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Functionalization of α-hydroxyphosphonates as a convenient route to *N*-tosyl-αaminophosphonates[†]

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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 K₂CO₃, *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.

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Introduction

α-Sulfonamide phosphonates constitute a very interesting class of compounds. They can be potential candidates for fluorescent-β-lactamase¹ and matrix metalloproteinase (MMPs) inhibitors² 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 reaction⁷ and its modifications,⁸ giving access to the synthesis of different types of α -functionalized phosphonates.⁹

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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 a-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 of α-hydroxyphosphonates into conversion 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 αhydroxyphosphonates 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 salt¹⁹ 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 a-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 a-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 transformed to *N*-unprotected 6a,b were 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. ¹⁹F, ³¹P 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 Nbenzyl 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-Pr₂EtN 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 BnNH₂ under acidic conditions, in the presence of Sc(OTf)₃, Yb(OTf)₃, Bi(OTf)₃, PBu₃, B(C₆F₅)₃, BiCl₃, TiCl₄ 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 K₂CO₃ and acetonitrile as a solvent. As a result, the phosphate **22** ($\delta = -5.01$ in ³¹P NMR) was formed (Scheme 2).

During the experiment, we observed the formation of diethyl phosphite ($\delta = 7.32$ in ³¹P NMR) and an aldehyde **1a** ($\delta = 9.30$ in ¹H 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 CF₃ 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





^{*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**, H₂/Pd/C, EtOH; 0 °C → rt; (iv) **7a,b**, Boc₂O, DMAP, MeCN, r.t., 1 d; (v) **7a,b**, CbzCl, NaHCO₃, CH₂Cl₂, 0 °C → rt, 1 d; (vi) HP(O)(OEt)₂, 1 eq. *i*-Pr₂EtN, CH₂Cl₂. ^{*b*} Isolated yield. ^{*c*} Crude reaction mixture (¹⁹F NMR and/or ³¹P NMR). ^{*d*} Configuration (2*S*). ^{*e*} Configuration (2*R*).

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



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 $\rm K_2CO_3$ 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 (TsNH₂) 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(1S,2R,3S)-**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 CaCl₂ with aniline was announced by Kaboudin *et al.*³¹ The results concerning the applied reaction conditions in the case of compounds **6a,b** with TsNH₂ 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 \rightarrow 60 °C), only signals of substrates were detected (¹⁹F, ³¹P 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% ¹⁹F, ³¹P 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 Bn Bn Bn TsNH₂, Base NHTs or/and Solvent, T, 8h P(O)(OEt)2 P(O)(OEt) rac 6a,b rac 23a,b rac 1a Solvent Yield^a [%] d.r.^b Entry d.r. Base (eq.) Temp. [°C] Product 1 20:1K₂CO₃ (1.2 eq.) MeCN Reflux 23a,b 74 6:1 2 1:1K₂CO₃ (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 20:1K₂CO₃ (12 eq.) MeCN Reflux 23a,b 80 9:14 Reflux MeCN 23a,b 96 9:1 5 1:1K₂CO₃ (12 eq.) 6 1:1K₂CO₃ (1.2 eq.) DMF 100 Decomp. 7 1:1K₂CO₃ (1.2 eq.) THF Reflux n.r. 7:1 8 K₂CO₃ (1.2 eq.) EtOH Reflux 23a,b 60 1:19 1:1None MeCN Reflux n.r. 10 TEA (1.2 eq.) MeCN Reflux 1:1n.r. TEA (1.2 eq.) Reflux 11 EtOH 1:1n.r. NaHCO₃ (1.2 eq.) 12 MeCN Reflux 1a 20 1:113 1:1NaHCO₃ (12 eq.) MeCN Reflux 1a 20 1:1NaH (1.2 eq.) THF Reflux 23a,b 18 8:1 14

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

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employment of other bases led to distinct results. In the presence of TEA, there were no reactions in MeCN, neither in EtOH. When NaHCO₃ 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 BnNH₂, MeNH₂ and BzNH₂. 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 TsNH₂ in detail using ¹⁹F 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 ¹⁹F NMR, which corresponded to the chemical shifts of β -CF₃imines 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 ³¹P NMR, with accompanying dominance of the diethyl phosphite signal). Finally, we decided to monitor the reactions of 6a,b with TsNH₂ and K₂CO₃ (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 ¹⁹F 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 -hydrox-yphosphonates **10a,b–12a,b** to *N*-tosylamide phosphonates **23a,b–37a,b**. Initially, we used 12 eq. of K₂CO₃ as a base, but



Scheme 3 Proposed reaction mechanism of 6a,b with TsNH₂ under K₂CO₃ conditions.

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-



^{*a*} Isolated yield. ^{*b*} Crude reaction mixture (¹⁹F NMR and/or ³¹P 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 Dgluco-configurations)³⁴ with TsNH₂ 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(1S,2R)-**34a** and rac(R,4S)-**36a** in the studied crystals. Apparently, during the reaction of **20a,b** (K₂CO₃, TsNH₂) 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



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.

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 (MeNH₂, BnNH₂) or benzamide (BzNH₂), 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 (K₂CO₃) 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 *a*-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 CF3 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

On the other hand, the reactions of **9a,b** (1 : 1.2, d.r.) with TsNH₂ (1.2 eq. K₂CO₃, 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 ³¹P 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** ($\delta_P = 15.89 \nu s$. 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 ¹⁹F and ³¹P NMR. Apparently, treatment of α -hydroxyphosphonate **9a** with base led to aziridine ring opening

P(O)(OEt)₂



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



NHTs

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 stereo-chemistry of **38** as rac(1S,2S,3S) were confirmed by NMR analysis and X-ray crystal structure determination (Fig. 5).

This aza-Payne rearrangement of non-fluorinated *N*-Boc³⁸ protected aziridinemethanols, as well as Ts,^{38,39} Mts⁴⁰ and Ms³⁸ protected aziridinemethanols, was previously reported. To the best of our knowledge, there are limited numbers of publications reporting the synthesis of trifluoromethylated epoxide phosphonates⁴¹ 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 TsNH₂ 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.*^{11*f*} Based on the detailed analysis of ¹H 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, *CHP*) and 4.33–4.25 ppm (m, *CHN*) in ¹H 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 TsNH₂, 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 P41212 space group as a single enantiomer (1R, 2S). 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, righthand screw axis). In all other crystal structures, the welldefined, 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

Experimental section

General methods

¹H NMR, ¹³C NMR, ¹⁹F NMR and ³¹P 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 ¹H NMR were expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard ($\delta = 0$) in CDCl₃ or using the residual solvent peak in the case of CD_3CN ($\delta = 1.96$). Chemical shifts of ¹³C NMR were expressed in parts per million downfield and upfield from $CDCl_3$ as an internal standard ($\delta = 77.0$). Chemical shifts of ¹⁹F NMR were expressed in parts per million upfield from CFCl₃ as an internal standard ($\delta = 0$) in CDCl₃. Chemical shifts of ³¹P NMR were expressed in parts per million in CDCl₃ and CD₃CN. All d.r. ratios were evaluated on the basis of ¹⁹F NMR or/and ³¹P NMR in the crude reaction mixture. Highresolution 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 \cdot (THF), CaH₂ \cdot (CH₂Cl₂, CH₃CN) and NaH \cdot (Et₂O), 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 N₂/n-hexane or liquid N₂/*i*-PrOH). TLC was performed on Merck Kieselgel 60-F254 with EtOAc/n-hexane and MeOH/CHCl₃ 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_a 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 SHELXT⁴⁹ and refined with the full-matrix least-squares procedure on F² 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**,^{27*b*} **4a**,⁵⁰ **4c**,⁵¹ **5a**,⁵² **5b**⁵³ were prepared as described. The NMR data for **2**–**3**,⁵⁴ **4b**,^{27*b*} **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% ¹H, ¹⁹F NMR): ¹H NMR (400 MHz, CDCl₃) δ = 9.30 (dq, *J* = 5.3, 2.6 Hz, 1H, CHO), 7.45–7.31 (m, 5H, Ph), 3.80 (d, *J* = 13.3 Hz, 1H, CHHPh), 3.75 (d, *J* = 13.4 Hz, 1H, CHHPh), 2.65 ("quintet", *J* = 6.3 Hz, 1H, CHCF₃), 2.50 (t, *J* = 6.1 Hz, 1H, CHCHCF₃). ¹H {/¹⁹F} NMR (376 MHz, CDCl₃) δ = 9.30 (d, *J* = 5.7 Hz, 1H, CHO), 7.44–7.24 (m, 5H, Ph), 3.79 (d, *J* = 13.4 Hz, 1H, CHHPh), 3.75 (d, *J* = 13.4 Hz, 1H, CHHPh), 2.68–2.61 (m, 1H, CHCF₃), 2.50 (t, *J* = 6.1 Hz, 1H, CHCHCF₃). ¹³C NMR (101 MHz, CDCl₃) δ = 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*F₃), 62.37 (s, *C*H₂Ph), 47.39 (s, *C*HCHCF₃), 44.47 (q, *J* = 40.8 Hz, CHCF₃). ¹⁹F NMR (376 MHz, CDCl₃) δ = -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%): ¹H NMR (400 MHz, CDCl₃) δ = 4.24 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 4.19 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 3.76 (br t, *J* = 7.8 Hz, 1H, CHP), 2.84–2.70 (m, 2H, CHCF₃, CHCHCF₃), 2.05 (br s, 1H, OH), 1.63 (br t, *J* = 8.8 Hz, 1H, NH), 1.38 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 1.37 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 124.58 (q, *J* = 274.0 Hz, CF₃), 66.79 (d, *J* = 158.9 Hz, CHP), 63.26 (d, *J* = 7.0 Hz, OCH₂CH₃), 63.18 (d, J = 6.9 Hz, OCH₂CH₃), 34.51 (d, J = 3.7 Hz, CHCHCF₃), 33.28 (dq, J = 39.7, 12.8 Hz, CHCF₃), 16.47 (d, J = 5.1 Hz, OCH₂CH₃), 16.43 (d, J = 5.3 Hz, OCH₂CH₃). ¹⁹F NMR (376 MHz, CDCl₃) $\delta = -66.75$ (br s). ¹⁹F{¹H} NMR (376 MHz, CDCl₃) $\delta = -66.76$ (d, J = 3.0 Hz). ³¹P{¹H} NMR (162 MHz, CDCl₃) $\delta = 22.53$ (d, J = 2.9 Hz). HRMS (ESI) calcd for C₈H₁₅-F₃NO₄PNa ([M + Na]⁺): 300.0589, found: 300.0589.

mixture diethyl((R)-hydroxy((2R,3S)-3-Racemic of (trifluoromethyl)aziridin-2-yl)methyl)phosphonate (rac 7b). Pale yellow oil (227 mg, 49%): ¹H NMR (400 MHz, CDCl₃) $\delta =$ 4.28–4.17 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 3.90 (t, J = 8.1 Hz, 1H, CHP), 2.94-2.75 (m, 2H, CHCF₃, CHCHCF₃), 1.86 (br s, 1H, OH), 1.81 (br t, J = 8.8 Hz, 1H, NH), 1.37 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.36(t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) $\delta =$ 124.29 (q, I = 273.6 Hz, CF_3), 65.72 (dd, I = 167.1, 1.5 Hz, CHP), $63.25 (d, J = 7.1 Hz, OCH_2CH_3), 62.98 (d, J = 7.3 Hz, OCH_2CH_3),$ 36.06 (d, J = 8.8 Hz, CHCHCF₃), 35.27 (q, J = 39.8 Hz, CHCF₃), 16.38 (d, J = 5.4 Hz, OCH₂CH₃), 16.34 (d, J = 5.4 Hz, OCH₂CH₃). ¹⁹F NMR (376 MHz, CDCl₃) $\delta = -66.65$ (d, J = 6.4 Hz). ¹⁹F{/¹H} NMR (376 MHz, CDCl₃) $\delta = -66,65$ (s). ³¹P{/¹H} NMR (162 MHz, CDCl_3) $\delta = 20.87$ (s). HRMS (ESI) calcd for $\text{C}_8\text{H}_{15}\text{F}_3\text{NO}_4\text{PNa}$ ([M + Na]⁺): 300.0589, found: 300.0585.

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

Aziridinyl phosphonates 7**a,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 CH₂Cl₂ (3 × 10 mL) and the layers were separated. The organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product **8b** was isolated using column chromatography (*n*-hexane/ethyl acetate 10 : 90, v/v \rightarrow ethyl acetate/methanol 99 : 1, v/v).

tert-butyl(2R,3S)-2-((R)-(diethox-Racemic mixture of yphosphoryl)(hydroxy)methyl)-3-(trifluoromethyl)aziridine-1carboxylate (rac 8b). Pale yellow oil (117 mg, 43%, 1.9 : 1 r.r. that could be isolated). Major rotamer: ¹H NMR (600 MHz, CDCl₃) δ = 5.03 (t, J = 9.6 Hz, 1H, CHP), 4.30–4.15 (m, 4H, 2 \times OCH₂CH₃), 2.97-2.84 (m, 2H, CHCF₃, CHCHCF₃), 1.53 (s, 9H, $C(CH_3)_3$, 1.36 (t, J = 7.1 Hz, 6H, $2 \times OCH_2CH_3$). ¹³C NMR (151 MHz, $CDCl_3$) $\delta = 152.13$ (s, C=O), 124.08 (q, I = 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_2CH_3), 62.95 (d, J = 6.7 Hz, OCH_2CH_3), 35.02 (q, J =41.4 Hz, CHCF₃), 34.27 (d, J = 8.9 Hz, CHCHCF₃), 27.68 (s, $C(CH_3)_3$, 16.36 (d, J = 5.9 Hz, OCH_2CH_3), 16.23 (d, J = 5.8 Hz, OCH₂*C*H₃). ¹⁹F NMR (565 MHz, CDCl₃) $\delta = -66.94$ (d, J = 6.6Hz). ¹⁹F{/¹H} NMR (565 MHz, CDCl₃) $\delta = -66.94$ (s). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = 16.47$ (s). HRMS (ESI) calcd for $C_{13}H_{23}F_{3}NO_{6}PNa$ ([M + Na]⁺): 400.1112, found: 400.1119. Minor rotamer: ¹H NMR (400 MHz, CDCl₃) $\delta = 4.88$ (t, J = 9.5 Hz, 1H, CHP), 4.32–4.18 (m, 4H, 2 \times OCH₂CH₃), 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 × OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) δ = 151.60 (s, *C*=O), 124.13 (q, *J* = 275.5 Hz, *C*F₃), 83.43 (s, *C*(CH₃)₃), 69.42 (d, *J* = 164.1 Hz, *C*HP), 63.32 (d, *J* = 7.1 Hz, OCH₂CH₃), 63.26 (d, *J* = 6.8 Hz, OCH₂CH₃), 33.58 (dq, *J* = 39.7, 11.2 Hz, *C*HCF₃), 32.66 (d, *J* = 2.6 Hz, *C*HCHCF₃), 27.54 (s, C(CH₃)₃), 16.43 (d, *J* = 5.8 Hz, OCH₂CH₃), 16.35 (d, *J* = 6.0 Hz, OCH₂CH₃). ¹⁹F NMR (376 MHz, CDCl₃) δ = -66.95 (br s). ¹⁹F{/¹H} NMR (376 MHz, CDCl₃) δ = -66.96 (s). ³¹P{/¹H} NMR (162 MHz, CDCl₃) δ = 17.64 (s). HRMS (ESI) calcd for C₁₃H₂₃F₃NO₆PK ([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. NaHCO₃ (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 MgSO₄, filtered and concentrated under reduced pressure. The crude products **9a,b** were isolated using column chromatography (*n*-hexane/ethyl acetate 10 : 90, v/v \rightarrow ethyl acetate/methanol 99 : 1, v/v).

benzyl(2R,3S)-2-((S)-(diethox-Racemic mixture of vphosphoryl)(hydroxy)methyl)-3-(trifluoromethyl)aziridine-1-carboxylate (rac 9a). Pale yellow oil, slowly crystallizing (118 mg, 34%): ¹H NMR (600 MHz, CDCl₃) $\delta = 7.42-7.33 \text{ (m, 5H, }$ Ph), 5.19 (d, J = 12.3 Hz, 1H, CHHPh), 5.16 (d, J = 12.3 Hz, 1H, CH*H*Ph), 4.25–4.10 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 3.80 (br t, J = 8.3 Hz, 1H, CHP), 3.17 (br q, J = 6.4 Hz, 1H, CHCHCF₃), 3.11 ("quintet", J = 5.7 Hz, 1H, CHCF₃), 1.28 (t, J = 7.0 Hz, 3H, OCH₂CH₃), 1.27 (t, J = 6.9 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) $\delta =$ 160.52 (s, C=O), 134.92, 128.61, 128.44, 128.16 (4 \times s, Ph), 122.98 (q, J = 275.0 Hz, CF_3), 69.06 (s, CH_2Ph), 65.22 (d, J =161.6 Hz, CHP), 63.42 (d, J = 7.3 Hz, OCH₂CH₃), 63.26 (d, J =7.0 Hz, OCH₂CH₃), 40.88 (d, J = 4.8 Hz, CHCHCF₃), 38.71 (dq, J $= 40.6, 12.4 \text{ Hz}, CHCF_3$, 16.34 (d, $J = 5.5 \text{ Hz}, OCH_2CH_3$), 16.28 (d, J = 5.6 Hz, OCH₂CH₃). ¹⁹F NMR (565 MHz, CDCl₃) $\delta =$ -67.26 (br s). ¹⁹F{/¹H} NMR (565 MHz, CDCl₃) $\delta = -67.27$ (d, J =2.2 Hz). ³¹P{/¹H} NMR (243 MHz, CDCl₃) 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-1carboxylate (rac 9b). Pale yellow oil, slowly crystallizing (101 mg, 40%) ¹H NMR (600 MHz, CDCl₃) 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 × OCH₂CH₃), 3.98 (br t, *J* = 8.4 Hz, 1H, CHP), 3.24 ("quintet", *J* = 6.2 Hz, 1H, CHCF₃), 3.21–3.15 (m, 1H, OH), 3.09 (dt, *J* = 9.3, 4.9 Hz, 1H, CHCHCF₃), 1.36 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃), 1.35 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) δ = 160.62 (s, *C*=O), 134.84, 128.52, 128.35, 128.06 (4 × s, Ph), 122.91 (q, *J* = 275.1 Hz, CF₃), 68.95 (s, CH₂Ph), 65.09 (dd, *J* = 161.7, 1.2 Hz, CHP), 63.32 (d, *J* = 7.3 Hz, OCH₂CH₃), 63.15 (d, J = 7.0 Hz, OCH₂CH₃), 40.82 (d, J = 5.2 Hz, CHCHCF₃), 38.61 (dq, J = 40.5, 12.6 Hz, CHCF₃), 16.25 (d, J = 5.7 Hz, OCH₂CH₃), 16.19 (d, J = 5.9 Hz, OCH₂CH₃). ¹⁹F NMR (565 MHz, CDCl₃) $\delta = -67.18$ (d, J = 6.0 Hz). ¹⁹F{/¹H} NMR (565 MHz, CDCl₃) $\delta = -67.18$ (s). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = 19.15$ (s). HRMS (ESI) calcd for C₁₆H₂₁F₃NO₆PNa ([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 \rightarrow chloroform/methanol 95 : 5).

Procedure B. Analogous treatment of aldehyde **4a** and diethyl phosphite (1 eq.) and *i*-Pr₂EtN (1.1 eq.) in CH₂Cl₂, (reflux) for 1 day gave crude products **16a,b**, which were isolated using column chromatography (chloroform/methanol 99 : 1, v/v \rightarrow chloroform/methanol 95 : 5).

tert-Butyl((1R,2S)-1-(diethoxyphosphoryl)-1-hydroxy-3phenylpropan-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%): ¹H NMR (600 MHz, CDCl₃) δ = 7.31–7.16 (m, 5H, Ph), 5.84 (d, I = 9.2 Hz, 1H, NH), 5.73-5.65 (m, 1H, OH), 4.32-4.00 (m, 5H, 100 H), 100 H) $2 \times OCH_2CH_3$, CHCH₂Ph), 3.92–3.82 (m, 1H, CHP), 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). ¹³C NMR (151 MHz, $CDCl_3$) $\delta = 155.50$ (s, C=O), 138.07, 129.37, 128.25, 126.22 $(4 \times s, Ph)$, 78.95 (s, $C(CH_3)_3$), 67.63 (d, J = 163.0 Hz, CHP), $62.96 (d, J = 7.1 Hz, OCH_2CH_3), 62.43 (d, J = 7.3 Hz, OCH_2CH_3),$ 52.89 (s, CHCH₂Ph), 38.12 (s, CH₂Ph), 28.26 (s, C(CH₃)₃), 16.42-16.27 (m, 2 × OCH₂*C*H₃). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta =$ 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). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 22.89$ (s).

Benzyl((1*R*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3phenylpropan-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%): ¹H NMR (600 MHz, CDCl₃) δ = 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, OCH₂Ph), 4.22-3.96 (m, 5H, 2 × OCH₂CH₃, CHCH₂Ph), 3.89-3.82 (m, 1H, CHP), 2.98 (d, *J* = 7.9 Hz, 2H, CH₂Ph), 1.38-1.24 (m, 3H, OCH₂CH₃), 1.23-1.17 (m, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) 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, CHP), 66.43 (s, OCH₂Ph), 63.15 (d, *J* = 7.0 Hz, OCH₂CH₃), 62.64 (d, *J* = 7.2 Hz, OCH₂CH₃), 53.51 (s, CHCH₂Ph), 38.03 (s, CH₂Ph), 16.28 (d, *J* = 4.5 Hz, OCH₂CH₃), 16.24 (d, *J* = 5.7 Hz, OCH₂CH₃). ³¹P{/¹H} NMR (243 MHz, CDCl₃) δ = 23.06 (s). HRMS (ESI) calcd for C₂₁H₂₈NO₆PNa ([M + Na]⁺): 444.1552, found: 444.1543.

Benzyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3-phenylpropan-2-yl)carbamate (12b). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = 22.63$ (s).

tert-Butyl((1R,2S)-1-(diethoxyphosphoryl)-1-hydroxy-3methylbutan-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%): ¹H NMR (600 MHz, CDCl₃) δ = 5.47 (d, J = 9.3 Hz, 1H, NH), 5.06 (d, J = 5.5 Hz, 1H, OH), 4.26–4.08 (m, 5H, 2 \times OCH_2CH_3 , CHP), 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(CH₃)₃), 1.38–1.30 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 0.97 ("t", J =6.3 Hz, 6H, $2 \times CH_3$). ¹³C NMR (151 MHz, CDCl₃) $\delta = 156.38$ (s, *C*==O), 79.14 (s, *C*(CH₃)₃), 68.32 (d, *J* = 162.7 Hz, *C*HP), 63.02 (d, J = 7.0 Hz, OCH₂CH₃), 62.55 (d, J = 7.6 Hz, OCH₂CH₃), 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, OCH₂*C*H₃), 16.45 (d, J = 4.2 Hz, OCH₂*C*H₃). ³¹P{/¹H} NMR (162 MHz, CDCl₃) δ = 23.47 (s). HRMS (ESI) calcd for C₁₄H₃₁NO₆P $([M + H]^{+})$: 340.1889, found: 340.1882.

tert-Butyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-1-hydroxy-3methylbutan-2-yl)carbamate (14b). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 23.04$ (s).

Benzyl((1R,2S)-1-(diethoxyphosphoryl)-1-hydroxy-3methylbutan-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%): ¹H NMR (600 MHz, CDCl₃) $\delta = 7.40$ -7.27 (m, 5H, Ph), 5.99 (d, J = 9.6 Hz, 1H, NH), 5.30 (dd, J = 8.1, 2.0 Hz, 1H, OH), 5.08 (s, 2H, CH_2Ph), 4.15–4.01 (m, 5H, 2× OCH_2CH_3 , CHP), 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, OCH₂CH₃), 1.20 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.00–0.95 (m, 6H, $2 \times CH_3$). ¹³C NMR (151 MHz, CDCl₃) $\delta = 156.57$ (s, C=O), 136.79, 128.35, 127.99, 127.96 ($4 \times s$, Ph), 67.84 (d, J = 163.3 Hz, CHP), 66.51 (s, CH_2Ph), 63.19 (d, J = 7.3 Hz, OCH_2CH_3), 62.57 $(d, J = 7.4 \text{ Hz}, OCH_2CH_3), 56.90 (s, CHCH(CH_3)_2), 30.39 (d, J =$ 12.3 Hz, $CH(CH_3)_2$, 19.54 (s, CH_3), 19.21 (s, CH_3), 16.40 (d, J =5.4 Hz, OCH₂CH₃), 16.30 (d, J = 6.1 Hz, OCH₂CH₃). ³¹P{/¹H} NMR (243 MHz, CDCl₃) δ = 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). ³¹P{/¹H} NMR (243 MHz, CDCl₃) 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%): ¹H NMR (600 MHz, CDCl₃) δ = 7.50-7.42 (m, 2H, Ph), 7.34-7.31 (m, 2H,

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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 \times OCH₂CH₃), 4.12 (ddd, J = 10.3, 8.3,7.1 Hz, 1H, CHP), 3.91 (d, J = 7.2 Hz, 1H, CHCHP), 3.67 (d, J = 13.3 Hz, 1H, CHHPh), 3.41 (m, 1H, NCHH), 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, CHHCH), 2.24 (dt, J = 13.5, 10.0 Hz, 1H, NCH₂CHH), 2.09 (ddd, J = 13.6, 8.7, 1.5 Hz, 1H, NCH₂CHH), 1.37 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.26 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) 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, OCH₂CH₃), 62.22 (d, *J* = 7.5 Hz, OCH₂CH₃), 53.56 (s, CH₂Ph), 53.12 (s, NCH₂), 36.25 (d, J = 12.6 Hz, CH_2CH), 23.17 (d, J = 2.0 Hz, NCH_2CH_2), 16.50 (d, J= 5.6 Hz, OCH₂CH₃), 16.36 (d, J = 5.2 Hz, OCH₂CH₃). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = 23.21$ (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, CDCl₃) $\delta = 7.48-7.43$ (m, 1H, Ph), 7.38-7.29 (m, 2H, Ph), 7.30-7.25 (m, 2H, Ph), 4.59 $(s, 1H, OH), 4.36-4.25 (m, 4H, 2 \times OCH_2CH_3), 4.26-4.16 (m, 1H, 2)$ CHP), 3.99 (d, *J* = 13.5 Hz, 1H, CHHPh), 3.97 (d, *J* = 6.2 Hz, 1H, CHCHP), 3.82 (d, *J* = 12.8 Hz, 1H, CHHPh), 3.38 (d, *J* = 14.2 Hz, 1H, NCHH), 3.05 (d, *J* = 14.3 Hz, 1H, NCHH), 2.82 (td, *J* = 9.0, 4.8 Hz, 1H, CHHCH), 2.35 (td, J = 9.6, 6.0 Hz, 1H, CHHCH), 2.26-2.19 (m, 1H, NCH₂CHH), 2.14 (ddd, J = 13.2, 9.3, 3.2 Hz, 1H, NCH₂CHH), 1.43 (s, 3H, OCH₂CH₃), 1.42 (s, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 139.02, 128.69, 128.13, 127.17 (4 \times s, Ph), 69.55 (d, I = 166.8 Hz, CHP), 69.51 (d, I = 5.0 Hz, CHCHP), 63.17 (d, J = 7.2 Hz, OCH₂CH₃), 62.15 (d, J = 6.8 Hz, OCH_2CH_3 , 52.22 (s, CH_2Ph), 51.13 (s, NCH_2), 30.18 (d, J =2.2 Hz, CH_2CH), 20.93 (s, NCH_2CH_2), 16.61 (d, J = 5.6 Hz, OCH₂*C*H₃), 16.57 (d, J = 5.7 Hz, OCH₂*C*H₃). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = 24.22$ (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: ¹H NMR (400 MHz, CDCl₃) $\delta = 7.39-7.29$ (m, 5H, Ph), 5.18 (d, J = 12.7 Hz, 1H, CHHPh), 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 × OCH₂CH₃, CHCHP), 3.64 (ddd, *J* = 11.3, 7.9, 4.0 Hz, 1H, NCHH), 3.46-3.41 (m, 1H, NCHH), 2.35-2.25 (m, 1H, CHHCH), 2.13-2.04 (m, 1H, CHHCH), 2.04–1.96 (m, 1H, NCH₂CHH), 1.77–1.70 (m, 1H, NCH₂CHH), 1.35 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.29 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) $\delta = 156.60$ (s, *C*=O), 136.46, 128.49, 128.06, 127.88 (4 × s, Ph), 70.16 (d, *J* = 156.0 Hz, CHP), 67.19 (s, CH_2Ph), 62.68 (d, J = 7.2 Hz, OCH_2CH_3), 62.53 (d, J = 6.8 Hz, OCH_2CH_3), 60.74 (d, J = 5.4 Hz, CHCHP), 47.58 (s, NCH₂), 27.51 (s, CH₂CH), 24.54 (s, NCH₂CH₂), 16.51–16.44 (m, $2 \times \text{OCH}_2\text{CH}_3$). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 21.90$ (s). Minor rotamer: ¹H NMR (400 MHz, CDCl₃) δ = 7.39–7.29 (m, 5H, Ph), 5.16 (d, J = 12.7 Hz, 1H, CHHPh), 5.11 (d, *J* = 12.6 Hz, 1H, CHHPh), 4.45 (d, *J* = 11.1 Hz, 1H, CHP), 4.15–4.05 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$, CHCHP), 3.61–3.57 (m, 1H, NCHH), 3.46-3.41 (m, 1H, NCHH), 2.35-2.25 (m, 1H, CHHCH), 2.13-2.04 (m, 1H, CHHCH), 2.04-1.96 (m, 1H, NCH₂CHH), 1.77-1.70 (m, 1H, NCH₂CHH), 1.29 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.24 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (101

MHz, CDCl₃) δ = 154.70 (s, *C*=O), 136.46, 128.49, 128.06, 127.88 (4 × s, Ph), 70.08 (d, *J* = 156.4 Hz, CHP), 67.19 (br s, *C*H₂Ph), 62.68 (d, *J* = 7.2 Hz, OCH₂CH₃), 62.53 (d, *J* = 6.8 Hz, OCH₂CH₃), 58.16 (d, *J* = 10.0 Hz, CHCHP), 47.58 (s, NCH₂), 26.53 (s, *C*H₂CH), 24.34 (s, NCH₂CH₂), 16.51–16.44 (m, 2 × OCH₂CH₃). ³¹P{/¹H} NMR (162 MHz, CDCl₃) δ = 22.47 (s). HRMS (ESI) calcd for C₁₇H₂₇NO₆P ([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: ¹H NMR (400 MHz, CDCl₃) δ = 7.39–7.32 (m, 5H, Ph), 5.21 (br s, 1H, OH), 5.17 (d, J = 12.0 Hz, 1H, CHHPh), 5.15 (d, J = 12.0 Hz, 1H, CHHPh), 4.32 (ddd, J = 10.1, 6.9, 3.7 Hz, 1H, CHCHP), 4.28–4.14 (m, 4H, $2 \times OCH_2CH_3$), 3.83 (dd, *J* = 9.4, 4.6 Hz, 1H, CHP), 3.53 (br q, *J* = 7.9 Hz, 1H, NCHH), 3.43 (ddd, J = 11.0, 7.5, 4.7 Hz, 1H, NCHH), 2.26–2.21 (m, 1H, CHHCH), 2.08-2.03 (m, 1H, CHHCH), 1.96-1.90 (m, 1H, NCH₂CHH), 1.90–1.85 (m, 1H, NCH₂CHH), 1.37 (br t, J = 6.6 Hz, 6H, 2 × OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 158.65 (s, *C*=O), 136.14, 128.54, 128.20, 127.96 (4 × s, Ph), 72.68 (d, *J* = 159.4 Hz, CHP), 67.77 (s, CH_2Ph), 63.14 (d, J = 7.3 Hz, OCH_2CH_3 , 62.55 (d, J = 7.0 Hz, OCH_2CH_3), 59.88 (d, J = 8.9 Hz, CHCHP), 46.96 (s, NCH₂), 28.27 (s, CH₂CH), 24.10 (s, NCH_2CH_2 , 16.51 (d, J = 6.1 Hz, OCH_2CH_3), 16.45 (d, J = 5.7 Hz, OCH₂*C*H₃). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 21.22$ (s). Minor rotamer: ${}^{31}P{/}^{1}H$ NMR (162 MHz, CDCl₃) $\delta = 22.08$ (s).

Diethyl((R)-((S)-3-benzyl-2,2-dimethyloxazolidin-4-yl)(hydroxy) methyl)phosphonate (19a). Slightly yellow oil (269 mg, 40%): ¹H NMR (600 MHz, CDCl₃) $\delta = 7.35 - 7.31$ (m, 4H, Ph), 7.30-7.26 (m, 1H, Ph), 4.23–4.18 (m, 2H, OCH₂CH₃), 4.20 (dd, *J* = 8.2, 3.8 Hz, 1H, CHP), 4.16 ("quintet", J = 7.0 Hz, 2H, OCH₂CH₃), 3.86 (d, J = 14.3 Hz, 1H, CHHPh), 3.57 (d, J = 14.3 Hz, 1H, CHHPh), 3.42-3.40 (m, 1H, OCHH), 3.40–3.39 (m, 1H, CHCHP), 3.28 (dd, J = 11.9, 3.8 Hz, 1H, OCHH), 1.38 (s, 3H, $C(CH_3)_2$), 1.36 (t, J =7.1 Hz, 3H, OCH_2CH_3), 1.33 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.32 (s, 3H, C(CH₃)₂). ¹³C NMR (151 MHz, CDCl₃) 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, OCH₂CH₃), 62.37 (d, J = 6.8 Hz, OCH₂CH₃), 59.47 (d, J= 2.9 Hz, OCH₂), 52.63 (s, CH₂Ph), 28.13 (s, C(CH₃)₂), 22.16 (s, $C(CH_3)_2$, 16.36 (d, J = 5.7 Hz, OCH_2CH_3), 16.34 (d, J = 5.5 Hz, OCH₂*C*H₃). ³¹P{/¹H} NMR (243 MHz, CDCl₃) 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: ¹H NMR (400 MHz, CDCl₃) $\delta =$ 7.34–7.25 (m, 4H, Ph), 7.27–7.18 (m, 1H, Ph), 4.16 ("quintet", J =7.0 Hz, 2H, OCH₂CH₃), 4.10 ("quintet", J = 7.0 Hz, 2H, OCH₂CH₃), 4.02–3.96 (m, 2H, OCH₂), 3.87 (d, J = 13.9 Hz, 1H, CHHPh), 3.57 (d, J = 13.8 Hz, 1H, CHHPh), 3.40–3.39 (m, 1H, CHP), 3.39–3.37 (m, 1H, CHCHP), 1.31 (s, 3H, C(CH₃)₂), 1.28 (t, J =7.1 Hz, 3H, OCH₂CH₃), 1.27 (s, 3H, C(CH₃)₂), 1.23 (t, J =7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) $\delta =$ 139.13, 128.56, 128.03, 127.44 (4 × s, Ph), 95.14 (s, C(CH₃)₂), 65.41 (d, J =1.3 Hz, OCH₂), 62.66 (d, J = 7.1 Hz, OCH₂CH₃), 62.27 (d, J = 6.7 Hz, OCH₂CH₃), 53.12 (s, CH₂Ph), 27.33 (s, C(CH₃)₂), 19.73 (s, C(CH₃)₂), 16.26 (d, J = 5.6 Hz, OCH₂CH₃), 16.20 (d, J = 5.9 Hz, OCH₂CH₃). ³¹P{¹H} NMR (243 MHz, CDCl₃) $\delta = 21.86$ (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: ¹H NMR (600 MHz, CD₃CN) δ = 7.45-7.36 (m, 5H, Ph), 5.17-5.11 (m, 2H, CH₂Ph), 4.36 (dd, J = 12.4, 7.2 Hz, 1H, CHP), 4.32 (br dd, *J* = 9.2, 2.6 Hz, 1H, OCHH), 4.26-4.21 (m, 1H, CHCHP), 4.15-4.10 (m, 2H, OCH₂CH₃), 4.08-3.96 (m, 3H, OCHH, OCH₂CH₃), 1.59 (s, 3H, C(CH₃)₂), 1.50 (s, 3H, C(CH₃)₂), 1.25 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.22 (t, J =7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CD₃CN) $\delta = 153.54$ (s, C=O), 138.28, 129.96, 129.45, 129.30 (4 \times s, Ph), 95.44 (s, $C(CH_3)_2$, 68.03 (d, J = 159.9 Hz, CHP), 67.78 (s, CH_2Ph), 64.80 $(s, OCH_2), 64.02 (d, J = 7.0 Hz, OCH_2CH_3), 63.56 (d, J = 6.9 Hz, OCH_2CH_3)$ OCH_2CH_3 , 59.04 (d, J = 13.6 Hz, CHCHP), 26.33 (s, $C(CH_3)_2$), 24.16 (s, $C(CH_3)_2$), 17.27 (d, J = 5.4 Hz, OCH_2CH_3), 17.25 (d, J =5.8 Hz, OCH₂CH₃). ³¹P{/¹H} (243 MHz, CD₃CN) $\delta = 21.72$ (s). ³¹P $\{/^{1}H\}$ NMR (243 MHz, CDCl₃) $\delta = 21.84$ (s). Minor rotamer: ¹H NMR (600 MHz, CD₃CN) δ = 7.45–7.36 (m, 5H, Ph), 5.20 (d, *J* = 12.5 Hz, 1H, CHHPh), 5.17–5.11 (m, 1H, CHHPh), 4.52 (dd, J = 11.4, 7.1 Hz, 1H, CHP), 4.28 (br dd, *J* = 8.3, 3.3 Hz, 1H, OCHH), 4.26-4.21 (m, 1H, CHCHP), 4.15-4.10 (m, 1H, OCHH), 4.08-3.96 (m, 4H, 2 \times OCH₂CH₃), 1.54 (s, 3H, C(CH₃)₂), 1.47 (s, 3H, $C(CH_3)_2$, 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.22 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CD₃CN) δ = 154.32 (s, C= O), 138.28, 129.96, 129.45, 129.30 ($4 \times s$, Ph), 95.12 (s, C(CH₃)₂), 68.12 (s, *C*H₂Ph), 66.70 (d, *J* = 159.9 Hz, *C*HP), 64.33 (s, OCH₂), 64.16 (d, J = 7.1 Hz, OCH₂CH₃), 63.56 (d, J = 6.9 Hz, OCH₂CH₃), 60.17 (d, J = 12.7 Hz, CHCHP), 26.99 (s, C(CH₃)₂), 25.94 (s, $C(CH_3)_2$, 17.27 (d, J = 5.4 Hz, OCH_2CH_3), 17.20 (d, J = 5.8 Hz, OCH_2CH_3). ³¹P{/¹H} NMR (243 MHz, CD₃CN) $\delta = 22.04$ (s). ³¹P $\{/^{1}H\}$ NMR (243 MHz, CDCl₃) $\delta = 22.13$ (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)-2,2dimethyloxazolidine-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, CD₃CN) δ = 21.72 (s). ${}^{31}P{/}^{1}H$ NMR (243 MHz, CDCl₃) δ = 22.13 (s).

Procedure for reactions of 6a,b, 10a,b and 20a,b with nitrogen nucleophiles (BnNH₂, MeNH₂, BzNH₂) and/or with K₂CO₃

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 CH₂Cl₂. The organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude products were isolated using column chromatography (chloroform/methanol or *n*hexane/ethyl acetate \rightarrow ethyl acetate/methanol).

Racemic mixture of (E)-3-(benzylamino)-4,4,4-trifluorobut-1en-1-yl-diethyl phosphate (rac 22). Pale yellow oil (33 mg, 65%): ¹H NMR (600 MHz, CDCl₃) δ = 7.40–7.27 (m, 5H, Ph), 6.68 (dd, J = 12.1, 6.7 Hz, 1H, OCH=CH), 5.33 (ddd, J = 12.1, 9.0, 0.8 Hz, 1H, OCH=CH), 4.23-4.15 (m, 4H, $2 \times OCH_2CH_3$), 3.93 (d, J =13.4 Hz, 1H, CHHPh), 3.79 (d, *J* = 13.4 Hz, 1H, CHHPh), 3.53 (m, 1H, CHCF₃), 1.38 (t, J = 6.8 Hz, 3H, OCH₂CH₃), 1.37 (t, J =6.7 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) $\delta = 141.86$ (d, *J* = 5.2 Hz, OCH=CH), 138.71, 128.62, 128.13, 127.45 (4 × s, Ph), 125.25 (q, J = 281.7 Hz, CF_3), 109.3 (d, J = 10.5, 1.8 Hz, OCH=CH), 64.74 (d, J = 6.0 Hz, $2 \times OCH_2CH_3$), 50.56 (s, CH_2Ph), 16.07 (d, J = 6.8 Hz, OCH_2CH_3), 16.06 (d, J = 6.5 Hz, OCH₂CH₃). ¹⁹F NMR (565 MHz, CDCl₃) $\delta = -75.84$ (d, I = 6.9Hz). ¹⁹F{/¹H} NMR (565 MHz, CDCl₃) $\delta = -75.84$ (s). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = -5.02$ (s). HRMS (ESI) calcd for $C_{15}H_{22}F_{3}NO_{4}P([M + H]^{+})$: 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 TsNH₂

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 H₂O (10 mL) and extracted with a few portions of CH₂Cl₂. The organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude products **23a,b–39** were isolated using column chromatography (chloroform/methanol or *n*-hexane/ethyl acetate \rightarrow ethyl acetate/methanol).

mixture Racemic diethyl((S)-((2R,3S)-1-benzylof 3-(trifluoromethyl)aziridin-2-yl)((4-methylphenyl)sulfonamido) methyl)phosphonate (rac 23a). Pale yellow oil, slowly crystallising (44 mg, 75%): ¹H NMR (400 MHz, CDCl₃) δ = 7.69 (d, J = 8.3 Hz, 2H, Ar), 7.30–7.10 (m, 7H, Ph, Ar), 6.30 (br s, 1H, NHSO₂), 4.30 (d, J = 13.6 Hz, 1H, CHHPh), 4.18–3.95 (m, 4H, 2 \times OCH_2CH_3 , 3.76 (dt, J = 17.8, 8.7 Hz, 1H, CHP), 2.94 (d, J =13.6 Hz, 1H, CH*H*Ph), 2.31 (s, 3H, ArC*H*₃), 2.12 (br t, *J* = 6.5 Hz, 1H, CHCHCF₃), 1.91 ("quintet", J = 5.8 Hz, 1H, CHCF₃), 1.25 (t, J = 7.0 Hz, 3H, OCH₂CH₃), 1.22 (t, J = 7.0 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 143.31, 138.08, 135.94, 129.39, 128.58, 128.46, 127.69, 127.08 (8 \times s, Ar, Ph), 124.12 (q, J =274.5 Hz, CF_3), 63.66 (d, J = 7.2 Hz, OCH_2CH_3), 63.31 (d, J =6.9 Hz, OCH_2CH_3), 61.98 (s, CH_2Ph), 47.95 (d, J = 153.7 Hz,

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CHP), 42.74 (d, J = 3.9 Hz, CHCHCF₃), 40.93 (dq, J = 38.6, 12.0 Hz, CHCF₃), 21.50 (s, ArCH₃), 16.33 (d, J = 6.0 Hz, 2 × OCH₂CH₃). ¹⁹F NMR (565 MHz, CDCl₃) $\delta = -65.85$ (d, J = 5.8Hz). ¹⁹F{/¹H} NMR (565 MHz, CDCl₃) $\delta = -65.85$ (s). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = 20.79$ (s). HRMS (ESI) calcd for C₂₂H₂₈F₃N₂O₅PS ([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 crystallis-

ing (7 mg, 12%): ¹H NMR (400 MHz, CDCl₃) δ = 7.74 (d, J = 8.1 Hz, 2H, Ar), 7.30-6.90 (m, 7H, Ph, Ar), 5.52 (br s, 1H, NHSO₂), 4.25–4.00 (m, 4H, 2 × OCH₂CH₃), 3.83 ("quintet", J = 9.5 Hz, 1H, CHP), 3.44 (d, J = 13.4 Hz, 1H, CHHPh), 2.63 (d, J = 13.5 Hz, 1H, CHHPh), 2.18 (s, 3H, ArCH₃), 2.10-2.02 (m, 1H, CHCHCF₃), 1.98 ("quintet", I = 6.1 Hz, 1H, CHCF₃), 1.29 (t, I = 7.1 Hz, 3H, OCH_2CH_3 , 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ¹³C NMR (151 MHz, CDCl_3) $\delta = 143.43, 138.30, 136.11, 129.45, 128.28, 128.10,$ 127.49, 127.41 (8 × s, Ar, Ph), 124.05 (q, J = 274.2 Hz, CF_3), 64.59 $(d, J = 7.0 \text{ Hz}, \text{OCH}_2\text{CH}_3), 62.90 (d, J = 6.6 \text{ Hz}, \text{OCH}_2\text{CH}_3), 62.61$ (s, CH_2Ph), 49.98 (dd, J = 157.8, 1.6 Hz, CHP), 43.29 (d, J =11.4 Hz, CHCHCF₃), 42.58 (q, J = 39.1 Hz, CHCF₃), 21.38 (s, Ar CH_3), 16.43 (d, J = 5.8 Hz, OCH₂ CH_3), 16.15 (d, J = 5.7 Hz, OCH₂CH₃). ¹⁹F NMR (376 MHz, CDCl₃) $\delta = -65.68$ (d, J = 6.1Hz). ¹⁹F{/¹H} NMR (565 MHz, CDCl₃) $\delta = -65.69$ (s). ³¹P{/¹H} NMR (162 MHz, CDCl₃) δ = 19.55 (s). HRMS (ESI) calcd for $C_{22}H_{28}F_{3}N_{2}O_{5}PSNa$ ([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%): ¹H NMR (600 MHz, CDCl₃) δ = 7.77 (d, J = 8.3 Hz, 2H, Ar), 7.27 (d, J = 8.3 Hz, 2H, Ar), 6.30 (br s, 1H, NHSO₂), 4.22–4.02 (m, 4H, $2 \times$ OCH₂CH₃), 3.76 (dt, J = 18.2, 8.6 Hz, 1H, CHP), 2.67–2.55 (m, 2H, CHCHCF₃, CHCF₃), 2.42 (s, 3H, ArCH₃), 1.32 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.27 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) $\delta = 143.25$, 138.28, 129.36, 126.98 (4 × s, Ar), 124.29 (q, J = 274.8 Hz, CF_3), 63.65 (d, J = 7.3 Hz, OCH_2CH_3), 63.50 (d, J = 6.8 Hz, OCH₂CH₃), 48.28 (d, J = 154.9 Hz, CHP), 35.15 (br s, CHCHCF₃), 34.16 (dq, J = 39.6, 13.2 Hz, CHCF₃), 21.51 (s, ArCH₃), 16.30 (d, J = 7.3 Hz, OCH₂CH₃), 16.26 (d, J = 6.8 Hz, OCH₂*C*H₃). ¹⁹F NMR (376 MHz, CDCl₃) $\delta = -67.10$ (d, J = 5.9 Hz). ¹⁹F{/¹H} NMR (376 MHz, CDCl₃) δ = -67.10 (s). ³¹P $\{/^{1}H\}$ NMR (162 MHz, CDCl₃) $\delta = 21.08$ (s). HRMS (ESI) calcd for $C_{15}H_{22}F_{3}N_{2}O_{5}PSNa$ ([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). ¹⁹F NMR (376 MHz, CDCl₃) $\delta = -66.98$ (d, *J* = 6.2 Hz). ¹⁹F{/¹H} NMR (376 MHz, CDCl₃) $\delta = -66.98$ (s). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 19.60$ (s).

Diethyl((1*R*,2*S*)-2-(dibenzylamino)-1-((4-methylphenyl) sulfonamido)-3-phenylpropyl)phosphonate (26a). Pale yellow solid (42 mg, 81%): ¹H NMR (400 MHz, CDCl₃) δ = 7.32– 7.03 (m, 19H, Ar, Ph), 5.28 (dd, *J* = 9.2, 1.9 Hz, 1H, NHSO₂), 4.13–3.74 (m, 6H, 2 × OCH₂CH₃, NHCH₂Ph), 3.61–3.45 (m, 3H, CHP, NHCH₂Ph), 3.24 (dd, *J* = 13.3, 9.7 Hz, 1H, CHHPh), 3.14– 2.94 (m, 1H, CHCH₂Ph), 2.80 (dd, *J* = 13.3, 5.6 Hz, 1H, CHHPh), 2.39 (s, 3H, ArCH₃), 1.17 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 1.14 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) $\delta = 142.89$, 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, CHCH₂Ph), 63.08 (d, J = 7.7 Hz, OCH₂CH₃), 62.38 (d, J = 6.7 Hz, OCH₂CH₃), 54.50 (s, NHCH₂Ph), 48.66 (d, J = 154.1 Hz, CHP), 31.46 (s, CHHPh), 21.50 (s, ArCH₃), 16.20 (d, J = 5.2 Hz, OCH₂CH₃), 16.18 (d, J = 6.0 Hz, OCH₂CH₃). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 22.27$ (s). HRMS (ESI) calcd for C₃₄H₄₂N₂O₅PS ([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%): ¹H NMR (600 MHz, CD₃CN) 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, NHSO₂), 5.41 (d, J= 9.4 Hz, 1H, NHBoc), 4.27–3.87 (m, 6H, $2 \times OCH_2CH_3$, CHP, CHCH₂Ph), 2.88 (dd, J = 13.9, 3.4 Hz, 1H, CHHPh), 2.60 (dd, J = 13.9, 10.6 Hz, 1H, CHHPh), 2.44 (s, 3H, ArCH₃), 1.31 (s, 9H, $C(CH_3)_3$, 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.22 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) δ = 155.56 (s, C=O), 143.40, 138.02, 137.54, 129.53, 129.36, 128.35, 127.17, 126.46 (8 \times s, Ar, Ph), 79.58 (s, C(CH₃)₃), 63.15–62.87 (m, 2 \times OCH₂CH₃), 53.37 (d, J = 153.7 Hz, CHP), 52.25 (s, CHCH₂Ph), 37.94 (s, CH_2Ph), 28.20 (s, C(CH_3)₃), 21.49 (s, Ar CH_3), 16.35 (d, J = 5.7 Hz, OCH₂*C*H₃), 16.24 (d, J = 5.8 Hz, OCH₂*C*H₃). ³¹P{/¹H} NMR (162) MHz, CDCl₃) $\delta = 21.41$ (s). HRMS (ESI) calcd for C₂₅H₃₇N₂O₇- $PSNa ([M + Na]^+): 563.1957, found: 563.1954.$

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%): ¹H NMR (400 MHz, CDCl₃) 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, NHSO₂), 5.18 (d, J = 8.6 Hz, 1H, NHBoc), 4.25-4.06 (m, 4H, 2 \times OCH₂CH₃), 3.83–3.62 (m, 2H, CHP, CHCH₂Ph), 2.96 (dd, *J* = 13.9, 7.6 Hz, 1H, *CH*HPh), 2.73 (dd, *J* = 14.0, 8.0 Hz, 1H, CHHPh), 2.42 (s, 3H, ArCH₃), 1.39 (s, 9H, C(CH₃)₃), 1.36-1.27 (m, 6H, 2 × OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) 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, OCH_2CH_3), 62.82 (d, J = 6.7 Hz, OCH_2CH_3), 53.39 (d, J =159.1 Hz, CHP), 51.92 (s, CHCH2Ph), 38.07 (s, CH2Ph), 28.27 (s, $C(CH_3)_3$, 21.55 (s, ArCH₃), 16.43 (d, J = 5.6 Hz, OCH₂CH₃), 16.30 $(d, J = 6.1 \text{ Hz}, \text{ OCH}_2CH_3)$. ³¹P $\{/^1H\}$ NMR (162 MHz, CDCl₃) $\delta =$ 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%): ¹H NMR (600 MHz, CDCl₃) δ = 7.75 (d, *J* = 7.9 Hz, 2H, Ar), 7.38–7.01 (m, 12H, Ar, Ph), 5.76 (s, 1H, NHSO₂), 5.31 (d, *J* = 9.6 Hz, 1H, NHCbz), 5.00 (d, *J* = 12.4 Hz, 1H, OCHHPh), 4.97 (d, *J* = 12.4 Hz, 1H, OCHHPh), 4.22–4.11 (m, 1H, CHCH₂Ph), 4.12–3.92 (m, 5H, 2 × OCH₂CH₃, CHP), 2.96 (dd, *J* = 14.0, 5.1 Hz, 1H, CHHPh), 2.81 (dd, *J* = 14.1, 9.3 Hz, 1H, CHHPh), 2.40 (s, 3H, ArCH₃), 1.26–1.18 (m, 6H, 2 × OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) 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, OCH₂Ph), 63.16 (d, *J* = 6.7 Hz, OCH₂CH₃), 63.12 (d, *J* = 7.0 Hz, OCH₂CH₃), 53.20 (d, *J* = 152.8 Hz, CHP), 52.73 (s, CHCH₂Ph), 37.66 (s, CH₂Ph), 21.51 (s, ArCH₃), 16.32 (d, *J* = 5.6 Hz, OCH₂CH₃), 16.20 (d, *J* = 5.9 Hz, OCH₂CH₃). ³¹P{/¹H} NMR (243 MHz, CDCl₃) δ = 20.97 (s). HRMS (ESI) calcd for C₂₈H₃₆N₂O₇PS ([M + H]⁺): 575.1981, found: 575.1980.

Benzyl((1*S*,2*S*)-1-(diethoxyphosphoryl)-1-((4-methylphenyl) sulfonamido)-3-phenylpropan-2-yl)carbamate (28b). ³¹P{/¹H} NMR (243 MHz, CDCl₃) δ = 19.66 (s).

((1R,2S)-1-(diethoxyphosphoryl)-3-methyl-1-((4*tert*-Butyl methylphenyl)sulfonamido)butan-2-yl)carbamate (30a). Pale yellow oil, slowly crystallising (37 mg, 51%): ¹H NMR (600 MHz, $CDCl_3$) $\delta = 7.77$ (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, NHSO₂), 4.85 (d, J = 10.1 Hz, 1H, NHBoc), 4.07–3.86 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 3.84 (ddd, J =18.9, 9.1, 5.4 Hz, 1H, CHP), 3.67 (ddd, J = 13.2, 10.6, 6.8 Hz, 1H, $CHCH(CH_3)_2$, 2.42 (s, 3H, Ar CH_3), 2.04 (sep, J = 6.8 Hz, 1H, $CH(CH_3)_2$, 1.43 (s, 9H, $C(CH_3)_3$), 1.21 (t, J = 7.1 Hz, 6H, 2 × OCH_2CH_3 , 0.95 (d, J = 6.6 Hz, 3H, CH_3), 0.88 (d, J = 6.8 Hz, 3H, CH₃). ¹³C NMR (151 MHz, CDCl₃) 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, $2 \times OCH_2CH_3$), 56.03 (d, J = 5.9 Hz, $CHCH(CH_3)_2$), 52.09 (d, J = 155.7 Hz, CHP), 29.21 $(d, J = 7.4 \text{ Hz}, CH(CH_3)_2)$, 28.30 (s, C(CH₃)₃), 21.48 (s, ArCH₃), 20.38 (s, CH₃), 17.45 (s, CH₃), 16.32 $(d, I = 5.7 \text{ Hz}, \text{OCH}_2C\text{H}_3), 16.23 (d, I = 5.7 \text{ Hz}, \text{OCH}_2C\text{H}_3).$ ³¹P $\{/^{1}H\}$ NMR (243 MHz, CDCl₃) $\delta = 22.29$ (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-((4methylphenyl)sulfonamido)butan-2-yl)carbamate (30b). Could not be separated by the chromatography techniques employed in this study, detected in the crude reaction mixture. ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 20.58$ (s).

Benzyl((1R,2S)-1-(diethoxyphosphoryl)-3-methyl-1-((4methylphenyl)sulfonamido)butan-2-yl)carbamate (31a). Pale yellow oil, slowly crystallising (26 mg, 42%): ¹H NMR (400 MHz, $CDCl_3$) $\delta = 7.75$ (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, NHSO₂), 5.22 (d, J = 9.9 Hz, 1H, NHCbz), 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, $2 \times OCH_2CH_3$, CHP), 3.82–3.68 (m, 1H, CHCH(CH₃)₂), 2.39 (s, 3H, ArCH₃), 2.06 (sep, J = 6.8 Hz, 1H, CH(CH₃)₂), 1.19 (t, J =6.0 Hz, 3H, OCH_2CH_3), 1.18 (t, J = 8.0 Hz, 3H, OCH_2CH_3), 0.95 $(d, J = 6.6 \text{ Hz}, 3H, CH_3), 0.86 (d, J = 6.8 \text{ Hz}, 3H, CH_3).$ ¹³C NMR (101 MHz, CDCl₃) δ = 156.98 (s, C=O), 143.29, 138.26, 136.43, 129.41, 128.45, 128.03, 127.98, 127.02 (8 \times s, Ar, Ph), 66.89 (s, OCH_2Ph), 62.95 (d, J = 7.5 Hz, OCH_2CH_3), 62.93 (d, J = 6.9 Hz, OCH_2CH_3 , 56.62 (d, J = 5.9 Hz, $CHCH(CH_3)_2$), 52.06 (d, J =155.4 Hz, CHP), 29.12 (d, J = 6.9 Hz, $CH(CH_3)_2$), 21.47 (s, ArCH₃), 20.39 (s, CCH₃), 17.45 (s, CCH₃), 16.28 (d, J = 6.0 Hz, OCH₂*C*H₃), 16.21 (d, J = 6.1 Hz, OCH₂*C*H₃). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 21.79$ (s). HRMS (ESI) calcd for C₂₄H₃₆N₂O₇PS $([M + H]^{+})$: 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: ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 20.24$ (s).

tert-Butvl (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, CDCl₃) 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, CHP), 4.18–4.05 (m, 4H, 2 \times OCH₂CH₃), 4.04–3.91 (m, 1H, CHCHP), 3.13-2.96 (m, 2H, NCH₂), 2.41 (s, 3H, ArCH₃), 2.10-1.98 (m, 1H, CHHCH), 1.98-1.81 (m, 2H, NCH₂CHH, CHHCH), 1.64–1.58 (m, 1H, NCH₂CHH), 1.48 (s, 9H, $C(CH_3)_3$), 1.33 (t, J =7.2 Hz, 3H, OCH₂CH₃), 1.31 (t, J = 7.2 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) $\delta = 155.34$ (s, C=O), 142.95, 138.36, 129.44, 127.18 (4 \times s, Ar), 79.66 (s, C(CH₃)₃), 62.74 (d, J = 6.8 Hz, $2 \times OCH_2CH_3$, 58.26 (d, J = 8.1 Hz, CHCHP), 52.25 (d, J =150.5 Hz, CHP), 47.10 (s, NCH₂), 28.47 (s, C(CH₃)₃), 27.99 (s, CH₂CH), 24.38 (s, NCH₂CH₂), 21.47 (s, ArCH₃), 16.52-16.22 (m, $2 \times \text{OCH}_2\text{CH}_3$). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 21.03$ (s). Minor rotamer: ¹H NMR (400 MHz, CDCl₃): $\delta = 7.68$ (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, CHP), 4.04–3.91 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 3.93–3.86 (m, 1H, CHCHP), 3.86-3.79 (m, 1H, NCHH), 3.36-3.25 (m, 1H, NCHH), 2.41 (br s, 3H, ArCH₃), 2.23-2.10 (m, 1H, CHHCH), 1.98-1.81 (m, 2H, NCH₂CHH, CHHCH), 1.64-1.58 (m, 1H, NCH₂CHH), 1.55 (s, 9H, C(CH₃)₃), 1.26 (t, J = 7.2 Hz, 3H, OCH_2CH_3 , 1.19 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ¹³C NMR (101 MHz, $CDCl_3$) $\delta = 153.67$ (s, C=O), 142.86, 138.91, 129.53, 126.58 $(4 \times s, Ar)$, 80.48 (s, $C(CH_3)_3$), 63.02 (d, J = 7.4 Hz, 2 \times OCH_2CH_3), 57.03 (d, J = 14.0 Hz, CHCHP), 52.17 (d, J =147.0 Hz, CHP), 46.01 (s, NCH2), 28.45 (s, C(CH3)3), 27.31 (s, CH₂CH), 23.92 (s, NCH₂CH₂), 21.47 (s, ArCH₃), 16.52–16.22 (m, $2 \times \text{OCH}_2C\text{H}_3$). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 21.54$ (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, $CDCl_3$) $\delta = 7.73$ (d, J = 8.1 Hz, 2H, Ar), 7.27 (d, J = 8.1 Hz, 2H, Ar), 4.18–4.05 (m, 5H, $2 \times \text{OCH}_2\text{CH}_3$, CHP), 3.55 (dd, J = 14.6, 10.4 Hz, 1H, CHCHP), 3.36-3.25 (m, 1H, NCHH), 2.79-2.71 (m, 1H, NCHH), 2.41 (s, 3H, ArCH₃), 2.23-2.10 (m, 1H, CHHCH), 1.81-1.74 (m, 1H, NCH₂CHH), 1.64-1.58 (m, 2H, CHHCH, NCH₂CHH), 1.46 (s, 9H, C(CH₃)₃), 1.26 (t, J = 7.2 Hz, 3H, OCH_2CH_3 , 1.19 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ¹³C NMR (101 MHz, $CDCl_3$) $\delta = 157.30$ (s, C=O), 142.90, 138.45, 129.37, 127.07 $(4 \times s, Ar)$, 80.05 (s, $C(CH_3)_3$), 62.50 (d, J = 6.8 Hz, 2 \times OCH_2CH_3), 56.62 (d, J = 11.1 Hz, CHCHP), 55.13 (d, J =156.8 Hz, CHP), 46.55 (s, NCH2), 29.47 (s, CH2CH), 28.41 (s, $C(CH_3)_3$, 23.38 (s, NCH₂CH₂), 21.47 (s, ArCH₃), 16.52–16.22 (m, $2 \times \text{OCH}_2\text{CH}_3$). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 21.27$ (s). Minor rotamer: ${}^{31}P{/}^{1}H$ NMR (162 MHz, CDCl₃) $\delta = 21.40$ (s).

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

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(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: ¹H NMR (600 MHz, CDCl₃) $\delta =$ 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, NH), 5.16 (d, J = 12.4 Hz, 1H, CHHPh), 5.12 (d, I = 12.5 Hz, 1H, CHHPh), 4.36 (dd, I = 22.1, 9.8 Hz, 1H, CHP), 4.17-4.09 (m, 2H, OCH₂CH₃), 4.07-4.00 (m, 2H, OCH₂CH₃), 3.97–3.91 (m, 1H, CHCHP), 3.43 (ddd, *J* = 12.0, 7.8, 4.7 Hz, 1H, NCHH), 3.15-3.11 (m, 1H, NCHH), 2.36 (br s, 3H, ArCH₃), 2.13-2.07 (m, 1H, CHHCH), 2.01-1.94 (m, 1H, CHHCH), 1.92-1.88 (m, 1H, NCH₂CHH), 1.66-1.59 (m, 1H, NCH₂CHH), 1.30 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 1.21 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) $\delta = 155.61$ (s, C=O), 143.05, 138.3, 136.63, 129.48, 128.45, 127.96, 127.83, 127.04 (8 \times s, Ar, Ph), 66.93 (s, CH₂Ph), 63.17 (d, J = 7.3 Hz, OCH_2CH_3), 62.89 (d, J = 7.0 Hz, OCH_2CH_3), 58.73 (d, J = 8.8 Hz, CHCHP), 51.94 (d, J = 150.4 Hz, CHP), 46.89 (s, NCH₂), 27.87 (s, CH_2CH), 24.45 (s, NCH₂ CH_2), 21.44 (s, Ar CH_3), 16.30 (d, J =5.9 Hz, 2 × OCH₂CH₃). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta =$ 20.49 (s). Minor rotamer: ¹H NMR (600 MHz, CDCl₃) 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, NH), 5.23 (d, J = 12.0 Hz, 1H, CHHPh), 5.12 (d, J = 12.0 Hz, 1H, CHHPh), 4.49 (ddd, J = 22.5, 9.7, 2.0 Hz, 1H, CHP), 4.24-4.20 (m, 2H, OCH₂CH₃), 4.00-3.91 $(m, 2H, OCH_2CH_3), 3.92-3.87 (m, 1H, CHCHP), 3.27 (dt, J = 9.8,)$ 6.6 Hz, 1H, NCHH), 2.61 (dt, J = 10.7, 6.8 Hz, 1H, NCHH), 2.41 (s, 3H, ArCH₃), 2.28-2.20 (m, 1H, CHHCH), 2.00-1.94 (m, 1H, CHHCH), 1.92-1.88 (m, 1H, NCH₂CHH), 1.66-1.59 (m, 1H, NCH₂CHH), 1.25 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.19 (t, J =7.0 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) $\delta = 154.15$ (s, C=O), 143.00, 138.56, 136.16, 129.48, 128.53, 127.96, 127.83, 126.65 (8 \times s, Ar, Ph), 67.43 (s, CH₂Ph), 63.17 (d, J = 7.3 Hz, OCH_2CH_3), 62.89 (d, J = 7.0 Hz, OCH_2CH_3), 57.13 (d, J =13.7 Hz, CHCHP), 51.71 (d, J = 146.6 Hz, CHP), 46.40 (s, NCH₂), 27.60 (s, CH₂CH), 23.94 (s, NCH₂CH₂), 21.50 (s, ArCH₃), 16.48 (d, $J = 5.6 \text{ Hz}, 2 \times \text{OCH}_2C\text{H}_3$). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta =$ 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: ¹H NMR (400 MHz, CDCl₃) 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, NH), 5.09 (d, *J* = 12.4 Hz, 1H, CHHPh), 5.02 (d, *J* = 12.4 Hz, 1H, CHHPh), 4.29–4.25 (m, 3H, CHCHP, OCH₂CH₃), 4.07–4.00 (m, 2H, OCH₂CH₃), 3.66–3.60 (m, 1H, CHP), 3.15–3.11 (m, 1H, NCHH), 2.72 (ddd, *J* = 10.3, 7.1, 3.1 Hz, 1H, NCHH), 2.31 (s, 3H, ArCH₃), 2.13–2.07 (m, 1H, CHHCH), 2.01–1.94 (m, 1H, CHHCH), 1.84–1.81 (m, 1H, NCH₂CHH), 1.74–1.70 (m, 1H, NCH₂CHH), 1.30 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 1.19 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) 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, CH_2Ph), 63.48 (d, J = 7.5 Hz, OCH_2CH_3), 62.63 (d, J = 6.9 Hz, OCH_2CH_3), 57.26 (d, J = 11.1 Hz, CHCHP), 55.15 (d, J = 156.3 Hz, CHP), 46.40 (s, NCH_2), 29.20 (s, CH_2CH), 23.37 (s, NCH_2CH_2), 21.38 (s, $ArCH_3$), 16.21 (d, J = 6.1 Hz, $2 \times OCH_2CH_3$). ³¹P{/¹H} NMR (162 MHz, $CDCl_3$) $\delta = 20.49$ (s). Minor rotamer: ³¹P{/¹H} NMR (162 MHz, $CDCl_3$) $\delta = 20.88$ (s).

Racemic mixture of tert-butyl(S)-4-((R)-(diethoxyphosphoryl)(4-methylphenylsulfonamido)methyl)-2,2dimethyloxazolidine-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: ¹H NMR (400 MHz, $CDCl_3$) $\delta = 7.78$ (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, NH), 4.53-4.45 (m, 1H, CHP), 4.28-4.22 (m, 2H, CHCHP, OCHH), 4.07-4.00 (m, 2H, OCHH, OCHHCH₃), 3.96-3.90 (m, 1H, OCHHCH₃), 3.90-3.86 (m, 1H, OCHHCH₃), 3.62–3.56 (m, 1H, OCHHCH₃), 2.42 (s, 3H, ArCH₃), 1.67 (s, 3H, C(CH₃)₂), 1.56 (s, 9H, C(CH₃)₃), 1.47 (s, 3H, $C(CH_3)_2$, 1.25–1.21 (m, 3H, OCH_2CH_3), 1.10 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, CDCl₃) $\delta = 152.57$ (s, C=O), 143.06, 138.47, 129.33, 127.35 (4 \times s, Ar), 94.30 (s, $C(CH_3)_2$), 80.80 (s, $C(CH_3)_3$), 63.83 (s, OCH_2), 62.66 (d, J = 7.1 Hz, OCH_2CH_3), 62.56 (d, J = 7.3 Hz, OCH_2CH_3), 57.28 (d, J =13.0 Hz, CHCHP), 49.80 (d, J = 151.6 Hz, CHP), 28.45 (s, C(CH₃)₃), 26.10 (s, C(CH₃)₂), 24.48 (s, C(CH₃)₂), 21.46 (s, ArCH₃), 16.29 (d, J = 5.6 Hz, OCH₂CH₃), 16.18 (d, J = 5.5 Hz, OCH₂CH₃). ${}^{31}P{/^{1}H}$ NMR (162 MHz, CDCl₃) $\delta = 21.34$ (s). Minor rotamer: ¹H NMR (400 MHz, CDCl₃) $\delta = 7.76$ (d, I = 8.4 Hz, 2H, Ar), 7.29 (d, J = 8.6 Hz, 2H, Ar), 5.08 (dd, J = 9.2, 3.4 Hz, 1H, NH), 4.53-4.45 (m, 1H, CHP), 4.28-4.22 (m, 2H, CHCHP, OCHH), 4.07-4.00 (m, 4H, OCHH, OCHHCH₃, OCH₂CH₃), 3.90-3.86 (m, 1H, OCHHCH₃), 2.42 (s, 3H, ArCH₃), 1.58 (s, 9H, C(CH₃)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, OCH₂CH₃), 1.25-1.21 (m, 3H, OCH₂CH₃). ¹³C NMR (101 MHz, $CDCl_3$) $\delta = 151.43$ (s, C=O), 143.27, 138.84, 129.44, 126.98 (4) \times s, Ar), 94.61 (s, C(CH₃)₂), 80.66 (s, C(CH₃)₃), 64.06 (s, OCH₂), 62.97 (d, *J* = 7.3 Hz, OCH₂CH₃), 62.45 (d, *J* = 7.0 Hz, OCH₂CH₃), 56.36 (d, J = 14.3 Hz, CHCHP), 51.59 (d, J = 152.1 Hz, CHP), 28.45 (s, C(CH₃)₃), 24.99 (s, C(CH₃)₂), 22.51 (s, C(CH₃)₂), 21.46 (s, ArCH₃), 16.35 (d, J = 5.6 Hz, OCH₂CH₃), 16.31 (d, J = 6.0 Hz, OCH₂*C*H₃). ³¹P{/¹H} NMR (162 MHz, CDCl₃) $\delta = 21.19$ (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, CDCl₃) $\delta = 21.03$ (s).

Benzyl(S)-4-((R)-(diethoxyphosphoryl)(4-

methylphenylsulfonamido)methyl)-2,2-dimethyloxazolidine-3carboxylate (37a). White solid (47 mg, 75%). Compound 37a is a mixture of two rotamers (1.2 : 1, r.r.). Major rotamer: ¹H NMR (600 MHz, CDCl₃) 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*HCH₃), 3.98-3.95 (m, 1H, OCH*H*CH₃), 3.90-3.85 (m, 1H, OCHHCH₃), 3.80–3.75 (m, 1H, OCHHCH₃), 2.40 (s, 3H, ArCH₃), 1.56 (s, 3H, C(CH₃)₂), 1.49 (s, 3H, C(CH₃)₂), 1.09 (t, J =7.1 Hz, 3H, OCH₂CH₃), 1.10 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) δ = 152.03 (s, C=O), 143.33, 138.51, 136.29, 128.67, 128.31, 128.08, 127.41, 127.14 (8 \times s, Ar, Ph), 95.19 (s, C(CH₃)₂), 67.39 (s, CH₂Ph), 64.37 (s, OCH₂), 63.02 (d, J = 7.7 Hz, OCH₂CH₃), 62.70 (d, J = 6.9 Hz, OCH₂CH₃), 56.41 (d, J= 14.6 Hz, CHCHP), 50.77 (d, I = 150.2 Hz, CHP), 25.06 (s, $C(CH_3)_2$, 23.03 (s, $C(CH_3)_2$), 21.57 (s, $ArCH_3$), 16.32 (d, J =5.9 Hz, OCH₂CH₃), 16.31 (d, J = 5.9 Hz, OCH₂CH₃). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = 20.56$. Minor rotamer: ¹H NMR (600 MHz, CDCl_3) $\delta = 7.77$ (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, NH), 5.23 (d, J = 12.3 Hz, 1H, CHHPh), 5.17 (d, J = 12.3 Hz, 1H, CHHPh), 4.58 (ddd, J = 19.7, 9.6, 2.5 Hz, 1H, CHP), 4.28-4.22 (m, 2H, OCHH, CHCHP), 4.07-4.02 (m, 1H, OCHH), 3.98-3.95 (m, 1H, OCHHCH₃), 3.75–3.62 (m, 3H, OCH₂CH₃, OCHHCH₃), 2.38 (s, 3H, ArCH₃), 1.54 (s, 3H, C(CH₃)₂), 1.42 (s, 3H, C(CH₃)₂), 1.24 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.14 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) $\delta = 153.42$ (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(CH₃)₂), 67.61 (s, CH₂Ph), 64.03 (s, OCH₂), 63.10 (d, J = 7.3 Hz, OCH₂CH₃), 62.94 (d, J = 6.9 Hz, OCH₂CH₃), 57.79 (d, J = 13.5 Hz, CHCHP), 49.63 (d, J = 151.2 Hz, CHP), 25.97 (s, C(CH₃)₂), 24.81 (s, C(CH₃)₂), 21.55 (s, ArCH₃), 16.36 (d, J = 5.8 Hz, OCH₂CH₃), 16.23 (d, J = 5.8 Hz, OCH₂CH₃). ³¹P{/¹H} NMR (243 MHz, CDCl₃) 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): ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = 20.50$ (s).

Racemic mixture of benzyl((S)-1-((2S,3S)-3-(diethoxyphosphoryl)oxiran-2-yl)-2,2,2-trifluoroethyl)carbamate (rac 38). Pale yellow oil slowly crystallising (44 mg, 74%): ¹H NMR (400 MHz, CDCl₃) $\delta =$ 7.44-7.32 (m, 5H, Ph), 5.16 (s, 2H, CH₂Ph), 4.81-4.70 (m, 1H, CHP), 4.28–4.11 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 3.69–3.64 (m, 1H, CHCHCF₃), 2.93 (dd, J = 27.6, 2.4 Hz, 1H, CHCF₃), 1.68 (s, 1H, OH), 1.38 (t, J = 7.1 Hz, 6H, $2 \times \text{OCH}_2\text{CH}_3$). ¹³C NMR (151 MHz, CDCl_3) $\delta = 155.58$ (s, C=O), 135.34, 128.68, 128.59, 128.25 (4 \times s, Ph), 124.04 (q, J = 282.4 Hz, CF_3), 68.04 (s, CH_2Ph), 63.59 (d, J = 6.2 Hz, OCH_2CH_3), 63.29 (d, J = 6.3 Hz, OCH₂CH₃), 51.72 (d, J = 1.6 Hz, CHCHCF₃), 51.24 (q, J = 31.5 Hz, CHCF₃), 45.81 (d, J = 204.2 Hz, CHP), 16.45 (d, J = 5.4 Hz, OCH₂CH₃), 16.43 (d, J = 5.6 Hz, OCH₂CH₃). ¹⁹F NMR (376 MHz, CDCl₃) $\delta = -75.49$ (d, J = 7.8 Hz). ¹⁹F{/¹H} NMR (565 MHz, CDCl₃) $\delta = -75.49$ (s). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta =$ 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%): ¹H NMR (600 MHz, CDCl₃) 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, NH), 4.45 (dd, *J* = 6.1, 0.7 Hz, 1H, CHP), 4.33–4.25 (m, 1H, CHCH₂Ph), 4.26–4.17 (m, 4H, 2 × OCH₂CH₃), 3.06 (dd, *J* = 13.6, 4.4 Hz, 1H, *CH*HPh), 2.80 (dd, *J* = 13.6, 9.1 Hz, 1H, *C*HHPh), 1.35 (m, 6H, 2 × OCH₂CH₃). ¹³C NMR (151 MHz, CDCl₃) δ = 157.05 (s, *C*=O), 135.46, 129.16, 129.13, 127.52 (4 × s, Ar), 74.98 (d, *J* = 171.9 Hz, CHP), 64.03 (d, J = 6.7 Hz, OCH₂CH₃), 63.54 (d, J = 6.8 Hz, OCH₂CH₃), 54.90 (s, CHCH₂Ph), 42.22 (d, J = 8.9 Hz, CH₂Ph), 16.49 (d, J = 4.4 Hz, OCH₂CH₃), 16.46 (d, J = 4.4 Hz, OCH₂CH₃). ³¹P{/¹H} NMR (243 MHz, CDCl₃) $\delta = 15.91$ (s). HRMS (ESI) calcd for C₁₄H₂₁NO₅P ([M + H]⁺): 314.1157, found: 314.1155.

Conflicts of interest

There are no conflicts to declare.

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