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Convenient, large-scale asymmetric synthesis of β-aryl-substituted α,α-difluoro-β-amino acids

Vadim A. Soloshonok,[a,*] Hironari Ohkura,[a] Alexander Sorochinsky,[b] Natalia Voloshin,[b] Andrey Markovsky,[b] Michael Belik[b] and Takashi Yamazaki[c]

[a]*Department of Chemistry and Biochemistry, University of Oklahoma, 620 Parrington Oval, Room 208, Norman, OK 73019-3051, USA*

[b]*Institute of Bioorganic Chemistry and Petrochemistry, Ukrainian Academy of Sciences, Kiev 94, 253660, Ukraine*

[c]*Department of Bioengineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan*

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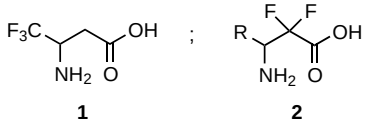
Abstract—The enantiopure *p*-toluenesulfinimines were found to be efficient as chiral imine equivalents in the high temperature Reformatsky-type additions with $BrZnCF_2COOEt$ affording an efficient approach to the enantiomerically pure α,α-difluoro-β-amino acids. High chemical and stereochemical yields (drs>9:1, and as high as 99:1) render this method immediately useful for preparing the target amino acids. © 2002 Elsevier Science Ltd. All rights reserved.

Taking into account the exciting benefits of fluorine substitution for hydrogen established in the series of α-amino acids and α-peptides, such as rational modification of lipophilicity/hydrophobicity, reactivity and stability of the peptides secondary structures,[1] preparation and study of fluorinated β-amino acids and β-peptides might be of particular interest. However, to the best of our knowledge, fluorine substitution for hydrogen in β-peptides has not been studied thus far.[2–4] Therefore, we set for ourselves a goal to design and synthesize fluorine-containing β-peptides and study their physicochemical and biological properties. In this context we envisioned two different strategies for fluorine substitution for hydrogen in β-peptides: the fluorinated outer-space and fluorinated inner-space, a peptide backbone. The former could be achieved using β-amino acids of type **1** (Fig. 1), while the latter could be realized with application of monomers **2**. To take on these targets, we needed convenient and reliable asymmetric methods for preparing both enantiomers of amino acids **1** and **2** on a relatively large scale. Recently we[5] and others[6] have independently developed several generalized approaches to enantiomerically pure β-fluoroalkyl-β-amino acids of type **1**. On the other hand, despite the considerable interests in α,α-difluoro-β-amino acids **2** as the precursors to a particular type of fluorinated β-lactam antibiotics,[7] only two,[8] to the best of our knowledge,[9] reports in the literature deal with a preparation of β-amino acids **2** in enantiomerically pure/enriched form. In the recent paper[8b] the authors reported Reformatsky addition reaction between in situ generated $XZnCF_2COOR$ (X = halogen) and chiral 1,3-oxazolidines. The reactions were shown to proceed with high diastereoselectivity furnishing the corresponding azetidin-2-ones with up to 99% de. However, the chemical yields were much less satisfactory ranging from 32 to 69%. Furthermore, the additional two to three steps required for transformation of the azetidin-2-ones to the target α,α-difluoro-β-amino acids **2** led to low overall yields rendering this approach synthetically problematic. In this communication we report that application of chiral *N*-sulfinimines in the addition reaction with the in situ generated $BrZnCF_2COOEt$ (**3**) offers a superior synthetic alternative to the previous methods[8,9] allowing an efficient large-scale preparation of enantiopure amino acids **2**.



1 **2**

Figure 1. Two different strategies for fluorine substitution for hydrogen in β-peptides.

Keywords: asymmetric synthesis; amino acids and derivatives; fluorine and compounds; sulfoxides; Reformatsky reactions/reagents.

* Corresponding author. E-mail: vadim@ou.edu

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Among a vast variety of synthetic approaches reported for asymmetric preparation of β-amino acids,[10] our attention was attracted by the method developed by Davis and co-workers.[11] Key step of their protocol consists in the highly diastereoselective Reformatsky type addition of methyl bromoacetate to the enantiopure *N*-*p*-toluenesulfinimines at −78°C in the presence of zinc. Hydrolysis of the corresponding addition products under mild conditions affords the target β-amino acids in high overall chemical yields.

First we conducted the reaction between **3** and (*S*)-*N*-benzylidene-*p*-toluenesulfinimine (**5a**) (Scheme 1). The reaction of sulfinimine **5a** with ethyl bromodifluoroacetate conducted in the presence of activated Zn powder in boiling THF was completed in 15 min furnishing the corresponding *p*-toluenesulfinamide **6a** as a sole reaction product. In a series of experiments designed to optimize chemical yield of addition product **6a**, we found that a 1/2 ratio of sulfinimine **5a** and $BrCF_2COOEt$ was required for complete transformation of the former to sulfinamide **6a**, isolated with over 80% yield. Diastereoselectivity of the addition, determined by 500 MHz NMR (^{19}F, ^{1}H) on crude reaction mixture, was found to be surprisingly high. Considering the high temperature of the addition, a 96/4 ratio of the diastereomers (Table 1, entry 1) is remarkable. Crystallization of the crude mixture afforded the major diastereomer in optically pure form.[12] To determine the absolute configuration of the newly formed stereogenic carbon in the major product **6a**, it was hydrolyzed to the target free amino acid **2a** (Scheme 1).[13] Enantiomeric purity (>99% ee) of the obtained amino acid **2a** was confirmed by HPLC analysis on chiral sorbents.[14] Comparison of the sign and magnitude of an optical rotation obtained for **2a** with the literature data revealed its (*S*) absolute configuration;[13] therefore, stereochemistry of the addition product **6a** was assigned to be (S_s,3*S*). Application of the (*R*)-configured starting sulfinimine **5a** in the reaction with **3**, mirrored the results obtained for (*S*)-**5a** giving rise to (R_s,3*R*)-**6a** in 92% de (entry 2). Next we studied generality of the reaction using aromatic sulfinimines **5b–f** bearing electron-releasing and electron-withdrawing substituents.[15] The addition between *p*-methoxy-containing (*S*)-**5b** afforded the product **6b** with unexpectedly improved diastereoselectivity (entry 3). Thus, only one diastereomeric product (S_s,3*S*)-**6b** was detected in the crude reaction mixture. On the other hand, the reactions of *p*-fluoro- and *p*-chloro-substituted (*S*)-**5c**,**d** gave rise to the diastereomeric products **6c**,**d** with the stereochemical outcome comparable with that of observed in the addition of unsubstituted *N*-benzylidene derivative **5a** (entries 1, 2 vs 4, 5). In contrast, the additions of *p*-trifluoromethyl- and 2-furyl-containing sulfinimines **5e**,**f** proceeded with lower stereochemical outcome as compared with the diastereoselectivity observed in the reactions of *N*-benzylidene derivative **5a** (entries 1, 2 vs 6, 7). These data clearly demonstrate that while the high-temperature Reformatsky addition reactions under study could be regarded as generalized and a practical approach to the target β-amino acids **2**, there is an unexpected and interesting issue of the stereochemical outcome influenced by electronic nature of a substituent on the starting sulfinimine **5**.

Hydrolysis of diastereomerically pure (column chromatography or recrystallization) sulfinamides **6b–f** was readily accomplished by refluxing with 6N HCl to afford, after treatment with propylene oxide, the target

Table 1. Addition reactions of Reformatsky reagent **3** with *N*-*p*-toluenesulfinimines (*S*)-**5a–e**[a]

Entry	**5a–e**	Products **6a–e**		
		Yield[b] (%)	de[c] (%)	Configuration[d]
1	**a**	82	92	(S_s,3*S*)
2	**a**	84	92	(R_s,3*R*)[e]
3	**b**	82	>98	(S_s,3*S*)
4	**c**	83	94	(S_s,3*S*)
5	**d**	85	93	(S_s,3*S*)
6	**e**	85	80	(S_s,3*S*)
7	**f**	76	86	(S_s,3*S*)

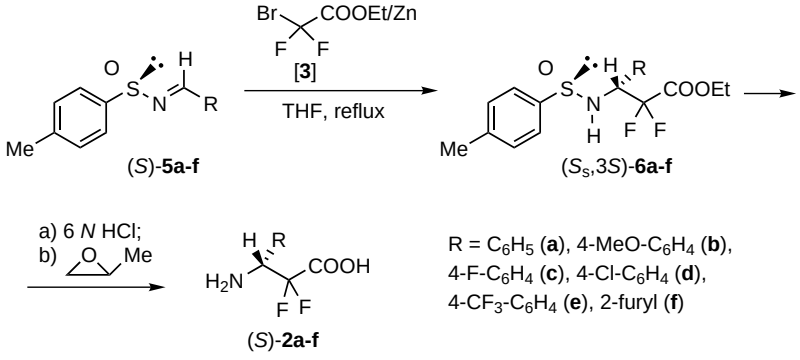
[a] All reactions were conducted by slow addition of a solution of 2 equiv. of ethyl 2-bromo-2,2-difluoroacetate and 1 equiv. of imine **5a–f** in THF to refluxing suspension of 2 equiv. of activated Zn powder in THF.

[b] Isolated yield of after column chromatography.

[c] Determined by NMR (500 MHz) analysis of the crude reaction mixtures.

[d] Determined by comparison of the sign and magnitude of the optical rotation compared with the literature data; see also the text.

[e] (*R*)-Configured imine **5a** was used.



Scheme 1.

α,α-difluoro-β-amino acids **2b**–**f**. The hydrolysis was typically carried out for 4 h to ensure complete removal of the sulfinamide as well as ester moieties. Enantiomeric purity of all amino acids **2a**–**f** obtained was controlled by the chiral HPLC analysis.[14]

Taking into consideration that the stereochemical outcome of the addition reactions under study, regarding the absolute configuration of the newly formed carbon stereogenic center, is similar[16] to the stereochemical preferences generally observed for the nucleophilic additions to sulfinimines of type **5**,[17] we can construct transition state **7** (Fig. 2) to account for the observed diastereoselectivity.

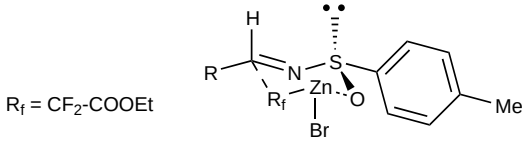


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Figure 2. Plausible transition state in the Reformatsky additions of **3** to **5**.

In summary, the results reported in this communication clearly demonstrate that the enantiopure *p*-toluenesulfinimines can be successfully used as chiral imine equivalents in the high temperature Reformatsky-type additions with $BrZnCF_2COOEt$ (**3**) affording an efficient approach to the enantiomerically pure α,α-difluoro-β-amino acids **2**. High chemical and stereochemical yields (drs>9:1, and as high as 99:1) render this method synthetically superior over previously reported approaches,[8,9] and immediately useful for preparing the target amino acids **2**. Extension of this method to the aliphatic series and α,α-difluoro-β-amino acids containing β-quaternary stereogenic carbon, as well as application of enantiopure *tert*-butanesulfinylimines as more powerful stereocontroling auxiliary,[17d,18] is currently under study.

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12. (*S*s,3*S*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluoro-3-phenylpropanoate (**6a**). Typical procedure. A solution of (*S*)-(+)-benzylidene-*p*-toluenesulfinamide **5a** (243 mg, 1.0 mmol) and ethyl bromodifluoroacetate (410 mg, 0.26 ml, 2.0 mmol) in THF (2 ml) was added dropwise to a refluxing suspension of Zn dust (131 mg, 2.0 mmol) in THF (5 ml). After refluxing for 15 min the reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (15 ml), and diluted with ethyl acetate. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic layers

were washed with water, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (hexane/ethyl acetate 3:1) gave 301 mg (82%) of **6a** as a 96:4 mixture of diastereomers. Recrystallization from mixture of hexane/ethyl acetate afforded 239 mg (65%) diastereomerically pure (*S*s,3*S*)-**6a** as a white solid; mp 119–120°C; $[\alpha]_D^{19}$ +116.2 (*c* 1.04 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (t, $J=7.2$ Hz, 3H), 2.43 (S, 3H), 4.09–4.26 (m, 2H), 4.84–5.04 (m, 2H), 7.32 (d, $J=8.2$ Hz, 2H), 7.38–7.43 (m, 5H), 7.57 (d, $J=8.2$ Hz, 2H). ^{19}F NMR ($CDCl_3$): δ −112.58 (dd, $J=253$ and 12.1 Hz, 1F), −114.74 (dd, $J=256$ and 12.1 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 162.39 (t, $J=31.1$), 141.76 (s), 141.02 (s), 133.21 (s), 129.56 (s), 129.20 (s), 128.72 (s), 128.65 (s), 125.52 (s), 113.78 (t, $J=256$), 63.26 (s), 59.69 (t, $J=23.6$), 21.48 (s), 13.77 (s). Anal. Calcd for $C_{18}H_{19}F_2NO_3S$: C, 58.84; H, 5.21; N, 3.81. Found: C, 58.57; H, 5.49; N, 3.85.

13. (*S*)-3-Amino-2,2-difluoro-3-phenylpropanoic acid (**2a**). Typical procedure. A solution of (*S*s,3*S*)-**6a** (197 mg, 0.54 mmol) in 6N HCl (11 ml) was reflux for 4 h. The aqueous phase was washed with ether (2×5 ml) and the aqueous solution was concentrated under reduce pressure to dryness. The resulting solid was treated with *i*-PrOH (3 ml) and propylene oxide (0.151 ml, 125 mg, 2.16 mmol) and reaction mixture was stirred for 5 h. Precipitate was filtered off and washed with ether to provide 95 mg (88%) of amino acid (*S*)-**2a** as a white solid; mp 242–244°C, $[\alpha]_D^{19}$ +7.71 (*c* 0.986, MeOH). Only one enantiomer was observed by HPLC analysis of (*S*)-**2a** [(*S*)-**2a** $t_r=6.9$ min, (*R*)-**2a** $t_r=8.5$ min]. ^1H NMR (CD_3OD): 4.85–4.93 (4H, m), 7.43–7.53 (5H, m). ^{19}F NMR (CD_3OD): 51.673 ppm (1F, dd, $J=13.14$, 258.72 Hz), 54.858 ppm (1F, dd, $J=9.70$, 257.86 Hz). Elemental analysis Calcd: C, 53.73; H, 4.51; N, 6.96. Found: C, 53.35; H, 4.21; N, 6.70. Literature (Ref. 8b): $[\alpha]_D^{25}$ +7.1 (*c* 1.0, MeOH).

S-3-Amino-2,2-difluoro-3-(*p*-methoxyphenyl)propanoic acid (**2b**). Hydrolysis of (*S*s,3*S*)-**6b** (199 mg, 0.5 mmol) gave 103 mg (96%) of amino acid (*S*)-**2b**, mp 261–263°C. Only one enantiomer was observed by HPLC analysis of (*S*)-**2b** [(*S*)-**2b** $t_r=7.0$ min, (*R*)-**2b** $t_r=8.6$ min]. ^1H NMR (DMSO-d_6): δ 3.76 (s, 3H), 4.74 (dd, $J=14.6$ and 8.4 Hz, 1H), 6.97 (d, $J=8.6$ Hz, 2H), 7.42 (d, $J=8.6$ Hz, 2H), 9.05 (broad s). ^{19}F NMR (DMSO-d_6): δ −106.05 (dd, $J=260$ and 8.4 Hz, 1F), −110.75 (dd, $J=260$ and 14.6 Hz, 1F). Anal. Calcd for $C_{10}H_{11}F_2NO_3$: C, 51.95; H, 4.80; N, 6.06. Found: C, 51.91; H, 5.02; N, 5.86.

S-3-Amino-2,2-difluoro-3-(*p*-trifluoromethylphenyl)-propanoic acid (**2d**). Hydrolysis of (*S*s,3*S*)-**6d** (298 mg, 0.68 mmol) gave 173 mg (94%) of amino acid (*S*)-**2d**, mp 252–254°C. Only one enantiomer was observed by HPLC analysis of (*S*)-**2d** [(*S*)-**2d** $t_r=11.6$ min, (*R*)-**2d** $t_r=15.8$ min]. ^1H NMR (DMSO-d_6): δ 5.01 (dd, $J=14.6$ and 8.8 Hz, 1H), 7.74 (d, $J=8.4$ Hz, 2H), 7.82 (d, $J=8.4$ Hz, 2H), 9.07 (broad s). ^{19}F NMR (DMSO-d_6): δ −60.74 (s, 3F), −106.22 (dd, $J=260$ and 8.8 Hz, 1F), −110.33 (dd, $J=260$ and 14.6 Hz, 1F). Anal. Calcd for $C_{10}H_8F_5NO_2$: C, 44.62; H, 2.99; N, 5.20. Found: 44.87; H, 3.18; N, 4.98.

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