warren [6] published a paper, where he considered some electrophilic reactions of organophosphorus compounds known at that time; however, the stereochemistry and chirality were not discussed. Consequently, there is a need to draw general conclusions on the stereochemistry and mechanisms of electrophilic reactions. This review discusses issues concerning the stereochemistry, mechanisms and applications of electrophilic reactions involving chiral phosphorus compounds.

The following abbreviations and designations are used in the review:

Ad — 1-adamantyl,
AIBN — azobis(isobutyronitrile),
o-An — *o*-anisyl (2-methoxyphenyl),
ARCM — asymmetric ring-closing metathesis,
B — base,
BINAP — 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl,
Boc — *tert*-butoxycarbonyl,
Cat — catalyst,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
dba — dibenzylideneacetone,
de — diastereomeric excess,
DIOP — 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane,
DIPAMP — 1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane,
DIPE — diisopropyl ether,
DIPEA — diisopropylethylamine,
DMAP — 4-dimethylaminopyridine,
DME — dimethoxyethane,
dmpe — 1,2-bis(dimethylphosphino)ethane,
DMT — 4,4′-dimethoxytrityl,
dppf — 1,1′-bis(diphenylphosphino)ferrocene,
DPTA — diisopropyl tartrate,
dr — diastereomeric ratio,
E — electrophile,
EA — elimination – addition,
ee — enantiomeric excess,
er — enantiomeric ratio,
es — enantiospecificity;
Fc — ferrocenyl,
Fu — furyl,
HBPin — 4,4,5,5-tetramethyl-1,3,2-dioxaborolane,
Inversion — inversion of the absolute configuration,
Ips — 2,4,6-triisopropylphenyl,
LDBB — lithium 4,4′-di-*tert*-butylbiphenylide,
L — ligand,
L* — chiral ligand,
LDA — lithium diethylamide,
Mes — mesityl (2,4,6-trimethylphenyl),
Mnt — (1*R*,2*S*,5*R*)-menthyl,
MTBE — methyl *tert*-butyl ether,
Naph — naphthyl,
NCS — *N*-chlorosuccinimide,
Ni-Ra — Raney nickel,
NMM — *N*-methylmorpholine,
PAMPOP — 4,5-bis[di(*o*-anisyl)phosphinomethyl]-2,2-dimethyl-1,3-dioxolane,
Phnt — phenanthryl,
PTC — phase-transfer catalysis,
Py — pyridyl,
QuinoxP — 2,3-bis(*tert*-butylmethylphosphino)quinoxaline,
rac — racemate,
Retention — retention of the absolute configuration,
rt — room temperature,
S_E2 — bimolecular electrophilic substitution,
S_N2 — bimolecular nucleophilic substitution,
TADDOL — α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol,
TBDMS — *tert*-butyldimethylsilyl,
TC — transition complex,
TEMPO — (2,2,6,6-tetramethylpiperidin-1-yl)oxyl,
Tf — trifluoromethanesulfonyl,
TFA — trifluoroacetic acid,
TMEDA — tetramethylethylenediamine,
TMS — trimethylsilyl,
Tol — tolyl,
Ts — 4-toluenesulfonyl (tosyl),
TS — transition state,
m-Xyl — *m*-xylyl (3,5-dimethylphenyl),
US — ultrasound.

2. Alkylation and arylation

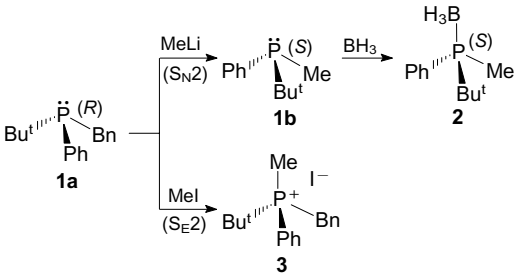
2.1. Electrophilic alkylation and arylation reactions

Electrophilic substitution reactions $S_E(P)$ are common and highly important transformations of trivalent phosphorus compounds. An electrophilic reaction is a reaction in which a phosphorus-containing substrate is initially attacked by an electrophile. In electrophilic substitution reactions, the leaving group of the substrate is removed without bonding electrons, and the vacant orbital of the electrophilic reagent accepts electrons, resulting in the formation of a new bond. Lewis acids are the most reactive electrophiles. Generally, electrophilic substitution reactions $S_E2(P)$ include the following two steps: the addition of an electrophile and the elimination of an electrofuge. In some cases, the reaction stops at the first step giving a stable phosphonium cation. The electrophile providing a vacant orbital to the substrate attacks the phosphorus reaction centre from the front side, where a lone pair is located. In most of $S_E(P)$ reactions, the

first step is rate-determining. Most often, electrophilic reactions of P^{III} compounds occur *via* addition–elimination, *i.e.*, the electrophile first adds to the phosphorus atom giving a positively charged intermediate followed by the removal of the leaving group.

In organic chemistry, a nucleophile and an electrophile are generally considered as attacking species for aliphatic and aromatic compounds, respectively. Electrophilic reactions of organophosphorus compounds proceed through the formation of a positively charged phosphonium intermediate, occur with retention of the absolute configuration at the phosphorus atom and involve a P^{III} compound as the substrate and an electrophile as the attacking reagent, which allows the consideration of the electrophilic attack on the phosphorus nucleophile. It should be noted that electrophilic reactions of P^{III} compounds, $S_E2(P)$, are similar to electrophilic substitution reactions of aromatic compounds, $S_E2(Ar)$, in that both types of reactions include two steps and proceed through the formation of a positively charged arenium intermediate. Trivalent phosphorus compounds can act as both electrophiles and nucleophiles. For example, both nucleophilic and electrophilic reactions of tertiary phosphine **1a** readily occur to form products **1b** and **2** or product **3**, respectively (Scheme 1).[4,5]

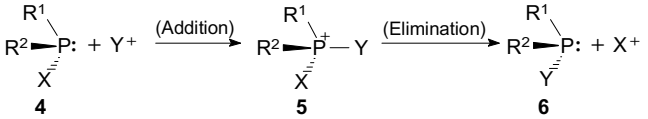
Scheme 1



In S_E2 reactions, the positively charged electrophile Y^+ interacts with the electron-rich phosphorus reaction centre of compound **4** from the front side, attracting the lone pair and forming a new P–Y bond. This gives rise to positively charged intermediate **5** with retention of the absolute configuration. The latter can be transformed into compound **6** or remain as a phosphonium salt (Scheme 2). For example, the reaction of tertiary phosphines **7** with borane leads to the formation of the additive bond, resulting in pyramidalization of the borane moiety to produce an approximately tetrahedral geometry, with a change in hybridization at boron from sp^2 to sp^3. Metal-substituted intermediate **8**, generated in the reaction of phosphine borane **9** with AlkM, is a trivalent phosphorus compound, which reacts stereospecifically with an electrophile. Both these pathways afford product **10** with retention of the absolute configuration at the phosphorus atom (Scheme 3).[5,6]

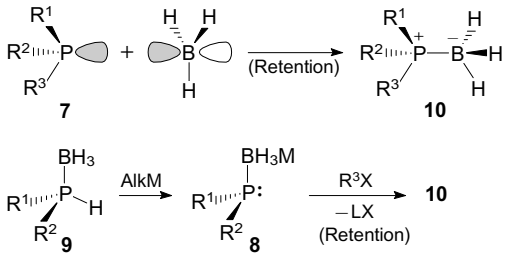
Therefore, as opposed to bimolecular nucleophilic reactions, which generally proceed with inversion of the chiral

Scheme 2



Here and below, unless otherwise indicated, R^n = Alk, Ar, OAlk, *etc.*

Scheme 3



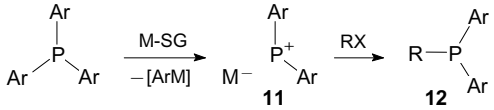
R^3X = AlkCl, AlkBr, AlkTs, *etc.*; M = Li, Na;
Ts is *p*-toluenesulfonyl (tosyl)

centre due to the orientation of bonding orbitals and electron pairs, the electrophilic substitution generally occurs with retention of the absolute configuration. An electrophile having a vacant orbital attacks the phosphorus centre from the front side, where the lone pair is located. This leads to electron density redistribution and the formation of a new bond without changing the arrangement of substituents at the phosphorus centre, *i.e.*, with retention of the absolute configuration, as shown in Scheme 2.

2.2. Alkylation and arylation of secondary phosphines

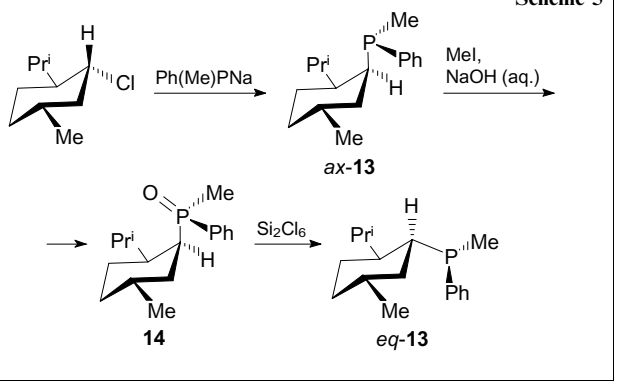
The alkylation and arylation of chiral tertiary phosphines are generally stereospecific and occur with retention of the absolute configuration at the phosphorus atom. The alkylation or arylation of metal phosphides provides a convenient route to tertiary phosphines.[5–9] Initial metal phosphides **11** can easily be prepared *via* a C–P bond cleavage of tri- and diarylphosphines with various reagents, such as alkali metals in mineral oil, sodium in liquid ammonia, sodium naphthalenide, sodium suspended in THF, sodium or potassium adsorbed on silica gel (M-SG reagent), and by other methods (Scheme 4).[8] Metal phosphides thus synthesized can be used as synthetic blocks for the preparation of various tertiary phosphines **12**. For example, menthyl(methylphenyl)phosphine *eq*-**13** was synthesized by the alkylation of neomenthyl(methylphenyl)-phosphine *ax*-**13** followed by the reduction of phosphine oxide **14** (Scheme 5).[10–15] The reaction of sodium methylphenylphosphide with (+)-(*R*)-1-chloroethylbenzene

Scheme 4

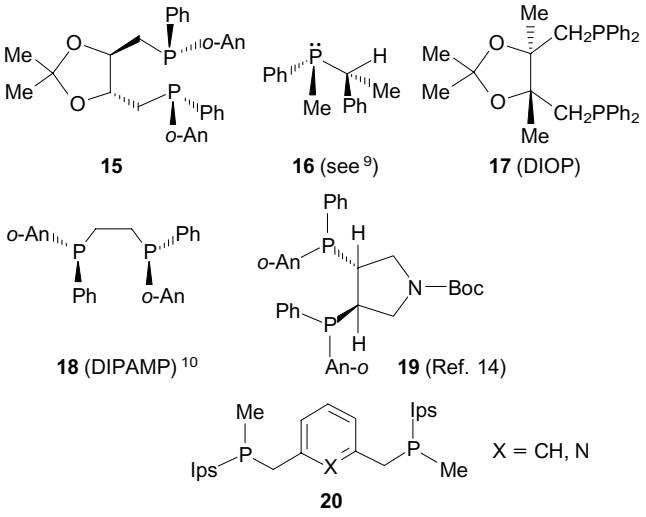


M = Li, Na

Scheme 5



Structures 15 – 20

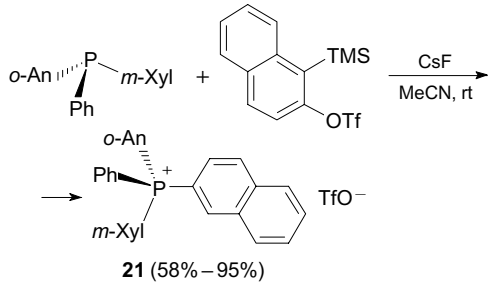


o-An is *o*-anisyl (2-methoxyphenyl), Boc is *tert*-butoxycarbonyl, Ips is 2,4,6-triisopropylphenyl, DIOP is 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, DIPAMP is 1,2-bis[(*o*-anisyl)phenylphosphino]ethane

afforded, after the oxidation, (−)-(S_P,S_C)-phosphine oxide with an enantiomeric excess (*ee*) of 25%.[9] This method was used to synthesize phosphine ligands **15** – **20**, including bisphosphines (4,5-bis[di(*o*-anisyl)phosphinomethyl)-2,2-dimethyl-1,3-dioxolane, PAMPOP), **17** (DIOP), **18** (DIPAMP), *etc*.[13,14] Some bisphosphines are applied in the chemical industry to perform catalytic asymmetric hydrogenation.[2,5,7] The alkylation and arylation of chiral tertiary phosphines afford chiral phosphonium salts, which have various applications in practice: as chiral phase-transfer catalysts, organocatalysts, ligands and chiral reagents.[9,16–18]

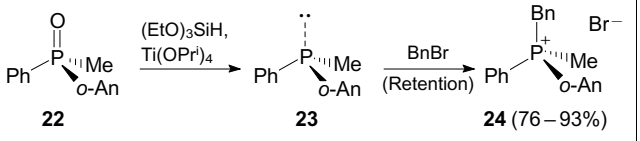
A method was developed for the synthesis of chiral phosphonium salts (*e.g.*, salt **21**) by the quaternization of the corresponding phosphine with arenes generated *in situ* from 2-(trimethylsilyl)aryl triflates (Scheme 6). Chiral phosphonium salts were synthesized from P-stereogenic phosphines. For example, compound **23** derived from phosphine oxide **22** gives salt **24** (Scheme 7). Phosphonium salts **25** – **27** were synthesized in a similar way. The reactions were stereospecific and occurred with retention of the absolute configuration at the P reaction centre and with high product yields.[16–20]

Scheme 6

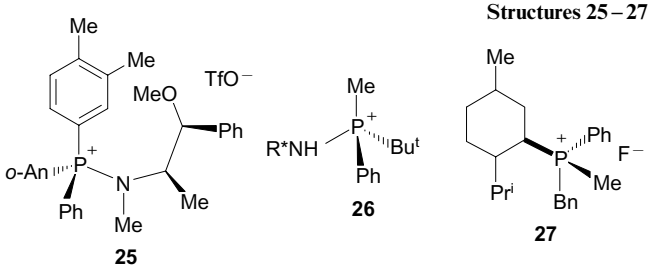


m-Xyl is *m*-xylyl (3,5-dimethylphenyl), TMS is trimethylsilyl, Tf is trifluoromethanesulfonyl (triflyl)

Scheme 7



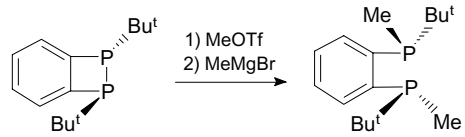
Structures 25 – 27



R* = (*S*)- or (*R*)-CH(Pr^i)CO_2Me

The successive electrophilic alkylation of benzodiphosphetane **28** with methyl triflate and nucleophilic alkylation with methylmagnesium bromide afford a symmetric P-stereogenic bisphosphine ligand. Benzodiphosphetane **28** is configurationally stable and does not undergo racemization when heated in toluene to 105 °C for 18 h. The formation of the C_2-symmetric P-stereogenic ligand BenzP* (**29**) is stereospecific and occurs with a diastereomeric excess (*de*) > 90% (Scheme 8).[21]

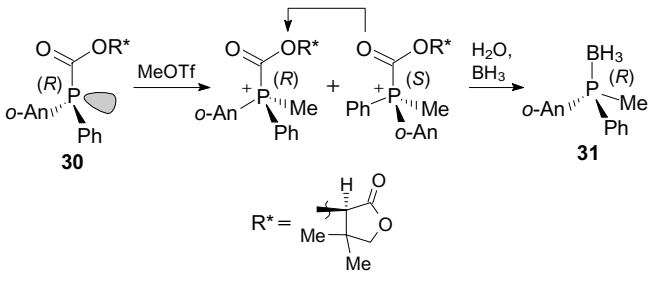
Scheme 8



er is enantiomeric ratio

Interesting observations were made in studying the P-alkylation of alkoxycarbonylphosphine **30** with methyl triflate.[22,23] This alkylation reaction in dichloromethane in the temperature range from −78 to 20 °C followed by hydrolysis of intermediate alkoxycarbonylphosphonium gave tertiary phosphine **31** as a mixture of (R_P)- and (S_P)-diastereomers with a low *de* value. However, stereoselective dynamic crystallization of the resulting mixture of diastereomers from ethanol at room temperature made it possible to enrich the mixture with one diastereomer. The diastereomeric ratio (*dr*) changed from 25 : 1 at room temperature to

Scheme 9



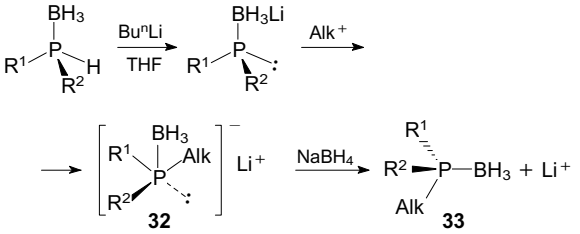
91 : 1 on heating to 50 °C for 22 h. After the removal of the BH_3 group, product **31** was transformed into the (*o*-anisyl)-methylphenylphosphine ligand (PAMP) with an enantiomeric purity of 99.5% *ee* in 74% yield (Scheme 9).[22,23]

2.3. Alkylation and arylation of phosphine boranes

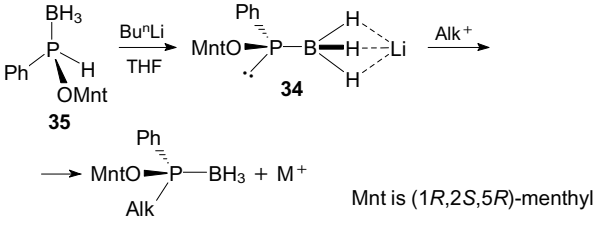
Phosphine boranes comprise an important class of organophosphorus compounds due to their high reactivity and extensive use in organic synthesis.[24,25] These compounds can be employed as precursors of chiral tertiary phosphines. Phosphine boranes readily form lithium or sodium derivatives, which undergo electrophilic substitution at the phosphorus atoms when treated with appropriate electrophiles (Scheme 10). Alkylation reactions generally proceed with retention of the absolute configuration, which indicates that the electrophile attacks the electron-rich phosphorus atom from the front side. Apparently, the reaction proceeds *via* the formation of unstable five-coordinate transition state **32**, which its stabilized through removal of an electrofuge (Li^+) giving final substitution product **33**. Phosphine boranes are Lewis acid – base complexes that are formed *via* an interaction between the phosphorus lone pair and the unoccupied molecular orbital of boron. In solution, lithium is coordinated by hydride ions of the BH_3 group in a η^3 fashion, as demonstrated in relation to structure **34** derived from complex **35** (Scheme 11).[26] Generally, phosphine boranes are quite easily available compounds, which are widely used in practice. A convenient procedure for their synthesis is based on the reduction of secondary phosphine oxides.[26–30] Phosphine boranes are configurationally stable and do not undergo racemization at room temperature, although racemization is sometimes observed at elevated temperature. Experimental studies showed that the racemization occurs *via* the pyramidal inversion mechanism (Scheme 12).[31–34]

A conventional method for the synthesis of tertiary phosphines involves the electrophilic substitution of phosphide anions with alkyl halides derived from phosphine borane complexes. Livinghouse and co-workers[35,36] developed a procedure for the enantioselective synthesis of chiral tertiary phosphine boranes from racemic secondary phosphine borane **36**.[35,36] Compound **37** was prepared by the deprotonation of phosphine borane **36** in the presence of (−)-sparteine. The subsequent alkylation of phosphide **37** was performed with high enantiocontrol *via* dynamic resolution. The predominant formation of a single enantiomer was accomplished *via* thermodynamic resolution induced by sparteine. The stirring of the suspended (−)-sparteine lithium complex at 25 °C for 1 h led to an increase in the optical purity of alkylation product **38** from 40% *ee* to 82% – 95% *ee* (Scheme 13).

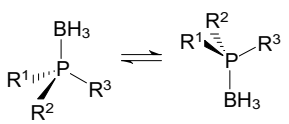
Scheme 10



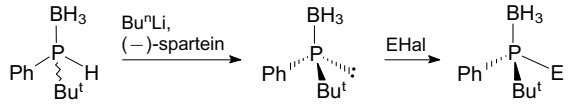
Scheme 11

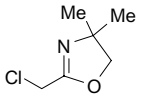
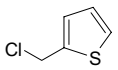
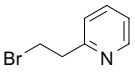


Scheme 12



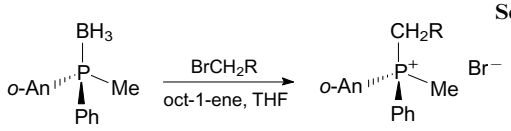
Scheme 13



EHal	Yield (%)	*ee* (%)
	90	82
	85	95
	90	92

Phosphine borane complexes react with alkyl(aryl) halides under mild conditions in the presence of alkene to form quaternary phosphonium salts. Thus, the reaction of the complex (*R*)-PAMP·BH_3 (**31**) with alkyl bromides affords enantiomerically pure phosphonium salts **24** and **39** with retention of configuration at the P reaction centre (Scheme 14).[37]

Scheme 14

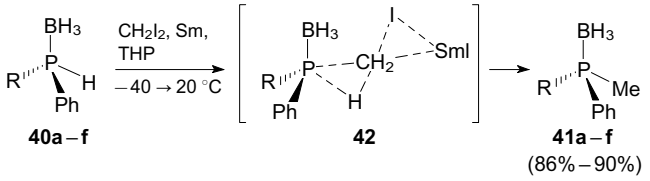


R = Ph (**24**), CN (**39**)

The samarium carbenoid, derived from diiodomethane and samarium, reacted with secondary phosphine boranes **40a**–**f** to give P-methylated tertiary phosphines **41a**–**f**. The reaction occurred with retention of configuration at the stereogenic phosphorus atom. Experiments with deuterium demonstrated that the methylene group is inserted directly into the P–H bond through transition state **42**. The P–H bonds in secondary phosphine boranes **40** are subjected to methylene insertion with the carbenoid (Scheme 15).[38]

Recently, a number of stereospecific methods were developed for the transformation of phosphine oxides into phosphine borane. For example, phosphine oxides and sulfides having the (*R*) configuration were transformed

Scheme 15

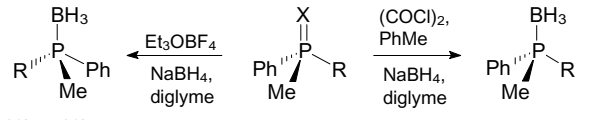


40a – f **42** **41a – f** (86% – 90%)

R = cyclo-C_6H_{11} (**a**), Me (**b**), Pr^n (**c**), Bu^n (**d**), Pr^i (**e**) , Ph (**f**)

into the corresponding phosphine boranes by the treatment with oxalyl chloride followed by the reduction with sodium borohydride. The reaction proceeded through the formation of secondary phosphine dichlorides, which were reduced to final phosphine boranes (*R*)-**2**, (*R*)-**31** and (*R*)-**43a – c** in high yields without loss of optical purity (Scheme 16).[39 – 44] The treatment of P-stereogenic phosphine oxides with Meerwein's salt (triethyloxonium tetrafluoroborate) and the subsequent reduction with sodium borohydride also yielded chiral phosphine boranes (*S*)-**2**, (*S*)-**31** and (*S*)-**43a – c** but with inversion of configuration.[41] Therefore, both optical antipodes of the corresponding phosphine borane can be derived from one and the same P-stereogenic phosphine oxide.

Scheme 16

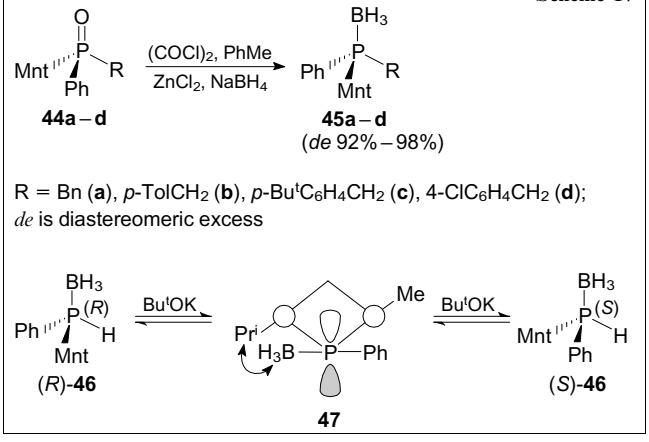


(*S*)-**2**, (*S*)-**31**, (*S*)-**43a – c** (62% – 76%) (*R*) Configuration (*R*)-**2**, (*R*)-**31**, (*R*)-**43a – c** (86% – 91%)

R = Bu^t (**2**), *o*-An (**31**); X = O,S;
43: R = *o*-Tol (**a**), 2-PhC_6H_4 (**b**), Mes (**c**); Tol is tolyl (methylphenyl), Mes is mesityl (2,4,6-trimethylphenyl)

Compounds **44a – d** and **45a – d** containing the L-menthyl group at the phosphorus atom are highly configurationally stable due to the presence of a bulky group preventing the interconversion of two stereoisomers (Scheme 17). The energy difference between the stereoisomers (S_P)-**46** and (R_P)-**46** evaluated by quantum chemical calculations is 91.47 kJ mol^{-1}.[39] Owing to the configurational stability, the transformation of phosphine borane **46** into different P-stereogenic compounds occurs stereospecifically under ambient conditions. The absolute configuration at the phosphorus atom was confirmed by an X-ray diffraction study of compound **45** (R = Bn), which showed that the alkylation proceeded with retention of the absolute configuration at the phosphorus atom.[40] In the presence of a base, the alkylation of phosphine boranes **46** occurs stereospecifically without loss of chirality to give P-stereogenic tertiary phosphine oxides through transition state **47**. Due to stabilization by the L-menthyl group, the alkylated products can be reduced stereospecifically to phosphine boranes without loss of optical purity.[39 – 41] These methods were applied to prepare bidentate and monofunctional phosphine ligands, including bisphosphine oxides as single stereoisomers.

Scheme 17



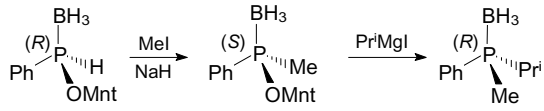
44a – d **45a – d** (*de* 92% – 98%)

R = Bn (**a**), *p*-TolCH$_2$ (**b**), *p*-$Bu^tC_6H_4CH_2$ (**c**), 4-$ClC_6H_4CH_2$ (**d**);
de is diastereomeric excess

(*R*)-**46** **47** (*S*)-**46**

The reaction of menthyloxyphenylphosphine borane **35** with alkyl halides in the presence of sodium hydride in THF proceeds with complete stereospecificity[40 – 43] to form menthyl (R_P)-methylphenylphosphinite borane **48** with retention of the absolute configuration. Then borane **48** was transformed into tertiary isopropyl(methyl)phenylphosphine borane **41e** by the treatment with Pr^iMgI (Scheme 18).[44 – 46]

Scheme 18

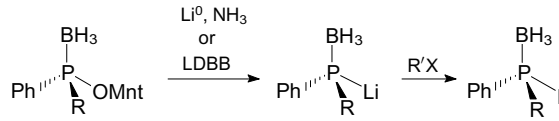


35 **48** (100% *de*) **41e**

Chiral menthylphosphinite boranes **48** and **49** were stereoselectively reduced to phosphine boranes **31**, **41b**, **50** and **51** with such reducing agents as lithium naphthalenide, lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) or lithium in liquid ammonia. The reaction proceeded through the formation of lithium derivatives **52**. Intermediate phosphide boranes **52** were alkylated with alkyl halides to prepare tertiary phosphines **31**, **41b**, **50** and **51** with retention of configuration at the phosphorus atom (Scheme 19).[33, 47 – 49]

The alkylation of compounds **53a – c** pretreated with butyllithium affords phosphine boranes **2** and **54a – j** with retention of configuration at the phosphorus atom and with high *ee* values (Table 1). The absolute configuration of some derivatives **54** was established by X-ray diffraction.[32]

Scheme 19

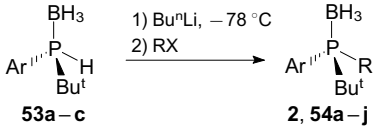


(*S*)-**48**, (*S*)-**49** (100% *de*) **52** (*S*)-**31**, (*S*)-**41b**, (*S*)-**50**, (*S*)-**51**

R = Me (**41b**, **48**, **50**), *o*-An (**31**, **49**, **51**); R′ = Me (**31**, **41b**), Bn (**50**, **51**)

The reductive elimination of the fluorenyl group of compound **55** using lithium naphthalenide produced the corresponding lithium derivative **56** with a diastereomeric ratio (*dr*) of 2.5 : 1. A mixture of diastereomers in a solution in heptane in the presence of alkyl halide underwent a

Table 1. Synthesis of optically active tertiary phosphine boranes **2** and **54a – j**.[32]

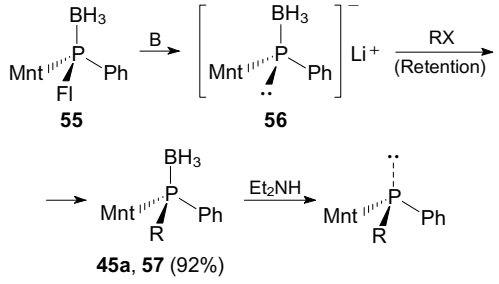


Substrate	Ar	RX	Product	Yield (%)	*ee* (%)
(*S*P)-**53a**	Ph	MeI	(*R*P)-**2**	85	99
(*S*P)-**53a**	Ph	BnBr	(*R*P)-**54a**	91	98
(*S*P)-**53a**	Ph	$CH_2{=}CHCH_2Br$	(*R*P)-**54b**	83	89
(*S*P)-**53a**	Ph	$CH{\equiv}CCH_2Br$	(*R*P)-**54c**	65	89
(*S*P)-**53a**	Ph	$TMSCH_2I$	(*R*P)-**54d**	93	86
(*S*P)-**53a**	Ph	2-$PyCH_2Cl$	(*R*P)-**54e**	68	99
(*S*P)-**53b**	*o*-Tol	MeI	(*R*P)-**54f**	77	98
(*S*P)-**53b**	*o*-Tol	BnBr	(*R*P)-**54g**	90	99
(*S*P)-**53b**	*o*-Tol	$CH_2{=}CHCH_2Br$	(*R*P)-**54h**	90	78
(*S*P)-**53b**	*o*-Tol	$CH{\equiv}CCH_2Br$	(*R*P)-**54i**	68	77
(*S*P)-**53c**	1-Naph	MeI	(*R*P)-**54j**	89	91

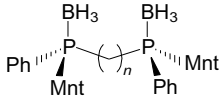
Naph is naphthyl, Py is pyridyl.

crystallization-induced asymmetric transformation into one major diastereomer upon slow evaporation of the solvent. This led to a change in the diastereomeric ratio to 20 : 1 towards more stable crystalline stereoisomer **45a** or **57** (Scheme 20).[23] The alkylation of lithium derivative **56** with alkyl dihalides was used to prepare bis(phosphine boranes) **58** (see Scheme 20).[39]

Scheme 20

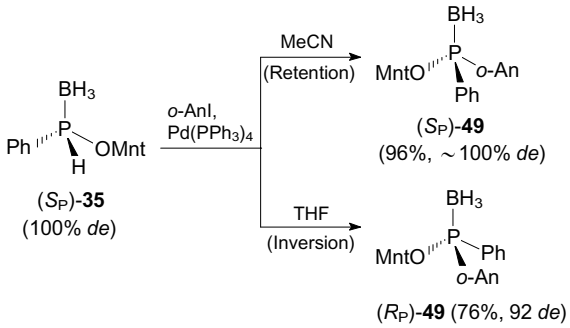


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Generally, the bimolecular electrophilic addition and substitution involving compound **35** occur with retention of the absolute configuration at the phosphorus atom. Nevertheless, there is one exception to this rule. The reaction of diastereomerically pure (*S*P)-(menthyloxy)phenylphosphine borane **35** with *o*-iodoanisole in the presence of 5 equiv. of 3% $Pd(PPh_3)_4$ in acetonitrile or dimethylformamide proceeds with retention of configuration giving product (*S*P)-**49**. Meanwhile, the reaction in tetrahydrofuran in the presence of K_2CO_3 or AcOK occurs with inversion of configuration and gives product (*R*P)-**49**, as shown in Scheme 21.

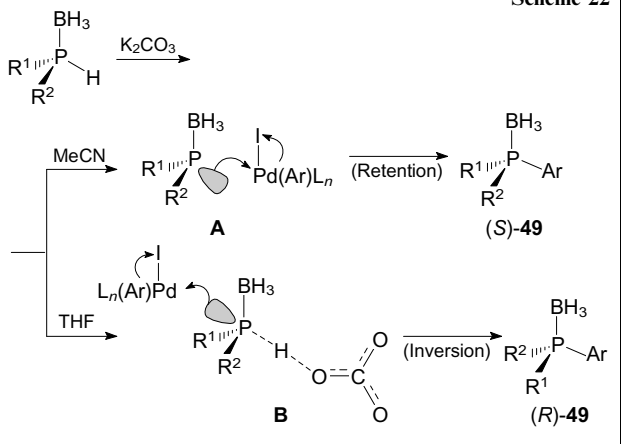
Scheme 21



Solvent	Ratio *S* : *R*	*ee* (%)
MeCN	100 : 0	100
THF	4 : 96	92

This is attributed to the fact that the deprotonation of secondary phosphine borane in a polar solvent (acetonitrile) in the reaction with K_2CO_3 occurs at a high rate. The resulting phosphorus-containing anion reacted with palladium with retention of configuration at the phosphorus atom in intermediate **A**. On the contrary, the deprotonation was slow in a less polar solvent (THF), resulting in the inversion of the absolute configuration of the product through the formation of intermediate **B** (Scheme 22).[33]

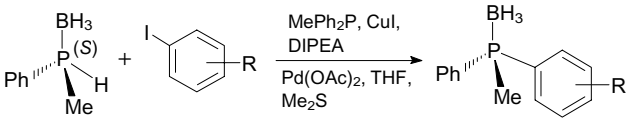
Scheme 22



Copper complexes and salts were used as cocatalysts in palladium-catalyzed phosphorylation reactions.[35] It was shown that the aromatic phosphorylation occurs at low temperatures and is accompanied by the addition of copper iodide. This method can be used to accomplish the $Pd^0 - Cu^I$-catalyzed reaction of enantiomeric methylphenylphosphine borane (*S*)-**40b** with aryl iodides giving products **31**, **43a** and **59a**,**b** (Scheme 23).

Halogen-substituted phosphine boranes having unique chemical properties are valuable chiral reagents for the synthesis of P-chiral phosphine ligands. Enantiomerically pure (*S*)-*tert*-butylmethylphosphine borane **60** can be deprotonated with Bu^nLi at −78 °C, and the subsequent halogenation with 1,2-dibromoethane or 1,2-diiodoethane gives halophosphine boranes **61** as crystalline compounds in

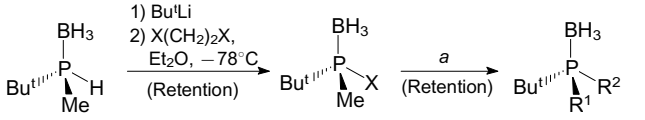
Scheme 23



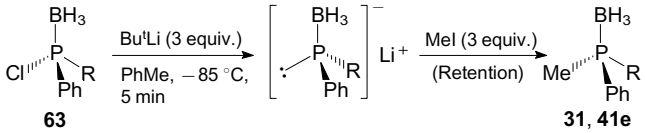
R = *o*-MeO (**31**), *o*-Me (**43a**), *p*-MeO (**59a**), *p*-CF_3 (**59b**); DIPEA is diisopropylethylamine

high yields.[49] The treatment of halophosphine boranes **61** affords ligands **62**, and the sequential reactions of chloride **63** with *tert*-butyllithium and alkyl halide through the formation of the corresponding phosphide ion produce tertiary phosphine boranes **31** and **41e** with high stereospecificity (Scheme 24).[34, 35, 45, 48] Bis(phosphines) **64** were synthesized from compounds **62**.[49]

Scheme 24

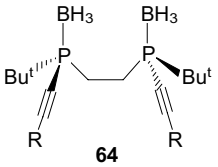


(*a*) R^1M or R^2M (R^1, $R^2 \neq Me$);
X = Br, I; R^2 = Me: R^1 = Bu^n, Bn; R^1 = Me: R^2 = C≡CR^3
(R^3 = Ph, Bu^t, Pr^i_3Si, TMS), Ph, *o*-An; M = Li, Mg



R = *o*-An (**31**, 75%, 92% *ee*), Pr^i (**41e**, 68%, 89% *ee*)

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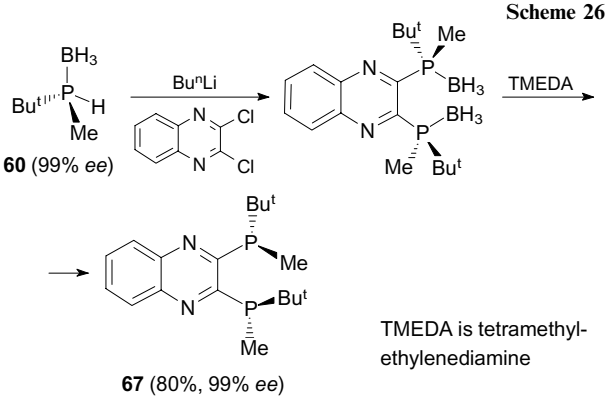


R = Ph, Pr^i_3Si, Bu^t

The stereoselective synthesis of secondary phosphine boranes **65** containing amino acid substituents was accomplished by alkylation of phenylphosphine borane with γ-iodo-α-amino ester under phase-transfer catalysis (PTC). Then compound **65** was hydrolyzed and treated with α,γ-diamine to prepare the corresponding dipeptides **66** in good yields. The hydrophosphination of fullerene C_{60} with phosphine borane proceeded under PTC to give P – C derivatives of C_{60} dipeptides in 80% yield. The addition of fullerene C_{60} was performed under mild conditions without racemization of the amino acid or peptide moiety (Scheme 25).[50]

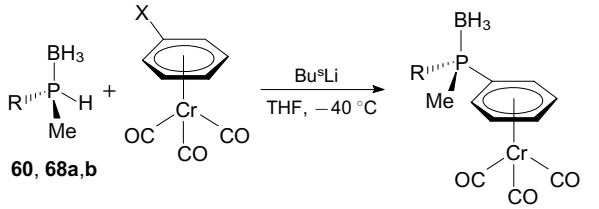
The P-chiral ligand (*R*,*R*)-QuinoxP* (**67**) was synthesized by the deprotonation of chiral secondary phosphine borane **60** with n-butyllithium followed by the nucleophilic substitution of Cl atoms in 2,3-dichloroquinoxaline at low temperature. The deboration afforded ligand **67**, which was isolated as an orange crystalline compound (Scheme 26).[51]

Scheme 26



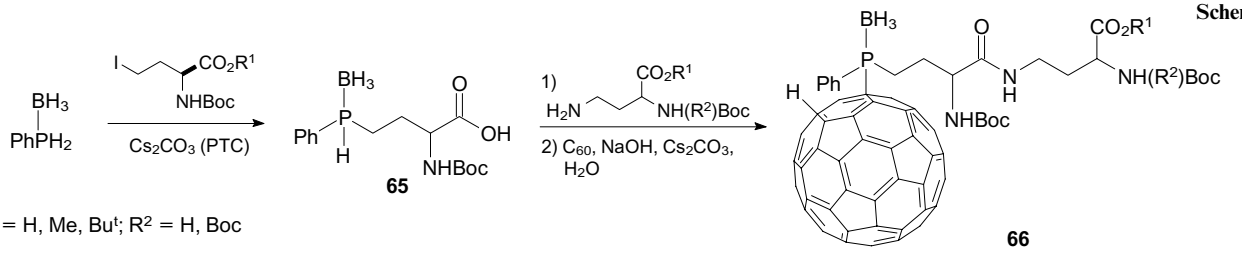
The reaction of P-chiral secondary phosphine boranes **60** and **68a**,**b** with halobenzene chromium complexes in the presence of *sec*-butyllithium *via* the $S_N(Ar)$ mechanism gave ligands **69** in 75% – 99% yields with complete retention of the absolute configuration (Scheme 27).[52] This method was used to prepare chiral phosphine ligands containing primary and secondary alkyl, as well as aromatic substituents including ferrocenyl (Fc) and phenyl groups (see, for example, Scheme 28). These ligands were utilized in the catalytic asymmetric reduction of alkynes and aldehydes to form chiral allyl alcohols with high regioselectivity and complete *E* selectivity.[53]

Scheme 27



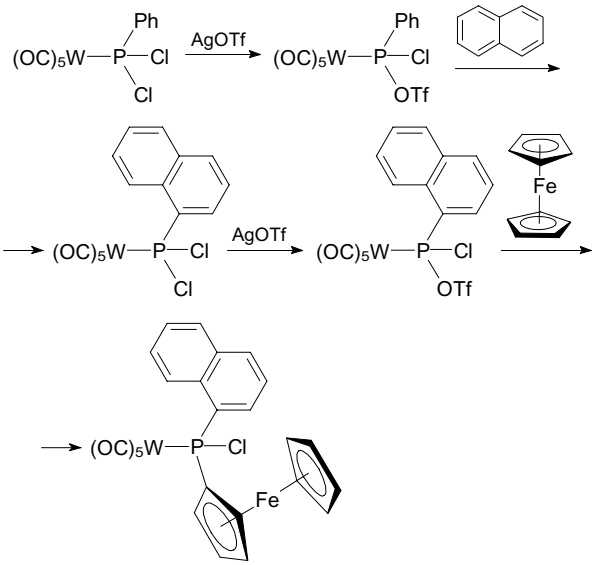
X = Cl, F; R = Bu^t (**60**), Ad (**68a**), Cy (**68b**); Ad is 1-adamantyl

Scheme 25



R^1 = H, Me, Bu^t; R^2 = H, Boc

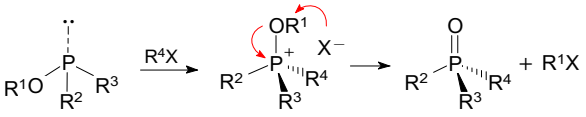
Scheme 28



2.4. Michaelis – Arbuzov reaction

The Michaelis – Arbuzov reaction (or rearrangement, also known as the Arbuzov reaction) provides a versatile approach to the formation of carbon – phosphorus bonds. The classical Michaelis – Arbuzov reaction involves the alkylation of trivalent phosphorus acid esters with alkyl halides giving the corresponding pentavalent phosphorus acid derivatives containing a new P – C bond and also phosphonates, phosphinates or tertiary phosphine oxides (Scheme 29).[54 – 67] Of particular interest is the stereochemistry of this reaction. The data on this issue have not been systematically considered as yet, although it has been extensively studied.

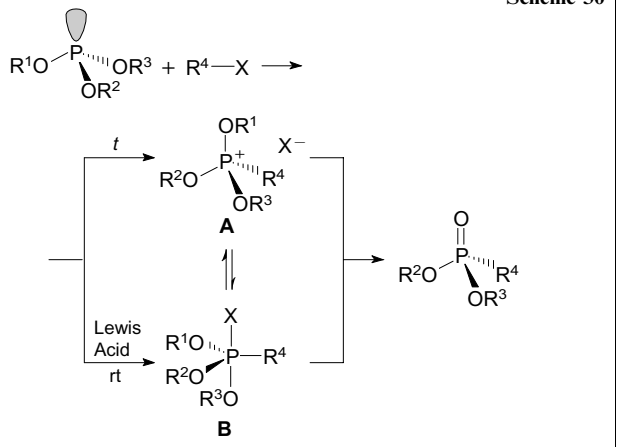
Scheme 29



R^1 = Alk, Ar; R^2 = AlkO or Alk, Ar; R^3 = AlkO, Alk, Ar

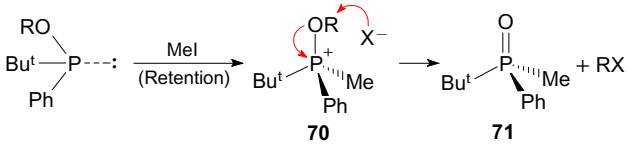
For example, the mechanism of the Michaelis – Arbuzov reaction was recently studied by ultrafast NMR spectroscopy (UF-HMBC).[58] The reaction of triethyl phosphite with benzyl bromide was investigated in the absence of catalysts on heating to 70 °C and in the presence of Lewis acids at room and low temperatures. At −70 °C, the UF-HMBC ^{1}H and ^{31}P NMR spectra show no signs of intermediates. At 25 °C, intermediate benzyltriethoxyphosphonium bromide was detected in the zinc bromide-catalyzed reaction. In the absence of the catalyst, the reaction took place only at high temperature through a two-step mechanism. The first step involves the slow formation of intermediates **A** ⇌ **B**, which are rapidly transformed into phosphonate. In the presence of such catalysts as $ZnBr_2$ or ZnI_2, the reaction is easily accomplished at room temperature. In the authors' opinion, the detection of the stable intermediates **A** is evidence of a unimolecular reaction mechanism (Scheme 30).

Scheme 30



Investigations of the mechanism and stereochemistry of the Michaelis – Arbuzov reaction showed that the first step occurs *via* the electrophilic addition of the starting compound to the trivalent phosphorus atom containing a lone pair to form positively charged alkoxyphosphonium salt **70**. This is followed by the intramolecular attack of the halide ion on the electrophilic carbon atom of the alkoxy group, resulting in the elimination of alkyl halide and the formation of phosphine oxide **71**. The Michaelis – Arbuzov reaction involving chiral phosphinites and alkyl halides is stereospecific and proceeds with complete retention of the absolute configuration at the phosphorus atom (Scheme 31).[56]

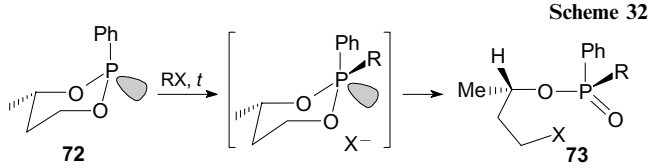
Scheme 31



R = Alk, X = I

The asymmetric version of the Michaelis – Arbuzov reaction was investigated by several research groups. For example, the reaction of cyclic phenylphosphinite **72**, derived from (*S*)-butane-1,3-diol, with alkyl halides is accompanied by the ring opening *via* the P – O bond cleavage in the intermediate giving acyclic products **73** (Scheme 32).[58]

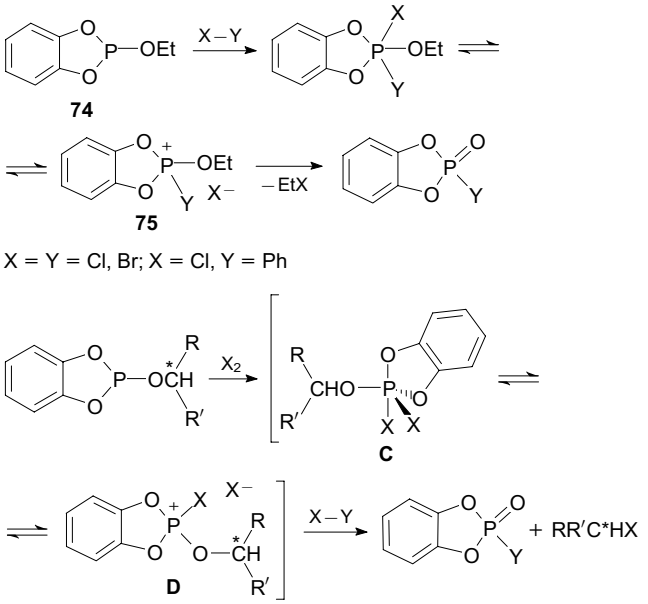
Scheme 32



RX	Yield (%)	$[\alpha]_D$/deg	RX	Yield (%)	$[\alpha]_D$/deg
MeI	86	10.6	AllBr	77	4.7
EtI	71	−15.9	BnCl	64	−11.8
Pr^{n}Br	51	−12.3	Ph_3CCl	56	−25.0
Bu^{n}Br	58	−8.1			

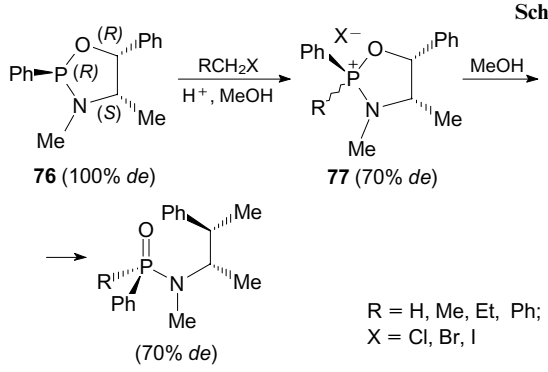
Michalski *et al.*[59] studied the stereochemistry of the Michaelis – Arbuzov reaction of dioxaphospholane **74** with alkyl halides and showed that phosphorane and phosphonium intermediates exist in equilibrium. The decomposition of intermediate alkoxyphosphonium salts **75** *via* the nucleophilic attack of the X^- anion on the alkoxy carbon atom gives rise to phosphoryl groups. The dealkylation of phosphonium intermediate **75** occurs by the S_N2 mechanism and is accompanied by inversion of configuration at the chiral carbon atom. The reaction of optically active secondary alcohol (R*OH) also produces alkyl halide with inversion of configuration in accordance with the S_N2 mechanism involving the phosphonium intermediate **D**. Evidently, the concerted dealkylation of the phosphonium intermediate **C** occurs with retention of configuration at the carbon atom of the resulting alkyl halide (Scheme 33).[59]

Scheme 33



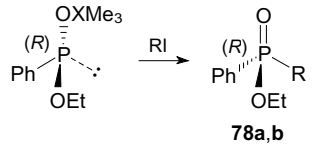
In some cases, the Michaelis – Arbuzov reaction proceeds with low stereospecificity. For example, the reaction of diastereomerically pure (2*R*,4*S*,5*R*)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine **76** with alkyl halides affords a mixture of two diastereomers of phosphonium salt **77** in a ratio of 85 : 15.[60] The formation of phosphonium intermediates with the same diastereomeric ratio as for the final phosphine oxides (Scheme 34) was detected by NMR spectroscopy. Meanwhile, the Michaelis – Arbuzov reaction involving propionyl chloride and 1,3,2-oxazaphosphorinanes gave cyclic acyl phosphonates in 81% yield with high stereoselectivity (*dr* = 92 : 8).[61]

Scheme 34



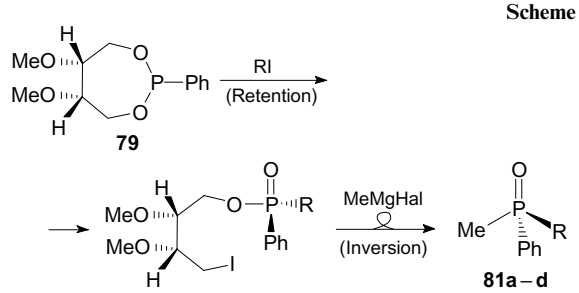
The alkylation of trimethylsilyl or trimethylstannyl ethylphenylphosphinate, like the free-radical addition to alkenes, was accomplished with complete (or nearly complete) retention of configuration and gave products **78a**,**b** in good yields (Scheme 35).[62]

Scheme 35



The Michaelis – Arbuzov reaction of (5*S*,6*S*)-dimethoxy-2-phenyl-1,2,3-dioxaphosphacycloheptane **79** with various alkyl halides afforded phosphinates **80** with a satisfactory enantiomeric excess. Products **80** were transformed into optically active phosphine oxides **81a – d** using Grignard reagents (Scheme 36).[55]

Scheme 36

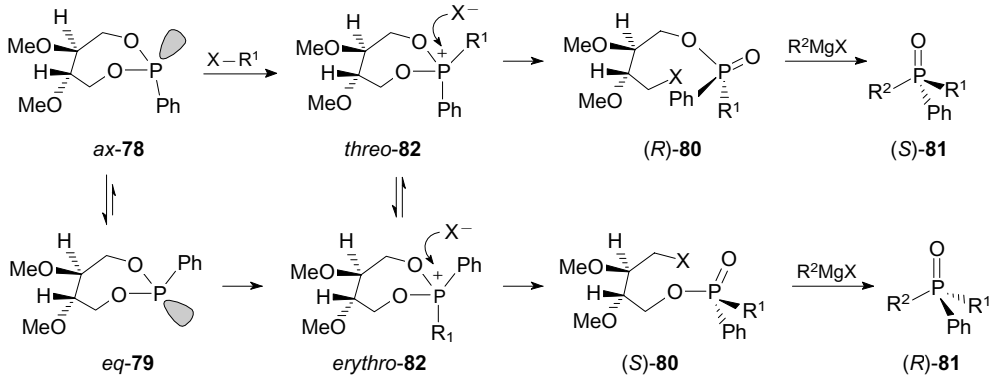


Compound **81**	RI	Temperature /°C	Yield (%)	*ee* (%)
a	$PhCH_2I$	rt	50	45
b	$4\text{-}BrC_6H_4CH_2I$	rt	46	50
c	$4\text{-}CNC_6H_4CH_2I$	36	63	99
d	$4\text{-}O_2NC_6H_4CH_2I$	36	100	99

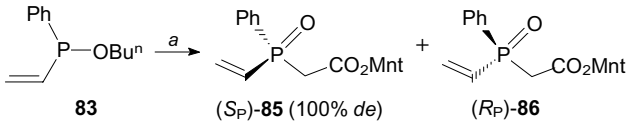
The reaction mechanism is presented in the general form in Scheme 37. The stereochemistry of the reaction is determined by the equilibrium between the *threo* and *erythro* isomers of intermediates **82**. The interaction of the lone pair of the phosphorus(III) atom with alkyl halide occurs through the attack on the axial position of the starting phosphinite **79** giving intermediate **82**. If the phosphonium ion is sufficiently long-lived to provide the thermodynamic equilibrium between the isomers *threo*-**82** and *erythro*-**82**, the diastereomeric excess of phosphinate **80** decreases. Therefore, the stereospecific Michaelis – Arbuzov reaction of (5*S*,6*S*)-5,6-dimethoxy-2-phenyl-1,3,2-dioxaphosphepanes **79** with alkyl halides through the intermediate formation of isomers **82** gives chiral tertiary phosphine oxides **80** and **81**.[55 – 57]

Pietrusiewicz[66] found that vinyl phosphine **83** reacts with (–)-menthyl homoacetate (**84**) to form a mixture of diastereomeric Michaelis – Arbuzov reaction products **85** and **86** (Scheme 38). Stereomers **85** and **86** were separated by crystallization of the crude reaction mixture. After the

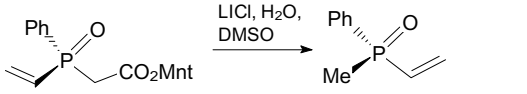
Scheme 37



Scheme 38



(*a*) $BrCH_2CO_2Mnt$ (**84**), 106 – 109 °C



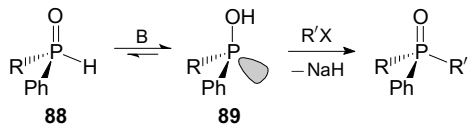
crystallization, the stereoisomer (S_P)-**85** was obtained with 100% *de*.

Johnson and Imamoto[67] demonstrated that menthyl esters **85** and **86** prepared by this method can easily be resolved into (S_P) and (R_P) stereomers and then alkylated at the α-carbon atom. The hydrolysis of these derivatives followed by decarboxylation produced tertiary phosphine oxide, *e.g.*, (S_P)-**87**, with a high *ee* value.[67]

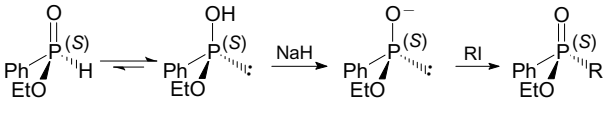
2.5. Michaelis – Becker reaction

The Michaelis – Becker reaction is an electrophilic substitution reaction of trivalent phosphorus acids giving alkyl phosphonates. Examples of the stereospecific Michaelis – Becker reaction with alkyl halides and aryl halides are shown in Schemes 39 – 42.[68 – 71] In the presence of strong bases, the tautomeric equilibrium **88** ⇌ **89** is shifted towards three-coordinate state **89**, which readily reacts with electrophiles (see Scheme 39). Sodium ethoxide, sodium in THF, sodium hydride, n-butyllithium, sodium naphthalenide, $Ca(OH)_2$ in DMF, KOH in acetonitrile and tertiary amines are utilized as bases (see Schemes 40 and 41). The Michaelis – Becker reaction is completely stereospecific. For instance, the alkylation of sodium salt of ethylphenylphosphinite **90** with iodomethane or iodoethane in dimethylformamide affords enantiomerically pure products **78a**,**b** according to stereospecificity of this reaction. The reaction of secondary phosphine oxides (*R*)-**91** and (R_P)-**92** with alkyl halides produces tertiary phosphine oxides **14** and **71** with retention of the absolute configuration at the P reaction centre (see Schemes 41 and 42). In the former case, the reaction proceeds through the formation of chiral metal phosphide derivatives **93** and **94**.

Scheme 39

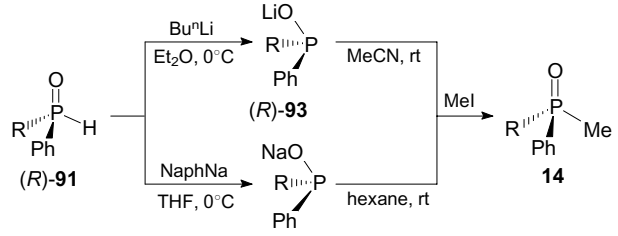


Scheme 40



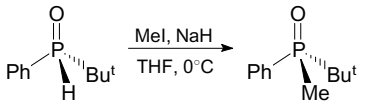
R = Me (**a**), Et (**b**)

Scheme 41



R = Mnt

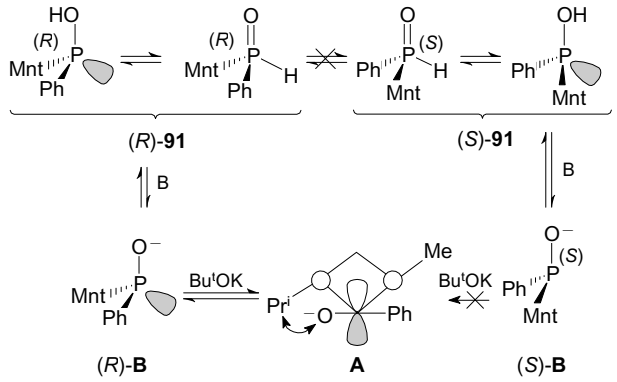
Scheme 42



The introduction of the (1*S*,2*R*,5*S*)-menthyl moiety at the phosphorus atom leads to an increase in the energy barrier between two stereoisomers in the Michaelis – Becker reaction, resulting in the stabilization of the major stereomer. High configurational stability of menthylphosphinic acids is due to the presence of the (−)-menthyl group preventing the interconversion between two stereoisomers. As shown in Scheme 43, the treatment of compound **91** with a base (B) resulted in the transformation of **91** into the phosphinite anion, in which a lone pair occupies more space. In the presumed transition state **A**, the gauche interaction between the oxygen anion and the phenyl or isopropyl group is responsible for a high energy barrier between the forms (*R*)-**B** and (*S*)-**B**.[39]

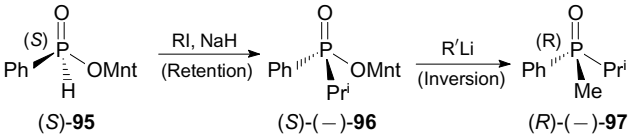
In the presence of bases, the alkylation of phosphine oxides **95** and **96** proceeds stereospecifically without loss of

Scheme 43



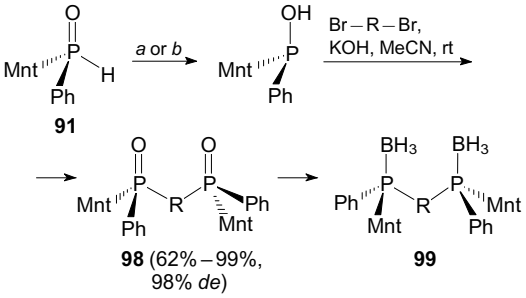
chirality to form P-stereogenic tertiary phosphine oxide **97**. Different bis(halomethyl)-substituted alkanes were successfully transformed into the corresponding tertiary bisphosphine oxides **98** and were isolated as pure stereoisomers of phosphine boranes **99** in high yields. For example, this method was applied to prepare propylene- and butylene(bisphosphine oxides) **98** [R = $(CH_2)_3$, $(CH_2)_4$] by the reaction of secondary phosphine oxide **91** with 1,3-dibromopropane or 1,4-dibromobutane, respectively, followed by the transformation of products **98** into bis(phosphine boranes) **99** [R = $(CH_2)_3$, $(CH_2)_4$] (Schemes 44 and 45).[40]

Scheme 44



R = Me, Pr^i; R′ = Me, Pr^i

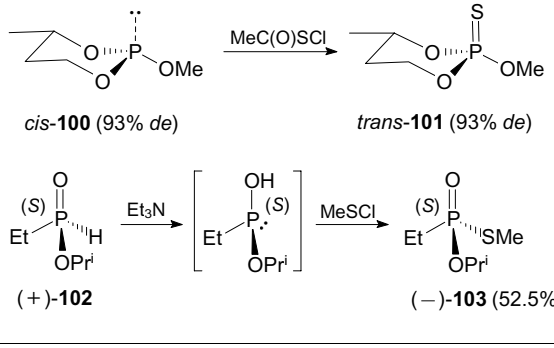
Scheme 45



(*a*) $Ca(OH)_2$, DMF; (*b*) KOH, MeCN;
R = $(CH_2)_n$ (*n* = 3, 4), *o*-, *m*- or *p*-$CH_2C_6H_4CH_2$

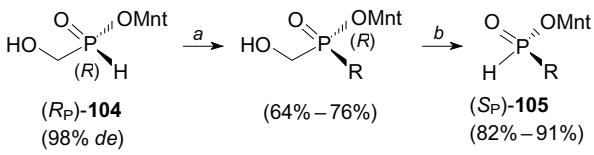
Cis- and *trans*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinanes **100** react with sulfenyl chlorides with retention of configuration at the phosphorus atom to form sulfide (−)-**101**. The same stereochemical outcome was observed in the reaction of optically active isopropyl ethylphosphinate (+)-**102** with methanesulfenyl chloride, resulting in the stereospecific formation of thiophosphonate (−)-**103** (Scheme 46).[72] Chiral H-hydroxymethylphosphonates are available P-chiral synthons for the preparation of optically active phosphines. H-Hydroxymethylphosphonates

Scheme 46



(R_P)-**104** can be considered as chiral equivalents of alkyl phosphinates $ROP(O)H_2$, which can be subjected to stereospecific alkylation followed by the removal of the hydroxymethyl moiety to prepare products (R_P)-**105** (Scheme 47).[73, 74]

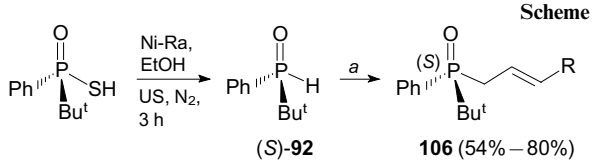
Scheme 47



(*a*) MeI or AllBr, TMSN=C(OTMS)Me;
(*b*) *N*-chlorosuccinimide, Me_2S, Et_3N, CH_2Cl_2;
R = Me, All (95% – 98% *de*)

In some cases, the ultrasonic (US) initiation of the reduction of compounds containing the P=O group increases the reaction rate and yields of enantiomerically pure (R_P)- and (S_P)-secondary phosphine oxides. For example, allyl- and but-2-enyl-*tert*-butylphenylphosphine oxides **106** were synthesized in two steps from (R_P)- and (S_P)-*tert*-butylphenylthiophosphinic acid. The initial ultrasonic treatment of the acid in the presence of Raney nickel (Ni-Ra) at room temperature resulted in the formation of (*S*)-*tert*-butyl(phenyl)phosphine oxide (*S*)-**92**. The latter compound was metallated and treated with lithium diethylamide (LDA) and alkenyl bromides, resulting in the formation of products **106** in good yields (Scheme 48).[75]

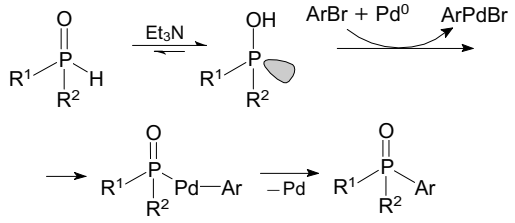
Scheme 48



(*a*) 1) RCH=CHCH$_2$Br, LDA, −50 °C; 2) NH_4Cl, H_2O; R = H, Me

The Hirao cross-coupling is a special case of the Michaelis – Becker reaction. This reaction involves the palladium [$Pd(PPh_3)_4$ or $Pd(OAc)_4 - PPh_3$]-catalyzed cross-coupling of trialkyl phosphite and aryl halide giving phosphonates containing a new P – C bond (Scheme 49). The cross-coupling is stereospecific, and the reaction of chiral H-phosphonates with aryl halides occurs with retention of the absolute configuration at the phosphorus atom.[76 – 83]

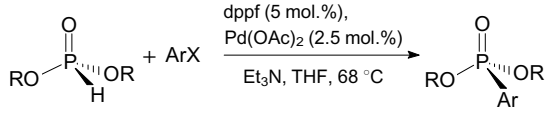
Scheme 49



R^1, R^2 = Ph, OAlk

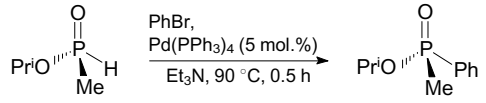
For example, the reaction of (*R*)-(+)-isopropyl methylphosphinate **107** with bromobenzene in the presence of tetra(triphenylphosphine)palladium as the catalyst and triethylamine occurs *via* the front-side attack of phenylpalladium bromide on the P reaction centre giving compound (*S*)-**108** (Schemes 50 and 51).[81]

Scheme 50



dppf is 1,1′-bis(diphenylphosphino)ferrocene

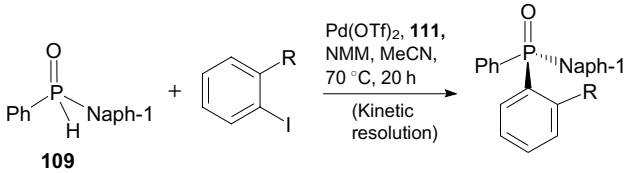
Scheme 51



(*R*)-(+)-**107** (*S*)-(−)-**108** (88%)

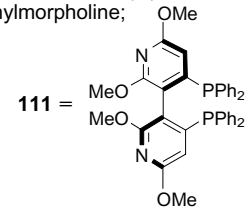
The enantioselective C−P cross-coupling of phosphine oxide **109** with *ortho*-substituted aryl iodides was accomplished *via* kinetic resolution strategy, resulting in the formation of chiral triarylphosphine oxides in high yields with good enantioselectivity. In acetonitrile, this reaction gave tertiary phosphines **110** (Scheme 52).[80] The highest enantioselectivity (61% – 83% *ee*) was achieved using such diarylphosphine oxides as (2-methoxyphenyl)phenylphosphine oxide, (*o*-tolyl)phenylphosphine oxide and (1,10-biphenyl-2-yl)phenylphosphine oxide in the presence of palladium triflate as the catalyst and bis(phosphine) **111** as the ligand at 70 – 80 °C.[80]

Scheme 52



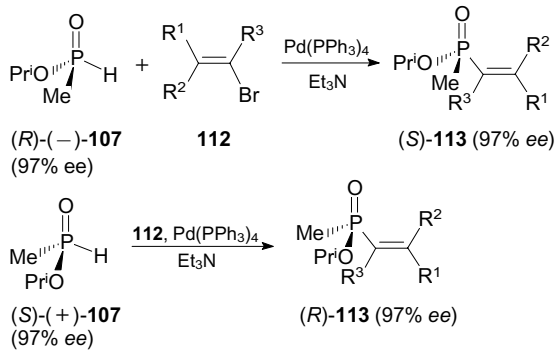
109 **110** (61% – 83% *ee*)

R = NHC(O)Bu^t, NHAc, NHC(O)CF_3, $NHSO_2Ph$;
NMM is *N*-methylmorpholine;



The reaction of (*R*)-(+)-isopropyl methylphosphinate **107** with vinyl bromides **112** in the presence of tetrakis(triphenylphosphine)palladium as the catalyst and triethylamine occurs *via* the front-side attack of alkenes on the phosphorus atom with complete retention of configuration at the chiral phosphorus centre.[79] Enantiomerically pure (*S*)- and (*R*)-isopropyl alkenylmethylphosphinates **113** were synthesized in good yields with high *ee* values. The absolute configuration of the compounds was determined by the chemical correlation method, which confirmed its complete retention (Scheme 53).[78]

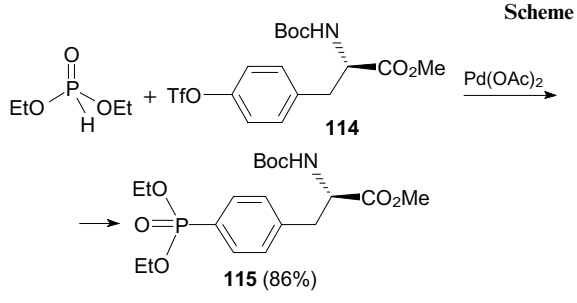
Scheme 53



R^1	R^2	R^3	Yield (%)	Configuration of the product	*ee* (%)
H	H	H	64	*S*	> 97
H	H	Me	71	*S*	> 97
Ph	H	H	98	*S*	> 97
H	H	Me	71	*R*	> 97
Ph	H	H	98	*R*	> 97
H	Ph	H	98	*R*	> 97

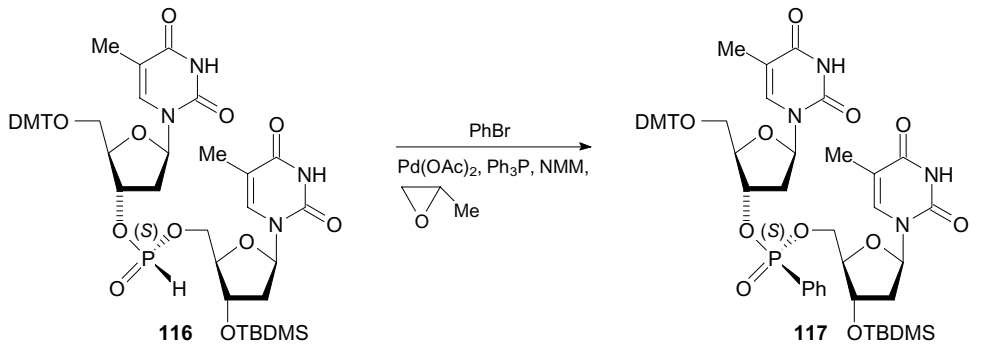
The Hirao cross-coupling is used in the synthesis of biologically active compounds. This reaction was performed with various electrophilic agents, such as aryl-substituted iodides, bromides and triflates, and H-phosphonates containing cholesterol or nucleoside substituents. For example, this method was applied to prepare aryl phosphonate **115** in high yield starting from tyrosine triflate **114** and diethyl phosphite (Scheme 54).[79]

Scheme 54



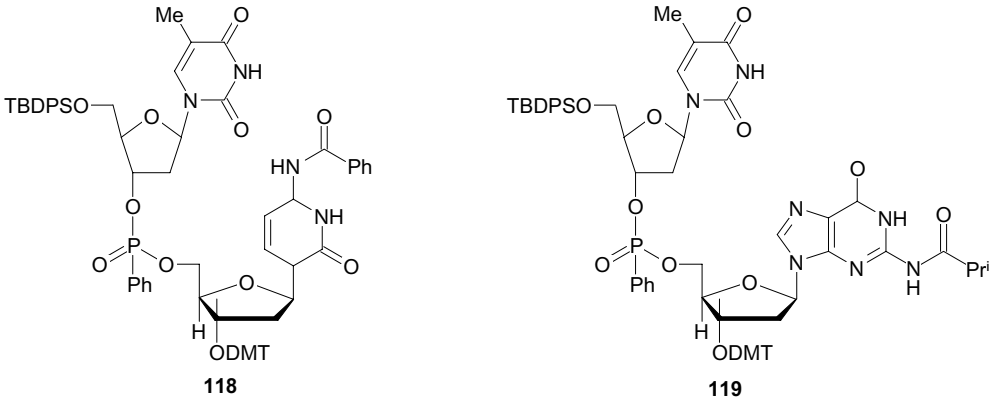
A series of P-stereogenic nucleosides were synthesized by the palladium-catalyzed cross-coupling of aryl halides (or triflates) with H-phosphonates. Thus, dinucleoside

Scheme 55

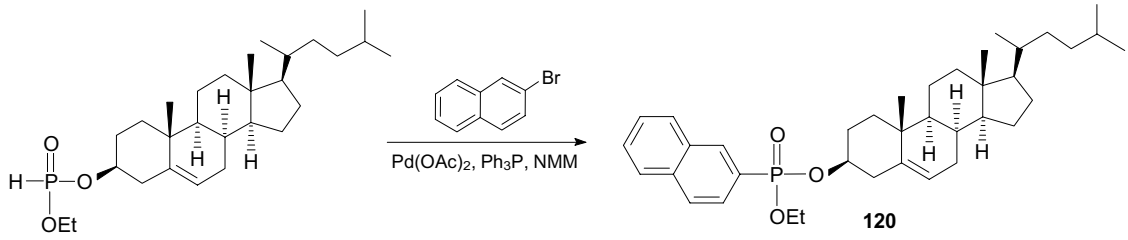


DMT is 4,4′-dimethoxytrityl, TBDMS is *tert*-butyldimethylsilyl

Structures 118, 119



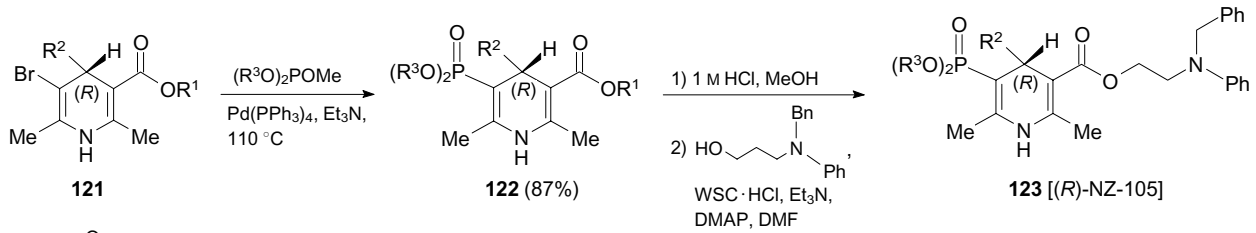
Scheme 56

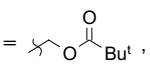
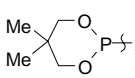


H-phosphonate **116** reacted with bromobenzene to form the corresponding dinucleoside phenylphosphonate **117** (Scheme 55).[79] Structures **118** and **119** are other examples of dinucleoside phosphonates. Cholesterol H-phosphonate was transformed into highly lipophilic 2-naphthyl phosphonate **120** in a similar way (Scheme 56).[79, 80, 83]

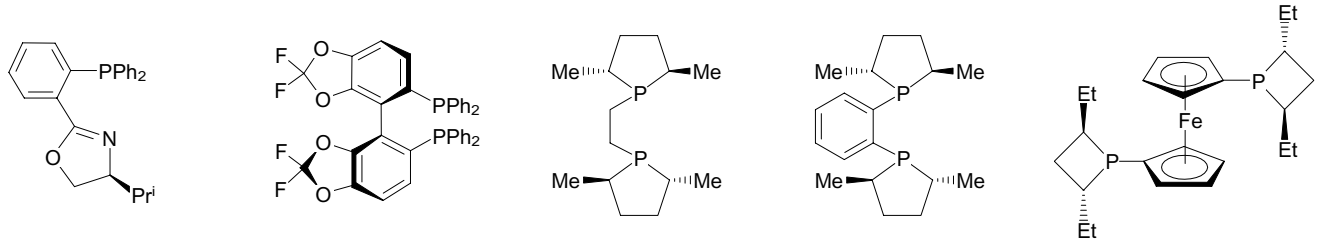
The asymmetric synthesis of enantiomers of the calcium antagonist, (*S*)-(+)- and (*R*)-(−)-NZ-105, from prochiral compound **121** was based on the modified Hunsdiecker–Borodin and Michaelis–Arbuzov reactions catalyzed by tetrakis(triphenylphosphine)palladium. The phosphination of bromide **121** was performed by heating with trialkyl phosphite in the presence of a palladium complex and triethylamine in toluene at 110 °C for 5 h. Product **122** was prepared in high yield. 1,4-Dihydropyridines **123** derived from **122** have a chiral centre at position 4, and their enantiomers exhibit different biological activity. For example, (*S*)-NZ-105 possesses 850 times higher calcium

Scheme 57

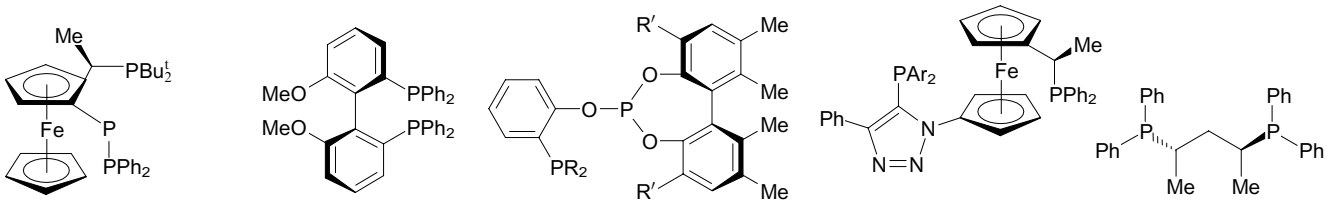


R^1 =  , R^2 = 3-$O_2NC_6H_4$, $(R^3O)_2P$ = ; DMAP is 4-dimethylaminopyridine, WSC is water-soluble carbodiimide

Structures 124 – 133



124 [(*R*)-Pr^i-PHOX] **125** [(*R*)-Diflluorophos] **126** (Me-BPE) **127** (Me-DuPhos) **128** (Et,Et-FerroTANE)



129 (Bu^t-Josiphos) **130** [(*R*)-MeO-BIPHEP] **131** (P – OP) **132** (ClickFerrophos II) **133** (Chiraphos)

Ar = *m*-Xyl

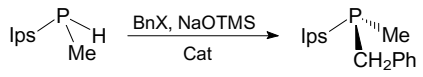
antagonistic activity compared to the *R* stereoisomer (Scheme 57).[71]

3. Asymmetric electrophilic catalysis

The catalytic electrophilic activation of organophosphorus compounds has attracted considerable attention of chemists. Lewis acids are commonly used as electrophilic catalysts and Lewis bases serve as nucleophilic catalysts. The addition of Lewis acid to a substrate containing a lone pair is accompanied by an increase in reactivity of the generated complex. Typical examples of the asymmetric electrophilic activation of organophosphorus compounds by chiral Lewis acids are catalytic alkylation, arylation and halogenation, enzyme catalysis, *etc*.[84 – 88] In many cases, the chiral Lewis acid-catalyzed asymmetric arylation (or alkylation) of racemic secondary phosphines affords enantiomerically enriched tertiary phosphines. These reactions are performed using ruthenium, platinum, palladium, copper and molybdenum complexes with chiral ligands (*e.g.*, compounds **124** – **133**).[84 – 94]

Chiral platinum complexes catalyze asymmetric alkylation of secondary phosphines with compounds RCH_2X (X = Cl, Br, I) giving tertiary phosphines (or their boranes) in good yields with an enantioselectivity of 50% – 93%.[86] Secondary phosphines containing bulky substituents react with *para*-substituted aryl iodides to form tertiary phosphines with an enantiomeric excess of up to 88% (Scheme 58).[84, 85]

Scheme 58

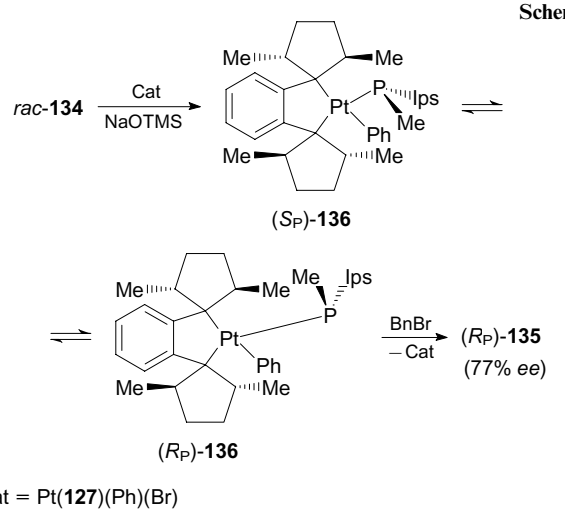


134 (R_P)-**135**

Ips is 2,4,6-triisopropylphenyl

Glueck and co-workers[85, 86] found that racemic secondary phosphine **134** is transformed into tertiary phosphine (R_P)-**135** in the presence of platinum complex Pt(**127**)(Ph)(Br) and NaOTMS in toluene. Apparently, the first reaction step gives adduct **136**, which rapidly undergoes a transformation *via* P inversion: (S_P)-**136** ⇌ (R_P)-**136** (Scheme 59). Adduct **136** was isolated and characterized by low-temperature NMR spectroscopy. According to the X-ray diffraction data, this compound has the R_P absolute configuration.[86] The treatment of **136** with benzyl bromide afforded product **135** with 72% – 78% *ee*. The fact that the alkylation of secondary phosphine occurred with retention of the absolute configuration at the chiral centre confirmed the reaction mechanism proposed by the authors. Based on these results, it was concluded that the enantioselectivity of electrophilic substitution is determined by the thermodynamic preference of one diastereomer in the equilibrium between the (S_P)- and (R_P)-complexes.

Scheme 59



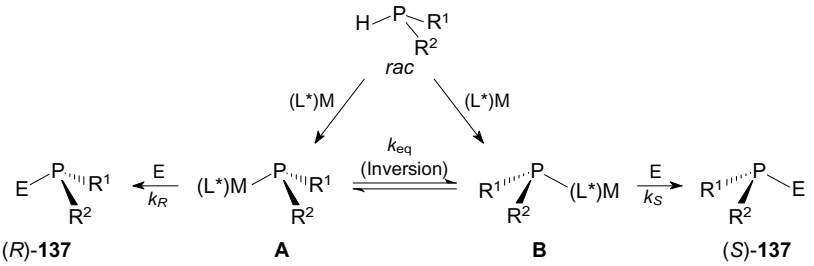
(S_P)-**136**

(R_P)-**136**

Cat = Pt(**127**)(Ph)(Br)

Metal phosphine complexes (MPR_2) undergo fast pyramidal inversion between the forms A and **B** (Scheme 60). As a result, the complexes M(L*)(PR^1R^2) exist as mixtures of diastereomers that are interconverted at different rates. If this equilibrium is established more rapidly than the rate of the electrophilic reaction, P-stereogenic phosphines **137** are

Scheme 60

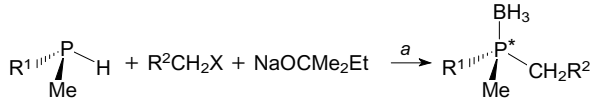


L* is a chiral ligand

produced in an enantioselective manner, and these compounds undergo slow pyramidal inversion. The ratio of the products in the dynamic equilibrium **A** ⇌ **B** depends on both the equilibrium constant (k_{eq}) and the rate constants of the formation of enantiomers (k_S and k_R). The alkylation of the complex occurs with complete stereoselectivity at −95 °C, because the reaction with EtI is more rapid than the inversion of phosphine. However, at 20 °C product **137** is generated with dr = 3.2 : 1, because the rate of phosphine inversion increases with increasing temperature, and the diastereomers **A** and **B** react with EtI at comparable rates.

The enantioselective alkylation of secondary phosphines with benzyl halides catalyzed by the ruthenium complexes $[RuH(\mathbf{124})_2]^+$ affords tertiary phosphines with *ee* values of 57% – 95%.[88,89] The complex [**125**(dmpe]Ru(H)][BPh_4] [dmpe is 1,2-bis(dimethylphosphino)ethane] efficiently catalyzes the asymmetric alkylation of secondary phosphines with benzyl bromides, whereas the ruthenium complex with the (*R*)-MeOBiPHEP (**130**) and dmpe ligands is more efficient in reactions with benzyl chlorides.[90] The asymmetric alkylation of secondary phosphines **138a**,**b** with benzyl bromides catalyzed by the ruthenium complex [**125**(dmpe)Ru(H)][BPh_4] gives phosphine boranes **139** in good yields with high *ee* values, while benzyl chlorides are preferred when using (*R*)-MeOBiPHEP (**130**) – dmpe ligands (Scheme 61).[87,88]

Scheme 61

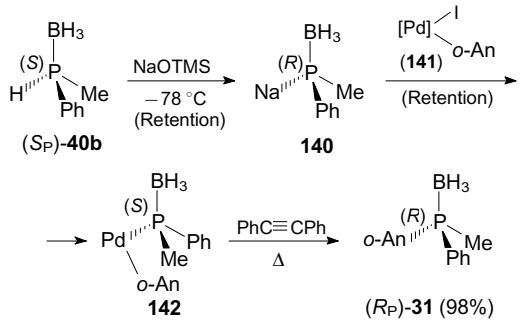


(*a*) [RuH(**125**)(dmpe)](BPh_4) (10 mol.%), BH_3 · THF;
R^1 = Pr^i (**a**), Ph (**b**); R^2 (*ee* for R^1 = Ph) = Ph (75%), *p*-An (85%), *o*-Tol (57%), 1-Naph (59%), Py (48%), Fu (68%), *m*-$ClCH_2C_6H_4$ (95%); X = Cl, Br; Fu is furyl

The reaction of secondary phosphine borane (*S*)-**40b** with *o*-anisyl iodide catalyzed by the chiral Pd complex with the (*S*,*S*)-Chiraphos ligand (**133**) occurred with retention of the absolute configuration at the phosphorus atom.[91] The first step of this reaction involves the formation of sodium derivative **140** from the enantiomerically enriched secondary phosphine in the presence of $NaOSiMe_3$. The addition of the complex Pd[(*S*,*S*)-Chiraphos)(*o*-An)] (**141**) to **140** gives stable complex **142**. The heating of the latter to 50 °C in excess diphenylacetylene affords borane (R_P)-**31** with 98% *ee* in 70% yield. The retention of configuration was established by X-ray diffraction (Scheme 62).

The enantioselective alkylation of secondary phosphine **138b** with alkyl halides catalyzed by the complex

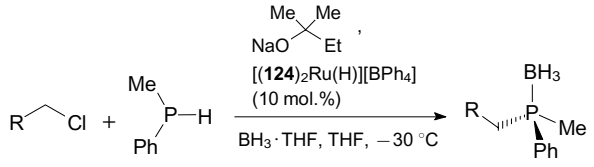
Scheme 62



[Pd] = Pd[(*S*,*S*)-**133**]

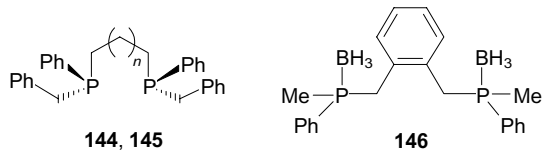
$[RuH(\mathbf{124})_2]^+$ produced tertiary phosphines **40c** (R = Et) and **143** (R = Ar, Het) with *ee* values of of 57% – 95%.[87,88] This method was used to prepare bisphosphines **144** – **148** with high *ee* values. The asymmetric alkylation can be accomplished using benzyl bromides instead of benzyl chlorides, but with a worse outcome. The ruthenium catalyst with the (*R*)-MeOBiPHEP (**130**) and dmpe ligands proved to be more efficient in the asymmetric alkylation of phosphine with benzyl chloride, whereas the (*R*)-Difluorophos (**125**) and dmpe ligands are preferred in the case

Scheme 63



R = Ar (80% – 90%, 41% – 85% *ee*), Het (80% – 94% *ee*), Et (**40c**, 70%, 57% *ee*)

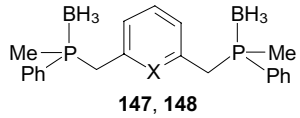
Structures 144 – 148



144, **145**

146

144: *n* = 0 (81%, 91% *ee*, 47% *de*);
145: *n* = 1 (87%, 93% *ee*, 59% *de*)



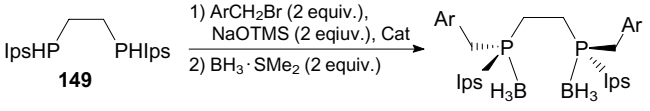
147, **148**

147: X = CH (86%, 95% *ee*, 48% *de*);
148: X = N (89%, 16% *de*)

of alkyl bromides (Scheme 63).[87] The alkylation of 1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]ethane (**126**) produced the corresponding alkyl derivatives with high diastereoselectivity.[88]

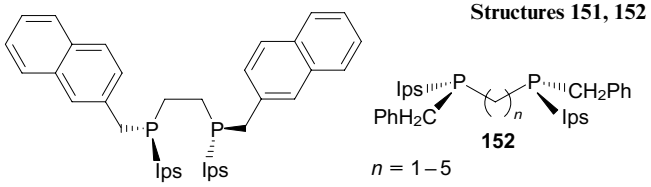
The catalytic asymmetric alkylation of secondary bisphosphines **149** with benzyl bromide in the presence of NaOTMS as the base and Pt[(*R*,*R*)-Me-Duphos](Ph)(Cl) as the catalyst gave tertiary bis(phosphine boranes) **150**. The use of 2-(bromomethyl)naphthalene as the alkylating agent, Pt[(*R*,*R*)-**127**](Ph)(Cl) (10 mol.%) as the catalyst and NaOTMS as the base allowed the synthesis of diastereomerically pure bisphosphines **151**. These conditions were employed to prepare compounds **152** (Scheme 64).[89 – 94]

Scheme 64



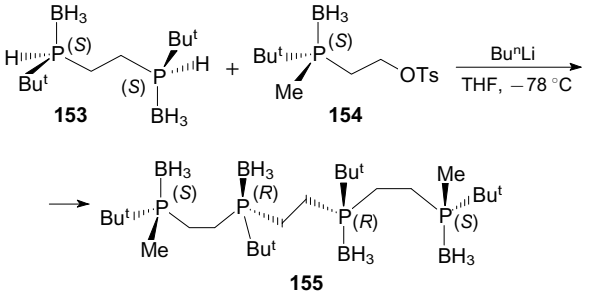
Cat = Pt[(*R*,*R*)-**127**](Ph)(Cl)

Structures 151, 152



The deprotonation of enantiomerically pure secondary bis(phosphine borane) **153** with n-butyllithium at low temperature followed by the reaction with tosylate **154** yielded tetraphosphine ligand **155**. This method provides a simple route to P-stereogenic tertiary phosphines using P-chiral substrates (Scheme 65).[95]

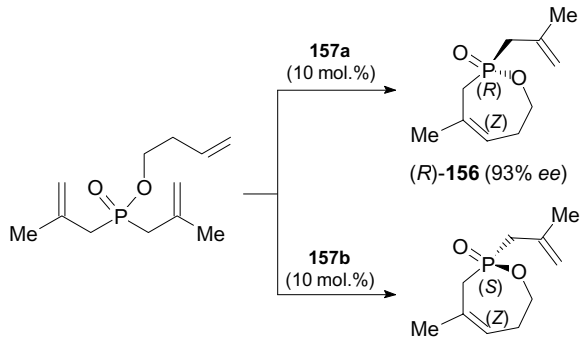
Scheme 65



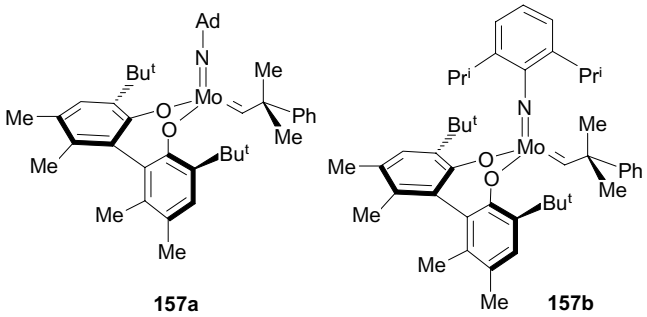
The enantioselective synthesis of P-stereogenic phosphinates and phosphine oxides was accomplished using molybdenum complexes. The asymmetric cyclization was performed *via* asymmetric ring-closing metathesis (ARCM). An increase in enantioselectivity was observed on changing the achiral imido ligand in a chiral molybdenum catalyst.[96] Enantiomerically enriched P-stereogenic phosphinates (*S*)-**156** and (*R*)-**156** were synthesized with a *ee* value of 98% by ARCM reactions catalyzed by molybdenum complex **157b** (Scheme 66).

In many cases, the arylation of secondary phosphines with aryl halides catalyzed by chiral copper,[97] platinum,[85, 89, 94, 98] ruthenium[87, 88] and palladium[82, 84, 91, 99 – 101] complexes occurs with good enantioselectivity and is a

Scheme 66



Structures 157

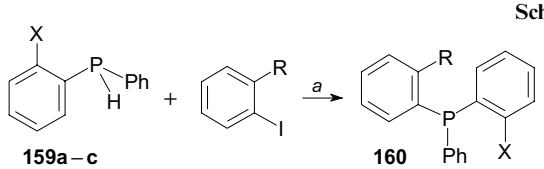


convenient method for the synthesis of tertiary phosphines. For example, the reaction of aryl iodides with secondary arylphosphine **138c** (R^1 = Ips, R^2 = Me) using the chiral complex Pd[(*R*,*R*)-**127**](*trans*-stilbene) or Pd[(*R*,*R*)-**127**](Ph)(I) as the catalyst precursor gives tertiary phosphines **158a**,**b** with an enantioselectivity of up to 88%.[84] The similar arylation of their phenyl analogues **159** using the *in situ* catalyst prepared from $Pd_2(dba)_3 - CHCl_3$ (dba is dibenzylideneacetone), the chiral ligand Et,Et-FerroTANE (**128**) and LiBr affords the corresponding tertiary phosphines **160a** – **d** with an enantioselectivity of 90% (Table 2).[54] The palladium complex $Pd_2(dba)_3$ with ligand **124** also showed high enantioselectivity in the arylation of tertiary phosphines in the presence of K_2CO_3 in acetonitrile.[100]

The Pd-catalyzed reactions of secondary phosphines **159a** – **c** with *ortho*-substituted aryl iodides produced chiral triarylphosphines **160** (Scheme 67).[54] Korff and Helmchen[54] studied the effect of the nature of the base and lithium salt additives on the product yield and *ee* (see Scheme 67, Table 3).

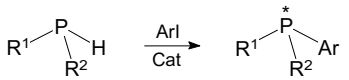
Similarly, the treatment of phosphine borane **40b** with *o*-anisyl iodide and sodium trimethylsilanoate in the pres-

Scheme 67



(*a*) $Pd_2(dba)_3 - CHCl_3$, **128**, Et_3N, LiBr, THF, rt;
R = CO_2Bu^t, CO_2Me, CHO, 3,4-dihydrooxazol-2-yl;
X = Ph (**a**), OMe (**b**), CF_3 (**c**)

Table 2. Arylation of secondary phosphines catalyzed by chiral palladium complexes.



138c, **159a – c** **158a**,**b**, **160a – e**

Substrate	R^1	ArI	Product	Catalytic system	Yield (%)	*ee* (%) (configuration)	Ref.
159a	2-PhC_6H_4	2-$Bu^tOC(O)C_6H_4I$	**160a**	**128** – $CHCl_3$ – $Pd_2(dba)_3$ – LiBr – NEt_3	76	90 (*S*)	54
159a	*o*-An	2-$Bu^tOC(O)C_6H_4I$	**160a**	**128** – $CHCl_3$ – $Pd_2(dba)_3$ – LiBr – *N*-Methylpiperidine	43	86 (*S*)	54
159b	*o*-An	2-$Bu^tOC(O)C_6H_4I$	**160b**	**128** – $CHCl_3$ – $Pd_2(dba)_3$ – LiBr – NEt_3	79	40 (+)	54
159c	2-$CF_3C_6H_4$	2-$Bu^tOC(O)C_6H_4I$	**160c**	**128** – $CHCl_3$ – $Pd_2(dba)_3$ – LiBr – NEt_3	39	93 (*R*)	54
159a	2-PhC_6H_4	2-$MeOC(O)C_6H_4I$	**160d**	**128** – $CHCl_3$ – $Pd_2(dba)_3$ – LiBr – NEt_3	69	85 (*S*)	54
159a	2-PhC_6H_4	2-$OCHC_6H_4I$	**160e**	**128** – $CHCl_3$ – $Pd_2(dba)_3$ – LiBr – NEt_3	71	63 (*S*)	54
138c	Ips	PhI	**158a**	Pd(**127**)(*trans*-stilbene) – NaOTMS	97	76 (*S*)	84
138c	Ips	PhI	**158a**	Pd(**127**)(Ph)(I) – NaOTMS	89	75 (*S*)	84
138c	Ips	*p*-AnI	**158b**	Pd(**127**)(Ph)(I) – NaOTMS	96	82 (*S*)	84

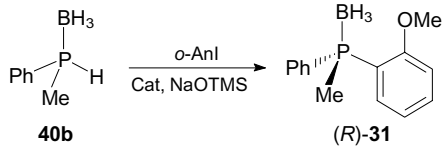
Note. R^2 = Me (**138**, **158**), Ph (**159**, **160**).

Table 3. Asymmetric arylation of secondary phosphines **159a – c** catalyzed by the Pd complex with ligand **128** (see Scheme 67).[54]

Substrate	X	R	Base	Li salt	Yield (%)	*ee* (%) (configuration)
159a	2-Ph	CO_2Bu^t	NEt_3	–	63	71 (*S*)
159a	2-Ph	CO_2Bu^t	$NBnMe_2$	–	45	77 (*S*)
159a	2-Ph	CO_2Bu^t	*N*-Methylpiperidine	–	76	84 (*S*)
159a	2-Ph	CO_2Bu^t	NEt_3	LiF	76	66 (*S*)
159a	2-Ph	CO_2Bu^t	NEt_3	LiCl	66	86 (S)
159a	2-Ph	CO_2Bu^t	NEt_3	LiBr	76	90 (*S*)
159a	2-Ph	CO_2Bu^t	NEt_3	LiI	58	87 (*S*)
159b	2-OMe	CO_2Bu^t	*N*-Methylpiperidine	LiBr	43	86 (*S*)
159c	2-CF_3	CO_2Bu^t	NEt_3	LiBr	39	93 (*R*)
159a	2-Ph	CO_2Bu^t	NEt_3	LiBr	69	85 (*S*)
159a	2-Ph	CHO	NEt_3	LiBr	71	63 (*S*)

Note. A dash indicates that the yield was not reported in the original publication.

Scheme 68



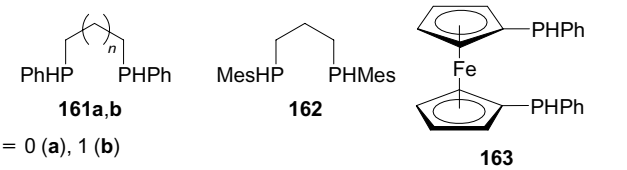
Cat = Pd((*R*)-Tol-BINAP)(*o*-An)(I);
BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl

ence of Pd[(*R*)-Tol-BINAP](*o*-An)(I) as the catalyst at room temperature gave phosphine borane **31** and Pd[(*R*)-Tol-BINAP] (Scheme 68). In the reaction performed at −78 °C, the formation of the product was observed by ^{31}P NMR spectroscopy even at −80 °C; in this case, intermediates were not detected.[99]

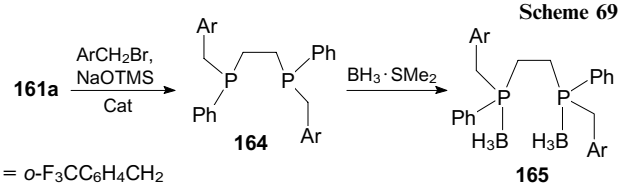
The alkylation and arylation of air-stable chiral primary phosphines PH_2Ar^* [Ar* is (S)-binaphthyl or (*R*)-MeO-binaphthyl] produced P-stereogenic phosphines with low stereoselectivity, which were isolated as diastereomerically pure products after chromatographic purification.[97] The platinum complex-catalyzed alkylation of diphosphine **161a** occurred at a higher rate and with a higher stereoselectivity compared to diphosphines **161b**, **162** and **163**. The alkylation of diphosphine **161a** with *o*-(trifluoromethyl)benzyl bromide in the presence of NaOTMS as the base and the platinum complexes {Pt[(*R*,*R*)-Me-DuPhos](Ph)(Cl) and Pt[(*R*,*R*)-Me-BPE](Ph)(Cl)} as the catalyst gave diphosphine **164**, which was isolated as optically pure borane complex **165** (Scheme 69).[82,97–99]

Silylated alkylarylphosphines are convenient starting reagents for the synthesis of chiral tertiary phosphines in

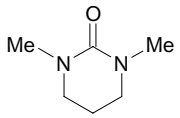
Structures 161 – 163



Scheme 69

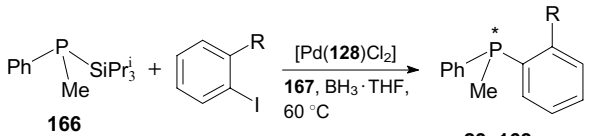


Structure 167



167 (DMPU)

Scheme 70



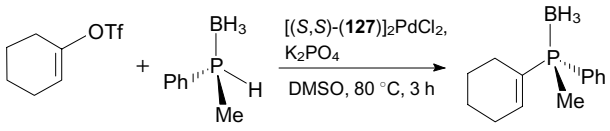
166 **23**, **168a – e**

Product	R	Yield (%)	*ee* (%)	Configuration
23	OMe	74	55	*R*
168a	SMe	73	63	*R*
168b	CO_2Bu^t	83	78	–
168c	$CO_2C_6H_3Me_2$-2,6	76	82	–
168d	$C(O)NEt_2$	63	79	–
168e	$C(O)NPr^i_2$	53	98	–

good yields with satisfactory enantioselectivity.[100] For example, the Pd(Et,Et-FerroTANE)Cl_2-catalyzed reaction of *ortho*-substituted aryl iodides with silylphosphine **166** in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU, **167**) affords P-chiral tertiary phosphines **23** and **168** with an enantioselectivity of up to 98% (Scheme 70).

P-Stereogenic benzophospholanes were synthesized by enantioselective intramolecular cyclization of secondary phosphine boranes in the presence of chiral (diphosphine)-palladium complexes as the catalyst.[101] The palladium-catalyzed asymmetric cross-coupling of racemic secondary methylphenylphosphine borane **40b** with achiral triflate affords chiral tertiary phosphine borane **169** in moderate optical yield.[102] The efficiency and selectivity of the reaction are influenced by such parameters, as the structure of the chiral ligand, the temperature and the nature of the solvent. The enantiomeric ratio of 78 : 22 for compound **169** was achieved using [(*S*,*S*)-Me-DUPHOS]$_2PdCl_2$ as the catalyst (Scheme 71).[26]

Scheme 71

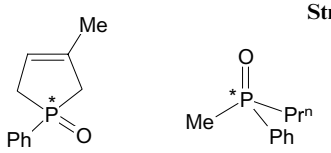


40b **169** (56% *ee*)

4. Reduction

The reduction of phosphorus compounds occurs through different mechanisms, including an electrophilic mechanism. Some processes are complex and multistep. The reaction can give products with retention or inversion of configuration at the phosphorus atom depending on the nature of the reducing agent.[103, 104] For instance, the reduction of tertiary phosphine oxides **170** and **171** with chiral aminoalanes [aluminium hydrides bound to chiral (*S*)-phenylethylamine] was described by Cernia *et al.*[105] This reaction affords chiral tertiary phosphines with a moderate enantiomeric excess. The hydride transfer from alane to the phosphorus atom can occur *via* two pathways: a unimolecular mechanism with retention of configuration and a bimolecular mechanism with inversion of the chiral centre. The predominance of a particular competitive mechanism defines the stereoselectivity of the reduction.

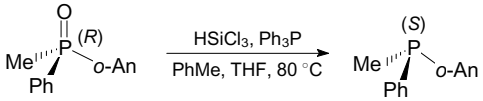
Structures 170, 171



170 **171**

Stereospecific methods were developed for the synthesis of optically pure tertiary phosphines from P-stereogenic phosphine oxides.[106 – 112] Some of these reactions proceed *via* an electrophilic mechanism with retention of configuration at the P atom. For example, the trichlorosilane – triphenylphosphine system reduces (*R*)-methyl(2-methoxyphenyl)phenylphosphine oxide **22** [(*R*)-PAMPO] to phosphine **23** [(*S*)-PAMP] with complete retention of configuration and optical purity (Scheme 72).[106]

Scheme 72

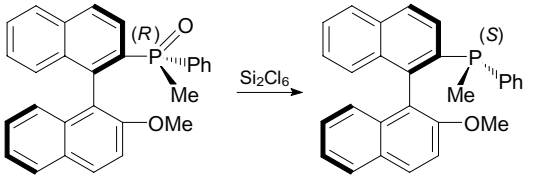


22 **23**

(*R*)-PAMPO (99% *ee*) (*S*)-PAMP (95%, 99% *ee*)

Meanwhile, the reduction with trichlorosilane in the presence of triethylamine leads to 50% inversion of configuration. On the contrary, hexachlorodisilane reduces monoxide **172** to tertiary phosphine **173** with high stereospecificity.[107] The reduction of this substrate with phenylsilane under similar conditions also occurs with retention of configuration at the phosphorus atom (Scheme 73).[109 – 111]

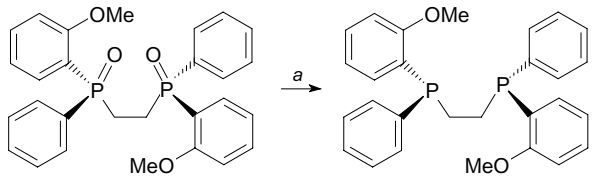
Scheme 73



172 (100% *ee*) **173** (60%, 100% *ee*)

The reactivity of silane can be enhanced using titanium(IV) isopropoxide as the catalyst. In this case, the reduction occurs with retention of configuration at the phosphorus atom. The catalytic cycle apparently includes the formation of an intermediate silyl radical, which reacts with phosphine oxide. For example, the reaction performed under these conditions produced diphosphine **174** with *ee* of

Scheme 74



175 (100% *ee*) **174** (85% *ee*)

(*a*) $(Me_2SiH)_2O$, $Ti(OPr^i)_4$, Na_2SO_4, methylcyclohexane, 60 °C

86% from optically pure diphosphine oxide **175** (Scheme 74).[107]

Keglevich *et al.*[108] used dimethyl sulfide borane under mild conditions for the direct transformation of cyclic phosphine oxides into phosphine borane. Thus, five-membered cyclic phosphine oxide **176** smoothly reacts with a 4 – 5-fold excess of the borane – dimethyl sulfide complex in chloroform at the temperature from 25 to 65 °C to form phosphine borane **177** in 39% – 92% yield. It is worth noting that under these conditions, the reduction of phosphine oxide proceeds with complete stereospecificity, which was confirmed by X-ray diffraction (Scheme 75).

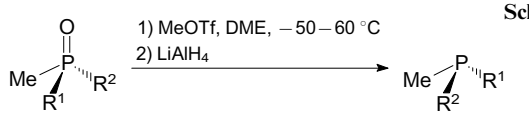
Scheme 75



176 **177** (86%)

The $MeOTf - LiAlH_4$ system proved to be a good reagent for the reduction of chiral phosphine oxides (Scheme 76).[103, 104] Chiral phosphines **23** and **178a – f** (from here and below the corresponding phosphine boranes) were synthesized with high enantiospecificity and inversion of configuration (88% – 98% *ee*). Methyl triflate, tosylates, mesylates and iodides were found to be the most efficient electrophiles, which reduced the corresponding

Scheme 76



23, **178a – f**

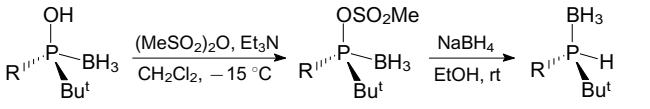
Table 4. Reduction of enantiomerically pure phosphine oxides to phosphines **23** and **178** (see Scheme 76).[103]

Product	R^1	R^2	Yield (%)	*ee* (%)	Configuration
178a	1-Naph	Ph	92	97	*S*
178a	1-Naph	Ph	90	98	*S*
23	Ph	*o*-An	85	98	*R*
178b	cyclo-C_6H_{11}	*o*-An	74	95	*R*
178c	cyclo-C_6H_{11}	1-Naph	81	88	*R*
178d	Ph	2-$Pr^iC_6H_4$	97	98	*R*
178e	$(CH_2)_2Ph$	Bu^t	55	97	*R*
178f	$(CH_2)_2Ph$	cyclo-C_6H_{11}	96	92	*R*

phosphine oxides to tertiary phosphines in good yields (Table 4).[103]

The reduction of phosphinite boranes with sodium borohydride and methanesulfonic anhydride gave phosphinic acid boranes. Thus, the reaction of optically pure boranes **179** with this anhydride resulted in the stereoselective formation of mesylates **180**, which were reduced with sodium borohydride in ethanol to chiral secondary phosphine boranes **60** and **181a**,**b** in 90% yield with complete stereospecificity and inversion of configuration (Scheme 77).[32, 103]

Scheme 77



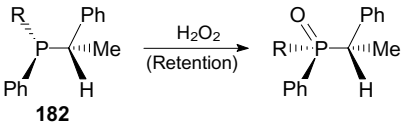
179 **180** **60**, **181a**,**b** (90%)

R = Me (**60**), Et (**181a**), MeO (**181b**)

5. Oxidation and thionization

The oxidation and thionization of trivalent phosphorus compounds generally occur with retention of the absolute configuration at the P reaction centre.[113 – 120] Despite the complexity of oxidation reactions, many of them can be assigned to electrophilic reactions. For example, the oxidation of chiral tertiary phosphines **182** with hydrogen peroxide (Scheme 78) or the addition of elemental sulfur to aminophosphines **183**, as well as their oxidation with hydrogen peroxide (Scheme 79), proceed in a stereospecific manner with retention of optical purity and absolute configuration at the carbon and phosphorus atoms.[120, 121]

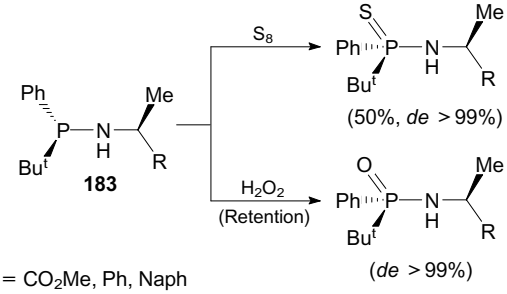
Scheme 78



182

R = Me, Ph

Scheme 79

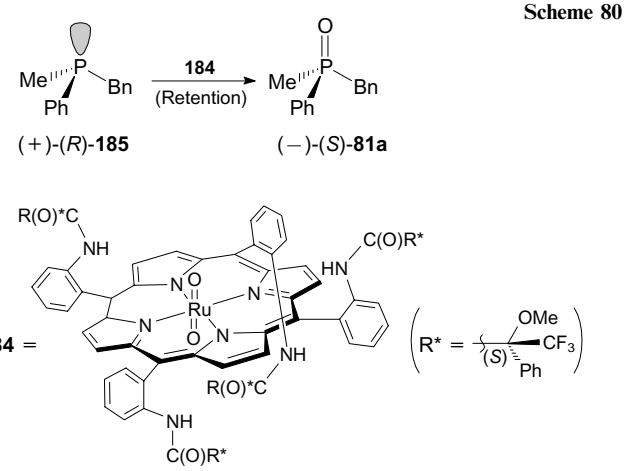


183

R = CO_2Me, Ph, Naph

The oxidation of racemic phosphines in the presence of chiral dioxoruthenium(VI) complex **184** containing optically active methoxy(trifluoromethyl)phenylacetyl groups on both sides of the porphyrin plane affords optically active phosphine oxides with 41% *ee*. Under these conditions, the reaction of chiral (+)-(*R*)-benzyl(methyl)phenylphosphine **185** affords (−)-(*S*)-benzyl(methyl)phenylphosphine oxide (−)-(*S*)-**81a** with retention of configuration. It was demon-

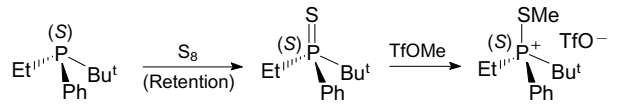
Scheme 80



strated that the reaction proceeds without racemization, with enantiospecific control of oxygen transfer (Scheme 80).[116]

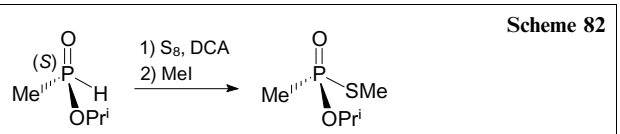
Chiral phosphines react with elemental sulfur with retention of configuration at the phosphorus atom. For example, optically active (−)-(*S*)-*tert*-butyl(methylthio)(phenyl)ethylphosphonium triflate **186** was prepared from methyl triflate and (+)-(*S*)-*tert*-butyl(phenyl)ethylphosphine sulfide **187**, which was synthesized from tertiary phosphine (*R*)-(−)-**188** and elemental sulfur (Scheme 81).[115]

Scheme 81



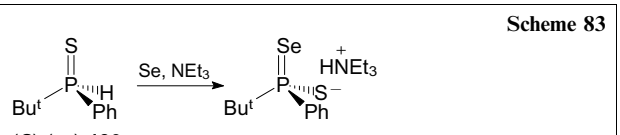
The addition of sulfur to phosphine oxide (*S*)-(−)-**107** in the presence of dicyclohexylamine (DCA) followed by methylation at the sulfur atom occurs with retention of configuration and affords (+)-isopropyl (*S*)-methylphosphonothioate (*S*)-**189**. The absolute configuration of this compound was established by X-ray diffraction (Scheme 82).[117]

Scheme 82



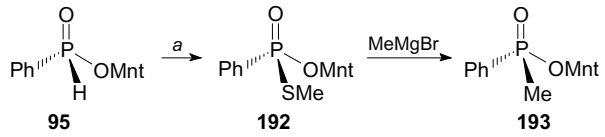
Sulfide **190** was transformed into optically active thioselenic acid in the form of salt **191** with a high *ee* value by the addition of selenium in the presence of triethylamine (Scheme 83). Another optically active selenic acid, Et(EtO)P(Se)SH, was resolved into enantiomers by crystallization of its salts with quinine.[114]

Scheme 83



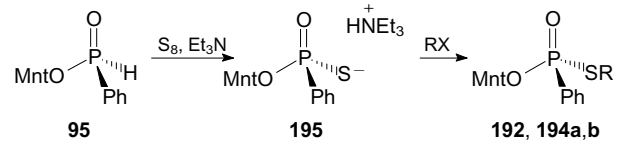
The thiomethylation of (*R*)-menthyl P-phenylphosphinate **95** followed by the reaction of menthyl *S*-methylphenylphosphonothioate **192** with methylmagnesium bromide gave menthyl (*R*)-P-methylphenylphosphinate **193** (Scheme 84). Following this, both the Grignard reaction and thiomethylation occur with retention of configuration at the phosphorus atom.[117] Besides, (*S*)-alkylphosphonothioates **192** and **194a**,**b** were synthesized in a stereospecific manner by the reaction of menthyl phenylphosphinate **95** with sulfur followed by S-alkylation of salts **195** with alkyl halides (Scheme 85).[113]

Scheme 84



(*a*) 1) S_8, $(n\text{-}C_6H_{13})_2NH$; 2) MeI

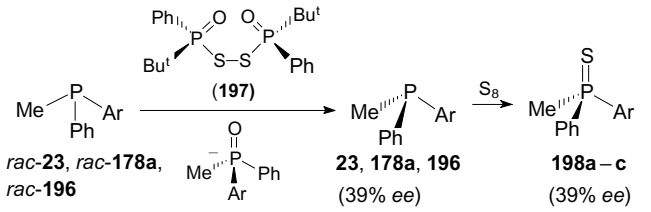
Scheme 85



R = Me (**192**), Et (**194a**), Ph (**194b**)

The treatment of racemic P-stereogenic tertiary phosphines **23**, **178a** and **196** with enantiomerically pure bisphosphoryl disulfide **197** under kinetic resolution conditions (the reactant ratio was 2 : 1) afforded the corresponding enantiomerically enriched tertiary phosphine oxides and phosphine sulfides **198a**–**c** with an enantioselectivity of 39% (Scheme 86).[118]

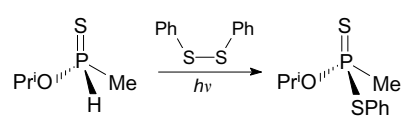
Scheme 86



Ar = *o*-An (**23**, **198a**), 1-Naph (**178a**, **198b**), *o*-Tol (**196**, **198c**)

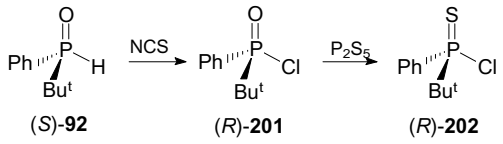
Under similar conditions, enantiomerically enriched (*S*)-phosphonite **199** reacts stereospecifically with diphenyl disulfide to form product (*R*)-**200** with equal *ee* values (Scheme 87).[114]

Scheme 87



The chlorination of secondary phosphine oxide (*S*)-**92** with *N*-chlorosuccinimide (NCS) gave chloride (*R*)-**201** with retention of configuration. The latter compound was stereospecifically transformed into sulfide (*R*)-**202** with retention of configuration by the treatment with phosphorus pentasulfide (Scheme 88). The synthesis of the following optically active phosphinodithioates was reported: methyl (*S*)-*tert*-butyl(phenyl)phosphinodithioate, (*S*)-*tert*-butyl(phenyl)-phosphinothioic iodide and (*R*)-*tert*-butyl(phenyl)phosphinoselenothioic acid.[119]

Scheme 88

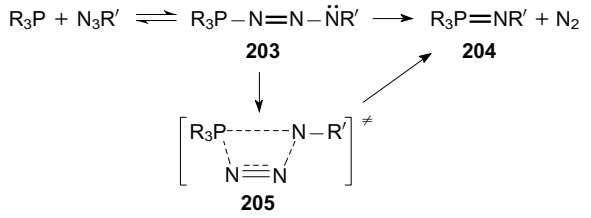


(*S*)-**92** (*R*)-**201** (*R*)-**202**

6. Staudinger imination and ligation

The Staudinger reaction is a two-step process involving the initial electrophilic addition of azide to a trivalent phosphorus compound followed by loss of nitrogen from intermediate phosphazide **203**, which is transformed into iminophosphorane **204**. The reaction rate is controlled by the inductive effect of substituents and the electrophilicity of the azide. The imination reaction is accelerated in the presence of electron-withdrawing groups in azide and electron-donating substituents in a trivalent phosphorus compound. Stability of intermediate phosphazide **203** defines the kinetic order of the Staudinger reaction. The reaction can follow either first- or second-order kinetics depending on whether the decomposition of the intermediate occurs *via* a unimolecular or bimolecular mechanism. Such phosphazides were found to dissociate into the starting reactants. The dissociation is slowed down in the presence of electron-withdrawing and electron-donating substituents in the azide and phosphorus components, respectively. The formation of phosphazides $(Me_2N)_3P-N_3R'$ (R′ = Me, Ph) is almost irreversible. The equilibrium of imination of phosphites with aryl azides is significantly shifted towards the formation of imines. Phosphazide **203** decomposes to the corresponding iminophosphoranes **204** *via* an intramolecular mechanism through four-membered cyclic transition state **205**, as was demonstrated by Gololobov and Kasukhin (Scheme 89).[122]

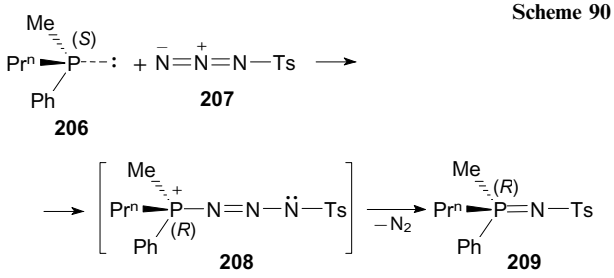
Scheme 89



203 **204** **205**

The Staudinger imination occurs with retention of the absolute configuration at the phosphorus atom.[123 – 129] This conclusion was confirmed by a number of imination reactions of optically active phosphines. Chiral phosphines were used to study the mechanisms of the Staudinger reaction with reactive nitrogen-containing compounds

Scheme 90

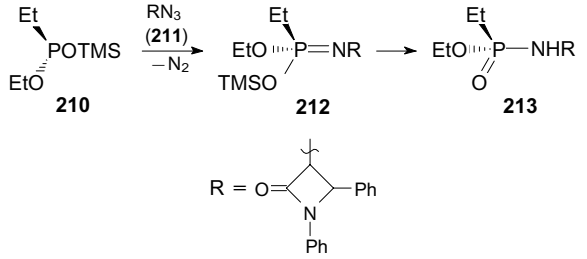


206 **207** **208** **209**

(Scheme 90).[124, 129] For example, chiral phosphine **206** reacts with tosyl azide **207** through the formation of intermediate **208**, which is transformed into chiral iminophosphorane **209** with retention of configuration at the phosphorus atom.

Dimukhametov and Nuretdinov [126, 127] studied the reaction of *O*-ethyl *O*-trimethylsilyl ethylphosphonite (**210**) with 3-azido-1,4-diphenylazetidin-2-one (**211**) in benzene. The reaction was accompanied by the removal of the silyl group from intermediate **212** to form (−)-*O*-ethyl(ethyl)-phosphonoamino-1,4-diphenylazetidin-2-one (**213**). The silyl group migrated from the oxygen atom to nitrogen. The Staudinger reaction involving silyl phosphinite and 3-azido-1,4-diphenylazetidin-2-one (**211**) was found to occur with retention of configuration at the phosphorus atom (Scheme 91).

Scheme 91



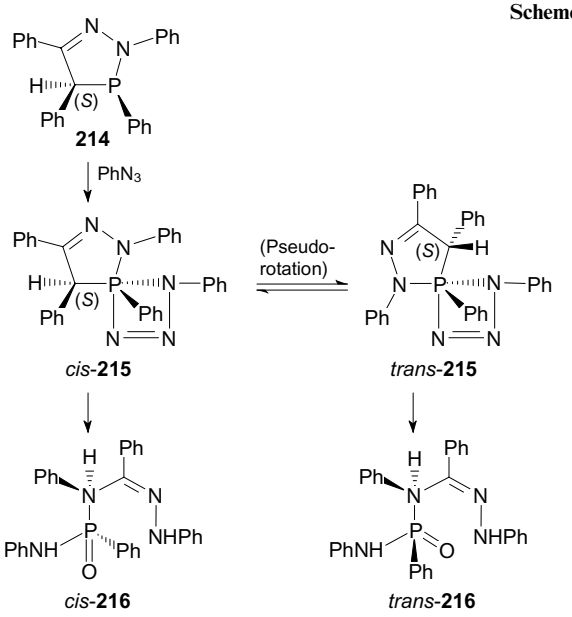
210 **212** **213**

The reaction of aromatic azides with diastereomeric diazaphospholenes **214** affords cyclic phosphazenes **215**. The hydrolysis of phosphazenes **215** gives the corresponding acyclic compounds **216**. The stereochemistry of the reaction and the *cis*–*trans* isomerization observed in the imination reaction of diazaphospole **214** are attributed to pseudorotation of the pentacoordinate phosphorane intermediate *cis*-**215** ⇌ *trans*-**215** (Scheme 92).[128]

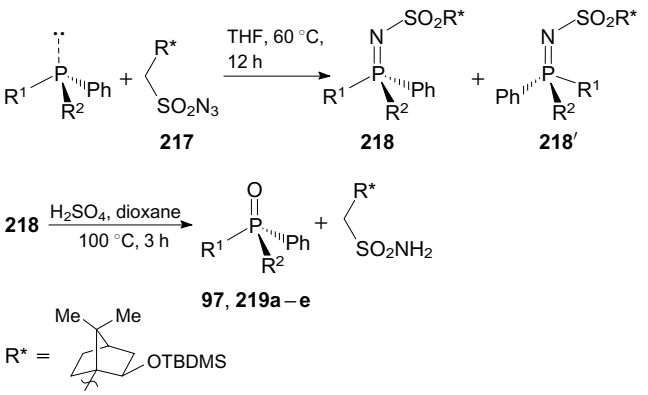
The resolution of racemic α-P-stereogenic phosphines into enantiomers was accomplished by the reaction of racemic phosphine with enantiomerically pure (1*S*,2*R*)-*O*-(*tert*-butyldimethylsilyl)isobornyl-10-sulfonyl azide (**217**). The resulting diastereomeric mixture of phosphine imines **218** was separated by fractional crystallization and flash chromatography. The subsequent acid hydrolysis produced the corresponding optically pure phosphine oxides **97** and **219a**–**e** in high yields with opposite configuration at the phosphorus atom (Scheme 93).[130] This method was applied to prepare phosphine ligands for rhodium(I) complexes.[131 – 133]

Saxon and Bertozzi [134] proposed a modification of the Staudinger reaction. This modification utilizes methyl carboxylate **220** as an electrophilic trap to capture aza-ylide intermediate **221**, which generates phosphine amide and oxide. As opposed to the classical Staudinger reaction,

Scheme 92



Scheme 93



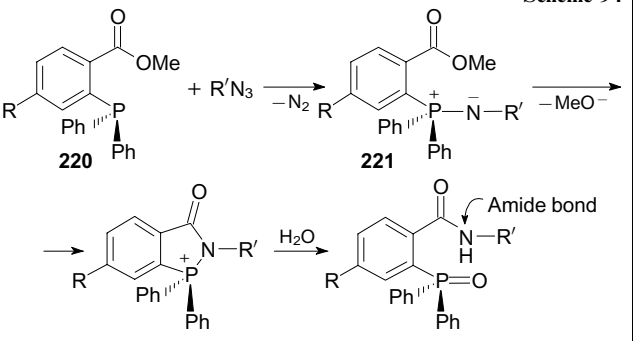
Compound	R^1	R^2	R*	Yield of **218** (%)	Yield of **218′** (%)	Configuration
219a	Ph	Me	cyclo-C_6H_{11}	94	93	R_P
219b	Ph	Me	cyclo-C_5H_9	90	93	–
97	Ph	Me	Pr^i	87	94	S_P
219c	Ph	Me	1-Naph	94	96	S_P
219d	Ph	Me	9-Phnt	89	> 99	–
219e	Ph	1-Naph	4-PhC_6H_4	91	93	R_P

Phnt is phenanthryl.

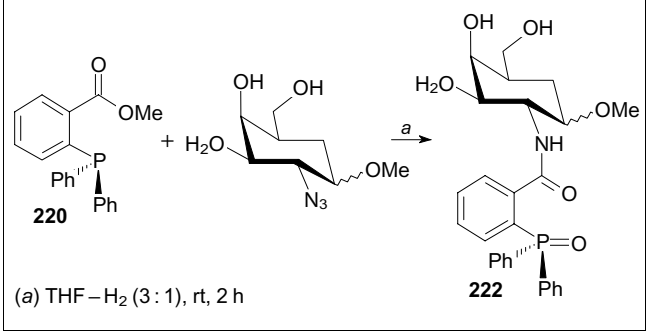
both products of this modification are covalently bound moieties. Hence, this modification was called Staudinger ligation and is widely used in chemical biology for bioconjugation (Scheme 94).[134 – 136]

Numerous examples of the Staudinger ligation demonstrate that this is a valuable method in chemistry and biology.[137, 138] Currently, the Staudinger reaction is one of the most mild and chemoselective ligation strategies. Besides, this reaction is applied to prepare bioconjugates in the case of chemical reactions in living cells.[136] Since the reactive partners, azide and phosphine, are absent in living organisms and are not prone to interact with natural compounds, the Staudinger ligation belongs to bioorthogonal reactions, which can proceed in living cells without interfering with biochemical processes. Hence, this reaction is considered as a 'gift to chemical biology'.[137] Examples of application of this method to the synthesis of amide derivatives of carbohydrates (**222**)[135] and nucleosides (**223**)[138] are given in Schemes 95 and 96.

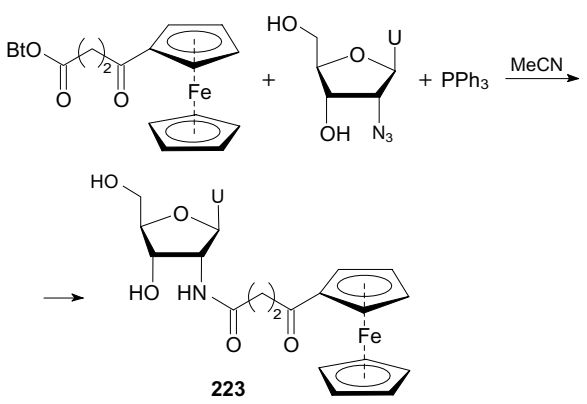
Scheme 94



Scheme 95



Scheme 96

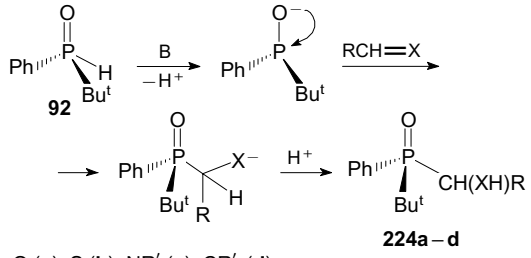


7. Electrophilic addition to multiple bonds

Unsaturated compounds are involved in electrophilic reactions at the C=X bond with phosphorus-containing reagents, being either anions or molecules, which donate an electron pair to form a new bond. In the chemistry of phosphorus, the most commonly used electrophilic addition reactions are phospha-aldol condensation, phospha-Mannich reaction and phospha-Michael reaction.[139 – 146] The latter reaction is known primarily as the Pudovik reaction.

Haynes *et al.*[147] studied the stereochemistry of the phospha-aldol reaction. The addition of configurationally stable chiral base-ionized *tert*-butylphenylphosphine oxide (**92**) to various saturated aldehydes or α,β-unsaturated carbonyl compounds was found to afford functionalized phosphonates **224a – d** with a diastereoselectivity from 33% to 98% and retention of the absolute configuration (Scheme 97).[100 – 102]

Scheme 97

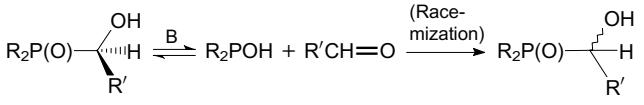


X = O (**a**), S (**b**), NR′ (**c**), CR'_2 (**d**)

7.1. Phospha-aldol condensation

The main method for the synthesis of hydroxyphosphonates is based on the phosphonylation of carbonyl compounds, primarily using the phospha-aldol reaction (the Abramov reaction, or the Pudovik reaction, or, more correctly, the Abramov – Pudovik reaction).[139 – 141] The addition of phosphorous acid esters to carbonyl compounds involves the following two steps: the formation of a P – C bond and the removal of the ester function giving a phosphonyl group. The first addition step is reversible.[141 – 145] In the presence of strong bases, hydroxyalkylphosphonates dissociate into the starting dialkyl phosphite and a carbonyl compound. This transformation is known as the retro-phospha-aldol reaction (or the retro-Abramov reaction). Cherkasov and coworkers[142, 143] and Gancarz[144] studied the retro-Abramov reaction by kinetic methods and NMR spectroscopy, respectively, and showed that this reaction has a considerable effect on the stereochemistry of hydroxyphosphonates. Chiral phosphonites containing a stereogenic phosphorus atom or phosphites, derived from chiral alcohols, amino alcohols or amines, can be used as chiral substrates in the asymmetric phospha-aldol condensation. The addition of achiral aldehydes to chiral dialkyl phosphites generally affords hydroxyphosphonates with moderate stereoselectivity (Scheme 98).[145 – 148]

Scheme 98



B = MeONa, Et_3N, *etc.*

The addition of P-chiral lithium-substituted *tert*-butylphenylphosphine oxide (**92**) to aldehydes and α,β-unsaturated carbonyl compounds produced hydroxyphosphonates **225a – m** with *de* values ranging from 33% to 98% (Scheme 99, Table 5).[147]

The diastereoselectivity of the reaction was additionally investigated by calculating the relative energies of diastereomeric five-membered transition states TS1 and TS2 taking into account O – Li contacts that generate products **225** and **225′**, respectively. In TS1 and TS2, *gauche* interactions involving the R group and the phenyl ring or the R substituent and the *tert*-butyl group, respectively, are apparent.[147] The reaction was found to be kinetically controlled (Scheme 100, arcs indicate *gauche* interactions).

Scheme 99

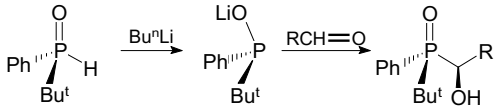
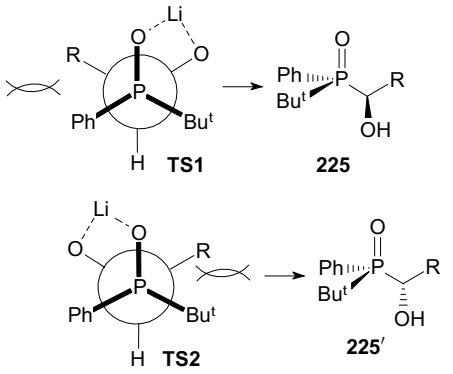


Table 5. Stereospecificity of the phospha-aldol reaction (see Scheme 99).[147]

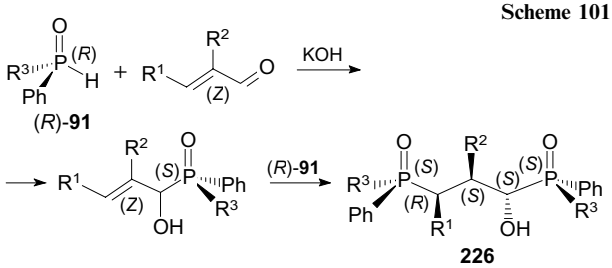
Compound **225**	R	Yield (%)	*dr*
a	PhCH=CH	77	80 : 20
b	MeCH=CH	63	80 : 20
c	CH_2=CH	65	78 : 22
d	MeC(=CH_2)	77.2	82 : 18
e	cyclo-C_6H_{11}	80	85 : 15
f	Ph	77	98 : 2
g	Me	80	70 : 30
h	2-Py	76	80 : 20
i	Bu^i	78	67 : 33
j	1-Naph	71	92 : 8
k	2-Naph	71	85 : 15
l	2-Th	68	82 : 18
m	2-Fu	76	90 : 10

Scheme 100



The KOH-catalyzed one-step reaction of (1*R*,2*S*,5*R*)-menthyl-(R_P)-phenylphosphine oxide (**91**) with α,β-unsaturated aldehydes at room temperature affords P,C-stereogenic 1,3-bis(phosphinyl)propane **226** as a single isomer

Scheme 101

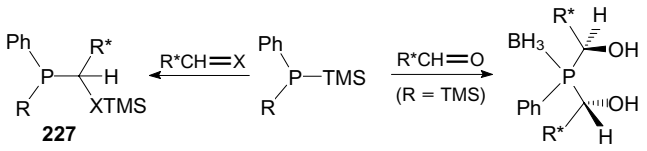


R^3 = (1*R*,2*S*,5*R*)-Mnt; R^1, R^2 = Ph, *o*-An, *m*-An, *p*-An, 4-ClC_6H_4, 4-FC_6H_4

containing five chiral centres. The reaction occurs with retention of the absolute configuration at the phosphorus atom (Scheme 101).[149]

The reaction of (trimethylsilyl)diphenylphosphine with chiral aldehydes and imines proceeds with high stereoselectivity to form diastereomerically pure tertiary α-(trimethylsilyl)oxyalkylphosphines **227**. Diastereomeric purity of the addition products was >90%. The products were purified through the formation of phosphine – borane complexes. The reaction of bis(trimethylsilyl)phenylphosphine with (*R*)-glyceraldehyde acetonide produces tertiary bis(glyceryl)phosphines **228** (Scheme 102).[150]

Scheme 102

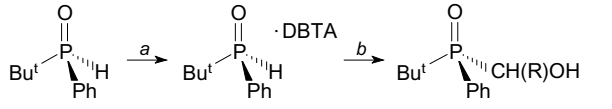


R*CHO = (*S*)-Leu, (*S*)-Phe, Gal, Gly, *etc.*;
X = O, NAlk; R = Ph, TMS

(90% – 96% *ee*)

The synthesis of stereochemically pure secondary phosphine oxides is based on the crystallization-induced asymmetric transformation (CIAT) involving radical-dynamic resolution.[148, 151] This strategy provides access to enantio- and diastereomerically pure *tert*-butyl(hydroxyalkyl)phenylphosphine oxides **225**.[148] The synthesis was accomplished by performing the reaction of an equimolar mixture of secondary phosphine oxide **92** and benzaldehyde in the presence of 0.05 M aqueous sodium hydroxide. This procedure gave diastereomeric *tert*-butyl(hydroxybenzyl)-phenylphosphine oxides **225f** in a ratio of 1 : 1. However,

Scheme 103



(*a*) (−)-DBTA (1 mol.%), I_2, DPE, Δ, 16 h (CIAT 1);
(*b*) RCH=O, 0.05 M NaOH (CIAT 2)

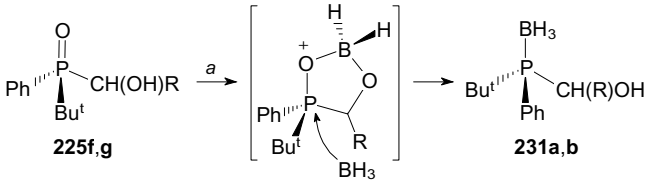
Table 6. Synthesis of *tert*-butyl(hydroxyalkyl)phenylphosphine oxides **225** *via* CIAT process (see Scheme 103).[148]

Compound **225**	R	*dr*	Configuration	Yield (%)
f	Ph	20 : 1	R_P, *R*	89
n	*p*-Tol	1 : 20	R_P, *S*	94
o	*o*-Tol	1 : 20	R_P, *S*	94
p	4-Pr^{i}C$_6$H$_4$	20 : 1	R_P, *R*	96
r	*p*-An	20 : 1	R_P, *S*	96
s	3-HOC$_6$H$_4$	1 : 20	R_P, *S*	90
t	4-ClC$_6$H$_4$	1 : 3.5	–	90
u	4-O$_2$NC$_6$H$_4$	1 : 4.4	–	93
v	Pr^i	1 : 20	R_P, *S*	95
w	Bu^t	1 : 20	R_P, *S*	89
x	H	–	–	100

heating of this mixture to 80 °C was accompanied by the reversible dynamic transformation, resulting in the predominant formation of a single diastereomer in 89% yield. The CIAT strategy involved the formation of complex **229** as a single diastereomer upon the treatment of phosphine oxide **92** with a 1% iodine solution and a stoichiometric amount of dibenzoyl-L-tartaric acid (DBTA) and its subsequent crystallization from a toluene – diisopropyl ether (DPE) mixture. The reaction of this complex with aldehydes produced compounds **225f**,**n** – **x** in good yields with high enantioselectivity (Scheme 103, Table 6).

Aromatic and enolizable aliphatic aldehydes proved to be the most suitable reagents because they give a single diastereomer as the major product at room temperature (see Table 5). The quantitative addition of formaldehyde to secondary phosphine oxide **92** afforded enantiomerically pure *tert*-butyl(hydroxymethyl)phenylphosphine oxide **225x** in quantitative yield.[148] The reaction of compounds **225f**,**g** with an excess of the borane complex ($BH_3 \cdot Me_2S$ or $BH_3 \cdot THF$) proceeds through the formation of intermediates **230** giving phosphine boranes **231a**,**b** (Scheme 104).[152]

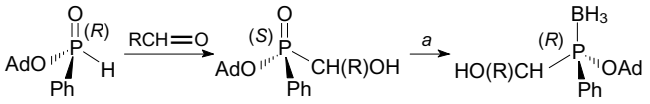
Scheme 104



(*a*) $BH_3 \cdot THF$, THF, 60 °C;
R = Ph (**225f**, **231a**), Me (**225g**, **231b**)

Optically pure hydroxyalkylphosphine boranes were synthesized from readily available adamantylphosphinate **232a** (Scheme 105). The one-pot two-step reaction gave enantiopure tertiary hydroxyalkylphosphine oxides **233** in good yield with high *ee* values. In the third step, their treatment with an excess of the complex $BH_3 \cdot THF$ produced phosphine boranes **234** with high stereospecificity.

Scheme 105



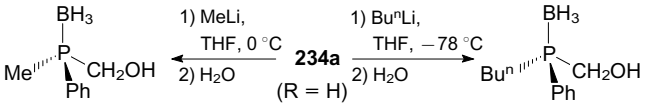
(*a*) $BH_3 \cdot THF$ (6 equiv.), THF, rt, 48 h; R = Bu^t, cyclo-C$_6$H$_{11}$, Ph, *o*-An, *etc.*

H-Adamantylphosphinates were proposed as convenient precursors for the synthesis of other P-stereogenic ligands. They can be synthesized in one step from commercially available chlorophosphines. Both enantiomers of these intermediates are air- and moisture-stable. They are easily separated by semipreparative chiral HPLC in gram amounts and can be subjected to stereoselective transformations, which makes it possible to isolate each enantiomeric P-stereogenic phosphine. Due to slow racemization of phosphinates **233** in the presence of bases, phosphine boranes 23**4** are produced with high stereospecificity.

The above-described strategy is based on the introduction of the hydroxymethyl protecting group at the phosphorus centre of phosphinate **232a**. The stereoselective transformation of tertiary hydroxyalkylphosphine oxides **233** into the corresponding tertiary hydroxyalkylphosphine boranes **234** was accomplished by the reduction of the P=O bond with excess BH_3 under mild conditions. The presence of an adjacent α- or β-hydroxy group is a key factor ensuring the reduction. The absence of this group or its distant position from the phosphorus atom leads to an inertness of the P=O bond towards BH_3. The intramolecular P=O···B complexation coordinated by α- or β-hydroxy groups that are present in phosphine oxide provides the possibility of reducing the P=O bond with BH_3. The transformation of hydroxyalkylphosphine oxides into hydroxyalkylphosphine boranes occurs with complete inversion of configuration at the phosphorus atom.[148, 152 – 155]

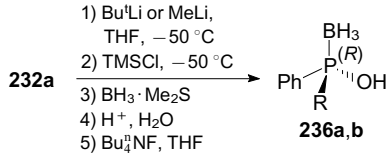
The P-alkylation reaction was found to proceed in good yield with high enantiospecificity (*ee* > 95%) involving various alkyl halides as electrophiles. The reactions of adamantylphosphinate **232** produced chiral phosphine boranes **235** and **236** (Schemes 106 and 107).[153, 155]

Scheme 106



235b (88%, 97% *ee*) **235a** (91%, 97% *ee*)

Scheme 107



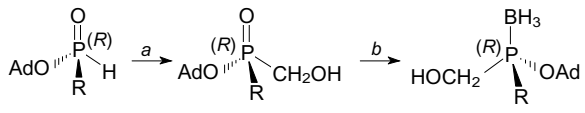
236a,**b**

236: R = Bu^t (**a**), Me (**b**)

An alternative method for the synthesis of P-stereogenic compounds **234**, **237** – **239** is based on the introduction of the hydroxymethyl group to the phosphorus centre of phosphinate **232** in order to control the stereoselectivity of the subsequent reduction in the reaction with a THF borane complex.[153, 155] The reaction of compounds **232a** – **f** with formaldehyde affords optically pure phosphinates **234a**, **237a** – **c** (Scheme 108).[153]

The synthesis of functionalized tertiary phosphine boranes **239** involves the transformation of (hydroxymethyl)-phosphine borane **237a** into secondary phosphine borane

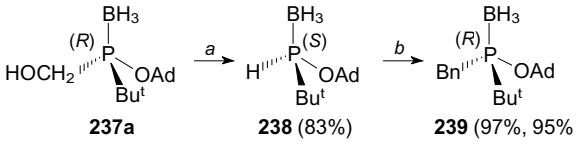
Scheme 108



232a – **d** **234**, **237a** – **c**

(*a*) $(CH_2O)_n$, LiOH, THF, H_2O; (*b*) $BH_3 \cdot THF$ (6 equiv.), THF, rt, 48 h; R = Ph (**232a**, **234a**), Bu^t (**232b**, **237a**), cyclo-C_6H_{11} (**232c**, **237b**), *o*-An (**232d**, **237c**)

Scheme 109



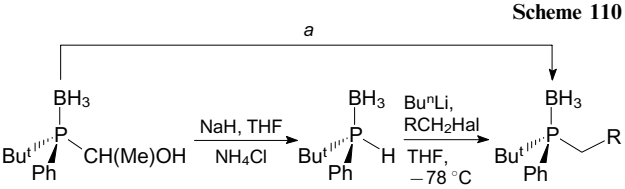
237a **238** (83%) **239** (97%, 95% *ee*)

(*a*) $RuCl_3$,$K_2S_2O_8$, KOH, MeCN, H_2O; (*b*) BnBr, Bu^{n}Li, THF, −78 °C

238 followed by alkylation of the latter. The P-alkylation of compound **238** affords phosphine borane **239** in good yield with high enantiospecificity (*es* > 95%) (Scheme 109). Other alkyl halides can also be used as electrophiles.

The highly regioselective synthesis of functionalized tertiary phosphine boranes **240a** – **g** under mild conditions was developed *via* a chemodivergent approach starting from readily available (hydroxymethyl)phosphine borane **231b**. This synthesis affords exclusively *O*-alkylation products. The P-alkylation reaction of secondary phosphine borane **53a** with a variety of alkyl halides as electrophiles proceeds in moderate to very good yield with very high enantiospecificity (*es* > 95%) (Scheme 110).[155]

Scheme 110



(S_P)-**231b** (*er* = 95 : 5) **53a** **240a** – **g** (95% *es*)

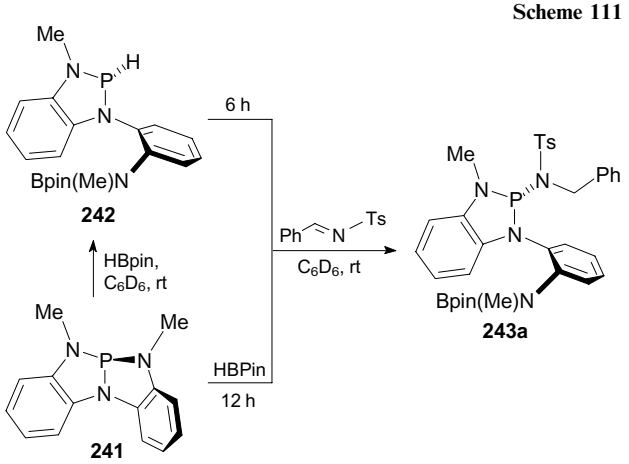
(*a*) NaH (1.5 equiv.), RCH_2Hal (1.2 equiv.), THF, 0 → 25 °C, 24 h; R = Me (**a**), All (**b**), Pr^i (**c**), 2-Py (**d**), *o*-An (**e**), *o*-Tol (**f**), H (**g**)

7.2. Phospha-Mannich reaction

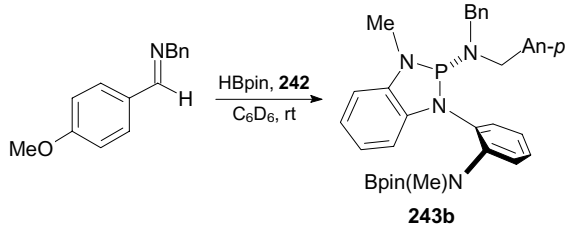
The synthesis of enantiomerically enriched aminophosphonates and aminophosphonic acids by the catalytic asymmetric hydrophosphonylation of imines has attracted significant research interest.[2] The addition of phosphites $(RO)_2P(O)H$ to imines (the phospha-Mannich reaction) is commonly used for the synthesis of chiral aminophosphonic acids exhibiting various biological activity. The stereochemistry of the phospha-Mannich reaction was studied and described in recent publications,[156 – 158] in particular using chiral compounds. For example, stoichiometric and catalytic activity of geometrically hindered phosphorous triamide **241** with pinacoloborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane, HBpin) under conditions of the phospha-Mannich reaction was reported. The addition of HBpin to triamide **241** affords P-hydrido-1,3,2-diazaphospholene **242** *via* the B – H bond cleavage in pinacoloborane. Compound **242** reacts with imine to form phosphorous triamide (*e.g.*, **243a**). This fact was confirmed by an independent synthesis. The first-order kinetics of this reaction attests to a unimolecular mechanism.[158] Compound **241** also reacts with *N*-tosylbenzaldimine and HBpin at room temperature in benzene, resulting in the complete transformation into addition product **243a** (Scheme 111).

The structure of compound **243a** was established by X-ray diffraction. This compound was shown to be a triamide with a three-coordinate phosphorus atom and the

Scheme 111



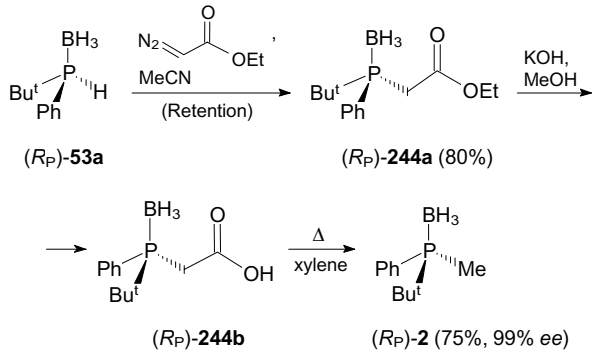
Scheme 112



Bpin moiety at the *N*-methylanilide group. Compound **243b** was synthesized directly from diazaphospholene **242** by the treatment with *N*-benzyl-*p*-methoxybenzaldimine and HBpin under ambient conditions (Scheme 112).

An efficient method was developed for the P – C bond formation in the presence of substoichiometric amounts of copper iodide as the catalyst. A series of sterically hindered phosphines were subjected to the addition reaction with diazo compounds. The corresponding products were prepared in high yields with retention of configuration at the asymmetric centre. The reaction proceeds under neutral conditions, thereby avoiding base-catalyzed racemization. For example, compound (*R*)-**53a** reacted with ethyl diazoacetate in the presence of 5 mol.% CuI in acetonitrile at ambient temperature to form product (R_P)-**244a**, which was isolated in 80% yield. In order to determine the stereointegrity of the phosphorus atom, compound (*R*)-**244a** was subjected to hydrolysis giving acid (*R*)-**244b** followed by decarboxylation, resulting in the formation of compound (R_P)-**2** in 75% yield (Scheme 113).[156]

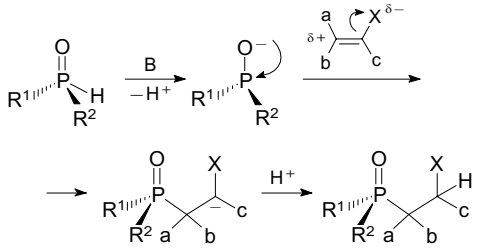
Scheme 113



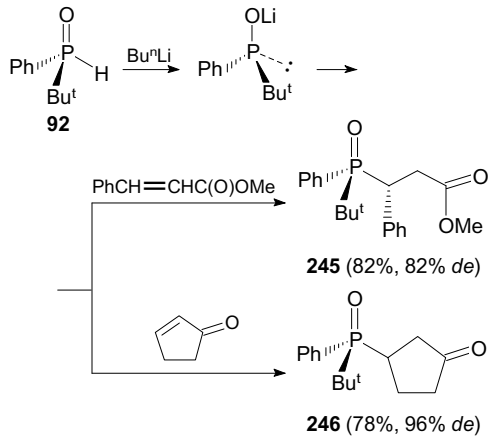
7.3. Phospha-Michael reaction (Pudovik reaction)

The phospha-Michael reaction (the Pudovik reaction) is a nucleophilic addition of anions, generated from trivalent phosphorus derivatives, to an activated multiple bond and is one of the most convenient methods for the P – C bond formation.[2, 159 – 167] The phospha-Michael reaction results in the addition of dialkyl phosphites to compounds with an activated C=C multiple bond in the presence of bases. Anions derived from compounds $R_2P(O)H$ or R_2PHB can be employed as P^{III} reagents. The asymmetric phospha-Michael reaction can be accomplished in two ways: by the substrate-controlled diastereoselective addition using chiral starting reagents and chiral inducers or by the catalytic enantioselective addition (Scheme 114; a, b, c are substituents in the alkene). For example, the addition of unsaturated carbonyl compounds to lithiated *tert*-butyl(phenyl)phosphine oxide affords chiral tertiary phosphines **245** and **246** in good yields with a diastereoselectivity of 82% – 96%. In most cases, the reaction occurs with retention of configuration at the phosphorus atom. The absolute configuration of the products was established by X-ray diffraction (Scheme 115).[147]

Scheme 114



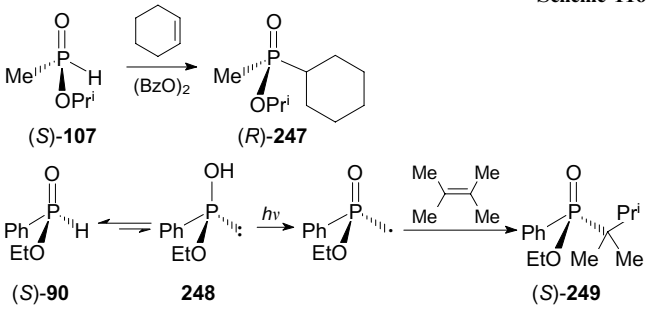
Scheme 115



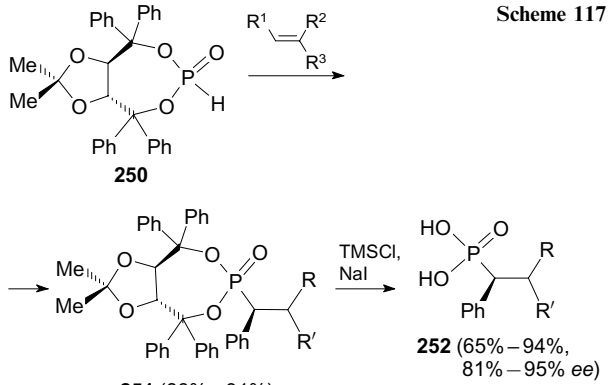
The free-radical addition of cyclohexene to isopropyl methylphosphinate (*S*)-**107** in the presence of dibenzoyl peroxides affords isopropyl cyclohexyl(methyl)phosphinate **247** with retention of configuration. The free-radical addition of alkenes (in particular, 2,3-dimethylbut-2-ene) to ethyl (*S*)-phenylphosphinate (*S*)-**90** proceeds through the formation of phosphinite **248** with complete retention of the absolute configuration at the phosphorus atom in addition product (*S*)-**249** (Scheme 116).[117]

Chiral phosphite **250**, which was synthesized from α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL), was used in addition reactions with aromatic alkylidene malonates and nitrostyrenes (Scheme 117).[158]

Scheme 116



Scheme 117

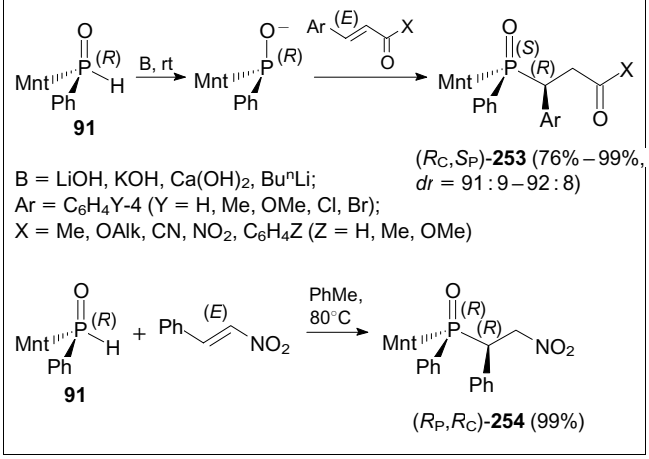


The reactions were performed under heterogeneous conditions in the presence of KOH supported onto solid Fe_2O_3. Phosphonates **251** were synthesized in moderate to high yields with very high stereoselectivity. The chiral inducer was removed by the treatment with a mixture of TMSCl and NaI followed by hydrolysis to form products **252**. Alkyl-substituted alkylidene malonates reacted in good yields, although with low diastereoselectivity. The stereoselective addition of nucleophiles to asymmetrically substituted *tert*-butyl(cyclohexa-1,4-dienyl)phosphine oxide and its derivatives proceeded with *ee* values of 65% – 94%.[159, 160]

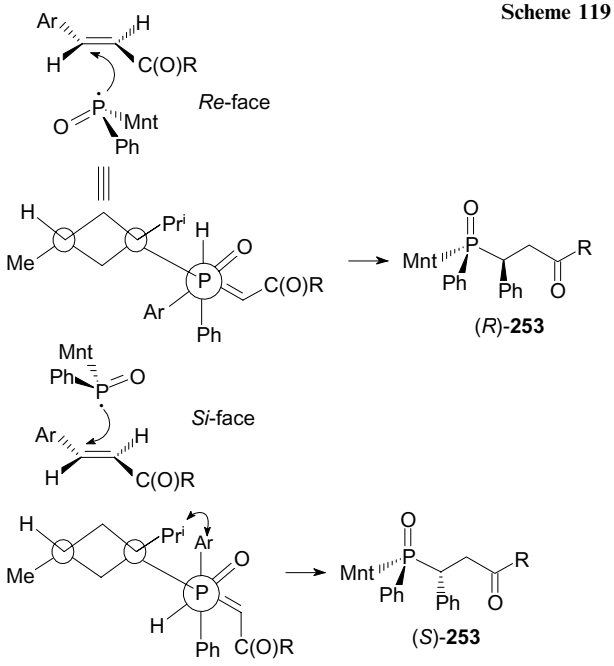
Functionalized P,C-stereogenic tertiary phosphine oxides **253** were synthesized in high yields with high *dr* values for P- and C-stereocentres by the addition of (R_P)-phenylphosphine oxide **91** to activated alkenes. The reaction was performed in the presence of metal hydroxides as catalysts or on heating. (R_P)-(−)-Menthylphenylphosphine oxide **91** was configurationally stable in electrophilic addition reactions because the (−)-menthyl group stabilizes the configuration at the phosphorus atom. The calcium hydroxide-catalyzed addition of secondary phosphine oxide **91** to a variety of activated alkenes at 20 °C was completely stereospecific and proceeded with retention of configuration at the P reaction centre. Functionalized P,C-stereogenic tertiary phosphine oxides **253** and **254** were synthesized with *dr* values ranging from 97 : 3 to 99 : 1. Optically pure stereoisomers were isolated in high yields and were transformed into P-stereogenic tertiary phosphines (Scheme 118).[161]

Since azobis(isobutyronitrile) (AIBN) catalyzed this reaction, while (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) acted as an inhibitor, it was concluded that the reaction proceeds *via* a mechanism of thermal free-radical addition. The phosphorus free radical attacks alkene from

Scheme 118



Scheme 119

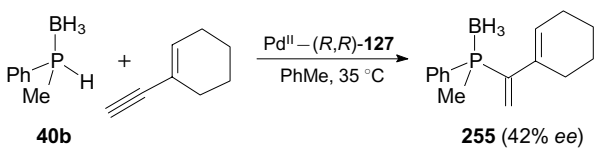


either the back or front side. The steric repulsion between the menthyl and aryl groups leads to the predominant formation of R_C-configured stereomer **253** (Scheme 119).[161]

Examples of the electrophilic addition of secondary phosphines to alkynes were reported. Thus, chiral palladium complexes with the (*R*,*R*)-Me-DuPhos ligand (**127**) catalyze the alkynylation of phosphine borane **40b** giving P-chirogenic phosphine **255** with moderate stereoselectivity and with a substrate conversion of 70% (Scheme 120).[162]

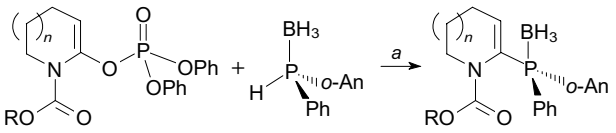
The use of α-amido enol phosphates for the activation of a vinylic bond in the palladium-catalyzed C – P-cross-coupling reaction proceeds with high *ee* values.[164] Enol phosphates **256**, which were derived from appropriate amides, were functionalized with a phosphinite group at the α

Scheme 120



position to the nitrogen atom. The reaction was performed under mild conditions due to activation of P – H bonds in phosphine boranes (or phosphine oxides) by palladium complexes involving enol phosphate linking reagents. Chiral and achiral α(β)-alkenylphosphinite boranes **257** were synthesized in yields of up to 70% with very high *ee* values (Scheme 121).

Scheme 121



256 **257** (99% *ee*)

(*a*) (dppf)$PdCl_2$, Cs_2CO_3, MeCN, 40 – 60 °C; *n* = 1, 2; R = Me, Bu^t

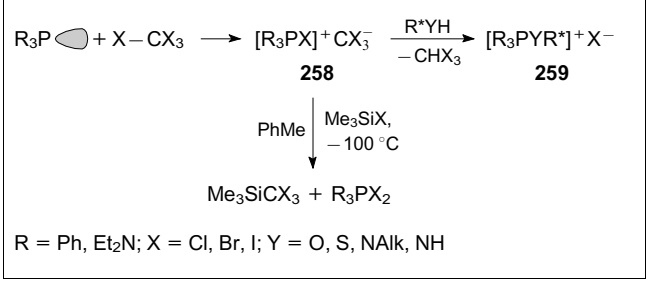
The review by Yorimitsu [165] addresses the homolytic radical substitution of organophosphorus compounds as a convenient method for C – P bond formation. The radical substitution of a halogen atom in organic phosphorus halides was considered as an alternative to the classical ionic substitution.

8. Halophilic reactions of phosphorus(III) compounds

Reactions of trivalent phosphorus compounds with tetrahalomethanes and other compounds containing a halogen atom with a partial positive charge belong to halophilic transformations. There are diverse reactions, in which a nucleophile interacts with a halogen atom and an organic substituent R in RHal serves as a leaving group forming a carbanion.[168 – 170] In halophilic reactions of P^{III} compounds with tetrahalomethanes, the nucleophilic phosphorus atom interacts with the electrophilic halogen atom to form quasiphosphonium salt **258** containing a phosphonium cation and a trihalomethyl anion.

The halophilic substitution reactions of P^{III} compounds involve two steps. The first step gives rise to highly reactive phosphonium-type intermediate **258** containing the CX_3^- anion, which was established by chemical and physicochemical methods.[169, 170] For example, the reaction of intermediate **258** with trimethylchlorosilane affords Me_3SiCX_3 (X = Cl, Br). These compounds were isolated and characterized. The reaction of triphenylphosphine with bromotrifluoromethane and trimethylchlorosilane produces trimethyl(trifluoromethyl)silane (Ruppert – Prakash reagent [168]). In the second step, compound **258** reacts with a nucleophile (ROH, RSH, R_2NH, RNH_2) giving phosphonium salt **259**, which can decompose to form phosphine oxide and alkyl halide or be rearranged into trihalomethylphosphonium salt.[169] The release of chloroform in halophilic reactions in the presence of a proton donor is also evidence in favour of the formation of quasiphosphonium intermediate **258** (Scheme 122).

Scheme 122



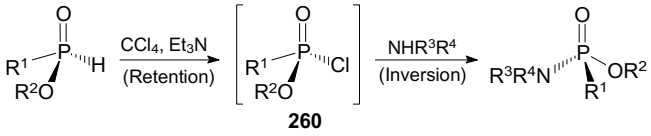
R = Ph, Et_2N; X = Cl, Br, I; Y = O, S, NAlk, NH

The reactions of P^{III} compounds with halogen donors bearing a partial positive charge are fairly diverse. Different versions of halophilic reactions are commonly applied in synthetic organic and organophosphorus chemistry to perform halogenation, dehydration and P – N bond formation reactions.[166 – 172] The Atherton – Todd, Appel and Corey – Fuchs reactions and the reaction of tertiary alkylphosphines with tetrahalomethanes are the most popular halophilic transformations in organic synthesis.[2]

8.1. Atherton – Todd reaction

The Atherton – Todd reaction is a conventional synthetic method used to prepare various phosphorus compounds.[173 – 181] This reaction was described in 1945.[173] Steinberg [174] studied the mechanism of this reaction and found that it involves the intermediate formation of phosphoryl chlorides **260** (Scheme 123). The Atherton – Todd reaction is a two-step process. The first step giving chloride **260** occurs with retention of configuration, whereas the second step (substitution) proceeds with inversion of configuration. This allows the synthesis of the final product with inverted configuration at the phosphorus atom.[175 – 178]

Scheme 123

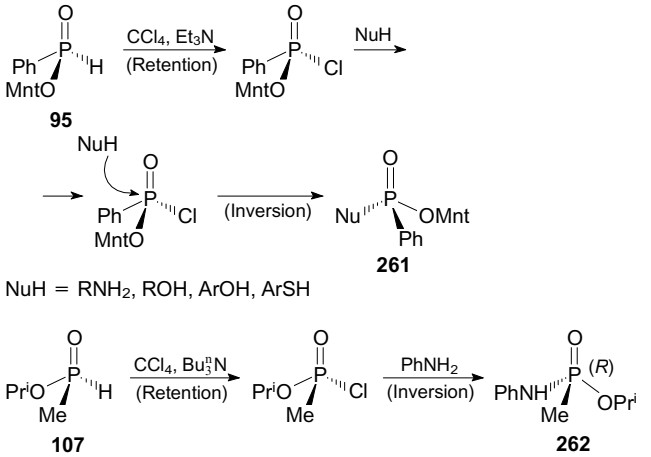


260

Reiff and Aaron [179] studied the stereochemistry of this process. They used enantiomeric *O*-isopropyl menthylphosphonite **95** as the substrate (Scheme 124). The Atherton – Todd reaction of compound **95** with CCl_4, tri-n-butylamine and aniline as the nucleophile gives products **261** with complete stereocontrol. Stec and Mikolajczyk [167] investigated the stereochemistry of the reaction of phosphoryl halides with alcohols and amines.

Optically active phosphonates were synthesized from menthylphosphinates (or other secondary phosphine oxides) and nucleophilic compounds (amines or alcohols)

Scheme 124



95 **261**

NuH = RNH_2, ROH, ArOH, ArSH

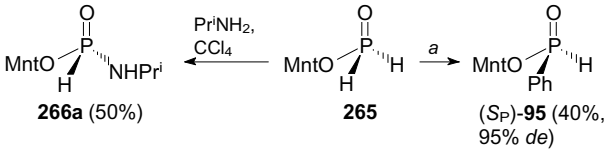
107 **262**

via the Atherton – Todd reaction.[175] The process occurred with complete stereoinversion at the phosphorus atom and afforded optically pure products **261** and **262** in nearly quantitative yield (94%). The authors concluded that in all cases, the first step (*i.e.*, the formation of intermediate phosphoryl chloride) proceeds *via* the S_E2 mechanism with retention of the absolute configuration. The subsequent attack of a nucleophilic substrate (amine, alcohol or thiophenol) proceeds *via* the S_N2 mechanism, *i.e.*, from the side opposite the phosphorus – chlorine bond giving the substituted product with high stereospecificity and inverted configuration (see Scheme 124).[175 – 179]

The Atherton – Todd reaction is usually performed in the presence of bases, due to which the three-coordinate form, *e.g.*, compound **92′** involved in the tautomeric equilibrium **92** ⇌ **92′**, readily reacts with tetrahalomethane. The first step of the reaction involves the electrophilic addition giving phosphonium intermediates **A** and **A′**, which are transformed into halide **263** with retention of the absolute configuration. In the second step, the reaction of bromide **263** with a nucleophile (dimethylamine) affords substituted product **264** with inverted configuration. It is worth noting that compound **263** was isolated in the pure form (Scheme 125).[178]

(1*R*,2*S*,5*R*)-Menthyl *H*-phosphinate (**265**) was synthesized by the treatment of (1*R*,2*S*,5*R*)-menthol with anhydrous hypophosphorous acid in the presence of trimethoxymethane. The Atherton – Todd reaction of compound **265** with CCl_4 and isopropylamine gave the corresponding amide **266a**. (1*R*,2*S*,5*R*)-Menthyl phosphinate **265** was also involved in the Heck reaction with iodobenzene in the presence of a palladium complex, resulting in the formation of diastereomerically enriched (S_P)-(−)-menthyl phenylphosphonite **95** (Scheme 126).[180]

Scheme 126

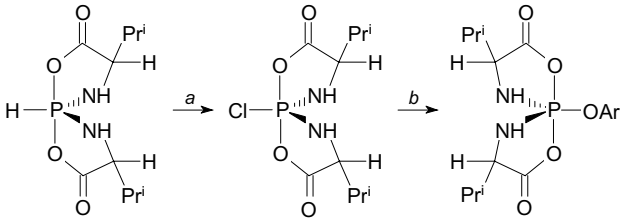


266a (50%) **265** (*S*$_P$)-**95** (40%, 95% *de*)

(*a*) PhI, $Pd(Ph_3P)_2Cl_2$, Et_3N

Cao *et al.*[181,182] studied the stereochemistry of the reaction of chiral hydrospirophosphorane **267** with CCl_4 and phenols. The first step affords chlorinated spirophosphorane **268** with retention of configuration at the phosphorus atom. In the second step, chloride **268** reacts with phenols with inversion of configuration, because the nucleophilic attack occurs *via* the S_N2 mechanism from the side opposite the phosphorus – chlorine bond to give phosphamides **269** (Scheme 127).

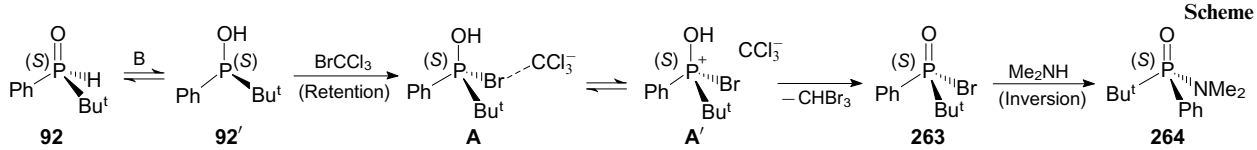
Scheme 127



267 **268** **269** (68% – 90%)

(*a*) CCl_4, K_2CO_3, MeCN (Retention); (*b*) ArOH (Inversion);
ArOH = Ph, *p*-Tol, *p*-An, 4-$O_2NC_6H_4$, 4-ClC_6H_4

Scheme 125



92 **92′** **A** **A′** **263** **264**

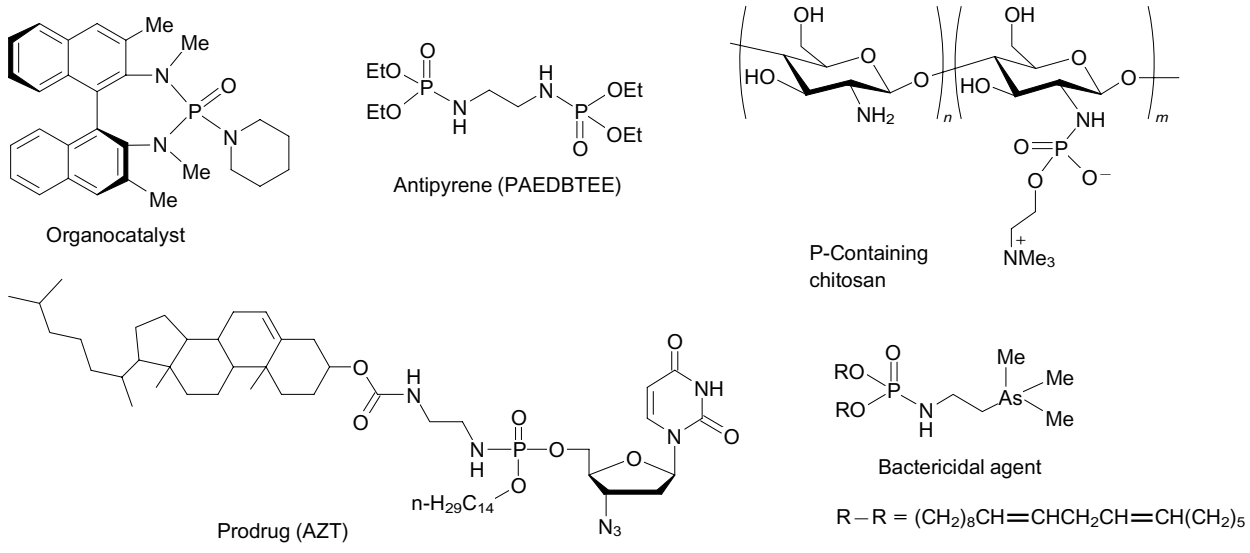


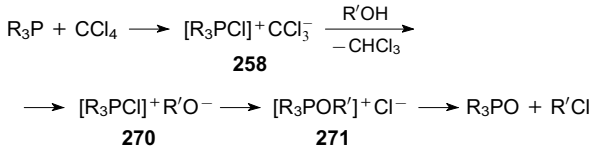
Figure 1. Examples of valuable phosphamides.

The Atherton – Todd reaction is commonly used in organic synthesis as a convenient method for the P – N bond formation. Many phosphoramidates and phosphonamidates prepared by this method are utilized in practice. Thus, chiral phosphamides are used as organocatalysts, antipyrenes (PAEDBTEE, PAPDBTEE, DMDAPR, *etc.*) and biologically active compounds, in particular, cationic lipophosphoramides, phosphorus derivatives of chitosan and bactericidal agents (*e.g.*, BSV77, BSV4, *etc.*). Some representatives of valuable phosphamides are shown in Fig. 1.[178]

8.2. Appel reaction

The Appel reaction is an important synthetic strategy for the conversion of alcohols into alkyl chlorides using triphenylphosphine and carbon tetrachloride (Scheme 128). The reactions utilizing carbon tetrabromide or bromine as a source of halogen afford alkyl bromides, while the application of tetraiodofuran, iodomethane or iodine allows the synthesis of alkyl iodides. This reaction was named for the German chemist Appel,[171] although it has earlier been described by Steinberg,[174] who considered this reaction as a special case of the Atherton – Todd reaction. The Appel reaction is commonly used in laboratory syntheses of natural products.[2] The reaction starts with the formation of phosphonium salt **258** (X = Cl), which exists as a contact ion pair[169, 182] and is not involved in the α-elimination reaction giving dichlorocarbene. The deprotonation of alcohol produces alkoxide **270** and chloroform. The nucleophilic substitution of chlorine with alkoxide affords intermediate compound **271**. The $S_N2(P)$ reaction of primary and secondary alcohols with tertiary phosphines and CX_4 produces alkyl halides and phosphine oxide. The formation of products **270** and **271** from tertiary alcohols proceeds *via* an intramolecular mechanism. The intramolecular nucleophilic displacement of chlorine by the alkoxy group in intermediate product **270** affords alkoxyphosphonium salt **271**. The reactions of optically active alcohols occur in a stereospecific manner to form alkyl halides with inversion of the absolute configuration.[169, 182]

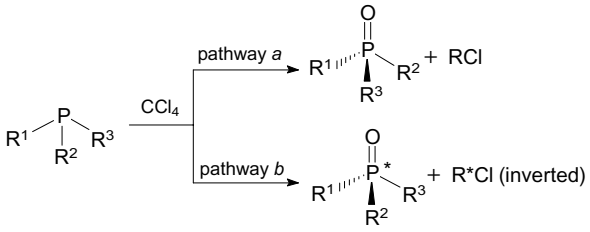
Scheme 128



Optically active tertiary phosphines react with tetrahalomethanes and achiral alcohols, to give chiral phosphine oxides with inversion of the absolute configuration of substituents at the phosphorus atom (Scheme 129, pathway *a*). Optically active alcohols give optically active alkyl halides with inversion of configuration and complete stereospecificity.[172] In some cases, the reaction of racemic tertiary phosphines with polyhalomethanes and chiral alcohols can produce chiral tertiary phosphine oxides *via* an asymmetric induction (see pathway *b* in Scheme 129).[170] Examples of the Appel reaction involving phosphines (*S*)-**272** and (*R*)-**1b** are presented in Schemes 130 and 131, respectively.

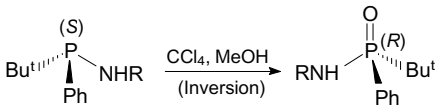
An asymmetric version of the Appel reaction was developed.[183, 184] The oxidation of aminophosphine **273** containing a chiral substituent (R*) in the amino group occurs in a stereoselective manner with chirality transfer

Scheme 129



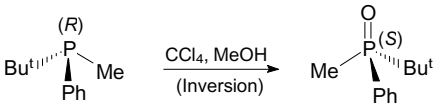
(*a*) Achiral ROH, chiral phosphine; (*b*) chiral R*OH, achiral phosphine (asymmetric synthesis)

Scheme 130



(*S*)-**272** (84% *ee*) (*R*)-**266** (80% *ee*)

Scheme 131

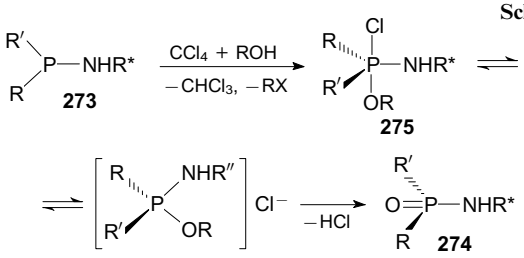


(*R*)-**1b** $[\alpha]_D$ = 29.5 (MeOH) (*S*)-**42e** $[\alpha]_D$ = −14.9 (MeOH)

from the R* group to the trivalent phosphorus atom giving phosphinamidate **274** in an optical yield of 50% – 98%. The crystallization of the products provided optically pure compounds. The study of the reaction mechanism by NMR spectroscopy showed that the reaction proceeds through chlorophosphoranes **275**. The formation of hydroxyhalophosphoranes **275** (R = H) or alkoxyhalophosphoranes (R = n-Alk) (the diastereomeric ratio was 94 : 6) was observed in the case of compounds containing the five-membered 1,3,2-oxaphospholane ring. It was established that the synthesized phosphoranes are in equilibrium with alkoxyphosphonium salts. Alkyl groups at the phosphorus atom favour the shift of the equilibrium of the compounds $P^V \rightleftharpoons P^{IV}$ towards the alkoxyphosphonium salt. The pseudorotation of the ligands at the P^V atom results in the formation of the thermodynamically most stable diastereomer of the halophosphonium intermediate, which is transformed into a single diastereomer of final product **274** (Scheme 132).[183]

Gilheany and co-workers[185 – 188] studied the asymmetric Appel reaction in relation to the oxidation of racemic tertiary phosphine **276** with polyhaloalkanes in the presence of chiral L-menthol (Scheme 133). The reaction afforded chiral phosphine oxide **42b** with a good *ee* value. The

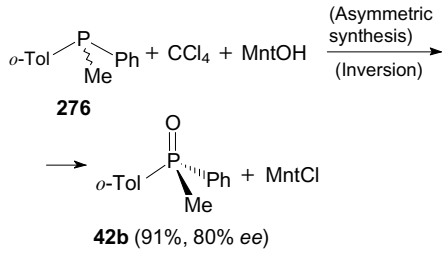
Scheme 132



R* = CH(Me)Ph, CH(Bu^i)CO_2Me

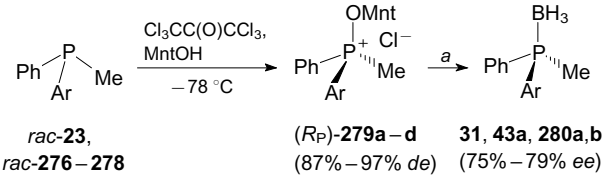
reaction of this phosphine oxide with LDA and copper chloride produced an analogue of the DiPAMP ligand, which is used in asymmetric catalysis. A small impurity of the meso isomer was removed by crystallization from benzene (see Scheme 133).[184]

Scheme 133



Interesting procedures for the isolation of both enantiomerically enriched reaction products (up to 94% *ee*) in good yields are based on the double resolution of phosphine oxides. Thus, the reaction of racemic phosphines **23**, **276** – **278** with hexachloroacetone and menthol *via* dynamic resolution gave salts **279a** – **d**, which were transformed into phosphine boranes accompanied by the elimination of chiral alcohol (Scheme 134).[188] Products **31**, **43a** and **280a**,**b** were obtained with *ee* values ranging from 75% to 79%.

Scheme 134



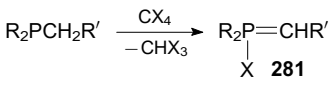
(*a*) 1) $LiAlH_4$ or $NaBH_4$; 2) $BH_3 \cdot THF$;
Ar = *o*-Tol (**276**, **279a**, **43a**), *o*-An (**23**, **279b**, **31**), 2-Pr^{i}C$_6$H$_4$ (**277**, **279c**, **280a**), 2,4-Me$_2$C$_6$H$_3$ (**278**, **279d**, **280b**)

Asymmetric induction in the Appel and Atherton – Todd reactions is attributed to the formation of the long-lived phosphorane intermediate and Berry pseudorotation. Van Kalkeren *et al.*[189] studied the mechanism of this reaction by theoretical calculations (Scheme 135).[189]

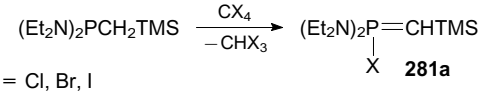
8.3. Reaction of tertiary alkylphosphines with tetrahalomethanes

Tertiary phosphines containing primary or secondary alkyl groups at the phosphorus atom react with halogen donors bearing a partial positive charge to form P-halogen ylides **281**.[190 – 192] Generally, the reactions of tertiary alkylphosphines with carbon tetrahalides (CCl_4, $CBrCl_3$, CBr_4) or C_2Cl_6 are performed in pentane, diethyl ether or dichloromethane on cooling below 0 °C. The reaction using carbon tetrachloride is accomplished at a temperature lower than 0 °C, while carbon tetrabromide and bromotrichloromethane readily react at −70 °C. The reaction of tertiary alkylphosphines with *N*-haloimides proceeds at room temperature. Generally, P-halogen ylides, *e.g.* compounds **281a**,**b**, are synthesized in very high yields (up to 99% – 100%; Scheme 136).

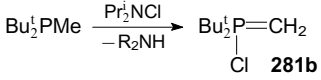
Scheme 136



X = Cl, Br; R = Alk, Ar, Et_2N, AlkO; R′ = H, Me, Ph, Cl, TMS и др.

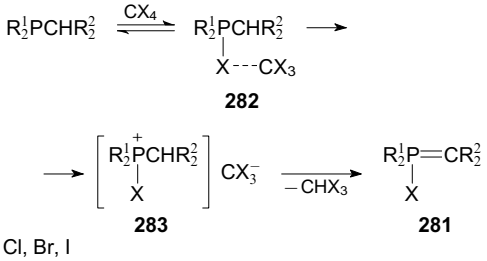


X = Cl, Br, I



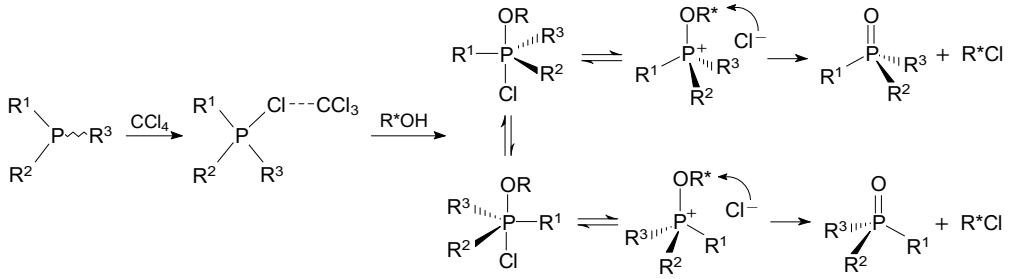
The substituents R and R′ can be electron-withdrawing, resulting in an increase in CH acidity of alkylphosphine, electroneutral or electron-donating (see Scheme 136).[193 – 196] Apparently, the reaction of tertiary alkylphosphines with CX_4 proceeds *via* the ionic mechanism. Intermediate complex **282** that is initially derived from tertiary phosphine and CX_4 (X = Hal) is transformed into quasiphosphonium salt **283** containing the trichloromethyl anion. The highly basic CX_3^- anion deprotonates carbon in phosphonium salt **283** to form ylide **281**. This mechanism was established by performing the reaction of sterically hindered tri-*tert*-butylphosphine with carbon tetrabromide at −120 °C in pentane, which afforded a phosphonium salt containing the tribromomethyl anion (Scheme 137).[197 – 199]

Scheme 137



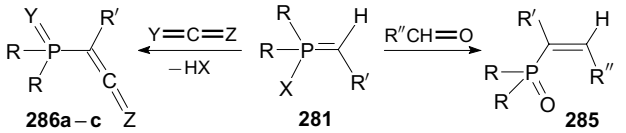
X = Cl, Br, I

Scheme 135



Chloro(fluoro) phosphorus ylides are highly reactive and undergo various transformations. These compounds readily react with aldehydes to form phosphorus-containing alkenes **285**, with carbon dioxide giving phosphorus-containing ketenes **286a**, with carbon disulfide to produce phosphorus-containing thioketenes **286b** and with phenyl iso(thio)cyanates yielding products **286c**. In the presence of a chiral centre at the phosphorus atom, the reaction proceeds in a stereospecific manner (Scheme 138).[172, 190, 191]

Scheme 138

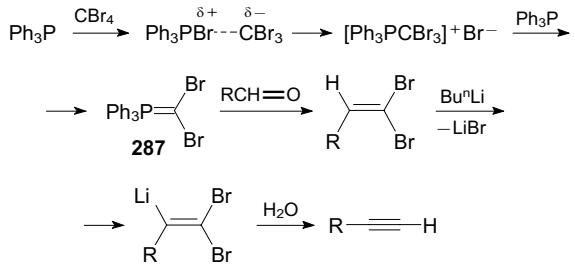


X = Cl, F; Y = O, S; Z = O (**a**), S (**b**), NPh (**c**)

8.4. Corey – Fuchs reaction

The Corey – Fuchs reaction, also known as the Ramirez – Corey – Fuchs reaction, is a two-step strategy for the conversion of aldehydes into alkynes.[200 – 208] The first step involves the reaction of triphenylphosphine with tetrabromomethane giving dibromo phosphonium ylide **287**, which reacts with aldehyde to form 1,1-dibromoalkene. In the second step, dibromoalkenes are transformed into alkynes in the presence of strong bases, *e.g.*, n-butyllithium (Scheme 139).

Scheme 139



The Corey – Fuchs reaction is employed in the synthesis of biologically active and natural products.[200 – 206] For example, this reaction, as the key step of the synthesis, produced polyunsaturated fatty acids and their amides, in particular, tetradecapentaenoic acid derivatives as efficient biological regulators of apoptosis.[203 – 206] Several reviews address applications of this reaction.[200 – 202]

9. Conclusion

An analysis of the literature data shows that the chemistry of electrophilic reactions involving phosphorus-containing compounds is being actively developed along different lines. The extension of the field of application of these reactions and investigation of their stereochemistry and mechanisms are important issues in organophosphorus chemistry, since they will provide a deeper insight into the electrophilicity and electrophilic substitution. Considerable progress was made in increasing the number of electrophilic reagents, resulting in the synthesis of a broad range of chiral organophosphorus derivatives structurally similar to known natural and synthetic physiologically active substances, including those with valuable properties. Numerous examples of application of electrophilic reactions involving chiral organophosphorus compounds demonstrate the popularity of these reactions among organic synthetic chemists. However, the synthetic potential of stereospecific electrophilic reactions has not yet been fully assessed. For example, electrophilic catalysis utilizing chiral metal complexes is not fully understood.

Phosphine boranes comprise an important class of organophosphorus compounds due to their high reactivity and extensive use in organic synthesis. Phosphine boranes easily produce lithium or sodium derivatives, which undergo electrophilic substitution at the phosphorus atom. The efficient application of phosphine boranes serves as an impetus to further research in this interesting field of chemistry. These compounds are valuable reagents, particularly as precursors of chiral tertiary phosphines.

The discovery of halophilic reactions and the subsequent establishment of the mechanism of attack of the phosphorus atom on halogen are considerable advances in organic chemistry in relation to knowledge of the electrophilic substitution. Halophilic reactions are characterized by a very low activation barrier and, under favourable thermodynamic conditions, they are among the most rapid heterolytic processes.

Electrophilic reactions occupy an important place in the industrial organic synthesis, in particular, in the production of agrochemicals, pharmaceuticals or materials. Of great interest are also P-chirogenic nucleotides, phospha-glucosides and other natural products with promising antiviral, antiproliferative, antibacterial and antimalarial properties. Considerable progress was made in the stereoselective synthesis of P-chirogenic compounds due to the design of versatile electrophilic building blocks, which were prepared using menthol or ephedrine as an auxiliary for the asymmetric synthesis. Methods of bioorthogonal conjugation and the Staudinger ligation are of interest for both biologists and chemists. This relatively new field of chemistry is being rapidly developed and is already in use in systematic biology. New conjugation strategies allow the modification of complex biological targets, which cannot be investigated by other available methods. The Staudinger ligation is one of the first reactions meeting the criteria of bioorthogonal chemistry. Consequently, this reaction proved to be particularly useful in labelling biomolecules in natural media because it is fast and allows the use of both azide and alkyne as chemical reactants.

Summarizing the above, it can be concluded that stereospecific electrophilic reactions of organophosphorus compounds provide an approach to the synthesis of a wide range of chiral products. The reaction mechanism of electrophilic substitution at the phosphorus atom has been extensively studied, and interesting results were obtained. Generally, these reactions involve two steps and proceed *via* addition – elimination. The reaction of an electrophilic reagent with a phosphorus-containing substrate affords a positively charged phosphonium-type intermediate followed by the elimination of an electrofuge, which leaves the substrate without bonding electrons. The vacant orbital of the electrophile accepts electrons, resulting in the formation of a new bond with the substrate. Generally, bimolecular electrophilic substitution reactions $S_E2(P)$ proceed in a stereospecfic manner with retention of the absolute configuration at the P centre, as opposed to bimolecular nucleophilic substitution reactions $S_N2(P)$, which occur with inversion of configuration through the formation of the

five-coordinate phosphorane intermediate that is susceptible to pseudorotation with a change in positions of substituents. Taking into account this fact and the possibility of combining stereospecific electrophilic reactions and stereoselective nucleophilic reactions, further investigations of these reactions hold great promise in relation to the synthesis of new classes of chiral organophosphorus compounds.[207 – 209]

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