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Asymmetric synthesis of phosphonotrifluoroalanine and its derivatives using *N-tert*-butanesulfinyl imine derived from fluoral

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ABSTRACT

Addition of dialkyl phosphites to (*S*)-*N*-*tert*-butanesulfinyl imine derived from fluoral afforded, under mild conditions, the corresponding *N*-*tert*-butanesulfinyl α-aminophosphonates in moderate to high yields and diastereoselectivity. The major diastereomers of *N*-*tert*-butanesulfinyl α-aminophosphonates of (S_S,*S*) configuration were isolated, and after partial or complete deprotection, converted into enantiomerically pure phosphonotrifluoroalanine and its dialkyl esters.

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α-Trifluoromethyl α-aminophosphonic acids and their phosphonate esters have been the subject of considerable attention in organic and bioorganic chemistry because of their potential utility as inhibitors of various proteolytic enzymes, as antimicrobial, antibacterial, antihypertensive, and anticancer agents and peptidomimetic units.[1] Several biological applications of α-aminophosphonates containing trifluoromethyl groups on the α-carbon as inhibitors of serine esterases, alanine racemase, and pyrimidine phosphorylases have been demonstrated.[2] Furthermore, due to the multidirectional pattern of hydrogen bonding and the presence of trifluoromethyl group attached to the stereogenic carbon, these compounds are of particular interest for the study of self-disproportionation of enantiomers via achiral chromatography[3] and sublimation.[4] Therefore the number of synthetic procedures resulting in the preparation of α-trifluoromethyl α-aminophosphonic acid derivatives has increased significantly.[1b,5] However, most of the available synthetic methods lead to the corresponding racemates and only a few examples deal with the synthesis of these compounds in optically active form.

Diastereoselective synthesis of phosphonotrifluoroalanine involves the reaction of enantiomerically pure *N*-(α-phenylethyl) trifluoroacetimidoyl chloride with trialkyl phosphites followed by a base-catalyzed [1,3]-proton shift of the imidoyl phosphonates with a relatively good stereochemical result.[6,7] The intermediate isomeric azomethines thus formed were transformed into the corresponding α-trifluoromethyl α-aminophosphonic acid by further hydrolysis in concentrated HCl. The enantioselective approach consists of the reduction of trifluoroacetimidoyl phosphonates with the oxaborolidine–catecholborane system giving rise to α-trifluoromethyl α-aminophosphonates in high yields and with moderate to good enantioselectivities.[5c] Additionally, enzymatic resolution using penicillin *G* acylase from *Escherichia coli* was used for the synthesis of optically pure phosphonotrifluoroalanine.[8] This enzyme catalyzes the hydrolysis of the *N*-phenylacetylated derivative of phosphonotrifluoroalanine with high enantioselectivity (ee 95%). In all these literature reports the absolute configuration of the products remained undetermined. Although diastereoselective nucleophilic addition of alkyl phosphites to chiral aldimines is the most frequently employed strategy for the asymmetric synthesis of α-aminophosphonates,[9] surprisingly the synthetic potential of chiral imines derived from fluoral[10] in these reactions remains largely unexplored.

Recently it has been demonstrated that *N*-*tert*-butanesulfinyl imine derived from fluoral is an extremely useful imine building block for the asymmetric synthesis of fluorinated amines and related molecules due to its excellent diastereocontrol of

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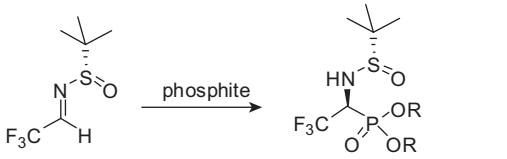
nucleophilic addition reactions across C=N double bonds and mild conditions for cleavage.[11] Moreover *N*-*tert*-butanesulfinyl imine derived from fluoral, in contrast to the *N*-acylimines of fluoral, is quite stable at room temperature under an inert atmosphere and can be easily purified by distillation.[12] In this context, it seemed quite reasonable to consider the addition of alkyl phosphites to this commercially available chiral reagent as a potentially convenient and straightforward approach for the preparation of optically active phosphonotrifluoroalanine and its derivatives.

Initially, we expected that the electron-withdrawing effect of the CF_3 group in *N*-*tert*-butanesulfinyl imine derived from fluoral would facilitate nucleophilic attack at the C=N double bond by the dialkyl phosphites without the need for any activation. However, treatment of *N*-*tert*-butanesulfinyl imine with dimethyl or diethyl phosphite in CH_2Cl_2 did not give any products at 0 °C to room temperature. On the other hand, when a combination of diethyl phosphite and potassium carbonate was used as required in the standard procedure for *N*-*tert*-butanesulfinyl imine mediated synthesis of chiral α-aminophosphonates[13] the reaction with trifluoroacetaldimine (*S*)-**1** proceeded at room temperature within 0.5 h affording *N*-*tert*-butanesulfinyl α-aminophosphonate (S_S,*S*)-**3** as the major diastereoisomer in moderate yield and diastereoselectivity (Table 1, entry 1). It should be mentioned that extension of the reaction time reduced the yield as well as the optical purity of *N*-*tert*-butanesulfinyl α-aminophosphonate (S_S,*S*)-**3**. Additionally, switching the solvent from dichloromethane to diethyl ether did not lead to a satisfactory result (Table 1, entry 2). We speculated that the instability of the trifluoromethyl group attached to the carbon atom possessing a highly acidic hydrogen atom under basic conditions, by analogy to *N*-protected esters of 3,3,3-trifluoroalanine,[14] might be the reason for moderate diastereoselectivity and yield of the reaction under study. Therefore hydrophosphorylation was repeated using weaker bases such as Li_2CO_3 and Na_2CO_3. However both Li_2CO_3 and Na_2CO_3 were ineffective in this reaction furnishing complex mixtures of products containing the target *N*-*tert*-butanesulfinyl α-aminophosphonate (S_S,*S*)-**3** in very small amounts (Table 1, entries 3 and 4). The diastereoselectivity could be raised to a more satisfactory level by converting diethyl phosphite in situ into its trimethylsilyloxy derivative in the presence of TMSCl and Et_3N.[15] The diethyl trimethylsilyl phosphite reacted with trifluoroacetaldimine (*S*)-**1** in a diastereoselective manner in CH_2Cl_2 at 0 °C yielding *N*-*tert*-butanesulfinyl α-aminophosphonate (S_S,*S*)-**3** in good yield and 84% de (Table 1, entry 5). We next investigated the reaction of trifluoroacetaldimine (*S*)-**1** with trimethylsilyl reagents derived from different dialkyl phosphites. Using dipropyl trimethylsilyl phosphite brought about a slight increase in the yield of the major diastereomer (S_S,*S*)-**4** while the trimethylsilyl reagent derived from dimethyl phosphite led to a lower overall yield and stereocontrol in favor of (S_S,*S*)-**2** (Table 1, entries 6 and 7). The best result was achieved with diisopropyl trimethylsilyl phosphite furnishing stereoisomer (S_S,*S*)-**5** in high yield and with good diastereoselectivity (Table 1, entry 8). The major diastereomers of *N*-*tert*-butanesulfinyl α-aminophosphonates (S_S,*S*)-**3–5** were isolated, after flash column chromatography or recrystallization, in excellent diastereomeric purity and subsequently used as precursors for the synthesis of enantiopure phosphonotrifluoroalanine. The stereochemistry of the major diastereomer **3** was determined to be (S_S,*S*) by X-ray analysis.[16] The stereochemistry of the remaining products (S_S,*S*)-**2,4,5** was assigned by analogy. Remarkably, we found that the configuration of the newly formed stereogenic carbon was opposite to that observed for dialkyl phosphite anion addition to non-fluorinated *N*-sulfinyl alkyl and aryl aldimines, which was proposed to proceed via chelated transition state **TS 1** (Fig. 1).[13,17] The formation of the major diastereomers with (S_S,*S*)-configuration in the addition of dialkyl phosphites to weakly coordinating trifluoroacetaldimine (*S*)-**1** may reasonably be explained by non-chelated transition state **TS 2** where dialkyl phosphites preferably add to the imine from the less hindered face occupied by the lone pair of electrons on sulfur to afford the major diastereomeric adduct (S_S,*S*) (Fig. 1). Such a transition state model rationalizes the greater diastereoselectivity observed for the more sterically hindered diisopropyl trimethylsilyl phosphite relative to other dialkyl trimethylsilyl phosphites as well as diethyl phosphite.

As further synthetic elaboration, the *N*-*tert*-butanesulfinyl group of the major diastereoisomers (S_S,*S*)-**3–5** was easily removed under acidic conditions at room temperature to furnish α-aminophosphonates (*S*)-**6–8** in a high yield (Scheme 1). The enantiomeric purity of α-aminophosphonate (*S*)-**6** was shown to be high by means of NMR analysis using the previously reported procedure.[5c] Only a single diastereomeric complex of α-aminophosphonate (*S*)-**6** with chiral europium shift reagents was detected in the ^{19}F and ^{31}P NMR spectra. The corresponding racemic α-aminophosphonate used as

Table 1
Addition of dialkyl phosphites to *N*-*tert*-butanesulfinyl imine derived from fluoral (*S*)-**1**



Entry	Phosphite	Conditions	Time (h)	Product	de[a] (%)	Yield (%)
1	$HP(O)(OEt)_2$	CH_2Cl_2, K_2CO_3, 20 °C	0.5	**3**	76	65[b] (51[c])
2	$HP(O)(OEt)_2$	Et_2O, K_2CO_3, 20 °C	0.5	**3**	65	67[b] (41[c])
3	$HP(O)(OEt)_2$	CH_2Cl_2, Li_2CO_3, 20 °C	1	**3**	—	trace
4	$HP(O)(OEt)_2$	CH_2Cl_2, Na_2CO_3, 20 °C	1	**3**	—	12[b]
5	$Me_3SiOP(OEt)_2$[d]	CH_2Cl_2, 0 °C	1	**3**	84	69[b] (54[c])
6	$Me_3SiOP(OMe)_2$[d]	CH_2Cl_2, 0 °C	1	**2**	68	56[b]
7	$Me_3SiOP(OPr)_2$[d]	CH_2Cl_2, 0 °C	1	**4**	83	65[c]
8	$Me_3SiOP(O\text{-}i\text{-}Pr)_2$[d]	CH_2Cl_2, 0 °C	1	**5**	88	83[c]

[a] From the ^{19}F and ^{31}P NMR spectra of the crude reaction mixture.
[b] Isolated total yield of both diastereomers.
[c] Isolated yield of the (S_S,*S*)-diastereomer.
[d] Dialkyl trimethylsilyl phosphites were generated in situ with $ClSiMe_3$ and Et_3N in CH_2Cl_2 at 0 °C.[15]

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