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Asymmetric synthesis of α,α-difluoro-β-amino phosphonic acids using sulfinimines

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Abstract—Addition of diethyl lithiodifluoromethylphosphonate to enantiopure sulfinimines afforded the corresponding *N*-sulfinyl α,α-difluoro-β-amino phosphonates with good diastereoselectivity. A two-step deprotection involving treatment of diastereomerically pure *N*-sulfinyl α,α-difluoro-β-amino phosphonates with trifluoroacetic acid in EtOH followed by refluxing with 10 N HCl afforded enantiopure α,α-difluoro-β-amino phosphonic acids.

Over the past two decades, amino phosphonic acids have been recognized as important structural analogues of amino acids because of their unique chemical and biological properties. Aminophosphonic acids have been shown to exhibit antibacterial, antiviral as well as pesticidal activities and act as transition-state analogue inhibitors of proteolytic enzymes.[1] Replacement of hydrogen atoms by fluorine atoms in amino carboxylic acids has been found to provide increased lipophilicity, hydrogen bonding, and reactivity.[2] For these reasons the incorporation of fluorine atoms into amino phosphonic acids is of interest for the screening of new bioactive compounds. In addition, the incorporation of fluorinated amino phosphonic acids into key positions in peptide chains plays an important role in rational design and synthesis of isosteric and isopolar phosphate mimics.[3] Current stereoselective approaches to biologically active fluorinated amino phosphonic acids include the reactions of dialkyl lithiodifluoromethylphosphonates with primary triflates, aldehydes, and esters derived from (*R*)-isopropylideneglycerol and D-serine,[3] high yield coupling of [(diethoxyphosphinyl)difluoromethyl]zinc bromide in the presence of CuBr–2LiBr with protected aspartic acid chloride[4] and fluoride catalyzed addition of trimethylsilyldifluoromethylphosphonate to protected L-aspartate semialdehyde.[5] Alternatively nucleophilic fluorination of benzylic α-oxophosphonate with (diethylamino)sulfur trifluoride followed by transition metal-mediated coupling of the corresponding benzylic α,α-difluorophosphonates with an iodoalanine derivative has also been used to prepare these amino phosphonic acids.[6] Recently synthetic methodology relying on the addition of methyl- and halomethylphosphonates anions to enantiopure sulfinimines has proved to be effective for the asymmetric syntheses of β-amino phosphonic acids.[7a,b] However, this attractive methodology has not been used for the synthesis of fluorinated β-amino phosphonic acids. In this communication we report that the use of the readily available and inexpensive chiral *N*-*p*-toluenesulfinylimines **1** in the addition reaction with diethyl lithiodifluoromethylphosphonate **2** offers a synthetic alternative to previous approaches affording a practical method for the preparation of enantiomerically pure a,a-difluoro-b-amino phosphonic acids **5**.

We have found that enantiomerically pure sulfinimine (*S*)-**1a** was easily reacted with 1.3 equiv of diethyl lithiodifluoromethylphosphonate **2** generated from diethyl

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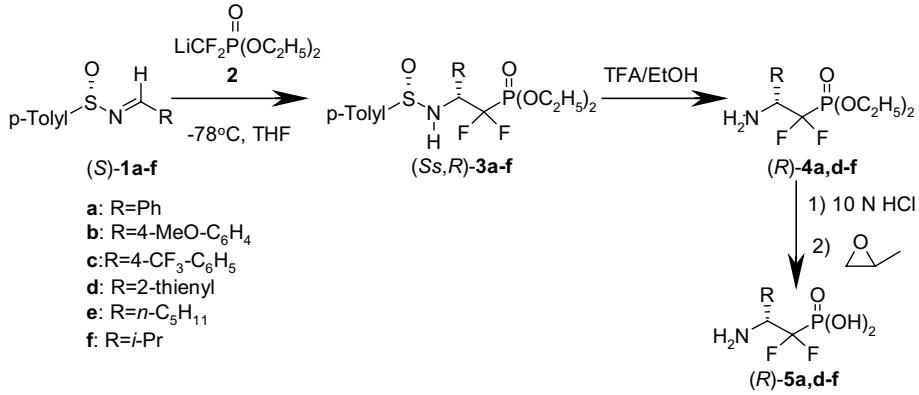

Scheme 1.

Table 1. Addition of diethyl lithiodifluoromethylphosphonate **2** to sulfinimines (*S*)-**1**

Entry	Sulfinimine **1**		β-Amino phosphonate **3**	
	Compound	R	(*Ss*,*R*):(*Ss*,*S*)[a]	Yield[b] (%)
1	(*S*)-**1a**	Ph	95:5	74
2	(*S*)-**1b**	*p*-MeO–C_6H_4	94:6	92[c]
3	(*S*)-**1c**	*p*-CF_3–C_6H_4	94:6	70
4	(*S*)-**1d**	2-Thienyl	92:8	67
5	(*S*)-**1e**	*n*-C_5H_{11}	92:8	72
6	(*S*)-**1f**	*i*-Pr	91:9	75

[a] Determined by ^{19}F NMR of the crude reaction mixtures.
[b] Isolated yield of major diastereoisomer.
[c] Yield of an inseparable mixture of diastereomers.

difluoromethylphosphonate and LDA in THF at −78 °C (Scheme 1). After 1 h the reaction mixture was quenched at this temperature with saturated aqueous NH_4Cl and the crude *N*-sulfinyl α,α-difluoro-β-amino phosphonate **3a** was isolated by simple extractive work-up in a diastereomeric ratio of 95:5 (Table 1, entry 1). Due to its crystalline nature, the major diastereomer of **3a** could be readily obtained in optically pure form by crystallization of the crude reaction mixture from ether.[8] The stereochemistry of the major diastereomer **3a** was determined to be (*Ss*,*R*) by X-ray analysis.[9] The sulfinimines (*S*)-**1b**,**c** having the 4-methoxyphenyl and 4-trifluoromethylphenyl groups afforded the expected addition adducts **3b**,**c** as mixtures of two diastereomers. The diastereoselectivity of the additions was independent of electronic factors and the adducts **3b**,**c** were obtained with the stereochemical outcome comparable with that observed for unsubstituted *N*-benzylidene derivative (*S*)-**1a** (Table 1, entries 2 and 3). The diastereoselectivity slightly decreased when the phenyl substituent in sulfinimine (*S*)-**1a** was replaced by 2-thienyl (*S*)-**1d**, *n*-alkyl (*S*)-**1e**, and *i*-propyl (*S*)-**1f** groups (Table 1, entries 4–6). The size of the alkyl group had no effect on the diastereoselectivity of the addition as illustrated by sulfinimines (*S*)-**1e**,**f** where R = *n*-pentyl and isopropyl. The isolation of the major products (*Ss*,*R*)-**3c**–**f** was achieved effectively either by crystallization or flash chromatography. On the other hand, all attempts to separate, by flash chromatography, the diastereomeric mixture of **3b**, which existed as an oil, were unsuccessful.

The (*R*) absolute configuration of the newly formed stereogenic center in the major diastereomers **3** corresponded to that observed for the addition of methyl- and halomethylphosphonate anions to sulfinimines (*S*)-**1**.[7] The observed selectivity for addition of diethyl lithiodifluoromethylphosphonate to sulfinimines is consistent with a transition-state model in which the sulfinimine is in the stereochemically favorable *E*-configuration and the organometallic reagent preferably attacks the C=N double bond from opposite to the *p*-tolylsulfinyl group direction.

Deprotection of the diastereomerically pure adducts (*Ss*,*R*)-**3a**,**d**–**f** was achieved in two steps. The *N*-sulfinyl group was selectively removed by treatment with trifluoroacetic acid in EtOH at 0 °C.[7c] Under these conditions, the phosphonate group remained intact and the α,α-difluoro-β-amino phosphonates (*R*)-**4a**,**d**–**f** were isolated by flash chromatography in 78–97% yields. Hydrolysis of (*R*)-**4a**,**d**–**f** was carried out by heating under reflux in 10 N HCl for 8 h. After concentration of reaction mixture in vacuo, the residue was treated with ethanol and propylene oxide and the mixture was stirred for 3 h. The resulting precipitate was filtered, washed with ether, and dried in vacuo affording the desired α,α-difluoro-β-amino phosphonic acids (*R*)-**5a**,**d**–**f** in 75–86% yields. On the other hand hydrolysis of fully protected (*Ss*,*R*)-**3a**,**d**–**f** in one-step to α,α-difluoro-β-amino phosphonic acids (*R*)-**5a**,**d**–**f** using 10 N HCl under reflux was a low yielding procedure, with typical yields of 30–35%. The enantiomeric purity of the α,α-difluoro-β-amino phosphonic acids (*R*)-**5a**,**d**–**f** so obtained was shown to be >98% ee (co-chromatography with racemic OPA/NAC derivatives by RP-HPLC[10]). Thus deprotection of *N*-sulfinyl α,α-difluoro-β-amino phosphonates (*Ss*,*R*)-**3a**,**d**–**f** occurred without epimerization at the β-position under these conditions.

In summary, an asymmetric synthesis of *N*-sulfinyl α,α-difluoro-β-amino phosphonates **3** from diethyl lithiodifluoromethylphosphonate **2** and enantiomerically pure *N*-*p*-toluenesulfinylimines **1** is described. The utility of diastereomerically pure *N*-sulfinyl α,α-difluoro-β-amino phosphonates **3** is illustrated by their transformation into the corresponding enantiomerically pure α,α-di-

fluoro-β-amino phosphonic acids **5**. Extension of this method to α,α-difluoro-β-amino phosphonic acids containing a β-quaternary stereogenic carbon is currently under study.

Acknowledgements

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8. (*Ss*,*R*) Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-phenylethylphosphonate (**3a**). To a solution of diethyl difluoromethylphosphonate (245 mg, 1.30 mmol) in THF (3 mL) at −78 °C was added LDA (1.8 M solution, 0.72 mL, 1.30 mmol). After 0.5 h (*S*)-*N*-benzylidene-*p*-toluenesulfinamide **1a** (243 mg, 1.00 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C and quenched at this temperature with satd NH_4Cl (10 mL). The organic phase was extracted with EtOAc (2×10 mL), washed with H_2O (10 mL), and brine (5 mL), dried (MgSO4), and concentrated under reduced pressure. Crystallization of the crude product from ether afforded 320 mg (74%) of (*Ss*,*R*)-**3a** as a white solid; mp 95–97 °C; $[\alpha]_D^{19}$ +53.7 (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, *J* 7.1 Hz, 3H), 1.26 (t, *J* 7.1 Hz, 3H), 2.32 (s, 3H), 3.94–4.23 (m, 4H), 4.87–5.02 (m, 1H), 5.43 (d, *J* 7.7 Hz, 1H), 7.12 (d, *J* 8.0 Hz, 2H), 7.24 (s, 5H), 7.51 (d, *J* 8.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.01 (ddd, *J* 302.2, 101.2, and 13.2 Hz, 1F), −115.58 (ddd, *J* 302.2, 103.6, and 15.0 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 5.90 (dd, *J* 103.6 and 101.2 Hz). Anal. Calcd for $C_{19}H_{24}F_2NO_4PS$: C, 52.90; H, 5.61; N, 3.25. Found: C, 53.14; H, 5.68; N, 3.30.
9. Crystallographic data (excluding structure factor) for (*Ss*,*R*)-**3a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 239237. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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