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Efficient asymmetric synthesis of trifluoromethylated β-aminophosphonates and their incorporation into dipeptides†

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Addition of anions derived from dialkyl methylphosphonates to (*Ss*)-*N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine afforded (*Ss*,*R*) addition adducts in moderate to good yield (53–75%) with excellent diastereoselectivity (94–95% de). After selective removal of the *N*-sulfinyl group, dipeptides containing enantiomerically pure diethyl 2-amino-3,3,3-trifluoropropylphosphonate were synthesized to investigate the influence of the trifluoromethyl substituent on *N*-terminal coupling.

Currently aminophosphonic acids and their derivatives are recognized as fundamental compounds in the area of medicine, biochemistry, and synthetic organic chemistry.[1] Taking into account that replacement of hydrogen atoms with fluorine atoms in bioactive agents greatly influences the bioavailability by improving the enzymatic stability and enhancing the lipophilicity the fluorinated aminophosphonic acids and their derivatives are becoming increasingly interesting for the development of enzyme inhibitors and modification of peptides of natural and synthetic origin.[2] As a result a large number of fluorinated aminophosphonic acid derivatives exhibiting enzyme inhibitory, antibiotic, antibacterial, antiviral, antifungal, and herbicidal activities were designed and synthesized.[3] Among them fluoroalkylated β-aminophosphonates have received less attention regardless of the fact that they are phosphorus analogues of the corre sponding β-fluoroalkyl-β-amino acids playing a key role in the design of β-peptides,[4] retropeptides[5] and a new class of proteasome inhibitors.[6] The most general approach to racemic fluoroalkylated β-aminophosphonates consists of reduction of β-enaminophosphonates containing fluoroalkyl substituents at the β position.[7] Other methods for the synthesis of racemic fluoroalkylated β-aminophosphonates are limited to some procedures developed for addition of amines or ammonia to α,β-unsaturated phosphonates,[8] ring opening of trifluoromethyl aziridine-2-phosphonates[9] and addition of carbanions generated from phosphonates to trifluoromethyl *N*-benzoyl and *N*-carbalkoxy imines.[10] To the best of our knowledge, there is only one report in the literature dealing with preparation of optically enriched fluoroalkylated β-aminophosphonates.[11] This synthetic route involves the reaction of enantiomerically pure *N*-(α-phenylethyl)trifluoroacetimidoyl chloride with carbanions derived from dialkyl methylphosphonates, followed by a base-catalyzed [1,3]-proton shift reaction of the intermediate *N*-substituted dialkyl 2-imino-3,3,3-trifluoropropylphosphonates and their isomeric enamines with enantioselectivities in the range of 60–83% ee. DBU-mediated isomerization of imine and enamine with *n*-propyl ester groups gave the best result in terms of yield and enantioselectivity.[12] The isomeric azomethines thus formed were hydrolyzed under mild conditions to the corresponding optically enriched trifluoromethylated β-aminophosphonates. However, in this report the absolute configuration of the products remained undetermined.

Considering the biological activities of the fluoroalkylated β-aminophosphonic acid derivatives, the availability of these compounds in enantiomerically pure form is highly desirable. We reasoned that addition of carbanions derived from phosphonates to (*Ss*)-*N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine, which displays high-level reactivity, asymmetric induction and is commercially available,[13] might represent a general method for the asymmetric synthesis of dialkyl 2-amino-3,3,3-trifluoropropylphosphonates. We report here the application of the (*Ss*)-*N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine as a versatile intermediate for the synthesis of dialkyl 2-amino-3,3,3-trifluoropropylphosphonates in optically pure form.

As a starting point, the reaction of *N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine (*Ss*)-**1** and diethyl methylphosphonate **2b** was investigated in THF using *n*-BuLi as a base. The addition occurred smoothly with 2.0 equiv. of the lithium diethyl methylphosphonate at −78 °C for 2 h giving rise to *N*-sulfinyl aminophosphonate (*Ss*,*R*)-**4b** in 60% overall yield and an excellent 97 : 3 diastereomeric ratio (Table 1, entry 1). In order to optimize the reaction conditions the effects of reaction parameters such as reactants ratio and reaction time were briefly investigated. However, when 1.2 equiv. of lithium

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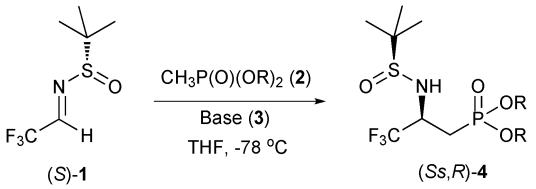
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data and copies of ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra of all compounds. CCDC 876310. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc36702e

Table 1 Synthesis of *N*-*tert*-butanesulfinyl 2-amino-3,3,3-trifluoropropylphosphonates (*Ss,R*)-**4** from *N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine (*Ss*)-**1**[a]



Entry	Phosphonate **2**	Base **3**	Molar ratio **1**/**2**/**3**	Time (h)	de[b] (%)	Yield[c] (%)
1	**2b** *R* = Et	*n*-BuLi	1.0 : 2.2 : 2.0	2	94	60
2	**2b** *R* = Et	*n*-BuLi	1.0 : 1.3 : 1.2	2	90	20
3	**2b** *R* = Et	*n*-BuLi	1.0 : 2.8 : 2.5	2	92	48
4	**2b** *R* = Et	LDA	1.0 : 2.2 : 2.0	2	93	56
5	**2b** *R* = Et	*n*-BuLi	1.0 : 2.2 : 2.0	0.5	94	76 (58)[d]
6	**2a** *R* = Me	*n*-BuLi	1.0 : 2.2 : 2.0	0.5	95	53
7	**2c** *R* = Pr	*n*-BuLi	1.0 : 2.2 : 2.0	0.5	94	68
8	**2d** *R* = *i*-Pr	*n*-BuLi	1.0 : 2.2 : 2.0	0.5	94	75

[a] The reactions were performed using the following procedure: a pre-cooled to −78 °C THF solution of (*S*)-**1** was quickly added to anions derived from dialkyl methylphosphonate **2** and base at −78 °C. [b] Determined by ^{19}F and ^{31}P NMR analysis of the crude reaction mixtures. [c] Isolated yield after chromatographic purification. [d] Yield of optically pure material after recrystallisation of the crude product.

diethyl methylphosphonate **2b** was employed, the yield of (*Ss,R*)-**4b** was significantly decreased with lower diastereoselectivity (Table 1, entry 2). On the other hand using 2.5 equiv. of lithium diethyl methylphosphonate obviously decreased the yield and had little effect on the diastereomeric ratio (Table 1, entry 3). In another experiment the use of LDA as a base only led to a slight decrease in yield of the product (*Ss,R*)-**4b** under the reaction conditions employed (Table 1, entry 3). The screening of the reaction time demonstrated that transformation could be carried out for 0.5 h and reducing the reaction time resulted in increase in yield to a synthetically useful level while not decreasing diastereoselectivity (Table 1, entry 5). Interestingly, formation of side products decreased when pre-cooled THF solution of (*S*)-**1** was quickly added in one portion to lithium diethyl methylphosphonate at −78 °C. Based on these results, we speculated that the diastereoselectivity of the reaction was kinetically controlled and the addition product was not stable under reaction conditions.

We then examined the effect of the phosphonate ester groups on the diastereoselectivity of addition to imine (*S*)-**1**. In general, various phosphonates **2a,c,d** participated successfully in the reaction under optimised reaction conditions providing the corresponding addition products (*Ss,R*)-**4a,c,d** in moderate to good yields and excellent diastereoselectivities (Table 1, entries 6–8). The use of the least hindered dimethyl methylphosphonate **2a** gave addition product with diastereoisomeric ratio similar to that found for the diisopropyl methylphosphonate **2d** albeit in lower yield. Similar diastereoselectivity for dimethyl and diisopropyl phosphonates indicated that the stereochemical outcome of addition reactions was independent of the alkyl moieties. The presence of excess of dialkyl methylphosphonates **2** complicated the isolation of the *N*-sulfinyl β-aminophosphonates (*Ss,R*)-**4** by flash chromatography on silica gel. To avoid this problem the crude products were dried using a high vacuum pump (0.5 mm Hg) at 30–35 °C. The major diastereoisomers (*Ss,R*)-**4** were then isolated by flash chromatography on silica gel with diastereomeric purity 96–98% de. Finally crystallisation of crude product (*Ss,R*)-**4b** allowed us to obtain optically pure material which was used in the next experiments. The stereochemistry of the major diastereomer **4b** was determined to be (*Ss,R*) by X-ray analysis.[14] The stereochemistry of the remaining products **4a,c,d** was assigned by analogy.

According to the literature, the addition of phenylmagnesium bromide, various aryllithium, phenyl boronic acids and ketone enolates to imine (*S*)-**1** proceeds *via* an open transition state model where reagents preferably add to the imine from the less hindered face occupied by the lone pair of electrons on sulfur to afford the major diastereomer adducts.[13] The stereochemical outcome of the phosphonate carbanions addition to weakly coordinating trifluoroacetaldimine (*S*)-**1** is also consistent with the open transition state model **TS 1** to result in *N*-sulfinyl β-aminophosphonates (*Ss,R*)-**4** as major diastereomers (Fig. 1). It is worth mentioning that addition of dialkyl methylphosphonates, halomethylphosphonate as well as ethyl (1,1-diethoxyethyl)-methylphosphinate carbanions to non-fluorinated aldehyde-derived *N*-sulfinyl imines exhibited a similar stereochemical outcome.[15]

One of the advantages of using the *tert*-butanesulfinyl group in aminophosphonates synthesis was that it could be removed under mild acidic conditions with complete chemoselectivity thus allowing further transformation. By performing the desulfinylation reaction of (*Ss,R*)-**4b** at room temperature with 4 N HCl solution in alcohol the β-aminophosphonate (*R*)-**5** could be isolated in high yield (Scheme 1). β-Aminophosphonate (*R*)-**5** was further quantitatively transformed upon refluxing in 10 N hydrochloric acid to free β-aminotrifluoropropylphosphonic acid (*R*)-**6**, which was isolated in the usual manner by the addition of propylene oxide. Because application of fluoroalkyl α- and β-aminophosphonates in peptide design is still in the early stages of development,[16] we decided to focus on incorporation of enantiopure trifluoromethylated β-aminophosphonate (*R*)-**5** into peptide chains by coupling with *N*-Cbz-L-alanine and *N*-Cbz-L-phenylalanine. As we anticipated that nucleophilicity of the nitrogen atom of β-aminophosphonate (*R*)-**5** was decreased by the neighbouring electron-withdrawing trifluoromethyl group, the activation of the Cbz-protected natural amino acids was achieved by exploiting a mixed anhydrides method, recently developed for *N*-terminal coupling of α-trifluoromethyl α-amino acids.[17] According to ^{19}F NMR as well as ^{31}P NMR analysis the diastereoisomerically pure *N*-Cbz protected β-aminophosphonic dipeptide derivatives (*S,R*)-**7** and (*S,R*)-**8** were conveniently obtained in good yield by this procedure. Coupling time was 18 h and purification of (*S,R*)-**7** and (*S,R*)-**8** was easily carried out by crystallization.

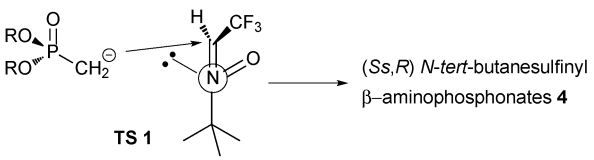
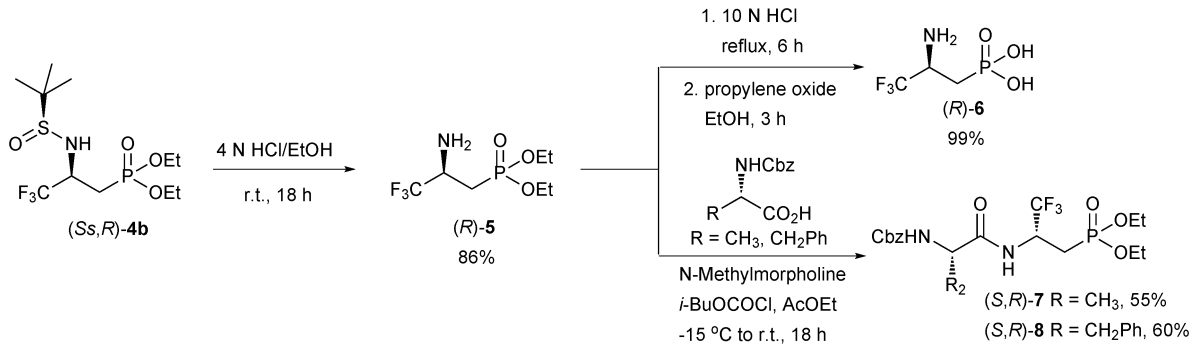


Fig. 1 Proposed transition state model for the diastereoselective addition of phosphonate carbanions to *N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine (*Ss*)-**1**.



Scheme 1 Deprotection of *N*-sulfinyl β-aminophosphonate (*Ss,R*)-**4b** and peptide coupling of β-aminophosphonate (*R*)-**5** with *N*-Cbz-L-alanine and *N*-Cbz-L-phenylalanine.

In summary, we have developed an asymmetric synthesis of 2-amino-3,3,3-trifluoropropylphosphonate esters *via* the addition of anions derived from dialkyl methylphosphonates to (*Ss*)-*N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine as chiral auxiliary. The excellent diastereoselectivity, good yield and short reaction time are the noteworthy advantages of the described method. Synthesis of phosphonodipeptides from enantiomerically pure 2-amino-3,3,3-trifluoropropylphosphonate ester using a coupling reaction at the deactivated N-terminal position was successfully performed.

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