Zinc-mediated Coupling Reaction of 2-Bromo-2,3,3,3-tetrafluoropropanoate with Various Chiral Imines. Simple and Effective Access to Optically Active α-Fluoro-α-(trifluoromethyl)-β-amino Esters

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The reactions of benzyl 2-bromo-2,3,3,3-tetrafluoropropanoate with various types of chiral imines in the presence of zinc in THF at room temperature were revealed to afford the *threo*- and *erythro*-isomers of α-fluoro-α-(trifluoromethyl)-β-amino esters with high diasteremeric excesses in fair to good chemical yields.

Since the introduction of fluorine groups, such as monofluoro, difluoromethylene, and trifluoromethyl, into bioactive compounds frequently exerts significant effects on their physical properties, physiological activities, and metabolic profiles,[1] a number of efforts have continuously been paid to synthesize many sorts of fluorine-containing biologically active compounds.[2] Recently, α- or β-fluorinated β-amino acids have attracted increasing attention owing to their biochemical or synthetic applications in medicinal and synthetic organic chemistry.[3] The literature embodies a limited number of stereoselective approaches to fluorinated and nonfluorinated β-amino acids using chiral imines.[4–6] However, the methods for synthesizing optically active α-fluorinated β-amino acid derivatives do not necessarily suffice for versatile applications. Therefore, development of a practical method for the asymmetric synthesis of such fluorinated β-amino carbonyl compounds would be exceedingly valuable. This communication discloses a simple and efficient access to the four diastereoisomers of α-fluoro-α-(trifluoromethyl)-β-amino esters **3** with high diastereomeric excesses, through the zinc-mediated coupling reaction between benzyl 2-bromo-2,3,3,3-tetrafluoropropanoate (**1**) and chiral imines **2** at ambient temperature.

Initially, the reaction of the α-bromo ester **1** (1.5 equiv.), prepared from commercially available 2-bromo-2,3,3,3-tetrafluoropropanoyl chloride, with (*S*)-*N*-(1-phenylethyl)imine **2a** (1.0 equiv.) was conducted in the presence of activated zinc (1.8 equiv.) in THF at room temperature for 3 h to result in almost no formation of the coupling product **3aa**, only bromine-reduced product, benzyl 2,3,3,3-tetrafluoropropanoate (**6**) being formed in a quantitative yield (Entry 1). The treatment of **1** with imine **2b** derived from (*S*)-valine methyl ester gave the desired coupling product **3ba**[7] in 13% yield, along with β-lactam derivative **4b**[7] (*cis*[8] 10%, *trans*[8] 10% yield) (Entry 2). On the other hand, treating **1** with imine **2c** derived from (*S*)-phenylglycine methyl ester under the similar conditions led to the corresponding α-fluoro-α-(trifluoromethyl)-β-amino ester **3ca**[7] in good yield as a 55:45 mixture of the *threo*- and *erythro*-isomers,[9] in which the (2*R*, 3*R*, 1′*S*)-*threo*- and (2*S*, 3*R*, 1′*S*)-*erythro*-isomers[10] were in 82 and 88% de, respectively (Entry 3). It is very interesting that the reactions with **2c** produced considerable amounts of pyrrolidine derivatives **5c**[11] as well as β-lactam **4c**,[7] in addition to **3c** (Entries 3 and 4). When the α-bromo ester **1** was allowed to react with (*S*)-sulfinimine **2d** under the same conditions, the corresponding coupling product **3da**[7] was afforded in high yield as an 83:17 mixture of the *threo*- and *erythro*-isomers. Of much synthetic value is that the *threo*- and *erythro*-isomers were formed as the (2*S*, 3*S*, S_S)-*threo*- and (2*R*, 3*S*, S_S)-*erythro*-isomers[10] with 92 and 92% de, respectively (Entry 5). Even performing this reaction at −15 °C for 6 h provided nearly comparable results with those of the reaction at room temperature for 3 h (Entry 6).

The reactions between **1** and various sulfinimines **2d** were examined, as shown in Table 1. Sulfinimines **2d** derived from aromatic and α,β-unsaturated aldehydes participated nicely in the coupling reaction of **1** to afford the corresponding α-fluoro-α-(trifluoromethyl)-β-amino esters **3d** in good to excellent yields (73–96%), without formation of β-lactams **4d**. The ratios of the *threo*- to *erythro*-isomer were in a range of 74:26 to 83:17 (Entries 7–10). The reaction with **2d** derived from aliphatic aldehydes, such as *n*-butanal and 2-methylpropanal, also proceeded in a good diastereoselective fashion to give the corresponding coupling products **3d** (Entries 11 and 12), but the reaction with imine **2d** from a sterically hindered aldehyde, 2,2-dimethylpropanal, did not take place at all to result in the formation of the reduced ester **6** and recovery of **1** (Entry 13). It is significant that the diastereomeric excesses in both *threo*- and *erythro*-isomers fall within 90–98% (Entries 1 and 5–12).

The general procedure for the reaction is as follows. To a suspension of zinc dust (1.8 equiv.) and imine **2** (1.0 equiv.) in THF was dropwise added a solution of benzyl 2-bromo-2,3,3,3-tetrafluoropropanoate (**1**) (1.5 equiv.) in THF at 0 °C under argon. The whole mixture was warmed to room temperature and stirred for 3 h, and then was poured into a cold aqueous NH_4Cl solution containing a third volume of aqueous 10% HCl solution. The resultant mixture was extracted three times with ethyl acetate. The organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to leave a residual oil. After high resolution ^{19}F NMR determination, the residue was subjected to purification by silica-gel column chromatography (hexane:ethyl acetate = 4/1–2/1) to afford analytically pure product **3**.[7,12] It should be noted that each major *threo*- and *erythro*-isomer of **3c** and **3d** can be isolated separately as optically pure forms by column chromatography.

In summary, we have demonstrated that the zinc-promoted coupling reaction of the α-bromo ester **1** with (*S*)-imines **2c** provided the (2*R*, 3*R*)-*threo*- and (2*S*, 3*R*)-*erythro*-isomers of α-fluoro-α-(trifluoromethyl)-β-amino esters **3c** with >82% de, while the similar reaction with (*S*)-sulfinimines **2d** led to the (2*S*, 3*S*)-*threo*- and (2*R*, 3*S*)-*erythro*-isomers of **3d** with >90% de. The present reactions will serve as an important protocol for synthesizing a number of regio- and stereoselectively fluorinated chiral compounds of biological interest.

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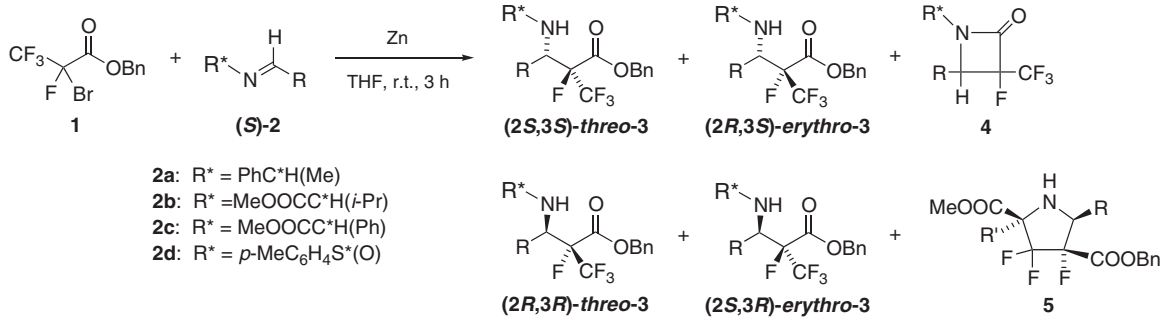
Table 1. Coupling reaction of **1** with various imines **2**

Entry[a]	Imine **2**	R	Yield[b]/% of **3**		Isomer ratio[c] of **3** *threo*:*erythro* (2*S*,3*S*:2*R*,3*R*) (2*R*,3*S*:2*S*,3*R*)	Yield[b]/% of **4** and/or **5**
1	**2a**	Ph	tr		-	0
2	**2b**	Ph	13	**(3ba)**	43:57	20 0
3	**2c**	Ph	71	**(3ca)**	55:45 (9:91) (6:94)	10 9
4	**2c**	*p*-ClC_6H_4	42	**(3cc)**	52:48 (8:92) (3:97)	33 25
5	**2d**	Ph	(89)	**(3da)**	83:17 (96:4) (96:4)	0
6[d]	**2d**	Ph	91	**(3da)**	78:22 (95:5) (97:3)	0
7	**2d**	*p*-$MeOC_6H_4$	(96)	**(3db)**	82:18 (97:3) (95:5)	0
8	**2d**	*p*-ClC_6H_4	(78)	**(3dc)**	74:26 (98:2) (96:4)	0
9	**2d**	*p*-FC_6H_4	(73)	**(3dd)**	78:22 (99:1) (99:1)	0
10	**2d**	MeCH–CH	(75)	**(3de)**	81:19 (98:2) (96:4)	0
11	**2d**	*n*-Pr	(89)	**(3df)**	80:20 (97:3) (95:5)	0
12	**2d**	*i*-Pr	(88)	**(3dg)**	89:11 (98:2) (95:5)	0
13	**2d**	*t*-Bu	0		-	0

[a] Unless otherwise noted, the molar ratio of **1**:**2**:Zn = 1.5:1.0:1.8. [b] Determined by ^{19}F NMR. Values in parentheses are of isolated yield based on **2**. [c] Measured by ^{19}F NMR (470 MHz). [d] Conducted at −15 °C for 6 h.



Scheme 1. Zinc-mediated coupling reaction of α-bromo ester **1** with chiral imines **2**.

References and Notes

1 "Biomedicinal Aspects of Fluorine Chemistry," ed. by R. Filler and Y. Kobayashi, Kodansha & Elsevier Biomedical, Tokyo (1982); J. T. Welch, *Tetrahedron*, **43**, 3123 (1987); J. T. Welch and S. Eswarakrishnan, "Fluorine in Bioorganic Chemistry," John Wiley & Sons, New York (1991); I. Ojima, J. R. McCarthy, and J. T. Welch, "Biomedical Frontiers of Fluorine Chemistry," American Chemical Society, Washington, D.C. (1996).

2 T. Yamazaki, K. Mizutani, and T. Kitazume, *J. Synth. Org. Chem. Jpn.*, **52**, 734 (1994); "Fluorine-containing Amino Acids. Synthesis and Properties," ed. by V. P. Kukhar and V. A. Soloshonok, John Wiley and Sons, Chichester (1995); "Enantiocontrolled Synthesis of Fluoro-Organic Compounds, Stereochemical Challenges and Biomedical Targets," ed. by V. A. Soloshonok, John Wiley & Sons, New York (1999).

3 D. Schirlin, S. Baltzer, J. M. Altenburger, C. Tarnus, and J. M. Remy, *Tetrahedron*, **52**, 305 (1996); K. Uoto, S. Ohsuki, H. Takenoshita, T. Ishiyama, S. Iimura, Y. Hirota, I. Mitsui, T. Hirofumi, and T. Soga, *Chem. Pharm. Bull.*, **45**, 1793 (1997); H. Chiba, H. Agematu, R. Kaneto, T. Terasawa, K. Sakai, K. Dobashi, and T. Yoshioka, *J. Antibiot.*, **52**, 695 (1999).

4 For the synthesis of α-fluorinated β-amino acids: T. Taguchi, O. Kitagawa, Y. Suda, S. Ohkawa, A. Hashimoto, Y. Itaka, and Y. Kobayashi, *Tetrahedron Lett.*, **29**, 5291 (1988); V. A. Soloshonok, H. Ohkura, A. Sorochinsky, N. Voloshin, A. Markovsky, M. Belik, and T. Yamazaki, *Tetrahedron Lett.*, **43**, 5445 (2002); D. D. Staas, K. L. Savage, C. F. Homnick, N. N. Tsou, and R. G. Ball, *J. Org. Chem.*, **67**, 8276 (2002).

5 For the synthesis of β-fluorinated β-amino acids: V. A. Soloshonok, I. V. Soloshonok, V. P. Kukhar, and V. K. Sveda, *J. Org. Chem.*, **63**, 1878 (1998); A. Volonterio, P. Bravo, and M. Zanda, *Org. Lett.*, **2**, 1827 (2000); S. Fustero, E. Salavert, B. Pina, A. C. Ramirez, and A. Asensio, *Tetrahedron*, **57**, 6475 (2001), and referenced cited therein.

6 For stereoselective nucleophilic addition to chiral imines: F. A. Davis, P. Zhou, and B. C. Chen, *Chem. Soc. Rev.*, **27**, 13 (1998); R. Bloch, *Chem. Rev.*, **98**, 1407 (1998); J. A. Ellman, T. D. Owens, and T. P. Tang, *Acc. Chem. Res.*, **35**, 984 (2002); F. A. Davis, J. Deng, Y. Zhang, and R. C. Haltianger, *Tetrahedron*, **58**, 7135 (2002).

7 The spectral (IR, ^1H (500 MHz), ^{13}C (125 MHz), and ^{19}F NMR (84.9 and 470 MHz), HRMS) and analytical data of the products were in good accord with the assigned structures including stereochemistry.

8 The isomer with a *cis* relationship between hydrogen and fluorine atoms on **4** was designated as cis, its stereochemical assignment being based on the relative magnitudes of $J_{H\text{-}F}$. T. Ishihara, K. Ichihara, and H. Yamanaka, *Tetrahedron*, **52**, 255 (1996).

9 The relative stereochemical nomenclature proposed by Noyori et al. is applied in this work. R. Noyori, I. Ishida, and J. Sakata, *J. Am. Chem. Soc.*, **105**, 1598 (1983).

10 The absolute configurations were determined on the basis of the X-ray crystallography for *p*-bromophenacyl esters prepared separately from the (2*R*, 3*R*, 1′*S*)-*threo*- and (2*S*, 3*R*, 1′*S*)-*erythro*-isomers of **3cc** and for the (2*S*, 3*S*, S_S)-*threo*- and (2*R*, 3*S*, S_S)-*erythro*-isomers of **3db**, whose data were collected on a Rigaku AFCR7R diffractometer with graphite monochromated Cu Kα radiation and a rotating anode generator.

11 The pyrrolidine derivatives **5c** were the 97:3 to 99:1 mixture of two diastereoisomers and the major one, depicted in Scheme 1, was found to be racemate by the X-ray crystallography for **5cc**.

12 Removal of the sulfinyl group for (2*S*, 3*S*, S_S)-*threo*-**3da** gave the corresponding β-amino ester in 60% yield. $[\alpha]^{21}_D$ −35.2° (*c* 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.82 (br s, 2H), 4.65 (d, J = 25.8 Hz, 1H), 4.99 (s, 2H), 7.08–7.13 (m, 2H), 7.24–7.39 (m, 8H); ^{19}F NMR ($CDCL_3$, $CFCl_3$) δ −73.2 (d, J = 6.6 Hz, 3F), −190.5 (dq, J = 6.6, 25.8 Hz, 1F); HRMS (FAB) calcd. for (M + H) $C_{17}H_{16}F_4NO_2$: 342.1117, found: 342.1117.

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