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Stereoselective Synthesis of 1,4,2-Oxazaphosphorines as Precursors of Chiral α-Aminophosphonic Acids by Intramolecular Heterocyclization of β-Aldiminoalkylphosphites

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ABSTRACT: *The intramolecular version of nucleophilic additon of phosphites to imines was carried out for the first time taking as an example* β-*aldiminoalkylphosphites, formed from chlorophosphites and* β-*aldiminoalcohols [N-(benzylidene)-2-aminoethanol and R-(+)-N-(benzylidene)-2-aminobutanol-1]. In these reactions, stereoisomeric 1,4,2-oxazaphosphorines were obtained in good yields. R-(+)-N-(benzylidene)-2-aminobutanol-1 being used as a precursor, nucleophilic attack by P(III) atom on electrophilic C atom of the C=N group proceeds stereospecifically with participation of only re-face of the two possible diastereotopic faces of the imine double bond to give the epimeric at phosphorus (3R,5R)-2-(*β-*chloroethyl)-2-oxo-3-phenyl-5-ethyl-1,4,2-oxazaphosphorines as precursors of nonracemic* α-*aminophosphonic acids*. © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:56–61, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10054

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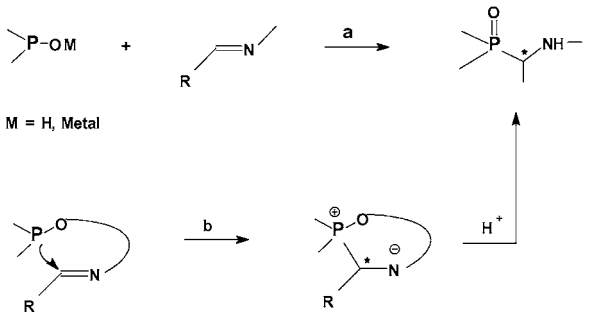
INTRODUCTION

The α-amino phosphonic acids, the phosphonic acid analogs of α-amino carboxylic acids, are interesting compounds because of their biological activity, particularly in connection with the design of enzyme inhibitors [1,2]. It is well known and is not surprising that the absolute configuration of a stereogenic α-carbon atom attached to phosphorus strongly influences the biological properties of derivatives of α-amino phosphonic acids [3]. Although several methods (the first synthesis of an optically active α-amino phosphonic acid was reported by Gilmore and McBride in 1972 [4]) for the synthesis of nonracemic α-aminophosphonates have been reported [5–8], there still exists a requirement for new methods which have greater simplicity and generality. The analysis of literature data shows that the most significant results in this field are obtained on the basis of stereoselective addition, including the catalytic one [9] of dialkyl or trialkyl phosphite derivatives to compounds, containing a C=N double bond (imines, nitrones). However, only intermolecular reactions were considered in terms of this approach (Scheme 1, route a). To develop a new, more effective



SCHEME 1

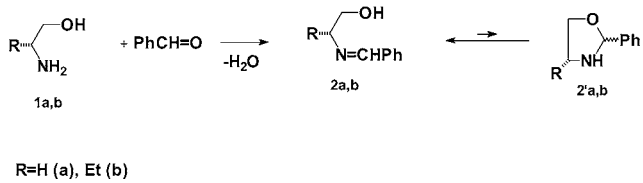
strategy of stereoselective synthesis of α-amino phosphonates we found it attractive to study reactions, allowing an intramolecular type of interaction of P(III) atom and an imino C=N unit (Scheme 1, route b). The following transformation of a cyclic intermediate, in particular via the Arbuzov reaction, could lead to nonracemic α-aminophosphonates. As the realization of such a process requires a strictly definite relative position of the P(III) atom to the imino group, possessing nonequivalent diastereotopic faces, one can anticipate a significant increase of diastereomeric excess of reaction products in terms of this approach.

To study the possibilities provided by this approach, we have chosen β-aldiminoalkylphosphites as model systems. The choice is explained by the fact that in this case potential cyclization will proceed via a six-membered intermediate which is most favorable for the stereodifferentiaton of diastereotopic faces of the C=N double bond. Possible products of the reaction—1,4,2-oxazaphosphorines, as it was shown by Royer and co-workers [10], can be easily converted into free α-amino phosphonic acids.

For the preparation of β-aldiminoalkylphosphites, we have focused our attention on the study of the reaction of monochlorophosphites with chiral β-aldiminoalcohols. However, to the best of our knowledge, no attempts have been made to investigate the reaction of halogen P(III) derivatives with β-iminoalcohols. We started our studies using *N*-(benzilydene)-2-aminoethanol (**2a**) as a model compound. In order to investigate the stereochemistry of the potentially possible intramolecular cyclization and to obtain optically active title compounds, we chose R-(+)-*N*-(benzylidene)-2-aminobutanol-1 (**2b**), which is easily preparable from commercially available R-(−)-2-aminobutanol-1 (**1b**) and benzaldehyde.

RESULTS AND DISCUSSION

β-Aldiminoalcohols **2** were prepared by the condensation of β-aminoalcohols **1** with benzaldehyde in



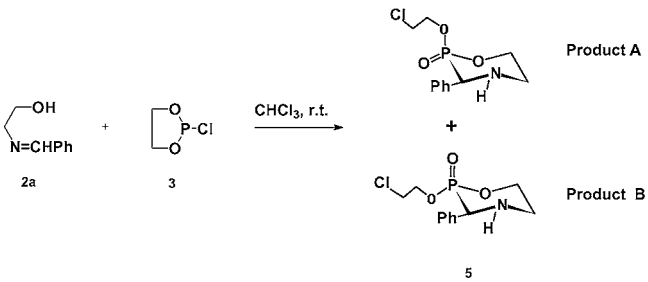
SCHEME 2

refluxing benzene, accompanied by simultaneous removal of water by azeotropic distillation (Scheme 2). The compounds **2** were found to be in equilibrium with 1,3-oxazolidines **2′**. The ^{1}H NMR spectra of the compounds **2** ⇌ **2′** exhibit a sharp singlet of the CH=N– moiety at $\delta = 8$ [11] and minor signals of the protons at the C-2 position of cyclic forms **2′** at $\delta =$ 5–6 with the following ratios –**2a:2′a** = 10:1(CCl_4), **2b:2′b** = 5.5:1(CCl_4).

We have chosen to study the reactions of β-aldimines **2** with ethylene chlorophosphite **3** and bis(β-chloroethyl) chlorophosphite **4**.

Slow addition of a chloroformic solution of **2a** to a stirred solution of **3** in chloroform at room temperature, according to a decoupled ^{31}P NMR spectrum of the crude reaction mixture, leads to the formation of unequal amounts of two reaction products **A** and **B** with δ = 12.7 (**A**) and 16.8 (**B**). The ratio of **A** and **B** is 2.8:1. Both reaction products were isolated from the reaction mixture by column chromatography (see Experimental). They are crystalline compounds stable to moisture and air. Recrystallization of **A** from benzene–ether (1:3) and **B** from acetone gave single crystals suitable for X-ray diffraction studies. It was found that these compounds are stereoisomeric 1,4,2-oxazaphosphorines **5**, shown in Scheme 3 and Figs. 1 and 2. Thus, the products of the reaction between **2a** and **3** are diastereomers **A** and **B**, which are distinguished from one another by the phosphorus atom configuration. (Each diastereomer is the racemic mixture of two enantiomers.)

The reaction between **2b** and **3**, conducted in a similar fashion, results in the formation of a



SCHEME 3

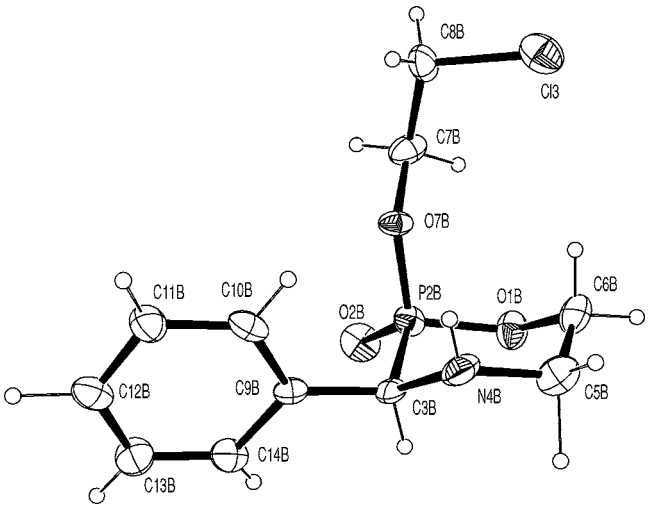


FIGURE 1 ORTEP drawing of **A** with atom numbering.

two-component product **6** (**C** and **D**) with $\delta = 12.4$ (**C**) and 16.8 (**D**) (Scheme 4) according to the decoupled ^{31}P NMR spectrum in $CHCl_3$ of the crude reaction mixture. The ratio of **C** and **D** is 2.4:1. Pure product **C** was isolated by column chromatography and was a crystalline solid stable towards the action of moisture and air. Single crystals of **C** suitable for X-ray diffraction studies were obtained by its recrystallization from benzene. It was found that 1,4,2-oxazaphosphorine **6** was formed (Scheme 4 and Fig. 3). The absolute configuration of all chiral centers **C** (2S, 3R, 5R) was determined by X-ray diffraction using the Hamilton test ratio, and was confirmed by the comparison with the known configuration of the C-5 atom.

It appeared to be impossible to isolate individual product **D** because of the close values of R_f of products **C** and **D**. The eluate fraction with the **C:D** ratio equal to 1:10 was obtained for spectral analysis. This mixture was a colorless oil.

The comparison of the structures **A,B** and **C,D**, and analysis of their NMR spectra gave us the basis

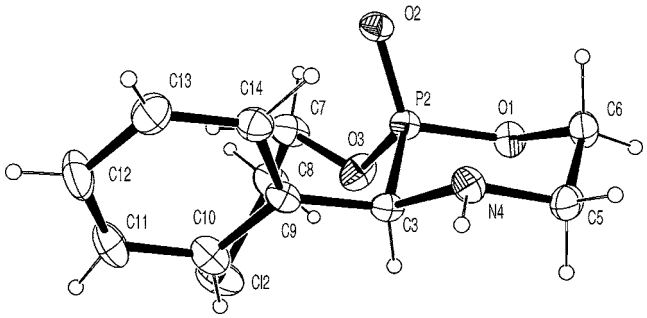
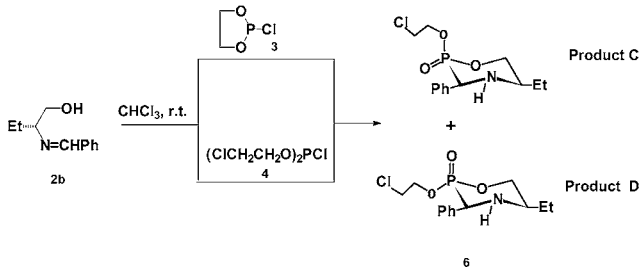


FIGURE 2 ORTEP drawing of **B** with atom numbering.



SCHEME 4

to assign the structure of 1,4,2-oxazaphosphorine **6** as the product **D**, shown in Scheme 4 with the absolute configurations of chiral centers (2R, 3R, 5R); that is, structure **D** is an analog of structure **B** (Scheme 3). Thus, the products **C** and **D** are epimers distinguished by the configuration of the phosphorus atom.

The above conclusions were additionally verified by the comparison of the ^1H NMR spectra of products **A,B** and **C,D**. One of the arguments is that the axial proton at C-3 in compounds **A,B,C** and the same proton in compound **D** have close values of chemical shifts and spin–spin coupling constants δ (ppm) and $^2J_{HP}$ (Hz): **A** (δ 4.33, $^2J_{HP} - 12.4$), **B** (δ 4.50, $^2J_{HP} - 11.4$), **C** (δ 4.25, $^2J_{HP} - 12.5$), **D** (δ 4.10, $^2J_{HP} - 10.7$). According to the literature [10,12], the proton at C-3 in 1,4,2-oxazaphosphorines has the values of $^2J_{HP} = -15.0$ to -19.2 Hz for an equatorial proton and $^2J_{HP} = -8.0$ to -11.4 Hz for an axial one. Other proofs are given by the comparison of the NMR spectra of compounds **C** and **D**. The proton at the endocyclic atom C-5 is axial in both compounds **C** and **D**, and the Et group is equatorial. This is proved by the large values of the spin–spin coupling

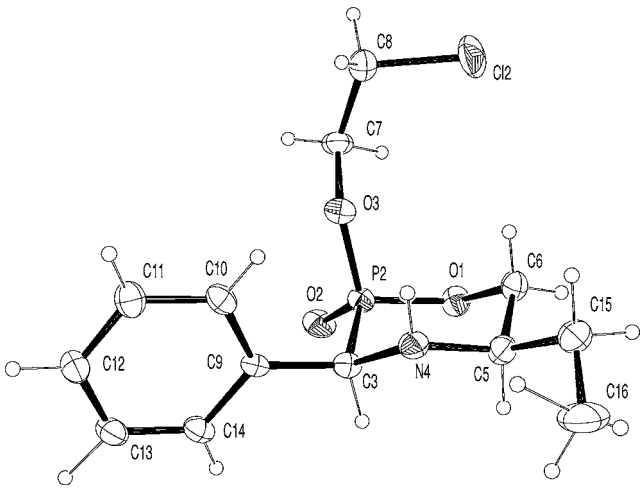


FIGURE 3 ORTEP drawing of **C** with atom numbering.

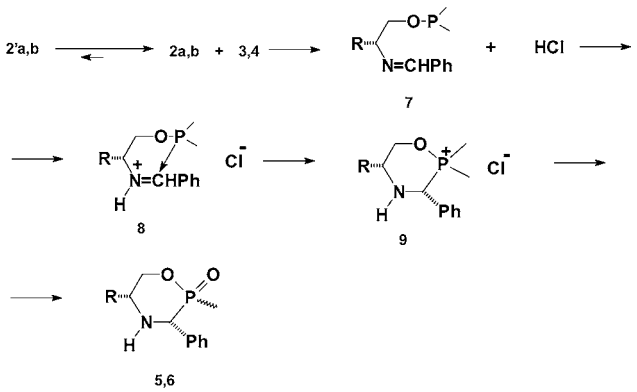
constants of the axial protons at C-5 and C-6: $^3J_{HH}$ = 11.0 Hz for **C**, $^3J_{HH}$ = 10.7 Hz for **D**, as well as by the close values of the NMR ^{13}C parameters for compounds **C** and **D**, being equal with respect to δ (ppm) and J_{HP} (Hz): C-3 δ 59.87, $^1J_{CP}$137.42; C-5 δ 57.66, $^3J_{CP}$2.5; C-6 δ 76.00, $^2J_{CP}$ 8.1 for **C** and C-3 δ 59.66, $^1J_{CP}$139.32; C-5 δ 58.01, $^3J_{CP}$0; C-6 δ 74.92, $^2J_{CP}$ 6.0 for **D**.

The interaction of **2b** and **4** also results in formation of epimeric **C,D** (Scheme 4). It should be noted that, in this case, epimer **C** is formed in larger quantities, the ratio **C:D** being equal to 4.3:1 in the reaction mixture.

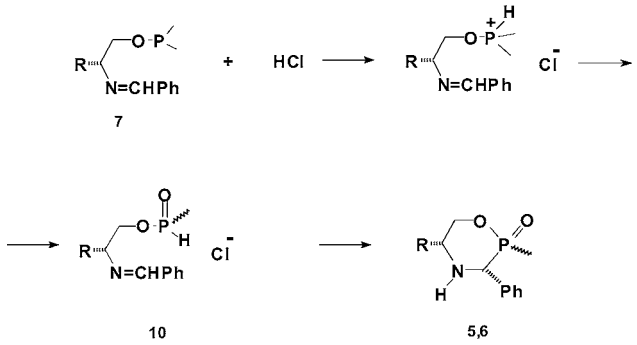
The comparison of the absolute configuration of the reaction products **C** and **D** witnesses that the formation of 1,4,2-oxazaphosphorine **6** proceeds stereospecifically at the endocyclic C-3 atom. In other words, formation of the P—C bond in the course of the reaction is totally stereoselective. This carbon atom has the R configuration in both **C** and **D** products. Furthermore, the phosphorus atom configuration is formed stereoselectively, which is clear from the nonstatistical **C** and **D** epimer ratio.

The scheme of the formation of 1,4,2-oxazaphosphorines **5** and **6** can be described in the following way. The first step involves nucleophilic substitution of the chlorine atom at P(III) in compounds **3** and **4** by β-aldiminoalcohols **2**, with formation of β-aldiminoalkylphosphites **7** (Scheme 5). Most probably, the acyclic form of β-aldiminoalcohols **2** participates in the reaction because no products of 1,3-oxazolidines **2′** are detected in the reaction mixtures.

Obviously, in the course of the reaction of **2** with **3** and **4**, upon the consumption of **2** the equilibrium **2′** ⇌ **2** is gradually shifted to the right until **2′** completely disappears. Phosphites **7**, possessing a strong basic center (imine nitrogen atom), can react with hydrogen chloride, which is evolved in the course of the reaction, with formation of the corresponding



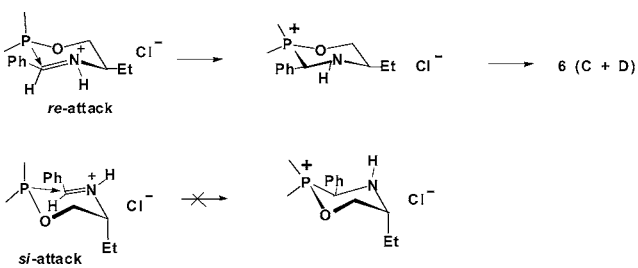
SCHEME 5



SCHEME 6

imine salts **8**. The latter undergo intramolecular cyclization with formation of quaziphosphonium salts **9**. They, in their turn, are stabilized via dealkylation following the Arbuzov reaction to give the final stereoisomeric 1,4,2-oxazaphosphorines **5** and **6**. Though the present reaction scheme is preferable, it is impossible to exclude the course of reaction with the initial protonation of P(III) by HCl in phosphites **7** and with preceeding formation of dialkyl phosphite **10** (Scheme 6). However, as the basicity of the imine nitrogen is much higher than the basicity of the P(III) atom in phosphites, the share of this reaction direction in the whole scheme is most probably very small.

As to the stereochemistry of this process, in accordance with the above scheme, the main stereocontrolling step is most probably heterocyclization, taking place owing to intramolecular nucleophilic attack on the electrophilic carbon atom of the —N=CHPh fragment by the P(III) atom (Scheme 7). Under similar conditions, the major stereodifferentiating factor of the diastereotopic faces of the C=N bond is the preferable equatorial position of the Et group for the formation of the six-membered cyclic transition state. The R configuration of the initial 2-aminobutanol-1 (**1b**) determines the *re*-face attack of the C=N bond by the P(III) atom generating the R configuration at the α-C atoms to phosphorus. The attack of the *si*-face is hindered, as in this case the Et



SCHEME 7

group would have to adopt an unfavorable axial position in the transition state. It should be noted that, in the case of the late transition state realization for this reaction, the fact of the diequatorial position of substituents Ph and Et in the final product suggests the intramolecular *re*-face attack of the P(III) atom on the C=N bond. The attack on the *si* face is less favorable, because it results in a less favorable final product with the axial–equatorial positions of substituents Et and Ph.

The preferable formation of stereoisomers **A** and **C** with the P=O group in the equatorial position is most probably explained by the fact that in the salts **9**, the Arbuzov reaction is realized by chloride anion attack at the carbon atom of the sterically less loaded equatorial P—O—C fragment.

Though, as it was indicated above, the share of the reaction direction starting from the protonation of the phosphorus atom in phosphites **7** in the course of the reaction of β-aldiminoalcohols **2** with chlorophosphites **3** and **4** in the overall reaction scheme is small, in this case, similar stereochemical considerations are also valid.

EXPERIMENTAL

Materials and Spectroscopy

All syntheses were performed under an atmosphere of dry argon. All solvents and starting reagents were distilled immediately prior to use. Commercial R-(−)-2-aminobutanol-1 (**1b**) has $[\alpha]_D^{20} = -7.01^\circ$ (neat). R-(+)-*N*-benzylidene-2-aminobutanol-1 (**2b**) derived from benzaldehyde and **1b** has $[\alpha]_D^{20} = +28.03^\circ$ (C, 13.25, CH_3OH), lit. [13] $[\alpha]_D^{20} = +39.30^\circ$. The optical purity of **2b** is 71.3%. Column chromatography and TLC were performed on silica gel L 100/160 μ and on Silufol 254 plates, respectively. ^{31}P NMR spectra were recorded with a Bruker MSL-400 spectrometer at 162 MHz (external standard 85% H_3PO_4). ^1H NMR spectra were obtained in CD_3CN on a Bruker WM-250 spectrometer at 250 MHz. Optical activity measurements were performed with a Polamat A Carl–Zeiss polarimeter.

The X-ray diffraction data for the crystals were collected on a CAD4 Enraf–Nonius automatic diffractometer. Further details consisting of the molecular and crystal structures of the studied compounds, as well as the crystal data, details of structure determination, atomic coordinates, and bond lengths and angles will be published elsewhere. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. All figures were made using the program PLATON [14].

*General Procedure for Reaction of P(III) Chlorides **3,4** with β-Aldiminoalcohols **2a,b***

Into a stirred solution of chlorophosphite **3** or **4** (10 mmol) in dry chloroform (10 ml), a solution of **2a** or **2b** (10 mmol) in chloroform (5 ml) was added dropwise at room temperature. Stirring was continued for 1 h. Chloroform was evaporated and the oily residue was submitted to a column chromatographic separation to give stereoisomeric 1,4,2-oxazaphosphorines **5** or **6**.

*2-(β-Chloroethyl)-2-oxo-3-phenyl-1,4,2-oxazaphosphorine (**5**).* Eluant, toluene–acetone 2:1; overall yield 83%. Diastereoisomer **A**: colorless solid; mp 78–79°C (from benzene–hexane, 1:1); ^{31}P NMR (CD_3CN) δ 13.7. Anal. Calcd. for $C_{11}H_{15}NO_3PCl$: C, 47.91; H, 5.44; N, 5.08; P, 11.25; Cl, 12.88. Found: C, 47.88; H, 5.40; N, 4.91; P, 11.15; Cl, 12.79. Diastereoisomer **B**: colorless solid; mp 107–107.5°C (from acetone); ^{31}P NMR (CD_3CN) δ 16.9. Anal. Found: C, 48.18; H, 5.25; N, 5.17; P, 11.41; Cl, 12.65.

*2-(β-Chloroethyl)-2-oxo-3-phenyl–5-ethyl-1,4,2-oxazaphosphorine (**6**) from Chlorophosphite **3**.* Eluant, toluene–acetone 4:1; overall yield 88%. Epimer **C**: colorless solid; mp 104–105°C (from benzene–dichloromethane, 4:1); $[\alpha a]_D^{20} = +115.9^\circ$ (C, 2.71, CH_3OH); ^{31}P NMR (CD_3CN) δ 13.6. Anal. Calcd. for $C_{13}H_{19}NO_3PCl$: C, 51.40; H, 6.26; N, 4.61; P, 10.21; Cl, 11.70. Found: C, 51.49; H, 6.10; N, 4.53; P, 10.02; Cl, 11.58. Mixture of epimers (**C:D** = 1:10): colorless oil; $n_d^{20} = 1.5302$; $[\alpha]_D^{20} = +16.2^\circ$ (C, 1.69, CH_3OH); ^{31}P NMR (CD_3CN) δ 17.4 (major), 13.5 (minor). Anal. Found: C, 51.55; H, 6.38; N, 4.73; P, 10.01; Cl, 11.89.

*2-(β-Chloroethyl)-2-oxo-3-phenyl–5-ethyl-1,4,2-oxazaphosphorine (**6**) from Chlorophosphite **4**.* Eluant, toluene:acetone 4:1; overall yield 62%. Physico-chemical constants, and spectral data of the pure epimer **C** are identical with those derived from chlorophosphite **3**.

CONCLUSIONS

Thus, we have found a new access to stereoselective synthesis of α-aminophosphonates based on the reaction of chiral β-aldiminoalcohols with chlorophosphites. The reactions take place under mild conditions with good yields, and this makes it possible to introduce a wide range of substituents at the α-position to the phosphorus atom. The intramolecular pathway of the formation of the P—C bond in the P—C—N fragment allows maximal control of the

diastereomeric excess of the reaction products. In addition, the method allows us to obtain both R and S α-aminophosphonates, depending on the absolute configuration of the β-aminoalcohols.

At present, we continue to study the reaction of chiral β-aldiminoalcohols with the P(III) halides for the asymmetric synthesis of various compounds containing the P—C—N fragment.

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