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Diastereoselective addition of diethyl difluoromethylphosphonate to enantiopure sulfinimines: synthesis of α,α-difluoro-β-aminophosphonates, phosphonic acids, and phosphonamidic acids

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Abstract—Addition of diethyl lithiodifluoromethylphosphonate to enantiomerically pure aromatic, heteroaromatic, and aliphatic aldehyde-derived sulfinimines afforded *N*-sulfinyl α,α-difluoro-β-aminophosphonates with generally good enantioselectivity and in high yield. The reaction with acetophenone-derived sulfinimine resulted in the formation of the addition product with high diastereoselectivity and in only moderate yield. A two-step deprotection involving treatment of diastereomerically pure *N*-sulfinyl α,α-difluoro-β-aminophosphonates with trifluoroacetic acid in EtOH followed by refluxing with 10 N HCl provided enantiopure α,α-difluoro-β-aminophosphonates and α,α-difluoro-β-aminophosphonic acids. The *N*-Cbz derivative of (*R*)-2-amino-1,1-difluoro-2-phenylethylphosphonate was a convenient starting point for the preparation of corresponding difluorophosphonate monoester, difluorophosphonic acid, and difluorophosphonamidic acid. At 21 °C difluorophosphonamidic acid was stable in aqueous solution at pH above 5.

1. Introduction

The importance of the aminophosphonic acids as structural analogs of amino carboxylic acids is well recognized.[1] Replacement of hydrogen atoms by fluorine atoms in amino carboxylic acids has been found to provide increased lipophilicity, resistance to oxidative and proteolytic degradation, changes in basicity or acidity of neighboring groups, conformational restrictions on the peptide chain, and modification of enzyme/substrate interaction,[2] therefore fluorinated aminophosphonic acids are of interest as biologically active compounds as well as building blocks for the preparation of peptidic materials with unique structural properties. Particular attention is devoted to aminophosphonic acids that contain a difluoromethylene group connected to a phosphorus atom in their role as hydrolytically stable phosphoamino acid mimetics in terms of both steric factors and pK_a value (Fig. 1).[3] Such mimetics have found application in the design of protein phosphatases, glycosyltransferases, and L-aspartate-β-semialdehyde dehydrogenase inhibitors.[4]

Current approaches to nonracemic difluoromethylene containing aminophosphonic acids have been largely based on the coupling of phosphonodifluoromethyl organometallic reagents with electrophilic substrates for the preparation of chain-extended adducts. The difluoromethylene analog of phosphoserine **1** was obtained in a multistep pathway using the reaction of dialkyl lithiodifluoromethylphosphonate with a primary triflate derived from (*R*)-isopropylideneglycerol as source of chirality.[5a] Owing to the inertness of dialkyl lithiodifluoromethylphosphonate toward secondary triflates, the condensation of dialkyl lithiodifluoromethylphosphonates with an ester, methyl Grignard addition, and radical deoxygenation of an intermediate tertiary alcohol sequence has been applied for the synthesis of difluoromethylene analogs of phosphothreonine **2** and *allo*-phosphothreonine **3** from L-glycerate and D-serine, respectively.[5b] Stereoselective synthesis of phosphothreonine **2** and *allo*-phosphothreonine **3** mimetics as well as their enantiomers was also achieved by applying a Cu(I)-mediated coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide and β-iodo-α,β-unsaturated ester followed by diastereoselective hydrogenation and amination using bornane-10,2-sultam as a chiral auxiliary.[5c] Nucleophilic opening of furanosylamines with diethyl lithiodifluoromethylphosphonate led to the formation of diastereomeric mixture of acyclic aminophosphonates with moderate diastereoselectivity. Separation of

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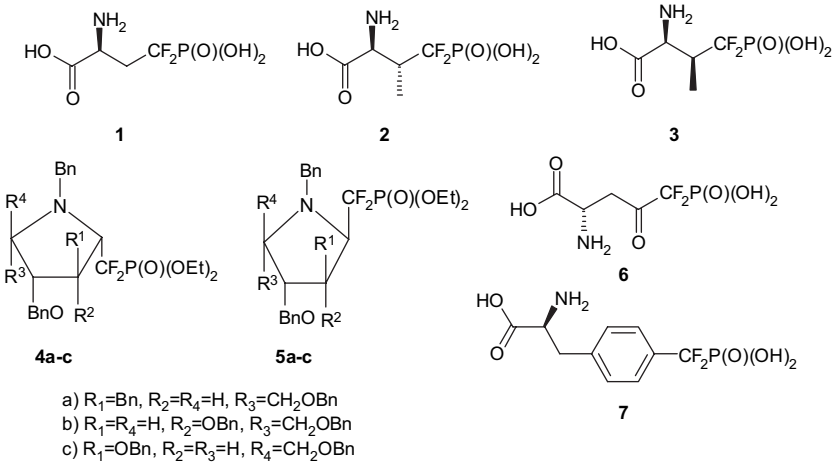


Figure 1.

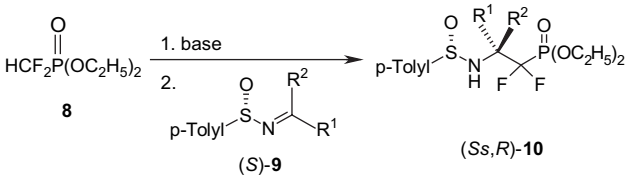
aminophosphonates followed by cyclization afforded azasugars **4** and **5** bearing difluoromethylenephosphonate group in good yields.[6]

Preparation of the difluoromethylene analog of β-aspartyl phosphate **6** was reported through addition of trimethylsilyl-difluoromethylphosphonate in the presence of a catalytic amount of TBAF to protected L-aspartate semialdehyde,[7a,b] or directly by Cu(I)-mediated coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide and protected aspartic acid chloride.[7c] Another methodology involving the use of benzylic α,α-difluorophosphonates in transition metal-catalyzed cross-coupling and alkylation reactions with L-alanine[8a] and glycine[8b] derivatives has been applied for the preparation of the difluoromethylene analog of phosphotyrosine **7**.

The nucleophilic addition of methyl- and chloromethylphosphonate carbanions to the C=N bond of enantiopure sulfinimines was found to be effective in the asymmetric syntheses of β-aminophosphonates and β-aminophosphonic acids due to exceptional characteristics of the chiral sulfinyl group.[9] The *N*-*p*-toluenesulfinyl substituent in imines provides high diastereofacial selectivity and activates the C=N bond for addition of different classes of nucleophiles.[10] Moreover a wide range of *N*-*p*-toluenesulfinylimines can be easily prepared by condensation of *p*-toluenesulfinamide, which is readily available in either configuration, with appropriate aldehydes and ketones according to the procedures reported by Davis et al.[11] Addition of a methylphosphonate carbanion to aldehyde-derived (*S*)-sulfinimines afforded *N*-sulfinyl β-aminophosphonates with the (*R*)-absolute configuration at the newly generated stereocenter of the major diastereomers. Stereoselectivity ranged between 66 and 82% de depending on the nature of the imine and the reaction conditions.[9a,b] The highest de was observed in the addition of dimethyl lithiomethylphosphonate to a benzaldehyde-derived sulfinimine in THF. In the analogous reactions of aldehyde-derived (*S*)-sulfinimines with chloromethylphosphonate carbanions, the corresponding α-chloro-β-amino adducts were isolated with the exclusive (*R*)-absolute configuration at the β-carbon atom.[9c] The induced configuration at the β-carbon atom in both cases was the opposite to that obtained in reaction of sulfinimines with organometallic reagents including enolates, Grignard reagents, metallo phosphite, and ethylaluminum cyanoisopropoxide.[10] Recently, in our preliminary communication, we reported that sulfinimines are also effective substrates for the addition of a difluoromethylphosphonate carbanion.[12] In this paper, we wish to report in full our studies concerning the addition reactions of difluoromethylphosphonate carbanion to sulfinimines with diverse steric and electronic properties. The effect of different methods for the preparation of the difluoromethylphosphonate carbanion on stereoselectivity is also discussed.

2. Results and discussion

Initially, we have found that addition of the phosphonodifluoromethyl carbanion, prepared by deprotonation of diethyl difluoromethylphosphonate **8** with LDA in THF at −78 °C, to enantiomerically pure sulfinimine (*S*)-**9a** proceeded smoothly within 1 h to afford, after mild acidic work-up, the corresponding *N*-sulfinyl α,α-difluoro-β-aminophosphonate **10a** with 90% de (Scheme 1, Table 1, entry 1). In spite of the relatively weak nucleophilicity and thermal instability of diethyl lithiodifluoromethylphosphonate,[13] *N*-sulfinyl α,α-difluoro-β-aminophosphonate **10a** was obtained in high combined yield. Direct crystallization of the crude reaction mixture from ether afforded the pure major diastereoisomer. Variation of the base (Table 1, entry 2) and the solvent (Table 1, entries 3 and 4) did not improve the selectivity of addition and resulted in incomplete conversion of the starting sulfinimine (*S*)-**9a**, as indicated by ^{1}H NMR and TLC analysis of crude products.



Scheme 1.

Table 1. Reaction of the diethyl lithiodifluoromethylphosphonate with sulfinimines (*S*)-**9a–h**[a]

Entry	Sulfinimine (*S*)-**9**			Conditions	Product (*Ss*,*R*)-**10**		
		R^1	R^2			de (%)[b]	Yield (%)[c]
1	**9a**	Ph	H	LDA, THF, −78 °C, 1 h	**10a**	90	74
2	**9a**	Ph	H	*t*-BuLi, THF, −78 °C, 1 h	**10a**	90	69
3	**9a**	Ph	H	LDA, Et_2O, −78 °C, 1 h	**10a**	70	[d]
4	**9a**	Ph	H	LDA, DME, −60 °C, 1 h	**10a**	82	[d]
5	**9b**	*p*-MeO–C_6H_4	H	LDA, THF, −78 °C, 1 h	**10b**	88	92[e]
6	**9c**	*p*-CF_3–C_6H_4	H	LDA, THF, −78 °C, 1 h	**10c**	88	70
7	**9d**	2-Thienyl	H	LDA, THF, −78 °C, 1 h	**10d**	84	67
8	**9e**	*n*-C_5H_{11}	H	LDA, THF, −78 °C, 1 h	**10e**	84	72
9	**9f**	*i*-Pr	H	LDA, THF, −78 °C, 1 h	**10f**	82	75
10	**9g**	*E*-PhCH=CH	H	LDA, THF, −78 °C, 1 h	**10g**	88	76
11	**9h**	Ph	CH_3	LDA, THF, −78 °C, 1 h	**10h**	92	40 (51)[f]
12	**9h**	Ph	CH_3	LDA, THF, −78 °C, 5 h	**10h**	92	42 (49)[f]
13	**9h**	Ph	CH_3	LDA, $CeCl_3$, THF, −78 °C, 1 h	**10h**	92	36 (45)[f]

[a] Reactions were performed using 1 equiv of sulfinimine (*S*)-**9** and 1.3 equiv of diethyl difluoromethylphosphonate **8**.
[b] Determined by ^1H and ^{19}F NMR analyses of the crude reaction mixtures.
[c] Isolated yield of major diastereoisomer.
[d] Not determined.
[e] Combined yield of diastereoisomers.
[f] Yield of the recovered starting sulfinimine (*S*)-**9h**.

The base and solvent optimizations outlined above permitted the use of LDA in THF for addition of diethyl difluoromethylphosphonate **8** to other sulfinimines. In the cases of 4-substituted benzaldehyde-derived sulfinimines (*S*)-**9b**,**c** with either electron-withdrawing or electron-donating groups, the corresponding adducts **10b**,**c** were obtained with the stereochemical outcome compared to that observed for *N*-benzylidene derivative (*S*)-**9a** (Table 1, entries 5 and 6). However, the use of heteroaromatic and alkyl-substituted sulfinimines (*S*)-**9d–f** as substrates provided lower stereoselectivity (Table 1, entries 7–9). The size of the alkyl group has no effect on the diastereoselectivity of addition as illustrated by sulfinimines (*S*)-**9e**,**f** where R=*n*-pentyl and isopropyl. When *trans*-cinnamaldehyde-derived sulfinimine (*S*)-**9g** was subjected to our reaction conditions, the 1,2-addition product **10g** was obtained exclusively in good yield and with high stereocontrol (Table 1, entry 10).

Attempts to expand the scope of the reaction by employing imines derived from ketones have met with limited success. Deprotonation of **8** with LDA in THF at −78 °C, followed by addition of acetophenone-derived sulfinimine (*S*)-**9h** led to the formation of adduct **10h** with a 92% de and in only moderate yield after 1 h (Table 1, entry 11). Purification by chromatography allowed the isolation of major diastereomer **10h** in 40% yield as well as unreacted starting sulfinimine (*S*)-**9h** in 51% yield. The diastereoselectivity and yield remained essentially unchanged with a longer reaction time (Table 1, entry 12). Competitive deprotonation of the sulfinimine (*S*)-**9h** was likely responsible for the moderate yield observed in the addition reaction. It was anticipated that the effect of a cerium salt on the reactivity of dialkyl lithiodifluoromethylphosphonate[14] might favor addition to acetophenone-derived sulfinimine (*S*)-**9h** over deprotonation. However, running the reaction in the presence of 1 M equiv of cerium(III) chloride did not significantly change both the yield and selectivity in this case (Table 1, entry 13).

The *N*-sulfinyl α,α-difluoro-β-aminophosphonate diastereomers **10c–h** were separated by chromatography or crystallization to give the pure major diastereomers. At the same time all attempts to separate the diastereomeric mixture of **10b**, which exists as an oil, by flash chromatography were unsuccessful. The stereochemistry of the major diastereomer of **10a** was determined to be (*Ss*,*R*) by X-ray analysis.[15] The stereochemistry of the remaining products (*Ss*,*R*)-**10b–h** have been assigned by analogy.

The (*R*)-absolute configuration of the newly formed stereocenter in the major diastereomers **10** corresponds to that observed for the addition of methylphosphonate carbanions to sulfinimines (*S*)-**9**. Thus, the stereochemical outcome is consistent with the transition state **TS** proposed in the nonfluorinated series by Mikolajczyk et al.:[9a,b] the lithium cation coordinates to both the phosphonate oxygen of **8** and the sulfinyl oxygen of the substrate (*S*)-**9** in an s-cis conformation, and addition to the C=N bond occurs on the side that is opposite to the *p*-tolyl group (Fig. 2).

With a high-yielding synthesis of *N*-sulfinyl α,α-difluoro-β-aminophosphonates (*Ss*,*R*)-**10** in hand, we proceeded to investigate its reactivity. A significant advantage of sulfinyl methodology is that *N*-sulfinyl β-aminophosphonates have the potential to undergo further synthetic manipulations.[9] The diastereomerically pure (*Ss*,*R*)-**10a**,**d–f**,**h** were *N*-desulfinylated by treatment with trifluoroacetic acid in EtOH at room temperature (Scheme 2). Under these conditions, the phosphonate group remained intact, and the α,α-difluoro-β-aminophosphonates (*R*)-**11a**,**d–f**,**h** were isolated by flash chromatography in good yields. Hydrolysis of (*R*)-**11a**,**d–f**,**h** in refluxing 10 N HCl provided, after treatment with propylene oxide, crystalline α,α-difluoro-β-aminophosphonic acids (*R*)-**12a**,**d–f**,**h** in good to excellent isolated yields.

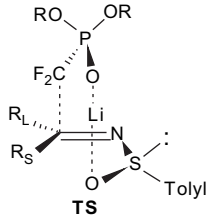
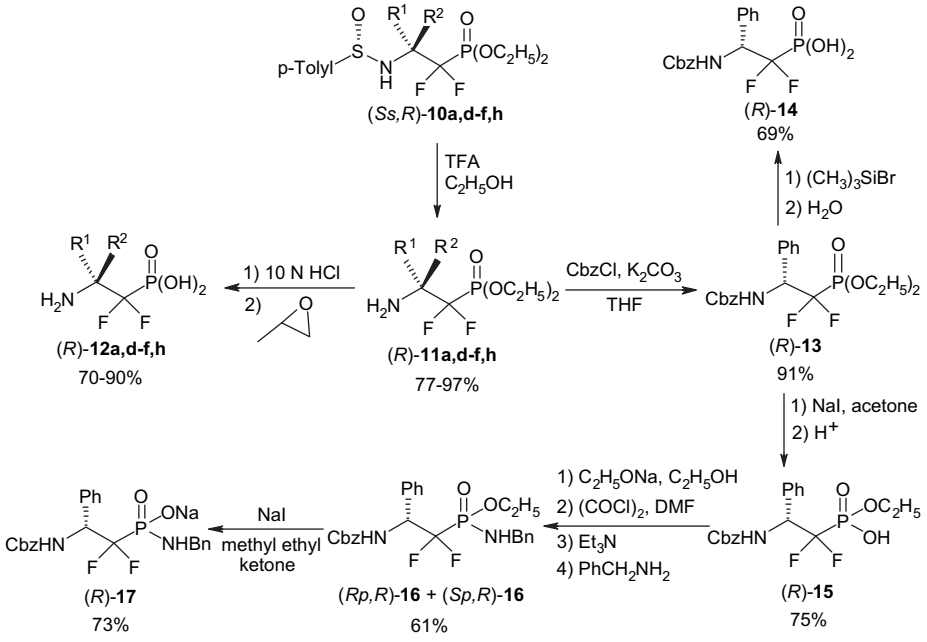


Figure 2.



Scheme 2.

The enantiomeric purity of α,α-difluoro-β-aminophosphonic acids (*R*)-**12a**,**d**–**f**,**h** so obtained was >98% ee. Consequently deprotection of *N*-sulfinyl α,α-difluoro-β-aminophosphonates (*Ss*,*R*)-**10a**,**d**–**f**,**h** occurred under the conditions described above without epimerization at the β-position. For the determination of enantiomeric purity of α,α-difluoro-β-aminophosphonic acids, we adopted previously developed method[16] of chiral precolumn derivatization followed by chromatographic separation of diastereomeric OPA/NAC derivatives. Racemic samples of α,α-difluoro-β-aminophosphonic acids **12a**,**d**–**f**,**h** were prepared according to the described method using racemic **9a**,**d**–**f**,**h** as starting compounds. The α,α-difluoro-β-aminophosphonate (*R*)-**11a** was further elaborated to the *N*-carbobenzyloxy derivative (*R*)-**13** by treatment with benzyloxycarbonyl chloride/potassium carbonate in 91% yield. Transformation of (*R*)-**13** into *N*-Cbz-protected α,α-difluoro-β-aminophosphonic acid (*R*)-**14** was achieved with bromotrimethylsilane and subsequent addition of water. The difluorophosphonic acid (*R*)-**14** was obtained after crystallization from acetone as solvate with 1 M equiv of acetone, which could not be completely removed from solvate by heating at 60 °C for 4 h under reduced pressure. Selective hydrolysis of difluorophosphonate diester (*R*)-**13** using sodium iodide in acetone afforded difluorophosphonate monoester (*R*)-**15**. The structural assignment for difluorophosphonate monoester (*R*)-**15** was based on ^{1}H NMR, which confirmed the loss of one ethyl group. The *N*-Cbz-protected difluorophosphonate monoester (*R*)-**15** was converted by treatment of the corresponding sodium salt with oxalyl chloride followed by triethylamine to give an intermediate phosphonyltriethylammonium salt.[17] The obtained reaction mixture was then treated with benzylamine to produce difluorophosphonamide **16**. Difluorophosphonamide **16** was purified chromatographically after standard work-up. The overall yield of the procedure was 61%. As the reaction generated a new stereogenic center at phosphorus, the product was obtained as mixture of diastereomers in ratio 1:1 according to ^{1}H, ^{19}F, and ^{31}P NMR analyses. Purification of difluorophosphonamide **16** by chromatography on silica gel did not alter the diastereomeric ratio. After repeated deprotection of difluorophosphonamide **16** with sodium iodide under more vigorous conditions in methyl ethyl ketone, the sodium salt of difluorophosphonamidic acid (*R*)-**17** was isolated in 73% yield as a nonhygroscopic yellow powder. The ^{1}H, ^{19}F, and ^{31}P NMR spectra are consistent with the assigned structure and have confirmed the absence of impurities in the product. Further characterization of sodium salt (*R*)-**17** involved the examination of the hydrolytic stability of the phosphonamide linkage. Previously it has been found that phosphonamides serve as analogs of the transition state of the enzyme-catalyzed amide bond hydrolysis owing to the tetrahedral configuration around the phosphorus, and therefore, act as inhibitors of zinc metalloproteases.[18] However, several publications have reported instability of phosphonamides at acidic pH.[18e,19] For example, the half-life of *N*-[[(benzyloxycarbonyl)amino]hydroxyphosphinyl]-L-phenylalanine at pH 7.5 is more than eight days, but at pH 6.2 it is 4 h; it is hydrolyzed in minutes at pH 2.3.[19a] The stability of phosphonamides can be increased by reducing the basicity of the nitrogen, as has been shown in the case of β-fluoro-α-amino phosphonamidic acids.[20] In our study sodium salt of difluorophosphonamidic acid (*R*)-**17** was stable at pH above 5.0 for two weeks at 21 °C. Only slow hydrolysis was observed at pH 2.18 (half-life was 36 h). Thus, introduction of fluorine atoms in the α-position relative to phosphorus increased the hydrolytic stability of phosphonamides.

3. Conclusion

In summary, we have described an efficient route to diastereomerically pure *N*-sulfinyl α,α-difluoro-β-aminophosphonates via addition of diethyl difluoromethylphosphonate to enantiopure sulfinimines. The usefulness

of *N*-sulfinyl α,α-difluoro-β-aminophosphonates has been demonstrated in its application to a concise synthesis of enantiomerically pure α,α-difluoro-β-aminophosphonates and α,α-difluoro-β-aminophosphonic acids. *N*-Cbz-protected (*R*)-2-amino-1,1-difluoro-2-phenylethylphosphonate was employed for the synthesis of the corresponding difluorophosphonate monoester, difluorophosphonic acid, and difluorophosphonoamidic acid. At 21 °C difluorophosphonoamidic acid was stable at pH above 5. Only slow hydrolysis was observed at pH 2.18 (half-life was 36 h). Hydrolytically stable at physiological pH, difluorophosphonamides may find applications as inhibitors in biochemical processes.

4. Experimental

4.1. General

All reagents were obtained from commercial suppliers and were used without further purification. THF and ether were distilled from sodium/benzophenone immediately before use. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. ^{1}H, ^{19}F, and ^{31}P NMR spectra were determined in the indicated solvent and referenced to TMS and $CFCl_3$ as internal standard and 85% H_3PO_4 as external standard, respectively. IR spectra were recorded on Specord M-80 spectrometer. Optical rotations were measured on a Perkin–Elmer 243 polarimeter. Column chromatography was carried out with Merck silica gel 60 (230–400 mesh) and Woelm Pharma neutral aluminum oxide activity grade Super I (type W 200). Thin-layer chromatography was performed on Merck TLC plates precoated with silica gel 60 F_{254} and aluminum oxide 60 F_{254} neutral of 0.25 mm thickness. TLC plates were visualized with ultraviolet light (254 nm) and/or in an iodine chamber. The sulfinimines were prepared by condensation of commercially available (*S*)-(+)-toluenesulfinamide with appropriate aldehyde or ketone as previously described.[11a]

4.1.1. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-phenylethylphosphonate (10a). *Typical procedure*: to a solution of diethyl difluoromethylphosphonate **8** (245 mg, 1.30 mmol) in THF (3 mL) at −78 °C was added LDA (1.8 M solution, 0.72 mL, 1.30 mmol). After 0.5 h sulfinimine (*S*)-**9a** (243 mg, 1.00 mmol) in THF (1 mL) was added dropwise and the solution was stirred at −78 °C for 1 h. At this time the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the solution was warmed to room temperature. After dilution with H_2O (2 mL) the solution was extracted with EtOAc (2×5 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave the crude phosphonate **10a** with 90% de. Crystallization from ether afforded 320 mg (74%) of (*Ss*,*R*)-**10a** as a white solid; mp 95–97 °C; $[\alpha]_D^{20}$ +53.7 (*c* 1.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, *J* 7.1 Hz, 3H), 1.26 (t, *J* 7.1 Hz, 3H), 2.32 (s, 3H), 3.97–4.21 (m, 4H), 4.87–5.02 (m, 1H), 5.43 (d, *J* 7.6 Hz, 1H), 7.12 (d, *J* 8.1 Hz, 2H), 7.24 (s, 5H), 7.51 (d, *J* 8.1 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.01 (ddd, *J* 302.2, 101.2, and 13.4 Hz, 1F), −115.58 (ddd, *J* 302.2, 103.6, and 15.0 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 5.9 (dd, *J* 103.6 and 101.2 Hz); IR (CH_2Cl_2): ν 3482, 2982, 1259, 1022 cm^{-1}. Anal. Calcd for $C_{19}H_{24}F_2NO_4PS$: C, 52.90; H, 5.61; N, 3.25. Found: C, 53.14; H, 5.68; N, 3.30.

4.1.2. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-(*p*-methoxyphenyl)ethylphosphonate (10b). Chromatography on silica gel (hexane/ethyl acetate 1:1); yield 92% (oil); 88% de; $[\alpha]_D^{20}$ +39.8 (*c* 1.17, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (t, *J* 7.0 Hz, 3H), 1.28 (t, *J* 7.0 Hz, 3H), 2.34 (s, 3H), 3.76 (s, 3H), 3.99–4.24 (m, 4H), 4.81–5.03 (m, 1H), 5.29 (d, *J* 7.6 Hz, 1H), 6.76 (d, *J* 8.2 Hz, 2H), 7.12–7.20 (m, 4H), 7.53 (d, *J* 8.2 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −114.73 (ddd, *J* 301.2, 101.5, and 14.0 Hz, 1F), −116.60 (ddd, *J* 301.2, 103.4, and 15.1 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 6.79 (dd, *J* 103.4 and 101.5 Hz); IR (CH_2Cl_2): ν 3159, 1512, 1253, 1052 cm^{-1}. Anal. Calcd for $C_{20}H_{26}F_2NO_5PS$: C, 52.06; H, 5.68; N, 3.04. Found: C, 52.21; H, 5.78; N, 3.09.

4.1.3. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-(*p*-trifluoromethylphenyl)ethylphosphonate (10c). Chromatography on neutral aluminum oxide (CH_2Cl_2/ethyl acetate 2:1); yield 70% (oil); $[\alpha]_D^{20}$ +25.38 (*c* 1.32, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (t, *J* 7.0 Hz, 3H), 1.24 (t, *J* 7.0 Hz, 3H), 2.19 (s, 3H), 3.93–4.24 (m, 4H), 4.84–5.05 (m, 1H), 5.70 (d, *J* 6.0 Hz, 1H), 6.94 (d, *J* 8.0 Hz, 2H), 7.22 (d, *J* 8.0 Hz, 2H), 7.30–7.36 (m, 4H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −63.30 (s, 3F), −113.12 (ddd, *J* 304.0, 99.2, and 12.1 Hz, 1F), −117.19 (ddd, *J* 304.0, 104.0, and 16.8 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 6.17 (dd, *J* 104.0 and 99.2 Hz); IR (CH_2Cl_2): ν 3149, 1249, 1019 cm^{-1}. Anal. Calcd for $C_{20}H_{23}F_5NO_4PS$: C, 48.10; H, 4.64; N, 2.80. Found: C, 48.30; H, 4.74; N, 3.08.

4.1.4. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-(2-thienyl)ethylphosphonate (10d). Crystallization from hexane/ether; yield 67%; mp 70–71 °C; $[\alpha]_D^{20}$ +58.7 (*c* 1.07, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (t, *J* 7.2 Hz, 3H), 1.24 (t, *J* 7.2 Hz, 3H), 2.29 (s, 3H), 3.86–4.26 (m, 4H), 5.07–5.29 (m, 2H), 6.82 (dd, *J* 5.0 and 3.6 Hz, 1H), 6.95 (d, *J* 3.6 Hz, 1H), 7.13 (d, *J* 8.0 Hz, 2H), 7.17–7.20 (m, 1H), 7.52 (d, *J* 8.0 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −114.21 (ddd, *J* 300.4, 100.8, and 11.2 Hz, 1F), −116.63 (ddd, *J* 300.4, 102.2, and 12.4 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 6.50 (dd, *J* 102.2 and 100.8 Hz); IR (CH_2Cl_2): ν 3457, 3137, 1260, 1018 cm^{-1}. Anal. Calcd for $C_{17}H_{22}F_2NO_4PS_2$: C, 46.68; H, 5.07; N, 3.20. Found: C, 47.01; H, 5.17; N, 3.21.

4.1.5. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoroheptylphosphonate (10e). Chromatography on silica gel (hexane/ethyl acetate 3:2); yield 72% (oil); $[\alpha]_D^{25}$ +68.38 (*c* 2.34, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* 7.0 Hz, 3H), 1.25–1.71 (m, 7H), 1.37 (t, *J* 7.0 Hz, 3H), 1.39 (t, *J* 7.0 Hz, 3H), 1.88–1.99 (m, 1H), 2.40 (s, 3H), 3.78–3.94 (m, 1H), 4.12 (d, *J* 8.8 Hz, 1H), 4.23–4.34 (m, 4H), 7.29 (d, *J* 8.0 Hz, 2H), 7.71 (d, *J* 8.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.22 (m, 1F), −115.61 (m, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 4.5 (t, *J* 100.2 Hz); IR (CH_2Cl_2): ν 3481, 3157, 1239, 1091 cm^{-1}. Anal. Calcd for $C_{18}H_{30}F_2NO_4PS$: C, 50.81; H, 7.11; N, 3.29. Found: C, 50.54; H, 7.32; N, 3.51.

4.1.6. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-3-methylbutylphosphonate (10f). Chromatography on silica gel (CH_2Cl_2/MeOH 10:0.2); yield 71%; mp 87–88 °C; $[\alpha]_D^{20}$ +51.34 (*c* 2.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, *J* 6.8 Hz, 3H), 1.16 (d, *J* 6.8 Hz, 3H), 1.38 (t, *J* 6.9 Hz, 3H), 1.40 (t, *J* 6.9 Hz, 3H), 2.41 (s, 4H), 3.76–3.90 (m, 1H), 4.22 (d, *J* 10.6 Hz, 1H), 4.26–4.35 (m, 4H), 7.31 (d, *J* 7.8 Hz, 2H), 7.76 (d, *J* 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −112.72 (ddd, *J* 305.2, 104.8, and 14.6 Hz, 1F), −115.35 (ddd, *J* 305.2, 104.8, and 12.8 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.00 (t, *J* 104.8 Hz); IR (CH_2Cl_2): ν 3484, 2978, 1240, 1068 cm^{-1}. Anal. Calcd for $C_{16}H_{26}F_2NO_4PS$: C, 48.36; H, 6.59; N, 3.52. Found: C, 48.11; H, 6.57; N, 3.92.

4.1.7. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-4-phenyl-3*E*-butenylphosphonate (10g). Chromatography on silica gel (hexane/ethyl acetate 2:1); yield 76% (oil); $[\alpha]_D^{20}$ +38.5 (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J* 7.1 Hz, 3H), 1.35 (t, *J* 7.1 Hz, 3H), 2.32 (s, 3H), 4.15–4.34 (m, 4H), 4.52–4.70 (m, 1H), 5.05 (d, *J* 8.2 Hz, 1H), 6.08 (dd, *J* 16.0 and 7.2 Hz, 1H), 6.58 (dd, *J* 16.0 and 1.0 Hz, 1H), 7.23 (d, *J* 8.2 Hz, 2H), 7.28–7.29 (m, 5H), 7.66 (d, *J* 8.2 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.52 (ddd, *J* 300.0, 103.4, and 12.2 Hz, 1F), −116.60 (ddd, *J* 300.0, 103.4, and 12.2 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.30 (t, *J* 103.4 Hz); IR (CH_2Cl_2): ν 3159, 1581, 1240, 1059 cm^{-1}. Anal. Calcd for $C_{21}H_{26}F_2NO_4PS$: C, 55.14; H, 5.73; N, 3.06. Found: C, 55.29; H, 5.61; N, 3.31.

4.1.8. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-phenylpropylphosphonate (10h). Chromatography on silica gel (hexane/ethyl acetate 1:1); yield 40% (oil); $[\alpha]_D^{20}$ +19.6 (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (t, *J* 7.2 Hz, 3H), 1.26 (t, *J* 7.2 Hz, 3H), 2.16 (s, 3H), 2.42 (s, 3H), 3.69–3.82 (m, 1H), 3.85–3.98 (m, 1H), 4.07–4.20 (m, 2H), 5.91 (s, 1H), 7.31–7.41 (m, 5H), 7.63–7.69 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.21 (dd, *J* 299.6 and 103.8 Hz, 1F), −116.75 (dd, *J* 299.6 and 103.8 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.08 (t, *J* 103.8 Hz); IR (CH_2Cl_2): ν 3457, 3137, 1238, 1067 cm^{-1}. Anal. Calcd for $C_{20}H_{26}F_2NO_4PS$: C, 53.93; H, 5.88; N, 3.14. Found: C, 53.72; H, 6.22; N 3.23.

4.1.9. (*R*)-Diethyl 2-amino-1,1-difluoro-2-phenylethylphosphonate (11a). *Typical procedure*: trifluoroacetic acid (0.38 mL, 4.93 mmol) was added to the solution of (*Ss*,*R*)-**10a** (425 mg, 0.99 mmol) in dry EtOH (30 mL) at 0 °C and the reaction mixture was stirred at room temperature for 4 h. The solution was concentrated, residue was dissolved in CH_2Cl_2 (30 mL), and neutralized to pH 7.5 with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), and concentrated. Purification by chromatography on silica gel (CH_2Cl_2/EtOH 10:0.4) afforded 0.266 g (92%) of (*R*)-**11a** as a white solid; mp 63–64 °C; $[\alpha]_D^{20}$ −13.1 (*c* 0.98, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J* 6.9 Hz, 3H), 1.21 (t, *J* 6.9 Hz, 3H), 1.85 (s, 2H), 3.91–4.21 (m, 4H), 4.29–4.46 (m, 1H), 7.27–7.32 (m, 5H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −116.13 (ddd, *J* 299.0, 103.5, and 11.4 Hz, 1F), −121.26 (ddd, *J* 299.0, 106.0, and 17.5 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 7.95 (dd, *J* 106.0 and 103.5 Hz); IR (CH_2Cl_2): ν 3294, 2979, 1236, 1026 cm^{-1}. Anal. Calcd for $C_{12}H_{18}F_2NO_3P$: C, 49.15; H, 6.19; N, 4.78. Found: C, 49.37; H, 6.13; N, 4.87.

4.1.10. (*R*)-Diethyl 2-amino-1,1-difluoro-2-(2-thienyl)-ethylphosphonate (11d). Chromatography on silica gel (CH_2Cl_2/EtOH 10:0.4); yield 97%; mp 69–70 °C; $[\alpha]_D^{20}$ −2.6 (*c* 0.96, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, *J* 7.1 Hz, 6H), 1.92 (br s, 2H), 3.96–4.27 (m, 4H), 4.59–4.75 (m, 1H), 6.94 (dd, *J* 5.0 and 3.4 Hz, 1H), 7.07 (d, *J* 3.4 Hz, 1H), 7.23 (dd, *J* 5.0 and 1.0 Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −115.17 (ddd, *J* 298.5, 103.0, and 10.0 Hz, 1F), −122.03 (ddd, *J* 298.5, 104.4, and 17.4 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 7.76 (dd, *J* 104.4 and 103.0 Hz); IR (CH_2Cl_2): ν 3360, 2986, 1232, 1015 cm^{-1}. Anal. Calcd for $C_{10}H_{16}F_2NO_3PS$: C, 40.13; H, 5.39; N, 4.68. Found: C, 40.22; H, 5.01; N, 4.31.

4.1.11. (*R*)-Diethyl 2-amino-1,1-difluoroheptylphosphonate (11e). Chromatography on silica gel (CH_2Cl_2/EtOH 10:0.2); yield 77% (oil); $[\alpha]_D^{20}$ +14.08 (*c* 1.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, *J* 6.7 Hz, 3H), 1.30–1.49 (m, 14H), 1.55–1.67 (m 1H), 1.74–1.83 (m, 1H), 3.07–3.23 (m, 1H), 4.24–4.34 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −117.74 (ddd, *J* 299.2, 108.2, and 11.0 Hz, 1F), −121.33 (ddd, *J* 299.2, 109.4, and 17.9 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 4.5 (dd, *J* 109.4 and 108.2 Hz); IR (CH_2Cl_2): ν 3482, 2982, 1236, 1090 cm^{-1}. Anal. Calcd for $C_{11}H_{24}F_2NO_3P$: C, 45.99; H, 8.42; N, 4.88. Found: C, 46.30; H, 8.36; N, 4.57.

4.1.12. (*R*)-Diethyl 2-amino-1,1-difluoro-3-methylbutylphosphonate (11f). Chromatography on silica gel (CH_2Cl_2/EtOH 10:0.2); yield 87% (oil); $[\alpha]_D^{25}$ +12.04 (*c* 1.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, *J* 6.8 Hz, 3H), 1.06 (d, *J* 6.8 Hz, 3H), 1.39 (t, *J* 7.0 Hz, 6H), 1.46 (br s, 2H), 2.20–2.30 (m, 1H), 3.11 (ddt, *J* 21.2, 11.0, and 3.0 Hz, 1H), 4.27 (q, *J* 7.0 Hz, 2H), 4.32 (q, *J* 7.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −116.28 (ddd, *J* 298.4, 110.4, and 11.0 Hz, 1F), −120.09 (ddd, *J* 298.4, 110.4, and 21.2 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.30 (t, *J* 110.4 Hz); IR (CH_2Cl_2): ν 3394, 2950, 1257, 1013 cm^{-1}. Anal. Calcd for $C_9H_{20}F_2NO_3P$: C, 41.70; H, 7.78; N, 5.40. Found: C, 41.78; H, 7.74; N, 5.15.

4.1.13. (*R*)-Diethyl 2-amino-1,1-difluoro-2-phenylpropylphosphonate (11h). Chromatography on silica gel (CH_2Cl_2/EtOH 10:0.4); yield 84% (oil); $[\alpha]_D^{20}$ +1.22 (*c* 1.47, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.94 (t, *J* 7.0 Hz, 3H), 1.23 (t, *J* 7.0 Hz, 3H), 1.56 (m, 3H), 2.26 (br s, 2H), 3.33–3.53 (m, 1H), 3.62–3.81 (m, 1H), 4.00–4.19 (m, 2H), 7.21–7.33 (m, 3H), 7.51–7.55 (m, 2H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −114.65 (dd, *J* 297.4 and 101.8 Hz, 1F), −116.94 (dd, *J* 297.4 and 109.2 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 7.63 (dd, *J* 109.2 and 101.8 Hz); IR (CH_2Cl_2): ν 3432, 3060, 1236, 1026 cm^{-1}. Anal. Calcd for $C_{13}H_{20}F_2NO_3P$: C, 50.82; H, 6.56; N, 4.56. Found: C, 51.02; H, 6.70; N, 4.69.

4.1.14. (*R*)-2-Amino-1,1-difluoro-2-phenylethylphosphonic acid (12a). *Typical procedure*: a solution of (*R*)-**11a** (850 mg, 2.90 mmol) in 10 N HCl (20 mL) was refluxed

for 8 h. The solution was concentrated under reduce pressure to dryness. The resulting solid was treated with EtOH (15 mL) and propylene oxide (0.61 mL, 8.7 mmol) and the reaction mixture was stirred for 3 h. Precipitate was filtered off and washed with ether to provide 580 mg (84%) of (*R*)-**12a** as a white solid; mp 286–288 °C (decomp.); $[\alpha]_D^{20}$ −11.9 (*c* 1.01, H_2O); ^{1}H NMR (200 MHz, D_2O): δ 4.75 (dd, *J* 19.4 and 9.4 Hz, 1H), 7.32 (s, 5H); ^{19}F NMR (188 MHz, D_2O): δ −114.45 (ddd, *J* 295.9, 85.0, and 9.4 Hz, 1F), −123.13 (ddd, *J* 295.9, 85.0, and 19.4 Hz, 1F); ^{31}P NMR (81 MHz, D_2O): δ 1.84 (t, *J* 85.0 Hz); IR (KBr): ν 3040, 1200, 1088, 1048 cm^{-1}. Anal. Calcd for $C_8H_{10}F_2NO_3P$: C, 40.52; H, 4.25; N, 5.91. Found: C, 40.62; H, 4.40; N, 5.92.

4.1.15. (*R*)-2-Amino-1,1-difluoro-2-(2-thienyl)ethylphosphonic acid (12d). Yield 86%; mp 265–266 °C (decomp.); $[\alpha]_D^{20}$ −1.9 (*c* 0.96, H_2O); ^{1}H NMR (200 MHz, D_2O): δ 5.18 (dd, *J* 20.3 and 8.2 Hz, 1H), 6.98 (dd *J* 5.0 and 3.4 Hz, 1H), 7.23 (d, *J* 3.4 Hz, 1H), 7.45 (d, *J* 5.0 Hz, 1H); ^{19}F NMR (188 MHz, D_2O): δ −115.26 (ddd, *J* 294.4, 84.9, and 8.2 Hz, 1F), −124.18 (ddd, *J* 294.4, 83.7, and 20.3 Hz, 1F); ^{31}P NMR (81 MHz, D_2O): δ 1.59 (dd, *J* 84.9 and 83.7 Hz); IR (KBr): ν 3144, 2857, 1208, 1100 cm^{-1}. Anal. Calcd for $C_6H_8F_2NO_3PS$: C, 29.64; H, 3.32; N, 5.76. Found: C, 29.70; H, 3.35; N, 5.80.

4.1.16. (*R*)-2-Amino-1,1-difluoroheptylphosphonic acid (12e). Yield 70%; mp 280–282 °C (decomp.); $[\alpha]_D^{20}$ +9.9 (*c* 1.01, 0.5 N NaOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, *J* 6.3 Hz, 3H), 1.17–1.51 (m, 6H), 1.53–1.67 (m, 1H), 1.72–1.87 (m, 1H), 3.41 (d, *J* 21.6 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ −118.95 (dd, *J* 292.4 and 79.6 Hz, 1F), −125.28 (ddd, *J* 292.4, 79.6, and 21.6 Hz, 1F); ^{31}P NMR (121 MHz, DMSO-d_6): δ 4.60 (t, *J* 79.6 Hz); IR (KBr): ν 3248, 2956, 1229, 1084, 1029 cm^{-1}. Anal. Calcd for $C_7H_{16}F_2NO_3P$: C, 36.37; H, 6.96; N, 6.06. Found: C, 36.48; H, 7.20; N, 6.19.

4.1.17. (*R*)-2-Amino-1,1-difluoro-3-methylbutylphosphonic acid (12f). Yield 75%; mp 264–266 °C (decomp.); $[\alpha]_D^{20}$ −5.9 (*c* 0.81, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 1.04 (d, *J* 7.0 Hz, 3H), 1.13 (d, *J* 7.0 Hz, 3H), 2.56–2.66 (m, 1H), 3.74 (dd, *J* 20.6 and 9.8 Hz, 1H); ^{19}F NMR (282 MHz, D_2O): δ −110.27 (dd, *J* 299.2 and 86.4 Hz, 1F), (ddd, *J* 299.2, 86.4, and 20.6 Hz, 1F); ^{31}P NMR (121 MHz, D_2O): δ 1.90 (t, *J* 86.4 Hz); IR (KBr): ν 3144, 2976, 1208, 1100, 1028 cm^{-1}. Anal. Calcd for $C_5H_{12}F_2NO_3P$: C, 29.57; H, 5.95; N, 6.90. Found: C, 29.60; H, 5.85; N, 6.71.

4.1.18. (*R*)-2-Amino-1,1-difluoro-2-phenylpropylphosphonic acid (12h). Yield 90%; mp 284–286 °C (decomp.); $[\alpha]_D^{20}$ −4.0 (*c* 0.75, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 1.97 (s, 3H), 7.48–7.54 (m, 5H); ^{19}F NMR (282 MHz, D_2O): δ −117.03 (dd, *J* 300.6 and 88.2 Hz, 1F), −118.13 (dd, *J* 300.6 and 88.2 Hz, 1F); ^{31}P NMR (121 MHz, D_2O): δ 2.50 (t, *J* 88.2 Hz); IR (KBr): ν 3100, 2930, 1150, 1075 cm^{-1}. Anal. Calcd for $C_9H_{12}F_2NO_3P$: C, 43.04; H, 4.82; N, 5.58. Found: C, 42.95; H, 4.73; N, 5.67.

4.1.19. (*R*)-Diethyl *N*-benzyloxycarbonyl-2-amino-1,1-difluoro-2-phenylethylphosphonate (13). To solution of (*R*)-**11a** (140 mg, 0.48 mmol) in THF (6 mL) and H_2O (0.5 mL) was added K_2CO_3 (95 mg, 0.69 mmol), followed by benzyl chloroformate (0.097 mL, 0.69 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then diluted with ethyl acetate (5 mL) and water (5 mL). The organic phase was separated and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were washed with 1 N HCl (4 mL), saturated aqueous $NaHCO_3$ (4 mL), water (4 mL), dried (Na_2SO_4), and concentrated. Purification by chromatography on silica gel (hexane/ethyl acetate 2:1) afforded 186 mg (91%) of (*R*)-**13** as a white solid; mp 104–105 °C; $[\alpha]_D^{20}$ +10.3 (*c* 1.07, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.21 (t, *J* 7.0 Hz, 3H), 1.22 (t, *J* 7.0 Hz, 3H), 3.96–4.21 (m, 4H), 5.04 (d, *J* 12.5 Hz, 1H), 5.14 (d, *J* 12.5 Hz, 1H), 5.36–5.51 (m, 1H), 7.30–7.43 (m, 8H), 7.54–7.56 (m, 2H); ^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ −112.90 (ddd, *J* 303.2, 99.2, and 11.8 Hz, 1F), −117.44 (ddd, *J* 303.2, 103.0, and 19.1 Hz, 1F); ^{31}P NMR (121 MHz, $(CD_3)_2CO$): δ 7.00 (dd, *J* 103.0 and 99.2 Hz); IR (CH_2Cl_2): ν 3432, 3060, 1730, 1248, 1222, 1027 cm^{-1}. Anal. Calcd for $C_{20}H_{24}F_2NO_5P$: C, 56.21; H, 5.66; N, 3.28. Found: C, 56.18; H, 5.67; N, 3.22.

4.1.20. (*R*)-*N*-Benzyloxycarbonyl-2-amino-1,1-difluoro-2-phenylethylphosphonic acid (14). Bromotrimethylsilane (0.55 mL, 4.2 mmol) was added dropwise to a solution of (*R*)-**13** (300 mg, 0.70 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for six days at room temperature and then evaporated under reduced pressure. The residue was treated with water (3 mL) and the mixture was stirred for 2 h. After the water was removed under reduced pressure the residue was crystallized from acetone. The precipitate was filtered, washed with acetone to give 209 mg (69%) of (*R*)-**14**·$(CH_3)_2CO$ as white crystals; mp 144–146 °C; $[\alpha]_D^{20}$ −24.96 (*c* 1.21, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.04 (s, 2H), 5.21–5.29 (m, 1H), 7.30–7.36 (m, 8H), 7.43–7.45 (m, 2H), 8.23 (d, *J* 9.8 Hz, 1H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −115.09 (ddd, *J* 295.6, 95.9, and 11.3 Hz, 1F), −120.20 (ddd, *J* 295.6, 95.9, and 19.2 Hz, 1F); ^{31}P NMR (202 MHz, DMSO-d_6): δ 7.70 (t, *J* 95.9); IR (KBr): ν 3293, 2982, 1710, 1259, 1022 cm^{-1}. Anal. Calcd for $C_{16}H_{16}F_2NO_5P \cdot C_3H_6O$: C, 53.15; H, 5.16; N, 3.26. Found: C, 53.11; H, 5.12; N, 2.86.

4.1.21. (*R*)-Monoethyl *N*-benzyloxycarbonyl-2-amino-1,1-difluoro-2-phenylethylphosphonate (15). A solution of diester (*R*)-**13** (850 mg, 1.99 mmol) and sodium iodide (328 mg, 2.19 mmol) in acetone (4 mL) was heated at reflux for 6 h. After cooling the reaction mixture was evaporated to dryness and residue was dissolved in water (3 mL). The aqueous solution was acidified with 1 N HCl until pH reaches 1 and extracted with EtOAc (2×30 mL). The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated. Crystallization from acetone gave 596 mg (75%) of (*R*)-**15** as white solid; mp 186–187 °C; $[\alpha]_D^{20}$ −9.8 (*c* 0.81, $(CH_3)_2CO$). ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.20 (t, *J* 7.2 Hz, 3H), 4.02–4.12 (m, 2H), 5.09 (d, *J* 12.6 Hz, 1H), 5.15 (d, *J* 12.6 Hz, 1H), 5.41–5.53 (m, 1H), 5.64 (br s, 1H), 7.34–7.44 (m, 8H), 7.57–7.60 (m, 2H); ^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ −113.46 (dd, *J* 302.2 and 100.8 Hz, 1F), −118.88 (ddd, *J* 302.2, 100.8, and 19.0 Hz, 1F); ^{31}P NMR (121 MHz, $(CD_3)_2CO$): δ 5.80 (t, *J* 100.8 Hz); IR (KBr): ν 3310, 2528, 1692, 1235, 1051 cm^{-1}. Anal. Calcd for

$C_{18}H_{20}F_2NO_5P$: C, 54.14; H, 5.05; N, 3.51. Found: C, 54.36; H, 5.09; N, 3.53.

4.1.22. (*Rp*,*R*) and (*Sp*,*R*)-Ethyl *N*-benzyl-2-(*N*′-benzyloxycarbonylamino)-1,1-difluoro-2-phenylethylphosphonoamidate (16). Sodium ethoxide (48 mg, 0.71 mmol) was added to suspension of (*R*)-**15** (282 mg, 0.71 mmol) in dry ethanol (6 mL). The resulting solution was stirred at room temperature for 2 h and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and DMF (two drops) was added. The solution was cooled to 0 °C and treated with oxalyl chloride (180 mg, 1.42 mmol). After stirring at 0 °C for 0.5 h the reaction mixture was concentrated to dryness, the residue was dissolved in CH_2Cl_2 (5 mL), and Et_3N (79 mg, 0.78 mmol) and then benzylamine (380 mg, 3.55 mmol) were added at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then treated with cold water (5 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), and dried (Na_2SO_4). Concentration afforded crude **16** as mixture of (*Rp*,*R*) and (*Sp*,*R*) diastereomers in ratio 1:1. Chromatography purification (CH_2Cl_2/Et_2O 10:1) gave 209 mg (61%) of **16** as white solid and did not alter the ratio of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (t, *J* 6.8 Hz, 1.5H), 1.26 (t, *J* 6.8 Hz, 1.5H), 2.59–2.64 (m, 0.5H), 3.06–3.11 (m, 0.5H), 3.88–3.96 (m, 2H), 4.04–4.19 (m, 2H), 5.12 (s, 2H), 5.36–5.48 (m, 1H), 6.34–6.42 (m, 1H), 7.12–7.14 (m, 1H), 7.25–7.38 (m, 12H), 7.42–7.45 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −112.17 (ddd, *J* 301.2, 94.2, and 8.6 Hz, 1F), −117.66 (ddd, *J* 301.2, 101.2, and 18.3 Hz, 1F) (first diastereomer); −113.17 (ddd, *J* 300.0, 106.0, and 10.2 Hz, 1F), −115.62 (ddd, *J* 300.0, 90.6, and 16.0 Hz, 1F) (second diastereomer); ^{31}P NMR (202 MHz, $CDCl_3$): δ 16.61 (dd, *J* 101.2 and 94.2 Hz) (first diastereomer); 17.14 (dd, *J* 106.0 and 90.6 Hz) (second diastereomer); IR (KBr): ν 3352, 3211, 1700, 1248, 1044 cm^{-1}. Anal. Calcd for $C_{25}H_{27}F_2N_2O_4P$: C, 61.47; H, 5.57; N, 5.73. Found: C, 61.62; H, 5.67; N, 5.70.

4.1.23. Sodium (*R*)-*N*-benzyl-(2-*N*′-benzyloxycarbonylamino)-1,1-difluoro-2-phenylethylphosphonoamidate (17). A solution of **16** (167 mg, 0.34 mmol) and sodium iodide (56 mg, 0.37 mmol) in methyl ethyl ketone (3 mL) was heated at reflux for 5 h. The reaction mixture was then cooled to room temperature, the precipitate was filtered, washed with cooled acetone, and dried to give 120 mg (73%) of (*R*)-**17**; mp 234–236 °C; $[\alpha]_D^{20}$ −11.55 (*c* 1.10, 20 mM H_3PO_4/NaOH pH 6.82); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.11 (br s, 1H), 3.76–3.92 (m, 2H), 4.85–4.94 (m, 1H), 4.98 (s, 2H), 7.12–7.40 (m, 15H), 8.58 (br s, 1H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −108.46 (dd, *J* 282.5 and 76.4 Hz, 1F), −115.75 (ddd, *J* 282.5, 76.4, and 16.0 Hz, 1F); ^{31}P NMR (202 MHz, DMSO-d_6): δ 9.16 (t, *J* 76.4 Hz); IR (KBr): ν 3383, 3288, 1706, 1230, 1067 cm^{-1}. Anal. Calcd for $C_{23}H_{22}F_2N_2NaO_4P$: C, 57.27; H, 4.60; N, 5.81. Found: C, 57.13; H, 4.67; N, 5.88.

4.1.24. Hydrolytic stability of sodium (*R*)-*N*-benzyl-(2-*N*′-benzyloxycarbonylamino)-1,1-difluoro-2-phenylethylphosphonoamidate (17). The hydrolytic stability of sodium salt (*R*)-**17** was studied chromatographically. The following buffering systems were employed: 20 mM phosphoric acid, pH 2.18; 20 mM phosphoric acid adjusted to pH 5.20 and 6.82 with concentrated sodium hydroxide. The stock solution of (*R*)-**17** (6 mM) was prepared by dissolving (*R*)-**17** in buffer at pH 6.82. Reactions were initiated by addition of aliquots of stock solution to 5 mL of buffers. The concentration of substrate ranged from 0.09 to 0.4 mM. At appropriate intervals three consecutive within 10-min samples were collected and injected onto C18 chromatographic column equipped with UV-detector monitoring at 220 nm. The absolute calibration method gave us acceptable level of quantitation accuracy. The sodium salt (*R*)-**17** was stable at pH above 5.00 for two weeks at 21 °C; the half-life of (*R*)-**17** at pH 2.18 was 36±1 h.

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