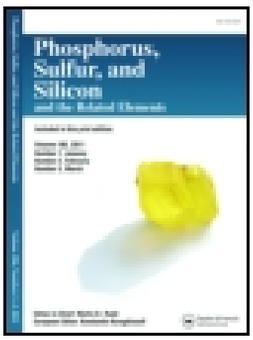

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Stereochemistry of electrophilic and nucleophilic substitution at phosphorus

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ABSTRACT

Stereochemistry and mechanisms of nucleophilic [$S_N2(P)$] and electrophilic [$S_E2(P)$} reactions have been analyzed, discussed and confirmed by experimental studies. $S_E2(P)$ reactions proceed with the retention of absolute configuration, while the $S_N2(P)$ reactions react with the inversion of the configuration at the phosphorus atom.

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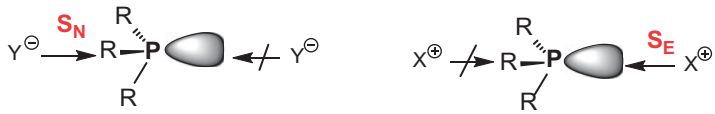
KEYWORDS
Electrophilic substitution; nucleophilic substitution; stereochemistry; halogenophilic reactions; mechanism of $S_N2(P)$ reaction

GRAPHICAL ABSTRACT



Introduction

Nucleophilic and electrophilic reactions are the most commonly used in organic chemistry. They are closely interconnected, because in a reacting pair always one reagent is an electrophile, and the other is a nucleophile.[1, 2] The electrophilic attack on the P(III) reaction center occurs from the front side, where a free pair of electrons and negative charge is localized, therefore the bond of electrophile with phosphorus is formed with retention of configuration. On the contrary, the negatively charged nucleophile is repulsed by a pair of electrons from the front-side, and therefore the attack occurs from the backside. As a result, the electrophilic attack proceeds with the retention of configuration, and the nucleophilic attack is accompanied by Walden inversion (Scheme 1).[3]

Results and discussion

The bimolecular $S_E2(P)$ mechanisms of electrophilic substitution reactions at phosphorus is similar to the S_N2 mechanism in the sense that new bonds form, when old bonds break (Scheme 2).

Usually the reaction of phosphorus (III) compounds with strong nucleophiles (Nu = Grignard reagents, alcoholates, alkyl lithium) proceeds stereospecifically *via* the formation of short-living intermediate **1** with inversion of absolute configuration. In the case of weak nucleophiles (Nu = alcohols in the presence of organic bases or primary amines), the reaction proceeds through the formation of a long-living pentacoordinated intermediate **2**, which undergoes the Berry pseudorotation with a change in the position of ligands at the phosphorus center (Scheme 3). In the case of a diastereoselective reaction of a chiral reagent with a racemic substrate, the existing chiral center influences the stereochemistry of new formed asymmetric center, therefore the formation of a more stable diastereomer is controlled by thermodynamic factors (Scheme 4). As a result, the reaction passes with partial racemization, the asymmetric induction at the phosphorus atom is also possible.[4, 5]

The reaction of P(III)-compounds with tetrahalomethanes plays an important role in chemical and biochemical synthesis, various versions of this reaction were described and used in organic and organophosphorus chemistry.[6–11] The most important versions of these reactions are the Atherton-Todd reaction, the Appel reaction, the Corey-Fuchs reaction, and the tertiary phosphine reaction proceeding with the formation of P-halogenylides.[11, 12]

These reactions consist of two steps. In the first step, an electrophilic attack of positivized halogen on a trivalent phosphorus atom is carried out to form a quasiphosphonium intermediate containing a CX_3-anion. In the second step, the intermediate reacts with the nucleophile or a rearrange with the formation of CX_3-phosphonium salt. The Appel and Atherton-Todd reactions are two-step processes resulting in the final product with inversion of absolute configuration.[8–10] The formation of the intermediate **3** containing the CX_3-anion was proved by chemical and physical methods.[12] For example, the CX_3-intermediate **3** reacts with trimethylchlorosilane to afford CX_3SiMe_3, or forms alkyl halides with alcohols under Appel reaction conditions. Optically active alcohols, in this case afford optically active alkyl halides with inversion of configuration (Scheme 5). Optically active tertiary phosphines under Appel reaction

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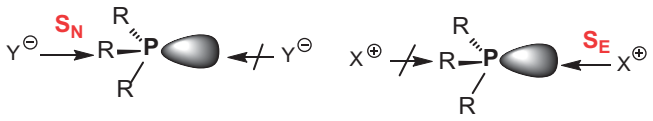
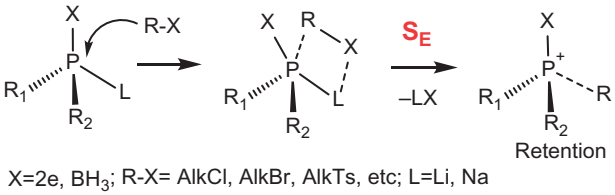
conditions give optically active phosphine oxides with inversion of absolute configuration. An asymmetric version of the Appel reaction was developed.[8] The oxidation of trivalent phosphorus compounds with alkane polyhalides in the presence of (-)-L-menthol led to the formation of chiral tertiary phosphine oxides (Scheme 6).

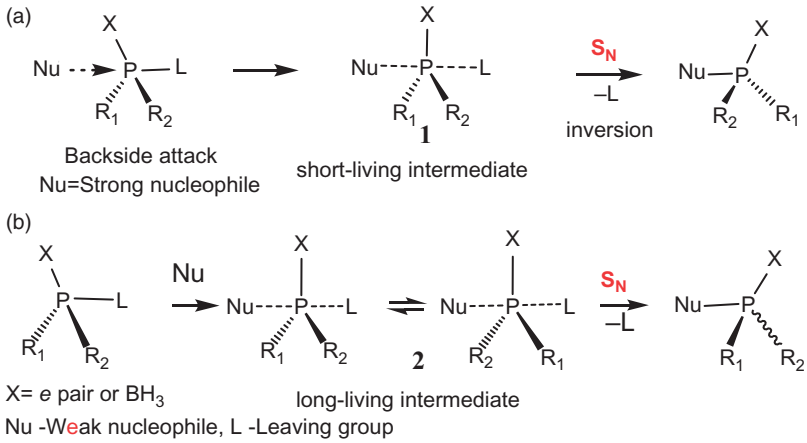
Reaction of chiral tertiary alkylphosphines with tetrachloromethane leads to the formation of P-halogenylides. These ylides are interesting reagents for organic synthesis. Scheme 7 shows the reaction mechanism. The deprotonation of the alkyl group in the phosphonium cation occurs by trichloromethyl anion, that leads to the formation of chloroform. As a result, the chiral P-halogenoylides, previously unknown, were obtained. These P-halogenylides can be used to prepare a number of novel chiral phosphorus compounds. The P-halogenylides react with aldehydes, ketones, CO_2 and CS_2 to form 1,2λ^5-oxaphosphetanes, some of which were isolated as stable compounds, as well as vinylphosphonates, allyl phosphonates, phosphoric ketenes and thioketenes. In this work, we synthesized some chiral P-halogenoylides. These compounds are analogs of the racemic P-halogenylides, which we have described earlier.[12–14] The sequential treatment of chiral alcoxylphosphine boranes with tetrachloromethane and



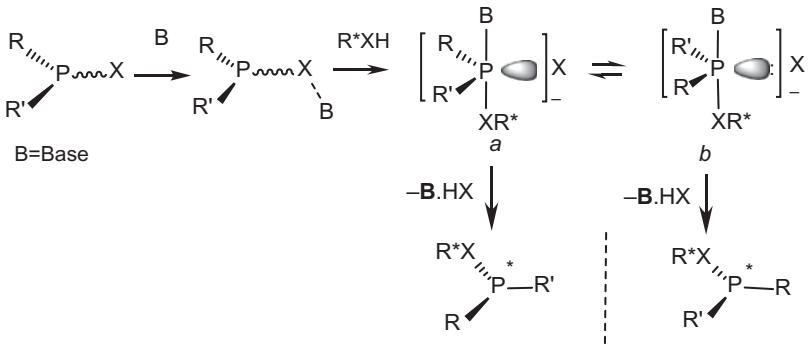
Scheme 1. Electrophilic and Nucleophilic attacks on the Phosphorus center.



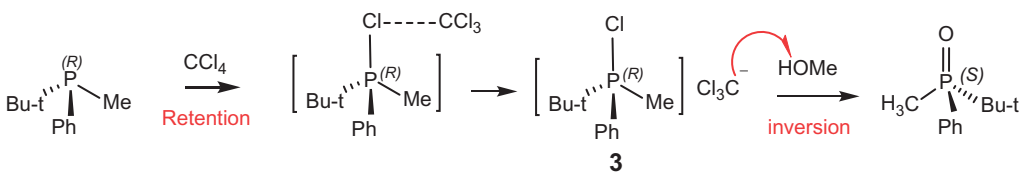
Scheme 2. Mechanism of electrophilic substitution of P(III)-compounds.



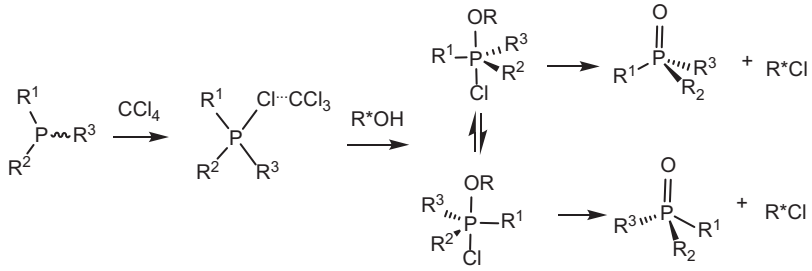
Scheme 3. The mechanism of nucleophilic substitution in P(III).



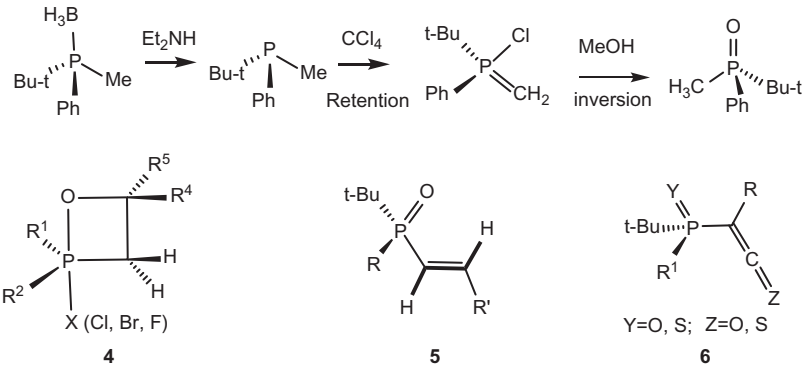
Scheme 4. The mechanism of nucleophilic substitution at the trivalent phosphorus atom.



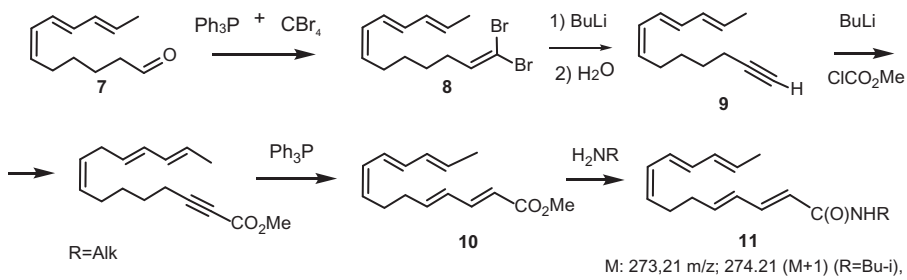
Scheme 5. Stereochemistry of the Appel reaction.



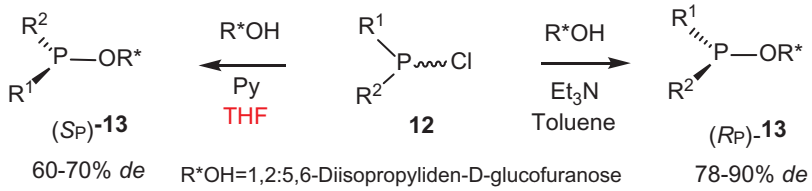
Scheme 6. The mechanism of asymmetric induction at the Phosphorus atom.



Scheme 7. Reaction of chiral tertiary alkylphosphines with tetrachloromethane.



Scheme 8. The Cory-Fuchs reaction and the Trost-Kazmaier methodology in the organic synthesis.



Scheme 9. Example of diastereoselective reaction of chiral alcohols with chlorophosphines.

carbon dioxide or carbon disulfide leads to the formation of chiral ketenes and thioketenes.

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.[15, 16] The reaction of tertiary phosphines with tetrabromomethane gives dibromomethylenephosphorane **7**, which reacts with aldehydes to form dibromalkenes **8**. The treatment of dibromalkenes **8** with butyl lithium gives terminal alkynes **9**. This reaction is used for the total synthesis of a number of important natural compounds. Using the Corey-Fuchs reaction on a key step, we obtained some polyunsaturated fatty acids and their amides, in particular of tetradecapentaenoic acid derivatives, which attract attention as bioregulators of apoptosis.[17] The treatment of dibromoalkene by triphenylphosphine using the method of Trost-Kazmaier led to the rearrangement of alkyne to 1,3-diene **10** and formation of tetradecapentaenoic acid **11** (Scheme 8).

The reaction of asymmetric chlorophosphines with chiral nucleophiles proceeds with asymmetric induction and lead to the formation of enantiomerically enriched phosphonates.[18] The reaction of chlorophosphines **12** with glucofuranose allows the production of phosphinites **13** with a high enantiomeric excess (Scheme 9). By changing the

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

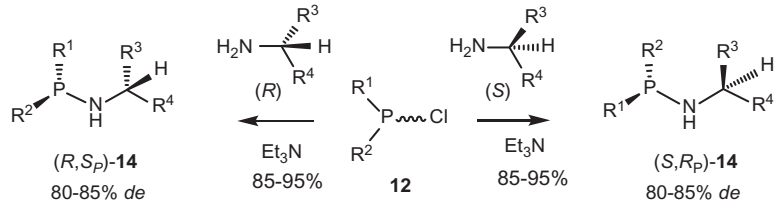
IIII	Solvent	Base	Temp. °C	1:2:Base	*dr*
1	Benzene	Et_3N	20	1:1:1	8:92
2	Benzene	Et_3N	20	1:1:2	13:87
3	Benzene	Et_3N	20	1:1:10	21:79
4	Toluene	Et_3N	30	1:1:1	10:90
5	Toluene	Et_3N	20	1:1:1	16:84
6	Toluene	Et_3N	0	1:1:1	20:80
7	Toluene	Et_3N	−20	1:1:1	26:74
8	Hexane	Et_3N	20	1:1:1	20:80
9	THF	Et_3N	20	1:1:1	38:62
10	Ether	Et_3N	20	1:1:1	36:64
!1	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

reaction conditions, it is possible to obtain the phosphinites of both absolute configurations (S_P)-**13** and (R_P)-**13**. The reactions of chlorophosphines with primary amines or with amino acid esters, or alpha-methylbenzylamine proceeds with the transfer of chirality from the chiral amine to the phosphorus atom (Scheme 10).[5–7] We have used these reactions as the object for investigation of mechanism of diastereoselective reaction at phosphorus. First of all we have found that the stereochemical result does not depend on the chirality of chlorophosphine, since the same diastereomeric values of aminophosphines were obtained with racemic and optically active chlorophosphines. The effect of various factors on stereochemistry of reaction of tert-butylphenylchlorophosphine with 1-methylbenzylamine in the presence of the organic bases shown in the Table 1 allowed to make some conclusions concerning the mechanism of reaction:

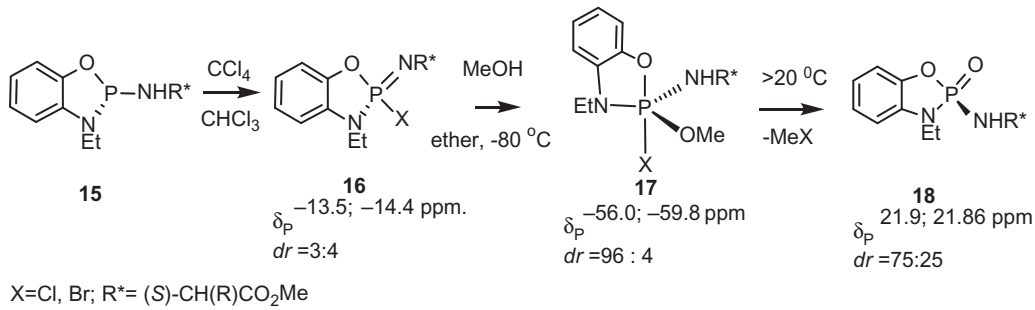
(1) stereoselectivity of reaction depends on the nature of solvent; (2) stereoselectivity of reaction depends on nature of organic bases; (3) increase in amount of chlorphosphine in the reaction mixture increases the stereoselectivity of reaction, while increase of methylbenzylamine concentration reduces stereoselectivity; (4) lowering temperature decreases the stereoselectivity of reaction; (5) the reaction of chlorophosphine with (*S*)-1-methylbenzylamine afforded phosphinites of (*R*)-configurations while (*R*)-1-methylbenzylamine gives a product having (*S*)-configuration.

The obtained results show significant effect of tertiary organic bases on stereochemistry of S_N2P reaction. The dependence of stereoselectivity on temperature shows that the reaction is not kinetically controlled because usually the decrease of temperature increases the stereoselectivity of kinetically controlled reactions.[19, 20] The dependence of the stereoselectivity on temperature shows that the mechanism of nucleophilic substitution at the trivalent phosphorus atom involves the Berry pseudorotation and the exchange of ligands in the pentacoordinated phosphorane intermediate, leading to the formation of a more stable diastereomer under thermodynamic control (Scheme 4). This mechanism was confirmed in the case of trivalent phosphorus compounds **15** containing a 1,3,2-oxazophospholane ring. Chloriminophosphoranes **16** stereoselectively add methanol to form pentacoordinated intermediate **17** (*dr* 96: 4), which is stable in solution. The ^{31}P NMR spectrum confirmed the presence of signals belonging to the diastereoisomers **17** in the negative field of the ^{31}P NMR spectra at δ_P −56 and −58 ppm, in accordance with the pentacoordinate state of phosphorus atom.

Upon heating, alkoxyphosphorane **17** was converted into cyclic amidophospholane **18** (*dr* 75:25). The (S_P,*S*)- and (R_P,*S*)-diastereomers **18** were separated and obtained in pure state (Scheme 11).



Scheme 10. Example of diastereoselective reaction of chiral amines with chlorophosphines.



Scheme 11. $S_N2(P)$ Mechanism of addition of methanol to chloriminophosphoranes.

Conclusions

So, the reactions of the electrophilic and nucleophilic substitution at the phosphorus center proceed through the formation of a pentacoordinated intermediate. The reaction with strong nucleophiles proceeds with formation of short-living intermediate, leading to products with inverted configuration. The reaction with weak nucleophiles proceeds with formation of long-living intermediates and accompanied by the Berry pseudorotation resulted in the formation of products with partial racemization or with the asymmetric induction at the phosphorus atom.[21] Reactions of bimolecular electrophilic substitution $S_E2(P)$ pass with retention of absolute configuration.

Disclosure statement

No potential conflict of interest was reported by the author.

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