Enantioselective Synthesis of α,α-Difluoro-β-amino Acid and 3,3-Difluoroazetidin-2-one via the Reformatsky-Type Reaction of Ethyl Bromodifluoroacetate with Chiral 1,3-Oxazolidines

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Chiral oxazolidines **2a**−**e** can be diastereoselectively alkylated with $BrCF_2CO_2Et$ to furnish 3,3-difluoroazetidin-2-ones **3a**−**e** with up to 99% de. Selective cleavage of the chiral appendage provided the corresponding unsubstituted azetidinones. Formation of optically pure α,α-difluoro-β-amino acids **5a**−**c** can be achieved by acidic hydrolysis of *N*-vinyl-azetidin-2-ones.

Introduction

In recent years, fluoro compounds have received a great deal interest. The presence of a fluorine atom introduces modifications to the physiological activity of bioactive compounds.[1] Indeed, fluorine's small van der Waals radius and its high electronegativity have important effects on the physical and chemical properties of the molecule. This led to the discovery of potent medicinal agents and development of original methods of preparation, especially in the asymmetric series.[2] Among them, *gem*-difluoro amino acids and derivatives have been the subject of an important area of research as the CF_2/CH_2 transposition has been recognized as a valuable tool in the blockage of metabolic processes. Replacement of various functional groups by a *gem*-difluoromethylene group has generated potent transition-state-type inhibitors.[3] Moreover, difluoroazetidin-2-ones have shown specific properties as an inhibitor of human leucocite elastase.[4] The importance of organofluorine compounds is reflected in the ever-increasing research activity in the field of their stereoselective synthesis.[5] Additionally, β-amino acids are now recognized as valuable tools for the generation of new derivatives[6] such as β-peptides[7] as well as building blocks for β-lactam antibiotics.[8]

In this context, the development of new synthetic methodology for preparing optically pure fluorine-containing β-amino acids is of particular interest. To the best of our knowledge, only two examples of such a strategy have been reported. Soloshonok[9] described the synthesis of optically pure β-(fluoroalkyl) β-amino acids via enantioselective biomimetic transamination of β-keto carboxylic acid derivatives. Kobayashi[10] used the asymmetric aldol addition of difluoroketenesilylacetal to aldehydes. However, this method suffered from a low yield for the preparation of the salt-free starting reagent from ethyl bromodifluoroacetate.

The aim of this study is the investigation of a new enantioselective route to α,α-difluoro-β-amino acids.

Results and Discussion

We first decided to evaluate the potentiality of ethyl-bromodifluoroacetate **1** in a Reformatsky-type reaction with aldimines as previously described by Kobayashi.[12] Only moderate diastereoselectivity (de <50%) was reported using α-methylbenzylamine as the source of chirality. We decided to perform the reaction with chiral 1,3-oxazolidines derived from chiral amino alcohols (Scheme 1). These stable equivalents of imines are known to furnish highly diastereoselective reactions with several organometallic reagents.[13] Oxazolidines **2a**−**e** were easily prepared in good yields by condensation of the corresponding amino alcohols and aldehydes and were then used without any purification. (*R*)-Phenylglycinol or the cheaper (*R*)-aminobutanol was used as the chiral auxiliary. Although these 1,3-oxazolidines were in equilibrium with the corresponding imino alcohol, reaction with ethyl bromodifluoroacetate (3.5 equiv) in the presence of activated Zn dust furnished 3,3-difluoroazetidin-2-ones **3a**−**e** as the major products (Scheme 1, Table 1). Even though we were unable to detect the intermediate β-amino acids, these results were encouraging as they allowed the synthesis of the corresponding azetidinones.

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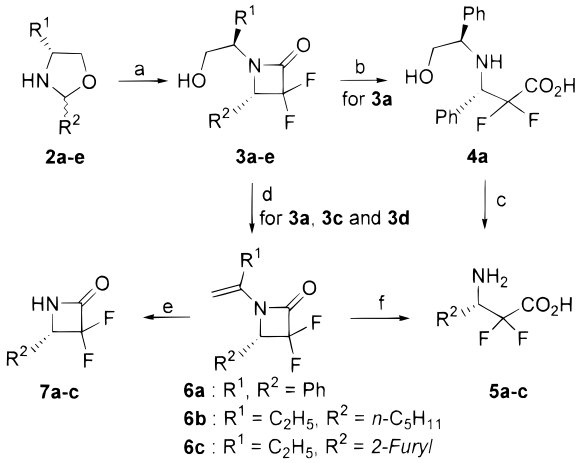
Scheme 1[a]



[a] (a) $BrCF_2CO_2Et$ (3.5 eq), Zn, THF; (b) HCl, 6N, 71%; (c) H_2, Pd/C, MeOH, 90%; (d) (i) Tf_2O, pyridine, (ii) for **6a**: DBU, 78%, for **5b**.**c**: *t*-BuOK, 71 and 69%; (e) 30 N H_2SO_4, Et_2O, **7a**: 53%, **7b**: 56%. **7c**: 61%; (f) 6 N HCl, 93−96%.

Table 1. Diastereoselective Formation of Fluoroazetidones 3a−e

entry	substrate	R_1	R_2	product	yield[a] (%)	selectivity (de, %)
1	**2**a	Ph	Ph	**3**a	65	>99[b]
2	**2b**	Et	Ph	**3b**	69[d]	96[b]
3	**2c**	Et	n-C_5H_{11}	**3c**	35	90[c]
4	**2d**	Et	2-Furyl	**3d**	62	85[b]
5	**2e**	Et	*trans*-CH=CHCH$_3$	**3e**	32	96[c]

[a] Isolated yields. [b] Diastereomeric excess was determined by HPLC-Mass spectrometry. [c] Diastereomeric excess were determined by ^{19}F NMR spectroscopy. [d] In this case 5% of the noncyclized coumpound was observed.

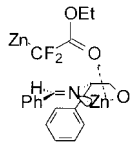


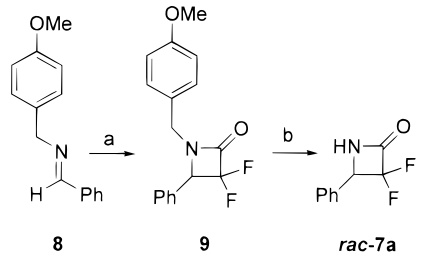
Figure 1.

The formation of the noncyclized product in small amounts (5%) was only observed during the preparation of compound **3b** (R^1 = ethyl, R^2 = phenyl). We can notice that the yields from nonaromatic imines (entries 3 and 5) are lower, in agreement with Kobayashi's results. But, in all cases, we were pleased to observe a very high diastereomeric excess, usually more than 90% except when R^2 is a furfuryl moiety (entry 4).

This high asymmetric induction, even at a quite high temperature (60 °C), can best be explained by the strongly rigid intermediate proposed by Pridgen[13] (Figure 1). In this model, the zinc of the alcoholate is chelated by the nitrogen atom, and the nucleophile attack occurs on the less hindered side opposite to the phenyl or ethyl group of the chiral auxiliary. As the stereochemistry of the imine is known to be *E*, this model led us to postulate the *S* absolute configuration for the newly created center as indicated in Figure 1. This hypothesis was confirmed by an X-ray analysis of *β*-amino acid **4a** (vide infra).[14]

(14) Toupet, L. Laboratoire de Chimie Cristalline, Faculté des Sciences, Rennes, France. Complete X-ray data will be published separately.

Scheme 2[a]



[a] (a) $BrCF_2CO_2Et$ (2 eq.), Zn, THF, 77%; (b) CAN, CH_3CN, H_2O, 83%.

Synthesis of α,α-difluoro-*β*-amino acids from azetidinones required removal of the chiral auxiliary and ring opening of the *β*-lactam. This was achieved in a two-step process from phenylglycinol derivative (−)-**3a**. Acidic treatment gave the amino acid (−)-**4a** without any trace of epimerization. Hydrogenolysis of the nitrogen appendage cleaved the phenylglycinol part of the molecule selectively, leading to 3-amino-2,2-difluoro-3-phenyl-propanoic acid **5a** as the *S* enantiomer having a dextrorotary sign ($[\alpha]_D$ +7.1).

Most of our results were obtained in the ethyl series (R^1 = Et) for which this strategy cannot be used. We then turned our attention to the deprotection method developed by Villieras,[15] who prepared an enamide that was then hydrolyzed with sulfuric acid. Application of this method to our compounds did not yield the corresponding azetidinones. Finally, we solved this problem by transforming the alcohol functionality to triflate, which was smoothly eliminated (DBU or *t*-BuOK) providing enamides **6a**−**c** (Scheme 1).[16] Acidic treatment (30 N sulfuric acid) furnished optically pure azetidinones **7a**−**c** in 53, 56, and 61% yield, respectively. When enamides **6a**−**c** were treated at reflux with 6 N aqueous hydrochloric acid, α,α-difluoro-*β*-amino acids **5a**−**c** were obtained in nearly quantitative yield as hydrochloric salts.

To establish the enantiomeric purity of the obtained compounds, we prepared racemic azetidinone **7a**. We used *p*-methoxybenzylamine in order to have a substituent on the nitrogen which could be cleaved under mild conditions. Compound **8** was reacted with **1** (2 equiv) in the presence of Zn dust (Scheme 2). The difluoroazetidin-2-one **9** was the only isolated product. Deprotection was realized by classical treatment with CAN, furnishing *rac*-**7a** in 83% yield. Chiral VPC analysis showed that **7a** was of very high (>99%) enantiomeric purity. Since the enantiomeric purity of **7a** was excellent, the other derivatives prepared in the same manner are expected to be of comparable purity. Furthermore, if any loss of stereochemical purity was to occur, the phenyl derivative would have been the most likely to epimerize.

In conclusion, we performed a diastereoselective route to the N-protected 3,3-difluoroazetidin-2-one with high diastereoselectivity using the Reformatsky-type reaction of ethyl bromodifluoroacetate with chiral 1,3-oxazolidines. These compounds furnished access to the corresponding α,α,difluoro-*β*-amino acid or 3,3-difluoroazetidinone after two or three steps.

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Experimental Section

All commercial solvents were distilled before using. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen atmosphere**.** Flash column chromatography purifications were carried out using silica gel (70−230 mesh). ^{1}H NMR, ^{13}C NMR and ^{19}F NMR ($CFCl_3$ as external reference) were recorded at 300.13, 75.47, and 282.40 MHz, respectively. Coupling constants (*J*) are reported in Hz. HPLC−Mass spectroscopy was done on a C18 HYPERSIL 5 μm column using CH_3CN/H_2O as solvent. Chiral VPC were performed on β-DEX 120 (10 m, 0.25 mm, ef 0.25 μm) with He as GV (30 mL s^{-1}).

Starting Materials. All substrate oxazolidines were readily synthesized by condensation of the appropriate aldehyde with the prerequiste chiral amino alcohol. They were used without purification but were dried before use by azeotropic distillation with toluene. The zinc was freshly activated and dried. Moisture-sensitive reactions were carried out in predried glassware and under argon atmosphere.

General Procedure for 3a−e. (4*S*)-3,3-Difluoro-1-((1*R*)-2-hydroxy-1-phenylethyl)-4-phenylazetidin-2-one (3a). To a refluxing suspension of freshly activated Zn dust (2.3 g, 35.4 mmol) in dry THF (10 mL) was added a solution of **2a** (1.66 g, 7.38 mmol) and ethyl bromodifluoroacetate (5.24 g, 25.83 mmol) in THF (1.5 mL) at a rate so as to maintain vigorous reflux. After 1 h, the reaction mixture was cooled and quenched by addition of a saturated NH_4Cl solution (20 mL). After filtration, the aqueous layer was extrated with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under vacuum. The residue was then purified by flash column chromatography using 10% ethyl acetate in cyclohexane, affording **3a** as a colorless oil (1.45 g, 4.79 mmol, 65%): $[\alpha]^{25}_D$ −15.4° (*c* 1, $CHCl_3$); IR (neat) 3436 (OH), 1778 cm^{-1}(C═O); ^{1}H NMR ($CDCl_3$) δ 2.71 (br, 1H), 3.74 (dd, 1H, *J* = 5.0, 11.5), 4.03 (dd, 1H, *J* = 9.1, 11.5), 4.64 (dd, 1H, *J* = 5.0, 9.1), 4.77 (dd, 1H, *J* = 2.2, 8.1), 7−7.5 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 64.0, 65.4, 72.6 (dd, *J* = 23.5, 29.2), 121.7 (dd, *J* = 292 Hz, 298 Hz),130.3, 130.7, 130.8, 130.9, 131.0, 132.0, 133.2, 137.1, 164.5 (dd, *J* = 30.7, 32.1); ^{19}F NMR ($CDCl_3$) δ −114.9 (dd, *J* = 8.1, *J* = 217.2), −121.8 (d, *J* = 217.2); HRMS (CI) calcd for $(M + 1)^+$ $C_{17}H_{16}F_2NO_2$ 304.1149, found 304.1144. Anal. Calcd for $C_{17}H_{15}F_2NO_2$: C, 67.32; H, 4.98; N, 4.62. Found: C, 67.11; H, 4.96; N, 4.42.

(4*S*)-3,3-Difluoro-1-((1*R*)-1-hydroxymethylpropyl)-4-phenylazetidin-2-one (3b). Flash chromatography (10% EtOAc in cyclohexane) yielded a colorless oil: 69%; $[\alpha]^{25}_D$ +16.9° (*c* 1, $CHCl_3$); IR (neat) 3417 (OH), 1769 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, *J* = 7.38), 1.58 (m, 2H), 2.50 (br,1H), 3.33−3.47 (m, 3H), 4.91 (dd, 1H, *J* = 2.1, 8.0), 7.2−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.9, 20.7, 57.4, 62.2, 68.2 (dd, *J* = 21.2, 23.0), 118.7 (dd, *J* = 287, 292),127.4, 127.9, 129.0, 130.5, 161.5 (dd, *J* = 30.4, 32); ^{19}F NMR ($CDCl_3$) δ −114.7 (dd, *J* = 8.0, 222.3), −122.0 (d, *J* = 222.3); HRMS (CI) calcd for $(M + 1)^+$ $C_{13}H_{16}F_2NO_2$ 256.1149 found 256.1145. Anal. Calcd for $C_{13}H_{15}F_2NO_2$: C, 61.17; H, 5.92; N, 5.49. Found: C, 61.33; H, 5.95; N, 5.28.

(4*S*)-3,3-Difluoro-1-((1*R*)-1-hydroxymethylpropyl)-4-pentylazetidin-2-one (3c). Flash chromatography (10% EtOAc in cyclohexane) yielded a yellow oil 35%: $[\alpha]^{25}_D$ +27.3° (*c* 1, $CHCl_3$); IR (neat) 3404 (OH), 1773 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 1.0 (m, 6H), 1.4 (m, 6H), 1.7 (m, 4H), 3.4 (m,1H), 3.5 (br, 1H), 3.8 (m, 2H), 4.4 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 9.7, 12.8, 20.6, 21.3, 24.0, 27.4, 30.5, 57.4, 62.4, 65.5 (dd, *J* = 24.2, 29.3), 119.2 (dd, *J* = 277, 290), 160.4 (t, *J* = 31.5); ^{19}F NMR ($CDCl_3$) δ −115.5 (dd, *J* = 8.1, 222.5), −128.1 (d, *J* = 222.5); HRMS (CI) calcd for $(M + 1)^+$ $C_{12}H_{21}F_2NO_2$ 250.1619, found 250.1622. Anal. Calcd for $C_{12}H_{21}F_2NO_2$: C, 57.81; H, 8.49; N, 5.62. Found: C, 57.61; H, 8.41; N, 5.43.

(4*S*)-3,3-Difluoro-1-((1*R*)-1-hydroxymethylpropyl)-4-furylazetidin-2-one (3d). Flash chromatography (20% EtOAc in cyclohexane) yielded a yellow oil: 62%; $[\alpha]^{25}_D$ +14.6° (*c* 1, $CHCl_3$); IR (neat) 3309 (OH), 1785 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 7.3), 1.52 (m, 2H), 3.09 (br, 1H), 3.43 (m, 1H), 3.50 (m, 2H), 4.96 (dd, 1H, *J* = 2.4, 7.0), 6.39 (dd, 1H, *J* = 1.7, 3.3), 6.52 (d, 1H, *J* = 3.3), 7.46 (d, 1H, *J* = 1.7); ^{13}C NMR ($CDCl_3$) δ 9.6, 20.3, 57.3, 60.9 (dd, *J* = 23.3, 27.6), 62.0, 110.2, 111.3, 118.7 (dd, *J* = 286, 293), 143.4, 144.0, 160.6 (t, *J* = 31.6), ^{19}F NMR ($CDCl_3$) δ −114.7 (dd, *J* = 7.0, 225.2), −120.4 (d, *J* = 225.2); HRMS (CI) calcd for $(M + 1)^+$ $C_{11}H_{14}F_2NO_2$ 246.0942, found 246.0946. Anal. Calcd for $C_{11}H_{13}F_2NO_2$: C, 53.88; H, 5.34; N, 5.71. Found: C, 53.61; H, 5.62; N, 5.68.

(4*S*)-3,3-Difluoro-1-((1*R*)-1-hydroxymethylpropyl)-4-propenylazetidin-2-one (3e). Flash chromatography (30% EtOAc in cyclohexane) yielded a colorless oil: 32%; $[\alpha]^{25}_D$ +12.9° (*c* 1, $CHCl_3$); IR (neat) 3452 (OH), 1654 (C═C), 1773 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 1.8 (m, 3H), 0.95 (t, 3H, *J* = 7.4), 1.65 (m, 2H), 1.8 (m, 3H), 2.1 (br,1H), 3.4 (m, 1H), 4.35 (m, 1H), 5.4 (m, 1H), 6.0 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 9.7, 17.1, 20.6, 57.2, 62.1, 67.1 (dd, *J* = 22.6, 26.4), 118.9 (dd, *J* = 286, 301), 121.6, 135.7, 160.5 (t, *J* = 32.3); ^{19}F NMR ($CDCl_3$) δ −118.3 (dd, *J* = 6.8, 222.0), −126.3 (d, *J* = 222.0); HRMS (CI) calcd for $(M + 1)^+$ $C_{10}H_{16}F_2NO_2$ 220.1149, found 220.1147. Anal. Calcd for $C_{10}H_{15}F_2NO_2$: C, 54.79; H, 6.90; N, 6.39. Found: C, 54.52; H, 6.58; N, 6.68.

(3*S*)-2,2 Difluoro-3-((1*R*)-2-hydroxy-1-phenylethylamino)-3-phenylpropanoic Acid (4a). A solution of **3a** (43 mg, 0.14 mmol) in HCl_{aq} (6 N, 6 mL) was heated at reflux for 5 h. The resulting mixture was concentrated in vacuo to dryness to obtain a white residue. After being triturated in ether, the solid was filtered and then washed with 2 × 5 mL of cold water and 5 mL of ether. It was recrystallized in MeOH to give **4a** as colorless prisms (32 mg, 0.1 mmol, 71%): mp 189−191 °C dec; $[\alpha]^{25}_D$ −6.4° (*c* 1, MeOH); IR (KBr) 3368 (OH), 1642 cm^{-1} (C═O); ^{1}H NMR (CD_3OD) δ 3.90 (m, 2H), 4.51 (m, 1H), 4.95 (masked by CD_3OH), 7−7.3 (m, 10H); ^{13}C NMR (DMSO) δ 62.2 (dd, *J* = 23.5, 29.2), 63.2, 64.0, 117.1 (dd, *J* = 286, 298), 128.9, 128.8, 129.0, 129.1, 129.7, 130.1, 134.9, 135.0, 163.0 (t, *J* = 30.4); ^{19}F NMR (DMSO) δ −107.0 (dd, *J* = 11.3, 245.1), −112.4 (dd, *J* = 14.1, 245.1). Anal. Calcd for $C_{17}H_{17}F_2NO_3$: C, 63.55; H, 5.33; N, 4.36. Found: C, 63.22; H, 5.24; N, 4.06.

(3*S*)-3-Amino-2,2-difluoro-3-phenylpropanoic Acid (5a). A solution of **4a** (69 mg, 0.216 mmol) in MeOH (10 mL) was hydrogenated (H_2, 1 bar) in the presence of 10% Pd/C. After filtration and concentration under vacuum, the crude material was washed with ether to remove phenylethanol. β-Amino acid **5a** was obtained as a white solid (39 mg, 0.194 mmol, 90%): mp 160−165 °C dec; $[\alpha]^{25}_D$ +7.1° (*c* 1, MeOH); IR (KBr) 1652 cm^{-1} (C═O); ^{1}H NMR (CD_3OD) δ 4.95 (masked by CD_3OH), 7.3−7.5 (m, 5H); ^{13}C NMR (CD_3OD) δ 58.6 (dd, *J* = 28.6, 29.7), 112.6 (t, *J* = 293), 129.9, 130.1, 131.1, 131.5, 166.9; ^{19}F NMR ($CDCl_3$) δ −110.8 (d, *J* = 258.4), −113.9 (d, *J* = 258.4). Anal. Calcd for $C_9H_9F_2NO_2$: C, 53.73; H, 4.51; N, 6.96. Found: C, 53.61; H, 4.45; N, 6.72.

(4*S*)-3,3-Difluoro-4-phenyl-1-(1-phenylvinyl)azetidin-2-one (6a). To CH_2Cl_2 (15 mL) and pyridine (0.311 mL, 3.84 mmol) at −10 °C was slowly added trifluoromethanesulfonic anhydride (0.354 mL, 2.10 mmol). A thick white precipitate began to form during the addition. After addition was complete, the suspension was allowed to stir for an additional 10 min. Then **3a** (320 mg, 1.05 mmol) in CH_2Cl_2 (7.5 mL) was added dropwise, and stirring was continued for 2 h. The reaction mixture was poured into ice−water (60 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried over magnesium sulfate, and the solvent was removed in vacuo. Flash chromatography (AcOEt/cyclohexane 10%) gave a colorless oil. The triflate was dissolved in CH_2Cl_2 (10 mL) at −10 °C, and DBU (188 μL, 1.26 mmol) was added. After 1 h, the mixture was poured into HCl_{aq} (2 N, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was purified on silica gel flash chromatography (ethyl acetate/cyclohexane 10%) to give **6a** as a white solid (235 mg, 0.82 mmol, 78%): mp = 56 °C; $[\alpha]^{25}_D$ +55.7° (*c* 1, $CHCl_3$); IR (neat) 1773 (C═O), 1626 cm^{-1} (C═C); ^{1}H NMR ($CDCl_3$) δ 4.91 (s,1H), 5.10 (s, 1H), 5.17 (dd, 1H, *J* = 2.0, 8.2), 7.1−7.3 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 68.3 (dd, *J* = 24.4, 26.5), 104.7, 118.5 (dd, *J* = 286, 274), 126.2, 126.5, 127.3,

127.9, 128.3, 128.6, 129.3, 132.7, 139.3, 157.1 (t, J = 31.7); ^{19}F NMR ($CDCl_3$) δ −113.7 (dd, J = 8.2, 226.1), −121.0 (d, J = 226.1). Anal. Calcd for $C_{17}H_{13}F_2NO$: C, 71.72; H, 4.62; N, 4.98. Found: C, 71.57; H, 4.59; N, 4.91.

(4*S*)-3,3-Difluoro-1-(1-ethylvinyl)-4-pentylazetidin-2-one (6b). Same procedure as above but the elimination reaction was carried out as follows. To a solution of the triflate (450 mg, 1.18 mmol) in THF (40 mL) at −10 °C was added potassium *tert*-butylate (158 mg, 1.4 mmol). After 10 min, the mixture was poured into HCl_{aq} (2 N, 50 mL). Then, the same procedure furnished **6b** as of a colorless oil (194 mg, 0.840 mmol, 71%): $[\alpha]^{25}_D$ +20.2° (*c* 1, $CHCl_3$); IR (neat) 1789 (C═O), 1636 cm^{-1}(C═C); ^{1}H NMR ($CDCl_3$) δ 0.83 (m, 3H), 1.05 (t, J = 7.3, 3H), 1.1−1.9 (m, 8H), 2.48 (q, J = 7.3, 2H), 4.04 (m, 1H), 4.42 (s, 1H), 4.47 (s,1H); ^{13}C NMR ($CDCl_3$) δ 11.0, 12.8, 21.7, 23.6, 24.7, 24.8, 30.5, 64.4 (dd, J = 23.6, 24.2), 95.6, 118.9 (dd, J = 281.5, 287.4), 143.1, 156.0 (t, J = 31.6); ^{19}F NMR ($CDCl_3$) δ −115.7 (dd, J = 11.2, 231.3), −126.4 (d, 231.3). Anal. Calcd for $C_{12}H_{19}F_2NO$: C, 62.32; H, 8.28; N, 6.06. Found: C, 62.53; H, 8.32; N, 6.11.

(4S)-3,3-Difluoro-1-(1-ethylvinyl)-4-furylazetidin-2-one (6c). Same procedure as **6b** afforded **6c** as a colorless oil (69%): $[\alpha]^{25}_D$ +46.0° (*c* 1, $CHCl_3$); IR (neat) 1788[1] (C═O), 1635 cm^{-1} (C═C); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.3, 3H), 2.45 (q, J = 7.3, 2H), 4.29 (s, 1H), 4.33 (s, 1H), 5.13 (dd, J = 1.77, 6.7), 6.38 (s, 1H), 6.46 (s, 1H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0, 24.56, 61.4 (dd, J = 24.1, 28.2), 96.4, 109.9, 110.8, 118.1 (dd, J = 282.1, 286.4), 142.8, 143.0, 143.2, 156.0 (t, J = 30.9); ^{19}F NMR ($CDCl_3$) δ −114.9 (dd, J = 6.5, 225.9), −126.4 (d, 225.9). Anal. Calcd for $C_{11}H_{11}F_2NO_2$: C, 58.15; H, 4.88; N, 6.16. Found: C, 58.37; H, 4.91; N, 6.13.

(4*S*)-3,3-Difluoro-4-phenylazetidin-2-one (7a). A solution of the enamide **6a** (65 mg, 0.228 mmol) in ether (20 mL) containing H_2SO_4 (30 N, 5 mL) was refluxed until no more starting material appeared on TLC monitoring. After the reaction was completed, the solution was neutralized with a saturated solution of $NaHCO_3$ (30 mL) and then addition of solid $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over $MgSO_4$. After concentration, the residue was flash chromatographed on silica gel with 15% ethyl acetate in cyclohexane. **7a** was obtained as a white solid (22 mg, 0.120 mmol, 53%): mp 64 °C; $[\alpha]^{25}_D$ +38.3° (*c* 1.01, $CHCl_3$); IR (neat) 3271 (OH), 1790 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 4.98 (dd, J = 2.4, 6.5, 1H), 6.94 (br, 1H), 7.1−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 64.2 (dd, J = 24.6, 26.4), 120.4 (dd, J = 279, 290), 126.1, 127.8, 128.6, 130.9, 160.5 (t, J = 31.5); ^{19}F NMR ($CDCl_3$) δ −114.0 (ddd, J = 6.5, 12.7, 224.1), −120.1 (ddd, J = 2.4, 11.2, 224.1). Anal. Calcd for $C_9H_7F_2NO$: C, 59.02; H, 3.85; N, 7.65. Found: C, 59.11; H, 3.63; N, 7.68

(4S)-3,3-Difluoro-4-pentylazetidin-2-one (7b). Flash chromatography (20% EtOAc in cyclohexane) yielded a colorless oil: 56%;. $[\alpha]^{20}_D$ −4.65° (*c* 0.36, $CHCl_3$); IR (neat) 3271 (NH), 1789 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 3H), 1.27 (m, 6H), 1.62 (m, 2H), 3.88 (m, 1H), 6.85 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 21.3, 24.0, 25.9, 30.3, 61.6 (t, J = 24.2), 120.7 (dd, J = 289, 293), 160.2 (t, J = 30.8); ^{19}F NMR ($CDCl_3$) δ −115.9 (ddd, J = 8.4, 14.1, 217.4), −120.1 (dd, J = 11.3, 217.4). Anal. Calcd for $C_8H_{13}F_2NO$: C, 54.23; H, 7.39; N, 7.90. Found: C, 54.53; H, 7.56; N, 7.77.

(4*S*)-3,3-Difluoro-4-furylazetidin-2-one (7c). Flash chromatography (30% EtOAc in cyclohexane) yielded a colorless oil: 61%; $[\alpha]^{20}_D$ −10.2° (*c* 0.5, $CHCl_3$); IR (neat) 3256 cm^{-1} (NH), 1802 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 4.98 (dd, J = 2.25, 5.62, 1H), 6.36 (s, 1H), 6.43 (s, 1H), 6.96 (br, 1H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 58.0 (dd, J = 24.1, 28.7), 109.8, 109.9, 120.2 (dd, J = 287, 294), 143.22, 144.63, 160.5 (t, J = 31.2); ^{19}F NMR ($CDCl_3$) δ −114.5 (ddd, J = 5.6, 11.3, 220.2), −119.3 (dd, J = 11.3, 220.2). Anal. Calcd for $C_7H_5F_2NO_2$: C, 48.57; H, 2.91; N, 8.09. Found: C, 48.72; H, 3.02; N, 8.51.

(3*S*)-3-Amino-2,2-difluoro-3-phenylpropanoic Acid, HCl Salt (5a). A solution of **6a** (56 mg, 0.196 mmol) in HCl_{aq} (6 N, 5 mL) was refluxed for 2 h. Water was removed under vacuum, and the resulting white solid was recrystallized from methanol−ether leading to **5a** HCl salt (45 mg, 0.19 mmol, 96%): mp 159 °C dec; $[\alpha]^{20}_D$ +3.3° (*c* 0.84, MeOH); IR (KBr) 3130 (NH, OH), 1657 cm^{-1} (COOH); ^{1}H NMR (CD_3OD) δ 5.05 (dd, J = 7.5, 19.7, 1H), 7.4 (m,5H); ^{13}C NMR (CD_3OD) δ 58.3 (t,J = 24.4), 114.9 (t, J = 260), 130.5, 130.9, 132.2, 132.4, 163.9 (t, J = 28.8); ^{19}F NMR (CD_3OD) δ −120.2 (dd, J = 19.7, 249.4), −110.5 (dd, J = 7.5, 249.4). Anal. Calcd for $C_9H_{10}ClF_2NO_2$: C, 45.49; H, 4.24; N, 5.89. Found: C, 45.32; H, 4.31; N, 5.93

(3*S*)-3-Amino-2,2-difluoro-3-octanoic Acid, HCl Salt (5b). A solution of **7b** (94 mg, 0.53 mmol) in HCl_{aq} (6 N, 8 mL) was refluxed for 2 h. Water was removed under vacuum, and the white solid was recrystallized from methanol−ether, furnishing **5b** (116 mg, 0.50 mmol, 95%): mp=190−194 °C; $[\alpha]^{20}_D$−9.2° (*c* 0.25, MeOH); IR (KBr) 3152 (NH, OH), 1655 cm^{-1} (COO); ^{1}H NMR ($CDCl_3$) δ 0.75 (m, 3H), 1.15−1.63 (m, 8H), 3.80 (m, masked by CD_3OH); ^{13}C NMR ($CDCl_3$) δ 14.7, 23.5, 25.9, 28.4, 32.6, 54.7 (t, J = 23.7), 115.0 (t, J = 255); 163.6 (t, J = 31.2); ^{19}F NMR ($CDCl_3$) δ −119.4 (dd, J = 16.9, 265.4), −110.5 (dd, J = 8.4, 265.4). Anal. Calcd for $C_8H_{16}ClF_2NO_2$: C, 41.48; H, 6.96; N, 6.05. Found: C, 41.22; H, 7.05; N, 6.22.

(3*S*)-3-Amino-2,2-difluoro-3-furylpropanoic acid, HCl salt (5c): white solid; mp 185−188 °C dec; $[\alpha]^{20}_D$ −19.8° (*c* 0.6, MeOH); IR (KBr) 3100[1] (NH, OH), 1659 cm^{-1} (COOH); ^{1}H NMR (CD_3OD) δ 5.43 (dd, J = 6.96, 17.46, 1H), 6.61 (dd, J = 1.3, 3.1), 6.79 (d, J = 3.1, 1H), 7.74 (d, J = 1.3, 1H); ^{13}C NMR (CD_3OD) δ_52.3 (t, J = 27.92), 112.73, 114.48, 114.8 (t, J = 261), 143.7, 146.8, 164.57 (t, J = 29); ^{19}F NMR (CD_3OD) δ −109.7 (dd, J = 6.9, 262), −117.6 (dd, J = 17.4, 262). Anal. Calcd for $C_7H_8ClF_2NO_3$: C, 36.94; H, 3.54; N, 6.15. Found: C, 37.12; H, 3.62; N, 6.23

***rac*-3,3-Difluoro-1-(4-methoxybenzyl)-4-phenylazetidin-2-one (9).** The synthesis of **9** was performed using the usual procedure with 2 equiv of ethyl bromodifluoroacetate. Silica gel flash chromatography, eluent 10% EtOAc in cyclohexane, provided a colorless oil (77%): IR (neat) 1790 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.81 (d, J = 15.3, 1H), 4.61 (dd, J = 1.8, 8.4, 1H), 4.77 (d, J = 15.3, 1H), 6.72 (m, 2H), 6.94 (m, 2H), 7.06 (m, 2H), 7.32 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 44.1, 55.7, 68.2 (t, J = 24.1), 114.8, 120.9 (dd, J = 291, 295), 125.7, 128.5, 129.1, 130.2, 130.4, 130.5, 160.0, 161.2 (t, J = 30.9); ^{19}F NMR ($CDCl_3$) δ −114.8 (dd, J = 8.4, 211.2), −121.9 (d, J = 211.2). Anal. Calcd for $C_{17}H_{15}F_2NO_2$: C, 67.32; H, 4.98; N, 4.62. Found: C, 67.12; H, 5.12; N, 4.83

***rac*-(4*S*)-3,3-Difluoro-4-phenylazetidin-2one (7a).** To **9** (53 mg, 0.23 mmol) in a mixture of CH_3CN/H_2O (9:1, 7 mL) at 0 °C was added CAN (385 mg, 0.70 mmol) in small portions. After 20 min at 0 °C and 6 h at room temperature, the mixture was poured on water (50 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with 5% $NaHCO_3$ (10 mL), 10% Na_2SO_3 (10 mL), 5% $NaHCO_3$ (10 mL), and finally brine (10 mL). After concentration and flash column chromatography with 15% ethyl acetate in cyclohexane, the desired racemic product **7a** was obtained in 83% yield (36 mg, 0.19 mmol) (IR, MS, and NMR identical to previously synthesized **(+)-7a)**.

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