Journal of Fluorine Chemistry 216 (2018) 47–56

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Diastereoselective synthesis of polyfluoroalkylated α-aminophosphonic acid derivatives

Oleg V. Stanko[a], Yuliya V. Rassukana[a,b], Kateryna A. Zamulko[a], Viktoriya V. Dyakonenko[c], Svitlana V. Shishkina[c], Petro P. Onys'ko[a,*]

[a] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmans'ka str., Kyiv 02660, Ukraine
[b] Department of Organic Chemistry, National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute", 37 prospect Pobedy, Kyiv 03056, Ukraine
[c] SSI "Institute for Single Crystals" National Academy of Sciences of Ukraine, 60 Nauky ave, Kharkiv 61001, Ukraine

ARTICLE INFO

Keywords:
Optically active α-aminophosphonates
Polyfluoroalkylated aminophosphonic acids
Iminophosphonates
Polyfluoroalkyl
Diastereoselective synthesis
Reduction

ABSTRACT

The asymmetric synthesis of biorelevant aminophosphonates and aminophosphonic acids bearing trifluoromethyl, tetrafluoroethyl, perfluoropropyl or chlorodifluoromethyl group in the α-position to phosphonyl group is developed. Diastereoselective reduction of α-(poly)fluoroalkylated iminophosphonates, bearing stereodirecting α-phenylethyl group at the nitrogen atom, with sodium borohydride produces diastereomeric N-(α-phenylethyl) polyfluoroalkylphosphonates, readily separated by column chromatography. The highly stereoselective reaction of (*R*)-N-tert-butylsulfinylimine of tetrafluoropropanal with generated in situ diethyltrimethysilylphosphite leads to (*R*,*R*)-N-(tert-butylsulfinyl)tetrafluopropylphosphonate. Sequential N- and O-deprotection affords enantiomerically pure polyfluoroalkylphosphonate and aminophosphonic acids. The presence of α-phenylethyl group at the nitrogen atom allows easy determination of absolute configuration of the newly formed stereogenic center by the ^{31}P,^{19}F NMR method.

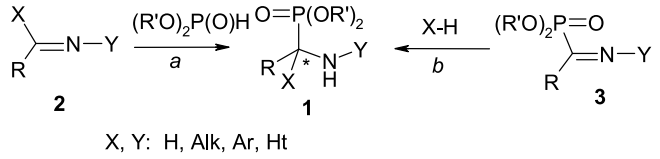
1. Introduction

α-Aminophosphonic acid derivatives are valuable targets in biomedical investigations. They are considered as the mimics of the corresponding α-aminocarboxylic acids and display the great variety of biological activities ranging from medicine to agriculture, for example, as antibiotics, peptide mimetics, haptens of catalytic antibodies, inhibitors of GABA receptors, inhibitors of various proteolyticenzymes and dialkylglycine decarboxylase, antitumor, antihypertensive and antibacterial agents and herbicides [1]. On the other hand, incorporation of the fluorinated group in organic molecules are widely used in the design and lead optimization of drug candidates in medicinal chemistry. These include an increase in binding interactions and membrane permeability, reduction of the pKa, modulation of conformation, improvement of pharmacokinetic properties of compounds and metabolic stability [2]. As for the other classes of chiral compounds, the biological activity of aminophosphonyl derivatives essentially depends on the absolute configuration of stereogenic carbon atom attached to the amino group. Different enantiomeric forms and racemic mixtures often show different and sometime opposite effects on biological target [3]. A variety of protocols for the preparation of scalemic aminophosphonic acids have been developed in the last decades. At the same time, there are only a few examples of synthesis of (poly)fluoroalkyl substituted nonracemic aminophosphonyl compounds [[4]] though the latter are the most interesting for biomedical studies. Most of the reported methods for the asymmetric synthesis of α-aminophosphonates **1** involve asymmetric addition of phosphites to non-phosphorylated imines **2** as a key step (Scheme 1, path a). In the last decades, an alternative general approach for the construction of α-aminophosphonates **1** based on the use of *C*-phosphorylated imines **3** as starting materials (Scheme 1, path b) has been developed by our group [4b,5]. With the use of this approach nonracemic aminophosphonates **1** can be accessed in several ways: (i) enantioselective addition of nucleophilic reagent to imine **2** bearing a chiral auxiliary group at the carbon or nitrogen atom of the C═N bond; (ii) the use of chiral reagent and/or catalyst; (iii) multiple stereoinduction with the use of chiral imine and chiral reagent and/or catalyst.

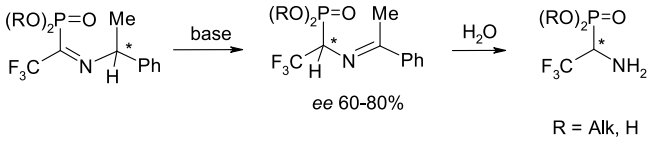
The first iminophosphonates with stereodirecting group were synthesized in our laboratory in 1990. It was established that scalemic α-(phenyl)ethylidenamino phosphonates undergo base catalyzed enantioselective proton transfer in the C = N–CH triad to afford enantiomerically enriched phosphorus analogs of trifluoroalanine derivatives (Scheme 2) [4a]. The similar results were reported later by Chinese researches [6]. Base-catalyzed intramolecular transamination

* Corresponding author.
E-mail address: onysko_@ukr.net (P.P. Onys'ko).

https://doi.org/10.1016/j.jfluchem.2018.10.001
Received 6 September 2018; Received in revised form 28 September 2018; Accepted 1 October 2018
Available online 04 October 2018
0022-1139/ © 2018 Published by Elsevier B.V.



Scheme 1. Synthesis of non-racemic aminophosphonates.



Scheme 2. Enantioslective 1,3-H transfer in trifluoroacetimidoyl phosphonates [4a].

in Scheme 2 is reducing agent-free process. At the same time, use of a base in Scheme 2 causes partial racemization of C–H stereogenic center [4a]. Diastereoselective reduction of the C=N bond of iminophosphonates bearing stereodirecting group represents another general approach to optically active aminophosphonyl derivatives, but such methodology was never used for scalemic iminophosphonates. The possibility for simple determination of diastereomeric ratio by NMR and separation of diastereomers by conventional methods is important advantage of this approach.

In the present work, we describe the synthesis of α-polyfluoroalkylated iminophosphonates bearing stereodirecting α-(phenyl) ethyl group at the nitrogen atom and their diastereoselective reduction to respective α-aminophosphonates. Alternative approach to enantiomerically pure α-(amino)tetrafluoropropylphosphonic acid by addition of phosphite to chiral N-(tert-butyl)sulfinylimine of tetrafluoropropopanal is also presented.

2. Results and discussion

The enantiopure iminophosphonates (*S*)-**6a-e** and (*R*)-**6a-e** bearing stereodirecting α-(phenyl)ethyl group at the nitrogen atom were prepared according to Scheme 3, starting from the esters of commercially accessible polyfluoroalkane carboxylic acids and (*S*)- and (*R*)-α-(phenyl)ethylamines.

Esters **4** were converted under mild conditions into amides **5** in almost quantitative yields. The latter reacted with phosphorus pentachloride to afford imidoyl chlorides **6**. It was found that imidoyl chlorides **6b-d**, similarly to their trifluoromethyl analogs (*S*)-**6a** [4a] or (*R*)-**6a** [7] react with triethyl phosphite by the Arbuzov reaction scheme with the formation of iminophosphonates (*S*)-**7b-d** and (*R*)-**7b-d** (Scheme 3). It is important to note that the alternative reaction route, involving the participation of halogen atom of the polyhaloalkyl group and formation of the N-phosphorylated product by the aza-Perkow reaction (cf. [8]) is not realized even in case of iminophosphonate **6d** bearing chlorodifluoromethyl group at the imine carbon atom. Iminophosphonates (*S*)-**6a** [4a] and (*R*)-**6a** [7] were described earlier. The crude enantiomers of **6b-d** and **7b-d** can be purified by distillation in vacuo allowing large-scale preparation of these novel chiral synthons in the analytically pure state.

Initially, we investigated the possibility for diastereoselective reduction of the C=N bond on the example of iminophosphonate (*S*)-**7a** (Scheme 4). It was found that upon palladium catalyzed hydrogenation (MeOH, 20 °C,) complete conversion of (*S*)-**7a** was achieved within 6 h to afford mixture of diastereomers (*S,S*)-**8a**, (*R,S*)-**8a** (Scheme 4) and N-unprotected aminophosphonate $CF_3CH[P(O)(OEt)_2]NH_2$ (**9a)** in the ratio of 0.8:1:3. More prolonged hydrogenation (10 h) resulted in complete conversion to **9a**. Since the removal of the N-protecting group does not involve the participation of newly generated CHP stereogenic center, the enantiomeric ratio in thus formed aminophosphonate **9a** is the same as diastereomeric ratio in the precursor **8a** [(*S*)-**9a**/(*R*)-**9a** = 0.8:1)]. It should be noted that previous attempts for the enantioselective hydrogenation of diethyl 4-(methoxyphenyl)iminotrifluoroethylphosphonate with the use of chiral rhodium catalysts were unsuccessful [9].

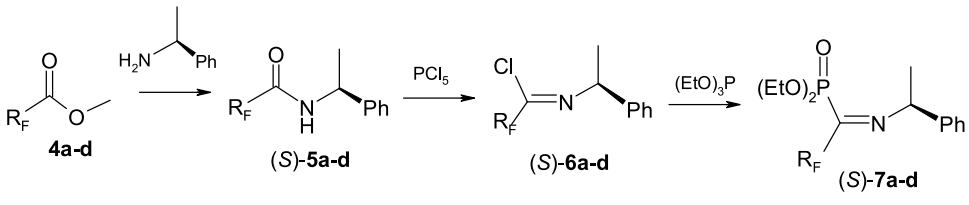
The reduction with sodium borohydride in methanol essentially improves the diastereoseletivity and results in the predominant formation of opposite diastereomer (*S,S*)-**8a** (Table 1, entry 2). Under these conditions N-protecting phenylethyl group is preserved. The use of lithium borohydride results in the decrease of diastereoslectivity (entry 3). Reduction with borane or sodium borohydride in THF does not take place at all (entries 4, 6). The reaction with $LiAlH_4$ is non-chemoselective and leads to the complex reaction mixture. As seen in Table 1, the best results were obtained with sodium borohydride in alcohols. The fraction of (*S,S*)-diastereomer and the rate of reduction increase with increasing of the relative polarity of alcoholic solvent (entries 2, 9, 10, 11). At the same time, the use of acetic acid or aqueous methanol leads to a decrease in diastereomeric ratio (entry 14). The opposite stereoselectivity was observed in methanol and *tert*-butanol. At the same time, aprotic solvents of different polarity are ineffective for the reduction (entries 6, 13). Fluorinated alcohols enhances diastereoselectivity as compared to their nonfluorinated analogs, although reactions in these cases are very slow (*cf*. entries 7 and 10, 8 and 9). Remarkably, the change of solvent allows controlling stereoselectivity and generating predominantly (*S*)- or (*R*)- stereogenic center.

It was found that established optimal conditions ($NaBH_4$, MeOH, -20 °C to r.t) can be applied for the diastereoselective reduction of optically active iminophosphonates bearing tetrafluoroethyl, heptafluoropropyl, and chlorodifluromethyl group at the imine carbon atom. Similarly to other fluoroalkylated iminophosphonates [11], compounds **7** exist predominantly in *Z* configuration. All of them reveal similar diastereoselectivity in the reaction with sodium borohydride (Table 2).

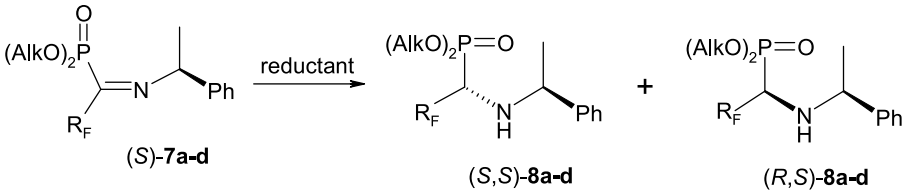
The rise in steric hindrance at the phosphorus atom has only a slight effect on stereoselectivity (Table 2, entries 1 and 2). At the same time, fluoroalkyl substituent at the imine carbon atom substantially affects the rates of hydrogenation: $CF_3 > CF_2Cl > n\text{-}C_3F_7 > HCF_2CF_2$.

Diastereomers (*S,S*)-**8a-d**, (*R,S*)-**8a-d** were separated by column chromatography. Consecutive N- and O-deprotection allows preparing both (*S*)- and (*R*)- enantiomers of aminophosphonates **9a-d** and aminophosphonic acids **10a-d**. The latter can be obtained also directly from aminophosphonates **8** by acid-catalyzed hydrolysis (Scheme 5). Individual diastereomers (*R,R*)-**8a,b,d** and (*S,R*)-**8a,b,d** were isolated similarly by column chromatography.

Enantio- or diastereoselective addition of phosphite to imines (Scheme 1, path a) is one of the most used methods in synthesis of optically active α-aminophosphonates. Imines with stereodirecting



Scheme 3. Synthesis of optically active α-polyfluoroalkylated iminophosphonates.



Scheme 4. Diastereoselective reduction of α-polyfluoroalkylated iminophosphonates.

Table 1
Reduction of iminophosphonates (*S*)-**7a**.

entry	reductant	solvent (relative polarity [10])	conditions	*dr* (*S,S*/*R,S*)	Conversion of **7**, %
1	H_2, Pd/C	MeOH (0.762)	20 °C, 6 h	0.8:1	100[a]
2	$NaBH_4$	MeOH (0.762)	–20 to 25 °C, 8 h	4.9:1	100
3	$LiBH_4$	MeOH (0.762)	–20 to 25 °C, 8 h	2.5:1	100
4	BH_3*Me_2S	THF	–20 to 65 °C, 24 h	–	0
5	$LiAlH_4$	THF	–40 to 0 °C, 2 h	–	-[b]
6	$NaBH_4$	THF	–20 to 65 °C, 24 h	–	0
7	$NaBH_4$	$(CF_3)_2CHOH$	–20 to 25 °C, 8 h	3.2:1	17
8	$NaBH_4$	CF_3CH_2OH	–20 to 25 °C, 8 h	2.6:1	8
9	$NaBH_4$	EtOH (0.654)	–20 to 25 °C, 8 h	1.6:1	100
10	$NaBH_4$	*i*-PrOH (0.546)	–20 to 25 °C, 8 h	0.75:1	100
11	$NaBH_4$	*t*-BuOH (0.389)	0 to 25 °C, 8 h	0.55:1	100
12	$NaBH_4$	MeOH-H_2O, 1:1	–20 to 25 °C, 8 h	2.6:1	100
13	$NaBH_4$	DMF (0.386)	–20 to 25 °C, 8 h	1:1	10
14	$NaBH_4$	AcOH (0.648)	20 °C, 0.5 h	2.4:1	17

[a] N-deprotected aminophosphonate **9a** is also formed: (*S,S*)-**8a**/(*R,S*)-**8a**/**9a** ~ 0.8:1:3.
[b] Complex reaction mixture is formed.

Table 2
Diastereoselective reduction of iminophosphonates (*S*)-**7a-d** ($NaBH_4$, MeOH, –20 to 25 °C).

R_F	CF_3	CF_3[c)]	HCF_2CF_2	*n*-C_3F_7	CF_2Cl
dr [a]	4.9:1	3.4:1	3.5:1	4.3:1	3.4:1
Relative reactivity [b)]	100	100	12	25	81

[a] The same values of *R,R*- to *S,R*- ratios were obtained in reduction of (*R*)-**7a-d**; [b)] determined by ^{19}F, ^{31}P NMR as conversion of **7**, %; [c)] O,O-diisopropyl ester.

sulfinyl moiety at the nitrogen atom are especially promising in this regard. At the same time, there is only one example of their use for the preparation of non-racemic fluoroalkylated tertiary α-aminophosphonates [4c].

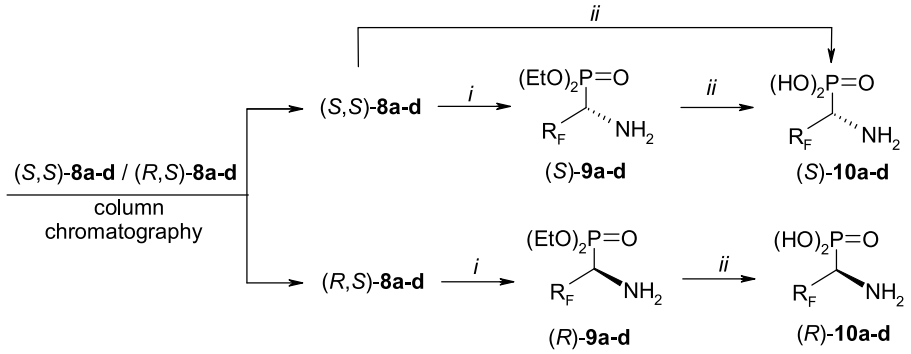
Based on commercially accessible reagents we have developed a convenient synthesis of previously unknown (*R*)-N-*tert*-butylsulfinimine **11** bearing tetrafluoroethyl group at the imine carbon atom (Sheme 6). After testing different conditions (classical azeotropic removal of water using Dean-Stark apparatus in the presence or absence of TsOH, heating with molecular sieves without solvent), it was found that heating in dichloromethane in the presence of $MgSO_4$-molecular sieves 4 Å dehydrating system followed by vacuum distillation are the optimal conditions to obtain enantiopure imine **11** (Scheme 6). Novel chiral synthon (*R*)-**11** is quite stable in anhydrous atmosphere and can be stored for a long time without decomposition and loss of optical activity.

It was found that diethyl trimethylsilyl phosphite, generated *in situ* by the reaction of diethyl phosphite with trimethylchlorosilane and triethylamine reacted with the imine (*R*)-**11** highly diastereoselectively to afford phosphonate **12** (R_CR_S/S_CR_S 92:8). The stereochemical outcome is similar to that described earlier for the analogous reaction of N-(*tert*-butylsulfinyl)imine of fluoral [4c]. Thus, the formation of the major diastereomer **12** with (*R,R*)-configuration can be explained by the same non-chelated transition state in which phosphite approaches to the imine (*R*)-**11** from the less hindered face occupied by a lone pair of electrons on sulfur.

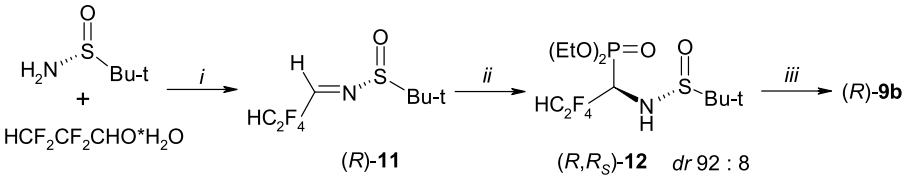
Analytically and diastereomerically pure (*R,R*)-**12** was isolated in 60% yield by crystallization from aqueous ethanol.

Consecutive removal of N-sulfinyl auxiliary and hydrolysis of ester groups in (*R,R*)-**12** affords enantiomerically pure aminophosphonate (*R*)-**9b** (Scheme 6) and aminophosphonic acid (*R*)-**10b** (Scheme 5).

Stereochemical assignments. The absolute configuration of N-(*tert*-



Scheme 5. Preparation of (*S*)- and (*R*)- enantiomers of aminophosphonates **9a-d** and aminophosphonic acids **10a-d**. *i*) H_2, Pd/C; *ii*) conc. HCl.



Scheme 6. Stereoselective synthesis of (*RR*)-**12** and (R)-**9b**. *i*) molecular sieves 4 A; *ii*) $(EtO)_2P(O)H$-Me_3SiCl-Et_3N; *iii*) 4 N HCl.

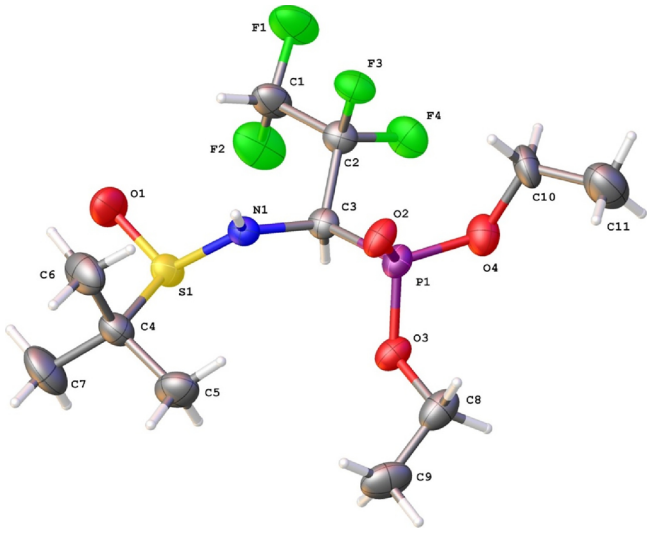


Fig. 1. Molecular structure of compound **12**. Thermal ellipsoids are shown at the 50% probability level.

butylsulfinyl) tetrafluoropropylphosphonate **12** was determined by XRD analysis of single crystals of the major diastereomer (Fig. 1). Compound **12** crystallizes in the chiral space group of $P2_12_12_1$ indicating the presence of one diastereoisomer in the crystal phase. There are two molecules A and B with similar geometric parameters as well as one water molecule in the asymmetric part of the unit cell. The molecules A and B of the diastereomer **12** have the R,R- configuration of the chiral centers at the P1 and C3 atoms what was determined using the Flack parameter (-0.04(7)).

Since in the conversions (*R,R*)-**12** → (*R*)-**9b**→ (*R*)-**10b** the bonds around the stereogenic carbon atom are not broken, it was possible to assign (*R*) configuration to phoshonate **9b** and aminophosphonic acid **10b** in Scheme 6. Similarly, the configurations of the newly formed stereogenic centers bonded with phosphorus atom are preserved during transformations **8** → **9**→ **10**. The configurations of the stereogenic α-carbon atoms in compounds **8a,b** were determined by their conversion into phosphonic acids **10a** and **10b** (Scheme 5) with known absolute configuration.

From configurational assignments in the compounds **8** it is very interesting to emphasize that ^{31}P NMR chemical shifts of all major diastereomers were found to be at the higher field and the ^{19}F NMR chemical shifts at the lower field concerning the minor diastereomers (Table 3). This clear relationship was taken as an indication that the newly generated α-carbon atom in all major diastereomers derived from (*S*) iminophosphonates **7a-d** has the (*S*) absolute configuration. Similarly, (*R*) enantiomers of iminophosphonates **7a-d** produce major diastereomers with (*RR*) configuration. To rationalize these spectral distinctions, we have calculated the preferred conformations for the diastereomers of **8a** with (*SS*) and (*RS*) configurations of the two stereogenic carbon atoms, respectively (Fig. 2), using m06-2x/cc-pvdz method within GAUSSIAN09 program. The *RS*-diastereomer is more stable by 2.79 kcal/mol as compared to *SS*-diastereomer. In compounds **8** phenyl group generates a diamagnetic anisotropy effect due to the ring current induced under the external magnetic field. As is seen from Fig. 2, phosphonyl group in (*SS*)-**8a** and trifluoromethyl group in (*RS*)-**8a** face the phenyl group in the preferred conformations and therefore undergo high-field shifts in the ^{31}P NMR and ^{19}F NMR spectra, respectively. In nice agreement with this, the experimental ^{31}P, ^{19}F NMR data for the compounds **8a-d** (Table 3) show that phosphonyl group in the diastereomers with the same [(*SS*) or (*RR*)] or polyfluoroalkyl group in the diastereomers with the different [(*RS*) or (*SR*)] absolute configurations of stereogenic carbon atoms, are shifted to higher field. The described above method can be applied for the determination of absolute configuration by ^{31}P NMR method for other aminophosphonates bearing enantiopure α-phenylethyl auxiliary at the nitrogen atom. For the α-fluoroalkylated aminophosphonates, both ^{31}P NMR and ^{19}F NMR can be utilized for the determination of absolute configuration.

Table 3
^{31}P, ^{19}F NMR data of the diastereomers **8a-d**.

	$\delta_P(S,S)$, ppm	$\delta_P(R,S)$, ppm	δ_F (*S,S*), ppm	δ_F (*R,S*), ppm
8a	17.5	19.3	–68.3	–69.8
8b	18.3	20.1	–123.0, –140.8	–125.0, –142.4
8c	17.1	18.8	–81.9, –112.7, –125.1	–82.1, –114.1, –124.7
8d	17.6	19.5	–52.1	–54.2

3. Conclusion

Based on the diastereoselective reduction of α-(poly)fluoroalkylated iminophosphonates with stereodirecting *α*-phenylethyl group at the nitrogen atom, we have developed an efficient synthetic protocol for the preparation of optically active derivatives of respective fluorinated α-aminophosphonic acids. The first representatives of enantiomerically pure (*S*) and (*R*) α-aminophosphonates and aminophosphonic acids bearing HCF_2CF_2, C_3F_7 or CF_2Cl group in α-position were prepared. The synthesis of novel chiral building block, (*R*)-*N*-*tert*-butylsulfinylimine of tetrafluoropropanal, was developed. The latter reacted with the system $(EtO)_2P(O)H$-Me_3SiCl-Et_3N highly stereoselectively to afford (*R,R*)-*N*-(*tert*-butylsulfinyl)tetrafluopropylphosphonate (*dr* 92:8) which was converted in enantiopure O,O-diethyl tetrafluopropylphosphonate and respective phosphonic acid. The ^{31}P, ^{19}F NMR chemical shifts in diastereomeric N-(α-phenylethyl) polyfluoroalkylphosphonates are affected by the diamagnetic anisotropy effect generated by the phenyl group allowing determination of absolute configuration of newly formed stereogenic center. The NMR spectral distinctions found for N-(α-phenylethyl)aminophosphonates can be used for determination of absolute configuration in related systems.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance DRX 500 (at 499.9 MHz for Protons, at 376.5 MHz for Fluorine and 124.9 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons and 100.7 MHz for Carbon-13). Chemical shifts are reported relative to internal TMS (^1H) or $CFCl_3$ (^{19}F) standards. The solvents were dried according to the standard procedures. All the starting materials were purchased from Acros, Merck, Fluka, and Enamine Ldt. Melting points are uncorrected. Column chromatography was performed using Kieselgel Merck 60 (400–630 mesh) as the stationary phase. Elemental analysis was carried out in the analytical laboratory of Institute of organic chemistry, NAS of Ukraine.

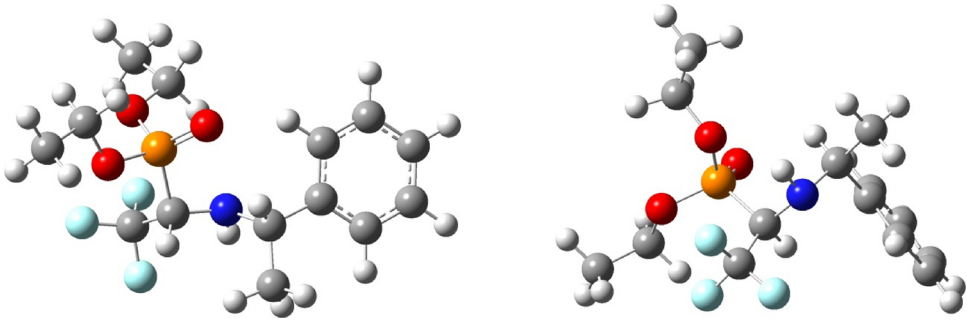


Fig. 2. Molecular structure of (*SS*) diastereomer **8a** (left) and (*RS*) diastereomer **8a** (right) according to data of quantum-chemical calculations.

4.2. N-(1-Phenylethyl)amides of polyfluoroalkyl carboxylic acids 5b–d

A solution of (*S*)-1-phenylethylamine (4.85 g, 40 mmol) in diethyl ether (7 mL) was added dropwise to stirring solution of respective methyl carboxylate **4** (40 mmol) in diethyl ether (10 mL) and left overnight at room temperature. The solvent was evaporated in *vacuo* and the residue was triturated with hexane. The product was filtered and dried in *vacuo* to give amides (*S*)-**5b-d.** The enantiomers (*R*)-**5b-d** were obtained similarly with the use of (*R*)-1-phenylethylamine.

4.2.1. (S)-2,2,3,3-Tetrafluoro-N-(1-phenylethyl)propanamide (S)-5b

Yield 9 g (97%). White solid: mp 76–78 °C. $[\alpha]_D^{20}$ = –118.4 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3), 5.16 (dq, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, C*H*CH_3), 6.13 (tt, $^2J_{HF}$ = 52.8, $^3J_{HF}$ = 5.6 Hz, 1H, CHF_2), 6.68 (br s, 1H, NH), 7.26–7.33 (m, 3H, Ph), 7.37–7.4 (m, 2H, Ph). ^{13}C NMR (125.7 MHz, $CHCl_3$) δ (ppm): 20.7 (s, CH_3), 49.1 (s, *C*HCH_3), 108.3 (tt, $^1J_{CF}$ = 251.4, $^2J_{CF}$ = 31.4 Hz, CF_2H), 108.5 (tt, $^1J_{CF}$ = 262.7, $^2J_{CF}$ = 28.9 Hz, *C*F_2CF_2H), 125.6 (s, C_{Ph}), 127.6 (s, $^4C_{Ph}$), 128.5 (s, C_{Ph}), 140.6 (s, $^1C_{Ph}$), 158.8 (t, $^2J_{CF}$ = 26.3 Hz, C = O). ^{19}F NMR (376.5 МГц, $CDCl_3$) δ (ppm): –126.4 (m, $^2J_{FAFB}$ = 271.1 Hz, 1 F), –126.2 (m, $^2J_{FBFA}$ = 271.1 Hz, 1 F), –139.9 (m, 2 F). Anal. calcd. for $C_{11}H_{11}F_4NO$: C 53.02; H 4.45; N 5.62. Found, %: C 52.88; H 4.42; N 5.71.

4.2.2. (R)-2,2,3,3-Tetrafluoro-N-(1-phenylethyl)propanamide (R)-5b

Yield 8.9 g (96%). White solid. $[\alpha]_D^{20}$ = +107.5 (*c* 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-5b.

4.2.3. (S)-2,2,3,3,4,4,4-Heptafluoro-N-(1-phenylethyl)butanamide (S)-5c

Yield 12.18 g (96%).White solid: mp 87–89 °C. (lit. mp 91–92 °C [12]. $[\alpha]_D^{20}$ = –97.3 (*c* 0.5, $CHCl_3$).

4.2.4. (R)-2,2,3,3,4,4,4-Heptafluoro-N-(1-phenylethyl)butanamide (R)-5c

Yield 11.93 g (94%).White solid. $[\alpha]_D^{20}$ = +97.6 (*c* 0.5, $CHCl_3$). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-5c.

4.2.5. (S)-2-Chloro-2,2-difluoro- N-(1-phenylethyl)ethanamide (S)-5d

Yield 8.97 g (96%).White solid: mp 79–82 °C. (lit. mp 70 °C [13]). $[\alpha]_D^{20}$ = –112.3 (*c* 0.5, $CHCl_3$).

4.2.6. (R)-2-Chloro-2,2-difluoro- N-)1-phenylethyl)ethanamide (R)-5d

Yield 8.88 g (95%).White solid. $[\alpha]_D^{20}$ = +113.9 (*c* 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-5d.

4.3. Imidoyl chlorides 6b-c

Phosphorus pentachloride (7.2 g, 34.5 mmol) was added to a solution of respective amide **5** (30 mmol) in toluene (10 mL) at room temperature. The mixture was refluxed until gas evolution stopped (~10 h). After then the mixture was distilled in *vacuo*, to give the compound **6**.

4.3.1. (S)-2,2,3,3-Tetrafluoro-N-(1-phenylethyl)propanimidoyl chloride (S)-6b

Yield 6.6 g (82%). Yellowish oil: bp 95–96 °C/12 Torr. $[\alpha]_D^{20}$ = −117.5 (*c* 1, C_6H_6). ^{1}H NMR (400 MHz, $_6D_6$) δ (ppm): 1.18 (d, $^3J_{HH}$ = 6.4 Hz, 3H, CH_3), 4.75 (q, $^3J_{HH}$ = 6.4 Hz, 1H, CH), 5.67 (tt, $^2J_{HF}$ = 52.8, $^3J_{HF}$ = 5.6 Hz, 1H, CHF_2), 7.06–7.19 (m, 5H, Ph). ^{13}C NMR (100 MHz, C_6D_6) δ (ppm): 22.2 (s, CH_3), 62.3 (s, CH), 108.7 (tt, $^1J_{CF}$ = 251.4, $^2J_{CF}$ = 31.4 Hz, CF_2H), 109.1 (tt, $^1J_{CF}$ = 255.2, $^2J_{CF}$ = 26.4 Hz, *C*F_2CF_2H), 125.8 (s, C_{Ph}), 127.2 (s, $^4C_{Ph}$), 128.2 (s, C_{Ph}), 133.9 (t, $^2J_{CF}$ = 33.9 Hz, C = N), 141.3 (s, $^1C_{Ph}$). ^{19}F NMR (376.5 MHz, C_6D_6) δ (ppm): –117.4 (m, $^2J_{FAFB}$ = 289.9 Hz, 1 F), –118.2 (m, $^2J_{FBFA}$ = 271.1 Hz, 1 F), –137.7 (m, 2 F). Anal. calcd. for $C_{11}H_{10}ClF_4N$: C 49.36; H 3.77; N 5.23. Found, %: C 49.58; H 3.80; N 5.33.

4.3.2. (R)-2,2,3,3-Tetrafluoro-N-(1-phenylethyl)propanimidoyl chloride (R)-6b

Yield 6.4 g (80%). Yellowish oil. $[\alpha]_D^{20}$ = +120.38 (*c* 1, C_6H_6). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-6b.

4.3.3. (S)-2,2,3,3,4,4,4-Heptafluoro-N-(1-phenylethyl)butanimidoyl chloride (S)-6c

Yield 7.85 g (78%). Yellowish oil: bp 81–82 °C/12 Torr. $[\alpha]_D^{20}$ = −84.1 (*c* 1, C_6H_6). ^{1}H NMR (400 MHz, C_6D_6) δ (ppm): 1.13 (d, $^3J_{HH}$ = 6.4 Hz, 3H, CH_3), 4.68 (q, $^3J_{HH}$ = 6.4 Hz, 1H, CH), 6.97 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ph), 7.04 (dd, $^3J_{HH}$ = 7.2, $^3J_{HH}$ = 6.8 Hz, 2H, Ph), 7.11 (d, $^3J_{HH}$ = 6.8 Hz, 2H, Ph). ^{13}C NMR (125 MHz, C_6D_6) δ (ppm): 22.6 (s, CH_3), 63.4 (s, CH), 108.8 (tq, $^1J_{CF}$ = 267.3, $^2J_{CF}$ = 35.2 Hz, *C*F_2CF_3), 109.1 (tt, $^1J_{CF}$ = 261.5, $^2J_{CF}$ = 30.2 Hz, *C*F_2CP), 117.8 (qt, $^1J_{CF}$ = 287.9, $^2J_{CF}$ = 33.9 Hz, CF_2CF_3), 126.2 (s, C_{Ph}), 127.5 (s, $^4C_{Ph}$), 128.5 (s, C_{Ph}), 131.0 (t, $^2J_{CF}$ = 31.4 Hz, *C*=N), 141.5 (s, $^1C_{Ph}$). ^{19}F NMR (376.5 MHz, C_6D_6) δ (ppm): –80.8 (t, $^3J_{FF}$ = 7.5 Hz, 3 F), –111.4 (q, $^3J_{FF}$ = 7.5 Гц, 2 F), –125.5 (м, 2 F). Anal. calcd. for $C_3H_6F_4NO_3P$: C 42.94; H 2.70; N 4.17. Found, %: C 42.87; H 2.74; N 4.12.

4.3.4. (R)-2,2,3,3,4,4,4-Heptafluoro-N-(1-phenylethyl)butanimidoyl chloride (R)-6c

Yield 7.55 g (75%). Yellowish oil. $[\alpha]_D^{20}$ = +86.6 (*c* 1, C_6H_6). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-**6c**.

4.3.5. (S)-2-Chloro-2,2-difluoro-N-(1-phenylethyl)ethanimidoyl chloride (S)-6d

Yield 5.67 g (75%). Yellowish oil: bp 94–95 °C/12 Torr. $[\alpha]_D^{20}$ = −108 (*c* 1, C_6H_6). ^{1}H NMR (400 MHz, C_6D_6) δ (ppm): 1.15 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3), 4.67 (q, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 6.98 (t, $^3J_{HH}$ = 6.8 Hz, 1H, Ph), 7.05–7.13 (m, $^3J_{HH}$ = 8.0, $^3J_{HH}$ = 6.8 Hz, 2H, Ph),

7.13 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ph). ^{13}C NMR (100 MHz, C_6D_6) δ (ppm): 23.1 (s, CH_3), 63.3 (s, CH), 120.8 (t, $^1J_{CF}$ = 293.8 Hz, CF_2Cl), 126.7 (s, C_{Ph}), 127.9 (s, C^4_{Ph}), 129.0 (s, C_{Ph}), 134.4 (t, $^2J_{CF}$ = 34.2 Hz, 1C, C = N), 142.2 (s, C^1_{Ph}). ^{19}F NMR (376.5 MHz, C_6D_6) δ (ppm): –58.02. Anal. calcd. for $C_{10}H_9ClF_2N$: C 47.65; H 3.60; N 5.56. Found, %: C 47.72; H 3.61; N 5.55.

4.3.6. (R)-2-Chloro-2,2-difluoro-N-(1-phenylethyl)ethanimidoyl chloride (R)-6d

Yield 5.89 g (78%). Yellowish oil. $[\alpha]_D^{20}$ = +115.3 (*c* 1, C_6H_6). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-6d.

4.4. Imidoyl phosphonates 7

Triethyl phosphite (5.6 g, 33.6 mmol) was added to respective imidoyl chloride **6** (28 mmol). The reaction mixture was stirred at 125 °C for 8 h. After then the mixture was distilled in *vacuo* to give the compound **7**.

*4.4.1. O,O-Diethyl (S)-[2,2,2-trifluoro-N-(1-phenylethyl)ethanimidoyl] phosphonate (S)-**6a***

Yield 7.93 g (84%). Yellowish oil. $[\alpha]_D^{20}$ = –52.5 (*c* 1, $CHCl_3$). The spectral data of (*S*)-**6a** were in agreement with those reported in the literature [4a].

*4.4.2. O,O-Diethyl (R)-[2,2,2-trifluoro-N-(1-phenylethyl)ethanimidoyl] phosphonate (R)-**6a***

Yield 7.65 (81%). Yellowish oil. $[\alpha]_D^{20}$ = +53.7 (*c* 1, $CHCl_3$). The spectral data of (*R*)-**6a** were in agreement with those reported in the literature [4a].

4.4.3. O,O-Diethyl (S)-[2,2,3,3-tetrafluoro-N-(1-phenylethyl)propanimidoyl] phosphonate (S)-7b

Yield 8.48 g (82%). Yellowish oil: bp 103–104 °C/0.07 Torr. $[\alpha]_D^{20}$ = −48.4 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_2CH_3,), 1.36 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_2CH_3,), 1.53 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CHCH_3$,), 4.09–4.31 (m, 4H, CH_2O) 5.71 (q, $^3J_{HH}$ = 6.4 Hz, 1H, -*CH*Ph), 6.37 (tt, $^2J_{HF}$ = 52.8, $^3J_{HF}$ = 5.6 Hz, 1H, CHF_2), 7.25–7.38 (m, 5H, Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 15.6 (d, $^3J_{CP}$ = 6.3 Hz. CH_2CH_3), 15.7 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 24.1 (s, $CHCH_3$), 63.1 (d, $^3J_{CP}$ = 12.5 Hz, CHPh), 63.1 (d, $^3J_{CP}$ = 6.3 Hz, CH_2O), 63.1 (d, $^3J_{CP}$ = 6.3 Hz, CH_2O), 108.9 (ttd, $^1J_{CF}$ = 250.1, $^2J_{CF}$ = 31.4, $^3J_{CP}$ = 3.8 Hz, CF_2H), 111.6 (tdt, $^1J_{CF}$ = 255.2, $^2J_{CP}$ = 31.4, $^2J_{CF}$ = 26.4 Hz, CF_2CF_2H), 126.0 (s, C_{Ph}), 126.9 (s, $^4C_{Ph}$), 128.1 (s, C_{Ph}), 142.6 (s, $^1C_{Ph}$), 153.8 (dt, $^1J_{CP}$ = 148.3, $^2J_{CF}$ = 31.4 Hz, C = N). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm): –118.1 (m, $^2J_{FAFB}$ = 301.2 Hz, 1 F), –118.9 (m, $^2J_{FBFA}$ = 301.2 Hz, 1 F), –140.0 (m, 2 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): –3.4. Anal. calcd. for $C_{15}H_{20}F_4NO_3P$: C 48.79; H 5.46; N 3.79; P 8.39. Found, %: C 49.06; H 5.35; N 3.63; P 8.41.

4.4.4. O,O-Diethyl (R)-[2,2,3,3-tetrafluoro-N-(1-phenylethyl)propanimidoyl] phosphonate (R)-7b

Yield 8.17 g (79%). Yellowish oil. $[\alpha]_D^{20}$ = +50.5 (c 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-**7b**.

*4.4.5. O,O-Diethyl (S)-[2,2,3,3,4,4,4-heptafluoro-N-(1-phenylethyl) butanimidoyl]phosphonate (S)-**7c***

Yield 9.92 g (81%). Yellowish oil: bp 88–89 °C/0.07 Torr. $[\alpha]_D^{20}$ = −33.3 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_2CH_3,), 1.36 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_2CH_3,), 1.53 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CHCH_3$,), 4.04–4.32 (m, 4H, CH_2O) 5.75 (q, $^3J_{HH}$ = 6.4 Hz, 1H, CHPh), 7.26 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ph), 7.33 (dd, $^3J_{HH}$ = 7.6, $^3J_{HH}$ = 7.2 Hz, 2H, Ph), 7.4 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 15.6 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 15.7 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 24.3 (s, $CHCH_3$), 63.1 (s, CHPh), 63.1 (d, $^3J_{CP}$ = 12.6 Hz, CH_2O), 63.4 (d, $^3J_{CP}$ = 12.6 Hz, CH_2O), 108.8–113.9 (m, CF_2CF_2), 117.9 (qt, $^1J_{CF}$ = 289.2, $^2J_{CF}$ = 37.7 Hz, CF_3), 126.0 (s, C_{Ph}), 126.9 (s, $^4C_{Ph}$), 128.0 (s, C_{Ph}), 142.6 (s, $^1C_{Ph}$), 152.0 (dt, $^1J_{CP}$ = 153.4, $^2J_{CF}$ = 30.2 Hz, C = N). ^{19}F NMR (376.5 MHz, C_6D_6) δ (ppm): –80.1 (t, $^3J_{FF}$ = 11.3 Hz, 3 F), –110.4 (m, $^2J_{FAFB}$ = 293.7 Hz, 1 F), –111.0 (m, $^2J_{FBFA}$ = 293.7 Hz, 1 F), –124.3 (m, 2 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 1.4. Anal. calcd. for $C_{16}H_{19}F_7NO_3P$: C 43.95; H 4.38; N 3.20; P 7.08. Found, %: C 44.04; H 4.35; N 3.23; P 7.12.

4.4.6. O,O-Diethyl (R)-[2,2,3,3,4,4,4-heptafluoro-N-(1-phenylethyl) butanimidoyl]phosphonate (R)-7c

Yield 10.16 g (83%). Yellowish oil. $[\alpha]_D^{20}$ = +36.7 (c 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-**7c**.

4.4.7. O,O-Diethyl (S)-[2-chloro-2,2-difluoro-N-(1-phenylethyl)ethanimidoyl] phosphonate (S)-7d

Yield 9.22 g (87%). Yellowish oil. Z/E = 8:1. Bp 114–115 °C/0.07 Torr. $[\alpha]_D^{20}$ = −44.3 (c 1, $CHCl_3$). **(*Z*)-isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (400 МГц, $CDCl_3$) δ: 1.3 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_2CH_3), 1.34 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_2CH_3), 1.54 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CHCH_3$), 4.11–4.31 (m, 4H, CH_2O) 5.63 (q, $^3J_{HH}$ = 6.4 Hz, 1H, CHPh), 7.25 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ph), 7.33 (dd, $^3J_{HH}$ = 7.6, $^3J_{HH}$ = 7.2 Hz, 2H, Ph), 7.41 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 16.5 (d, $^3J_{CP}$ = 5 Hz, CH_2CH_3), 16.6 (d, $^3J_{CP}$ = 5 Hz, CH_2CH_3), 24.8 (s, $CHCH_3$), 63.5 (d, $^3J_{CP}$ = 12.5 Hz, CHPh), 63.9 (d, $^2J_{CP}$ = 6.3 Hz, CH_2O), 64.1 (d, $^2J_{CP}$ = 6.3 Hz, CH_2O), 123.8 (td, $^1J_{CF}$ = 293.7, $^2J_{CP}$ = 52.5 Hz, CF_2Cl), 126.8 (s, C_{Ph}), 127.7 (s, C^4_{Ph}), 128.9 (s, C_{Ph}), 143.5 (s, C^1_{Ph}), 153.8 (dt, $^1J_{CP}$ = 156.3, $^2J_{CF}$ = 28.8 Hz, C = N). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm): –56.8. ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): –2.6. **(*E*)-isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.3 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_2CH_3), 1.34 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH_2CH_3), 1.54 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CHCH_3$), 4.11–4.31 (m, 4H, CH_2O) 5.25–5.31 (m, 1H, CHPh), 7.25 (t, $^3J_{HH}$ = 7.2 Hz, 1H, Ph), 7.33 (dd, $^3J_{HH}$ = 7.6, $^3J_{HH}$ = 7.2 Hz, 2H, Ph), 7.41 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm): –52.4 (d, $^2J_{FAFB}$ = 169.4 Hz, 1 F), –53.3 (d, $^2J_{FBFA}$ = 169.4 Hz, 1 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 2.5. Anal. calcd. for $C_{14}H_{19}ClF_2NO_3P$: C 47.54; H 5.41; N 3.96, P 8.76. Found, %: C 47.62; H 5.38; N 3.95; P 8.85.

*4.4.8. O,O-Diethyl (R)-[2-chloro-2,2-difluoro-N-(1-phenylethyl)ethanimidoyl] phosphonate (R)-**7d***

Yield 9.02 g (85%). Yellowish oil. $[\alpha]_D^{20}$ = +42.9 (c 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-7d.

4.5. N-(1-Phenylethyl)aminophosphonates 8a–c

$NaBH_4$ (0.115 g, 2.98 mmol) was added to stirring solution of respective imine **7** (2.98 mmol) in MeOH (15 mL) at –20 °C. The reaction mixture was allowed to warm to room temperature. The procedure was repeated three times for compounds **7b** and **7c** [total amount of $NaBH_4$ 0.46 g (11.92 mmol)]. The mixture was stirred at room temperature for 2 h and 15% solution of HCl (5 mL) was added dropwise. Then the mixture was washed with a saturated solution of $NaHCO_3$ (10 mL), and volatile compounds were evaporated, the mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated in *vacuo* to give the product as a diastereomeric mixture. Diastereomers were separated by column chromatography.

*4.5.1. O,O-Diethyl ((1S)-2,2,2-trifluoro-1-{[(1S)-1-phenylethyl]amino} ethyl)phosphonate (S,S)-**8a***

Obtained from (S)-**7a**. Yield 0.54 g (54%). Colorless oil. $[\alpha]_D^{20}$ = −19.6 (c 1, $CHCl_3$). R_f = 0.56 (EtOAC–Hexane 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3), 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3), 1.37 (d, $^3J_{HH}$ = 7.2 Hz, 3H, $CHCH_3$), 2.08 (br s, 1H, NH), 3.27 (dt, $^3J_{HH}$ = 23, $^3J_{HH}$ = 7.2 Hz, 1H, CHP), 4.01–4.18 (m, 1H, CHPh), 4.01–4.18 (m, 4H, OCH_2), 7.24–7.29 (m, 1H, Ph), 7.31–7.35 (m, 4H, Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 16.2 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 16.4 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 24.5 (s, $-CHCH_3$), 54.9 (dq, $^1J_{CP}$ = 155.9, $^2J_{CF}$ = 28.9 Hz, CHP), 56.8 (d, $^3J_{CP}$ = 11.3 Hz, CHPh), 63.2 (d, $^2J_{CP}$ = 6.3 Hz, CH_2O), 63.6 (d, $^2J_{CP}$ = 6.3 Hz, CH_2O), 125.0 (qd, $^1J_{CF}$ = 284.1, $^2J_{CP}$ = 10.1 Hz, CF_3), 127.2 (s, C_{Ph}), 127.6 (s, $^4C_{Ph}$), 128.6 (s, C_{Ph}), 143.1 (s, $^1C_{Ph}$). ^{19}F NMR (376.55 MHz, $CDCl_3$) δ (ppm): –67.6 (d, $^3J_{FP}$ = 11.3 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 17.0 (q, $^3J_{PF}$ = 11.3 Hz). Anal. calcd. for $C_{14}H_{21}F_3NO_3P$: C 49.56; H 6.24; N 4.13; P 9.13. Found, %: C 50.72; H 6.14; N 4.18; P 9.11.

4.5.2. O, O-Diethyl ((R)-2,2,2-trifluoro-1-{[(1R)-1-phenylethyl]amino} ethyl)phosphonate (R,R)-8a

Obtained from (R)-7a. Yield: 0.56 g (56%). Colorless oil. $[\alpha]_D^{20}$ = +20.4 (c 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of diastereomer (S,S)-8a.

4.5.3. O,O-Diethyl ((1S)-2,2,3,3-tetrafluoro-1-{[(1S)-1-phenylethyl] amino}propyl) phosphonate (S,S)-8b and O,O-diethyl ((R)-2,2,3,3-tetrafluoro-1-{[(1S)-1-phenylethyl]amino}propyl) phosphonate (R,S)-8b

The diastereomeric mixture of (*S,S*)-8b/(*R,S*)-8b (3.5:1) was obtained by reduction of (*S*)-7b. Yield 0.98 g (89%). Diastereomers were separated by column chromatography (silica gel, hexane-EtOAc 1:1).

(S,S)-**8b**: Yield 0.55 g (50%). Colorless oil. $[\alpha]_D^{20}$ = −18.1 (*c* 1, $CHCl_3$). R_f = 0.58 (hexane-EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3,), 1.33 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $-CH_2CH_3$,), 1.36 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CHCH_3$,), 1.96 (br s, 1H, NH), 3.39 (dt, $^2J_{HF}$ = 10.4 Гц, $^3J_{HF}$ = 5.2 Hz, 1H, CHP), 3.91–4.20 (m, 4H, CH_2O), 3.91–4.20 (m, 1H, CHPh), 6.35 (tt, $^2J_{HF}$ = 53.2, $^3J_{HF}$ = 5.6 Hz, 1H, CHF_2), 7.26–7.30 (m, 1H, Ph), 7.33–7.36 (m, 4H, Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 16.2 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 16.3 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 23.0 (s, $CHCH_3$), 54.3 (dt, $^1J_{CP}$ = 153.4, $^2J_{CF}$ = 30.2 Hz, CHP), 56.6 (d, $^3J_{CP}$ = 6.3 Hz, $CHCH_3$), 63.0 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 63.2 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 109.2 (tq, $^1J_{CF}$ = 266.5, $^2J_{CF}$ = 37.7 Hz, CF_2CF_3), 116.0 (tt, $^1J_{CF}$ = 260.2, $^2J_{CF}$ = 30.2 Hz, CF_2CP), 117.9 (qt, $^1J_{CF}$ = 289.1, $^2J_{CF}$ = 35.2 Hz, CF_2CF_3), 127.1 (s, C_{Ph}), 127.6 (s, $^4C_{Ph}$), 128.5 (s, C_{Ph}), 143.9 (s, $^1C_{Ph}$). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm): –121.9 (dd, $^2J_{FAFB}$ = 267.3, $^3J_{FF}$ = 11.3 Hz 1 F), –123.7 (m, $^2J_{FBFA}$ = 267.3 Hz, 1 F), –139.1 (dd, $^2J_{FAFB}$ = 297.4, $^3J_{FF}$ = 11.3 Hz, 1 F), –140.9 (dd, $^2J_{FBFA}$ = 297.4 Hz, $^3J_{FF}$ = 11.3 Hz, 1 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 17.3 (m, *J* = 22.3 Hz). Anal. calcd. for $C_{15}H_{22}F_4NO_3P$: C 48.52; H 5.97; N 3.77; P 8.34. Found, %: C 48.84; H 5.74; N 3.82; P 8.43.

(R,S)-**8b:** Yield 0.16 g (15%). Colorless oil. $[\alpha]_D^{20}$ = −78.7 (*c* 1, $CHCl_3$). R_f = 0.45 (EtOAc–hexane 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.36–1.4 (m, 6H, CH_2CH_3,), 1.36–1.4 (m, 3H, $CHCH_3$,), 1.96 (br s, 1H, NH), 3.15–3.27 (m, 1H, CHP), 4.15–4.26 (m, 4H, CH_2O), 4.15–4.26 (m, 1H, CHPh), 6.02–6.31 (m, $^2J_{HF}$ = 53.2 Hz, 1H, CHF_2), 7.26–7.35 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 16.4 (d, $^3J_{CP}$ = 5.0 Hz, CH_2CH_3), 16.5 (d, $^3J_{CP}$ = 5.0 Hz, CH_2CH_3), 24.2 (s, $CHCH_3$), 53.7 (dt, $^1J_{CP}$ = 139.8, $^2J_{CF}$ = 25.2 Hz, CHP), 56.5 (s, $CHCH_3$), 62.7 (d, $^2J_{CP}$ = 6.0 Hz, CH_2O), 63.2 (d, $^2J_{CP}$ = 6.0 Hz, CH_2O), 108.7 (tt, $^1J_{CF}$ = 250.5, $^2J_{CF}$ = 34.2 Hz, CF_2CF_3), 115.9 (tt, $^1J_{CF}$ = 252.5, $^2J_{CF}$ = 26.2 Hz, CF_2CP), 117.9 (qt, $^1J_{CF}$ = 289.1, $^2J_{CF}$ = 35.2 Hz, CF_2CF_3), 127.5 (s, C_{Ph}), 127.8 (s, $^4C_{Ph}$), 128.6 (s, C_{Ph}), 142.7 (s, $^1C_{Ph}$). ^{19}F NMR (376,5 MHz, $CDCl_3$) δ (ppm): –124.1 (m, $^2J_{FF}$ = 263.6 Hz, 1 F), –125.0 (m, $^2J_{FF}$ = 263.6 Hz, 1 F), –137.4 (m, $^2J_{FF}$ = 297.4, $^3J_{FF}$ = 11.3 Hz, 1 F), –145.3 (m, $^2J_{FF}$ = 297.4 Hz, 1 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 19.9. Anal. calcd. for $C_{15}H_{22}F_4NO_3P$: C 48.52; H 5.97; N 3.77; P 8.34. Found, %: C 48.62; H 6.11; N 3.81; P 8.28.

*4.5.4. O,O- Diethyl ((1R)-2,2,3,3-tetrafluoro-1-{[(1R)-1-phenylethyl] amino}propyl) phosphonate (R,R)-**8b** and O,O-diethyl ((R)-2,2,3,3-tetrafluoro-1-{[(1S)-1-phenylethyl]amino}propyl) phosphonate (S,R)-**8b**.*

The diastereomeric mixture of (*R,R*)-**8b**/(*S,R*)-**8b** (3.5:1) was obtained by reduction of (*R*)-**7b.** Yield 0.91 g (82%). Individual diastereomers were isolated by column chromatography (silica gel, hexane–EtOAc 1:1).

(*R,R*)-**8b**: Yield 0.54 g (49%). Colorless oil. $[\alpha]_D^{20}$ = +19.4 (*c* 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of diastereomer *(S,S)*-**8b**.

(S,R)-**8b**: Yield 0.17 g (16%). Colorless oil, $[\alpha]_D^{20}$ = +80.5 (*c* 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of diastereomer *(R,S)*-**8b**.

*4.5.5. O,O-Diethyl ((S)-2,2,3,3,4,4,4-heptafluoro-1-{[(1S)-1-phenylethyl] amino}butyl) phosphonate (S,S)-**8c** and O,O-Diethyl ((R)-2,2,3,3,4,4,4-heptafluoro-1-{[(1S)-1-phenylethyl]amino}butyl) phosphonate (R,S)-**8c***

The diastereomeric mixture of (*S,S*)-**8c**/*(R,S)*-**8c** (4.3:1) was obtained by reduction of (*S*)-**7c.** Yield 0.96 g (73%). Enantiopure diastereomer (*S,S*)-**8c** isolated by column chromatography (silica gel, hexane–EtOAc 1:1).

(*S,S*)-**8c**: Yield 0.58 g (44%). Colorless oil, $[\alpha]_D^{20}$ = −18.7 (*c* 1, $CHCl_3$). Rf = 0.4 (EtOAc : Hex = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3,), 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3,), 1.34 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CHCH_3$,), 2.2 (br s, 1H, NH), 3.58–3.71 (m, 1H, CHP), 4.02–4.17 (m, 4H, CH_2O), 4.02–4.17 (m, 1H, CHPh), 7.26–7.36 (m, 5H, Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 16.2 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 16.3 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 23.0 (s, $CHCH_3$), 54.3 (dt, $^1J_{CP}$ = 153.4, $^2J_{CF}$ = 30.2 Hz, CHP), 56.6 (d, $^3J_{CP}$ = 6.3 Hz, $CHCH_3$), 63.0 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 63.2 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 109.2 (tq, $^1J_{CF}$ = 266.5, $^2J_{CF}$ = 37.7 Hz, CF_2CF_3), 116.0 (tt, $^1J_{CF}$ = 260.2, $^2J_{CF}$ = 30.2 Hz, CF_2CP), 117.9 (qt, $^1J_{CF}$ = 289.1, $^2J_{CF}$ = 35.2 Hz, CF_2CF_3), 127.1 (s, C_{Ph}), 127.6 (s, $^4C_{Ph}$), 128.5 (s, C_{Ph}), 143.9 (s, $^1C_{Ph}$). ^{19}F NMR (3765 MHz, $CDCl_3$) δ (ppm): –81.0 (t, $^3J_{FF}$ = 11.3 Hz, 3 F), –110.2 (m, $^2J_{FF}$ = 286.1 Hz, 1 F), –115.4 (m, $^2J_{FF}$ = 286.1 Hz, 1 F), –123.3 (m, $^2J_{FF}$ = 289.9 Hz, 1 F), –126.2 (m, $^2J_{FF}$ = 289.9, $^3J_{FF}$ = 18.8 Hz, 1 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 17.3. Anal. calcd. for $C_{16}H_{19}F_7NO_3P$: C 43.75; H 4.82; N 3.19; P 7.05. Found, %: C 43.82; H 4.85; N 3.15; P 6.96.

*4.5.6. O,O-Diethyl ((R)-2,2,3,3,4,4,4-heptafluoro-1-{[(1R)-1-phenylethyl] amino}butyl) phosphonate (R,R)-**8c** and O,O-Diethyl ((S)-2,2,3,3,4,4,4-heptafluoro-1-{[(1R)-1-phenylethyl]amino}butyl) phosphonate (S,R)-**8c***

The diastereomeric mixture of (*R,R*)-**8c**/*(S,R)*-**8c** (4.3:1) was obtained by reduction of (*R*)-**7c.** Yield 0.98 g (75%). Enantiopure diastereomer (*R,R*)-**8c** was isolated by column chromatography (silica gel, hexane–EtOAc 1:1).

(R,R)-**8c**: Yield 0.58 g (44%). Colorless oil. $[\alpha]_D^{20}$ = +17.7 (*c* 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of diastereomer *(S,S)*-**8c**.

*4.5.7. O,O-Diethyl ((S)-2-chloro-2,2-difluoro-1-{[(1S)-1-phenylethyl] amino}ethyl)phosphonate (S,S)-**8d** and O,O-diethyl ((R)-2-chloro-2,2-difluoro-1-{[(1S)-1-phenylethyl]amino}ethyl)-phosphonate (R,S)-**8d***

The diastereomeric mixture of (*S,S*)-**8d**/*(R,S)*-**8d** (3.4:1) was obtained by reduction of (*S*)-**7d.** Yield 0.63 g (59%). Individual diastereomers were isolated by column chromatography (silica gel, hexane–EtOAc 1:1).

(*S,S*)-**8d**: Yield 0.34 g (32%). Colorless oil. $[\alpha]_D^{20}$ = −24.8 (*c* 1, $CHCl_3$). Rf = 0.57 (EtOAc : Hex = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3), 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3), 1.39 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CHCH_3$), 1.98 (br s, 1H, NH),

3.36–3.46 (m, 1H, CHP), 3.99–4.25 (m, 1H, CHPh), 3.99–4.25 (m, 4H, OCH_2), 7.23–7.30 (m, 1H, Ph), 7.33–7.36 (m, 4H, Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 16.3 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 16.4 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 24.4 (s, $CHCH_3$), 56.7 (d, $^3J_{CP}$ = 11.3 Hz, $CHCH_3$), 60.3 (dt, $^1J_{CP}$ = 157.1, $^2J_{CF}$ = 25.1 Hz, CHP), 63.2 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 63.5 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 127.3 (s, C_{Ph}), 127.6 (s, $^4C_{Ph}$), 128.6 (s, C_{Ph}), 129.4 (qd, $^1J_{CF}$ = 301.7, $^2J_{CP}$ = 13.8 Hz, CF_3), 143.2 (s, $^1C_{Ph}$). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm): –49.6 (dd, $^2J_{FAFB}$ = 169.2, $^3J_{FP}$ = 26.3 Hz, 1 F), –52.8 (d, $^2J_{FBFA}$ = 169.2 Hz, 1 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 17.1 (d, $^3J_{PF}$ = 26.3 Hz). Anal. calcd. for $C_{14}H_{21}ClF_2NO_3P$: C 47.27; H 5.95; N 3.94, P 8.71. Found, %: C 47.33; H 5.96; N 3.95; P 8.67.

(*R,S*)-**8d**: Yield 0.13 g (12%). Colorless oil. $[\alpha]_D^{20}$ = −64.2 (*c* 1, $CHCl_3$). Rf = 0.48 (EtOAc–hexane 1:1). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35–1.40 (m, 6H, CH_2CH_3), 1.35–1.40 (m, 3H, $-CHCH_3$), 2.07 (br s, 1H, NH), 3.33–3.42 (m, 1H, CHP), 4.13–4.28 (m, 1H, CHPh), 4.13–4.28 (m, 4H, OCH_2), 7.25–7.39 (m, 5H, Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm): 16.4 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 16.4 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 24.2 (s, $-CHCH_3$), 56.7 (s, $CHCH_3$), 60.7 (dt, $^1J_{CP}$ = 144.6, $^2J_{CF}$ = 26.4 Hz, CHP), 63.2 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 63.6 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 127.6 (s, C_{Ph}), 127.7 (s, $^4C_{Ph}$), 128.0 (td, $^1J_{CF}$ = 296.7, $^2J_{CP}$ = 15.1 Hz, CF_3), 128.5 (s, C_{Ph}), 143.1 (s, $^1C_{Ph}$). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm): –52.4 (dd, $^2J_{FAFB}$ = 165.7, $^3J_{FP}$ = 15.1 Hz, 1 F), –55.3 (d, $^2J_{FBFA}$ = 165.7 Hz, 1 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 18.8 (d, $^3J_{PF}$ = 15.1 Hz). Anal. calcd. for $C_{14}H_{21}ClF_2NO_3P$: C 47.27; H 5.95; N 3.94, P 8.71. Found, %: C 47.29; H 5.91; N 3.88; P 8.76.

4.5.8. O,O-Diethyl ((S)-2-chloro-2,2-difluoro-1-{[(1S)-1-phenylethyl] amino}ethyl)phosphonate (R,R)-8d and O,O-diethyl ((R)-2-chloro-2,2-difluoro-1-{[(1S)-1-phenylethyl]amino}ethyl)-phosphonate (S,R)-8d

The diastereomeric mixture of (*S,S*)-**8d**/(*R,S*)-**8d** (3.4:1) was obtained by reduction of (*R*)-**7d.** Yield 0.68 g (64%). Individual diastereomers were isolated by column chromatography (silica gel, hexane–EtOAc 1:1).

(*R,R*)-**8d**: Yield 0.33 g (31%). Colorless oil. $[\alpha]_D^{20}$ = +25.0 (*c* 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of enantiomer *(S,S)*-**8d**.

(*S,R*)-**8d**: Yield 0.12 g (11%). Colorless oil. $[\alpha]_D^{20}$ = +62.6 (*c* 1, $CHCl_3$). Other physicochemical and spectral data were identical to those of diastereomer *(R,S)*-**8d**.

4.6. Aminophosphonates 9

Pd/C (0.1 g) was added to a degassed solution of respective aminophosphonate **8** (13.5 mmol) in MeOH (10 mL). A hydrogen pressure of ca. 1.05 bar was applied, and the reaction mixture was stirred at r.t. for 12 h. The catalyst was filtered off, washed with methanol and the filtrate was evaporated to give **9** as colorless oil.

4.6.1. O,O-Diethyl (S)-(1-amino-3,3,3-trifluoroethyl)phosphonate (S)-9a

Yield 0.27 g (85%). Colorless oil. $[\alpha]_D^{20}$ = –3.5 (*c* 1, $CHCl_3$). The spectral data of (*S*)-**9a** were in agreement with those reported in the literature [14].

4.6.2. O,O-Diethyl (R)-(1-amino-3,3,3-trifluoroethyl)phosphonate (R)-9a

Yield 0.29 g (91%). Colorless oil. $[\alpha]_D^{20}$ = +3.4 (*c* 1, $CHCl_3$). The spectral data of (*S*)-**9a** were in agreement with those reported in the literature [14].

4.6.3. O,O-Diethyl (S)-(1-amino-2,2,3,3-tetrafluoropropyl)phosphonate (S)-9b

Yield 0.29 g (81%). Colorless oil. $[\alpha]_D^{20}$ = +52.4 (*c* 1, CH_3COCH_3). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35–1.39 (m, 6H, CH_2CH_3,), 1.36 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CHCH_3$,), 1.89 (br s, 2H, NH_2), 3.54 (dt, $^2J_{HP}$ = 18.0, $^3J_{HF}$ = 16.0 Hz, 1H, CHP), 4.20–4.24 (m, 4H, CH_2O), 6.35 (tt, $^2J_{HF}$ = 53.2, $^3J_{HF}$ = 5.6 Hz, 1H, CHF_2). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm): –125.1 (dd, $^2J_{FAFB}$ = 267.3, $^3J_{FF}$ = 11.3 Hz, 1 F), –126.5 (ddd, $^2J_{FBFA}$ = 267.3, $^3J_{FP}$ = 16.2, $^3J_{FF}$ = 11.3 Hz, 1 F), –138.7 (dd, $^2J_{FAFB}$ = 300.0, $^3J_{FF}$ = 11.3 Hz, 1 F), –141.1 (dd, $^2J_{FBFA}$ = 297.4 Hz, $^3J_{FF}$ = 11.3 Hz, 1 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 18.2 (d, $^3J_{PF}$ = 16.2 Hz). Anal. calcd. for $C_7H_{14}F_4NO_3P$: C 31.47; H 5.28; N 5.24; P 11.59. Found, %: C 31.28; H 5.19; N 5.16 P 11.63.

4.6.4. O,O-Diethyl (R)-(1-amino-2,2,3,3-tetrafluoropropyl)phosphonate (R)-9b

Method A. Phosphonate (*R*)-**9b** was obtained from (*R,R*)-**8b** according to described above general procedure (see item 4.6). Yield 0.31 g (86%). Colorless oil. $[\alpha]_D^{20}$ = −54.5 (*c* 1, acetone).

Method B. 4 N HCl (2 mL) was added to a stirring solution of sulfinamide (*R,R*)-**12** (0.125 g, 0.34 mmol) in EtOH (2 mL) and the mixture was left at r.t. overnight. The volatile products were evaporated, and dichloromethane (15 mL) was added, the mixture was washed with a saturated solution of $NaHCO_3$ (5 mL). The mixture was extracted with dichloromethane (5 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated in *vacuo* to give product (*R*)-**9b**. Yield 0.074 g (81%). Colorless oil. $[\alpha]_D^{20}$ = −53.6 (*c* 1, acetone).

4.6.5. O,O-Diethyl (S)-(1-amino-2,2,3,3,4,4,4-heptafluorobutyl) phosphonate (S)-9c

Yield 0.38 g (84%). White solid. $[\alpha]_D^{20}$ = +6.8 (*c* 0.3, acetone). Mp = 46–49 °C. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.36 (t, $^3J_{HH}$ = 7.2 Hz, 6H, CH_2CH_3), 1.93 (br s, 1H, NH), 3.75 (m, $^3J_{HF}$ = 21.6 Hz, 1H, CHP) 4.18–4.27 (m, 4H, CH_2O). ^{13}C NMR (125.7 МГц, $CDCl_3$) δ (ppm): 16.2 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 16.3 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 50.9 (dt, $^1J_{CP}$ = 153.4, $^2J_{CF}$ = 30.2 Hz, CHP), 63.3 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 63.6 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 109.4 (tq, $^1J_{CF}$ = 266.5, $^2J_{CF}$ = 37.7 Hz, CF_2CF_3), 115.3 (tt, $^1J_{CF}$ = 258.9, $^2J_{CF}$ = 30.2 Hz, CF_2CP), 117.7 (qt, $^1J_{CF}$ = 289.1, $^2J_{CF}$ = 32.7 Hz, CF_2CF_3). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): –80.7 (t, $^3J_{FF}$ = 11.3 Hz, 3 F), –112.7 (m, $^2J_{FF}$ = 282.2 Hz, 1 F), –120.6 (m, $^2J_{FF}$ = 282.2 Hz, 1 F), –123.4 (m, $^2J_{FF}$ = 291.6 Hz, 1 F), –126.0 (dd, $^2J_{FF}$ = 291.6, $^3J_{FF}$ = 18.8 Hz, 1 F). ^{31}P NMR (202 MHz, $CDCl_3$) δ (ppm): 17.2. Anal. calcd. for $C_8H_{13}F_7NO_3P$: C 28.67; H 3.91; N 4.18; P 9.24. Found, %: C 28.72; H 3.85; N 4.25; P 9.16.

4.6.6. O,O-Diethyl (R)-(1-amino-2,2,3,3,4,4,4-heptafluorobutyl) phosphonate (R)-9c

Yield 0.37 g (82%). White solid. $[\alpha]_D^{20}$ = −7.1 (*c* 0.3, acetone). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-**9c**.

4.7. Aminophosphonic acids 10a–c

Conc. HCl (3 ml) was added to respective aminophosphonate **9**. The reaction mixture was refluxed for 6 h and evaporated in vacuo. The residue was dissolved in MeOH (3 ml), and 2-methyloxirane (1 mL) was added dropwise. The mixture was allowed to stand at room temperature for 2 days. The precipitated aminophosphonic acid **6** was isolated by filtration. 4.7.1. (S)-*(1-Amino-2,2,2-trifluoroethyl)phosphonic acid* (*S*)-**10a.**

Yield 0.16 g (89%). White solid: mp = 238–240 °C (with decomposition) (lit. mp 237–239 °C [4c]). $[\alpha]_D^{20}$ = –2.31 (c 1.5, H_2O). The spectral data of (*S*)-**6a** are in agreement with those reported in the literature [4c,13].

4.7.1. (R)-(1-Amino-2,2,2-trifluoroethyl)phosphonic acid (R)-10a

Yield 0.15 g (84%). White solid. $[\alpha]_D^{20}$ = +2.31 (c 1.5, H_2O). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-**10a**.

*4.7.2. (S)-(1-Amino-2,2,3,3-tetrafluoropropyl)phosphonic acid (S)-**10b***

Yield 0.19 g (92%). White solid: mp = 175–180 °C (with decomposition). $[\alpha]_D^{20}$ = −1.45 (*c* 0.2, H_2O). ^1H NMR (400 MHz, D_2O) δ (ppm): 3.54 (m, $^2J_{HP}$ = 16.0, $^3J_{HF}$ = 16.0 Hz, 1H, CHP), 6.53 (tt, $^2J_{HF}$ = 52.0, $^3J_{HF}$ = 6.0 Hz, 1H, CHF_2). ^{19}F NMR (376.5 MHz, D_2O) δ (ppm): –120.9 (m, $^2J_{FAFB}$ = 285.0 Hz, 2 F), –135.4 (m, $^2J_{FBFA}$ = 301.0 Hz, 1 F), –141.2 (dt, $^2J_{FF}$ = 301.0, $^3J_{FF}$ = 9.0 Hz, 1 F), –141.1 (dd, $^2J_{FBFA}$ = 297.4 Hz, $^3J_{FF}$ = 11.3 Hz, 1 F). ^{31}P NMR (202 MHz, D_2O) δ (ppm): 2.16 (d, $^3J_{PF}$ = 11.0 Hz). Anal. calcd. for $C_3H_6F_4NO_3P$: C 17.07; H 2.87; N 6.64; P 14.68. Found, %: C 17.22; H 2.73; N 6.77; P 14.53.

*4.7.3. (R)-(1-Amino-2,2,3,3-tetrafluoropropyl)phosphonic acid (R)-**10b***

Yield: 0.18 g (87%). White solid: mp = 175–180 °C (with decomposition). $[\alpha]_D^{20}$ = +1.55 (*c* 0.2, H_2O). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-**10b**

*4.7.4. (S)-(1-Amino-2,2,3,3,4,4,4-heptafluorobutyl)phosphonic acid (S)-**10c***

Yield: 0.25 g (91%). White solid: mp = 246–250 °C (with decomposition). $[\alpha]_D^{20}$ = −7.3 (*c* 0.5, CH_3OH). ^1H NMR (400 MHz, CD_3OD) δ (ppm): 4.06 (m, $^2J_{HP}$ = $^3J_{HF}$ = 15.6 Hz, 1H, CHP). Спектр ЯМР ^{19}F (470.3 MHz, CD_3OD) δ (ppm): –82.6 (t, $^3J_{FF}$ = 9.4 Hz, 3 F), –116.1 (m, $^2J_{FF}$ = 291,6 Hz, 1 F), –117.1 (m, $^2J_{FF}$ = 291.6 Hz, 1 F), –127.3 (dd, $^2J_{FF}$ = 291.6, $^3J_{FF}$ = 9.4 Hz, 1 F), –128.1 (dd, $^2J_{FF}$ = 291.6, $^3J_{FF}$ = 9.4 Hz, 1 F). ^{31}P NMR (202 MHz, CD_3OD) δ (ppm): 2.1(m, *J* = 8.1 Hz). Anal. calcd. for $C_4H_5F_7NO_3P$: C 17.22; H 1.81; N 5.02; P 11.10. Found, %: C 17.12; H 1.85; N 4.95; P 11.16.

*4.7.5. (R)-(1-Amino-2,2,3,3,4,4,4-heptafluorobutyl)phosphonic acid (R)-**10***

Yield: 0.24 g (86%). White solid: mp = 246–250 °C (with decomposition). $[\alpha]_D^{20}$ = +8.0 (*c* 0.5, CH_3OH). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-**10c**.

4.8. Aminophosphonic acids (S)-10d and (R)-10d

Aminophosphonate (*S*)-**8d** or (*R*)-**8d** was refluxed in conc. HCl (3 mL) for 10 h. The mixture was evaporated in vacuo, the residue was dissolved in MeOH (3 mL), and 2-methyl oxirane (1 mL) was added dropwise. The mixture was allowed to stand at room temperature for 2 days. Precipitated was filtered to give aminophosphonic acid was isolated by filtration.

*4.8.1. (S)-(1-amino-2-chloro-2,2-difluoroethyl)phosphonic acid (S)-**10d***

Yield 0.16 g (82%). White solid: mp = 175–180 °C (with decomposition). $[\alpha]_D^{20}$ = −1.12 (*c* 0.5, CH_3OH). ^1H NMR (400 MHz, CD_3OD) δ (ppm): 4.02 (dt, $^2J_{HP}$ = 14.8, $^3J_{HF}$ = 10.8 Hz, 1H, CHP). ^{13}C NMR (125.7 MHz, CD_3OD) δ: 55.2 (dt, $^1J_{CP}$ = 129.5, $^2J_{CF}$ = 28.9 Hz, CHP), 124.9 (t, $^1J_{CF}$ = 292.9 Hz, CF_2Cl). ^{19}F NMR (376.5 MHz, CD_3OD) δ: –49.6 (dd, $^2J_{FAFB}$ = 169.2 Hz, $^3J_{FP}$ = 26.3 Hz, 1 F), –52.8 (d, $^2J_{FBFA}$ = 169.2 Hz, 1 F). ^{31}P NMR (202 MHz, CD_3OD) δ: 2.2 (m, *J* = 16.2 Hz). Anal. calcd. for $C_2H_5ClF_2NO_3P$: C 12.29; H 2.58; N 7.16, P 15.82. Found, %: C 12.32; H 2.51; N 7.18; P 15.76.

*4.8.2. (R)-(1-amino-2-chloro-2,2-difluoroethyl)phosphonic acid (R)-**10d***

Yield: 0.17 g (87%). White solid: mp = 175–180 °C (with decomposition). $[\alpha]_D^{20}$ = +1.04 (*c* 0.5, CH_3OH). Other physicochemical and spectral data were identical to those of enantiomer (*S*)-**10d**.

*4.9. (R)-N-(2,2,3,3-tetrafluoropropiliden)-tert-butylsulfinamide (R)-**11***

To a stirring solution of (*R*)-*tert*-butanesulfinamide (1.2 g, 9.8 mmol) in dichloromethane (50 mL) was added tetrafluoropropionaldehyde hydrate (1.7 g, 10.8 mmol) and 4.9 g of anhydrous $MgSO_4$. The mixture was refluxed for 4 h. After cooling to cooling to room temperature, $MgSO_4$ was filtered off. Molecular sieves 4 A (5.0 g) were added to the filtrate, and the mixture was refluxed for 8 h. The solvent was evaporated, and the residue was distilled in *vacuo*. Yield 1.46 g (64%). Yellowish oil: bp 84–85 °C/18 Torr. $[\alpha]_D^{20}$ = −284.2 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (s, 9H, t-Bu), 6.05 (tt, $^2J_{HF}$ = 53.4, $^3J_{HF}$ = 3.0 Hz, 1H, CHF_2), 8.07 (t, $^3J_{HF}$ = 4.0 Hz, 1H, CH = N). ^{13}C NMR (125.7 МГц, $CDCl_3$) δ (ppm): 22.4 (s, $(CH_3)_3C$), 58.8 (s, $(CH_3)_3C$), 109.4 (tt, $^1J_{CF}$ = 251.0, $^2J_{CF}$ = 36.3 Hz, CF_2H), 111.3 (tt, $^1J_{CF}$ = 251.6, $^2J_{CF}$ = 36.2, CF_2CN), 155.7 (t, $^2J_{CF}$ = 30.6 Hz, C = N). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm): –116.4 (m, $^2J_{FF}$ = 292 Hz, $^2J_{FH}$ = 56.3 Hz, $^3J_{FF}$ = 5.0 Hz, 1 F), –118.3 (m, $^2J_{FF}$ = 292, $^2J_{FH}$ = 56.0 Hz, $^3J_{FF}$ = 5.0 Hz, 1 F), –133.8 (m, $^2J_{FF}$ = 290, $^2J_{FH}$ = 53, $^3J_{FF}$ = 5.0 Hz, 1 F), –135.5 (m, $^2J_{FF}$ = 290, $^2J_{FH}$ = 53, $^3J_{FF}$ = 5.0 Hz, 1 F). Anal. calcd. for $C_7H_{11}F_4NOS$: C 36.05; H 4.75; N 6.01. Found, %: C 36.21; H 4.95; N 6.12.

*4.10. O,O-Diethyl 1-[(tert-butylsulfinyl)amino]-2,2,3,3-tetrafluoropropyl phosphonate (R,R_S)-**12***

Trimethylchlorosilane (0.16 g, 1.4 mmol) was added dropwise to a mixture of diethylphosphite (0.17 g, 1.28 mmol) and Et_3N (0.13 g, 1.4 mmol) in dichloromethane (6 mL) at 0 °C. The mixture was stirred for 15 min. After then imine (*R*)-**11** (0.3 g, 1.28 mmol) was added, the mixture was allowed to warm to room temperature and left overnight. The mixture was washed with water (2 x 5 mL), dried over Na_2SO_4 and evaporated in *vacuo* to give the product as a diastereomeric mixture (92:8). Individual diastereomer (*R*,R_S)-**12** (*de* > 99%), was isolated by crystallization from EtOH-H_2O (1:2). Yield 0.28 g (59%). Colourless crystals: mp = 90 °C. $[\alpha]_D^{20}$ = +10.0 (*c* 1, CH_3COCH_3). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27 (s, 9H, t-Bu), 1.37 (t, $^3J_{HH}$ = 7 Hz, 6H, CH_2CH_3), 3.91 (br d, $^3J_{HH}$ = 7 Hz, 1H, NH), 3.97–4.06 (m, 1H, CHP), 4.18–4.22 (m, 4H, OCH_2), 6.47 (tt, $^2J_{HF}$ = 53.2, $^3J_{HF}$ = 6.1 Hz, 1H, CHF_2). ^{13}C NMR (125.7 МГц, acetone-d_6) δ (ppm): 15.8 (d, $^3J_{CP}$ = 6 Hz, CH_2CH_3), 15.9 (d, $^3J_{CP}$ = 6.3 Hz, CH_2CH_3), 21.9 (s, $(CH_3)_3C$), 55.0 (m, $^1J_{CP}$ = 157.0, $^2J_{CF}$ = 25.1, $^3J_{CF}$ = 3 Hz, CHP), 57.1 (s, $(CH_3)_3C$), 63.1 (d, $^2J_{CP}$ = 6.1 Hz, CH_2O), 63.2 (d, $^2J_{CP}$ = 6.1 Hz, CH_2O), 109.6 (ttd, $^1J_{CF}$ = 250.5, $^2J_{CF}$ = 31.2, $^3J_{CP}$ = 5.3 Hz, CF_2H), 115.3 (ttd, $^1J_{CF}$ = 250.3, $^2J_{CF}$ = 26.2, $^3J_{CP}$ = 8.1 Hz, CF_2CP). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm): –122.5 (m, $^2J_{FF}$ = 274.1 Hz, 1 F), –124.8 (m, $^2J_{FF}$ = 274.1 Hz, 1 F), –138.5 (m, $^2J_{FF}$ = 303.4, $^2J_{FH}$ = 53, $^3J_{FF}$ = 10.0 Hz, 1 F), –141.6 (m, $^2J_{FF}$ = 303.4, $^2J_{FH}$ = 53, $^3J_{FF}$ = 10.0 Hz, 1 F). ^{31}P NMR (202 MHz, acetone-d_6) δ (ppm): 15.7. Anal. calcd. for $C_{11}H_{22}F_4NO_4PS$: C 35.58; H 5.97; N 3.77; P 8.34. Found, %: C 35.81; H 5.95; N 3.72; P 8.37.

*4.10.1. X-ray structure determination of (R,R_S)-**12***

The colourless crystals of 12 ($C_{11}H_{22}F_4NO_4PS$, $0.5H_2O$) are orthorhombic. At 293 K a = 9.9339(9), b = 19.192(1), c = 19.305(1) Å, V = 3680.6(5) Å^3, M_r = 760.67, Z = 4, space group $P2_12_12_1$, d_{calc} = 1.373 g/cm^3, m(MoK_a) = 0.316 mm^{-1}, F(000) = 1592. Intensities of 31,226 reflections (6472 independent, R_{int} = 0.087) were measured on the «Xcalibur-3» diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 60°). The structure was solved by direct method using SHELXTL package [15]. Positions of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with U_{iso} = nU_{eq} (n = 1.5 for methyl groups and water molecule and n = 1.2 for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 6472 reflections was converged to wR_2 = 0.203 (R_1 = 0.087 for 5010 reflections with F > 4σ(F), S = 1.207). The final atomic coordinates, and crystallographic data for compound 12 have been deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition number CCDC 1865710.

4.11. Quantum-chemical calculations

The geometrical structures of (*SS*)-**8a** and (*RS*)-**8b** diastereomers were optimized using M06-2X [16] theory with the cc-pVDZ basis set [17] in the GAUSSIAN09 program [18]. Character of stationary points on the potential energy surface was verified by calculations of vibrational frequencies within the harmonic approximation, using analytical second derivatives at the same level of theory. All stationary points possess zero imaginary frequencies.

References

[1] (a) N.S. Zefirov, E.D. Matveeva, Catalytic Kabachnik-Fields reaction: new horizons for old reaction, Arkivoc (i) (2008) 1–17;
(b) R.M. Abdel-Rahman, T.E. Ali, S.M. Abdel-Kariem, Methods for synthesis of *N*-heterocyclyl/heteroaryl- α-aminophosphonates and α-(azaheterocyclyl)phosphonates, Arkivoc i (2016) 183–211 and references therein.

[2] (a) B.E. Smart, Fluorine substituent effects (on bioactivity), J. Fluorine Chem. 109 (2001) 3–11;
(b) F.M.D. Ismail, Important fluorinated drugs in experimental and clinical use, J. Fluorine Chem. 118 (2002) 27–33 and references therein;
(c) R. Filler, Y. Kobayshi, L.M. Yagupolskii (Eds.), Organofluorine Compounds in Medicinal Chemistry and Biomedicinal Applications, Elsevier, Amsterdam, 1993;
(d) D. O'Hagan, Fluorine in health care: organofluorine containing blockbuster drugs, J. Fluorine Chem. 131 (2010) 1071–1081;
(e) P.A. Procopiou, R.J.D. Hatley, S.M. Lynn, R.C.B. Copley, Y. He, D.J. Minick, Determination of the absolute configuration of (+)- and (−)-N-CBZ-3-fluoropyrrolidine-3-methanol using vibrational circular dichroism and confirmation of stereochemistry by conversion to (R)-tert-butyl 3-fluoro-3-(((R)-1-phenylethyl)carbamoyl)pyrrolidine-1-carboxylate, Tetrahedron Asymmetry 27 (2016) 1222–1230;
(f) E.P. Gillis, K.J. Eastman, M.D. Hill, D.J. Donnelly, N.A. Meanwell, Applications of fluorine in medicinal chemistry, J. Med. Chem. 58 (2015) 8315–8359.

[3] M. Mikolajczyk, Acyclic and cyclic aminophosphonic acids: asymmetric syntheses mediated by chiral sulfinyl auxiliary, J. Organomet. Chem. 690 (2005) 2488–2496.

[4] (a) P.P. Onys'ko, T.V. Kim, E.I. Kiseleva, A.D. Sinitsa, M.Y. Kornilov, Sigmatropic isomerizations in phosphorylated 2-azaalyl systems. VII. Asymmetric induction in 1,3-H shift in diethyl 2,2,2-trifluoro-N-(α-methyl-benzyl)acetimidoyl phosphonate, J. Gen. Chem USSR (Engl. Transl.) 60 (1990) 1165–1168;
(b) Yu.V. Rassukana, P.P. Onys'ko, M.V. Kolotylo, A.D. Sinitsa, P. Lyzwa, M. Mikolajczyk, A new strategy for asymmetric synthesis of aminophosphonic acid derivatives: the first enantioselective catalytic reduction of C-phosphorylated imines, Tetrahedron Lett. 50 (2009) 288–290;
(c) G. Roschenthaler, V.P. Kukhar, I.B. Kulik, M.Yu. Belik, A.E. Sorochinsky, E.B. Rusanov, V.A. Soloshonok, Asymmetric synthesis of phosphonotrifluoroalanine and its derivatives using N-tert-butanesulfinyl imine derived from fluoral, Tetrahedron Lett. 53 (2012) 539–542.

[5] (a) P.P. Onys'ko, T.V. Kim, E.I. Kiseleva, A.D. Sinitsa, Phosphorylated 2-azaallylic systems. Synthesis, properties, and rearrangements, Phosphorus Sulfur Silicon Relat. Elem. 109 (110) (1996) 397–400;
(b) P.P. Onys'ko, Yu.V. Rassukana, O.A. Sinitsa, Prototropic isomerizations in the 2-azaallylic triad of imidoylphosphonates, Curr. Org. Chem. 14 (2010) 1223–1233;
(c) P.P. Onys'ko, Yu.V. Rassukana, Y.Y. Khomutnyk, I.P. Yelenich, D.V. Klukovsky, A.D. Sinitsa, A new strategy for synthesis of compounds bearing biorelevant α-aminophosphonate functionalities, Phosphorus Sulfur Silicon Relat. Elem. 190 (2015) 725–728.

[6] J. Xiao, X. Zhang, C. Yuan, A facile asymmetric synthesis of 1-amino-2,2,2-trifluoroethanephosphonic acid, Heteroatom Chem. 11 (2000) 536–540.

[7] Yu.V. Rassukana, L.V. Bezgubenko, O.V. Stanko, E.B. Rusanov, I.B. Kulik, P.P. Onys'ko, Diastereoselective cycloaddition of (S)-N-(1-phenylethylimino) trifluoropropionate and trifluoroethylphosphonate with diazomethane, Tetrahedron Asymmetry 28 (2017) 555–560.

[8] P.P. Onys'ko, Yu.V. Rassukana, A.D. Sinitsa, Phosphorylation of α-haloimines: P-C vs. P-N bond formation, Curr. Org. Chem. 12 (2008) 2–24.

[9] N.S. Gouliokina, G.N. Bondarenko, S.E. Lyubimov, V.A. Davankov, K.N. Gavrilov, I.P. Beletskaya, Catalytic hydrogenation of α-iminophosphonates as a method for the synthesis of racemic and optically active α-aminophosphonates, Adv. Synth. Catal. 350 (2008) 482–492.

[10] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed., Wiley-VCH Publishers, 2003, https://sites.google.com/site/miller00828/in/solvent-polarity-table.

[11] (a) Ya.Ya. Khomutnik, P.P. Onys'ko, Yu.V. Rassukanaya, V.V. Pirozhenko, A.D. Sinitsa, N-Aryltrifluoroacetimidoylphosphonates, Russ. J. Gen. Chem. 83 (2013) 445–452;
(b) Yu.V. Rassukana, O.V. Stanko, I.P. Yelenich, P.P. Onys'ko, Silylated iminophosphonates: novel reactive synthons for the preparation of fluorinated aminophosphonates and aminophosphonic acids, Tetrahedron Lett. 58 (2017) 3449–3452.

[12] A. Katritzky, H.-Y. He, K. Suzuki, N-Acylbenzotriazoles: neutral acylating reagents for the preparation of primary, secondary, and tertiary amides, J. Org. Chem. 65 (2000) 8210–8213.

[13] M. Bordeau, F. Frebault, M. Gobet, J.-P. Picard, Ethyl difluoro(trimethylsilyl) acetate and difluoro(trimethylsilyl)acetamides – precursors of 3,3-difluoroazetidinones, Eur. J. Org. Chem. 18 (2006) 4147–4154.

[14] P.P. Onys'ko, T.V. Kim, E.I. Kiseleva, A.D. Sinitsa, Sigmatropic isomerizations in azaallyl systems: XXI. Alkanimidoylphosphonates and their prototropic and phosphorotropic isomers, Russ. J. Gen. Chem. 74 (2004) 1868–1878.

[15] G.M. Sheldrick, Acta Crystallogr., A short history of SHELX. Sect. A 64 (2008) 112-122.

[16] Y. Zhao, D.G. Truhlar, The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals, Theor. Chem. Accounts 120 (2008) 215–241.

[17] R.A. Kendall, T.H. Dunning, R.J. Harrison, Electron affinities of the first-row atoms revisited. Systematic basis sets and wave functions, J.Chem.Phys. 96 (1992) 6796–6806.

[18] M.J. Frisch, G.W.H. Trucks, B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr, J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision B.01, Gaussian, Inc., Wallingford CT, 2010.