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Efficient synthesis of an optically pure β-bromo-β,β-difluoroalanine derivative, a general precursor for β,β-difluoroamino acids

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Abstract—A highly efficient enantioselective preparation of a β-bromo-β,β-difluoroalanine derivative, a promising general precursor for optically active β,β-difluoroamino acids, is described. Alkylation of the hydroxypinanone glycinate Schiff base **2a** with CF_2Br_2 resulted in the production of undesired dehydrobrominated product **4a** promoted by the lithium alkoxide moiety on the hydroxypinanone chiral auxiliary. Dehydrobromination was prevented by protection of the hydroxyl group on the chiral auxiliary. Utilization of TMSOTf resulted in production of (*S*,*S*,*S*,*S*)-**3b** as the sole diastereomer without dehydrobromination. Further transformations of (*S*,*S*,*S*,*S*)-**3b** to other optically active β,β-difluoroamino acids were demonstrated.

1. Introduction

Fluorinated chiral amino acids and peptides[1,2] are an important class of unnatural bioactive molecules in medicinal and agricultural sciences. Among them, β,β-difluoroalanine acts as an inhibitor for pyridoxal phosphate dependent enzymes.[3] In spite of these interests in their potential biological activities, few methods are available for the synthesis of these β,β-difluoroamino acids[4] and enantioselective syntheses of optically active β,β-difluoroamino acids have been especially scarce.[5]

Recently, we reported the preparation of (±)-β-bromo-β,β-difluoroalanine derivatives by bromodifluoromethylation of *N*-diphenylmethylene glycinate Schiff base.[6] Optically pure β-bromo-β,β-difluoroalanine **1** would be an efficient and general synthetic precursor for a number of chiral α-difluoromethylene-α-amino acids. For the asymmetric syntheses of chiral amino acids, the diastereoselective nucleophilic alkylation of hydroxypinanone glycinate Schiff base **2a** with alkyl monohalides is known to be one of the most efficient methodologies.[7] However, the alkylation of Schiff base **2a** with alkyl *gem*-dihalides causes dehydrohalogenation of the alkylated products to give alkylidene glycine under basic conditions with the deprotonated hydroxyl group of Schiff base **2a**. Herein, we report the asymmetric bromodifluoromethylation of Schiff base **2** to give β-bromo-β,β-difluoroalanine enantioselectively. Further transformations of the β-bromo-β,β-difluoroalanine derivative to give β,β-difluoroamino acids are also reported.

2. Results and discussion

2.1. Preparation of bromodifluoromethylated compound 3

Schiff base **2a** was prepared using the reported (BF_3–etherate-catalyzed) procedure.[7] The results for the alkylation of **2a** with CF_2Br_2 under a number of conditions are summarized in Table 1. The reaction at −78°C with LTMP base gave the undesired dehydrobrominated product **4a** (derived from **3**) (entry 1). When the reaction was conducted at −100°C with LTMP or LHMDS base, the desired bromodifluoromethylated adduct **3a** was obtained as the sole diastereomer without dehydro-

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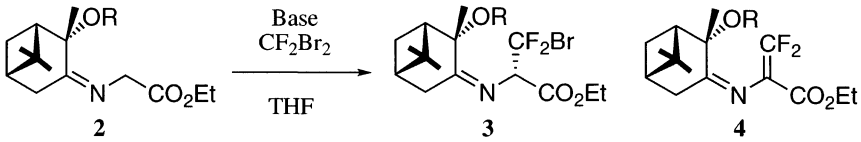
Table 1. Bromodifluoromethylation of Schiff base **2**



2 **3** **4**

Entry	Schiff base **2**	Base (equiv.)	Conditions	Yield (%)[a]		
				3 (d.e., %)	**4**	**2**
1	**2a** (R = H)	LTMP (2.0)	−78°C, 4 h		38	–
2	**2a** (R = H)	LTMP (2.0)	−100°C, 5 h	20 (>99)	–	72
3	**2a** (R = H)	LHMDS (2.0)	−100°C, 7 h	20 (>99)	–	–
4	**2b** (R = TMS)	LTMP (1.0)	−78°C, 4 h	45 (64)	16	–
5	**2b** (R = TMS)	LTMP (1.0)	−100°C, 7 h	30 (68)	7	–
6	**2b** (R = TMS)	LHMDS (1.0)	−78°C, 4 h	81[b] (64)	Trace	–
7	**2c** (R = TBDMS)	LTMP (1.0)	−78°C, 4 h	48 (64)	10	–
8	**2c** (R = TBDMS	LHMDS (1.0)	−78°C, 4 h	75[b] (64)	–	–

[a] Chemical yields and diastereomeric excesses were determined by ^{19}F NMR using 1,3-bis(trifluoromethyl)benzene as an internal standard.
[b] Isolated yields.

bromination, but the conversion was low (entries 2 and 3). The absolute configuration of the diastereomer **3b** was found to be (*S*,*S*,*S*,*S*) as determined by X-ray crystallographic analysis (the ORTEP structure is shown in Fig. 1).

To avoid dehydrohalogenation of the alkylated product **3a** to **4a** (which would be promoted by the lithium alkoxide moiety of the chiral auxiliary), the hydroxyl group of the hydroxypinanone was masked using protective groups. Silyl-protected Schiff bases **2b** and **2c** were prepared easily in high yields by the reported general procedures.[8] The yields of the bromodifluoromethylation products **3b** and **3c** from the silyl protected **2b** and **2c** respectively were improved markedly, although the diastereoselectivity was moderate (entries 4–8). The reaction of **2b** with LHMDS resulted in the formation of **3b** (81%) as a mixture of two diastereomers (82:18) (entry 6). Purification by silica-gel chromatography followed by recrystallization gave the diastereomer, (*S*,*S*,*S*,*S*)-**3b**, in 62% yield. These results imply that the hydroxyl group of the

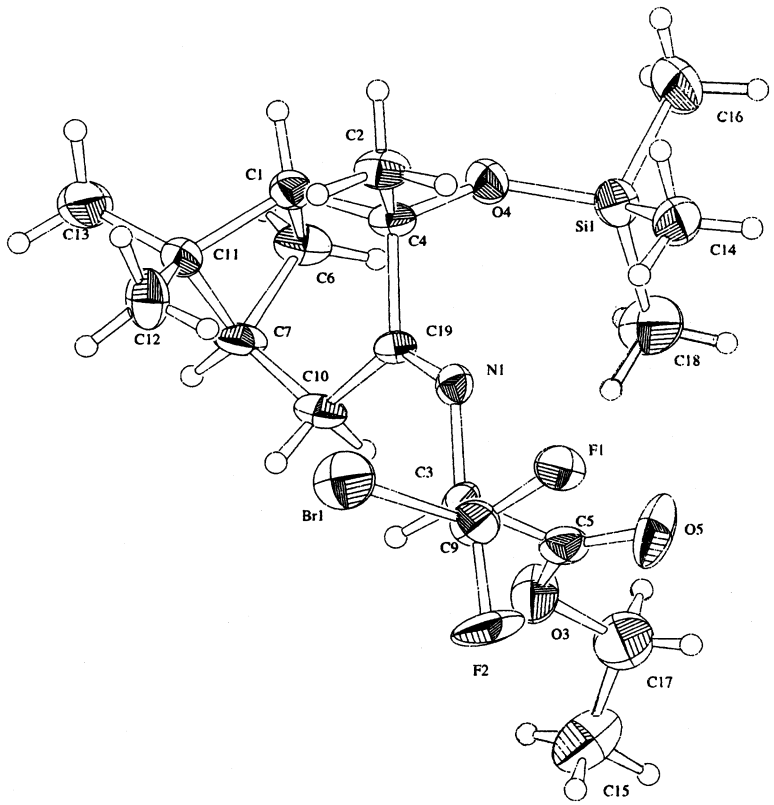


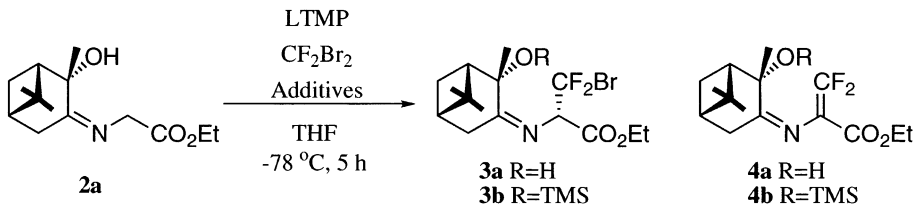
Figure 1. ORTEP structure of **3b**.

hydroxypinanone chiral auxiliary plays an essential role in the diastereoselective reaction, which is consistent with our previous results regarding the base effects on diastereoselectivity.[7h]

To overcome the depression of diastereomeric excess of **3** by prior protection of the hydroxyl moiety of Schiff bases **2b** and **2c**, in situ protection by the addition of silyl halides and triflate was investigated[9] (Table 2). Fortunately, silyl protection by the addition of silyl halides or triflate was effective in preventing the dehydrobromination of **3**, which resulted in the production of the desired product **3** with excellent diastereoselectivity. Optimization of the silyl additive reactions revealed that the addition of 6 equiv. of TMSCl to the reaction mixture excluded dehydrobromination of **3** to **4** (entry 3). Utilization of the more reactive TMSBr, TMSI, or TMSOTf instead of TMSCl led to improved yields of **3** (entries 2 and 4–6). Among them, TMSOTf was found to be the most effective protecting reagent of the chiral auxiliary hydroxyl moiety to give **3** in moderate 38% yield with complete diastereoselectivity (entry 6). Further optimization of the reaction conditions resulted in the preparation of **3** in 54% yield with >98% d.e. (entry 9).

To date, there are two hypotheses on the high diastereoselectivity of reactions utilizing the hydroxypinanone moiety. One is a simple diastereoselective alkylation of Schiff base **2**,[7c,7e,7f] and the other is a diastereoselective protonation of lithium keteneacetal **5** generated from bromodifluoromethylated compound **3**.[7g] To investigate the contribution of the second possibility, lithium keteneacetal **5** was generated in situ. It is noteworthy that **5** underwent immediate debromination even at −78°C to give **4b** (Scheme 1). Therefore, in the present case, the diastereoselective protonation of lithium keteneacetal **5** was not involved. The high diastereoselectivity of the present reaction must therefore be due to diastereoselective alkylation of Schiff base **2** and not diastereoselective protonation.

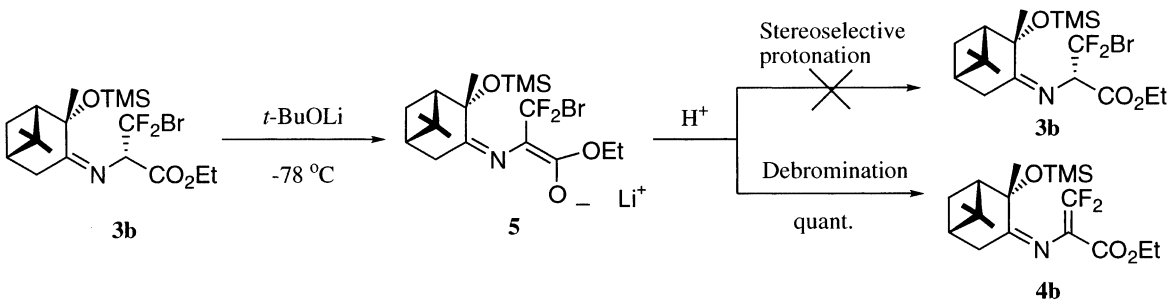
Table 2. Bromodifluoromethylation of Schiff base **2a** with additives



2a **3a** R=H, **3b** R=TMS **4a** R=H, **4b** R=TMS

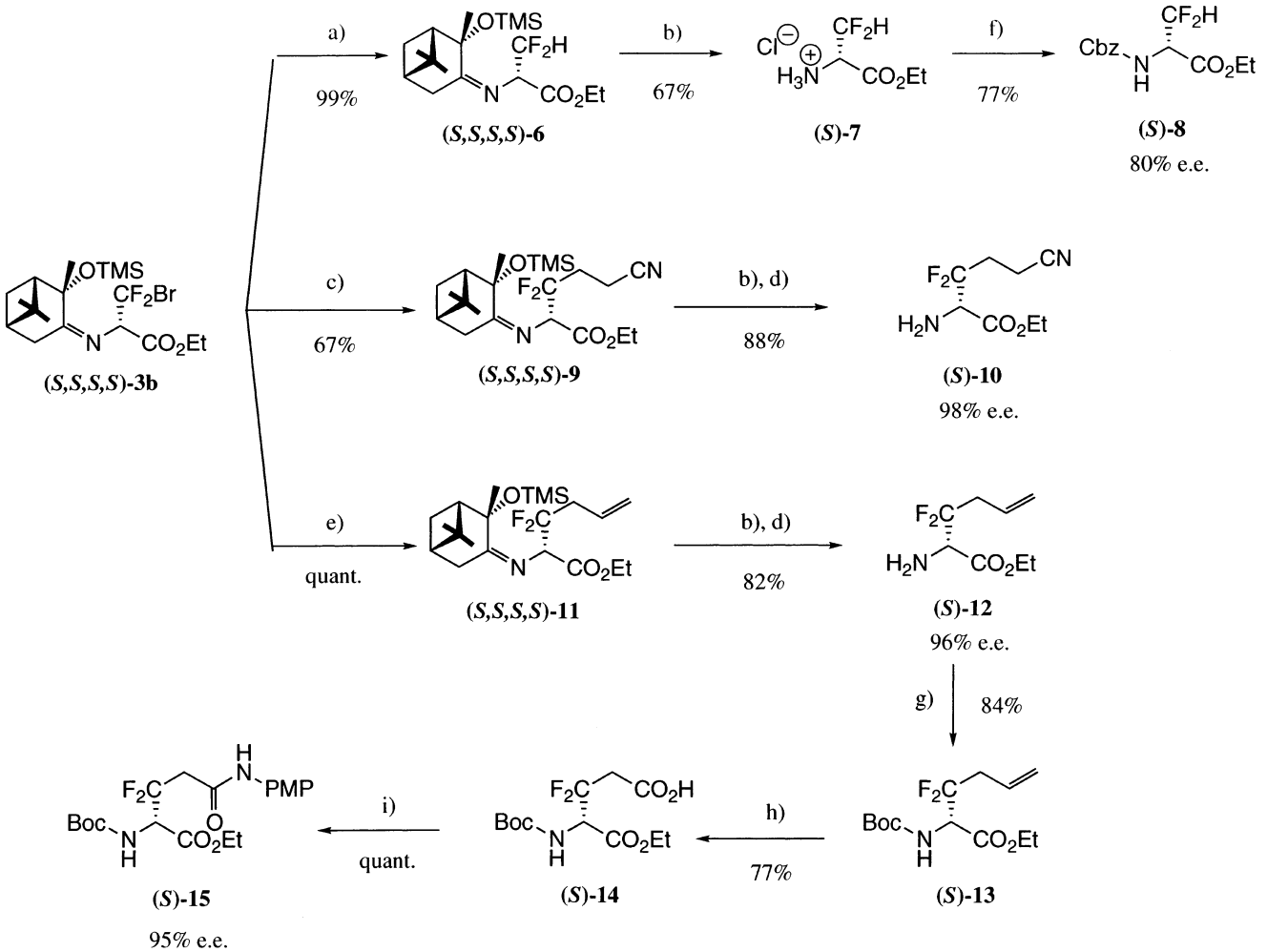
Entry	Additives (equiv.)	Yields of products (%)[b]		
		3a+**3b** (d.e., %)	**4a**+**4b**	**2**
1	None (2.0)	–	38	–
2	TMSCl (2.0)	19 (>98)	41	–
3	TMSCl (6.0)	37 (>98)	–	–
4	TMSBr (2.0)	32 (>98)	25	–
5	TMSI (2.0)	35 (>98)	30	–
6	TMSOTf (2.0)	38 (>98)	7	–
7	TMSOTf (3.0)	43 (>98)	9	–
8[a]	TMSOTf (3.0)	52 (>98)	12	–
9[a,d]	TMSOTf (3.0)	54[c] (>98)	–	39

[a] 10 equiv. of CF_2Br_2 was used.
[b] Chemical yields and diastereomeric excesses were determined by ^{19}F NMR.
[c] Isolated yield was 48% as **3b**.
[d] Reaction was quenched by imidazole in anhydrous THF solution.



3b **5** **3b** **4b**

Scheme 1.



Scheme 2. (a) Tri-*n*-butyltin hydride, AIBN; (b) 1N HCl aq., 91–92% chiral auxiliary was recovered; (c) tri-*n*-butyltin hydride, AIBN, acrylonitrile; (d) $NaHCO_3$; (e) allyltri-*n*-butyltin, AIBN; (f) Cbz-Cl, $NaHCO_3$; (g) $(Boc)_2O$, $NaHCO_3$; (h) RuO_2, $NaIO_4$; (i) DCC, *p*-anisidine.

2.2. Synthetic application of compound 3b

To demonstrate the synthetic applications of (*S*)-β-bromo-β,β-difluoroalanine derivative **3b**, we investigated hydride reduction and C–C bond formation reactions. The precursor **3b** was reduced quantitatively to **6** using tri-*n*-butyltin hydride under radical conditions. Subsequent hydrolysis of the imino groups gave β,β-difluoroalanine derivative **7** (67%) with recovery of chiral auxiliary (91%). Because compound **7** was epimerized and/or dehydrofluorinated in a basic HPLC column for optical purity determinations, the enantiomeric excess (e.e.) of β,β-difluoroalanine derivative **8** was determined instead. The e.e. of **8** was found to be 80%. Next, the difluoromethylene radical of **3b** was generated and underwent C–C bond formation with acrylonitrile in moderate yield (67%) to give **9**. Similarly, the bromine atom of **3b** was transformed quantitatively into an allylic group on reaction with allyltributyltin under radical conditions to give **11**. Subsequent hydrolysis of these alkylated products **9** and **11** gave the new β,β-difluorinated amino acid derivatives **10** and **12** without epimerization at the α-position (96–98% e.e.). Additionally, the chiral auxiliary was recovered in high yields of 91–92% (Scheme 2). Further transformation of the allylated compound **12** gave β,β-difluoroglutamine derivative **15** via β,β-difluoroglutamic acid derivative **14**. Oxidative cleavage of the double bond in *N*-protected amino acid derivative **13** by RuO_2 (cat.)/$NaIO_4$ afforded the β,β-difluoroglutamic acid derivative **14**. Further amidation of the carboxylic group in **14** afforded the β,β-difluoroglutamine derivative **15** with 95% e.e.

3. Conclusion

(*S*)-β-Bromo-β,β-difluoroalanine derivative **3** as a chiral amino acid precursor was efficiently synthesized by trimethylsilyl-assisted stereoselective alkylation of Schiff base **2**. The facile syntheses of some difluoroamino acid derivatives from (*S*)-β-bromo-β,β-difluoroalanine derivative were demonstrated by radical transformation of the bromine atom.

4. Experimental

^{19}F (188 MHz) and ^{1}H (200 MHz) NMR spectra were

recorded on a Varian VXR-200 spectrometer (δ in ppm referred to C_6F_6 for ^{19}F NMR spectra and to TMS for ^1H NMR spectra, J in Hz). Infrared spectra were recorded on a Hitachi model 270-30 infrared spectrometer (ν in cm^{-1}). Melting points were determined on a Yanako MP-S3 melting point measurement apparatus. Optical rotation was measured in a cell with 50 mm length and 1 mL capacity using a Horiba SEPA-300 highly sensitive polarimeter. A Perkin–Elmer Series II CHNS/O Analyzer 2400 was employed for elemental analysis. X-Ray intensity measurements were carried out on a Rigaku RAXIS-IV imaging-plate area detector. Enantiomeric excesses were determined by GC analysis equipped with a chiral column (CP-Cyclodex-β-256M) on a Shimadzu GC-12A and HPLC analysis equipped with Chiral columns (Daicel Chemical Industries: Chiralcel OJ and Chiralcel OD-H) on Shimadzu LC-10AT VP and SPD-10A VP. For the preparation of **2a**, see Ref. 7.

4.1. (1′*S*,2′*S*,5′*S*)-Ethyl 2-[(2′-trimethylsiloxypinylidene)amino]acetate (*S*,*S*,*S*)-2b

To a mixture of the iminoester Schiff base (*S*,*S*,*S*)-**2a** (10.1 g, 40 mmol) and imidazole (5.45 g, 80 mmol) in DMF (60 mL) was added trimethylsilyl chloride (TMSCl: 6.1 mL, 48 mmol) slowly at 0°C under an argon atmosphere. After 1.5 h, the reaction was quenched with water. The reaction mixture was extracted with ether, and the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Then the crude products were purified by silica-gel column chromatography (hexane:AcOEt = 15:1) to afford (*S*,*S*,*S*)-**2b** as a colorless oil (12.0 g, 36.8 mmol, 92%); $[\alpha]_D^{25} = +15.9$ (*c* 1.21, $CHCl_3$); IR (neat): 2924, 1748, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.06 (s, 9H), 0.81 (s, 3H), 1.28 (s, 3H), 1.28 (t, $J = 7$, 3H), 1.50 (s, 3H), 1.61 (d, $J = 11$, 1H), 1.95–2.11 (m, 2H), 2.15–2.35 (m, 1H), 2.30–2.50 (m, 2H), 4.10 (s, 2H), 4.22 (q, $J = 7$, 2H); EI-MS (rel. int.): 325 (50), 310 (100), 282 (60), 256 (100), 198 (55), 183 (100). Anal. calcd for $C_{17}H_{31}NO_3Si$: C, 62.73; H, 9.60; N, 4.30. Found: C, 62.35; H, 9.74; N, 3.95%.

4.2. (1′*S*,2′*S*,5′*S*)-Ethyl 2-[(2′-*tert*-butyldimethylsiloxypinylidene)amino]acetate (*S*,*S*,*S*)-2c

To a mixture of the iminoester Schiff base (*S*,*S*,*S*)-**2a** (0.506 g, 2 mmol) and 2,6-lutidine (0.885 mL, 7.6 mmol) in CH_2Cl_2 (5.0 mL) was added *tert*-butyldimethylsilyl triflate (TBDMSOTf: 0.82 mL, 3.6 mmol) slowly at 0°C under an argon atmosphere. After 1 h, the reaction was quenched by addition of water. The reaction mixture was extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 15:1) to afford (*S*,*S*,*S*)-**2c** as a colorless oil (0.720 g, 1.96 mmol, 97%); $[\alpha]_D^{25} = +10.2$ (*c* 0.58, $CHCl_3$); IR (neat): 2932, 1748, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): δ −0.11 (s, 3H), 0.18 (s, 3H), 0.79 (s, 3H), 0.80 (s, 9H), 1.27 (s, 3H), 1.28 (td, $J = 7$, 3H), 1.46 (br, 3H), 1.55–1.65 (m, 1H), 1.95–2.01 (m, 2H), 2.10–2.31 (m, 1H), 2.32–2.49 (m, 2H), 4.07 (s, 2H), 4.24 (q, $J = 7$, 2H); EI-MS (rel. int.): 367 (2), 352 (5), 310 (100), 224 (10), 185 (12), 73 (34). Anal. calcd for $C_{20}H_{37}NO_3Si$: C, 65.35; H, 10.15; N, 3.81. Found: C, 65.49; H, 10.02; N, 3.98%.

4.3. (1′*S*,2′*S*,5′*S*,2*S*)-Ethyl 2-[(2′-trimethylsiloxypinylidene)amino]-3-bromo-3,3-difluoropropanoate (*S*,*S*,*S*,*S*)-3b

4.3.1. Method A. To a solution of the iminoester Schiff base (*S*,*S*,*S*)-**2b** (6.49 g, 20 mmol) in anhydrous THF (40 mL) was added a solution of the lithium bis(trimethylsilyl)amide in THF (1.0 M, 20 mL, 20 mmol) at −78°C under an argon atmosphere. The mixture was stirred for 0.5 h at −78°C, and then CF_2Br_2 (22 mmol, 2.0 mL) was added. After 4 h, the reaction was quenched with satd aqueous NH_4Cl at −78°C. The reaction mixture was extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 20:1) to afford two diastereomeric isomers **3b** (16.1 mmol, 7.35 g, 81%; (*S*,*S*,*S*,*S*)-**3b**:(*S*,*S*,*S*,*R*)-**3b** = 82:18 determined by ^{19}F NMR of the crude mixture) with a trace amount of (*S*,*S*,*S*)-**4b**. Another purification by silica-gel column chromatography (hexane:AcOEt = 30:1) gave a sole diastereomer (*S*,*S*,*S*,*S*)-**3b**, and crystallization from pentane solution at −10°C gave a pure diastereomer (*S*,*S*,*S*,*S*)-**3b** as colorless crystals (5.60 g, 12.3 mmol, 62%).

4.3.2. Method B. To a solution of lithium tetramethylpiperidide in THF [LTMP: 2.0 mmol, freshly prepared from MeLi in ether (1.0 M, 2.0 mmol, 2.0 mL) and tetramethylpiperidine (0.34 mL, 2.0 mmol)] was added a solution of the iminoester Schiff base (*S*,*S*,*S*)-**2a** (0.252 g, 1 mmol) in anhydrous THF (2.0 mL) at −78°C under an argon atmosphere. The mixture was stirred for 0.5 h at −78°C, and CF_2Br_2 (2.2 mmol, 0.20 mL) was added, immediately followed by the addition of TMSOTf (3 mmol, 0.60 mL). After stirring the mixture for 4 h, the reaction was quenched at −78°C with a solution of imidazole (0.133 g, 2.0 mmol) in THF. The reaction mixture was extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 20:1) to afford (*S*,*S*,*S*,*S*)-**3b** (0.124 g 0.48 mmol, 48%). The diastereomeric excess was determined by ^{19}F NMR of the crude mixture. Recrystallization from pentane solution at −10°C gave (*S*,*S*,*S*,*S*)-**3b** as colorless crystals; $[\alpha]_D^{24} = +91.3$ (*c* 0.74, $CHCl_3$); mp 58.0–58.5°C; IR (KBr): 2936, 1744, 1650 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 107.0 (dd, $J = 159$, 11, 1F), 109.5 (dd, $J = 159$, 7, 1F); ^1H NMR ($CDCl_3$): δ 0.07 (s, 9H), 0.80 (s, 3H), 1.29 (s, 3H), 1.30 (t, $J = 7$, 3H), 1.53 (s, 3H), 1.63 (d, $J = 11$, 1H), 1.94–2.10 (m, 2H), 2.18–2.44 (m, 1H), 2.40–2.75 (m, 2H), 4.23 (q, $J = 7$, 2H), 4.80 (dd, $J = 11$, 7, 1H); EI-MS (rel. int.): 454 (1), 440 (3), 374 (5), 284 (5), 238 (27), 143 (100), 73 (74). Anal. calcd for $C_{18}H_{30}BrF_2NO_3Si$: C, 47.58; H, 6.65; N, 3.08. Found: C, 47.85; H, 6.77; N, 3.21%.

Crystal data for bromodifluoroalanine: $C_{18}H_{30}BrF_2NO_3Si$; $M_w=454.43$; orthorhombic; $P2_12_12_1$ (no. 19); $a=10.205(1)$, $b=20.934(2)$, $c=10.5370(6)$ Å, $V=2251.1(3)$ Å^3, $Z=4$, $D_{calcd}=1.341$ g/cm^3; $\mu=19.16$ cm^{-1} for Mo Kα radiation ($\lambda=0.7107$ Å). The structure was solved by a direct method (SIR-92), and refined by a full-matrix least-squares method. Final R was 0.067 and R_w was 0.067 for 1436 reflections with $I_0>3.00\sigma$ (I_0), reflection/parameter = 6.01, GOF = 2.33, max. shift/error 0.02.

4.4. (1′*S*,2′*S*,5′*S*,2*S*)-Ethyl 2-[(2′-*tert*-butyldimethylsiloxypinylidene)amino]-3-bromo-3,3-difluoropropanoate (*S*,*S*,*S*,*S*)-3c

Under the same conditions used in method A as described in Section 4.3 ((*S*,*S*,*S*,*S*)-**3b**), (*S*,*S*,*S*,*S*)-**2c** (1.0 mmol, 0.367 g) was alkylated with CF_2Br_2 to afford (*S*,*S*,*S*,*S*)-**3c** (0.372 g, 0.75 mmol; (*S*,*S*,*S*,*S*)-**3c**:(*S*,*S*,*S*,*R*)-**3c** = 82:18 as determined by ^{19}F NMR of the crude mixture). Another purification by silica-gel column chromatography (hexane:AcOEt = 30:1) gave the diastereomer (*S*,*S*,*S*,*S*)-**3c** as a colorless oil (0.297 g, 0.60 mmol); $[\alpha]_D^{27}=-12.5$ (*c* 0.58, $CHCl_3$); IR (neat): 2992, 2932, 1752, 1660 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 107.1 (dd, *J* = 159, 12 Hz, 1F), 109.3 (dd, *J* = 159, 7 Hz, 1F); ^{1}H NMR ($CDCl_3$): δ −0.01 (s, 3H), 0.13 (s, 3H), 0.79 (s, 3H), 0.80 (s, 9H), 1.29 (t, *J* = 7, 3H), 1.29 (s, 3H), 1.51 (s, 3H), 1.66 (d, *J* = 10, 1H), 1.94–2.10 (m, 2H), 2.20–2.35 (m, 1H), 2.40–2.75 (m, 2H), 4.21 (q, *J* = 7, 2H), 4.80 (dd, *J* = 12, 7, 1H); EI-MS (rel. int.): 497 (1), 441 (10), 440 (36), 439 (10), 438 (33), 185 (49), 73 (100). Anal. calcd for $C_{21}H_{36}BrF_2NO_3Si$: C, 50.80; H, 7.31; N, 2.82. Found: C, 50.40; H, 7.64; N, 3.04%.

4.5. (1′*S*,2′*S*,5′*S*)-Ethyl 2-[(2′-hydroxypinylidene)amino]-3,3-difluoro-2-propeno-1-ate (*S*,*S*,*S*)-4a

To a solution of lithium tetramethylpiperidide in THF [LTMP: 2 mmol, freshly prepared from MeLi in ether (1.0 M, 2 mmol, 2.0 mL) and tetramethylpiperidine (0.34 mL, 2 mmol)] was added the iminoester Schiff base (*S*,*S*,*S*)-**2a** (0.252 g, 1 mmol) in anhydrous THF (2 mL) at −78°C under an argon atmosphere. The mixture was stirred for 0.5 h at −78°C, and then CF_2Br_2 (2.2 mmol, 0.20 mL) was added. After 4 h, the reaction was quenched with satd aqueous NH_4Cl at −78°C. Then the reaction mixture was extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 5:1) to afford (*S*,*S*,*S*)-**4a** as a yellow oil (0.112 g, 0.38 mmol, 38%); $[\alpha]_D^{27}=-9.37$ (*c* 0.72, $CHCl_3$); IR ($CHCl_3$): 3400, 2988, 2936, 1750 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 75.8 (d, *J* = 9, 1F), 81.7 (d, *J* = 9, 1F); ^{1}H NMR ($CDCl_3$): δ 0.88 (s, 3H), 1.29 (t, *J* = 7, 3H), 1.33 (s, 3H), 1.56 (s, 3H), 1.62 (br, 1H), 2.00 (ddd, *J* = 10, 6, 2, 1H), 2.10 (t, *J* = 6, 1H), 2.30–2.44 (m, 1H), 2.47 (br, 1H), 2.39–2.62 (m, 2H), 4.25 (q, *J* = 7, 2H); EI-MS (rel. int.): 301 (1), 272 (15), 258 (20), 232 (65), 203 (76), 147 (100), 111 (77). Anal. calcd for $C_{15}H_{21}F_2NO_3$: C, 59.79; H, 7.02; N, 4.65. Found: C, 60.08; H, 7.36; N, 4.98%.

4.6. (1′*S*,2′*S*,5′*S*)-Ethyl 2-[(2′-trimethylsiloxypinylidene)amino]-3,3-difluoro-2-propeno-1-ate (*S*,*S*,*S*)-4b

$[\alpha]_D^{27}=+7.19$ (*c* 1.40, $CHCl_3$); IR (neat): 2964, 1748, 1654 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 74.5 (d, *J* = 10, 1F), 81.2 (d, *J* = 10, 1F); ^{1}H NMR ($CDCl_3$): δ 0.10 (s, 9H), 0.84 (s, 3H), 1.28 (t, *J* = 7, 3H), 1.30 (s, 3H), 1.57 (s, 3H), 1.67 (d, *J* = 10, 1H), 1.90–2.02 (m, 1H), 2.07 (t, *J* = 6, 1H), 2.20–2.38 (m, 1H), 2.44 (br, 1H), 2.45 (br, 1H), 4.24 (q, *J* = 7, 1H), 4.24 (q, *J* = 7, 1H); EI-MS (rel. int.): 373 (1), 358 (8), 300 (10), 183 (46), 143 (63), 130 (30), 73 (100). Anal. calcd for $C_{18}H_{29}F_2NO_3Si$: C, 57.88; H, 7.83; N, 3.75. Found: C, 57.62; H, 7.92; N, 4.09%.

4.7. (1′*S*,2′*S*,5′*S*,2*S*)-Ethyl 2-[(2′-trimethylsiloxypinylidene)amino]-3,3-difluoropropano-1-ate (*S*,*S*,*S*,*S*)-6

To a mixture of (*S*,*S*,*S*,*S*)-**3b** (0.454 g, 1.0 mmol) and tri-*n*-butyltin hydride (0.30 mL, 1.2 mmol) in toluene (1.0 mL) was added cat. AIBN (ca. <10 mg) at 90°C under an argon atmosphere. After 1 h, to the reaction mixture were added satd KF aq. and AcOEt (10 mL), and the mixture was then stirred for 1 h at rt. The reaction mixture was then filtered, extracted with ether, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 20:1 at −10°C) to afford (*S*,*S*,*S*,*S*)-**6** as a colorless oil (0.373 g, 0.99 mmol, 99%); $[\alpha]_D^{24}=+90.8$ (*c* 1.53, $CHCl_3$); IR (neat): 2860, 1762, 1654 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 34.6 (ddd, *J* = 286, 56, 11, 1F), 37.7 (ddd, *J* = 286, 56, 7, 1F); ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 9H), 0.78 (s, 3H), 1.29 (t, *J* = 7, 3H), 1.29 (s, 3H), 1.48 (s, 3H), 1.60 (d, *J* = 11, 1H), 1.94–2.10 (m, 2H), 2.20–2.34 (m, 1H), 2.42–2.79 (m, 2H), 4.20 (q, *J* = 7, 2H), 4.52 (dt, *J* = 11, 7, 1H), 6.19 (td, *J* = 56, 7, 1H); EI-MS (rel. int.): 375 (tr), 355 (4), 340 (15), 326 (5), 312 (6), 286 (15), 282 (27), 183 (67), 143 (50), 73 (100). Anal. calcd for $C_{18}H_{31}F_2NO_3Si$: C, 57.57; H, 8.32; N, 3.73. Found: C, 57.27; H, 8.27; N, 3.65%.

4.8. (2*S*)-Ethyl 2-amino-3,3-difluoropropano-1-ate hydrochloride (*S*)-7

To (*S*,*S*,*S*,*S*)-**6** (1.0 mmol, 0.373 g) in EtOH (1.0 mL) was added HCl aq. (1N, 6.0 mL) at 50°C. After 1 h, the reaction mixture was extracted with ether. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 4:1) to afford the chiral auxiliary as a colorless oil (0.152 g, 0.91 mmol, 91%). The aqueous phase was concentrated under reduced pressure. Recrystallization of the crude products from EtOH gave (*S*)-**7** as a white powder (0.125 g, 0.67 mmol, 67%); $[\alpha]_D^{25}=-8.1$ (*c* 2.20, MeOH); mp 109.5°C; IR (KBr): 3200 (br), 1758 cm^{-1}; ^{19}F NMR (DMSO-d_6): δ 36.2 (ddd, *J* = 286, 53, 19, 1F), 38.4 (ddd, *J* = 286, 53, 11, 1F); ^{1}H NMR (DMSO-d_6): δ 1.24 (t, *J* = 7, 3H), 4.27 (q, *J* = 7, 2H), 4.82 (ddd, *J* = 18, 12, 2, 1H), 6.61 (td, *J* = 53, 2, 1H), 9.30 (br, 3H). Anal. calcd for $C_5H_{10}ClF_2NO_2$: C, 31.68; H, 5.32; N, 7.39. Found: C, 31.98; H, 5.62; N, 7.19%.

4.9. (2*S*)-Ethyl 2-[*N*-(benzyloxycarbonyl)amino]-3,3-difluoropentano-1-ate (*S*)-8

To a mixture of (*S*)-**7** (0.191 g, 1.0 mmol) and carbobenzoxy chloride (0.436 g, 2.0 mmol) in water (2.0 mL) and dioxane (2.0 mL) was added $NaHCO_3$ (0.150 g, 2.0 mmol) at 0°C. The reaction mixture was stirred for 1 h, then extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 7:1) and recrystallization to afford (*S*)-**8** as colorless needles (0.226 g, 0.79 mmol, 79%); e.e. = 80% as determined by HPLC analysis: OJ column, hexane:^{i}PrOH = 5:1; $[\alpha]_D^{27} = -13.0$ (*c* 2.30, $CHCl_3$); mp 52.5°C; IR (neat): 3300, 2988, 1730 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 34.6 (ddd, $J = 283$, 55, 18, 1F), 35.0 (ddd, $J = 283$, 55, 12, 1F); ^1H NMR ($CDCl_3$): δ 1.31 (t, $J = 7$, 3H), 4.28 (q, $J = 7$, 2H), 4.72–4.94 (m, 1H), 5.16 (s, 2H), 5.51 (d (br), 1H), 6.12 (t (br), $J = 55$, 1H), 7.37 (br, 5H); EI-MS (rel. int.): 287 (1), 108 (96), 91 (100). Anal. calcd for $C_{13}H_{15}F_2NO_4$: C, 54.35; H, 5.26; N, 4.88. Found: C, 54.26; H, 5.33; N, 5.11%.

4.10. (1′*S*,2′*S*,5′*S*,2*S*)-Ethyl 2-[(2′-trimethylsiloxypinylidene)amino]-5-cyano-3,3-difluoropentano-1-ate (*S*,*S*,*S*,*S*)-9

To a mixture of (*S*,*S*,*S*,*S*)-**3b** (0.454 g, 1.0 mmol), tri-*n*-butyltin hydride (0.30 mL, 1.2 mmol) and acrylonitrile (1.0 mL, 15 mmol) in toluene (10 mL) was added cat. AIBN at 90°C under an argon atmosphere. After 1 h, to the reaction mixture were added satd KF aq. and AcOEt (10 mL), and this was then stirred for 1 h at rt. The reaction mixture was filtered, extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (hexane:AcOEt = 9:1) to afford (*S*,*S*,*S*,*S*)-**9** as a colorless oil (0.286 g, 0.67 mmol, 67%); $[\alpha]_D^{24} = +104.8$ (*c* 0.41, $CHCl_3$); IR (neat): 2948, 2256, 1748, 1652 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 59.2 (ddt, $J = 251$, 27, 7, 1F), 62.5 (ddt, $J = 251$, 27, 13, 1F); ^1H NMR ($CDCl_3$): δ 0.04 (s, 9H), 0.75 (s, 3H), 1.28 (t, $J = 7$, 3H), 1.29 (s, 3H), 1.47 (s, 3H), 1.61 (d, $J = 10$, 1H), 1.98–2.08 (m, 2H), 2.20–3.04 (m, 7H), 4.19 (q, $J = 7$, 2H), 4.69 (dd, $J = 12$, 7, 1H); EI-MS (rel. int.): 428 (tr), 427 (1), 373 (1), 238 (27), 143 (100), 73 (43). Anal. calcd for $C_{21}H_{34}F_2N_2O_3Si$: C, 58.85; H, 8.00; N, 6.54. Found: C, 58.57; H, 8.18; N, 6.55%.

4.11. (2*S*)-Ethyl 2-amino-5-cyano-3,3-difluoropentano-1-ate (*S*)-10

To a solution of (*S*,*S*,*S*,*S*)-**9** (0.428 g, 1.0 mmol) in EtOH (1.0 mL) was added aq. HCl (1N, 8 mL) at 50°C. After 1 h, the reaction mixture was extracted with ether. The organic phase was dried over $MgSO_4$ and concentrated under reduce pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 4:1) to afford the chiral auxiliary as a colorless oil (0.154 g, 0.91 mmol, 91% recovery). The water phase was concentrated under reduced pressure. To the crude products in water (2.0 mL) and ether (2.0 mL) was added $NaHCO_3$ (0.100 g, 1.2 mmol) at 0°C. After 1 h, the reaction mixture was extracted with ether, dried over $MgSO_4$ and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 9:1) to afford (*S*)-**10** as a colorless oil (0.180 g, 0.88 mmol, 88%); e.e. = 98% as determined by GC analysis: oven temp. 165°C; $[\alpha]_D^{27} = -30.9$ (*c* 1.00, $CHCl_3$); IR (neat): 3424, 3348, 2992, 2256, 1738, 1612 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 51.5–54.8 (m, 2F); ^1H NMR ($CDCl_3$): δ 1.31 (t, $J = 7$, 3H), 1.74 (br, 2H), 2.30–2.68 (m, 4H), 3.77 (t, $J = 12$, 1H), 4.27 (q, $J = 7$, 2H); EI-MS (rel. int.): 207 (1, $M^+ + 1$), 133 (100), 113 (10), 102 (53). Anal. calcd for $C_8H_{12}F_2N_2O_2$: C, 46.60; H, 5.87; N, 13.59. Found: C, 46.83; H, 5.96; N, 13.97%.

4.12. (1′*S*,2′*S*,5′*S*,2*S*)-Ethyl 2-[(2′-trimethylsiloxypinylidene)amino]-3,3-difluoro-5-hexeno-1-ate (*S*,*S*,*S*,*S*)-11

To a mixture of (*S*,*S*,*S*,*S*)-**3b** (5.0 mmol, 2.27 g) and allyltri-*n*-butyltin (15 mmol, 4.7 mL) in toluene (5.0 mL) was added cat. AIBN several times at 90°C under an argon atmosphere. After 1 h, to the reaction mixture were added satd KF aq. and AcOEt (40 mL), and this was then stirred for 1 h at rt. The reaction mixture was filtered, extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (hexane:AcOEt = 20:1) to afford (*S*,*S*,*S*,*S*)-**11** as a colorless oil (5.0 mmol, 2.07 g, quant.); $[\alpha]_D^{24} = +109.7$ (*c* 1.20, $CHCl_3$); IR (neat): 2928, 1754, 1650 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 59.3 (ddt, $J = 249$, 26, 9, 1F), 62.2 (ddt, $J = 249$, 26, 12, 1F); ^1H NMR ($CDCl_3$): δ 0.06 (s, 9H), 0.76 (s, 3H), 1.28 (s, 3H), 1.29 (t, $J = 7$, 3H), 1.49 (s, 3H), 1.61 (d, $J = 10$, 1H), 1.94–2.06 (m, 2H), 2.18–2.34 (m, 1H), 2.35–2.76 (m, 2H), 2.80–3.28 (m, 2H), 4.20 (q, $J = 7$, 2H), 4.61 (dd, $J = 11$, 9, 1H), 5.16–5.45 (m, 2H), 5.88 (ddt, $J = 18$, 11, 7, 1H); EI-MS (rel. int.): 415 (27), 400 (18), 372 (20), 346 (20), 183 (34), 143 (92), 73 (100). Anal. calcd for $C_{21}H_{35}F_2NO_3Si$: C, 60.69; H, 8.49; N, 3.37. Found: C, 60.51; H, 8.86; N, 3.53%.

4.13. (2*S*)-Ethyl 2-amino-3,3-difluoro-5-hexeno-1-ate (*S*)-12

Under the same conditions as described in Section 4.11 ((*S*)-**10**), (*S*,*S*,*S*,*S*)-**11** (3.0 mmol, 1.25 g) was hydrolyzed with aq. 1N HCl to afford (*S*)-**12** (2.5 mmol, 0.48 g, 82%); e.e. = 96% as determined by GC analysis: oven temp. 110°C; $[\alpha]_D^{27} = -55.4$ (*c* 0.82, $CHCl_3$); IR (neat): 3428, 3352, 2992, 1744, 1612 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 55.4 (q, $J = 15$, 2F); ^1H NMR ($CDCl_3$): δ 1.31 (t, $J = 7$, 3H), 1.69 (br, 2H), 2.58–2.95 (m, 2H), 3.76 (t, $J = 12$, 1H), 4.25 (q, $J = 7$, 2H), 5.23 (br, 1H), 5.26–5.34 (m, 1H), 5.72–5.85 (m, 1H); EI-MS (rel. int.): 193 (1), 120 (100), 102 (100), 100 (60), 80 (40), 74 (74). Anal. calcd for $C_8H_{13}F_2NO_2$: C, 49.74; H, 6.78; N, 7.25. Found: C, 49.35; H, 7.10; N, 6.99%.

4.14. (2*S*)-Ethyl 2-[*N*-(*tert*-butoxycarbonyl)amino]-3,3-difluoro-5-hexeno-1-ate (*S*)-13

To a mixture of (*S*)-**12** (0.286 g, 2.0 mmol) and di-*tert*-butyldicarbonate (0.872 g, 4.0 mmol) in water (4.0 mL)

and dioxane (4.0 mL) was added $NaHCO_3$ (0.150 g, 2.0 mmol) at 0°C. The reaction mixture was stirred for 1 h, and then extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 9:1) to afford (*S*)-**13** as a colorless oil (0.462 g, 1.58 mmol, 84%); $[\alpha]_D^{25} = -22.6$ (*c* 0.62, $CHCl_3$); IR (neat): 3392, 2984, 1722, 1648, cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 56.5 (dq, $J = 247$, 17, 1F), 56.8 (dq, $J = 247$, 15, 1F); ^1H NMR ($CDCl_3$): δ 1.31 (t, $J = 7$, 3H), 1.45 (s, 9H), 2.74 (td, $J = 17$, 7, 2H), 4.27 (q, $J = 7$, 1H), 4.28 (q, $J = 7$, 1H), 4.60–4.82 (m, 1H), 5.20–5.36 (m, 3H), 5.72–5.90 (m, 1H); EI-MS (rel. int.): 294 (1, $M^+ + 1$), 237 (4), 220 (5), 193 (13), 120 (22), 102 (20), 57 (100). Anal. calcd for $C_{13}H_{21}F_2NO_4$: C, 53.23; H, 7.22; N, 4.78. Found: C, 53.42; H, 7.53; N, 4.65%.

4.15. (2*S*)-Ethyl 2-[*N*-(*tert*-butoxycarbonyl)amino]-4-carboxyl-3,3-difluoro-butano-1-ate (*S*)-14

To a solution of (*S*)-**13** (0.246 g, 0.84 mmol) in AcOEt (2.0 mL) was added a solution of $RuO_2 \cdot xH_2O$ (15 mol%, 0.0180 g) and 20% $NaIO_4$ aq. at 0°C. The reaction mixture was stirred at 25°C for 7 days during which several additional aliquots of $NaIO_4$ aq. were added from time to time to maintain the yellow color of RuO_4. The reaction mixture was then filtered, extracted with AcOEt, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (AcOEt) to afford (*S*)-**14** as a colorless oil (0.203 g, 0.65 mmol, 77%); $[\alpha]_D^{25} = +14.8$ (*c* 2.95, $CHCl_3$); IR (neat): 3400 br, 2988, 1734, 1680 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 59.4 (q, $J = 15$, 2F); ^1H NMR ($CDCl_3$): δ 1.32 (t, $J = 7$, 3H), 1.45 (s, 9H), 3.15 (t, $J = 15$, 2H), 4.28 (m, 2H), 5.08 (m, 1H), 5.48 (d (br), 2H), 4.65–6.19 (br, 1H). Anal. calcd for $C_{12}H_{19}F_2NO_6$: C, 46.30; H, 6.15; N, 4.50. Found: C, 46.00; H, 6.47; N, 4.66%.

4.16. (2*S*)-Ethyl 2-[*N*-(*tert*-butoxycarbonyl)amino]-3,3-difluoro-4-[*N*-(4′-methoxyphenyl)carbamoyl]butano-1-ate (*S*)-15

To a mixture of (*S*)-**14** (0.125 g, 0.38 mmol) and *p*-anisidine (0.100 g, 0.76 mmol) in CH_2Cl_2 was added a solution of DCC (0.113 g, 0.55 mmol) in CH_2Cl_2 at 0°C. After 1 h, the reaction mixture was filtered, extracted with AcOEt, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica-gel column chromatography (hexane:AcOEt = 2:1) to afford (*S*)-**15** as a white powder (0.155 g, 0.38 mmol, quant.); e.e. = 95% as determined by HPLC analysis: OD-H column, hexane:^{i}PrOH = 5:1; $[\alpha]_D^{23} = +7.1$ (*c* 0.64, $CHCl_3$); mp 120°C; IR (KBr): 3328, 2988, 1752, 1706, 1690, 1606 cm^{-1}; ^{19}F NMR ($CDCl_3$): δ 60.3 (m, 2F); ^1H NMR ($CDCl_3$): δ 1.29 (t, $J = 7$, 3H), 1.47 (s, 9H), 2.95–3.25 (m, 2H), 3.78 (s, 3H), 4.28 (m, 2H), 4.88 (m, 1H), 5.69 (d (br), $J = 9$, 2H), 6.85 (d, $J = 9$, 2H), 7.49 (d, $J = 9$, 2H), 8.91 (br, 1H). Anal. calcd for $C_{19}H_{26}F_2N_2O_6$: C, 54.80; H, 6.29; N, 6.73. Found: C, 54.94; H, 6.60; N, 6.78%.

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