Conference paper

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Stereochemistry of electrophilic and nucleophilic substitutions at phosphorus

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Abstract: Nucleophilic and electrophilic substitutions are the most often applied reactions in organophosphorus chemistry. They are closely interrelated, because in a reacting pair always one reagent is an electrophile, and another nucleophile. The reactions of electrophilic and nucleophilic substitutions at the phosphorus center proceed via the formation of a pentacoordinated intermediate. The mechanism of nucleophilic substitution involves the exchange of ligands in the pentacoordinate phosphorane intermediate, leading to the more stable stereomer under the thermodynamic control. Electrophilic substitution proceeds with retention of absolute configuration, whereas nucleophilic substitution with inversion of configuration at the phosphorus center.

Keywords: electrophilic substitution; halogenophilic reactions; ICPC-22; nucleophilic substitution; stereochemistry.

Introduction

Nucleophilic and electrophilic reactions are the most commonly used reactions in organophosphorus chemistry. They are closely interrelated, because in a reacting pair always one reagent is an electrophile, and another nucleophile [1–4].

There is a similarity and a difference between these two types of reactions, which are the most noticeable in the case of chiral compounds. For example, both electrophilic and nucleophilic substitutions include the breaking of existing bonds and the forming of new bonds replacing the previous bonds. In electrophilic substitution reactions, the electrophile (a positive ion or partially positive center of polar compound) attacks the electrophilic center of the molecule, whereas in the nucleophilic substitution reaction, the nucleophile (a molecule rich in electrons) attacks the nucleophilic center by removing the leaving group. The difference between these types of reactions proceeding at phosphorus or carbon center is determined by the structure and the electron shell of these elements. First of all by free pair of electrons and high coordination number of phosphorus. All this makes theoretically interesting the stereochemistry of electrophilic and nucleophilic reactions of organophosphorus compounds, since previously this problem was not generalized and analyzed in spite of a large number of publications.

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Results and discussion

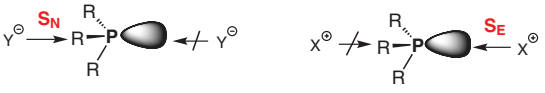
The bimolecular mechanism of the electrophilic substitution of S_E2 on phosphorus is analogous to the $S_N2(P)$ mechanism in that a new bond is formed, when the old bond is broken. However, in the S_N2 mechanism, the incoming group contains a pair of electrons, and its orbital can overlap with the orbital of the phosphorus atom to the extent that the leaving group departs with its electrons.

Stereochemistry of nucleophilic and electrophilic reactions

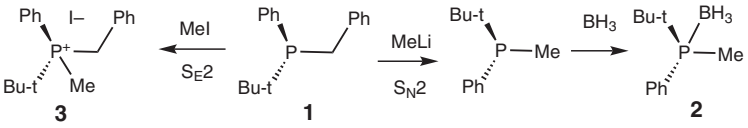
The negatively charged electrophile and the electron pair of P(III)-phosphorus at the frontside repel each other, so the incoming group attacks the substrate from the backside at the angle of 180° to the leaving group with the inversion of configuration of the stereogenic center. If the attacking reagent is an electrophile carrying a vacant orbital to the substrate, then it attacks the frontside of phosphorus center, where a free electron pair is located (Scheme 1). In many cases, the electrophilic reaction with P(III) proceeds according to the type of addition-elimination, that is, first the electrophile is linking with the phosphorus to form an adduct, and then the leaving group is removed.

The P(III) compounds can be electrophiles and nucleophiles. For example, the tertiary phosphine **1** equally easily enters into the reactions of electrophilic and nucleophilic substitution with the formation of products **2** and **3**, respectively (Scheme 2) [3, 5].

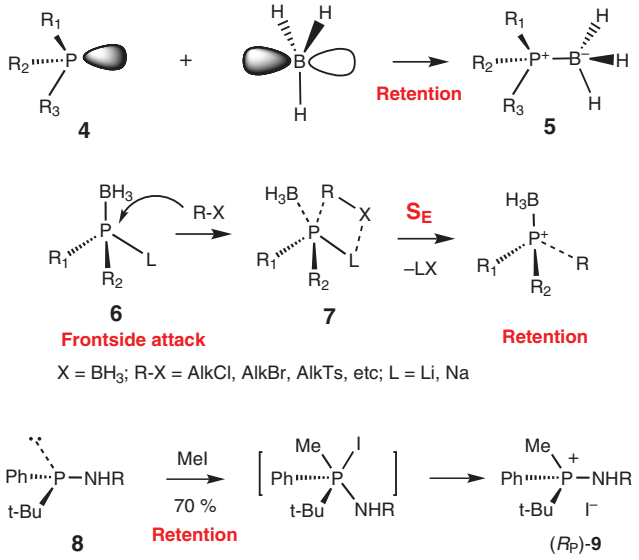
The difference between the reactions of nucleophilic and electrophilic addition is that the intermediates have opposite charges: a negative one at the nucleophilic addition and a positive one at the electrophilic addition. Therefore, the influence of substituents on these reactions is of an opposite nature. The electron-withdrawing group deactivates the phosphorus center with respect to electrophilic addition, and activates the phosphorus center in the case of nucleophilic addition. The electron-withdrawing groups, due to the participation in the delocalization of negative charge, stabilize the transition state, which leads to the formation of an intermediate anion in the nucleophilic reaction. In the case of substrates for which these two versions distinguishable, the configuration is retained if the reaction passes through the first mechanism, and in the second case it is inverted (Scheme 3). The electrophilic substitution through the backside attack is theoretically possible in the case of metal-substituted phosphines, although this is unlikely, since it must pass with the inversion of the configuration. However, examples of such reactions are absent in chemical literature. In reactions S_E2, the positively charged electrophile attacks the phosphorus center from the frontside, attracting the electron pair. The simplest and the most logical geometry of the transition state for S_E2 reactions is shown in Scheme 3. The transition state **7** in the S_E2 reaction has an electrophilic atom attacking the front side of the phosphorus center without preliminary or simultaneous coordination of P(III). In the case of reaction of tertiary phosphines **4** with borane, the formation of additive bond leads to pyramidalization of the borane part to produce approximately tetrahedral geometry with a change in the hybridization of boron from sp^2 to



Scheme 1: Mechanism of electrophilic and nucleophilic reactions.



Scheme 2: P(III) compounds reacting as nucleophiles and electrophiles.



Scheme 3: The mechanism of electrophilic substitution at P(III).

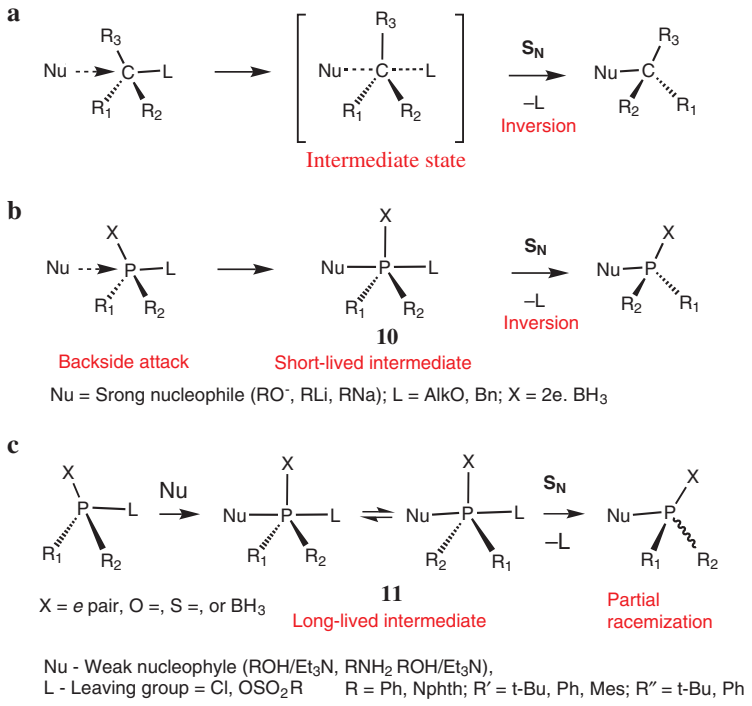
sp³. Alternatively, the intermediate **7** has a "four-center" geometry with an anionic Y atom that coordinates the electropositive metal. Both these paths lead to products with the retention of the absolute configuration at the group R [5, 6].

Unlike the carbon reacting under conditions of $S_N2(C)$ substitution through the formation of a pentacoordinate transition state, the vacant orbitals and high coordination numbers of phosphorus lead to the reaction proceeds through the formation of a pentacoordinated intermediate, which is relatively stable and has a more or less prolonged lifetime. Strong nucleophiles (lithium alkyls, Grignard reagents, alcoholates) react with phosphorus compounds with formation of a short-lived pentacoordinate intermediate **10** converting into the substitution product with complete inversion. However, with weak nucleophiles, for example with alcohols in the presence of tertiary amines or with primary amines, the reaction proceeds through the formation of the long-lived intermediate **11**, which undergoes the Berry pseudorotation with a change in the position of ligands. As a result, racemization occurs, and in some cases the reaction proceeds with asymmetric induction at the phosphorus atom [4, 5].

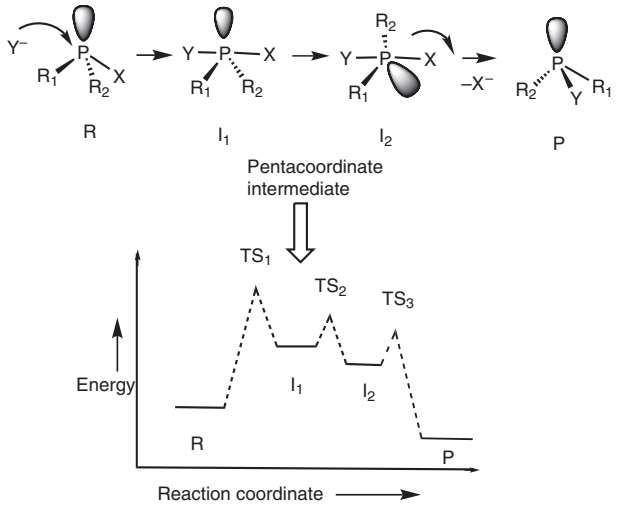
In S_N2 reactions, a nucleophile cannot attack a negatively charged frontside reaction center carrying the electron pair, therefore it attacks the phosphorus from the backside (Scheme 4). In many cases, electrophilic substitution reactions begin with electrophilic addition to form an adduct that easily cleaves the leaving group, converting to P(III) or P(IV)-compounds. Therefore, two types of reactions are possible at the phosphorus atom – nucleophilic addition-substitution or addition-elimination (Scheme 5). Many of the important reactions in organophosphorus chemistry take place by the addition-elimination mechanism (for example, the reactions of Arbuzov, Michaelis-Becker, Appel, Todd-Atterton, etc.). Thus, electrophilic substitution at phosphorus provides an unified classification of some well-known reactions (for example, the reaction of dialkyl phosphites with electrophiles) and a few "abnormal" reactions (for example, cleavage of the P–C bond in phosphonates) [1, 2, 5, 6].

Examples of $S_E2(P)$ reactions

The alkylation and arylation of chiral tertiary phosphines **12** proceed, as a rule, stereospecifically with retention of the absolute configuration, as shown in Scheme 6. This indicates the frontside electrophilic attack to the electron-enriched phosphorus atom, with the formation of an unstable pentacoordinated intermediate that is stabilized by cleavage of the electrofug X^+ and the formation of the final product **13**. It is most con-

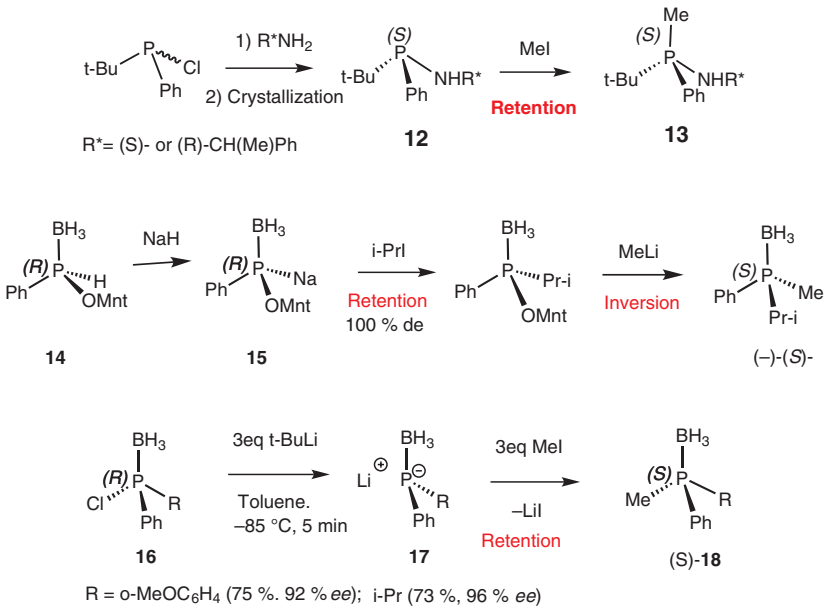


Scheme 4: The mechanism of nucleophilic substitution at P(III).



Scheme 5: Nucleophilic substitution of $S_N2(P3)$ at phosphorus with formation of P(V)-intermediate.

venient to carry out the alkylation and arylation of lithium or sodium substituted phosphine boranes [7, 8]. These compounds are conformationally stable under the reaction conditions, therefore, products with a high degree of stereospecificity are formed. Of great interest are the P-chirogenous chlorophosphines boranes **14**, which were obtained by HCl-acidolysis of the corresponding aminophosphine boranes. Then, the chlorophosphine boranes **16** were converted to lithium derivatives **17**, which were introduced into the electrophilic alkylation with a retention of configuration and formation of product **18** (Scheme 6) [9, 10]. The Michaelis-Becker reaction represents a reaction of a hydrophosphonate with a base and the subsequent electrophilic substitution of trivalent phosphorus with formation of the alkyl phosphonate **19**. In alkaline media, as well as in the presence of strong bases, the tautomeric equilibrium P(IV)⇌P(III) shifts towards the trivalent form,

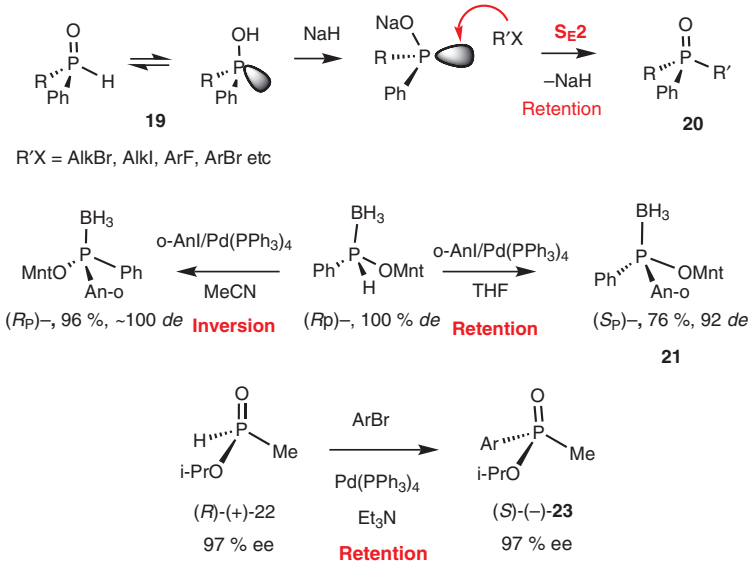


Scheme 6: Stereospecific alkylation reactions.

which easily reacts with the electrophile. Sodium and lithium derivatives of P(III)-acids exist completely in a trivalent, three-coordinated form (Scheme 7).

Therefore, the alkylation of chiral acids P(III) in alkaline media, as well as their metal salts, proceeds with the retention of the absolute configuration. Examples of the stereospecific Michaelis-Becker reaction with alkyl halides and aryl halides are described [11–14].

The Michaelis-Arbuzov [9, 10] is the reaction of trialkyl phosphites with alkyl halides which results in alkoxyphosphonates or tertiary phosphine oxides. The reaction consists of two steps. In the first step, an electron-deficient reagent, an electrophile, attacks the trivalent phosphorus atom of the compound **24**, containing a free pair of electrons, to form stereospecifically with retention of absolute configuration the phosphonium salt **25**. In the next step, the nucleophilic attack of the halide ion on the electrophilic carbon atom



Scheme 7: The Michaelis-Becker reaction.

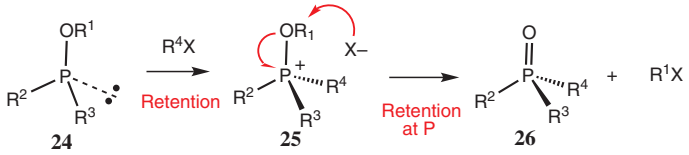
of alkoxy group occurs, with the elimination of alkyl halide and the formation of the dialkylphosphonate **26**, which is known as the Arbuzov rearrangement. The Arbuzov reaction of chiral phosphinites with halogen alkyls proceeds stereospecifically with retention of absolute configuration of phosphorus atom and inversion of configuration of alkoxyl (if the alkoxy group is chiral) (Scheme 8) [15, 16].

Examples of $S_N2(P)$ nucleophilic reactions

Reactions of nucleophilic substitution proceed with inversion of configuration, which was confirmed by a number of examples. Thus, lithium alkyls react with tertiary phosphines and their borane complexes with substitution of benzyl or alkoxy groups to form the new optically active phosphorus compounds **27–29** with good stereospecificity (Scheme 9) [10, 21].

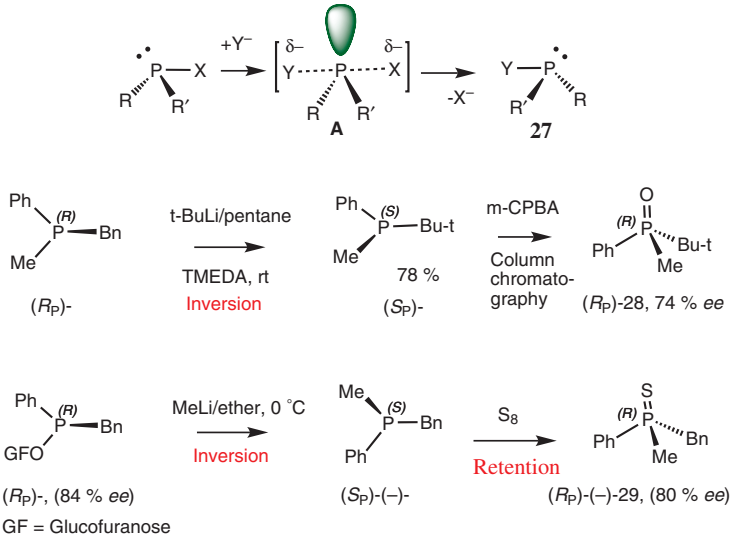
In some cases, exceptions to the rule are possible, when S_E2 reactions proceed with the inversion of absolute configuration and the S_N2 reactions with retention. Although in case of S_E2-reactions, exceptions are very rare. Only in the case of catalytic arylation, Imamoto unexpectedly found that the reaction of anisyl iodide with the (*S*)-chiral tertiary phosphine in the presence of $Pd(PPh_3)_4$ in hexane gave the product of the (*S*)–configuration, however, this reaction in the THF resulted in the (R_p)-product [17].

$S_N2(P)$ reactions of some cyclic products, in particular phosphacyclobutanes **30** [18], as well as ephedrine derivated phosphines [19], proceed with the retention of configuration. There is also an example of the S_N2 reaction of 2,3-$(MeO)C_6H_3Li$ with Ph(o-An)(MeO)P-BH_3 proceeding with the retention of configuration, that is, with an attack on the front side of the molecule, because the attack on the backside is sterically hampered (Scheme 10) [20].

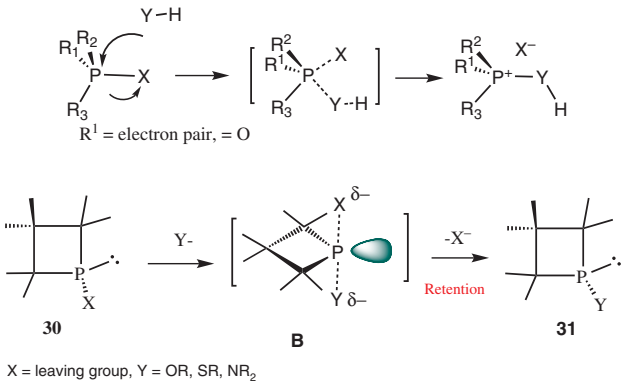


R^2 = AlkO or Alk, Ar; R^3 = AlkO, Alk, Ar

Scheme 8: The Michaelis-Arbuzov reaction.



Scheme 9: $S_N2(P)$ nucleophilic substitution.



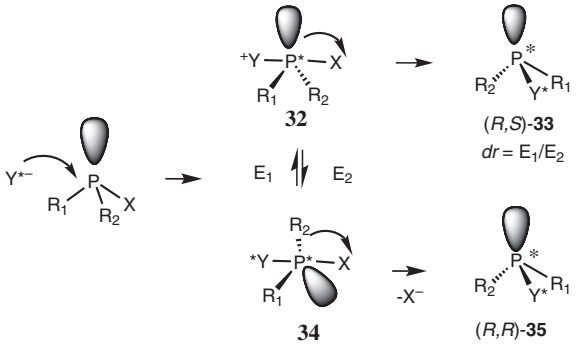
Scheme 10: Examples of anomalous reactions of nucleophilic substitution.

Diastereoselective $S_N2(P)$ reactions

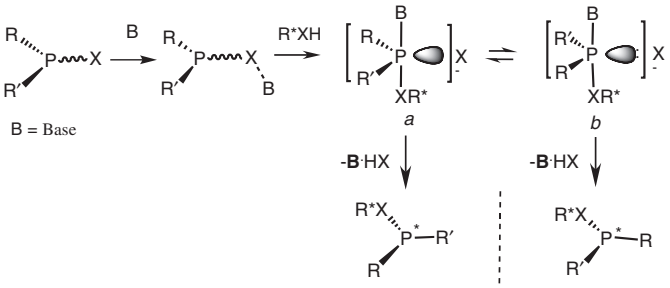
In diastereoselective reactions, one diastereomer is formed in a larger amount than the second. In this case, two or more chiral centers are formed. The final result of the diastereoselective reaction may depend on the pseudorotation, which in turn depends on the nature of substrate and reagent, on the stability and life-time of intermediate. There is a competition between the kinetic factors at the first step of the reaction and the thermodynamic factors in the second step, which depends on the pseudorotation of the ligands. In diastereoselective reactions, substrate chirality largely controls the stereoselectivity, although the role of reagent and catalyst is important. In principle, asymmetric synthesis assumes the formation of a new stereogenic center. The effect of reaction conditions on the ratio of diastereoisomeric products shows that in the overwhelming majority of cases, the nucleophilic substitution of $S_N2(P)$ in chiral trivalent phosphorus occurs with the inversion of the configuration, which is associated with the formation of pentacoordinated anionic intermediates containing the attacking and leaving groups in the apical positions (Scheme 11).

Thus, the mechanism of nucleophilic substitution at the trivalent phosphorus atom involves the exchange of ligands in the pentacoordinate phosphorane intermediate, so a thermodynamically more stable diastereomer is formed. The stability of intermediate *b*, the apicophilicity of ligands, and the asymmetric induction of the chiral auxiliary determine the stereochemical result of the reaction (Scheme 12) [2–5, 21].

An interesting example of the combination of electrophilic and nucleophilic substitution is the halogenophilic reactions at P(III). The halogenophilic are reactions in which the nucleophile attacks the halogen atom, while the organic moiety R in RHal acts as a leaving group, forming a carbanion [the $S_N2(Hal)$ mechanism]. Such reactions, named halogenophilic, demonstrate the ambident behavior of a C–Hal bond as an electrophile, in spite of the $C^{\delta+}$-$Hal^{\delta-}$ polarization, which seems unsuitable for a halogenophilic attack, The reaction of P(III) compounds with donors of positivated halogen is rather diverse, various versions of this



Scheme 11: Diastereoselective nucleophilic substitution.

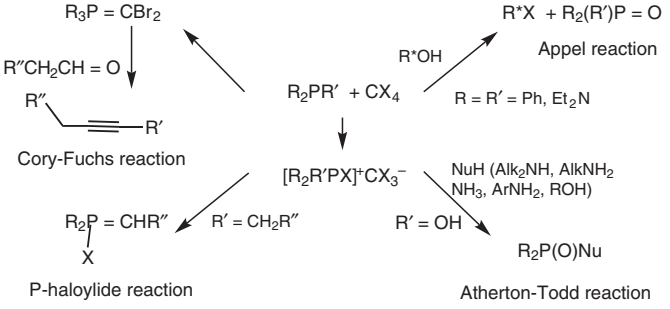


Scheme 12: The mechanism of nucleophilic substitution in the trivalent phosphorus atom.

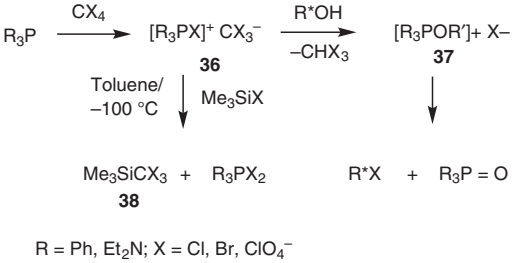
reaction are known and are widely used in synthetic organic and organophosphorus chemistry (Scheme 13) [4, 6, 22–24].

The halogenophilic substitution at trivalent phosphorus consists of two steps. In the first step, an electrophilic attack of positivated halogen on a P(III)-atom is carried out to form a highly active *quasi*phosphonium intermediate **36** containing a CX_3^- anion. Previously we have proved the formation of the intermediate **36** by chemical and physicochemical methods [22]. For example, the reaction of intermediate **36** with trimethylchlorosilane led to the formation of Me_3SiCX_3 (X=Cl, Br), which was isolated and characterized. In the second step, the intermediate reacts with a nucleophile, such as ROH, RSH, R_2NH, RNH_2, or is rearranged with formation of the trihalomethylphosphonium salt (Scheme 14) [23].

The Appel and Atherton-Todd reactions are stereospecific, two-step and give the final product with a inversed absolute configuration [21, 23, 25, 26]. The Atherton-Todd reaction is carried out in a basic medium in which the tautomeric equilibrium of the tetracoordinated P(O)H form shifts toward the three-coordinated POH form, which readily reacts with methane tetrahalogenide. As a result, the intermediate chloride **39** is formed. In the second step, the reaction of the chloride **39** with a nucleophile leads to the formation of the substitution product **40**. The use of optically active substrates **41** allowed to define the mechanism and stereochemistry of the Atherton-Todd reaction. The first step of reaction is an electrophilic addition proceeding



Scheme 13: The halogenophilic reactions of the compounds P(III).



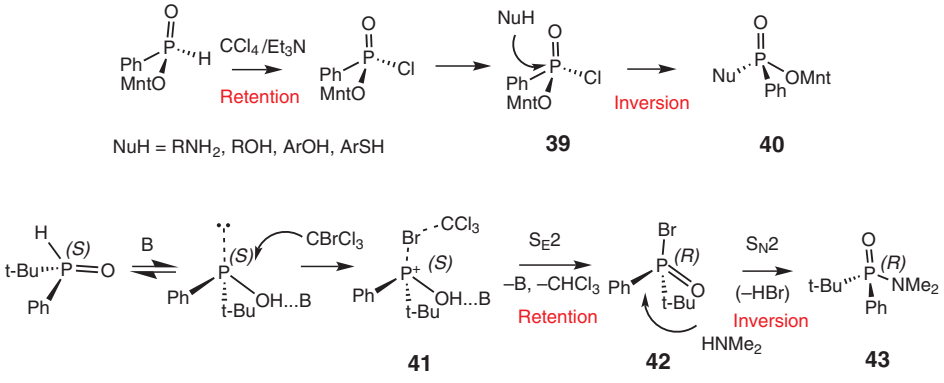
Scheme 14: The mechanism of halogenophilic reactions of P(III) compounds.

via the formation of a CX_3-phosphonium intermediate **41** and leading to the bromide **42** with retention of the absolute configuration. Then, bimolecular nucleophilic substitution of bromide **42** with $HNMe_2$ afforded the product **43** with inversion of configuration (Scheme 15) [23, 25, 26].

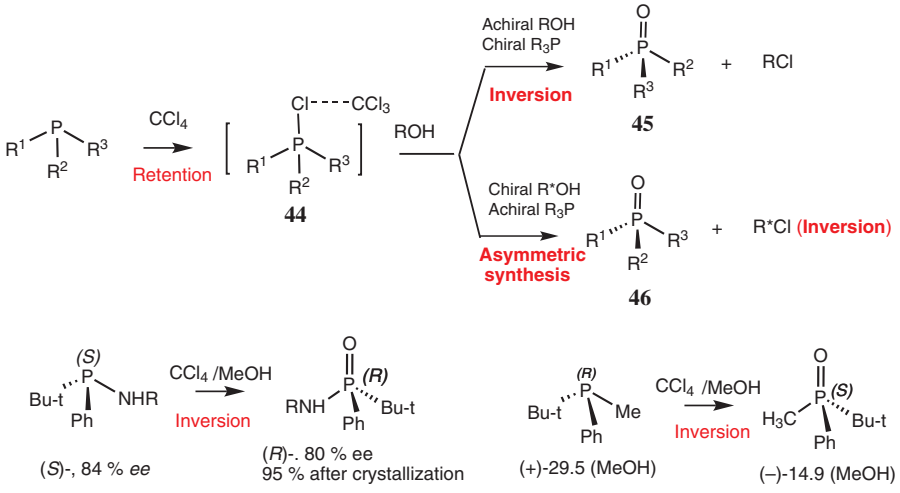
In the first step of the Appel reaction the electrophilic attack of CCl_4 on tertiary phosphine gives an unstable *quasi*phosphonium complex **44** containing a trichloromethyl anion [22, 23]. Then, in the second step the complex **44** reacts with a nucleophile (alcohol or amine) to afford the phosphine oxides **45,46** with the inversion of configuration at the phosphorus atom. Optically active alcohols under the Appel reaction conditions form optically active alkyl halides with inversion of configuration and with very good stereospecificity (Scheme 16) [24]. The asymmetric version of the Appel reaction was developed [27]. Reaction of racemic tertiary phosphines with polyhalogen methanes in the presence of chiral (–)-L-menthol resulted in the formation of chiral tertiary phosphine oxides, which were used as starting compounds for the preparation of phosphine ligands (Scheme 17).

Asymmetric induction under Appel and Atherton-Todd reactions is explained by the formation of a long-lived phosphorane intermediate and Berry pseudorotation (Scheme 18).

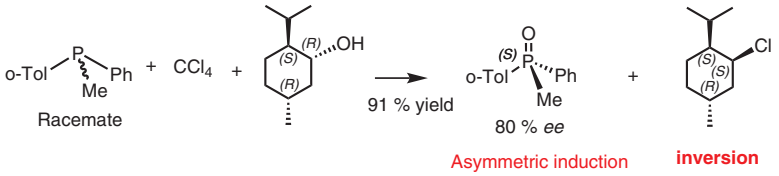
Tertiary alkylphosphines, bearing hydrogen atoms in the α-position of alkyl groups, react with tetrahalogenmethanes with formation of P-halogenylides. These ylides are interesting reagents for organic synthesis [24, 28–32]. They react with aldehydes, ketones, CO_2 and CS_2 to form 1,2λ^5-oxaphosphetanes, a few of which were isolated as stable compounds [32], as well as vinylphosphonates, allyl phosphonates, phosphorous ketenes and thioketenes. The reaction of chiral tertiary alkylphosphines with CCl_4 leads to the formation of



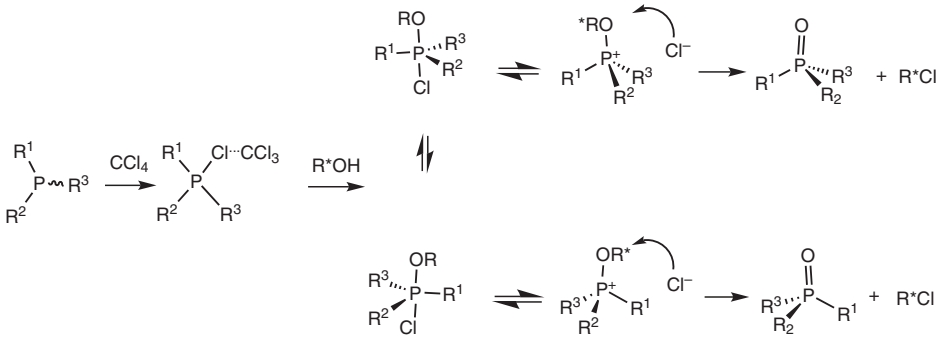
Scheme 15: Stereochemistry of the Atherton-Todd reaction.



Scheme 16: The stereochemistry of the Appel reaction.



Scheme 17: The asymmetric Appel reaction.

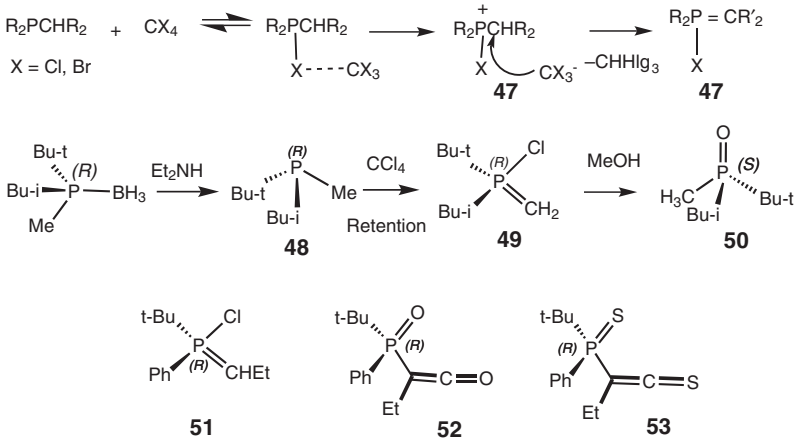


Scheme 18: Mechanism of the Appel reaction.

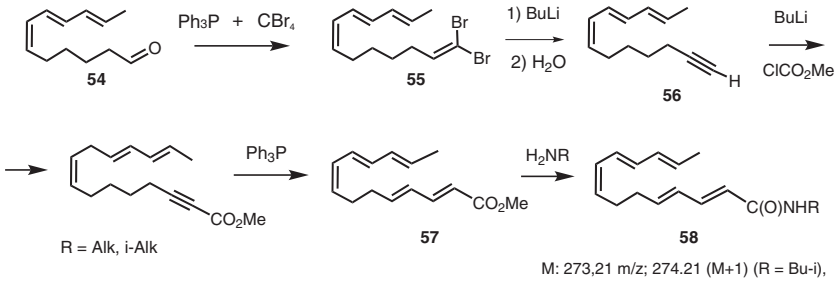
chiral P-halogenylides with retention of configuration. Scheme 20 explains the mechanism of reaction, which proceeds via the deprotonation of alkyl group in the phosphonium intermediate **47** by trichloromethyl anion leading to the formation of P-chloroylide and chloroform (Scheme 19).

The sequential treatment of chiral alkoxylphosphines with carbon tetrachloride and carbon dioxide or carbon disulfide leads to the formation of the chiral ketenes **52** and thioketenes **53**. The synthesized phosphorus ketenes and thioketenes are stable compounds, they can be purified by distillation under vacuum. At the same time, they are chemically very active, add alcohols and amines. These phosphorus compounds are interesting starting reagents for the preparation of a number of optically active phosphorus compounds.

The considerable interest from the point of view of organic synthesis represent also the Corey-Fuchs reaction as a method for the synthesis of terminal alkynes (Scheme 13) [33, 34]. The reaction of tertiary phosphines with tetrabromomethane gives dibromomethylenephosphorane, which reacts with aldehydes **54** to form dibromalkenes **55**. The treatment of dibromalkenes **55** with butyllithium gives terminal alkynes **56**. This reaction is used in total syntheses of a number of important natural compounds. Using the Corey-Fuchs



Scheme 19: Chiral P-chloroylides.

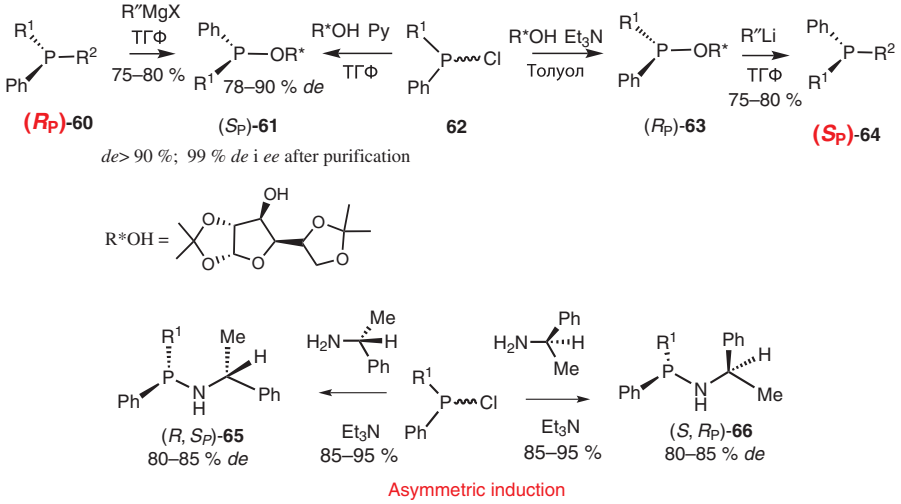


Scheme 20: Synthesis of tetradecapentaenoic acid derivatives **58** using the Corey-Fuchs reaction in the key step.

reaction on a key step, we obtained some polyunsaturated fatty acids and their amides, in particular the tetradecapentaenoic acid derivatives, which attract attention as bioregulators of apoptosis [35]. The treatment of alkynes by triphenylphosphine using the method of Trost-Kazmaier led to the rearrangement of alkyne to 1,3-diene **57** and to the formation of tetradecapentaenoic acid **58**. The Scheme 20 is interesting as an example of stereodirected synthesis of compound with the exact position of E and Z double bonds.

Reactions of asymmetric chlorophosphines with chiral nucleophiles proceed with asymmetric induction leading to the formation of enantiomerically enriched phosphinites [36–41]. For example, the reaction of chlorophosphines with glucofuranose allows to obtain phosphinites with high enantiomeric excesses [36] (Scheme 21). Using various bases and solvents in the preparation of phosphinites, the diastereoisomers (S_p)-**61** or (R_p)-**63** were obtained with good stereoselectivity: (R_p)-phosphinites **63** were prepared in toluene with Et_3N as a base, and (-)-(S_p)-phosphinites **61** were obtained in THF with pyridine as a base. Esters **61,63** were converted into the corresponding tertiary phosphines (R_p)-**60** or (S_p)-**64** by reaction with organomagnesium.

Reactions of chlorophosphines with primary amines or with amino acid esters or alpha-methylbenzylamine proceed with the transfer of chirality from the chiral amine to the phosphorus atom. Unsymmetric chlorophosphines react diastereoselectively with chiral 1-methylbenzylamine to form diastereomeric aminophosphines **65** and **66** (up to 80–85 % *de*), which after crystallization were isolated as stereochemically pure compounds [4, 6, 37, 38]. It was found that the reaction of (*S*)-1-methylbenzylamine with chlorophosphines leads to the formation of (R_p)-aminophosphines, whereas (*R*)-1-methylbenzylamine gives aminophosphines of (S_p)-configuration [37, 38]. These reactions were previously described by us [36–40]. In this work, these reactions were used as objects for the studying of mechanism of diastereoselective substitution at phosphorus (Scheme 21).



Scheme 21: Examples of diastereoselective reactions at the phosphorus atom.

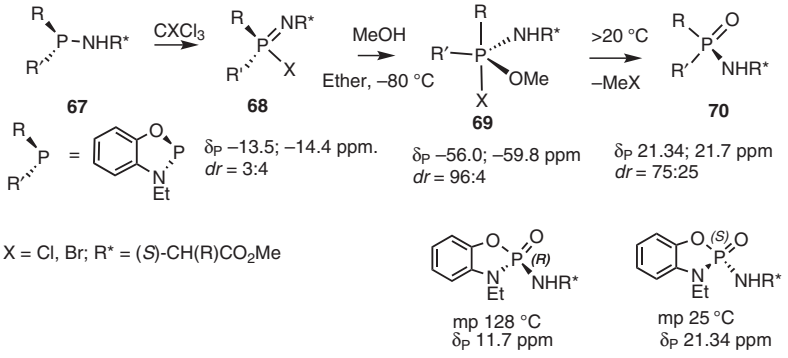
We studied the effect of reaction conditions on the stereochemistry of the reaction of tert-butylphenylchlorophosphine with 1-methylbenzylamine. The obtained data are collected in Table 1. These data allow to make some conclusions about the reaction mechanism. The most important observations are as follows:

(1) The stereoselectivity of the reaction depends on the nature of solvents and the nature of organic bases (item 15–17, Table 1); (2) an excess of chlorophosphine and methyl benzylamine does not affect the stereoselectivity (item 13, 14); (3) a decrease in temperature reduces the stereoselectivity of the reaction, because the reaction proceeds intramolecularly (item 4–7). Evidently, the stereoselectivity of reaction is determined by pseudorotation, and the increase of temperature allows faster to achieve the equilibrium of reaction proceeding under the thermodynamic control [42].

Besides, we have studied the mechanism of nucleophilic addition of alcohols to 1,3,2-oxazophospholanes using NMR spectroscopy. The methanol is stereoselectively added to chloriminophosphoranes **68** with formation of the pentacoordinate intermediates **69** (*dr* 96:4), which are stable in solution. The presence of the diastereoisomers **69** was confirmed by signals in the negative field of the ^{31}P NMR spectra, at δ_P –56 and –58 ppm, in accordance with the pentacoordinate state of the phosphorus atom. Upon heating, the alkoxyphosphoranes **69** are converted into the cyclic amidophospholanes **70** (*dr* 75:25). The diastereomers **70** were isolated in a pure form (Scheme 22) [5, 39].

Table 1: The reaction of tert-butyl(phenyl)chlorophosphine with 1-methylbenzylamine in depending on reaction conditions.

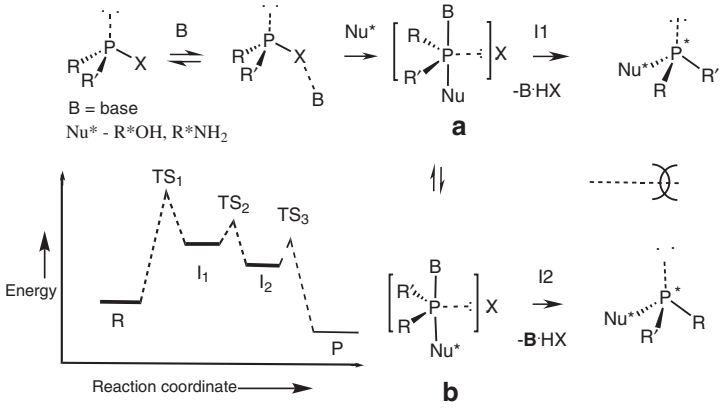
Item	Solvent	Base	Temperature	Chlorophosphine: Primary amine: Base	*dr*
1	Benzene	Et_3N	20 °C	1:1:1	8:92
2	Benzene	Et_3N	20	1:1:2	13:87
3	Benzene	Et_3N	20	1:1:10	21:79
4	Toluene	Et_3N	30	1:1:1	10:90
5	Toluene	Et_3N	20	1:1:1	16:84
6	Toluene	Et_3N	0	1:1:1	20:80
7	Toluene	Et_3N	–20	1:1:1	26:74
8	Hexane	Et_3N	20	1:1:1	20:80
9	THF	Et_3N	20	1:1:1	38:62
10	Ether	Et_3N	20	1:1:1	36:64
11	Benzene	Et_3N	20	1:1:1	75:25
12	Toluene	Et_3N	20	2:1:1	15:85
13	Toluene	Et_3N	20	4:1:1	14:86
14	Benzene	Et_3N	20	1:1:4	18:82
15	Toluene	DABCO	20	1:1:1	25:75
16	Toluene	PEA	20	1:1:1	17.5:82.5
17	Toluene	DBU	20	1:1:1	42:58



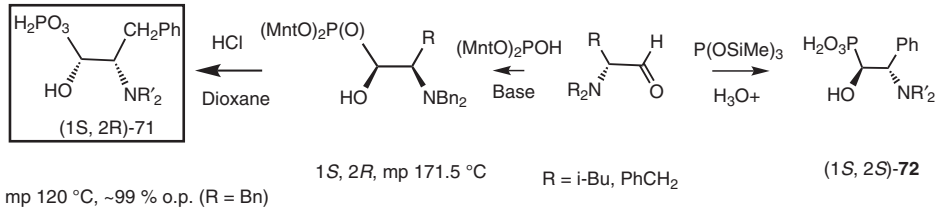
Scheme 22: The mechanism of nucleophilic addition of methanol to 1,3,2-oxazophospholanes.

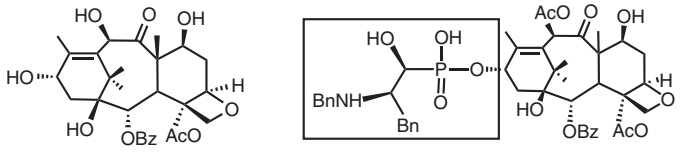
So, the stereochemical course of reaction proceeds under thermodynamic control through the formation of a pentacoordinate intermediate [36–39], which can be registered in some cases. The pseudorotation of ligands in phosphorane intermediate leads to the thermodynamically most stable diastereomer. The stereoselectivity of the reaction depends on the structure of reagents and reaction conditions (bases, solvents, temperature), which affects the position of ***a*⇌*b*** equilibrium and the difference in free energies $\mathbf{I}_1$, $\mathbf{I}_2$ of the diastereomeric products (Scheme 23) [42].

Chiral inductors that are present in the reacting system can enhance the resulting stereoselectivity (matched asymmetric induction) or, conversely, weaken it, opposing each other (uncoordinated asymmetric induction). The strategy of multiple stereoselectivity is an effective method of stereochemical control in the asymmetric synthesis of organic compounds [43]. Stereochemical control of newly formed stereogenic centers of compounds is achieved by selecting (*R*)- or (*S*)-chiral reagents, as well as by summarizing their stereoselectivities. Using strategy of double stereoselectivity we have synthesized both stereomers of the lateral chain of C-13 taxoid, starting from natural amino acids [44]. The reaction of aldehydes with dibornyl phosphite gave (1*S*,2*R*)–stereoisomer, while dimenthylphosphite gave (1*R*,2*R*)-stereoisomer. The reaction of dibenzylphenylalanyl with tris(trimethylsilyl)phosphite afforded (1*R*,2*S*)-1-hydroxy-2-aminoalkylphosphonic acid [45–49]. The chiral 1-hydroxy-2-aminophosphonic acids have been used to modify Baccatin III in the synthesis of new



Scheme 23: The mechanism of S_N2 (P) nucleophilic substitution.





Scheme 24: Synthesis of (1*S*,2*R*)-phosphonotaxol.

phosphono-taxoids [50, 51]. Taxoids are important anti-cancer substances of natural origin, a few of which, for example, docetaxel and paclitaxel, are used in clinical medical practice (Scheme 24) [52, 53].

Conclusions

So, the reaction of electrophilic and nucleophilic substitution at the phosphorus center proceeds through the formation of a pentacoordinate intermediate. $S_N2(P)$-Reaction of P(III) compounds with strong nucleophiles proceeds through the formation of a short-lived intermediate, which leads to products with an inverted configuration. The reaction of P(III) compounds with weak nucleophiles proceeds through the formation of long-lived intermediate and is accompanied by a Berry pseudorotation that leads to the formation of products with partial racemization or asymmetric induction at the phosphorus atom. The mechanism of $S_N2(P)$ substitution and transfer of chirality from reactant to phosphorus atom was studied by NMR. P(V)-phosphorane intermediates were registered in some cases. Electrophilic substitution proceeds with retention of absolute configuration, and nucleophilic substitution with inversion of configuration of substituents at the asymmetric phosphorus center.

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