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Synthesis of trifluoromethyl *γ*-aminophosphonates by nucleophilic aziridine ring opening

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Phosphonated derivatives of trifluoromethyl aziridine were obtained with good yield from aziridine-2-carbaldehyde by two distinct methods, which resulted in different diastereoselectivity. Using thiols as nucleophiles ring opening reactions of trifluoromethylated derivatives of aziridines-2-phosphonates proceeded regio- and diastareoselectively, giving rise to *γ*-amino-*γ*-trifluoromethyl phosphonates.

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Introduction

Aminophosphonates are an important class of compounds, because of their unique utilities as antibiotics, herbicides, antifungal agents, enzyme inhibitors, and pharmacological agents.[1] They can also act as analogues of amino acids, and as such they constitute important motifs in medicinal chemistry.[2] Among the various types of aminophosphonates, *α*-amino and *β*-aminophosphonates and their biological importance have been widely described in literature.[1,2] With regard to *γ*-aminophosphonates, only a few examples of biological activity have been found (e.g. receptors agonists and antagonists).[3]

Aziridine derivatives are valuable functionalized building blocks for the asymmetric synthesis of aminophosphonates because of their ability to undergo highly regio- and stereospecific ring opening reactions.[4] Furthermore, the presence of CF_3 group, attached to aziridine ring, constitutes a promising route to obtain fluorinated amino acids analogues. The introduction of fluorine atoms in organic molecules often results in a deep modification of physical, chemical and biological properties of the parent compounds.[5] Amongs them, fluorinated phosphonates structurally and functionally mimic the phosphate compounds. In contrast, they are resistant to phosphatase cleavage. The replacement of oxygen for CH_2 makes phosphonates hydrolytically stable. However the electronegativity of oxygen is distinctly different from CH_2, but the incorporation of one or two fluorine atoms onto methylene group changes the acidity of the compound due to electron withdrawing effect of the fluorine atom. Moreover, CF_2-phosphonate analogues are structurally most closely resemble to the phosphate ester, due to similarity of the C-CF_2-P (117°) angle to the C-O-P system (119°).[6] Recently, Berkowitz et al. reported the state of research on developing and application CF_2-phosphonate analogs as tools for the study of protein phosphorylation, showing their potential importance in chemical biology by regulation of protein functions.[6b] From the other side, bulky liphophilic CF_3 group is numerously used to mimic side chain of miscellaneous amino acids involved in ligands interactions or in enzyme inhibitors,[5e] and also in modification of the agonist/antagonist nature of the ligands when the binding activity remains unchanged.[5d] Moreover, the hydrophobic nature of the CF_3 group prefers complementarity with the liphophilic pockets of the proteins.[5b] Furthermore, CF_3 group can replace the C=O group of peptides and create a stable, nonbasic, amine that preserves excellent hydrogen bonding, as has been used in the design of various enzymes inhibitors.[5a,c,g]

According to huge synthetic utility of aziridine, this three-member ring is applied to synthesis of various aminophosphonates.[7] One of the most useful approaches for synthesis of aminophosphonates is the addition of dialkyl phosphites to *N*-protected amino aldehydes known as Pudovik type reaction,[8] which is a modification of Abramov reaction.[9] However, to the best of our knowledge, there are only a few reports of synthesis of fluorinated aminophosphonates using aziridine-2-phosphonate route.[10]

Considering reactivity of aziridine-2-carboxylates, a regio- and stereoselective synthesis of fluorinated *anti*-*α*-functionalised-*β*-amino acids through nucleophilic ring opening of racemic ethyl *trans*-*N*-benzyl-3-trifluoromethylaziridine-2-carboxylate in acidic conditions was described by Davoli.[11] The ring opening reactions occurred with nucleophilic attack at the C2 carbon atom to give only one

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regioisomer in a single *anti* diasteromeric form. Regiochemistry of this reaction is governed by CF_3 group. In contrast, non fluorinated 3-alkyl-aziridine-2-carboxylates underwent nucleophilic attack at C3 carbon atom.[12] Stereochemistry is a consequence of the displacement mechanism involved the ring opening reactions of aziridine carboxylates.[13] These assumptions were confirmed using opposite isomer, *cis*-*N*-benzyl-3-trifluoromethylaziridine-2-carboxylate which led to *syn* stereoisomer of α-functionalized-β-amino trifluoromethyl esters.[14] These ring opening reactions of non activated CF_3-substituted aziridines are limited to only a few nucleophiles such as thiols, halides and carboxylates. Reactions with other nucleophiles, such as amines are more problematic and even with Lewis acids catalysts are mostly inert,[15] except a method, described by D'hooghe *et al*., involving activation of aziridine ring by *N*-alkylation, towards *N*-benzylmethylamines.[16]

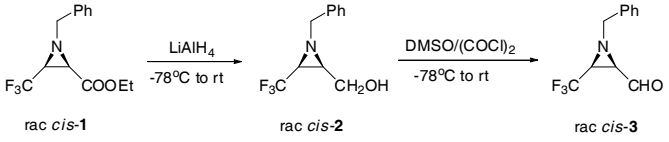
Results and discussion

In the course of our studies we were able to synthesize trifluoromethyl aziridine derivatives of phosphonates which were subsequently used in ring opening reactions, leading to series of new derivatives of γ-amino-γ-trifluoromethyl phosphonates with high regio- and diastereoselectivity.

Racemic *cis*-*N*-benzyl-trifluoromethylaziridine **1** was prepared in two steps from commercially available fluoral *via* trifluoromethylated *N*-benzylimine, as described in the literature.[14,17] Then, an ester group was reduced to provide the corresponding alcohol **2** in 84% yield.[18,19] Swern oxidation of **2** gave the respective aldehyde **3** (Scheme 1).

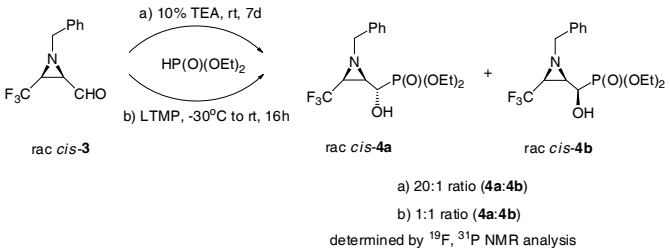
Aldehyde **3** was used directly to introduce C-P bond by two distinct methods, using different bases and conditions, to yield 1-hydroxyphosphonates (Scheme 2). In the first one, aldehyde **3** was subjected to the TEA-catalyzed (10%) addition of diethyl phosphite to carbonyl group to furnish phosphonates **4a** and **4b** with 77% isolated yield (20:1 ^{19}F, ^{31}P NMR ratio), which were very difficult to separate.[7h] In the second route, aldehyde **3** was used in the reaction with lithium diethyl phosphate, generated *in situ* from diethyl phosphite/LTMP, in dry THF at -30°C, to afford phosphonates **4a** and **4b** (1:1 ^{19}F, ^{31}P NMR ratio) with 84% isolated yield.[20]

^{19}F and ^{31}P NMR analysis of mixtures of **4a** and **4b** showed P-F coupling only for **4a** diastereomer $^5J_{P\text{-}F}$ = 2.6 Hz.



rac *cis*-**1** rac *cis*-**2** rac *cis*-**3**

Scheme 1 Reduction of the ester group of racemic aziridine **1** to alcohol **2** and Swern oxidation to corresponding aldehyde **3**.



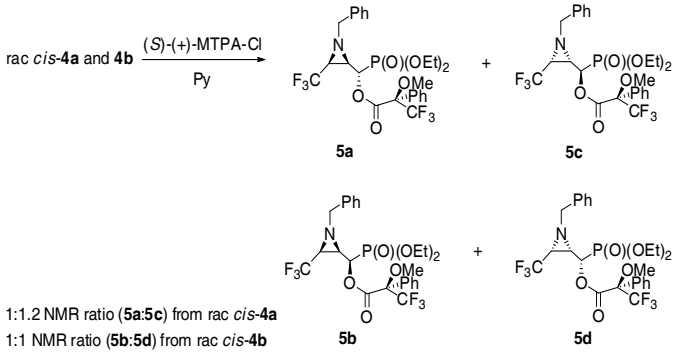
rac *cis*-**3** rac *cis*-**4a** rac *cis*-**4b**

Scheme 2 Addition of diethyl phosphite to carbonyl group of **3** by two methods, using different bases and conditions.

In order to determine geometry of phosphonates **4a** and **4b**, a reaction with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-(+)-MTPA-Cl] according to Mosher method was applied,[21] yielding two diastereomer **5a**, **5c** (1:1.2 ^1H, ^{31}P NMR ratio) from rac-**4a** and **5b**, **5d** (1:1 ^1H, ^{31}P NMR ratio) from rac-**4b**, respectively (Scheme 3).

According to the literature, for 1-hydroxyphosphonates exist two models for configuration assignment, using MTPA chloride.[22] The first method is double derivatization, in which one enantiomer of 1-hydroxyphosphonate is converted separately with two enantiomers (*S* and *R*) of MTPA chloride. Then the absolute configuration is assigned on the basis of the $\Delta\delta^{SR}$ signs.[23] The second method is performed with the mixture of enantiomers of 1-hydroxyphosphonate using only one enantiomer (*S* or *R*) of the MTPA chloride. Then the absolute configuration is assigned by comparison of the chemical shifts of the corresponding nuclei.[24]

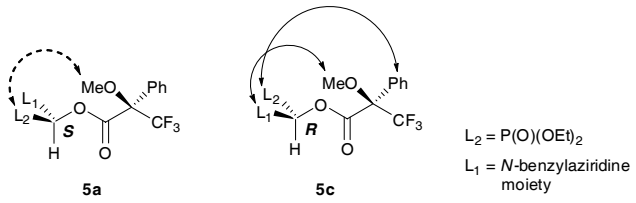
Using the second model, comparative ^{31}P NMR analysis of crude mixtures of (2*R*)-esters **5a**-**d** showed that chiral C1 carbon atom (in the phosphonate moiety) has configuration *S* for **5a** and **5d**, *R* for **5b** and **5c** (Table 1). It is due to the fact that dialkylphosphono group is situated on the same side of the plane as the phenyl ring of the MTPA ester moiety and it is more shielded and moves upfield (δ^R of **5b** and **5c**). When the dialkylphosphono group is on the opposite side of the plane as the phenyl ring of the MTPA ester moiety, the chemical shift of the phosphorus signal is located downfield (δ^S of **5a** and **5d**).[24,25]



1:1.2 NMR ratio (**5a**:**5c**) from rac *cis*-**4a**
1:1 NMR ratio (**5b**:**5d**) from rac *cis*-**4b**

Scheme 3 Reaction of aziridin-2-yl(hydroxy)phosphonates **4a** and **4b** with (*S*)-(+)-MTPA-Cl].

Table 1 Model for the assignment of the configuration of 1-hydroxyphosphonates **4a**, **4b** from the ^{1}H, ^{31}P NMR spectra of their (*R*)-MTPA on the basis of the shielding and deshielding effects.



^{31}P NMR [P(O)(OEt)$_2$]: $\delta^R < \delta^S$

^{1}H NMR (OMe): $\delta^R < \delta^S$

Entry	Product	^{31}P NMR[a]	^{1}H NMR[b]
1	2*R*-(1*S*,2*R*,3*S*)-**5a**	16.36 (dd)	3.59 (s)
2	2*R*-(1*R*,2*R*,3*S*)-**5b**	14.73 (s)	3.55 (s)
3	2*R*-(1*R*,2*S*,3*R*)-**5c**	16.04 (dd)	3.55 (s)
4	2*R*-(1*S*,2*S*,3*R*)-**5d**	15.21 (s)	3.63 (s)

[a] Chemical shifts of ^{31}P NMR in ppm ($CDCl_3$). [b] Chemical shifts of OMe group in ^{1}H NMR in ppm ($CDCl_3$)

Another diagnostic signals are observed for methoxy group of the MTPA esters moiety, when L1 substituent, in the α position to the phosphonate part, contains bulky aryl group. The methoxy group is more shielded by the aryl ring when both are on the same side of the MTPA plane (**5a** and **5d**). Beside, in the opposite enantiomer, the methoxy group is deshielded by the phosphorus substituent, which is on the same side of the plane (**5b** and **5c**).[24,26]

Moreover, when mixture of **4a**,**b** (1:1 NMR ratio) was used in this reaction, diastereomer rac-**4b** was proved to be more reactive, yielding **5a**,**c**:**5b**,**d** with 1:3.5 ratio (75% total yield; ^{1}H, ^{31}P NMR), due to less steric hindrance around the hydroxyl group (further distance from CF_3 group) than in case of **4a** (Figure 1,2).

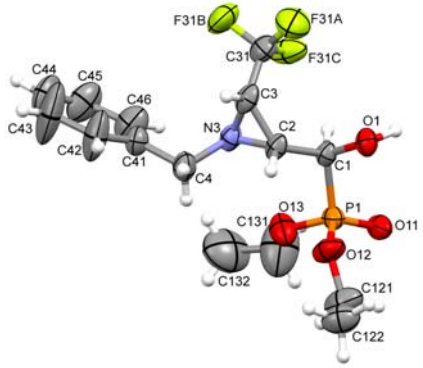


Figure 1 A perspective view of **4a** with numbering scheme. Ellipsoids are drawn at the 50% probability level, hydrogen atoms are represented by spheres of arbitrary radii (ORTEP).

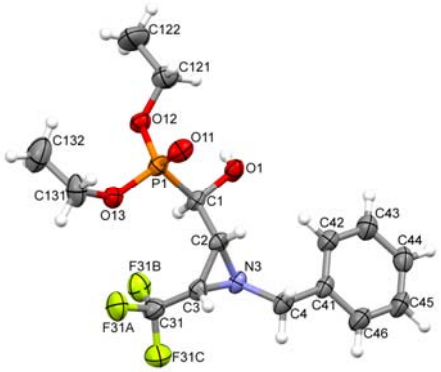


Figure 2 A perspective view of **4b** with numbering scheme. Ellipsoids are drawn at the 50% probability level, hydrogen atoms are represented by spheres of arbitrary radii (ORTEP).

The structure and relative stereochemistry of compounds **4a** and **4b** were determined by X-ray diffraction analysis. Interestingly, **4a** and **4b** crystallize with different shape, **4a** as a flat plate, **4b** as a needle. Both compounds crystallize in the stereosymmetric space which means, that both enantiomers are present in the crystals. Analysis of crystal structures of racemic diastereomers showed that phosphonates **4a** have *syn*/*cis* (*syn*/*syn*) conformation which is equal to (1*S*,2*R*,3*S*)-**4a** and (1*R*,2*S*,3*R*)-**4a** (Figure 1). Phosphonates **4b** have *anti*/*cis* (*anti*/*syn*) conformation which is equal to (1*R*,2*R*,3*S*)-**4b** and (1*S*,2*S*,3*R*)-**4b** (Figure 2).

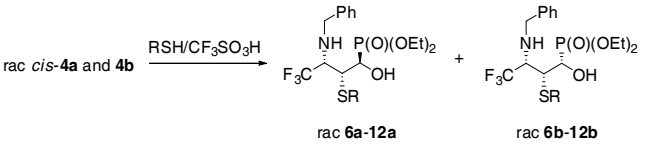
The reactivity of aziridine-2-phosphonates **4a** and **4b** was then investigated in nucleophilic ring opening reactions with representative number of thiols and catalyzed by the addition of trifluoromethanesulphonic acid.[27] A large excess of thiol was necessary. The yield was dramatically increased when 3 eqiv of thiol was used. The reaction provided a variety to number of sulfides **6a**,**b**-**12a**,**b** (Table 2) with regio- and diastereoselectivity. Reaction of *syn*/*cis* isomer **4a** led to *anti*/*syn* products **6a**-**12a**, whereas *anti*/*cis* isomer **4b** gave *syn*/*syn* products **6b**-**12b**. It is noteworthy that the major product of ring opening is always *anti*/*syn* isomer due to steric hindrance of bulky phosphonate group. Using mixture of **4a**,**b** (20:1 NMR ratio) led to obtain corresponding sulfides **6a**-**12a** with slightly better yields than from the mixture of **4a**,**b** (1:1 NMR ratio). Regio- and stereochemistry was confirmed by NMR analysis and X-ray crystal structure determination in case of racemic **6a** (Figure 3) and **8a.**

Compounds **6a**, **8a** crystallize in the centrosymmetric space groups, which means that both enantiomers are present in the crystals, with *R*(C1)-*R*(C2)-*S*(C3) (and *SSR*) combination of the chirality centers. Molecules **6a** and **8a** have very similar conformations (tables in supporting information list some relevant geometrical features).

In all the crystal structures the principal, directional interaction is the O-H···O11 hydrogen bond (table in supporting information); interestingly in **6a**, **8a** and **4a** the hydrogen bonds forming the centrosymmetric dimers are built of different enantiomers, while in **4b** the unichiral chains of

molecules along *y* directions are formed from a sole enantiomer (neighbouring chains are enantiomeric). In **6a** and **8a** additional N-H···O11 intermolecular hydrogen bonds add to the creation of crystal structures.

Table 2 Ring opening of aziridine-2-phosphonates **4a** and **4b** with thiols.



Entry	Substrate[a]	RSH[b]	Time [h]	Temp. [°C]	Isolated product	Yield[c] [%]
1	**4a**,**b**	4-FPhSH	3	90	**6a**	95
					6b	38
2	**4a**,**b**	4-MePhSH[d]	3	90	**7a**	84
					7b	32
3	**4a**,**b**	PhSH	3	90	**8a**	74
					8b	29
4	**4a**,**b**	BnSH	3	90	**9a**	80
					9b	26
5	**4a**,**b**	*i*-PnSH	3	90	**10a**	90
					10b	41
6	**4a**,**b**	*t*-BuSH	72	50	**11a**	60
					11b	14
7	**4a**,**b**	EtSH	48	25	**12a**	68
					12b	18

[a] Mixture of **4a**:**4b** (1:1, d.r). [b] 20 equiv of RSH were used. [c] Isolated yields of products **6a**-**12a** were calculated according to substrate **4a** and products **6b**-**12b** according to substrate **4b**. [d] 2 mL of CH_2Cl_2 was added to a reaction mixture, to dilute solid thiol.

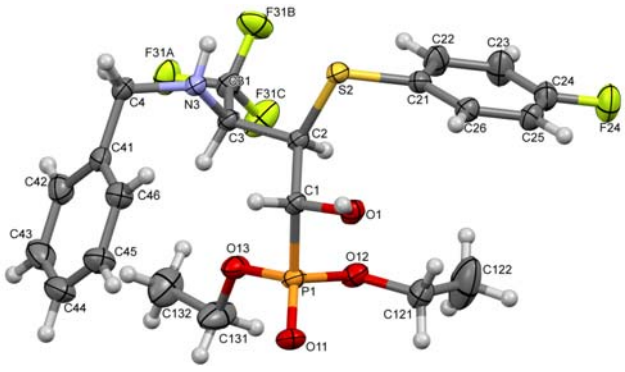


Figure 3 A perspective view of **6a** with numbering scheme. Ellipsoids are drawn at the 50% probability level, hydrogen atoms are represented by spheres of arbitrary radii (ORTEP).

Considering only a few examples of ring opening reactions of trifluoromethylated *N*-benzyl aziridines in the literature,[15a] we have tried to undergo ring opening reaction of aziridine-2-phosphonates with $BnNH_2$ and piperidine under acid conditions, in the presence of $Sc(OTf)_3$, $Yb(OTf)_3$, $Bi(OTf)_3$, PBu_3, $B(C_6F_5)_3$, $BiCl_3$, $TiCl_4$ and under basic conditions as well, using TEA as catalyst. Unfortunately, no ring opening occurred.

Conclusions

In summary, our results demonstrated synthesis of trifluoromethyl aziridine derivatives of phosphonates, as a mixture of diastereomers, by two distinct methods, different in diastereoselectivity. When equimolar amounts of strong and bulky base (LTMP) was used during addition reaction of diethyl phosphite to carbonyl group, reaction proceeded with lack of diastereoselectivity led to obtain two diastereomers in 1:1 ratio. Using catalytic amounts of TEA, at room temperature, reaction distinguished high diastereoselectivity, gave two diastereomers in 20:1 ratio. We suggest that, in the first method, the conditions of the reaction affect that kinetically controlled pathway reaction is favoured, when in the second method, the reaction carried out with thermodynamic control towards, almost purely, the major diastereomer. This study also explore the versatility of functionalized aziridines as building blocks for the phosphorylation of lateral groups by highly regio- and diastereoselectivity nucleophilic ring-opening under acidic conditions with aliphatic and aromatic thiols, that ultimately furnished γ-amino-γ-trifluoromethyl phosphonates. Further deprotection of amino group could be considered in a design of important trifluoromethyl phosphonated building blocks employed in the synthesis of useful compounds such as peptide analogs.

Experimental

General Methods

^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were performed on Varian GEMINI 300 (300 MHz), Varian 400 (400 MHz), Bruker ASCEND 400 (400 MHz), Bruker ASCEND 600 (600 MHz) and Bruker ULTRASHIELD 600 (600 MHz) spectrometers. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard (δ = 0) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ = 77.0). Chemical shifts of ^{19}F NMR were expressed in parts per million upfield from $CFCl_3$ as an internal standard (δ = 0) in $CDCl_3$. Chemical shifts of ^{31}P NMR were expressed in parts per million in $CDCl_3$. Low-resolution resolution mass spectra were recorded by electron impact (MS-EI) techniques using AMD-402 spectrometer. High-resolution resolution mass spectra were recorded by electron spray (MS-ESI) techniques using micrOToF-Q Bruker spectrometer. Reagent grade chemicals were used. Solvents were dried by refluxing with sodium metal-benzophenone (THF), with $CaCl_2$ (CH_2Cl_2), NaH (Et_2O) and distilled under argon

atmosphere. All moisture sensitive reactions were carried out under argon atmosphere using ovendried glassware. Reaction temperatures below 0°C were performed using a cooling bath (liquid N_2/hexane or CO_2/isopropanol). TLC was performed on Merck Kieselgel 60-F254 with EtOAc/ hexane and MeOH/ $CHCl_3$ as developing systems, and products were detected by inspection under UV light (254 nm) and with a solution of potassium permanganate. Merck Kieselgel 60 (230–400 mesh) was used for column chromatography. X-ray diffraction data were collected the ω-scan technique on Agilent Technologies four-circle on diffractometers: for **4a** and **4b** at room temperature on Xcalibur (Eos) with graphite-monochromatized MoKα radiation (λ=0.71073Å), for **6a** at 130(1) K, and for **8a** at room temperature on SuperNova (Atlas detector) with mirror-monochromatized CuKα radiation (λ=1.54178Å). The data were corrected for Lorentz-polarization and absorption effects.[28] Accurate unit-cell parameters were determined by a least-squares fit of 1219 (**4a**), 867 (**4b**), 1568 (**6a**) and 2213 (**8a**) reflections of highest intensity, chosen from the whole experiment. The structures were solved with SIR92[29] and refined with the full-matrix least-squares procedure on F^2 by SHELXL97.[30] Scattering factors incorporated in SHELXL97 were used. All non-hydrogen atoms were refined anisotropically, majority of hydrogen atoms were placed in the calculated positions, all H-atoms were then refined as 'riding model' with the isotropic displacement parameters set at 1.2 (1.5 for methyl groups) times the U_{eq} value for appropriate non-hydrogen atom. Only OH (**4a**, **6a**, **8a**) and NH (**6a**, **8a**) hydrogen atoms were located in difference Fourier maps and isotropically refined. Relevant crystal data are listed in tables in supporting information, together with refinement details.
Crystallographic data (excluding structure factors) for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, Nos. CCDC – 990787 (**4a**), CCDC - 990788 (**4b**), CCDC - 990786 (**6a**) and CCDC - 990785 (**8a**). Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44(1223)336-033, e-mail:deposit@ccdc.cam.ac.uk, or www: www.ccdc.cam.ac.uk.

Procedure of reduction of aziridine 1

Aziridine **1** (2.77 mmol, 756 mg) was added dropwise to a solution of $LiAlH_4$ (2.77, 105 mg) in anhydrous Et_2O (10 mL) under argon at -78°C and the reaction mixture was stirred for 5 hours and left overnight at room temperature. Then, the reaction mixture was cooled to 0°C and carefully quenched by dropwise addition of water (0.25 mL), followed by an aqueous 0.15N NaOH solution (0.25 mL). The reaction mixture was then diluted with H_2O (10 mL), extracted with Et_2O (4 x 10 mL) and the organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to gave 618 mg (96%) of product **2**, used in the next step without additional purification.
(1-Benzyl-3-(trifluoromethyl)aziridin-2-yl)methanol (rac *cis*-2): Pale yellow oil (500 mg, 82%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.40 – 7.25 (m, 5H, C_6H_5), 3.82 – 3.65 (m, 3H, CH_2OH, CHPh), 3.59 (d, 1H, J = 13.1 Hz, CHPh), 2.26 („pentet", 1H, J = 6.5 Hz, $CHCF_3$), 2.18 (br dd, 1H, J = 11.7, 6.8 Hz, $CHCHCF_3$), 1.77 – 1.69 (m, 1H, OH) ppm. ^{1}H {/^{19}F}NMR (600 MHz, $CDCl_3$) δ = 7.42 – 7.27 (m, 5H, C_6H_5), 3.76 (dd, 1H, J = 12.1, 4.7 Hz, CHOH) 3.73 – 3.67 (m, 2H, CHOH, CHPh), 3.64 (d, 1H, J = 13.3 Hz, CHPh), 2.26 (d, 1H, J = 6.5 Hz, $CHCF_3$), 2.18 (td, 1H, J = 6.9, 5.0 Hz, $CHCHCF_3$) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.03, 128.58, 128.19, 127.73 (4 x s, C_6H_5), 124.40 (q, J = 274.0 Hz, CF_3), 63.56 (s, CH_2Ph), 60.30 (q, J = 2.0 Hz, CH_2OH), 44.37 (s, $CHCHCF_3$), 41.68 (q, J = 39.4 Hz, $CHCF_3$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.09 (d, J = 6.2 Hz) ppm. MS (EI) m/z: 232 ($[M+H]^+$).

Procedure for Swern oxidation of 2

DMSO (2.60 mmol, 0.23 mL) was added dropwise to a stirred solution of oxalyl chloride (4.33 mmol, 0.31 mL) in CH_2Cl_2 (20 mL) under argon at -78°C and the reaction mixture was stirred for 5 min. Then a solution of aziridinyl alcohol **2** (2.16 mmol, 500 mg) in CH_2Cl_2 (2 mL) were added. After 30 min of stirring at -78°C, triethylamine (8.63 mmol, 1.2 mL) was added, and mixtures were allowed to warm to room temperature over 30 min. The reaction mixture was then diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were washed with 1% HCl (15 mL), H_2O (15 mL), 5% $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting crude aziridine carbaldehyde **3** was used in next step without additional purification.

Procedure for addition of diethyl phosphite to 3

Method a

A mixture of crude aldehyde **3** (2.16 mmol, 495 mg) and diethyl phosphite (2.59 mmol, 0.335 mL) containing triethylamine (0.23 mmol, 0.032 mL) was stirred at room temperature for 7 days. The crude product was isolated using column chromatography (chloroform/methanol 100:1, v/v) to give phosphonates **4a** and **4b** in unseparable mixture (20:1 ^{19}F, ^{31}P NMR ratio) (610 mg, 77%) as yellow oil, slowly crystallising.

Method b

Lithium 2,2,6,6-tetramethylpiperidine was prepared by adding of *n*-BuLi (2.16 mmol, 138 mg, 2 M in cyclohexane) to a stirred solution of 2,2,6,6-tetramethylpiperidine (2.16 mmol, 304 mg) in dry THF (25 mL) under an atmosphere of argon at -78°C. The solution was stirred for additional 30 min. Then a solution of diethyl phosphite (2.16 mmol, 0.276 mL) in THF (2 mL) was added dropwise to the reaction mixture at -78°C. After 15 min the solution was allowed to warm to room temperature over 30 min and then cooled to -30°C. Crude aldehyde **3** (2.16 mmol, 495 mg) in THF (2 mL) were added dropwise into the solution. After the addition, the reaction mixtures were slowly allowed to warm to room temperature and stirred overnight, quenched by addition of saturated solution of NH_4Cl (10 mL). Crude products were extracted to AcOEt (3 x10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified using column chromatography (chloroform/methanol 100:1, v/v) to give phosphonates **4a** and **4b** as a mixture (1:1

^{19}F, ^{31}P NMR ratio) (666 mg, 84%), which could not be separated by the chromatography techniques employed in this study. Another attempts of separation of **4a** and **4b** by column chromatography (hexane/ethyl acetate 70:30, v/v) led to two fractions of compounds **4a**:**4b** (4:1 ^{19}F, ^{31}P NMR ratio) and **4a**:**4b** (1:4 ^{19}F, ^{31}P NMR ratio).

Diethyl 1-benzyl-3-(trifluoromethyl)aziridin-2-yl)(hydroxy)methylphosphonate (rac *cis*-4a): Yellow oil, slowly crystallising (508 mg, 77% in two steps): ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.40 – 7.25 (m, 5H, C_6H_5), 4.25 – 4.10 (m, 5H, CH_3CH_2O, *CH*HPh), 3.87 (dd, 1H, *J* = 9.7, 5.6 Hz, C*H*P), 3.23 (d, 1H, *J* = 13.5 Hz, CH*H*Ph), 2.34 (br dd, 1H, *J* = 15.1, 6.3 Hz, C*H*CHCF$_3$), 2.17 („pentet", 1H, *J* = 6.1 Hz, C*H*CF$_3$), 1.35 and 1.33 (2 x t, 6H, *J* = 7.2 and 7.1 Hz, CH_3CH$_2$O) ppm ^{1}H {/^{19}F}NMR (403 MHz, $CDCl_3$) δ = 7.46 – 7.15 (m, 5H, C_6H_5), 4.27 – 4.13 (m, 5H, CH_3CH_2O, *CH*HPh), 3.87 (dd, 1H, *J* = 9.7, 6.3 Hz, C*H*P), 3.27 (d, 1H, *J* = 13.5 Hz, CH*H*Ph), 2.33 (dt, 1H, *J* = 9.6, 6.3 Hz, C*H*CHCF$_3$), 2.20 (d, 1H, *J* = 5.9 Hz, C*H*CF$_3$), 1.37 (m, 6H, CH_3CH$_2$O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.11, 128.57, 128.37, 127.61 (4 x s, C_6H_5), 124.39 (dq, *J* = 274.2, 0.8 Hz, *C*F$_3$), 65.99 (dd, *J* = 158.5, 1.4 Hz, *C*HP), 63.14 and 62.96 (2 x d, *J* = 7.0 Hz, CH_3CH_2O), 62.06 (s, CH_2Ph), 42.29 (d, *J* = 5.0 Hz, *C*HCHCF$_3$), 40.34 (dq, *J* = 39.0, 12.1 Hz, *C*HCF$_3$), 16.46 and 16.38 (2 x d, *J* = 5.4 Hz, CH_3CH_2O), ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.84 (dd, *J* = 5.3, 2.4 Hz) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 22.68 (d, *J* = 2.6 Hz) ppm. HRMS (ESI) calcd for $C_{15}H_{22}F_3NO_4P$ ($[M+H]^+$): 368.1233, found: 368.1173.

Diethyl 1-benzyl-3-(trifluoromethyl)aziridin-2-yl)(hydroxy)methylphosphonate (rac cis-4b): Yellow oil, slowly crystallising: ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.43 – 7.22 (m, 5H, C_6H_5), 4.25 – 4.05 (m, 4H, CH_3CH_2O), 3.92 (t, 1H, *J* = 8.1 Hz, C*H*P), 3.85 (d, 1H, *J* = 13.1 Hz, C*H*HPh), 3.56 (d, 1H, *J* = 13.2 Hz, CH*H*Ph), 2.40 – 2.34 (m, 1H, C*H*CHCF3), 2.31 („pentet", 1H, *J* = 6.4 Hz, C*H*CF$_3$), 1.33 and 1.31 (2 x t, 6H, *J* = 7.1 Hz, CH_3CH$_2$O) ppm. ^{1}H {/^{19}F}NMR (403 MHz, $CDCl_3$) δ = 7.40 – 7.25 (m, 5H, C_6H_5), 4.25 – 4.05 (m, 4H, CH_3CH_2O), 3.97 – 3.89 (m, 2H, C*H*HPh, C*H*P), 3.51 (d, 1H, *J* = 13.2 Hz, CH*H*Ph), 2.33 (dt, 1H, *J* = 9.0, 5.5 Hz, C*H*CHCF$_3$), 2.29 (d, 1H, *J* = 6.0 Hz, C*H*CF$_3$), 1.37 (m, 6H, CH_3CH$_2$O) ppm ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.52, 128.58, 128.54, 127.79 (4 x s, C_6H_5), 124.16 (q, *J* = 273.6 Hz, *C*F$_3$), 65.71 (dd, *J* = 165.8, 1.4 Hz, *C*HP), 63.54 (s, CH_2Ph), 63.19 and 62.94 (2 x d, *J* = 7.1 and 7.2 Hz, CH_3CH_2O), 44.53 (d, *J* = 8.6 Hz, *C*HCHCF$_3$), 42.39 (q, *J* = 39.6 Hz, *C*HCF$_3$), 16.35 and 16.31 (2 x d, *J* = 5.4 and 5.5 Hz, *C*H_3CH$_2$O) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -65.74 (d, *J* = 6.3 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ = 20.79 (s) ppm. HRMS (ESI) calcd for $C_{15}H_{21}F_3NO_4P$ ($[M+Na]^+$): 390.1053, found: 390.1065.

Procedure for preparation of Mosher esters from 4a,b

Mosher esters of **4a**,**b** were prepared according to Dale and Mosher method.[21] Thus, mixture of aziridinyl phosphonates **4a**,**b** (1:1 or 20:1 ^{19}F, ^{31}P NMR ratio) (0.14 mmol, 51 mg) was dissolved in the mixture of dry dichlorometane (5mL) and dry pyridine (0,72 mL) followed by addition of (*S*)-(+)MTPA-Cl (0.32 mmol, 0.06 mL) The mixture was left for 3 days at room temperature with slowly shaking. Then the excess of 3-dimethylamino-1-propylamine (1 mmol, 0.1 mL) was added and after 10 minutes reaction mixture was diluted with ethyl eter (15 mL) and washed once with cold diluted HCl and then water. Organic layer was dried over anhydrous $MgSO_4$ and evaporated. The 1:1 NMR ratio mixture of **4a**,**b** yielded **5a**,**c**:**5b**,**d** with 1:3.5 ^{1}H, ^{31}P NMR ratio, where the ratio of **5a:5c** was 1:1.2 and **5b:5d** was 1:1. The 20:1 NMR ratio mixture of **4a**,**b** yielded **5a**,**c**:**5b**,**d** with 20:1 ^{1}H, ^{31}P NMR ratio, where the ratio of **5a:5c** was 1:1.2 and **5b:5d** was 1:1.

General Procedure for ring opening of aziridynyl phosphonates (4a, 4b) with thiols

Aziridinyl phosphonates **4a**, **4b** (1:1 ^{19}F, ^{31}P NMR ratio) (0.14 mmol, 51 mg) were dissolved in an excess of thiol (2.8 mmol, 20 equiv) and then trifluoromethanesulfonic acid (0.16 mmol, 0.014 mL) was added. The solution was heated (Table 2) without any additional solvent (except reaction with 4-MePhSH which is solid at room temperature and addition of CH_2Cl_2 was needed). The reaction mixtures were then diluted with $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 20 mL) and the organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude products were isolated using column chromatography (chloroform/methanol 100:1, v/v).

Diethyl 3-(benzylamino)-4,4,4-trifluoro-2-(4-fluorophenylthio)-1-hydroxybutylphosphonate (rac 6a): Pale yellow crystals (32.9 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.62 (dd, 2H, *J* = 8.9, 5.2 Hz, SCC*H*), 7.40 – 7.25 (m, 5H, C_6H_5), 6.98 (dd, 2H, *J* = 8.7, 8.7 Hz SCCHC*H*), 4.33 – 4.08 (m, 6H, C*H*P, CH_3CH_2O, *CH*HPh), 3.86 (d, 1H, *J* = 12.3 Hz, CH*H*Ph), 3.82 (ddd, 1H, *J* = 8.4, 4.8, 1.8 Hz, C*H*S), 3.71 (br q, 1H, *J* = 6.8 Hz, C*H*CF$_3$), 1.34 and 1.32 (2 x t, 6H, *J* = 7.0 Hz, CH_3CH$_2$O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.49 (d, *J* = 248.1 Hz, *C*F), 138.17, 128.66, 128.44, 127.71 (4 x s, C_6H_5), 134.64 (d, *J* = 8.2 Hz, *C*HCHCF), 129.24 (d, *J* = 3.3 Hz, S*C*CHCHCF), 125.21 (dq, *J* = 287.8, 3.6 Hz, *C*F$_3$), 116.05 (d, *J* = 21.9 Hz, *C*HCF), 71.67 (d, *J* = 170.2 Hz, *C*HP), 63.54 and 62.44 (2 x d, *J* = 7.0 and 6.9 Hz, CH_3CH_2O), 61.46 (dq, *J* = 26.9, 12.2. Hz, *C*HCF$_3$), 53.95 (s, *C*HS), 51.77 (s, CH_2Ph), 16.39 and 16.34 (2 x d, *J* = 5.5 and 5.6 Hz, *C*H_3CH$_2$O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -114.09 – -113.97 (m), -69.11 (d, *J* = 6.8 Hz) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 20.49 (s) ppm. HRMS (ESI) calcd for $C_{21}H_{27}F_4NO_4PS$ ($[M+H]^+$): 496.1329, found: 496.1281.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-2-(4-fluorophenylthio)-1-hydroxybutylphosphonate (rac 6b): Pale yellow crystals (13.2 mg, 38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 (dd, 2H, *J* = 8.9, 5.2 Hz, SCC*H*), 7.40 – 7.25 (m, 5H, C_6H_5), 7.03 (dd, 2H, *J* = 8.8, 8.5 Hz SCCHC*H*), 4.69 (br q, 1H, *J* = 7.2 Hz, C*H*CF$_3$), 4.30 – 4.05 (m, 6H, C*H*P, CH_3CH_2O, *CH*HPh), 3.98 (d, 1H, *J* = 12.3 Hz, CH*H*Ph), 3.64 (dd, 1H, *J* = 5.0, 2.9 Hz, C*H*S), 1.34 and 1.29 (2 x t, 6H, *J* = 7.1 Hz, CH_3CH$_2$O) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.99 (d, *J* = 249.4 Hz, *C*F), 137.85, 128.78, 128.52, 127.88 (4 x s, C_6H_5), 135.99 (d, *J* = 8.4 Hz, *C*HCHCF), 127.70 (d, *J* = 3.3 Hz, S*C*CHCHCF), 125.03 (q, *J* = 287.6 Hz, *C*F$_3$),

116.37 (d, *J* = 17.4 Hz, *C*HCF), 71.46 (d, *J* = 159.0 Hz, *C*HP), 63.70 and 62.38 (2 x d, *J* = 6.9 and 7.5 Hz, CH_3CH_2O), 60.13 (q, *J* = 27.5 Hz, *C*HCF$_3$), 52.23 (s, *C*H$_2$Ph), 49.36 (d, *J* = 7.4 Hz, *C*HS), 16.50 and 16.38 (2 x d, *J* = 5.4 and 5.5 Hz, *C*H$_3$CH$_2$O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -112.80 – -112.66 (m), -68.67 (d, *J* = 6.8 Hz) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 20.94 (s) ppm. HRMS (ESI) calcd for $C_{21}H_{27}F_4NO_4PS$ ($[M+H]^+$): 496.1329, found: 496.1311.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(p-tolylthio)butylphosphonate (rac 7a): Pale yellow oil, slowly crystallising (28.9 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49 (d, 2H, *J* = 8.1 Hz, SCC*H*), 7.42 – 7.27 (m, 5H, C$_6$*H*$_5$), 7.10 (d, 2H, *J* = 7.9 Hz, SCCHC*H*), 4.32 – 4.07 (m, 6H, C*H*P, CH$_3$C*H*$_2$O, C*H*HPh), 3.91 – 3.83 (m, 2H, CH*H*Ph, C*H*S), 3.76 (dq, 1H, *J* = 7.2, 1.7 Hz, C*H*CF$_3$), 2.32 (s, 1H, PhC*H*$_3$), 1.35 and 1.32 (2 x t, 6H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.46, 128.58, 128.40, 127.57 (4 x s, *C*$_6$H$_5$), 137.72, 132.31, 130.47, 129.74 (4 x s, *C*$_6$H$_4$), 125.40 (dq, *J* = 287.8, 3.3 Hz, *C*F$_3$), 70.92 (d, *J* = 169.4 Hz, *C*HP), 63.42 and 62.47 (2 x d, *J* = 7.0 and 6.8 Hz, CH$_3$*C*H$_2$O), 61.14 (dq, *J* = 26.9, 10.7. Hz, *C*HCF$_3$), 53.87 (s, *C*HS), 51.82 (s, *C*H$_2$Ph), 21.02 (s, Ph*C*H$_3$), 16.37 and 16.33 (2 x d, *J* = 5.6 and 5.8 Hz, *C*H$_3$CH$_2$O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.27 (s) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 20.79 (s) ppm. HRMS (ESI) calcd for $C_{22}H_{30}F_3NO_4PS$ ($[M+H]^+$): 492.1580, found: 492.1554.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(p-tolylthio)butylphosphonate (rac 7b): Pale yellow oil, slowly crystallising (8.5 mg, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42 – 7.25 (m, 7H, C$_6$*H*$_5$, SCC*H*), 7.12 (d, 2H, *J* = 8.5 Hz SCCHC*H*), 4.68 (br q, 1H, *J* = 7.2 Hz, C*H*CF$_3$), 4.29 – 4.03 (m, 6H, C*H*P, CH$_3$C*H*$_2$O, C*H*HPh), 3.97 (d, 1H, *J* = 12.3 Hz, CH*H*Ph), 3.68 (dd, 1H, *J* = 4.8, 2.5 Hz, C*H*S), 2.34 (s, 3H, PhC*H*$_3$), 1.36 and 1.28 (t, 6H, *J* = 7.0 and 7.1 Hz, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.58, 128.77, 128.41, 127.75 (4 x s, *C*$_6$H$_5$), 138.35, 133.60, 130.05, 129.82 (4 x s, *C*$_6$H$_4$), 125.23 (q, *J* = 287.7 Hz, *C*F$_3$), 71.74 (d, *J* = 158.0 Hz, *C*HP), 63.59 and 62.34 (2 x d, *J* = 6.9 and 7.5 Hz, CH$_3$*C*H$_2$O), 60.32 (dq, *J* = 27.4, 1.3. Hz, *C*HCF$_3$), 52.23 (s, *C*H$_2$Ph), 48.88 (dd, *J* = 7.3, 1.3 Hz, *C*HS), 21.14 (s, Ph*C*H$_3$), 16.50 and 16.39 (2 x d, *J* = 5.4 Hz, *C*H$_3$CH$_2$O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -68.74 (s) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 21.24 (s) ppm. HRMS (ESI) calcd for $C_{22}H_{30}F_3NO_4PS$ ($[M+H]^+$): 492.1580, found: 492.1571.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(phenylthio)butylphosphonate (rac 8a): Pale yellow crystals (24.7 mg, 74%): ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.62 – 7.20 (2 x m, 10H, C$_6$*H*$_5$), 4.31 – 4.07 (m, 6H, C*H*P, CH$_3$C*H*$_2$O, C*H*HPh), 3.94 (ddd, 1H, *J* = 9.1, 5.4, 1.8 Hz, C*H*S), 3.88 (d, 1H, *J* = 12.8 Hz, CH*H*Ph), 3.76 (dq, 1H, *J* = 7.0, 1.7 Hz, C*H*CF$_3$), 1.33 and 1.30 (2 x t, 6H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.23, 128.67, 128.49, 127.61 (4 x s, *C*$_6$H$_5$), 134.08, 132.05, 129.00, 127.70 (4 x s, S*C*$_6$H$_5$), 125.28 (q, *J* = 287.8 Hz, *C*F$_3$), 71.23 (d, *J* = 169.6 Hz, *C*HP), 63.52 and 62.53 (2 x d, *J* = 6.8 Hz, CH$_3$*C*H$_2$O), 61.33 (dq, *J* = 27.8, 11.6. Hz, *C*HCF$_3$), 53.32 (s, *C*HS), 51.83 (s, *C*H$_2$Ph), 16.41 and 16.37 (2 x d, *J* = 5.6 and 5.5 Hz, *C*H$_3$CH$_2$O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.34 (d, *J* = 7.0 Hz) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 20.60 (s) ppm. HRMS (ESI) calcd for $C_{21}H_{28}F_3NO_4PS$ ($[M+H]^+$): 478.1423, found: 478.1378.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(phenylthio)butylphosphonate (rac 8b): Pale yellow crystals (9.7 mg, 29%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.51 – 7.25 (2 x m, 10H, C$_6$*H*$_5$), 4.70 (br q, 1H, *J* = 6.9 Hz, C*H*CF$_3$), 4.30 – 4.02 (m, 6H, C*H*P, CH$_3$C*H*$_2$O, C*H*HPh), 3.98 (d, 1H, *J* = 12.4 Hz, CH*H*Ph), 3.76 (br dd, 1H, *J* = 4.7, 3.0 Hz, C*H*S), 1.34 and 1.33 (2 x t, 6H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.22, 128.77, 128.44, 127.79 (4 x s, *C*$_6$H$_5$), 133.10, 132.86, 129.26, 128.05 (4 x s, S*C*$_6$H$_5$), 125.19 (q, *J* = 287.7 Hz, *C*F$_3$), 71.89 (d, *J* = 158.3 Hz, *C*HP), 63.63 and 62.35 (2 x d, *J* = 6.9 and 7.5 Hz, CH$_3$*C*H$_2$O), 60.23 (q, *J* = 27.0 Hz, *C*HCF$_3$), 52.24 (s, *C*H$_2$Ph), 48.65 (d, *J* = 7.5 Hz, *C*HS), 16.49 and 16.38 (2 x d, *J* = 5.4 and 5.5 Hz, *C*H$_3$CH$_2$O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -68.81 (d, *J* = 7.0 Hz) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 21.06 (s) ppm. HRMS (ESI) calcd for $C_{21}H_{28}F_3NO_4PS$ ($[M+H]^+$): 478.1423, found: 478.1449.

Diethyl 3-(benzylamino)-2-(benzylthio)-4,4,4-trifluoro-1-hydroxybutylphosphonate (rac 9a): Pale yellow oil (27.5 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 – 7.21 (2 x m, 10H, C$_6$*H*$_5$), 4.24 – 4.00 (m, 6H, C*H*P, CH$_3$C*H*$_2$O, NC*H*HPh), 3.89 (s, 2H, SC*H*$_2$Ph), 3.83 (d, 1H, *J* = 12.8 Hz, NCH*H*Ph), 3.81 – 3.71 (m, 1H, C*H*CF$_3$), 3.47 (ddd, 1H, *J* = 10.0, 6.3, 1.8 Hz, C*H*S), 1.32 and 1.30 (2 x t, 6H, *J* = 6.8 Hz, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.65, 136.91, 129.18, 128.60, 128.54, 128.37, 127.52, 127.48 (8 x s, *C*$_6$H$_5$), 125.73 (dq, *J* = 287.7, 2.5 Hz, *C*F$_3$), 70.04 (d, *J* = 168.3 Hz, *C*HP), 63.34 and 62.51 (2 x d, *J* = 7.0 and 6.7 Hz, CH$_3$*C*H$_2$O), 60.77 (dq, *J* = 26.4, 9.6. Hz, *C*HCF$_3$), 51.88 (s, *C*HS), 48.54 (s, NC*H*$_2$Ph), 37.94 (s, SC*H*$_2$Ph), 16.44 and 16.40 (2 x d, *J* = 5.4 and 5.5 Hz, *C*H$_3$CH$_2$O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.83 (br s) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 21.00 (s) ppm. HRMS (ESI) calcd for $C_{22}H_{30}F_3NO_4PS$ ($[M+H]^+$): 492.1580, found: 492.1564.

Diethyl 3-(benzylamino)-2-(benzylthio)-4,4,4-trifluoro-1-hydroxybutylphosphonate (rac 9b): Pale yellow oil (8.9 mg, 26%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40 – 7.18 (2 x m, 10H, C$_6$*H*$_5$), 4.59 (br q, 1H, *J* = 6.9 Hz, C*H*CF$_3$), 4.25 – 3.85 (m, 8H, C*H*P, CH$_3$C*H*$_2$O, C*H*S, NC*H*HPh, NCH*H*Ph), 3.81 (s, 2H, SC*H*$_2$Ph), 1.32 (t, 3H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.27 – 1.20 (m, 3H, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.32, 136.93, 129.17, 128.73, 128.61, 128.40, 127.71, 127.43 (8 x s, *C*$_6$H$_5$), 125.32 (q, *J* = 287.9 Hz, *C*F$_3$), 73.45 (d, *J* = 157.9 Hz, *C*HP), 63.60 and 62.14 (2 x d, *J* = 6.9 and 7.5 Hz, CH$_3$*C*H$_2$O), 59.87 (q, *J* = 26.8 Hz, *C*HCF$_3$), 51.95 (s, NC*H*$_2$Ph), 43.00 (d, *J* = 7.0 Hz, *C*HS), 36.50 (s, SC*H*$_2$Ph), 16.50 and 16.39 (2 x d, *J* = 5.4 and 5.6 Hz, *C*H$_3$CH$_2$O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -68.69 (br s) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 20.50 (s) ppm. HRMS (ESI) calcd for $C_{22}H_{30}F_3NO_4PS$ ($[M+H]^+$): 492.1580, found: 492.1581.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(isopentylthio)butylphosphonate (rac 10a): Pale yellow oil (25.8 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 – 7.18 (m,

5H, C_6H_5), 4.20 – 3.89 (m, 6H, C*H*P, CH_3CH_2O, C*H*HPh), 3.77 (d, 1H, *J* = 12.8 Hz, CH*H*Ph), 3.68 (br q, 1H, *J* = 6.8 Hz, C*H*CF_3), 3.34 (ddd, 1H, *J* = 9.7, 6.5, 1.4 Hz, C*H*S), 2.64 – 2.56 (m, 2H, SCH_2), 1.65 – 1.50 (m, 1H, $(CH_3)_2CH$), 1.44 – 1.34 (m, 2H, SCH_2CH_2), 1.27 and 1.26 (2 x t, 6H, *J* = 7.1 Hz, CH_3CH_2O), 0.82 and 0.81 (2 x d, 6H, *J* = 6.5 Hz, $(CH_3)_2CH$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.75, 128.48, 128.33, 127.43 (4 x s, C_6H_5), 124.39 (dq, *J* = 288.1, 2.5 Hz, *C*F_3), 69.72 (d, *J* = 168.8 Hz, *C*HP), 63.18 and 62.43 (2 x d, *J* = 7.0 and 6.8 Hz, CH_3CH_2O), 60.64 (dq, *J* = 26.3, 8.9. Hz, *C*HCF_3), 51.78 (s, *C*H_2Ph), 49.71 (s, *C*HS), 38.36 (s, SCH_2CH_2), 32.05 (s, SCH_2), 27.24 (s, $(CH_3)_2CH$), 22.19 and 22.01 (2 x s, $(CH_3)_2CH$), 16.39 and 16.34 (2 x d, *J* = 5.6, *C*H_3CH_2O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.81 (d, *J* = 7.1 Hz) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 21.13 (s) ppm. HRMS (ESI) calcd for $C_{20}H_{34}F_3NO_4PS$ ($[M+H]^+$): 472.1893, found: 472.1884.

Diethyl 3-(benzylamino)-4,4,4-trifluoro-1-hydroxy-2-(isopentylthio)butylphosphonate (rac 10b): Pale yellow oil (11.8 mg, 41%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37 – 7.27 (m, 5H, C_6H_5), 4.56 (br q, 1H, *J* = 6.9 Hz, C*H*CF_3), 4.30 – 4.15 (m, 5H, C*H*P, CH_3CH_2O), 4.05 (d, 1H, *J* = 12.3 Hz, C*H*HPh), 3.94 (d, 1H, *J* = 12.4 Hz, CH*H*Ph), 3.34 (br dd, 1H, *J* = 4.8, 2.9 Hz, C*H*S), 2.64 (br t, 2H, *J* = 7.6 Hz, SCH_2), 1.72 – 1.59 (m, 1H, $(CH_3)_2CH$), 1.45 (dd, 2H, *J* = 15.2, 6.9 Hz, SCH_2CH_2), 1.37 and 1.36 (2 x t, 6H, *J* = 7.1 Hz, CH_3CH_2O), 0.89 (d, 6H, *J* = 6.6 Hz, $(CH_3)_2CH$) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.47, 128.72, 128.37, 127.67 (4 x s, C_6H_5), 125.36 (q, *J* = 287.8 Hz, *C*F_3), 73.52 (d, *J* = 157.5 Hz, *C*HP), 63.55 and 62.34 (2 x d, *J* = 7.0 and 7.5 Hz, CH_3CH_2O), 59.91 (q, *J* = 27.3 Hz, *C*HCF_3), 51.85 (s, *C*H_2Ph), 44.41 (d, *J* = 5.1 Hz, *C*HS), 38.27 (s, SCH_2CH_2), 30.86 (s, SCH_2), 27.26 (s, $(CH_3)_2CH$), 22.26 and 22.11 (2 x s, $(CH_3)_2CH$), 16.54 and 16.49 (2 x d, *J* = 5.6, *C*H_3CH_2O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -68.83 (d, *J* = 7.2 Hz) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 21.04 (s) ppm. HRMS (ESI) calcd for $C_{20}H_{34}F_3NO_4PS$ ($[M+H]^+$): 472.1893, found: 472.1864.

Diethyl 3-(benzylamino)-2-(tert-butylthio)-4,4,4-trifluoro-1-hydroxybutylphosphonate (rac 11a): Pale yellow oil (19.2 mg, 60%): ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.40 – 7.27 (m, 5H, C_6H_5), 4.20 – 4.05 (m, 5H, CH_3CH_2O, C*H*HPh), 3.87 – 3.78 (m, 2H, C*H*CF_3, CH*H*Ph), 3.59 (dd, 1H, *J* = 10.1, 2.4 Hz, C*H*P), 3.53 (ddd, 1H, *J* = 14.4, 10.1, 1.1 Hz, C*H*S), 1.35 – 1.28 (m, 15H, $(CH_3)_3C$, CH_3CH_2O) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.33, 128.40, 128.37, 127.26 (4 x s, C_6H_5), 126.32 (q, *J* = 287.5 Hz, *C*F_3), 64.99 (d, *J* = 166.1 Hz, *C*HP), 62.88 and 62.70 (2 x d, *J* = 7.1 and 6.6 Hz, *C*H_3CH_2O), 58.97 (q, *J* = 26.3 Hz, *C*HCF3), 52.04 (s, *C*H_2Ph), 46.79 (s, *C*HS), 44.92 (s, *C*$(CH_3)_3$), 31.48 (s, C(*C*$H_3)_3$), 16.38 and 16.36 (2 x d, *J* = 5.9 and 5.7 Hz, *C*H_3CH_2O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.99 (d, *J* = 7.2 Hz) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 22.92 (s) ppm. HRMS (ESI) calcd for $C_{19}H_{32}F_3NO_4PS$ ($[M+H]^+$): 458.1736, found: 458.1691.

Diethyl 3-(benzylamino)-2-(tert-butylthio)-4,4,4-trifluoro-1-hydroxybutylphosphonate (rac 11b): Pale yellow oil (4.5 mg, 14%): ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.35 – 7.25 (m, 5H, C_6H_5), 4.65 (br q, 1H, *J* = 6.9 Hz, C*H*CF_3), 4.32 – 4.02 (m, 6H, C*H*P, CH_3CH_2O, C*H*HPh), 3.92 (d, 1H, *J* = 12.5 Hz, CH*H*Ph), 3.40 (br s, 1H, C*H*S), 1.37 – 1.21 (m, 15, CH_3CH_2O, $(CH_3)_3C$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.10, 128.73, 128.59, 127.88 (4 x s, C_6H_5), 129.50 – 120.50 (m, *C*F_3), 79.00 – 75.00 (m, *C*HP), 63.64 and 62.19 (2 x d, *J* = 6.8 and 6.9 Hz, CH_3CH_2O), 61.00 – 59.00 (m, *C*HCF_3), 51.96 (s, *C*H_2Ph), 44.96 (s, *C*HS), 40.05 (s, *C*$(CH_3)_3$), 30.94 (s, C(*C*$H_3)_3$), 16.50 and 16.48 (2 x d, *J* = 5.7 and 5.4 Hz, *C*H_3CH_2O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -68.73 (br s) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 20.74 (s) ppm. HRMS (ESI) calcd for $C_{19}H_{32}F_3NO_4PS$ ($[M+H]^+$): 458.1736, found: 458.1716.

Diethyl 3-(benzylamino)-2-(ethylthio)-4,4,4-trifluoro-1-hydroxybutylphosphonate (rac 12a): Pale yellow oil (20.4 mg, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39 – 7.24 (m, 5H, C_6H_5), 4.26 – 3.95 (m, 6H, C*H*P, CH_3CH_2O, C*H*HPh), 3.85 (d, 1H, *J* = 12.8 Hz, CH*H*Ph), 3.76 (br q, 1H, *J* = 7.3 Hz, C*H*CF_3), 3.45 (ddd, 1H, *J* = 9.9, 6.3, 1.4 Hz, C*H*S), 2.70 (q, 2H, *J* = 7.4 Hz, SCH_2CH_3), 1.32 and 1.30 (2 x t, 6H, *J* = 7.0 Hz, CH_3CH_2O), 1.25 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.18, 128.60, 128.52, 127.66 (4 x s, C_6H_5), 125.63 (q, *J* = 287.8 Hz, *C*F_3), 69.78 (d, *J* = 168.3 Hz, *C*HP), 63.36 and 62.53 (2 x d, *J* = 7.0 and 6.8 Hz, CH_3CH_2O), 60.72 (dq, *J* = 26.7, 9.5 Hz, *C*HCF_3), 51.75 (s, *C*H_2Ph), 48.92 (s, *C*HS), 27.97 (s, SCH_2CH_3), 16.44 and 16.38 (2 x d, *J* = 5.9 and 6.0 Hz, *C*H_3CH_2O, 14.59 (s, SCH_2CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.69 (br s) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 21.09 (s) ppm. HRMS (ESI) calcd for $C_{17}H_{28}F_3NO_4PS$ ($[M+H]^+$) 430.1423, found 430.1427.

Diethyl 3-(benzylamino)-2-(ethylthio)-4,4,4-trifluoro-1-hydroxybutylphosphonate (rac 12b): Pale yellow oil (5.4 mg, 18%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43 – 7.24 (m, 5H, C_6H_5), 4.60 (br q, 1H, *J* = 6.9 Hz, C*H*CF_3), 4.33 – 4.05 (m, 6H, C*H*P, CH_3CH_2O, C*H*HPh), 3.98 (d, 1H, *J* = 12.4 Hz, CH*H*Ph), 3.39 (br s, 1H, C*H*S), 2.67 (q, 2H, *J* = 7.4 Hz, SCH_2CH_3), 1.36 and 1.35 (2 x t, 6H, *J* = 7.1 Hz, CH_3CH_2O), 1.25 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.25, 128.70, 128.39, 127.69 (4 x s, C_6H_5), 125.26 (q, *J* = 287.8 Hz, *C*F_3), 73.43 (d, *J* = 158.5 Hz, *C*HP), 63.55 and 62.35 (2 x d, *J* = 7.0 and 7.4 Hz, CH_3CH_2O), 59.89 (q, *J* = 27.5 Hz, *C*HCF_3), 51.84 (s, *C*H_2Ph), 43.94 (br s, *C*HS), 26.75 (s, SCH_2CH_3), 16.53 and 16.48 (2 x d, *J* = 5.1 and 5.4 Hz, *C*H_3CH_2O), 14.43 (s, SCH_2CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -68.52 (br s) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ = 20.99 (s) ppm. HRMS (ESI) calcd for $C_{17}H_{28}F_3NO_4PS$ ($[M+H]^+$): 430.1423, found: 430.1462.

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