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Functionalization of α-hydroxyphosphonates as a convenient route to *N*-tosyl-α-aminophosphonates†

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Direct conversion of the α-hydroxyl group by *para*-toluenesulfonamide to yield α-(*N*-tosyl) aminophosphonates is reported. α-Aminophosphonates **23a,b–37a,b** were obtained from the corresponding α-hydroxyphosphonates **6a,b–21a,b** in the presence of K_2CO_3, *via* the retro-Abramov reaction of the appropriate aldehydes, **1–5**. The subsequent formation of imines with simultaneous addition of diethyl phosphite provided access to the α-sulfonamide phosphonates **23a,b–37a,b** with better diastereoselectivity than in the case of the Pudovik reaction. The mechanism for this transformation is proposed herein. When Cbz *N*-protected aziridine **9a,b** and phenylalanine analogue **12a,b** were exploited, intramolecular substitution was observed, leading to the corresponding epoxide **38** as the sole product, or oxazolidin-2-one **39** as a minor product. Analogous substitution was not observed in the case of proline **18a,b** and serine **21a,b** derivatives.

Introduction

α-Sulfonamide phosphonates constitute a very interesting class of compounds. They can be potential candidates for fluorescent-β-lactamase[1] and matrix metalloproteinase (MMPs) inhibitors[2] such as compounds containing carboxylate and hydroxamate moieties, which are well known MMP inhibitors. Moreover, these compounds are promising substrates for the synthesis of *N*-deprotected α-aminophosphonates, which are important isosteres of α-amino acids, possessing a wide range of biological activities. They act as antibiotics, herbicides, antifungal agents, enzyme inhibitors, and pharmacological agents.[3]

There are several routes for the synthesis of α-aminophosphonates. One of the most important protocols is the Kabachnik–Fields (or phospha-Mannich) reaction involving the condensation of dialkyl phosphite, carbonyl compounds and primary or secondary amines;[4] however, the reaction mechanism is still under investigation.[5] There are several other possibilities for the preparation of α-aminophosphonates, among which a very convenient route is the addition of phosphite nucleophiles to imines or enamines.[6] The major disadvantage of this approach is the stability of the imine/enamine prepared from the aliphatic amine. Transformation of the α-hydroxyphosphonates seems to provide an encouraging method for achieving α-aminophosphonates. These compounds are easily obtained using the Abramov reaction[7] and its modifications,[8] giving access to the synthesis of different types of α-functionalized phosphonates.[9]

α-Hydroxyphosphonates exhibit interesting medicinal properties as potential antibacterial, antiviral and anticancer agents,[10] as well as enzyme inhibitors such as protease, EPSP synthase, human rennin, human calpain I and tyrosine-specific protein kinase.[11] Among the methods of synthesis of α-aminophosphonates utilizing α-hydroxyphosphonates, Mitsunobu azidation followed by the Staudinger reduction is commonly applied with good yields and is well-known in the literature.[12] Unfortunately, using the volatile and highly toxic hydrazoic acid is the main disadvantage of this method. Another type of conversion of α-hydroxyphosphonates into α-aminophosphonates is nucleophilic substitution at C1, but this method is rather difficult due to the hindered hydroxy function,[13] although substitution of the hydroxyl group in primary α-hydroxyphosphonates by a good leaving group, *e.g.* triflate,[14] mesylate,[15] tosylates,[16] or *via* acid-mediated displacement,[17] has been described in the literature. To our knowledge, only one paper reported the substitution of the hydroxyl group by an amine at the secondary centre, under microwave-assisted and solvent-free conditions.[18]

In the literature there exist methods of conversion of primary α-hydroxyphosphonates to α-amino analogues, such as

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intramolecular cyclodehydration *via* the alkoxyphosphonium salt[19] or phosphonation *via* the retro-Abramov reaction,[13d] which is an effort to explain the Kabachnik–Fields reaction mechanism (Scheme 1).

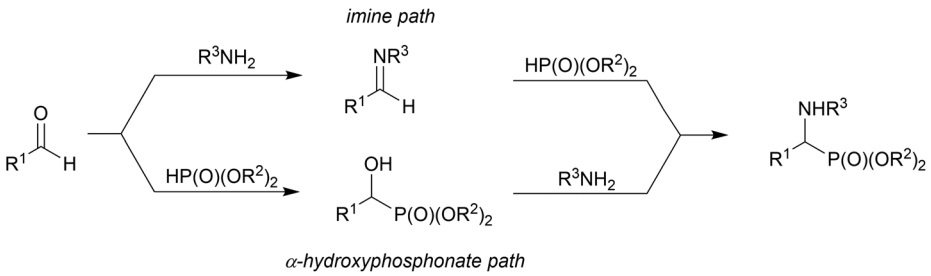
In this mechanism, one possibility is that an imine is formed from the carbonyl compound and primary amine (or iminium salt when a secondary amine is applied). Then, the addition reaction of dialkyl phosphite to the imine leads to α-aminophosphonate.[4b] The second possibility is based on the amine promoted (especially by the highly basic amines) addition of dialkyl phosphite to the carbonyl group, leading to α-hydroxyphosphonate, in a reversible step, and then nucleophilic substitution of the hydroxyl group by an amine moiety.[20] The first approach is based on the reversibility of the addition of dialkyl phosphite to the carbonyl group (retro-Abramov reaction) with subsequent irreversible imine formation followed by immediate dialkyl phosphite addition.[21] The second approach argues that α-aminophosphonates are obtained at high temperatures. During heating, the disappearance of the α-hydroxyphosphonate in favour of the α-aminophosphonate formation is postulated.[22] On the basis of kinetic studies, it is suggested that the mechanism depends on the nature of the reacting substrates.[5a] The reaction of benzaldehyde, aniline and dialkyl phosphite supports the imine pathway. The formation of the hydrogen bond between the phosphoryl group of the dialkyl phosphite and amine promotes the formation of imine without additional catalyst.[23] On the other hand, aniline is too weak a base to promote the addition of dialkyl phosphite to the carbonyl group. Cherkasov *et al.* performed the reaction of the more nucleophilic cyclohexylamine with benzaldehyde and dialkyl phosphite and they suggested the hydroxyphosphonate path where the amine was basic enough to interact with the hydrogen of the phosphite to promote the attack of phosphite on the carbonyl carbon.[5a,24] Subsequent papers provided more evidence supporting the imine pathway, even when hard nucleophilic amines were applied to the reaction.[24,25]

Results and discussion

In the course of our studies, we were able to synthesize a wide range of α-hydroxyphosphonates that were subsequently used in reactions with *para*-toluenesulfonamide towards obtaining α-aminophosphonate derivatives.

As the convenient starting materials, the *N*-protected amino aldehydes such as aziridine **1**, as well as aldehydes **2–5** originating from amino acids, possessing various amino protecting groups, *e.g.* benzyl (Bn) **1a–5a**, *tert*-butoxycarbonyl (Boc) **2b–5b**, carboxybenzyl (Cbz) **2c–5c** were chosen. All aldehydes were prepared from the corresponding alcohols according to the literature data (see Experimental section). The introduction of a new C–P bond, yielding α-hydroxyphosphonates, was conducted by the three main methodologies. First, aldehydes **1a**, **2**, **3** were used in the reactions with lithium diethyl phosphite in dry THF at −30 °C. This strategy afforded phosphonates **6a,b**, **10a,b–12a,b** and **13a,b–15a,b**. The yields varied from moderate in the case of (*S*)-phenylalanine **10a,b–12a,b** and (*S*)-valine analogues **13a,b–15a,b**, to very good for aziridines **6a,b**, while the diastereoselectivity of this reaction varied from poor in the case of **6a,b**, to very good for **10a,b**. Moreover, phosphonates **6a,b** were transformed to *N*-unprotected α-hydroxyphosphonates **7a,b** with the subsequent introduction of the protecting groups, Boc **8a,b** and Cbz **9a,b**. In the case of transformations of **7a,b** yielding **9a,b**, due to steric hindrance between the Cbz group and the phosphonate moiety in **9a**, we observed a small predominance of diastereoisomer **9b** (1 : 1.2, d.r. ^{19}F, ^{31}P NMR). Thus, the stereochemistry of aziridine **9a** was analogous to the major diastereoisomer of **6a** and parallel to a study reported previously (for comparison see Fig. 1 and *N*-benzyl protected aziridines **6a,b**).[26] In the case of Boc protected aziridine, the reaction gave only one diastereoisomer **8b** as the sole product, where **7a** was left unreacted in the reaction mixture. Moreover, **8b** existed as a mixture of two rotamers (1.9 : 1 NMR ratio) that could be separated by chromatography techniques. In the second route, the TEA-catalyzed addition of $HP(O)(OEt)_2$ to appropriate aldehydes at room temperature with 0.1 eq. TEA or 0.2 eq. TEA at r.t. or 50 °C led to products **6a,b**, **17a,b–21a,b**, in yields ranging from moderate for **19a,b** to excellent in the case of **20a,b**; there was also good diastereoselectivity for **18a,b** and excellent diastereoselectivity in the case of aziridines **6a,b** and serine analogues **20a,b**. Only in case of the synthesis of **16a,b** was the application of *i*-Pr_2EtN needed (Table 1).

The stereochemistry of the addition of dialkyl phosphite to *N*-protected (*S*)-amino aldehydes [or (*R*)- in the case of **4c**] was a consequence of the steric hindrance on the adjacent stereogenic centre. Moreover, the Pudovik reaction conducted on *N*-protected aldehydes **2**, **3** derived from phenylalanine and valine led to anti addition, giving rise to major diastereoisomers (1*R*,2*S*) according to the data reported for nucleophilic additions to (*N*,*N*-dibenzylamino)aldehydes.[27] These assumptions



Scheme 1 Kabachnik–Fields reaction.

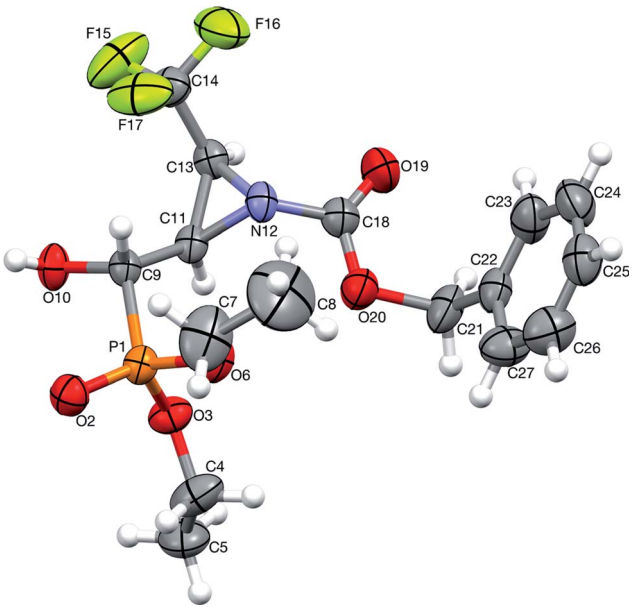


Fig. 1 A perspective view of **9a**, showing the numbering scheme. Ellipsoids were drawn at the 30% probability level, hydrogen atoms are represented by spheres of arbitrary radii.

were confirmed by the absolute stereochemistry of compound **10a** determined by X-ray diffraction analysis (Fig. 2).

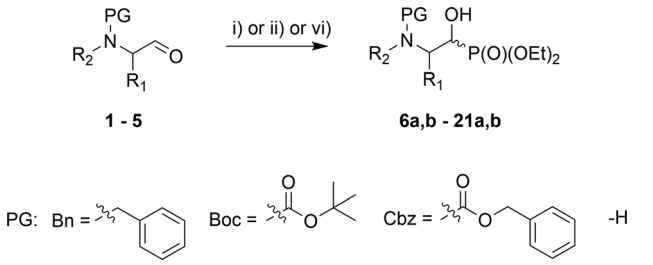
At the same time, the addition performed on (2*S*)-prolinal and (4*S*)-serial derivatives yielded (1*R*,2*S*)**16a–17a**, and (*R*,4*S*) **19a–21a** as major diastereoisomers, confirmed by NOESY experiments or X-ray diffraction analysis. The diastereoselectivity of the Pudovik reaction in the case of **20a,b–21a,b** was analogous to that obtained by Wróblewski *et al.*[28]

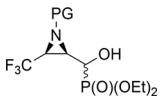
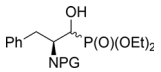
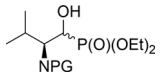
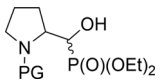
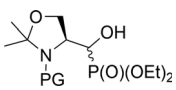
Considering only a few examples of ring opening reactions of trifluoromethylated *N*-unactivated aziridines with nitrogen nucleophiles in the literature,[29] we tried to open the ring of aziridin-2-ylphosphonates **6a,b** with $BnNH_2$ under acidic conditions, in the presence of $Sc(OTf)_3$, $Yb(OTf)_3$, $Bi(OTf)_3$, PBu_3, $B(C_6F_5)_3$, $BiCl_3$, $TiCl_4$ in different solvents, but all attempts failed. Only unreacted **6a,b** were observed in the reaction mixtures. Then, we decided to carry out the reaction under basic conditions in the presence of K_2CO_3 and acetonitrile as a solvent. As a result, the phosphate **22** ($\delta = -5.01$ in ^{31}P NMR) was formed (Scheme 2).

During the experiment, we observed the formation of diethyl phosphite ($\delta = 7.32$ in ^{31}P NMR) and an aldehyde **1a** ($\delta = 9.30$ in ^{1}H NMR), which vanished at the end of the reaction. Apparently, besides the rearrangement of the α-hydroxyphosphonate, due to proton extraction from the hydroxyl group by base the aldehyde was formed with concomitant phosphonate elimination, supporting the retro-Abramov reaction mechanism proposed by Gancarz.[13d] Furthermore, the presence of the electron-withdrawing CF_3 moiety in the aziridine ring allowed the α-hydroxyphosphonate intramolecular rearrangement with subsequent aziridine ring opening to phosphate **22**. The phosphonate/phosphate conversion was already studied in the case of the fluorene molecule when stronger amines were used by Gancarz *et al.*[30]

Moreover, the application of $MeNH_2$ or $BzNH_2$ (instead of $BnNH_2$), under the same conditions, as well as using K_2CO_3

Table 1 Preparation of α-hydroxyphosphonates[a]



Aldehyde	Product		PG	Cond.	Yield[b] [%]	d.r.[c]
1a		**6a,b**	Bn	i	84	1 : 1
1a		**6a,b**	Bn	ii	77	20 : 1
1a		**7a,b**	H	iii	97	1 : 1
1a		**8a,b**	Boc	iv	43	1 : 99
1a		**9a,b**	Cbz	v	74	1 : 1.2
2a		**10a,b**	Bn_2	i	52	11 : 1
2b		**11a,b**	Boc	i	61	2.1 : 1
2c		**12a,b**	Cbz	i	52	2.3 : 1
3a		**13a,b**	Bn_2	i	44	1.9 : 1
3b		**14a,b**	Boc	i	55	3.4 : 1
3c		**15a,b**	Cbz	i	41	2.3 : 1
4a[d]		**16a,b**[d]	Bn	vi	61	1.3 : 1
4b[d]		**17a,b**[d]	Boc	ii	77	3.7 : 1
4c[e]		**18a,b**[e]	Cbz	ii	76	2.9 : 1
5a		**19a,b**	Bn	ii	40	3.1 : 1
5b		**20a,b**	Boc	ii	94	95 : 5
5c		**21a,b**	Cbz	ii	67	13 : 1

[a] (i) $LiP(O)(OEt)_2$, −30 °C → rt, 16–18 h; (ii) $HP(O)(OEt)_2$, 0.1 or 0.2 eq. TEA, neat, r.t. or 50 °C, 1 d or 7 d; (iii) **6a,b**, H_2/Pd/C, EtOH; 0 °C → rt; (iv) **7a,b**, Boc_2O, DMAP, MeCN, r.t., 1 d; (v) **7a,b**, CbzCl, $NaHCO_3$, CH_2Cl_2, 0 °C → rt, 1 d; (vi) $HP(O)(OEt)_2$, 1 eq. *i*-Pr_2EtN, CH_2Cl_2. [b] Isolated yield. [c] Crude reaction mixture (^{19}F NMR and/or ^{31}P NMR). [d] Configuration (2*S*). [e] Configuration (2*R*).

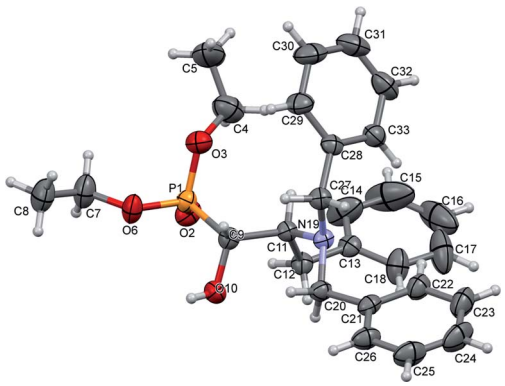
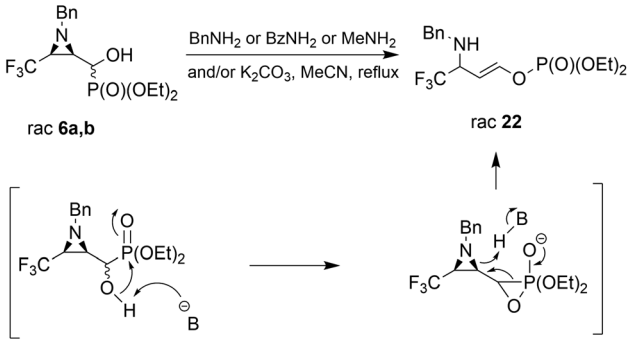


Fig. 2 A perspective view of **10a**, showing the numbering scheme. Ellipsoids were drawn at the 30% probability level; hydrogen atoms are represented by spheres of arbitrary radii.



Scheme 2 Reactions of **6a,b** with different nitrogen nucleophiles under K_2CO_3 conditions.

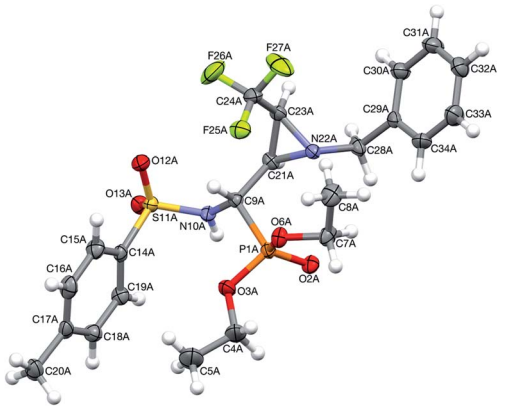


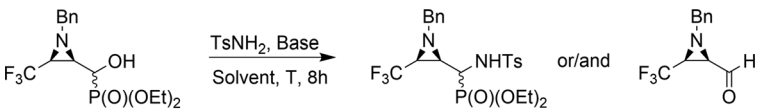
Fig. 3 A perspective view of **23a**, showing the numbering scheme. Ellipsoids were drawn at the 50% probability level and hydrogen atoms are represented by spheres of arbitrary radii.

without nitrogen nucleophiles, gave phosphate **22** (Scheme 2). Surprisingly, when *para*-toluenesulfonamide ($TsNH_2$) was used along with K_2CO_3, aminophosphonates **23a,b** were obtained as the sole products. The structure and stereochemistry of compound **23a** was determined by X-ray diffraction analysis and indicated the rac(1*S*,2*R*,3*S*)-**23a** configuration, analogous to **6a**,[26] obtained by Pudovik addition (Fig. 3).

The obtained results were contrary to known methods leading to *N*-tosylamide derivatives. Usually, the hydroxyl group reacts with sulfonamides under acidic conditions,[17] or under basic conditions the substitution of leaving groups such as *O*-mesyl is applied.[15a] On the other hand, a similar transformation of hydroxyphosphonates to aminophosphonates with amines in a basic environment was reported by Gancarz.[20] Likewise, the application of Lewis bases such as $CaCl_2$ with aniline was announced by Kaboudin *et al.*[31] The results concerning the applied reaction conditions in the case of compounds **6a,b** with $TsNH_2$ are presented below (Table 2).

The presented experiments indicate that the best conditions leading to **23a,b** involved 1.2 eq. (5 eq.) of K_2CO_3 and MeCN as a solvent, while the reaction mixture was refluxed for 8 h. When we monitored this reaction at lower temperatures (40 °C → 60 °C), only signals of substrates were detected (^{19}F, ^{31}P NMR). Besides, increasing the amount of K_2CO_3 from 1.2 eq. to 12 eq. led to slightly better yields and higher diastereoselectivity (Table 2, entry 2, 5). The application of THF as a solvent gave no reaction, while reaction in DMF led to the decomposition of the starting material to a number of undefined products. Moreover, reaction in EtOH, contrary to results reported by Gancarz,[13d] decreased the reaction yield (60% ^{19}F, ^{31}P NMR). On the other hand, the reaction without base failed. Surprisingly, the

Table 2 Optimization of the reaction of compounds **6a,b** with *para*-toluenesulfonamide



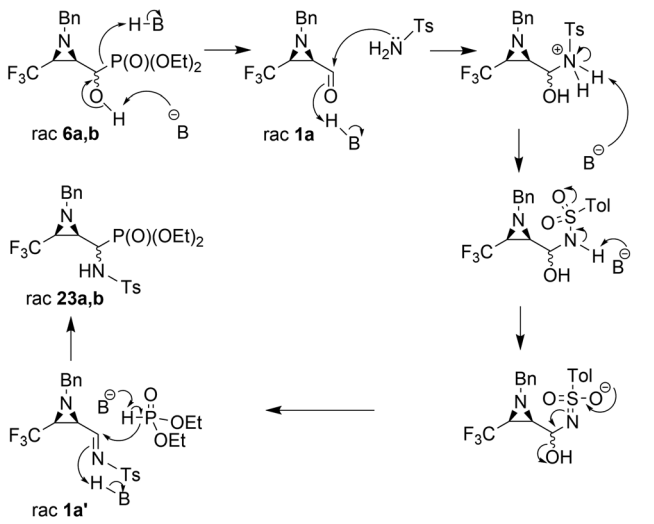
Entry	d.r.	Base (eq.)	Solvent	Temp. [°C]	Product	Yield[a] [%]	d.r.[b]
1	20 : 1	K_2CO_3 (1.2 eq.)	MeCN	Reflux	**23a,b**	74	6 : 1
2	1 : 1	K_2CO_3 (1.2 eq.)	MeCN	Reflux	**23a,b**	87	6 : 1
3	1 : 1	K_2CO_3 (5 eq.)	MeCN	Reflux	**23a,b**	73	9 : 1
4	20 : 1	K_2CO_3 (12 eq.)	MeCN	Reflux	**23a,b**	80	9 : 1
5	1 : 1	K_2CO_3 (12 eq.)	MeCN	Reflux	**23a,b**	96	9 : 1
6	1 : 1	K_2CO_3 (1.2 eq.)	DMF	100	Decomp.	—	—
7	1 : 1	K_2CO_3 (1.2 eq.)	THF	Reflux	n.r.	—	—
8	1 : 1	K_2CO_3 (1.2 eq.)	EtOH	Reflux	**23a,b**	60	7 : 1
9	1 : 1	None	MeCN	Reflux	n.r.	—	—
10	1 : 1	TEA (1.2 eq.)	MeCN	Reflux	n.r.	—	—
11	1 : 1	TEA (1.2 eq.)	EtOH	Reflux	n.r.	—	—
12	1 : 1	$NaHCO_3$ (1.2 eq.)	MeCN	Reflux	**1a**	20	—
13	1 : 1	$NaHCO_3$ (12 eq.)	MeCN	Reflux	**1a**	20	—
14	1 : 1	NaH (1.2 eq.)	THF	Reflux	**23a,b**	18	8 : 1

[a] ^{19}F NMR and/or ^{31}P NMR yield. [b] Crude reaction mixture (^{19}F NMR and/or ^{31}P NMR).

employment of other bases led to distinct results. In the presence of TEA, there were no reactions in MeCN, neither in EtOH. When $NaHCO_3$ was used, mainly unreacted substrates were observed, together with diethyl phosphite and aldehyde **1a** (NMR) but with lower yield, likewise in the case of reactions with $BnNH_2$, $MeNH_2$ and $BzNH_2$. The last examined base, NaH (in anhydrous THF), allowed α-aminophosphonates **23a,b**, but with very poor yields (Table 2, entry 14). Additionally, we decided to examine the reaction of **1a** with $TsNH_2$ in detail using ^{19}F NMR monitoring. Similar to studies reported by Keglevich *et al.*,[5b] the appropriate *N*-tosylaldimine **1a′** as a transient species was detected during the reaction in a crude mixture but in very low concentration ($\delta = -78.16$ ppm in ^{19}F NMR, which corresponded to the chemical shifts of β-CF_3–imines in the literature ref. 32). Subsequent addition of diethyl phosphite and K_2CO_3 (1.2 eq.) to the reaction led to **23a,b** but in poor yields (30% in ^{31}P NMR, with accompanying dominance of the diethyl phosphite signal). Finally, we decided to monitor the reactions of **6a,b** with $TsNH_2$ and K_2CO_3 (1.2 eq.). In the employed basic conditions, the elimination of the hydroxyl group gave rise to aldimine **1a′**, which most probably occurred by the E1cB mechanism involving the participation of the sulfonimidate anion; we observed the same signal of imine **1a′** in the ^{19}F NMR during the reaction. This signal was completely suppressed at the end of the reaction. Subsequent nucleophilic addition of dialkyl phosphite to the C=N bond of imine **1a′** (Pudovik reaction) gave **23a,b** (Scheme 3). These observations support the imine path of the Kabachnik–Fields reaction (KFR), proving that the imine is the most rational intermediate in the synthesis of α-aminophosphonates.

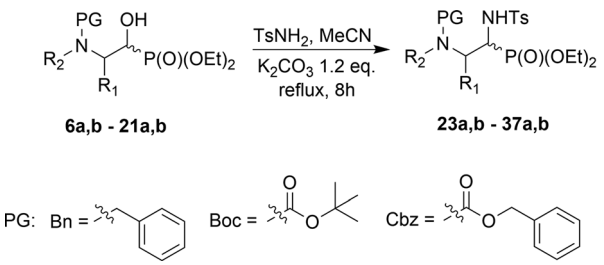
The optimized results prompted us to examine the scope of this particular transformation in the reactions of aziridines **6a,b–9a,b** as well as the amino acid origin of α-hydroxyphosphonates **10a,b–12a,b** to *N*-tosylamide phosphonates **23a,b–37a,b**. Initially, we used 12 eq. of K_2CO_3 as a base, but decreasing yields in some cases led us to choose 1.2 eq. as a standard base concentration (Table 3).

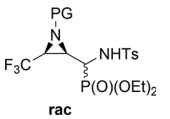
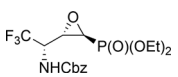
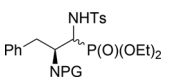
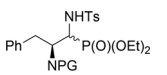
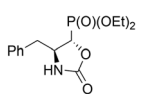
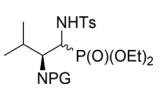
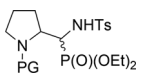
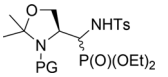
It is noteworthy that the stereoselectivity as well as the stereochemistry of the major diastereoisomers of **23a,b–37a,b** were always analogous to the ratio and configurations of those obtained in the Pudovik reaction, the major isomers of **6a,b–21a,b**; slightly different results were reported by Dimukhametov.[33] Thus, higher stereoselectivity was obtained in the case of the application of chiral imines in the Pudovik reaction, compared to the use of chiral amines in the three-component Kabachnik–Fields reaction. The employment of two diastereoisomers of **6a,b** (1 : 1, NMR ratio) under standard conditions led to the corresponding **23a,b** with very good yield. On the contrary, in the case of **12a,b** and **15a,b**, the reactions proceeded with moderate yields. The stereochemistry of **24a,b**, **26a,b–**



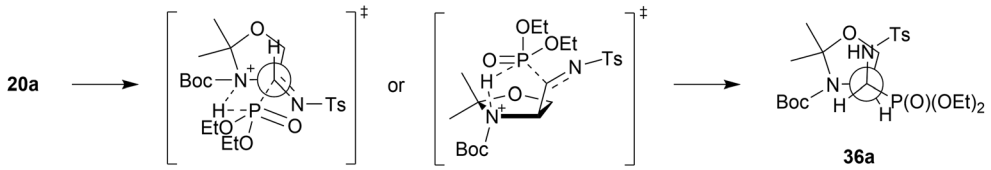
Scheme 3 Proposed reaction mechanism of **6a,b** with $TsNH_2$ under K_2CO_3 conditions.

Table 3 Preparation of α-(*N*-tosyl)aminophosphonates



Substrate	d.r.	Product		PG	Yield[a] [%]	d.r.[b]
6a,b	1 : 1		**23a,b**	Bn	87	6 : 1
7a,b	1 : 1		**24a,b**	H	80	6 : 1
8a,b	1 : 99	rac	**25a,b**	Boc	—	—
9a,b	3 : 1		**38**	Cbz	41(74)[c]	—
10a,b	19 : 1		**26a,b**	Bn_2	81	99 : 1
11a,b	1.9 : 1		**27a,b**	Boc	78	2.5 : 1
			**28a,b**		40	2.4 : 1
12a,b	2.7 : 1	+ 	**39**	Cbz	11	99 : 1
13a,b	9 : 1		**29a,b**	Bn_2	—	—
14a,b	5.4 : 1		**30a,b**	Boc	51	3.6 : 1
15a,b	1.7 : 1		**31a,b**	Cbz	42	5.2 : 1
16a,b[d]	1.3 : 1		**32a,b**	Bn	—	—
17a,b[d]	4 : 1		**33a,b**[d]	Boc	59	4.4 : 1
18a,b[e]	3.3 : 1		**34a,b**[e]	Cbz	75	3.7 : 1
19a,b	2.6 : 1		**35a,b**	Bn	—	—
20a,b	99 : 1		**36a,b**	Boc	72	12 : 1
21a,b	13 : 1		**37a,b**	Cbz	75	12 : 1

[a] Isolated yield. [b] Crude reaction mixture (^{19}F NMR and/or ^{31}P NMR). [c] After additional 10 hours of heating. [d] Configuration (2*S*). [e] Configuration (2*R*).



Scheme 4 The Felkin–Ahn model of the addition of diethyl phosphite to α-hydroxyphosphonate **20a**.

31a,b/**33a,b**, **37a,b** was confirmed by NMR as well as NOESY experimental analysis. Moreover, the steric hindrance in **8b**, between the *N*-Boc substituent and the phosphonate moiety (confirmed by interactions between protons on 1D ROESY experiments) caused no access to the hydroxyl group by the base (K_2CO_3) and subsequently, only the substrate **8b** was observed in the reaction mixture. On the other hand, the very good diastereoselectivity of the addition, yielding **36a,b** and **37a,b**, can be explained by the Felkin–Ahn model as well as additional interactions substantiated the addition of the dialkyl phosphite on the C=N unit of *N*-tosylimine **5a**′ derived from the appropriate aldehyde **5a**. According to this, a H-bond was formed between the P(O)H moiety of the phosphite and the nitrogen atom of the pyrrolidine, arranging the five-membered transition state (Scheme 4). It seems probable that the actual mechanism is dependent on the components of the reaction since the reaction of carbohydrate derived α-hydroxyphosphonates (*e.g.* two epimeric carbohydrates, 5C-phosphonate with L-*ido*- or D-*gluco*-configurations)[34] with $TsNH_2$ failed, presumably due to a lack of nitrogen heteroatoms in the analogous neighborhood of the reaction center.

Additionally, the X-ray crystal structure determinations in the case of **34a** and **36a** (Fig. 4) were performed. Interestingly, both compounds existed as a racemic mixture rac(1*S*,2*R*)-**34a** and rac(*R*,4*S*)-**36a** in the studied crystals. Apparently, during the reaction of **20a,b** (K_2CO_3, $TsNH_2$) yielding **36a,b**, besides the *N*-tosylimine formation *via* aldehyde **5b**, the competitive enolization took place, followed by proton addition from both sides of the enol double bond leading to racemization at C4. The phenomenon of partial racemization during aldehyde formation was already reported in the case of serine derivatives.[35]

In the case of the reactions of **13a,b**, **16a,b** and **19a,b** with $TsNH_2$ in the presence of K_2CO_3, the retro-Abramov reactions took place. Thus, in the reaction mixture only diethyl phosphite and the appropriate aldehydes **3a–5a** were detected (monitored by NMR). Additionally, in the case of reactions of **10a,b** and **20a,b** [(*R*,*S*)/(*S*,*S*) 19 : 1 and 99 : 1 ratios, respectively] with K_2CO_3 (1.2 eq.) as well as with K_2CO_3 and amines ($MeNH_2$, $BnNH_2$) or benzamide ($BzNH_2$), partial racemization at carbon α regarding phosphonate moieties occurred, leading to **10a,b** and **20a,b** [(*R*,*S*)/(*S*,*S*) in 1.5 : 1 ratio and 3.6 : 1 ratio, respectively]. These results confirmed the formation of aldehydes due to base treatment (K_2CO_3) during the analyzed reactions. Similar observations were reported by Wróblewski *et al.*[36] Thus, treatment of the single diastereomeric 1,2-oxaphospholane derivative with sodium methoxide led to the retro-Abramov reaction followed by phosphite addition and cyclization, yielding the corresponding mixture of diastereoisomers. On the other hand, these observations were in contradiction to the results of the analogous reactions of **6a,b**, which led almost exclusively to phosphate **22**. Gancarz *et al.* explained the distinction between the retro-Abramov reaction yielding aldehyde and the intramolecular rearrangement towards phosphate, based on kinetic and NMR studies.[30] Their observations were based on the reactions between various α-hydroxyphosphonates and amines, assuming that the differentiation of these two routes was dependent on the electronic effect of the substituents. They concluded that the retro-Abramov reaction is preferred when the electron-donating substituents appear in the α-hydroxyphosphonates. In our case, the presence of the strongly electron-withdrawing CF_3 group in **6a,b** facilitated the intramolecular rearrangement over the retro-Abramov reaction. In this particular reaction, the *in situ* formed alkoxide ion substituted the phosphorus atom, leading to the formation of the three-membered cyclic intermediate. Subsequent electron pair transfer led to phosphate while stabilization of the partial negative charge on the α-carbon atom followed by aziridine ring opening finally gave the vinyl phosphate **22**.[37]

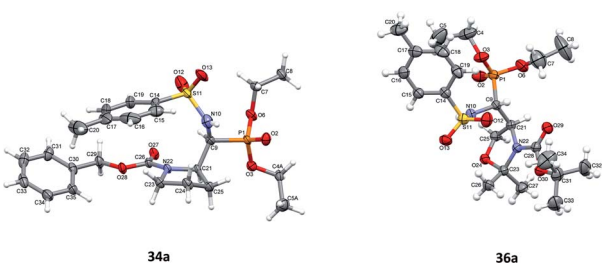
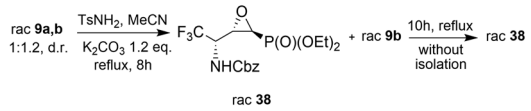
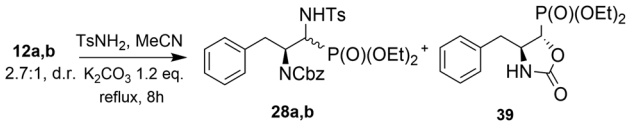


Fig. 4 A perspective view of **34a** and **36a** showing the numbering scheme. Ellipsoids were drawn at the 50% probability level and hydrogen atoms are represented by spheres of arbitrary radii. Only one of the alternative conformations of the C4–C5 ethyl group is shown.

On the other hand, the reactions of **9a,b** (1 : 1.2, d.r.) with $TsNH_2$ (1.2 eq. K_2CO_3, MeCN, reflux) after 8 h of heating, gave only one diastereoisomer of epoxide **38** (41%), while the remaining diastereoisomer **9b** was present in the reaction mixture. In the ^{31}P NMR spectrum, the signal of epoxide **38** was shifted distinctly upfield compared to the aziridinyl substrates **9a,b** and α-sulfonamide derivatives **23a,b–24a,b** ($\delta_P = 15.89$ *vs.* approx. 20 ppm). Furthermore, additional heating of the remaining reaction mixture for 10 h under the same reaction conditions led to **38** (74% after isolation), due to the total consumption of starting materials **9a,b**. The reaction was monitored by ^{19}F and ^{31}P NMR. Apparently, treatment of α-hydroxyphosphonate **9a** with base led to aziridine ring opening



Scheme 5 Reaction of *N*-Cbz protected aziridines **9a,b** under K_2CO_3 conditions.



Scheme 6 Reaction of *N*-Cbz protected phenylalanine derivatives **12a,b** under K_2CO_3 conditions.

by the attack of a previously formed alkoxide anion on an adjacent nitrogen atom (anti to alkoxide ion) of the Cbz moiety. Furthermore, due to proton abstraction followed by aldehyde **1c** (PG = Cbz) formation, the racemization, such as in case of **5b**, *via* enol took place. Subsequent phosphite addition to the C=O bond of aldehyde **1c** led to **9a,b** as an equilibrating mixture of diastereoisomers, where only one diastereoisomer **9a** reacted with base to give **38** (Scheme 5). The structure and stereochemistry of **38** as rac(1*S*,2*S*,3*S*) were confirmed by NMR analysis and X-ray crystal structure determination (Fig. 5).

This aza-Payne rearrangement of non-fluorinated *N*-Boc[38] protected aziridinemethanols, as well as Ts,[38,39] Mts[40] and Ms[38] protected aziridinemethanols, was previously reported. To the best of our knowledge, there are limited numbers of publications reporting the synthesis of trifluoromethylated epoxide phosphonates[41] that could be biologically promising derivatives of non-fluorinated epoxide phosphonates possessing antibiotic activity.[42] On the other hand, epoxide **38** can easily provide trifluoromethylated hydroxyphosphonates, whose biological activities were already evaluated.[43]

When phenylalanine *N*-Cbz protected derivatives **12a,b** (2.7 : 1, d.r.) were subjected to the reaction with $TsNH_2$ under the same conditions, the α-(*N*-tosyl)aminophosphonates **28a,b** were obtained as major products, together with compound **39** (Scheme 6). Apparently, the alkoxide ion formed from α-hydroxyphosphonate attacked the carbonyl carbon atom of the Cbz moiety, instead of the adjacent carbon, as was in the case of **9b** where the formation of fused three and five membered rings was excluded. Subsequent leaving of the benzyloxide ion led to the formation of the oxazolidin-2-one function in **39**. A similar displacement of the *N*-amide group leading to the corresponding oxazolidin-2-one was reported by Patel *et al.*[11f] Based on the detailed analysis of ^{1}H NMR data we were able to assign the stereochemistry of compound **39**. Thus, diagnostic signals appeared at 4.45 (dd, J = 6.1, 0.7 Hz, C*H*P) and 4.33–4.25 ppm (m, C*H*N) in ^{1}H NMR, which corresponded to the (1*S*,2*S*) diastereoisomer of **39**.[44] These data indicated that during the reaction of Cbz protected phenylalanine derivatives **12a,b** under basic conditions with $TsNH_2$, only the (1*S*,2*S*)-**12b** diastereoisomer reacted towards (1*S*,2*S*)-**39**.

Fig. 1–5 show the perspective views of the molecules. Of all six compounds, only **10a** crystallized in the chiral $P4_12_12$ space group as a single enantiomer (1*R*,2*S*). All other compounds crystallized in the centrosymmetric space group, which means that both enantiomers were present in the crystals. This difference was also visible in the supramolecular motifs created by hydrogen bonds in the crystal structures. In **10a** the O–H···O hydrogen bonds connect molecules into infinite chains (Fig. 1 and Table 2 in ESI†), expanding along the *z*-direction (molecules related by fourfold, right-hand screw axis). In all other crystal structures, the well-defined, directional O–H···O or N–H···O (Fig. 2 and Table 2 in ESI†) hydrogen bonds made centrosymmetric dimers, arranged by two different enantiomers. In compound **23a**, each of the symmetry-independent molecules made the dimer with its own symmetry-related mate (*i.e.* A–A and B–B). It is possible that the relative ease of making centrosymmetric dimers is one of the reasons that all these compounds crystallized as racemates.

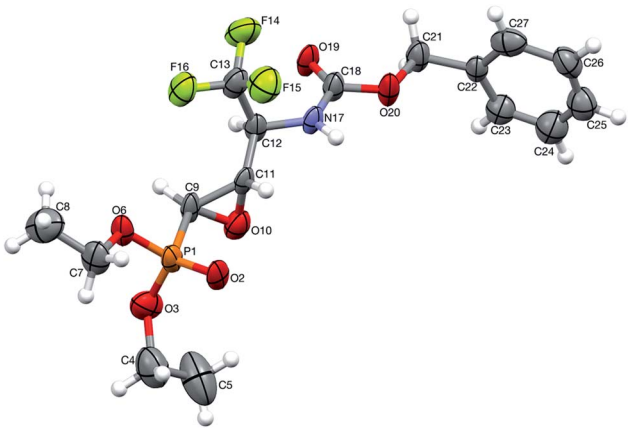


Fig. 5 A perspective view of **38** showing the numbering scheme. Ellipsoids were drawn at the 50% probability level, hydrogen atoms are represented by spheres of arbitrary radii.

Conclusions

In summary, our results demonstrate the synthesis of a wide range of α-hydroxyphosphonates that subsequently underwent reactions with nitrogen nucleophiles. Only *para*-toluenesulfonamide provided access to fluorinated[3k,45] and non-fluorinated α-aminophosphonates,[46] an important group of compounds that are mimics of the naturally occurring α-amino acids,[47] and could be explored as versatile substrates in the synthesis of biologically active species. Further deprotection of the α-amino group could be considered in the design of important phosphonated building blocks employed in the synthesis of useful compounds such as peptide analogues. According to the establishments concerning the reaction mechanism, this study gives further proof that the Kabachnik–Fields reaction occurs *via* the imine intermediate, which immediately undergoes the

addition of dialkyl phosphite towards *N*-tosyl-α-aminophosphonates.

Experimental section

General methods

^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectral measurements were performed on Bruker ASCEND 400 (400 MHz), Bruker ASCEND 600 (600 MHz) spectrometers. All 2D and 1D selective NMR spectra were recorded on the Bruker ASCEND 600 (600 MHz) spectrometer. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard ($\delta = 0$) in $CDCl_3$ or using the residual solvent peak in the case of CD_3CN ($\delta = 1.96$). Chemical shifts of ^{13}C NMR were expressed in parts per million downfield and upfield from $CDCl_3$ as an internal standard ($\delta = 77.0$). Chemical shifts of ^{19}F NMR were expressed in parts per million upfield from $CFCl_3$ as an internal standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{31}P NMR were expressed in parts per million in $CDCl_3$ and CD_3CN. All d.r. ratios were evaluated on the basis of ^{19}F NMR or/and ^{31}P NMR in the crude reaction mixture. High-resolution mass spectra were recorded by electron spray (MS-ESI) techniques using a QToF Impact HD Bruker spectrometer. The melting points were measured on a Boetius apparatus and were uncorrected. Reagent grade chemicals were used. Solvents were dried by refluxing with sodium metal-benzophenone·(THF), CaH_2·(CH_2Cl_2, CH_3CN) and NaH·(Et_2O), then distilled under an argon atmosphere. Absolute ethanol was stored under argon and over molecular sieves (3 Å). All moisture sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. Reactions at temperatures below 0 °C were performed using a cooling bath (liquid N_2/*n*-hexane or liquid N_2/*i*-PrOH). TLC was performed on Merck Kieselgel 60-F254 with EtOAc/*n*-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 (0.063–0.200 μm), Merck Kieselgel 60 (0.040–0.063 μm), Merck Kieselgel 60 (0.015–0.004 μm), were used for column chromatography. X-ray diffraction data were collected by the ω-scan technique on a Rigaku four-circle Xcalibur (Eos detector) diffractometer with graphite-monochromatized MoK_α radiation ($\lambda = 0.71073$ Å): for **9a**, **10a** and **36a** at room temperature, for **23a** and **38** at 130(1) K, and for **34a** at 100(1) K. The data were corrected for Lorentz-polarization and absorption effects.[48] Accurate unit-cell parameters were determined by a least-squares fit of 7906 (**9a**), 4321 (**10a**), 6595 (**23a**), 3219 (**34a**), 7252 (**36a**) and 1078 (**38**) reflections of highest intensity, chosen from the whole experiment. The structures were solved with SHELXT[49] and refined with the full-matrix least-squares procedure on F^2 by SHELXL-2014/7.[49] All non-hydrogen atoms were refined anisotropically, hydrogen atoms were placed in the calculated positions and refined as the 'riding model' with the isotropic displacement parameters set at 1.2 (1.5 for methyl groups) times the $U_{eq.}$ value for the appropriate non-hydrogen atoms. In **9a**, **34a**, **36a** and **38**, the lengths of terminal C–C bonds in the ethyl groups C4–C5 and C7–C8 were constrained to the typical values, due to the significant shortening resulting from large thermal motion; additionally, in **9a**, **34a** and **38** weak constraints were applied to the selected anisotropic displacement parameters. Relevant crystal data are listed in Table 1 (see ESI†), together with refinement details. In structure **34a** one of the ethyl groups was disordered over two alternative conformations; an s.o.f. of 0.5 was assigned to both positions.

Crystallographic data for the structural analysis was deposited with the Cambridge Crystallographic Data Centre, no. CCDC – 1568454 (**9a**), CCDC – 1569663 (**10a**), CCDC – 1568455 (**23a**), CCDC – 1568456 (**34a**), CCDC – 1568457 (**36a**) and CCDC – 1568458 (**38**).

Procedure for the synthesis of aldehydes 1–5

All aldehydes were prepared from the corresponding alcohols. Compounds **1a**,[26] **2–3**,[27b] **4a**,[50] **4c**,[51] **5a**,[52] **5b**[53] were prepared as described. The NMR data for **2–3**,[54] **4b**,[27b] **5c**[55] were in good agreement.

Racemic mixture of (2*R*,3*S*)-1-benzyl-3-(trifluoromethyl) aziridine-2-carbaldehyde (rac 1a). Pale yellow oil (1 g, >99% ^{1}H, ^{19}F NMR): ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.30$ (dq, $J = 5.3$, 2.6 Hz, 1H, C*H*O), 7.45–7.31 (m, 5H, Ph), 3.80 (d, $J = 13.3$ Hz, 1H, C*H*HPh), 3.75 (d, $J = 13.4$ Hz, 1H, CH*H*Ph), 2.65 ("quintet", $J = 6.3$ Hz, 1H, C*H*CF_3), 2.50 (t, $J = 6.1$ Hz, 1H, C*H*CHCF_3). ^{1}H {/^{19}F} NMR (376 MHz, $CDCl_3$) $\delta = 9.30$ (d, $J = 5.7$ Hz, 1H, C*H*O), 7.44–7.24 (m, 5H, Ph), 3.79 (d, $J = 13.4$ Hz, 1H, C*H*HPh), 3.75 (d, $J = 13.4$ Hz, 1H, CH*H*Ph), 2.68–2.61 (m, 1H, C*H*CF_3), 2.50 (t, $J = 6.1$ Hz, 1H, C*H*CHCF_3). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 196.74$ (q, $J = 1.9$ Hz, *C*=O), 135.66, 128.77, 128.23, 128.14 (4 × s, Ph), 123.46 (q, $J = 274.7$ Hz, *C*F_3), 62.37 (s, *C*H_2Ph), 47.39 (s, *C*HCHCF_3), 44.47 (q, $J = 40.8$ Hz, *C*HCF_3). ^{19}F NMR (376 MHz, $CDCl_3$) $\delta = -66.26$ (dd, $J = 6.2$, 2.7 Hz).

Procedure for the addition of diethyl phosphite to aldehyde 1a

Compounds **6a,b**[26] were prepared as described. The NMR data for **6a** were in good agreement.

Procedure for *N*-deprotection of 6a,b

To a round-bottom flask with aziridinyl phosphonates **6a,b** (1 : 1, d.r.) (1.68 mmol, 616 mg) dissolved in ethanol (10 mL), a catalytic amount of palladium hydroxide was added. The flask was then connected by three-way valve to a vacuum pump and a gasbag filled with gaseous hydrogen. Hydrogen was then introduced inside the flask at 0 °C and vigorously stirred. This cycle was repeated 10 times and the reaction mixture was stirred overnight at room temperature. The catalyst was then filtered out and crude products **7a,b** were isolated using column chromatography (chloroform/methanol 99 : 1, v/v).

Racemic mixture of diethyl((*S*)-hydroxy((2*R*,3*S*)-3-(trifluoromethyl)aziridin-2-yl)methyl)phosphonate (rac 7a). Pale yellow oil (228 mg, 49%): ^{1}H NMR (400 MHz, $CDCl_3$) $\delta =$ 4.24 (q, $J = 7.2$ Hz, 2H, OC$H_2$$CH_3$), 4.19 (q, $J = 7.2$ Hz, 2H, OC$H_2$$CH_3$), 3.76 (br t, $J = 7.8$ Hz, 1H, C*H*P), 2.84–2.70 (m, 2H, C*H*CF_3, C*H*CHCF_3), 2.05 (br s, 1H, O*H*), 1.63 (br t, $J = 8.8$ Hz, 1H, N*H*), 1.38 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3), 1.37 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 124.58$ (q, $J =$ 274.0 Hz, *C*F_3), 66.79 (d, $J = 158.9$ Hz, *C*HP), 63.26 (d, $J = 7.0$ Hz,

OCH$_2$CH$_3$), 63.18 (d, J = 6.9 Hz, OCH$_2$CH$_3$), 34.51 (d, J = 3.7 Hz, CHCHCF$_3$), 33.28 (dq, J = 39.7, 12.8 Hz, CHCF$_3$), 16.47 (d, J = 5.1 Hz, OCH$_2$CH$_3$), 16.43 (d, J = 5.3 Hz, OCH$_2$CH$_3$). ^{19}F NMR (376 MHz, CDCl$_3$) δ = −66.75 (br s). ^{19}F{/^{1}H} NMR (376 MHz, CDCl$_3$) δ = −66.76 (d, J = 3.0 Hz). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 22.53 (d, J = 2.9 Hz). HRMS (ESI) calcd for $C_8H_{15}F_3NO_4PNa$ ([M + Na]$^+$): 300.0589, found: 300.0589.

Racemic mixture of diethyl((*R*)-hydroxy((2*R*,3*S*)-3-(trifluoromethyl)aziridin-2-yl)methyl)phosphonate (rac 7b). Pale yellow oil (227 mg, 49%): ^{1}H NMR (400 MHz, CDCl$_3$) δ = 4.28–4.17 (m, 4H, 2 × OCH$_2$CH$_3$), 3.90 (t, J = 8.1 Hz, 1H, CHP), 2.94–2.75 (m, 2H, CHCF$_3$, CHCHCF$_3$), 1.86 (br s, 1H, OH), 1.81 (br t, J = 8.8 Hz, 1H, NH), 1.37 (t, J = 7.1 Hz, 3H, OCH$_2$CH$_3$), 1.36 (t, J = 7.1 Hz, 3H, OCH$_2$CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ = 124.29 (q, J = 273.6 Hz, CF$_3$), 65.72 (dd, J = 167.1, 1.5 Hz, CHP), 63.25 (d, J = 7.1 Hz, OCH$_2$CH$_3$), 62.98 (d, J = 7.3 Hz, OCH$_2$CH$_3$), 36.06 (d, J = 8.8 Hz, CHCHCF$_3$), 35.27 (q, J = 39.8 Hz, CHCF$_3$), 16.38 (d, J = 5.4 Hz, OCH$_2$CH$_3$), 16.34 (d, J = 5.4 Hz, OCH$_2$CH$_3$). ^{19}F NMR (376 MHz, CDCl$_3$) δ = −66.65 (d, J = 6.4 Hz). ^{19}F{/^{1}H} NMR (376 MHz, CDCl$_3$) δ = −66,65 (s). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 20.87 (s). HRMS (ESI) calcd for $C_8H_{15}F_3NO_4PNa$ ([M + Na]$^+$): 300.0589, found: 300.0585.

Procedure for the introduction of the Boc protecting group into 7a,b

Aziridinyl phosphonates **7a,b** (1 : 1, d.r.) (0.72 mmol, 200 mg, 1 eq.) were dissolved in acetonitrile (5 mL) under argon at 0 °C. DMAP (0.87 mmol, 106 mg, 1.2 eq.) was added and the reaction mixture was stirred for 15 min. Next, di-*tert*-butyl dicarbonate (99%, 1.08 mmol, 238 mg, 1.5 eq.) was introduced and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then diluted with water (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the layers were separated. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product **8b** was isolated using column chromatography (*n*-hexane/ethyl acetate 10 : 90, v/v → ethyl acetate/methanol 99 : 1, v/v).

Racemic mixture of *tert*-butyl(2*R*,3*S*)-2-((*R*)-(diethoxyphosphoryl)(hydroxy)methyl)-3-(trifluoromethyl)aziridine-1-carboxylate (rac 8b). Pale yellow oil (117 mg, 43%, 1.9 : 1 r.r. that could be isolated). Major rotamer: ^{1}H NMR (600 MHz, CDCl$_3$) δ = 5.03 (t, J = 9.6 Hz, 1H, CHP), 4.30–4.15 (m, 4H, 2 × OCH$_2$CH$_3$), 2.97–2.84 (m, 2H, CHCF$_3$, CHCHCF$_3$), 1.53 (s, 9H, C(CH$_3$)$_3$), 1.36 (t, J = 7.1 Hz, 6H, 2 × OCH$_2$CH$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 152.13 (s, C=O), 124.08 (q, J = 274.5 Hz, CF$_3$), 83.54 (s, C(CH$_3$)$_3$), 69.87 (d, J = 169.3 Hz, CHP), 63.43 (d, J = 6.8 Hz, OCH$_2$CH$_3$), 62.95 (d, J = 6.7 Hz, OCH$_2$CH$_3$), 35.02 (q, J = 41.4 Hz, CHCF$_3$), 34.27 (d, J = 8.9 Hz, CHCHCF$_3$), 27.68 (s, C(CH$_3$)$_3$), 16.36 (d, J = 5.9 Hz, OCH$_2$CH$_3$), 16.23 (d, J = 5.8 Hz, OCH$_2$CH$_3$). ^{19}F NMR (565 MHz, CDCl$_3$) δ = −66.94 (d, J = 6.6 Hz). ^{19}F{/^{1}H} NMR (565 MHz, CDCl$_3$) δ = −66.94 (s). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 16.47 (s). HRMS (ESI) calcd for $C_{13}H_{23}F_3NO_6PNa$ ([M + Na]$^+$): 400.1112, found: 400.1119. Minor rotamer: ^{1}H NMR (400 MHz, CDCl$_3$) δ = 4.88 (t, J = 9.5 Hz, 1H, CHP), 4.32–4.18 (m, 4H, 2 × OCH$_2$CH$_3$), 3.00–2.70 (m, 2H, CHCF$_3$, CHCHCF$_3$), 1.51 (s, 9H, C(CH$_3$)$_3$), 1.38 (t, J = 7.1 Hz, 6H, 2 × OCH$_2$CH$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 151.60 (s, C=O), 124.13 (q, J = 275.5 Hz, CF$_3$), 83.43 (s, C(CH$_3$)$_3$), 69.42 (d, J = 164.1 Hz, CHP), 63.32 (d, J = 7.1 Hz, OCH$_2$CH$_3$), 63.26 (d, J = 6.8 Hz, OCH$_2$CH$_3$), 33.58 (dq, J = 39.7, 11.2 Hz, CHCF$_3$), 32.66 (d, J = 2.6 Hz, CHCHCF$_3$), 27.54 (s, C(CH$_3$)$_3$), 16.43 (d, J = 5.8 Hz, OCH$_2$CH$_3$), 16.35 (d, J = 6.0 Hz, OCH$_2$CH$_3$). ^{19}F NMR (376 MHz, CDCl$_3$) δ = −66.95 (br s). ^{19}F{/^{1}H} NMR (376 MHz, CDCl$_3$) δ = −66.96 (s). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 17.64 (s). HRMS (ESI) calcd for $C_{13}H_{23}F_3NO_6PK$ ([M + K]$^+$): 416.0852, found: 416.0846.

Procedure for the introduction of the Cbz protecting group into 7a,b

Aziridinyl phosphonates **7a,b** (1 : 1, d.r.) (0.72 mmol, 200 mg, 1 eq.) were dissolved in CH_2Cl_2 (5 mL) under argon at 0 °C. $NaHCO_3$ (0.87 mmol, 67 mg, 1.2 eq.) was added and the reaction mixture was stirred for 15 min. Benzyl chloroformate (95%, 1.08 mmol, 194 mg, 162 μL, 1.5 eq.) was introduced and the reaction mixture was stirred overnight at room temperature. Next, the reaction mixture was diluted with water (10 mL) then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products **9a,b** were isolated using column chromatography (*n*-hexane/ethyl acetate 10 : 90, v/v → ethyl acetate/methanol 99 : 1, v/v).

Racemic mixture of benzyl(2*R*,3*S*)-2-((*S*)-(diethoxyphosphoryl)(hydroxy)methyl)-3-(trifluoromethyl)aziridine-1-carboxylate (rac 9a). Pale yellow oil, slowly crystallizing (118 mg, 34%): ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.42–7.33 (m, 5H, Ph), 5.19 (d, J = 12.3 Hz, 1H, CHHPh), 5.16 (d, J = 12.3 Hz, 1H, CHHPh), 4.25–4.10 (m, 4H, 2 × OCH$_2$CH$_3$), 3.80 (br t, J = 8.3 Hz, 1H, CHP), 3.17 (br q, J = 6.4 Hz, 1H, CHCHCF$_3$), 3.11 ("quintet", J = 5.7 Hz, 1H, CHCF$_3$), 1.28 (t, J = 7.0 Hz, 3H, OCH$_2$CH$_3$), 1.27 (t, J = 6.9 Hz, 3H, OCH$_2$CH$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 160.52 (s, C=O), 134.92, 128.61, 128.44, 128.16 (4 × s, Ph), 122.98 (q, J = 275.0 Hz, CF$_3$), 69.06 (s, CH$_2$Ph), 65.22 (d, J = 161.6 Hz, CHP), 63.42 (d, J = 7.3 Hz, OCH$_2$CH$_3$), 63.26 (d, J = 7.0 Hz, OCH$_2$CH$_3$), 40.88 (d, J = 4.8 Hz, CHCHCF$_3$), 38.71 (dq, J = 40.6, 12.4 Hz, CHCF$_3$), 16.34 (d, J = 5.5 Hz, OCH$_2$CH$_3$), 16.28 (d, J = 5.6 Hz, OCH$_2$CH$_3$). ^{19}F NMR (565 MHz, CDCl$_3$) δ = −67.26 (br s). ^{19}F{/^{1}H} NMR (565 MHz, CDCl$_3$) δ = −67.27 (d, J = 2.2 Hz). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 20.68 (s). HRMS (ESI) calcd for $C_{16}H_{21}F_3NO_6PNa$ ([M + Na]$^+$): 434.0956, found: 434.0952.

Racemic mixture of benzyl(2*R*,3*S*)-2-((*R*)-(diethoxyphosphoryl)(hydroxy)methyl)-3-(trifluoromethyl)aziridine-1-carboxylate (rac 9b). Pale yellow oil, slowly crystallizing (101 mg, 40%) ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.41–7.36 (m, 5H, Ph), 5.23 (d, J = 12.2 Hz, 1H, CHHPh), 5.20 (d, J = 12.3 Hz, 1H, CHHPh), 4.28–4.18 (m, 4H, 2 × OCH$_2$CH$_3$), 3.98 (br t, J = 8.4 Hz, 1H, CHP), 3.24 ("quintet", J = 6.2 Hz, 1H, CHCF$_3$), 3.21–3.15 (m, 1H, OH), 3.09 (dt, J = 9.3, 4.9 Hz, 1H, CHCHCF$_3$), 1.36 (t, J = 7.0 Hz, 3H, OCH$_2$CH$_3$), 1.35 (t, J = 7.0 Hz, 3H, OCH$_2$CH$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 160.62 (s, C=O), 134.84, 128.52, 128.35, 128.06 (4 × s, Ph), 122.91 (q, J = 275.1 Hz, CF$_3$), 68.95 (s, CH$_2$Ph), 65.09 (dd, J = 161.7, 1.2 Hz, CHP), 63.32 (d, J = 7.3 Hz, OCH$_2$CH$_3$),

63.15 (d, $J = 7.0$ Hz, OCH_2CH_3), 40.82 (d, $J = 5.2$ Hz, $CHCHCF_3$), 38.61 (dq, J = 40.5, 12.6 Hz, $CHCF_3$), 16.25 (d, J = 5.7 Hz, OCH_2CH_3), 16.19 (d, $J = 5.9$ Hz, OCH_2CH_3). ^{19}F NMR (565 MHz, $CDCl_3$) $\delta = -67.18$ (d, $J = 6.0$ Hz). ^{19}F{/^{1}H} NMR (565 MHz, $CDCl_3$) $\delta = -67.18$ (s). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) $\delta = 19.15$ (s). HRMS (ESI) calcd for $C_{16}H_{21}F_3NO_6PNa$ ([M + Na]$^+$): 434.0956, found: 434.0935.

Procedure for the addition of diethyl phosphite to aldehydes 2–5

Compounds **10–15** were prepared according to the previously reported procedure.[27b] The NMR data for **10**,[27b] **13**,[27b] **17**,[56] **20**[28] were in good agreement.

Procedure A. To the respective aldehydes, diethyl phosphite (1 eq.) and TEA (0.2 eq.) were added and the reaction mixture was kept at 50 °C for 1 day (monitored by TLC or NMR). The reaction mixture was then diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with aqueous sodium bicarbonate then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude products were isolated using column chromatography (chloroform/methanol 99 : 1, v/v → chloroform/methanol 95 : 5).

Procedure B. Analogous treatment of aldehyde **4a** and diethyl phosphite (1 eq.) and *i*-Pr_2EtN (1.1 eq.) in CH_2Cl_2, (reflux) for 1 day gave crude products **16a,b**, which were isolated using column chromatography (chloroform/methanol 99 : 1, v/v → chloroform/methanol 95 : 5).

***tert*-Butyl((1*R*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3-phenylpropan-2-yl)carbamate (11a).** A white solid was isolated as a mixture with **11b**, which could not be separated by the chromatography techniques employed in this study (396 mg, 61%): ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 7.31$–7.16 (m, 5H, Ph), 5.84 (d, $J = 9.2$ Hz, 1H, N*H*), 5.73–5.65 (m, 1H, O*H*), 4.32–4.00 (m, 5H, 2 × OCH_2CH_3, $CHCH_2Ph$), 3.92–3.82 (m, 1H, C*H*P), 2.97 (d, J = 7.9 Hz, 2H, CH_2Ph), 1.40 (s, 9H, $C(CH_3)_3$), 1.32 (t, $J = 6.6$ Hz, 3H, OCH_2CH_3), 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) $\delta = 155.50$ (s, *C*=O), 138.07, 129.37, 128.25, 126.22 (4 × s, Ph), 78.95 (s, $C(CH_3)_3$), 67.63 (d, J = 163.0 Hz, *C*HP), 62.96 (d, $J = 7.1$ Hz, OCH_2CH_3), 62.43 (d, $J = 7.3$ Hz, OCH_2CH_3), 52.89 (s, $CHCH_2Ph$), 38.12 (s, CH_2Ph), 28.26 (s, $C(CH_3)_3$), 16.42–16.27 (m, 2 × OCH_2CH_3). ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) δ = 23.25 (s). HRMS (ESI) calcd for $C_{18}H_{30}NO_6PNa$ ([M + Na]$^+$): 410.1708, found: 410.1701.

***tert*-Butyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3-phenylpropan-2-yl)carbamate (11b).** ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) $\delta = 22.89$ (s).

Benzyl((1*R*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3-phenylpropan-2-yl)carbamate (12a). Pale yellow oil, isolated as a mixture with **12b**, which could not be separated by the chromatography techniques employed in this study (412 mg, 52%): ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 7.33$–7.17 (m, 10H, Ph), 6.19 (d, $J = 9.1$ Hz, 1H, N*H*), 5.41 (d, $J = 8.4$ Hz, 1H, O*H*), 5.07–4.99 (m, 2H, OCH_2Ph), 4.22–3.96 (m, 5H, 2 × OCH_2CH_3, $CHCH_2Ph$), 3.89–3.82 (m, 1H, C*H*P), 2.98 (d, J = 7.9 Hz, 2H, CH_2Ph), 1.38–1.24 (m, 3H, OCH_2CH_3), 1.23–1.17 (m, 3H, OCH_2CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.09 (s, *C*=O), 137.84, 136.66, 129.43, 128.43, 128.39, 128.34, 127.88, 126.44 (8 × s, Ph), 67.52 (d, $J = 162.7$ Hz, *C*HP), 66.43 (s, OCH_2Ph), 63.15 (d, $J = 7.0$ Hz, OCH_2CH_3), 62.64 (d, $J = 7.2$ Hz, OCH_2CH_3), 53.51 (s, $CHCH_2Ph$), 38.03 (s, CH_2Ph), 16.28 (d, $J = 4.5$ Hz, OCH_2CH_3), 16.24 (d, $J = 5.7$ Hz, OCH_2CH_3). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) $\delta = 23.06$ (s). HRMS (ESI) calcd for $C_{21}H_{28}NO_6PNa$ ([M + Na]$^+$): 444.1552, found: 444.1543.

Benzyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3-phenylpropan-2-yl)carbamate (12b). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) δ = 22.63 (s).

***tert*-Butyl((1*R*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3-methylbutan-2-yl)carbamate (14a).** The white solid was isolated as a mixture with **14b** that could not be separated by the chromatography techniques employed in this study (351 mg, 55%): ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 5.47$ (d, $J = 9.3$ Hz, 1H, N*H*), 5.06 (d, J = 5.5 Hz, 1H, O*H*), 4.26–4.08 (m, 5H, 2 × OCH_2CH_3, C*H*P), 3.52 (tdd, J = 8.5, 4.5, 2.6 Hz, 1H, $CHCH(CH_3)_2$), 2.11 (dq, $J = 13.4$, 7.0 Hz, 1H, $CH(CH_3)_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.38–1.30 (m, 6H, 2 × OCH_2CH_3), 0.97 ("t", J = 6.3 Hz, 6H, 2 × CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) $\delta = 156.38$ (s, *C*=O), 79.14 (s, $C(CH_3)_3$), 68.32 (d, $J = 162.7$ Hz, *C*HP), 63.02 (d, $J = 7.0$ Hz, OCH_2CH_3), 62.55 (d, $J = 7.6$ Hz, OCH_2CH_3), 56.76 (s, $CHCH(CH_3)_2$), 29.89 (d, J = 11.9 Hz, $CH(CH_3)_2$), 28.38 (s, $C(CH_3)_3$), 19.67 (s, CH_3), 19.19 (s, CH_3), 16.48 (d, J = 4.6 Hz, OCH_2CH_3), 16.45 (d, $J = 4.2$ Hz, OCH_2CH_3). ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) $\delta = 23.47$ (s). HRMS (ESI) calcd for $C_{14}H_{31}NO_6P$ ([M + H]$^+$): 340.1889, found: 340.1882.

***tert*-Butyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3-methylbutan-2-yl)carbamate (14b).** ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) $\delta = 23.04$ (s).

Benzyl((1*R*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3-methylbutan-2-yl)carbamate (15a). A white oil, slowly crystallizing, was isolated as a mixture with **15b** that could not be separated by the chromatography techniques employed in this study (298 mg, 41%): ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 7.40$–7.27 (m, 5H, Ph), 5.99 (d, $J = 9.6$ Hz, 1H, N*H*), 5.30 (dd, $J = 8.1$, 2.0 Hz, 1H, O*H*), 5.08 (s, 2H, CH_2Ph), 4.15–4.01 (m, 5H, 2× OCH_2CH_3, C*H*P), 3.64 (tdd, J = 9.1, 4.6, 2.3 Hz, 1H, $CHCH(CH_3)_2$), 2.07–2.01 (m, 1H, $CH(CH_3)_2$), 1.29 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.20 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.00–0.95 (m, 6H, 2 × CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) $\delta = 156.57$ (s, *C*=O), 136.79, 128.35, 127.99, 127.96 (4 × s, Ph), 67.84 (d, $J = 163.3$ Hz, *C*HP), 66.51 (s, CH_2Ph), 63.19 (d, $J = 7.3$ Hz, OCH_2CH_3), 62.57 (d, $J = 7.4$ Hz, OCH_2CH_3), 56.90 (s, $CHCH(CH_3)_2$), 30.39 (d, J = 12.3 Hz, $CH(CH_3)_2$), 19.54 (s, CH_3), 19.21 (s, CH_3), 16.40 (d, J = 5.4 Hz, OCH_2CH_3), 16.30 (d, J = 6.1 Hz, OCH_2CH_3). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) $\delta = 23.23$ (s). HRMS (ESI) calcd for $C_{17}H_{29}NO_6P$ ([M + H]$^+$): 374.1732, found: 374.1736.

Benzyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3-methylbutan-2-yl)carbamate (15b). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) δ = 23.17 (s).

Diethyl((*R*)-((*S*)-1-benzylpyrrolidin-2-yl)(hydroxy)methyl) phosphonate (16a). A white solid was isolated as a mixture with **16b**, which could not be separated by the chromatography techniques employed in this study (1062 mg, 61%): ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 7.50$–7.42 (m, 2H, Ph), 7.34–7.31 (m, 2H,

Ph), 7.24–7.26 (m, 1H, Ph), 4.73 (d, J = 13.3 Hz, 1H, C*H*HPh), 4.35–4.20 (m, 4H, 2 × OCH_2CH$_3$), 4.12 (ddd, J = 10.3, 8.3, 7.1 Hz, 1H, C*H*P), 3.91 (d, J = 7.2 Hz, 1H, C*H*CHP), 3.67 (d, J = 13.3 Hz, 1H, CH*H*Ph), 3.41 (m, 1H, NC*H*H), 3.00 (d, J = 13.6 Hz, 1H, NCH*H*), 2.96 (ddd, J = 10.0, 7.5, 2.9 Hz, 1H, C*H*HCH), 2.49 (td, J = 9.3, 7.2 Hz, 1H, CH*H*CH), 2.24 (dt, J = 13.5, 10.0 Hz, 1H, NCH$_2$C*H*H), 2.09 (ddd, J = 13.6, 8.7, 1.5 Hz, 1H, NCH$_2$CH*H*), 1.37 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.26 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 138.26, 128.41, 128.21, 126.71 (4 × s, Ph), 71.76 (d, J = 154.6 Hz, *C*HP), 69.42 (d, J = 2.9 Hz, *C*HCHP), 62.75 (d, J = 7.4 Hz, O*C*H$_2$CH$_3$), 62.22 (d, J = 7.5 Hz, O*C*H$_2$CH$_3$), 53.56 (s, *C*H$_2$Ph), 53.12 (s, NCH$_2$), 36.25 (d, J = 12.6 Hz, *C*H$_2$CH), 23.17 (d, J = 2.0 Hz, NCH$_2$*C*H$_2$), 16.50 (d, J = 5.6 Hz, OCH$_2$*C*H$_3$), 16.36 (d, J = 5.2 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 23.21 (s). HRMS (ESI) calcd for $C_{16}H_{27}NO_4P$ ([M + H]$^+$): 328.1672, found: 328.1667.

Diethyl((*S*)-((*S*)-1-benzylpyrrolidin-2-yl)(hydroxy)methyl) phosphonate (16b). δ ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.48–7.43 (m, 1H, Ph), 7.38–7.29 (m, 2H, Ph), 7.30–7.25 (m, 2H, Ph), 4.59 (s, 1H, O*H*), 4.36–4.25 (m, 4H, 2 × OCH_2CH$_3$), 4.26–4.16 (m, 1H, C*H*P), 3.99 (d, J = 13.5 Hz, 1H, C*H*HPh), 3.97 (d, J = 6.2 Hz, 1H, C*H*CHP), 3.82 (d, J = 12.8 Hz, 1H, CH*H*Ph), 3.38 (d, J = 14.2 Hz, 1H, NC*H*H), 3.05 (d, J = 14.3 Hz, 1H, NCH*H*), 2.82 (td, J = 9.0, 4.8 Hz, 1H, C*H*HCH), 2.35 (td, J = 9.6, 6.0 Hz, 1H, CH*H*CH), 2.26–2.19 (m, 1H, NCH$_2$C*H*H), 2.14 (ddd, J = 13.2, 9.3, 3.2 Hz, 1H, NCH$_2$CH*H*), 1.43 (s, 3H, OCH$_2$CH_3), 1.42 (s, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, CDCl$_3$) δ = 139.02, 128.69, 128.13, 127.17 (4 × s, Ph), 69.55 (d, J = 166.8 Hz, *C*HP), 69.51 (d, J = 5.0 Hz, *C*HCHP), 63.17 (d, J = 7.2 Hz, O*C*H$_2$CH$_3$), 62.15 (d, J = 6.8 Hz, O*C*H$_2$CH$_3$), 52.22 (s, *C*H$_2$Ph), 51.13 (s, NCH$_2$), 30.18 (d, J = 2.2 Hz, *C*H$_2$CH), 20.93 (s, NCH$_2$*C*H$_2$), 16.61 (d, J = 5.6 Hz, OCH$_2$*C*H$_3$), 16.57 (d, J = 5.7 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 24.22 (s).

Benzyl(*R*)-2-((*S*)-(diethoxyphosphoryl)(hydroxy)methyl) pyrrolidine-1-carboxylate (18a). White solid (860 mg, 76%). Compound **18a** is a mixture of two rotamers (3 : 1, r.r.). Major rotamer: ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.39–7.29 (m, 5H, Ph), 5.18 (d, J = 12.7 Hz, 1H, C*H*HPh), 5.12 (d, J = 12.6 Hz, 1H, CH*H*Ph), 4.35 (br d, J = 5.6 Hz, 1H, C*H*P), 4.26–4.14 (m, 5H, 2 × OCH_2CH$_3$, C*H*CHP), 3.64 (ddd, J = 11.3, 7.9, 4.0 Hz, 1H, NC*H*H), 3.46–3.41 (m, 1H, NCH*H*), 2.35–2.25 (m, 1H, C*H*HCH), 2.13–2.04 (m, 1H, CH*H*CH), 2.04–1.96 (m, 1H, NCH$_2$C*H*H), 1.77–1.70 (m, 1H, NCH$_2$CH*H*), 1.35 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.29 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, CDCl$_3$) δ = 156.60 (s, *C*═O), 136.46, 128.49, 128.06, 127.88 (4 × s, Ph), 70.16 (d, J = 156.0 Hz, *C*HP), 67.19 (s, *C*H$_2$Ph), 62.68 (d, J = 7.2 Hz, O*C*H$_2$CH$_3$), 62.53 (d, J = 6.8 Hz, O*C*H$_2$CH$_3$), 60.74 (d, J = 5.4 Hz, *C*HCHP), 47.58 (s, NCH$_2$), 27.51 (s, *C*H$_2$CH), 24.54 (s, NCH$_2$*C*H$_2$), 16.51–16.44 (m, 2 × OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 21.90 (s). Minor rotamer: ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.39–7.29 (m, 5H, Ph), 5.16 (d, J = 12.7 Hz, 1H, C*H*HPh), 5.11 (d, J = 12.6 Hz, 1H, CH*H*Ph), 4.45 (d, J = 11.1 Hz, 1H, C*H*P), 4.15–4.05 (m, 5H, 2 × OCH_2CH$_3$, C*H*CHP), 3.61–3.57 (m, 1H, NC*H*H), 3.46–3.41 (m, 1H, NCH*H*), 2.35–2.25 (m, 1H, C*H*HCH), 2.13–2.04 (m, 1H, CH*H*CH), 2.04–1.96 (m, 1H, NCH$_2$C*H*H), 1.77–1.70 (m, 1H, NCH$_2$CH*H*), 1.29 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.24 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, CDCl$_3$) δ = 154.70 (s, *C*═O), 136.46, 128.49, 128.06, 127.88 (4 × s, Ph), 70.08 (d, J = 156.4 Hz, *C*HP), 67.19 (br s, *C*H$_2$Ph), 62.68 (d, J = 7.2 Hz, O*C*H$_2$CH$_3$), 62.53 (d, J = 6.8 Hz, O*C*H$_2$CH$_3$), 58.16 (d, J = 10.0 Hz, *C*HCHP), 47.58 (s, NCH$_2$), 26.53 (s, *C*H$_2$CH), 24.34 (s, NCH$_2$*C*H$_2$), 16.51–16.44 (m, 2 × OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 22.47 (s). HRMS (ESI) calcd for $C_{17}H_{27}NO_6P$ ([M + H]$^+$): 372.1571, found: 372.1579.

Benzyl(*R*)-2-((*R*)-(diethoxyphosphoryl)(hydroxy)methyl) pyrrolidine-1-carboxylate (18b). Mixture of two rotamers (8.3 : 1, r.r.). Major rotamer: ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.39–7.32 (m, 5H, Ph), 5.21 (br s, 1H, O*H*), 5.17 (d, J = 12.0 Hz, 1H, C*H*HPh), 5.15 (d, J = 12.0 Hz, 1H, CH*H*Ph), 4.32 (ddd, J = 10.1, 6.9, 3.7 Hz, 1H, C*H*CHP), 4.28–4.14 (m, 4H, 2 × OCH_2CH$_3$), 3.83 (dd, J = 9.4, 4.6 Hz, 1H, C*H*P), 3.53 (br q, J = 7.9 Hz, 1H, NC*H*H), 3.43 (ddd, J = 11.0, 7.5, 4.7 Hz, 1H, NCH*H*), 2.26–2.21 (m, 1H, C*H*HCH), 2.08–2.03 (m, 1H, CH*H*CH), 1.96–1.90 (m, 1H, NCH$_2$C*H*H), 1.90–1.85 (m, 1H, NCH$_2$CH*H*), 1.37 (br t, J = 6.6 Hz, 6H, 2 × OCH$_2$CH_3). ^{13}C NMR (101 MHz, CDCl$_3$) δ = 158.65 (s, *C*═O), 136.14, 128.54, 128.20, 127.96 (4 × s, Ph), 72.68 (d, J = 159.4 Hz, *C*HP), 67.77 (s, *C*H$_2$Ph), 63.14 (d, J = 7.3 Hz, O*C*H$_2$CH$_3$), 62.55 (d, J = 7.0 Hz, O*C*H$_2$CH$_3$), 59.88 (d, J = 8.9 Hz, *C*HCHP), 46.96 (s, NCH$_2$), 28.27 (s, *C*H$_2$CH), 24.10 (s, NCH$_2$*C*H$_2$), 16.51 (d, J = 6.1 Hz, OCH$_2$*C*H$_3$), 16.45 (d, J = 5.7 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 21.22 (s). Minor rotamer: ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 22.08 (s).

Diethyl((*R*)-((*S*)-3-benzyl-2,2-dimethyloxazolidin-4-yl)(hydroxy) methyl)phosphonate (19a). Slightly yellow oil (269 mg, 40%): ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.35–7.31 (m, 4H, Ph), 7.30–7.26 (m, 1H, Ph), 4.23–4.18 (m, 2H, OCH_2CH$_3$), 4.20 (dd, J = 8.2, 3.8 Hz, 1H, C*H*P), 4.16 ("quintet", J = 7.0 Hz, 2H, OCH_2CH$_3$), 3.86 (d, J = 14.3 Hz, 1H, C*H*HPh), 3.57 (d, J = 14.3 Hz, 1H, CH*H*Ph), 3.42–3.40 (m, 1H, OC*H*H), 3.40–3.39 (m, 1H, C*H*CHP), 3.28 (dd, J = 11.9, 3.8 Hz, 1H, OCH*H*), 1.38 (s, 3H, C(CH_3)$_2$), 1.36 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.33 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.32 (s, 3H, C(CH_3)$_2$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 139.38, 128.59, 127.84, 127.43 (4 × s, Ph), 98.14 (d, J = 6.0 Hz, *C*(CH$_3$)$_2$), 72.09 (d, J = 170.1 Hz, *C*HP), 65.43 (d, J = 4.4 Hz, *C*HCHP), 62.97 (d, J = 7.0 Hz, O*C*H$_2$CH$_3$), 62.37 (d, J = 6.8 Hz, O*C*H$_2$CH$_3$), 59.47 (d, J = 2.9 Hz, O*C*H$_2$), 52.63 (s, *C*H$_2$Ph), 28.13 (s, C(*C*H$_3$)$_2$), 22.16 (s, C(*C*H$_3$)$_2$), 16.36 (d, J = 5.7 Hz, OCH$_2$*C*H$_3$), 16.34 (d, J = 5.5 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 22.36 (s). HRMS (ESI) calcd for $C_{17}H_{29}NO_5P$ ([M + H]$^+$): 358.1778, found: 358.1775.

Diethyl((*S*)-((*S*)-3-benzyl-2,2-dimethyloxazolidin-4-yl)(hydroxy) methyl)phosphonate (19b). Isolated as a mixture with **19a**, which could not be separated by the chromatography techniques employed in this study: ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.34–7.25 (m, 4H, Ph), 7.27–7.18 (m, 1H, Ph), 4.16 ("quintet", J = 7.0 Hz, 2H, OCH_2CH$_3$), 4.10 ("quintet", J = 7.0 Hz, 2H, OCH_2CH$_3$), 4.02–3.96 (m, 2H, OCH_2), 3.87 (d, J = 13.9 Hz, 1H, C*H*HPh), 3.57 (d, J = 13.8 Hz, 1H, CH*H*Ph), 3.40–3.39 (m, 1H, C*H*P), 3.39–3.37 (m, 1H, C*H*CHP), 1.31 (s, 3H, C(CH_3)$_2$), 1.28 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.27 (s, 3H, C(CH_3)$_2$), 1.23 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 139.13, 128.56, 128.03, 127.44 (4 × s, Ph), 95.14 (s, *C*(CH$_3$)$_2$), 65.41 (d, J = 166.2 Hz, *C*HP), 63.68 (d, J = 5.2 Hz, *C*HCHP), 63.37 (d, J = 1.3 Hz, O*C*H$_2$), 62.66 (d, J = 7.1 Hz, O*C*H$_2$CH$_3$), 62.27 (d, J =

6.7 Hz, OCH_2CH_3), 53.12 (s, CH_2Ph), 27.33 (s, C(CH_3)$_2$), 19.73 (s, C(CH_3)$_2$), 16.26 (d, J = 5.6 Hz, OCH_2CH_3), 16.20 (d, J = 5.9 Hz, OCH_2CH_3). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) δ = 21.86 (s).

Benzyl(*S*)-4-((*R*)-(diethoxyphosphoryl)(hydroxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (21a). Pale yellow oil (477 mg, 67%). Compound **21a** is a mixture of two rotamers (1.8 : 1, r.r.). Major rotamer: ^{1}H NMR (600 MHz, CD_3CN) δ = 7.45–7.36 (m, 5H, Ph), 5.17–5.11 (m, 2H, CH_2Ph), 4.36 (dd, J = 12.4, 7.2 Hz, 1H, C*H*P), 4.32 (br dd, J = 9.2, 2.6 Hz, 1H, OC*H*H), 4.26–4.21 (m, 1H, C*H*CHP), 4.15–4.10 (m, 2H, OCH_2CH$_3$), 4.08–3.96 (m, 3H, OCH*H*, OCH_2CH$_3$), 1.59 (s, 3H, C(CH_3)$_2$), 1.50 (s, 3H, C(CH_3)$_2$), 1.25 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.22 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (151 MHz, CD_3CN) δ = 153.54 (s, *C*=O), 138.28, 129.96, 129.45, 129.30 (4 × s, Ph), 95.44 (s, *C*(CH$_3$)$_2$), 68.03 (d, J = 159.9 Hz, *C*HP), 67.78 (s, CH_2Ph), 64.80 (s, OCH_2), 64.02 (d, J = 7.0 Hz, OCH_2CH$_3$), 63.56 (d, J = 6.9 Hz, OCH_2CH$_3$), 59.04 (d, J = 13.6 Hz, *C*HCHP), 26.33 (s, C(CH_3)$_2$), 24.16 (s, C(CH_3)$_2$), 17.27 (d, J = 5.4 Hz, OCH$_2$CH_3), 17.25 (d, J = 5.8 Hz, OCH$_2$CH_3). ^{31}P{/^{1}H} (243 MHz, CD_3CN) δ = 21.72 (s). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) δ = 21.84 (s). Minor rotamer: ^{1}H NMR (600 MHz, CD_3CN) δ = 7.45–7.36 (m, 5H, Ph), 5.20 (d, J = 12.5 Hz, 1H, C*H*HPh), 5.17–5.11 (m, 1H, CH*H*Ph), 4.52 (dd, J = 11.4, 7.1 Hz, 1H, C*H*P), 4.28 (br dd, J = 8.3, 3.3 Hz, 1H, OC*H*H), 4.26–4.21 (m, 1H, C*H*CHP), 4.15–4.10 (m, 1H, OCH*H*), 4.08–3.96 (m, 4H, 2 × OCH_2CH$_3$), 1.54 (s, 3H, C(CH_3)$_2$), 1.47 (s, 3H, C(CH_3)$_2$), 1.25 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.22 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (151 MHz, CD_3CN) δ = 154.32 (s, *C*=O), 138.28, 129.96, 129.45, 129.30 (4 × s, Ph), 95.12 (s, *C*(CH$_3$)$_2$), 68.12 (s, CH_2Ph), 66.70 (d, J = 159.9 Hz, *C*HP), 64.33 (s, OCH_2), 64.16 (d, J = 7.1 Hz, OCH_2CH$_3$), 63.56 (d, J = 6.9 Hz, OCH_2CH$_3$), 60.17 (d, J = 12.7 Hz, *C*HCHP), 26.99 (s, C(CH_3)$_2$), 25.94 (s, C(CH_3)$_2$), 17.27 (d, J = 5.4 Hz, OCH$_2$CH_3), 17.20 (d, J = 5.8 Hz, OCH$_2$CH_3). ^{31}P{/^{1}H} NMR (243 MHz, CD_3CN) δ = 22.04 (s). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) δ = 22.13 (s). HRMS (ESI) calcd for $C_{18}H_{28}NO_7PNa$ ([M + Na]$^+$): 424.1496, found: 424.1495.

Benzyl(*S*)-4-((*S*)-(diethoxyphosphoryl)(hydroxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (21b). Detected in the crude reaction mixture as one rotamer (not isolated, signals in NMR overlapped by major diastereoisomer): ^{31}P{/^{1}H} NMR (243 MHz, CD_3CN) δ = 21.72 (s). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) δ = 22.13 (s).

Procedure for reactions of 6a,b, 10a,b and 20a,b with nitrogen nucleophiles ($BnNH_2$, $MeNH_2$, $BzNH_2$) and/or with K_2CO_3

To a solution of benzylamine or methylamine (HCl salt) or benzamide (1.2 eq.) in acetonitrile (5 mL), potassium carbonate (1.2 eq. or 2.2 eq. in the case of methylamine HCl) was added. After 30 min, the α-hydroxyphosphonates (1 eq.) were added to the stirred solution. The reaction mixture was refluxed for 8 h. When the reaction was completed, water was added (10 mL) followed by extraction with a few portions of CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were isolated using column chromatography (chloroform/methanol or *n*-hexane/ethyl acetate → ethyl acetate/methanol).

Racemic mixture of (*E*)-3-(benzylamino)-4,4,4-trifluorobut-1-en-1-yl-diethyl phosphate (rac 22). Pale yellow oil (33 mg, 65%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.40–7.27 (m, 5H, Ph), 6.68 (dd, J = 12.1, 6.7 Hz, 1H, OC*H*=CH), 5.33 (ddd, J = 12.1, 9.0, 0.8 Hz, 1H, OCH=C*H*), 4.23–4.15 (m, 4H, 2 × OCH_2CH$_3$), 3.93 (d, J = 13.4 Hz, 1H, C*H*HPh), 3.79 (d, J = 13.4 Hz, 1H, CH*H*Ph), 3.53 (m, 1H, C*H*CF$_3$), 1.38 (t, J = 6.8 Hz, 3H, OCH$_2$CH_3), 1.37 (t, J = 6.7 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 141.86 (d, J = 5.2 Hz, O*C*H=CH), 138.71, 128.62, 128.13, 127.45 (4 × s, Ph), 125.25 (q, J = 281.7 Hz, *C*F$_3$), 109.3 (d, J = 10.5, 1.8 Hz, OCH=*C*H), 64.74 (d, J = 6.0 Hz, 2 × OCH_2CH$_3$), 50.56 (s, *C*H$_2$Ph), 16.07 (d, J = 6.8 Hz, OCH$_2$CH_3), 16.06 (d, J = 6.5 Hz, OCH$_2$CH_3). ^{19}F NMR (565 MHz, $CDCl_3$) δ = −75.84 (d, J = 6.9 Hz). ^{19}F{/^{1}H} NMR (565 MHz, $CDCl_3$) δ = −75.84 (s). ^{31}P{/^{1}H} NMR (243 MHz, $CDCl_3$) δ = −5.02 (s). HRMS (ESI) calcd for $C_{15}H_{22}F_3NO_4P$ ([M + H]$^+$): 368.1239, found: 368.1236.

Note 1: An analogous reaction of **6a,b** with K_2CO_3 (1.2 eq.) in acetonitrile (reflux, 8 h) according to the above procedure gave **22**.

Note 2: Reaction of **10a,b** (19 : 1, d.r.) with K_2CO_3 (1.2 eq.) or K_2CO_3 (1.2 eq.) and $BzNH_2$ (1.2 eq.) or with K_2CO_3 (1.2 eq.) and $BnNH_2$ (1.2 eq.) in acetonitrile (reflux, 8 h) according to the above procedure gave a partially racemized mixture of **10a,b** (1.5 : 1, d.r.).

Note 3: Reaction of **20a,b** (99 : 1, d.r.) with K_2CO_3 (1.2 eq.) or K_2CO_3 (1.2 eq.) and $BzNH_2$ (1.2 eq.) or with K_2CO_3 (1.2 eq.) and $BnNH_2$ (1.2 eq.) in acetonitrile (reflux, 8 h) according to the above procedure gave a partially racemized mixture of **20a,b** (3.6 : 1, d.r.).[12]

Procedure for the reactions of 6a,b–21a,b with $TsNH_2$

To a solution of *para*-toluenesulfonamide (1.2 eq.) in acetonitrile (5 mL), potassium carbonate (1.2 eq.) was added. After 30 min, the α-hydroxyphosphonates **6a,b–21a,b** (1 eq.) were added to the stirred reaction mixture. The solution was refluxed for 8 hours. When the reaction was completed, the reaction mixture was diluted with H_2O (10 mL) and extracted with a few portions of CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products **23a,b–39** were isolated using column chromatography (chloroform/methanol or *n*-hexane/ethyl acetate → ethyl acetate/methanol).

Racemic mixture of diethyl((*S*)-((2*R*,3*S*)-1-benzyl-3-(trifluoromethyl)aziridin-2-yl)((4-methylphenyl)sulfonamido)methyl)phosphonate (rac 23a). Pale yellow oil, slowly crystallising (44 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, J = 8.3 Hz, 2H, Ar), 7.30–7.10 (m, 7H, Ph, Ar), 6.30 (br s, 1H, N*H*SO$_2$), 4.30 (d, J = 13.6 Hz, 1H, C*H*HPh), 4.18–3.95 (m, 4H, 2 × OCH_2CH$_3$), 3.76 (dt, J = 17.8, 8.7 Hz, 1H, C*H*P), 2.94 (d, J = 13.6 Hz, 1H, CH*H*Ph), 2.31 (s, 3H, ArCH_3), 2.12 (br t, J = 6.5 Hz, 1H, C*H*CHCF$_3$), 1.91 ("quintet", J = 5.8 Hz, 1H, C*H*CF$_3$), 1.25 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 1.22 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.31, 138.08, 135.94, 129.39, 128.58, 128.46, 127.69, 127.08 (8 × s, Ar, Ph), 124.12 (q, J = 274.5 Hz, *C*F$_3$), 63.66 (d, J = 7.2 Hz, OCH_2CH$_3$), 63.31 (d, J = 6.9 Hz, OCH_2CH$_3$), 61.98 (s, *C*H$_2$Ph), 47.95 (d, J = 153.7 Hz,

*C*HP), 42.74 (d, J = 3.9 Hz, *C*HCHCF$_3$), 40.93 (dq, J = 38.6, 12.0 Hz, *C*HCF$_3$), 21.50 (s, Ar*C*H$_3$), 16.33 (d, J = 6.0 Hz, 2 × OCH$_2$*C*H$_3$). ^{19}F NMR (565 MHz, CDCl$_3$) δ = −65.85 (d, J = 5.8 Hz). ^{19}F{/^{1}H} NMR (565 MHz, CDCl$_3$) δ = −65.85 (s). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 20.79 (s). HRMS (ESI) calcd for $C_{22}H_{28}F_3N_2O_5PS$ ([M + H]$^+$): 521.1487, found: 521.1500.

Racemic mixture of diethyl((*R*)-((2*R*,3*S*)-1-benzyl-3-(trifluoromethyl)aziridin-2-yl)((4-methylphenyl)sulfonamido)methyl)phosphonate (rac 23b). Pale yellow oil slowly crystallising (7 mg, 12%): ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.74 (d, J = 8.1 Hz, 2H, Ar), 7.30–6.90 (m, 7H, Ph, Ar), 5.52 (br s, 1H, N*H*SO$_2$), 4.25–4.00 (m, 4H, 2 × OC*H*$_2$CH$_3$), 3.83 ("quintet", J = 9.5 Hz, 1H, C*H*P), 3.44 (d, J = 13.4 Hz, 1H, C*H*HPh), 2.63 (d, J = 13.5 Hz, 1H, CH*H*Ph), 2.18 (s, 3H, ArC*H*$_3$), 2.10–2.02 (m, 1H, C*H*CHCF$_3$), 1.98 ("quintet", J = 6.1 Hz, 1H, C*H*CF$_3$), 1.29 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.25 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 143.43, 138.30, 136.11, 129.45, 128.28, 128.10, 127.49, 127.41 (8 × s, Ar, Ph), 124.05 (q, J = 274.2 Hz, *C*F$_3$), 64.59 (d, J = 7.0 Hz, O*C*H$_2$CH$_3$), 62.90 (d, J = 6.6 Hz, O*C*H$_2$CH$_3$), 62.61 (s, *C*H$_2$Ph), 49.98 (dd, J = 157.8, 1.6 Hz, *C*HP), 43.29 (d, J = 11.4 Hz, *C*HCHCF$_3$), 42.58 (q, J = 39.1 Hz, *C*HCF$_3$), 21.38 (s, Ar*C*H$_3$), 16.43 (d, J = 5.8 Hz, OCH$_2$*C*H$_3$), 16.15 (d, J = 5.7 Hz, OCH$_2$*C*H$_3$). ^{19}F NMR (376 MHz, CDCl$_3$) δ = −65.68 (d, J = 6.1 Hz). ^{19}F{/^{1}H} NMR (565 MHz, CDCl$_3$) δ = −65.69 (s). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 19.55 (s). HRMS (ESI) calcd for $C_{22}H_{28}F_3N_2O_5PSNa$ ([M + Na]$^+$): 543.1306, found: 543.1290.

Racemic mixture of diethyl((*S*)-((4-methylphenyl)sulfonamido)((2*R*,3*S*)-3-(trifluoromethyl)aziridin-2-yl)methyl) phosphonate (rac 24a). Pale yellow oil, isolated as a mixture with rac **24b**, which could not be separated by the chromatography techniques employed in this study (35 mg, 80%): ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.77 (d, J = 8.3 Hz, 2H, Ar), 7.27 (d, J = 8.3 Hz, 2H, Ar), 6.30 (br s, 1H, N*H*SO$_2$), 4.22–4.02 (m, 4H, 2 × OC*H*$_2$CH$_3$), 3.76 (dt, J = 18.2, 8.6 Hz, 1H, C*H*P), 2.67–2.55 (m, 2H, C*H*CHCF$_3$, C*H*CF$_3$), 2.42 (s, 3H, ArC*H*$_3$), 1.32 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.27 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 143.25, 138.28, 129.36, 126.98 (4 × s, Ar), 124.29 (q, J = 274.8 Hz, *C*F$_3$), 63.65 (d, J = 7.3 Hz, O*C*H$_2$CH$_3$), 63.50 (d, J = 6.8 Hz, O*C*H$_2$CH$_3$), 48.28 (d, J = 154.9 Hz, *C*HP), 35.15 (br s, *C*HCHCF$_3$), 34.16 (dq, J = 39.6, 13.2 Hz, *C*HCF$_3$), 21.51 (s, Ar*C*H$_3$), 16.30 (d, J = 7.3 Hz, OCH$_2$*C*H$_3$), 16.26 (d, J = 6.8 Hz, OCH$_2$*C*H$_3$). ^{19}F NMR (376 MHz, CDCl$_3$) δ = −67.10 (d, J = 5.9 Hz). ^{19}F{/^{1}H} NMR (376 MHz, CDCl$_3$) δ = −67.10 (s). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 21.08 (s). HRMS (ESI) calcd for $C_{15}H_{22}F_3N_2O_5PSNa$ ([M + Na]$^+$): 453.0837, found: 453.0839.

Racemic mixture of diethyl((*R*)-((4-methylphenyl)sulfonamido)((2*R*,3*S*)-3-(trifluoromethyl)aziridin-2-yl)methyl) phosphonate (rac 24b). ^{19}F NMR (376 MHz, CDCl$_3$) δ = −66.98 (d, J = 6.2 Hz). ^{19}F{/^{1}H} NMR (376 MHz, CDCl$_3$) δ = −66.98 (s). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 19.60 (s).

Diethyl((1*R*,2*S*)-2-(dibenzylamino)-1-((4-methylphenyl) sulfonamido)-3-phenylpropyl)phosphonate (26a). Pale yellow solid (42 mg, 81%): ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.32–7.03 (m, 19H, Ar, Ph), 5.28 (dd, J = 9.2, 1.9 Hz, 1H, N*H*SO$_2$), 4.13–3.74 (m, 6H, 2 × OC*H*$_2$CH$_3$, NHC*H*$_2$Ph), 3.61–3.45 (m, 3H, C*H*P, NHC*H*$_2$Ph), 3.24 (dd, J = 13.3, 9.7 Hz, 1H, *CH*HPh), 3.14–2.94 (m, 1H, C*H*CH$_2$Ph), 2.80 (dd, J = 13.3, 5.6 Hz, 1H, CH*H*Ph), 2.39 (s, 3H, ArC*H*$_3$), 1.17 (t, J = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.14 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ = 142.89, 139.09, 138.97, 136.84, 129.51, 129.38, 128.87, 128.40, 128.31, 127.18, 127.11, 126.17 (12 × s, Ar, Ph), 63.44 (d, J = 2.9 Hz, *C*HCH$_2$Ph), 63.08 (d, J = 7.7 Hz, O*C*H$_2$CH$_3$), 62.38 (d, J = 6.7 Hz, O*C*H$_2$CH$_3$), 54.50 (s, NH*C*H$_2$Ph), 48.66 (d, J = 154.1 Hz, *C*HP), 31.46 (s, *C*HHPh), 21.50 (s, Ar*C*H$_3$), 16.20 (d, J = 5.2 Hz, OCH$_2$*C*H$_3$), 16.18 (d, J = 6.0 Hz, O*C*H$_2$CH$_3$). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 22.27 (s). HRMS (ESI) calcd for $C_{34}H_{42}N_2O_5PS$ ([M + H]$^+$): 621.2552, found: 621.2560.

***tert*-Butyl((1*R*,2*S*)-1-(diethoxyphosphoryl)-1-((4-methylphenyl) sulfonamido)-3-phenylpropan-2-yl)carbamate (27a).** White solid (37 mg, 72%): ^{1}H NMR (600 MHz, CD$_3$CN) δ = 7.89–7.78 (d, J = 8.0 Hz, 2H, Ar), 7.40 (d, J = 8.0 Hz, 2H, Ar), 7.26–7.15 (m, 3H, Ar), 7.03–6.93 (d, J = 6.8 Hz, 2H, Ar), 6.41 (br s, 1H, N*H*SO$_2$), 5.41 (d, J = 9.4 Hz, 1H, N*H*Boc), 4.27–3.87 (m, 6H, 2 × OC*H*$_2$CH$_3$, C*H*P, C*H*CH$_2$Ph), 2.88 (dd, J = 13.9, 3.4 Hz, 1H, *CH*HPh), 2.60 (dd, J = 13.9, 10.6 Hz, 1H, CH*H*Ph), 2.44 (s, 3H, ArC*H*$_3$), 1.31 (s, 9H, C(C*H*$_3$)$_3$), 1.27 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.22 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ = 155.56 (s, *C*═O), 143.40, 138.02, 137.54, 129.53, 129.36, 128.35, 127.17, 126.46 (8 × s, Ar, Ph), 79.58 (s, *C*(CH$_3$)$_3$), 63.15–62.87 (m, 2× O*C*H$_2$CH$_3$), 53.37 (d, J = 153.7 Hz, *C*HP), 52.25 (s, *C*HCH$_2$Ph), 37.94 (s, *C*H$_2$Ph), 28.20 (s, C(*C*H$_3$)$_3$), 21.49 (s, Ar*C*H$_3$), 16.35 (d, J = 5.7 Hz, OCH$_2$*C*H$_3$), 16.24 (d, J = 5.8 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 21.41 (s). HRMS (ESI) calcd for $C_{25}H_{37}N_2O_7$-PSNa ([M + Na]$^+$): 563.1957, found: 563.1954.

***tert*-Butyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-1-((4-methylphenyl) sulfonamido)-3-phenylpropan-2-yl)carbamate (27b).** White solid, isolated as a mixture with **27a**, which could not be separated by the chromatography techniques employed in this study (3 mg, 6%): ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.59 (d, J = 8.0 Hz, 2H, Ar), 7.26–7.19 (m, 5H, Ar), 6.96 (dd, J = 6.7, 2.8 Hz, 2H, Ar), 6.02–5.93 (br d, 1H, N*H*SO$_2$), 5.18 (d, J = 8.6 Hz, 1H, N*H*Boc), 4.25–4.06 (m, 4H, 2 × OC*H*$_2$CH$_3$), 3.83–3.62 (m, 2H, C*H*P, C*H*CH$_2$Ph), 2.96 (dd, J = 13.9, 7.6 Hz, 1H, *CH*HPh), 2.73 (dd, J = 14.0, 8.0 Hz, 1H, CH*H*Ph), 2.42 (s, 3H, ArC*H*$_3$), 1.39 (s, 9H, C(C*H*$_3$)$_3$), 1.36–1.27 (m, 6H, 2 × OCH$_2$C*H*$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ = 156.10 (s, *C*═O), 143.44, 137.17, 137.04, 129.76, 129.08, 128.50, 127.25, 126.63 (8 × s, Ar, Ph), 79.95 (s, *C*(CH$_3$)$_3$), 64.08 (d, J = 7.4 Hz, O*C*H$_2$CH$_3$), 62.82 (d, J = 6.7 Hz, O*C*H$_2$CH$_3$), 53.39 (d, J = 159.1 Hz, *C*HP), 51.92 (s, *C*HCH$_2$Ph), 38.07 (s, *C*H$_2$Ph), 28.27 (s, C(*C*H$_3$)$_3$), 21.55 (s, Ar*C*H$_3$), 16.43 (d, J = 5.6 Hz, OCH$_2$*C*H$_3$), 16.30 (d, J = 6.1 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, CDCl$_3$) δ = 20.34 (s). HRMS (ESI) calcd for $C_{25}H_{37}N_2O_7PSNa$ ([M + Na]$^+$): 563.1957, found: 563.1964.

Benzyl((1*R*,2*S*)-1-(diethoxyphosphoryl)-1-((4-methylphenyl) sulfonamido)-3-phenylpropan-2-yl)carbamate (28a). White solid, isolated as a mixture with **28b**, which could not be separated by the chromatography techniques employed in this study (26 mg, 40%): ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.75 (d, J = 7.9 Hz, 2H, Ar), 7.38–7.01 (m, 12H, Ar, Ph), 5.76 (s, 1H, N*H*SO$_2$), 5.31 (d, J = 9.6 Hz, 1H, N*H*Cbz), 5.00 (d, J = 12.4 Hz, 1H, OC*H*HPh), 4.97 (d, J = 12.4 Hz, 1H, OCH*H*Ph), 4.22–4.11 (m, 1H, C*H*CH$_2$Ph), 4.12–3.92 (m, 5H, 2 × OC*H*$_2$CH$_3$, C*H*P), 2.96 (dd, J = 14.0, 5.1 Hz, 1H, C*H*HPh), 2.81 (dd, J = 14.1, 9.3 Hz, 1H, CH*H*Ph), 2.40 (s, 3H, ArC*H*$_3$), 1.26–1.18 (m, 6H, 2 × OCH$_2$C*H*$_3$). ^{13}C NMR

(151 MHz, $CDCl_3$) δ = 156.11 (s, *C*=O), 143.56, 139.10, 137.99, 137.23, 136.36, 129.69, 129.63, 129.23, 128.41, 127.88, 127.14, 126.46 (12 × s, Ar, Ph), 66.67 (s, O*C*H_2Ph), 63.16 (d, J = 6.7 Hz, O*C*H_2CH$_3$), 63.12 (d, J = 7.0 Hz, O*C*H_2CH$_3$), 53.20 (d, J = 152.8 Hz, *C*HP), 52.73 (s, *C*HCH$_2$Ph), 37.66 (s, *C*H_2Ph), 21.51 (s, Ar*C*H$_3$), 16.32 (d, J = 5.6 Hz, OCH$_2$*C*H$_3$), 16.20 (d, J = 5.9 Hz, OCH$_2$*C*H$_3$). $^{31}P\{/^1H\}$ NMR (243 MHz, $CDCl_3$) δ = 20.97 (s). HRMS (ESI) calcd for $C_{28}H_{36}N_2O_7PS$ ($[M + H]^+$): 575.1981, found: 575.1980.

Benzyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-1-((4-methylphenyl) sulfonamido)-3-phenylpropan-2-yl)carbamate (28b). $^{31}P\{/^1H\}$ NMR (243 MHz, $CDCl_3$) δ = 19.66 (s).

***tert*-Butyl ((1*R*,2*S*)-1-(diethoxyphosphoryl)-3-methyl-1-((4-methylphenyl)sulfonamido)butan-2-yl)carbamate (30a).** Pale yellow oil, slowly crystallising (37 mg, 51%): ^1H NMR (600 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.1 Hz, 2H, Ar), 7.29 (d, J = 8.2 Hz, 2H, Ar), 5.83 (dd, J = 9.4, 4.6 Hz, 1H, N*H*SO$_2$), 4.85 (d, J = 10.1 Hz, 1H, N*H*Boc), 4.07–3.86 (m, 4H, 2 × OCH_2CH$_3$), 3.84 (ddd, J = 18.9, 9.1, 5.4 Hz, 1H, C*H*P), 3.67 (ddd, J = 13.2, 10.6, 6.8 Hz, 1H, C*H*CH(CH$_3$)$_2$), 2.42 (s, 3H, ArCH_3), 2.04 (sep, J = 6.8 Hz, 1H, C*H*(CH$_3$)$_2$), 1.43 (s, 9H, C(CH_3)$_3$), 1.21 (t, J = 7.1 Hz, 6H, 2 × OCH$_2$CH_3), 0.95 (d, J = 6.6 Hz, 3H, CH_3), 0.88 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.43 (s, *C*=O), 143.23, 138.29, 129.38, 127.09 (4 × s, Ar), 79.58 (s, *C*(CH$_3$)$_3$), 62.87 (d, J = 7.1 Hz, 2 × O*C*H$_2$CH$_3$), 56.03 (d, J = 5.9 Hz, *C*HCH(CH$_3$)$_2$), 52.09 (d, J = 155.7 Hz, *C*HP), 29.21 (d, J = 7.4 Hz, *C*H(CH$_3$)$_2$), 28.30 (s, C(*C*H$_3$)$_3$), 21.48 (s, Ar*C*H$_3$), 20.38 (s, *C*H$_3$), 17.45 (s, *C*H$_3$), 16.32 (d, J = 5.7 Hz, OCH$_2$*C*H$_3$), 16.23 (d, J = 5.7 Hz, OCH$_2$*C*H$_3$). $^{31}P\{/^1H\}$ NMR (243 MHz, $CDCl_3$) δ = 22.29 (s). HRMS (ESI) calcd for $C_{21}H_{37}N_2O_7PSNa$ ($[M + Na]^+$): 515.1957, found: 515.1952.

***tert*-Butyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-3-methyl-1-((4-methylphenyl)sulfonamido)butan-2-yl)carbamate (30b).** Could not be separated by the chromatography techniques employed in this study, detected in the crude reaction mixture. $^{31}P\{/^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 20.58 (s).

Benzyl((1*R*,2*S*)-1-(diethoxyphosphoryl)-3-methyl-1-((4-methylphenyl)sulfonamido)butan-2-yl)carbamate (31a). Pale yellow oil, slowly crystallising (26 mg, 42%): ^1H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, J = 8.3 Hz, 2H, Ar), 7.35 (m, 4H, Ph), 7.28–7.22 (m, 3H, Ph, Ar), 5.83 (dd, J = 9.3, 4.6 Hz, 1H, N*H*SO$_2$), 5.22 (d, J = 9.9 Hz, 1H, N*H*Cbz), 5.13 (d, J = 12.3 Hz, 1H, OC*H*HPh), 5.02 (d, J = 12.3 Hz, 1H, OCH*H*Ph), 4.07–3.80 (m, 5H, 2 × OCH_2CH$_3$, C*H*P), 3.82–3.68 (m, 1H, C*H*CH(CH$_3$)$_2$), 2.39 (s, 3H, ArCH_3), 2.06 (sep, J = 6.8 Hz, 1H, C*H*(CH$_3$)$_2$), 1.19 (t, J = 6.0 Hz, 3H, OCH$_2$CH_3), 1.18 (t, J = 8.0 Hz, 3H, OCH$_2$CH_3), 0.95 (d, J = 6.6 Hz, 3H, CH_3), 0.86 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.98 (s, *C*=O), 143.29, 138.26, 136.43, 129.41, 128.45, 128.03, 127.98, 127.02 (8 × s, Ar, Ph), 66.89 (s, O*C*H$_2$Ph), 62.95 (d, J = 7.5 Hz, O*C*H$_2$CH$_3$), 62.93 (d, J = 6.9 Hz, O*C*H$_2$CH$_3$), 56.62 (d, J = 5.9 Hz, *C*HCH(CH$_3$)$_2$), 52.06 (d, J = 155.4 Hz, *C*HP), 29.12 (d, J = 6.9 Hz, *C*H(CH$_3$)$_2$), 21.47 (s, Ar*C*H$_3$), 20.39 (s, C*C*H$_3$), 17.45 (s, C*C*H$_3$), 16.28 (d, J = 6.0 Hz, OCH$_2$*C*H$_3$), 16.21 (d, J = 6.1 Hz, OCH$_2$*C*H$_3$). $^{31}P\{/^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 21.79 (s). HRMS (ESI) calcd for $C_{24}H_{36}N_2O_7PS$ ($[M + H]^+$): 527.1981, found: 527.1978.

Benzyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-3-methyl-1-((4-methylphenyl)sulfonamido)butan-2-yl)carbamate (31b). Could not be separated by the chromatography techniques employed in this study, detected in the crude reaction mixture: $^{31}P\{/^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 20.24 (s).

***tert*-Butyl (*S*)-2-((*R*)-(diethoxyphosphoryl)(4-methylphenylsulfonamido)methyl)pyrrolidine-1-carboxylate (33a).** Transparent oil, slowly crystallising, isolated as a mixture with **33b**, which could not be separated by the chromatography techniques employed in this study (68 mg, 59%). Compound **33a** is a mixture of two rotamers (1.5 : 1, r.r.), mp. 119–121 °C. Major rotamer: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, J = 8.1 Hz, 2H, Ar), 7.27 (d, J = 8.1 Hz, 2H, Ar), 4.30 (dd, J = 21.4, 0.9 Hz, 1H, C*H*P), 4.18–4.05 (m, 4H, 2 × OCH_2CH$_3$), 4.04–3.91 (m, 1H, C*H*CHP), 3.13–2.96 (m, 2H, NCH_2), 2.41 (s, 3H, ArCH_3), 2.10–1.98 (m, 1H, C*H*HCH), 1.98–1.81 (m, 2H, NCH$_2$C*H*H, CH*H*CH), 1.64–1.58 (m, 1H, NCH$_2$CH*H*), 1.48 (s, 9H, C(CH_3)$_3$), 1.33 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3), 1.31 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.34 (s, *C*=O), 142.95, 138.36, 129.44, 127.18 (4 × s, Ar), 79.66 (s, *C*(CH$_3$)$_3$), 62.74 (d, J = 6.8 Hz, 2 × O*C*H$_2$CH$_3$), 58.26 (d, J = 8.1 Hz, *C*HCHP), 52.25 (d, J = 150.5 Hz, *C*HP), 47.10 (s, N*C*H$_2$), 28.47 (s, C(*C*H$_3$)$_3$), 27.99 (s, *C*H$_2$CH), 24.38 (s, NCH$_2$*C*H$_2$), 21.47 (s, Ar*C*H$_3$), 16.52–16.22 (m, 2 × OCH$_2$*C*H$_3$). $^{31}P\{/^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 21.03 (s). Minor rotamer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 8.1 Hz, 2H, Ar), 7.27 (d, J = 8.1 Hz, 2H, Ar), 4.60 (dd, J = 22.9, 1.4 Hz, 1H, C*H*P), 4.04–3.91 (m, 4H, 2 × OCH_2CH$_3$), 3.93–3.86 (m, 1H, C*H*CHP), 3.86–3.79 (m, 1H, NC*H*H), 3.36–3.25 (m, 1H, NCH*H*), 2.41 (br s, 3H, ArCH_3), 2.23–2.10 (m, 1H, C*H*HCH), 1.98–1.81 (m, 2H, NCH$_2$C*H*H, CH*H*CH), 1.64–1.58 (m, 1H, NCH$_2$CH*H*), 1.55 (s, 9H, C(CH_3)$_3$), 1.26 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3), 1.19 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.67 (s, *C*=O), 142.86, 138.91, 129.53, 126.58 (4 × s, Ar), 80.48 (s, *C*(CH$_3$)$_3$), 63.02 (d, J = 7.4 Hz, 2 × O*C*H$_2$CH$_3$), 57.03 (d, J = 14.0 Hz, *C*HCHP), 52.17 (d, J = 147.0 Hz, *C*HP), 46.01 (s, N*C*H$_2$), 28.45 (s, C(*C*H$_3$)$_3$), 27.31 (s, *C*H$_2$CH), 23.92 (s, NCH$_2$*C*H$_2$), 21.47 (s, Ar*C*H$_3$), 16.52–16.22 (m, 2 × OCH$_2$*C*H$_3$). $^{31}P\{/^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 21.54 (s). HRMS (ESI) calcd for $C_{21}H_{36}N_2O_7PS$ ($[M + H]^+$): 491.1975, found: 491.1986.

***tert*-Butyl(*S*)-2-((*S*)-(diethoxyphosphoryl)(4-methylphenylsulfonamido)methyl)pyrrolidine-1-carboxylate (33b).** Mixture of two rotamers (2.2 : 1, r.r.). Major rotamer: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, J = 8.1 Hz, 2H, Ar), 7.27 (d, J = 8.1 Hz, 2H, Ar), 4.18–4.05 (m, 5H, 2 × OCH_2CH$_3$, C*H*P), 3.55 (dd, J = 14.6, 10.4 Hz, 1H, C*H*CHP), 3.36–3.25 (m, 1H, NC*H*H), 2.79–2.71 (m, 1H, NCH*H*), 2.41 (s, 3H, ArCH_3), 2.23–2.10 (m, 1H, C*H*HCH), 1.81–1.74 (m, 1H, NCH$_2$CH*H*), 1.64–1.58 (m, 2H, CH*H*CH, NCH$_2$C*H*H), 1.46 (s, 9H, C(CH_3)$_3$), 1.26 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3), 1.19 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.30 (s, *C*=O), 142.90, 138.45, 129.37, 127.07 (4 × s, Ar), 80.05 (s, *C*(CH$_3$)$_3$), 62.50 (d, J = 6.8 Hz, 2 × O*C*H$_2$CH$_3$), 56.62 (d, J = 11.1 Hz, *C*HCHP), 55.13 (d, J = 156.8 Hz, *C*HP), 46.55 (s, N*C*H$_2$), 29.47 (s, *C*H$_2$CH), 28.41 (s, C(*C*H$_3$)$_3$), 23.38 (s, NCH$_2$*C*H$_2$), 21.47 (s, Ar*C*H$_3$), 16.52–16.22 (m, 2 × OCH$_2$*C*H$_3$). $^{31}P\{/^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 21.27 (s). Minor rotamer: $^{31}P\{/^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 21.40 (s).

Racemic mixture of benzyl (*R*)-2-((*S*)-(diethoxyphosphoryl)(4-methylphenylsulfonamido)methyl)pyrrolidine-1-carboxylate

(rac 34a). Transparent oil, slowly crystallising (60 mg, 75%). Isolated as a mixture with rac **34b**, which could not be separated by the chromatography techniques employed in this study. Compound rac **34a** is a mixture of two rotamers (2.5 : 1, r.r.), mp. 136–138 °C. Major rotamer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.74 (d, J = 8.3 Hz, 2H, Ar), 7.42–7.35 (m, 5H, Ph), 7.22 (d, J = 8.3 Hz, 2H, Ar), 6.35 (br s, 1H, N*H*), 5.16 (d, J = 12.4 Hz, 1H, C*H*HPh), 5.12 (d, J = 12.5 Hz, 1H, CH*H*Ph), 4.36 (dd, J = 22.1, 9.8 Hz, 1H, C*H*P), 4.17–4.09 (m, 2H, OCH_2CH$_3$), 4.07–4.00 (m, 2H, OCH_2CH$_3$), 3.97–3.91 (m, 1H, C*H*CHP), 3.43 (ddd, J = 12.0, 7.8, 4.7 Hz, 1H, NC*H*H), 3.15–3.11 (m, 1H, NCH*H*), 2.36 (br s, 3H, ArCH_3), 2.13–2.07 (m, 1H, C*H*HCH), 2.01–1.94 (m, 1H, CH*H*CH), 1.92–1.88 (m, 1H, NCH$_2$CH*H*), 1.66–1.59 (m, 1H, NCH$_2$CH*H*), 1.30 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3), 1.21 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.61 (s, *C*=O), 143.05, 138.3, 136.63, 129.48, 128.45, 127.96, 127.83, 127.04 (8 × s, Ar, Ph), 66.93 (s, *C*H$_2$Ph), 63.17 (d, J = 7.3 Hz, O*C*H$_2$CH$_3$), 62.89 (d, J = 7.0 Hz, O*C*H$_2$CH$_3$), 58.73 (d, J = 8.8 Hz, *C*HCHP), 51.94 (d, J = 150.4 Hz, *C*HP), 46.89 (s, N*C*H$_2$), 27.87 (s, *C*H$_2$CH), 24.45 (s, NCH$_2$*C*H$_2$), 21.44 (s, Ar*C*H$_3$), 16.30 (d, J = 5.9 Hz, 2 × OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) δ = 20.49 (s). Minor rotamer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.57 (d, J = 8.0 Hz, 2H, Ar), 7.42–7.35 (m, 5H, Ph), 7.22 (d, J = 8.0 Hz, 2H, Ar), 5.55 (dd, J = 9.7, 6.9 Hz, 1H, N*H*), 5.23 (d, J = 12.0 Hz, 1H, C*H*HPh), 5.12 (d, J = 12.0 Hz, 1H, CH*H*Ph), 4.49 (ddd, J = 22.5, 9.7, 2.0 Hz, 1H, C*H*P), 4.24–4.20 (m, 2H, OCH_2CH$_3$), 4.00–3.91 (m, 2H, OCH_2CH$_3$), 3.92–3.87 (m, 1H, C*H*CHP), 3.27 (dt, J = 9.8, 6.6 Hz, 1H, NC*H*H), 2.61 (dt, J = 10.7, 6.8 Hz, 1H, NCH*H*), 2.41 (s, 3H, ArCH_3), 2.28–2.20 (m, 1H, C*H*HCH), 2.00–1.94 (m, 1H, CH*H*CH), 1.92–1.88 (m, 1H, NCH$_2$C*H*H), 1.66–1.59 (m, 1H, NCH$_2$CH*H*), 1.25 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.19 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.15 (s, *C*=O), 143.00, 138.56, 136.16, 129.48, 128.53, 127.96, 127.83, 126.65 (8 × s, Ar, Ph), 67.43 (s, *C*H$_2$Ph), 63.17 (d, J = 7.3 Hz, O*C*H$_2$CH$_3$), 62.89 (d, J = 7.0 Hz, O*C*H$_2$CH$_3$), 57.13 (d, J = 13.7 Hz, *C*HCHP), 51.71 (d, J = 146.6 Hz, *C*HP), 46.40 (s, N*C*H$_2$), 27.60 (s, *C*H$_2$CH), 23.94 (s, NCH$_2$*C*H$_2$), 21.50 (s, Ar*C*H$_3$), 16.48 (d, J = 5.6 Hz, 2 × OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) δ = 20.71 (s). HRMS (ESI) calcd for $C_{24}H_{34}N_2O_7PS$ ([M + H]$^+$): 525.1819, found: 525.1834.

Racemic mixture of benzyl(*R*)-2-((*R*)-(diethoxyphosphoryl)(4-methylphenylsulfonamido)methyl)pyrrolidine-1-carboxylate (rac 34b). Isolated as a mixture with rac **34a**, which could not be separated by the chromatography techniques employed in this study. Mixture of two rotamers (4.5 : 1, r.r.). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, J = 8.2 Hz, 2H, Ar), 7.42–7.35 (m, 5H, Ph), 7.16 (d, J = 8.0 Hz, 2H, Ar), 6.22 (d, J = 8.3 Hz, 1H, N*H*), 5.09 (d, J = 12.4 Hz, 1H, C*H*HPh), 5.02 (d, J = 12.4 Hz, 1H, CH*H*Ph), 4.29–4.25 (m, 3H, C*H*CHP, OCH_2CH$_3$), 4.07–4.00 (m, 2H, OCH_2CH$_3$), 3.66–3.60 (m, 1H, C*H*P), 3.15–3.11 (m, 1H, NC*H*H), 2.72 (ddd, J = 10.3, 7.1, 3.1 Hz, 1H, NCH*H*), 2.31 (s, 3H, ArCH_3), 2.13–2.07 (m, 1H, C*H*HCH), 2.01–1.94 (m, 1H, CH*H*CH), 1.84–1.81 (m, 1H, NCH$_2$C*H*H), 1.74–1.70 (m, 1H, NCH$_2$CH*H*), 1.30 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.19 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.43 (s, *C*=O), 143.05 (br s), 138.36, 136.40, 129.52, 128.57, 127.83, 126.14, 126.69 (8 × s, Ar, Ph), 67.38 (s, *C*H$_2$Ph), 63.48 (d, J = 7.5 Hz, O*C*H$_2$CH$_3$), 62.63 (d, J = 6.9 Hz, O*C*H$_2$CH$_3$), 57.26 (d, J = 11.1 Hz, *C*HCHP), 55.15 (d, J = 156.3 Hz, *C*HP), 46.40 (s, N*C*H$_2$), 29.20 (s, *C*H$_2$CH), 23.37 (s, NCH$_2$*C*H$_2$), 21.38 (s, Ar*C*H$_3$), 16.21 (d, J = 6.1 Hz, 2 × OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) δ = 20.49 (s). Minor rotamer: ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) δ = 20.88 (s).

Racemic mixture of *tert*-butyl(*S*)-4-((*R*)-(diethoxyphosphoryl)(4-methylphenylsulfonamido)methyl)-2,2-dimethyloxazolidine-3-carboxylate (rac 36a). White solid (54 mg, 72%). Compound rac **36a** is a mixture of two rotamers (1.4 : 1, r.r.), mp. 152–153 °C. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, J = 8.1 Hz, 2H, Ar), 7.29 (d, J = 8.6 Hz, 2H, Ar), 5.39 (dd, J = 10.0, 4.2 Hz, 1H, N*H*), 4.53–4.45 (m, 1H, C*H*P), 4.28–4.22 (m, 2H, C*H*CHP, OC*H*H), 4.07–4.00 (m, 2H, OCH*H*, OC*H*HCH$_3$), 3.96–3.90 (m, 1H, OCH*H*CH$_3$), 3.90–3.86 (m, 1H, OC*H*HCH$_3$), 3.62–3.56 (m, 1H, OCH*H*CH$_3$), 2.42 (s, 3H, ArCH_3), 1.67 (s, 3H, C(CH_3)$_2$), 1.56 (s, 9H, C(CH_3)$_3$), 1.47 (s, 3H, C(CH_3)$_2$), 1.25–1.21 (m, 3H, OCH$_2$CH_3), 1.10 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.57 (s, *C*=O), 143.06, 138.47, 129.33, 127.35 (4 × s, Ar), 94.30 (s, *C*(CH$_3$)$_2$), 80.80 (s, *C*(CH$_3$)$_3$), 63.83 (s, O*C*H$_2$), 62.66 (d, J = 7.1 Hz, O*C*H$_2$CH$_3$), 62.56 (d, J = 7.3 Hz, O*C*H$_2$CH$_3$), 57.28 (d, J = 13.0 Hz, *C*HCHP), 49.80 (d, J = 151.6 Hz, *C*HP), 28.45 (s, C(*C*H$_3$)$_3$), 26.10 (s, C(*C*H$_3$)$_2$), 24.48 (s, C(*C*H$_3$)$_2$), 21.46 (s, Ar*C*H$_3$), 16.29 (d, J = 5.6 Hz, OCH$_2$*C*H$_3$), 16.18 (d, J = 5.5 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) δ = 21.34 (s). Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, J = 8.4 Hz, 2H, Ar), 7.29 (d, J = 8.6 Hz, 2H, Ar), 5.08 (dd, J = 9.2, 3.4 Hz, 1H, N*H*), 4.53–4.45 (m, 1H, C*H*P), 4.28–4.22 (m, 2H, C*H*CHP, OC*H*H), 4.07–4.00 (m, 4H, OCH*H*, *OCH*HCH$_3$, OCH_2CH$_3$), 3.90–3.86 (m, 1H, *OCH*HCH$_3$), 2.42 (s, 3H, ArCH_3), 1.58 (s, 9H, C(CH_3)$_3$), 1.44 (s, 3H, C(CH_3)$_2$), 1.39 (s, 3H, C(CH_3)$_2$), 1.28 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.25–1.21 (m, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.43 (s, *C*=O), 143.27, 138.84, 129.44, 126.98 (4 × s, Ar), 94.61 (s, *C*(CH$_3$)$_2$), 80.66 (s, *C*(CH$_3$)$_3$), 64.06 (s, O*C*H$_2$), 62.97 (d, J = 7.3 Hz, O*C*H$_2$CH$_3$), 62.45 (d, J = 7.0 Hz, O*C*H$_2$CH$_3$), 56.36 (d, J = 14.3 Hz, *C*HCHP), 51.59 (d, J = 152.1 Hz, *C*HP), 28.45 (s, C(*C*H$_3$)$_3$), 24.99 (s, C(*C*H$_3$)$_2$), 22.51 (s, C(*C*H$_3$)$_2$), 21.46 (s, Ar*C*H$_3$), 16.35 (d, J = 5.6 Hz, OCH$_2$*C*H$_3$), 16.31 (d, J = 6.0 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) δ = 21.19 (s). HRMS (ESI) calcd for $C_{22}H_{38}N_2O_8PS$ ([M + H]$^+$): 521.2081, found: 521.2090.

***tert*-Butyl(*S*)-4-((*S*)-(diethoxyphosphoryl)(4-methylphenylsulfonamido)methyl)-2,2-dimethyloxazolidine-3-carboxylate (36b).** Detected in the crude reaction mixture as one rotamer (not isolated): ^{31}P{/^{1}H} NMR (162 MHz, $CDCl_3$) δ = 21.03 (s).

Benzyl(*S*)-4-((*R*)-(diethoxyphosphoryl)(4-methylphenylsulfonamido)methyl)-2,2-dimethyloxazolidine-3-carboxylate (37a). White solid (47 mg, 75%). Compound **37a** is a mixture of two rotamers (1.2 : 1, r.r.). Major rotamer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.60 (d, J = 8.3 Hz, 2H, Ar), 7.50–7.47 (m, 2H, Ph), 7.41–7.36 (m, 3H, Ph), 7.22 (d, J = 8.0 Hz, 2H, Ar), 5.47 (dd, J = 9.6, 4.1 Hz, 1H, N*H*), 5.26 (d, J = 12.0 Hz, 1H, C*H*HPh), 5.12 (d, J = 12.0 Hz, 1H, CH*H*Ph), 4.36 (ddd, J = 19.2, 9.5, 2.6 Hz, 1H, C*H*P), 4.28–4.22 (m, 2H, OC*H*H, C*H*CHP), 4.07–4.02 (m, 2H, OCH*H*, OC*H*HCH$_3$), 3.98–3.95 (m, 1H, OCH*H*CH$_3$), 3.90–3.85

(m, 1H, OC*H*HCH$_3$), 3.80–3.75 (m, 1H, OCH*H*CH$_3$), 2.40 (s, 3H, ArC*H*$_3$), 1.56 (s, 3H, C(C*H*$_3$)$_2$), 1.49 (s, 3H, C(C*H*$_3$)$_2$), 1.09 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.10 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 152.03 (s, *C*=O), 143.33, 138.51, 136.29, 128.67, 128.31, 128.08, 127.41, 127.14 (8 × s, Ar, Ph), 95.19 (s, *C*(CH$_3$)$_2$), 67.39 (s, *C*H$_2$Ph), 64.37 (s, O*C*H$_2$), 63.02 (d, J = 7.7 Hz, O*C*H$_2$CH$_3$), 62.70 (d, J = 6.9 Hz, O*C*H$_2$CH$_3$), 56.41 (d, J = 14.6 Hz, *C*HCHP), 50.77 (d, J = 150.2 Hz, *C*HP), 25.06 (s, C(*C*H$_3$)$_2$), 23.03 (s, C(*C*H$_3$)$_2$), 21.57 (s, Ar*C*H$_3$), 16.32 (d, J = 5.9 Hz, OCH$_2$*C*H$_3$), 16.31 (d, J = 5.9 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 20.56. Minor rotamer: ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.77 (d, J = 8.3 Hz, 2H, Ar), 7.41–7.34 (m, 5H, Ph), 7.24 (d, J = 8.1 Hz, 2H, Ph), 5.65 (dd, J = 9.7, 4.6 Hz, 1H, N*H*), 5.23 (d, J = 12.3 Hz, 1H, C*H*HPh), 5.17 (d, J = 12.3 Hz, 1H, CH*H*Ph), 4.58 (ddd, J = 19.7, 9.6, 2.5 Hz, 1H, C*H*P), 4.28–4.22 (m, 2H, OC*H*H, C*H*CHP), 4.07–4.02 (m, 1H, OCH*H*), 3.98–3.95 (m, 1H, OC*H*HCH$_3$), 3.75–3.62 (m, 3H, OC*H*$_2$CH$_3$, OCH*H*CH$_3$), 2.38 (s, 3H, ArC*H*$_3$), 1.54 (s, 3H, C(C*H*$_3$)$_2$), 1.42 (s, 3H, C(C*H*$_3$)$_2$), 1.24 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.14 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 153.42 (s, *C*=O), 143.29, 138.42, 136.14, 128.67, 128.23, 128.08, 127.41, 127.14 (8 × s, Ar, Ph), 94.71 (s, *C*(CH$_3$)$_2$), 67.61 (s, *C*H$_2$Ph), 64.03 (s, O*C*H$_2$), 63.10 (d, J = 7.3 Hz, O*C*H$_2$CH$_3$), 62.94 (d, J = 6.9 Hz, O*C*H$_2$CH$_3$), 57.79 (d, J = 13.5 Hz, *C*HCHP), 49.63 (d, J = 151.2 Hz, *C*HP), 25.97 (s, C(*C*H$_3$)$_2$), 24.81 (s, C(*C*H$_3$)$_2$), 21.55 (s, Ar*C*H$_3$), 16.36 (d, J = 5.8 Hz, OCH$_2$*C*H$_3$), 16.23 (d, J = 5.8 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 20.89 (s). HRMS (ESI) calcd for $C_{25}H_{36}N_2O_8PS$ ([M + H]$^+$): 555.1924, found: 555.1919.

Benzyl(*S*)-4-((*S*)-(diethoxyphosphoryl)(4-methylphenylsulfonamido)methyl)-2,2-dimethyloxazolidine-3-carboxylate (37b). Detected in the crude reaction mixture as one rotamer (not isolated): ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 20.50 (s).

Racemic mixture of benzyl((*S*)-1-((2*S*,3*S*)-3-(diethoxyphosphoryl)-oxiran-2-yl)-2,2,2-trifluoroethyl)carbamate (rac 38). Pale yellow oil slowly crystallising (44 mg, 74%): ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.44–7.32 (m, 5H, Ph), 5.16 (s, 2H, C*H*$_2$Ph), 4.81–4.70 (m, 1H, C*H*P), 4.28–4.11 (m, 4H, 2 × OC*H*$_2$CH$_3$), 3.69–3.64 (m, 1H, C*H*CHCF$_3$), 2.93 (dd, J = 27.6, 2.4 Hz, 1H, C*H*CF$_3$), 1.68 (s, 1H, O*H*), 1.38 (t, J = 7.1 Hz, 6H, 2 × OCH$_2$C*H*$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 155.58 (s, *C*=O), 135.34, 128.68, 128.59, 128.25 (4 × s, Ph), 124.04 (q, J = 282.4 Hz, *C*F$_3$), 68.04 (s, *C*H$_2$Ph), 63.59 (d, J = 6.2 Hz, O*C*H$_2$CH$_3$), 63.29 (d, J = 6.3 Hz, O*C*H$_2$CH$_3$), 51.72 (d, J = 1.6 Hz, *C*HCHCF$_3$), 51.24 (q, J = 31.5 Hz, *C*HCF$_3$), 45.81 (d, J = 204.2 Hz, *C*HP), 16.45 (d, J = 5.4 Hz, OCH$_2$*C*H$_3$), 16.43 (d, J = 5.6 Hz, OCH$_2$*C*H$_3$). ^{19}F NMR (376 MHz, CDCl$_3$) δ = −75.49 (d, J = 7.8 Hz). ^{19}F{/^{1}H} NMR (565 MHz, CDCl$_3$) δ = −75.49 (s). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 15.89 (s). HRMS (ESI) calcd for $C_{16}H_{21}F_3NO_6P$ ([M + Na]$^+$): 434.0956, found: 434.0955.

Diethyl((4*S*,5*S*)-4-benzyl-2-oxooxazolidin-5-yl)phosphonate (39). Pale yellow oil, slowly crystallising (4 mg, 11%): ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.35 (t, J = 7.4 Hz, 2H, Ph), 7.29 (t, J = 7.4 Hz, 1H, Ph), 7.20 (d, J = 7.2 Hz, 2H, Ph), 5.06 (s, 1H, N*H*), 4.45 (dd, J = 6.1, 0.7 Hz, 1H, C*H*P), 4.33–4.25 (m, 1H, C*H*CH$_2$Ph), 4.26–4.17 (m, 4H, 2 × OC*H*$_2$CH$_3$), 3.06 (dd, J = 13.6, 4.4 Hz, 1H, *CH*HPh), 2.80 (dd, J = 13.6, 9.1 Hz, 1H, CH*H*Ph), 1.35 (m, 6H, 2 × OCH$_2$C*H*$_3$). ^{13}C NMR (151 MHz, CDCl$_3$) δ = 157.05 (s, *C*=O), 135.46, 129.16, 129.13, 127.52 (4 × s, Ar), 74.98 (d, J = 171.9 Hz, *C*HP), 64.03 (d, J = 6.7 Hz, O*C*H$_2$CH$_3$), 63.54 (d, J = 6.8 Hz, O*C*H$_2$CH$_3$), 54.90 (s, *C*HCH$_2$Ph), 42.22 (d, J = 8.9 Hz, *C*H$_2$Ph), 16.49 (d, J = 4.4 Hz, OCH$_2$*C*H$_3$), 16.46 (d, J = 4.4 Hz, OCH$_2$*C*H$_3$). ^{31}P{/^{1}H} NMR (243 MHz, CDCl$_3$) δ = 15.91 (s). HRMS (ESI) calcd for $C_{14}H_{21}NO_5P$ ([M + H]$^+$): 314.1157, found: 314.1155.

Conflicts of interest

There are no conflicts to declare.

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