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Enantioselective synthesis of α,α-difluoro-β-lactams using amino alcohol ligands

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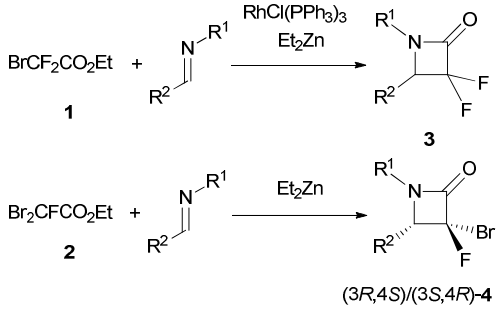
A practical and highly enantioselective Reformatsky reaction of ethyl bromodifluoroacetate with imines using a cheap and commercially available amino alcohol ligand is described. A variety of α,α-difluoro-β-lactams were obtained in up to 74% yield with high enantioselectivity in excess of 99% ee. The use of ethyl bromodifluoroacetate provides for ease of operation because of the inherent chemical stability of this reagent.

Introduction

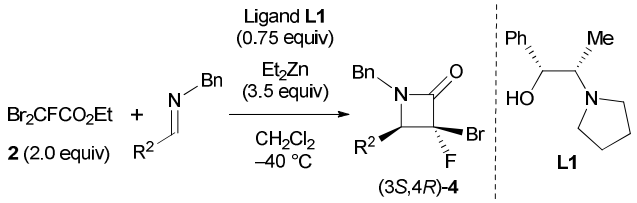
The incorporation of fluorine atoms in organic molecules can substantially alter the physical and biological properties of the molecules, leading to useful biological and pharmacological effects.[1] Organofluorine compounds have been used extensively in the medicinal,[2] agrochemical,[3] and material science fields.[4] In particular, fluorine-containing compounds have been successful as pharmaceutical drugs.[5] The β-lactam structure has been used not only in antibiotics,[6] but also in bioactive compounds, including a hypercholesterol therapeutic agent.[7] Incorporation of CF_2 group into a β-lactam ring to create an α-fluorinated β-lactam is expected to enhance the antibiotic activity of the parent β-lactam due to increased electrophilicity and structural strain of an amide bond. In fact, fluoro-β-lactams and difluoro-β-lactams have been shown to be effective in the inhibition of β-lactamases[8] and human leukocyte elastase.[9] Furthermore, it is important that α-fluorinated β-lactams have been used as building blocks to introduce α-fluorinated β-amino acid moieties into bioactive compounds.[10] To date, fluorinated β-lactams have been synthesized by various approaches, including cycloaddition of an halofluoroacetate with Schiff bases,[11] [2+2] fluoroketene-imine condensation,[12] Mitsunobu ring closure of 3-hydroxy-2,2-difluoropropaneamides,[10a-b,13] intramolecular hydroamination of difluoropropargyl amides,[14] cycloaddition of a nitrone to hexafluoropropene,[15] and direct electrophilic fluorination of β-lactam nuclei.[16] The Reformatsky reaction of an halofluoroacetate with an imine is the simplest and most direct approach toward a fluoro-β-lactam. Recently, we reported the syntheses of several fluorinated β-lactams, including the α,α-difluoro-β-lactam (**3**) and α-bromo-α-fluoro-β-lactam (**4**), using the Reformatsky reaction of bromofluoroacetate (**1**) or di



Scheme 1 Imino-Reformatsky reaction of halofluoroacetate **1** and **2**.

bromofluoroacetate (**2**) with imines (Scheme 1).[17,18] Although fluorinated β-lactams are important in medicinal chemistry, stereoselective syntheses of these molecules remain scarce. Stereoselective approaches have been limited to starting from chiral imines, chiral oxazolines, or chiral halodifluoroacetates in a diastereoselective manner.[19] α,α-Difluoro-β-amino esters, which are non-cyclized Reformatsky adducts, have also been synthesized using the Reformatsky reaction of **1** with chiral imines.[20] Akiyama et al. have reported an asymmetric Mannich reaction using difluoroenol silyl ethers with *N*-Boc imines in the presence of a 1,1'-bi-2-naphthol derived chiral phosphoric acid catalyst, providing α,α-difluoro-β-lactams enantio-selectively from the Mannich-adducts.[21] Recently, high enantioselectivity has been achieved through the reaction of ethyl iododifluoroacetate or ethyl iodofluoroacetate with ketones in the presence of a stoichiometric amount of a chiral ligand.[22,23] Unfortunately, despite giving the desired products in high yield with good enantioselectivity, the poor chemical stability of the iodoacetate reagents has impaired the convenience of this approach. Recently, we published an asymmetric imino-Reformatsky reaction of **2** with an imine

using a substoichiometric amount of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-propan-1-ol (**L1**) as a chiral ligand (eqn (1)).[24] In this reaction, a variety of different imines were used to provide the chiral (3*S*,4*R*)-α-bromo-α-fluoro-β-lactams (**4**) in good yields with high enantio- and diastereoselectivities. As part of our ongoing work toward the stereoselective synthesis of fluorinated β-lactams, we herein report the asymmetric synthesis of α,α-difluoro-β-lactams by a convenient approach using the chemically stable reagent **1** in the presence of a chiral amino alcohol ligand.



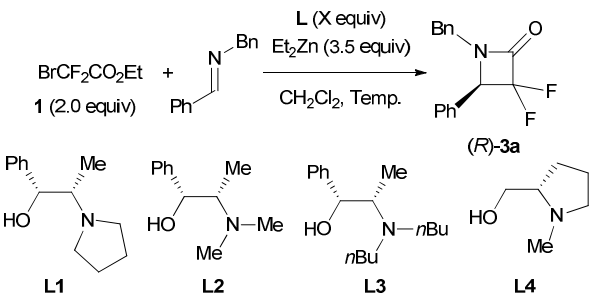
Result and discussion

Optimization of the enantioselective synthesis of difluoro-β-lactams

Based on our previous research, we envisioned that the imino-Reformatsky reaction of **1** using a chiral amino alcohol ligand would proceed enantioselectively to provide a new approach to enantioenriched α,α-difluoro-β-lactam **3**. We initially investigated the enantioselective Reformatksy reaction with the modified conditions of our previously reported reaction (Table 1, entry 1). The reaction of **1** with benzylidenebenzylamine was carried out in CH_2Cl_2 at 0 °C in the presence of 0.75 equiv of **L1**. The reaction provided the desired product (**3a**) with excellent enantiomeric excess (96%), but the reaction was slow and the yield of **3a** was moderate (63%). To improve the yield of **3a**, the reaction conditions were optimized. When a stoichiometric amount of **L1** was used, the yield of **3a** was slightly increased (entry 2). This improvement in yield was also observed when the reaction was carried out at room temperature (entry 3). Different chiral ligands were also explored to find the optimal ligand. (1*R*,2*S*)-2-(Dimethylamino)-1-phenylpropan-1-ol (**L2**) was effective, although the stereoselectivity was slightly decreased (entry 4). (1*R*,2*S*)-2-(Dibutylamino)-1-phenylpropan-1-ol (**L3**) was found to be an inferior catalyst with respect to the chemical yield and enantioselectivity of the product compared with **L1** (entry 5). The prolinol ligand (**L4**) also led to lower enantioselectivity of the desired product, although the yield of product was comparable to that of **L1** (entry 6). Based on these results, the optimal reaction conditions were determined to be a stoichiometric amount of ligand **L1** at room temperature.

Scope and limitations for the enantioselective syntheses of difluoro-β-lactams

Table 1 Screening of reaction conditions.



Entry	Ligand (equiv)		Temp (°C)	Yield (%)[a]	ee (%)[b]
1	**L1**	0.75	0	63	96
2	**L1**	1	0	67	91
3	**L1**	1	r.t.	72	91
4	**L2**	1	r.t.	76	85
5	**L3**	1	r.t.	39	62
6	**L4**	1	r.t.	73	21

[a] Isolated yields.

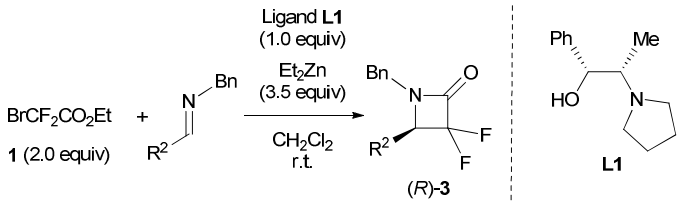
[b] Determined by HPLC.

With the optimal conditions in hand, we investigated the generality of our protocol using a variety of differently substituted aromatic imines. The results of these investigations are listed in Table 2. In comparison with the reaction of **2**, high enantioselectivity was observed regardless of the substituents on the aromatic rings. In particular, imines bearing an electron-withdrawing substituent on the aromatic ring gave rise to the corresponding products with high enantioselectivity (**3c**–**3f**). However, the yields of the products were lower than those of the products in the reaction with **2**. These results suggest that the low yields of **3** were caused by the low reactivity of **1** with the diethyl zinc. In fact, generation of the Reformatsky reagent from **1** required the use of heat or an additive, such as diethylaluminum chloride,[19,25] whereas the Reformatsky reagent of **2** can be generated below room temperature without the presence of a promotor.[18,24,26,27] In all cases, the decomposition products of imine were recovered, after column chromatography. The opposite enantiomer was also obtained, using the (1*S*,2*R*)-isomer of the ligand, in 67% yield and 86% ee.

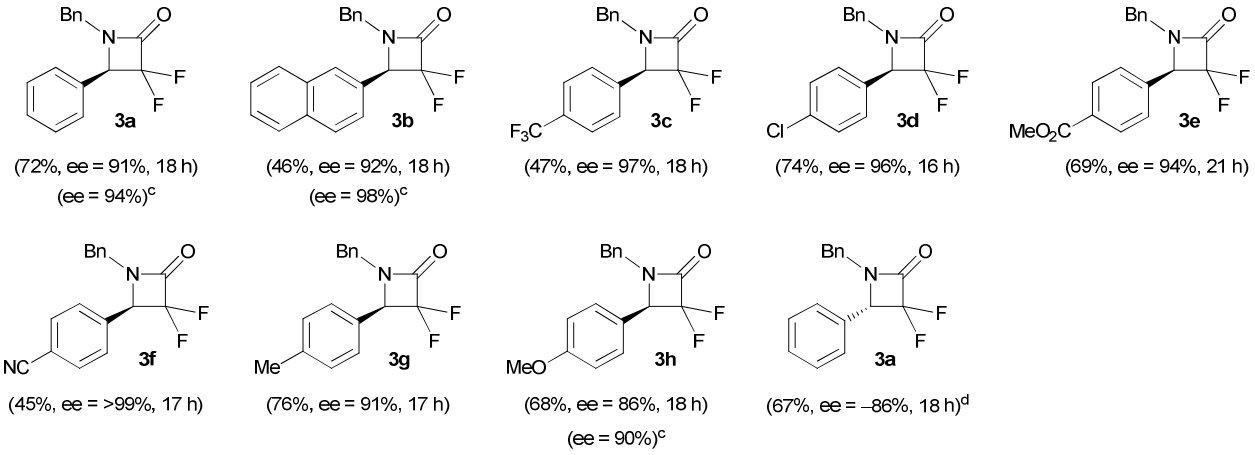
Absolute configuration of the products and the proposed reaction mechanism

The absolute configuration of the product **3a** was determined by comparison of the order of elution by chiral HPLC analysis and the sign of the optical rotation with (*S*)-**3a** obtained from the reaction of (−)-menthyl bromodifluoroacetate with benzyli-

Table 2 Scope and limitations of asymmetric syntheses of **3**



products (yield[a], ee[b], time)



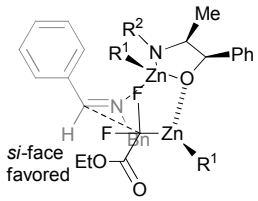
[a] Isolated yields.

[b] Determined by HPLC.

[c] The values indicate the ee after recrystallization of the products.

[d] The(1*S*,2*R*)-isomer of ligand **L1** was used.

denebenzylamine.[19d] The results indicated that the absolute configuration of the product obtained through the Reformatsky reaction is (*R*)-**3a**. Absolute configurations of the other products were also assigned in the same manner. Considering these results, we proposed the reaction mechanism as shown in Scheme 2, which is the same model that we have previously proposed.[24] This transition model is supported by Noyori's representative transition model as well as Soai's model.[28] However, the exact mechanism of this reaction remains unclear. Hence, a detailed investigation on the mechanism will be presented in a future paper.



Scheme 2 Proposed stereoinduction model of the Reformatksy reaction

Conclusions

We have presented a convenient method for an enantioselective imino-Reformatsky reaction of ethyl bromodifluoroacetate (**1**) using a stoichiometric amount of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-propan-1-ol (**L1**) as a chiral ligand. This approach provides for not only convenient experimental operation, as it uses the chemically stable reagent **1**, but also easy access to a chiral fluorinated building block. The reaction gave rise to chiral α,α-difluoro-β-lactams with excellent enantioselectivity up to in excess of 99% ee under mild conditions at room temperature.

Experimental

NMR spectra were obtained from a solution in $CDCl_3$ using 600 and 400 MHz for ^{1}H, 150 and 100 MHz for ^{13}C and 564 and 84 MHz for ^{19}F. Chemical shifts of ^{1}H NMR and ^{13}C NMR are reported in ppm from tetramethylsilane (TMS) as an internal standard. Chemical shifts of ^{19}F NMR are reported in ppm from benzotrifluoride (BTF) as an internal standard. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet doublet, br = broad, brs = broad-singlet, m = multiplet), coupling constants (Hz). High-resolution mass spectroscopy (HRMS) experiments were measured on a double-

focusing mass spectrometer with an ionization mode of EI. Infrared (IR) spectra were recorded in KBr tablets or thin films on KBr disks. Melting points were measured uncorrected. Analytical high performance liquid chromatography (HPLC) was performed on a Shimadzu 10A instrument using Daicel Chiralpak AD-H (0.46 cm I.D. × 25 cm). Optical rotations were recorded on a JASCO P1020.

All experiments were carried out under an argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted. Anhydrous THF and diethyl ether (Et_2O) were distilled over benzophenone ketyl sodium just before use. Anhydrous dichloromethane were distilled over P_2O_5 just before use. All commercially available materials were used as received without further purification. Diethyl zinc 1.0 M in hexane was purchased from Aldrich. All imines were synthesized from amines and aldehydes using $MgSO_4$ as a desiccant. The ligand (**L2**) was synthesized following the procedure described in the literature.[29]

General procedure for the enantioselective imino-Reformatsky reaction of ethyl bromodifluoroacetate.

Ethyl bromodifluoroacetate (**2**) (2.0 mmol, 0.26 mL) was added to a solution of the corresponding imine (1 mmol) and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-propan-1-ol (**L1**) (1.0 mmol, 205 mg) in CH_2Cl_2 (8 mL) at ambient temperature. Then, the mixture was cooled to 0 °C, and 1.0 M Et_2Zn in hexane (3.5 mmol, 3.5 mL) was slowly added to the mixture at 0 °C. The reaction mixture was allowed to warm to ambient temperature, and the whole mixture was stirred at the same temperature for the appropriate time. The mixture was quenched with saturated aqueous $NaHCO_3$, and was filtered through a Celite pad. The filtrate was extracted with AcOEt, and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt/hexane) to afford the corresponding α,α-difluoro-β-lactam **3**.

Racemates **3** were synthesized following the procedure described in the literature.[17]

(*R*)-1-Benzyl-3,3-difluoro-4-phenylazetidin-2-one 3a. The titled product **3a** was obtained as a colorless liquid (181 mg, 67%), after column chromatography (AcOEt/hexane = 1:9). $[\alpha]_D^{25}$ −92.3 (c 1.05 in $CHCl_3$); IR (neat) cm^{-1} 1790; δ_H ($CDCl_3$, 600 MHz) 3.93 (1H, dd, *J* 14.8, 2.0 Hz), 4.72 (1H, dd, *J* 7.3, 2.1 Hz), 4.95 (1H, d, *J* 14.8 Hz), 7.11–7.13 (2H, m), 7.22–7.23 (2H, m), 7.31–7.33 (3H, m), 7.42–7.44 (3H, m); δ_C ($CDCl_3$, 150 MHz) 44.2 (m), 68.0 (dd, *J* 26, 24 Hz), 120.5 (dd, *J* 293, 290 Hz), 128.1, 128.4, 128.6, 129.0, 129.1, 129.8, 130.0, 133.4, 160.9 (m); δ_F NMR ($CDCl_3$, 90 MHz) −58.9 (1F, d, *J* 224 Hz), −51.8 (1F, dd, *J* 224, 7 Hz); *m*/*z* (EI) 273.0963 (M^+. $C_{16}H_{13}F_2NO$ requires 273.0965). The ee was determined to be 91% by HPLC (Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 9:1, 0.7 mL/min, 254 nm, major 10.1 min and minor 9.0 min).

(*R*)-1-Benzyl-3,3-difluoro-4-(naphthalen-2-yl)azetidin-2-one 3b. The titled product **3b** was obtained as a colorless solid (143 mg, 46%), after column chromatography (AcOEt/hexane = 1:9). mp 94.5–95.0 °C; $[\alpha]_D^{25}$ −109 (c 1.00 in $CHCl_3$); IR (KBr) cm^{-1} 1800; δ_H ($CDCl_3$, 600 MHz) 3.99 (1H, dd, *J* 14.9, 1.9 Hz), 4.89 (1H, dd, *J* 7.4, 2.0 Hz), 4.98 (1H, d, *J* 14.9 Hz), 7.12–7.13 (2H, m), 7.31–7.33 (4H, m), 7.54–7.56 (2H, m), 7.70 (1H, m), 7.83–7.91 (3H, m); δ_C ($CDCl_3$, 150 MHz) 44.4 (m), 68.3 (dd, *J* 27, 24 Hz), 120.7 (dd, *J* 293, 290 Hz), 124.5, 126.9, 127.1, 27.5, 127.9, 128.1, 128.4, 128.5, 128.7, 129.0, 129.1, 133.1, 133.5, 133.9, 161.0 (m); δ_F ($CDCl_3$, 90 MHz) −58.6 (1F, d, *J* 225 Hz), −51.5 (1F, dd, *J* 225, 7 Hz); *m*/*z* (EI) 323.1121 (M^+. $C_{20}H_{15}F_2NO$ requires 323.1122). The ee was determined to be 92% by HPLC (Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 95:5, 0.7 ml/min, 254 nm, major 16.2 min and minor 14.8 min).

(*R*)-1-Benzyl-3,3-difluoro-4-{4-(trifluoromethyl)phenyl}azetidin-2-one 3c. The titled product **3c** was obtained as a colorless solid (162 mg, 47%), after column chromatography (AcOEt/hexane = 1:9). mp 142.0–143.0 °C; $[\alpha]_D^{25}$ −77 (c 1.00 in $CHCl_3$); IR (KBr) cm^{-1} 1771; δ_H ($CDCl_3$, 400 MHz) 3.98 (1H, dd, *J* 14.9, 2.2 Hz), 4.77 (1H, dd, *J* 7.3, 1.9 Hz), 4.95 (1H, d, *J* 14.9 Hz), 7.10–7.13 (2H, m), 7.32–7.36 (5H, m), 7.68 (2H, d, *J* 7.8 Hz); δ_C ($CDCl_3$, 100 MHz) 44.6 (m), 67.3 (dd, *J* 27, 24 Hz), 120.3 (dd, *J* 293, 290 Hz), 123.4 (q, *J* 271 Hz) 125.8 (q, *J* 4 Hz), 128.3, 128.4, 128.5, 129.0, 131.8 (q, *J* 33 Hz), 132.8, 134.1 (m), 160.4 (m); δ_F ($CDCl_3$, 90 MHz, Hexafluorobenzene) 41.2 (1F, d, *J* 225 Hz), 48.1 (1F, dd, *J* 225, 7 Hz), 99.3 (3F, s); *m*/*z* (EI) 341.0839 (M^+. $C_{17}H_{12}F_5NO$ requires 341.0839). The ee was determined to be 97% by HPLC (Daicel CHIRALPAK AD-H, hexane/EtOH = 98:2, 1.0 mL/min, 254 nm, major 10.4 min and minor 9.5 min).

(*R*)-1-Benzyl-4-(4-chlorophenyl)-3,3-difluoroazetidin-2-one 3d. The titled product **3d** was obtained as a colorless solid (226 mg, 74%), after column chromatography (AcOEt/hexane = 1:9). mp 76.5–77.5 °C; $[\alpha]_D^{25}$ −109 (c 1.04 in $CHCl_3$); IR (KBr) cm^{-1} 1814; δ_H ($CDCl_3$, 400 MHz) 3.93 (1H, dd, *J* 14.7, 2.0 Hz), 4.68 (1H, dd, *J* 7.2, 2.2 Hz), 4.92 (1H, d, *J* 14.7 Hz), 7.10–7.13 (2H, m), 7.16 (2H, d, *J* 8.4 Hz), 7.31–7.34 (3H, m), 7.40 (2H, d, *J* 8.4 Hz); δ_C ($CDCl_3$, 100 MHz) 44.3 (m), 67.2 (dd, *J* 26, 24 Hz), 120.2 (dd, *J* 293, 290 Hz), 128.3, 128.4, 128.9, 129.1, 129.2, 132.9, 135.8, 160.5 (m); δ_F ($CDCl_3$, 90 MHz) −58.4 (1F, d, *J* 225 Hz), −51.8 (1F, dd, *J* 225, 7 Hz); *m*/*z* (EI) 307.0575 (M^+, 100%. $C_{16}H_{12}ClF_2NO$ requires 307.0575), 309.0538 (34). The ee was determined to be 96% by HPLC (Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 9:1, 0.7 mL/min, 254 nm, major 11.2 min and minor 10.1 min).

(*R*)-1-Benzyl-3,3-difluoro-4-(4-methoxycarbonylphenyl)azetidin-2-one 3e. The titled product **3e** was obtained as a colorless solid (230 mg, 69%), after column chromatography (AcOEt/hexane = 1:4). mp 98.0–99.0 °C; $[\alpha]_D^{25}$ −92 (c 1.00 in $CHCl_3$); IR (KBr) 1812, 1715 cm^{-1}; δ_H ($CDCl_3$, 600 MHz) 3.94 (3H, s), 3.96 (1H, dd, *J* 14.8, 2.0 Hz), 4.75 (1H, dd, *J* 7.3, 1.8 Hz), 4.95 (1H, d, *J* 14.8 Hz), 7.09–7.11 (2H, m), 7.30 (2H, d, *J* 8.3 Hz), 7.32–7.33 (3H, m), 8.08 (2H, d, *J* 8.3 Hz); δ_C ($CDCl_3$, 150 MHz) 44.6 (m), 52.4, 67.6 (dd, *J* 27, 24 Hz), 120.4 (dd, *J* 293, 291 Hz), 128.1, 128.6, 128.6, 129.2, 130.2, 131.6, 133.1,

135.0, 160.7 (m), 166.3; δ_F ($CDCl_3$, 90 MHz) −58.1 (1F, d, *J* 224 Hz), −51.5 (1F, dd, *J* 224, 7 Hz); *m/z* (EI) 331.1014 (M^+. $C_{18}H_{15}F_2NO_3$ requires 331.1020). The ee was determined to be 94% by HPLC (Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 4:1, 1.0 mL/min, 254 nm, major 9.5 min and minor 7.0 min).

(*R*)-4-(1-Benzyl-3,3-difluoro-4-oxoazetidin-2-yl)benzonitrile 3f. The titled product **3f** was obtained as a colorless solid (133 mg, 45%), after column chromatography (AcOEt/hexane = 1:4). mp 66.0–67.0 °C; $[\alpha]_D^{25}$ −154 (c 1.00 in $CHCl_3$); IR (KBr) cm^{-1} 2228, 1811; δ_H ($CDCl_3$, 400 MHz) 4.01 (1H, dd, *J* 14.9, 2.0 Hz), 4.76 (1H, dd, *J* 7.3, 1.9 Hz), 4.92 (1H, d, *J* 14.9 Hz), 7.09–7.12 (2H, m), 7.31–7.35 (5H, m), 7.71 (2H, d, *J* 8.3 Hz); δ_C ($CDCl_3$, 100 MHz) 44.8 (m), 67.3 (dd, *J* 26, 24 Hz), 113.7, 117.8, 120.2 (dd, *J* 293, 291 Hz), 128.4, 128.5, 129.0, 132.5, 132.7, 135.3, 135.3, 160.2 (m); δ_F ($CDCl_3$, 90 MHz) −57.7 (1F, d, *J* 225 Hz), −51.2 (1F, dd, *J* 225, 7 Hz); *m/z* (EI) 298.0909 (M^+. $C_{17}H_{12}F_2N_2O$ requires 298.0918). The ee was determined to be >99% by HPLC (Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 4:1, 1.0 mL/min, 254 nm, major 9.3 min and minor 8.4 min).

(*R*)-1-Benzyl-3,3-difluoro-4-(*p*-tolyl)azetidin-2-one 3g. The titled product **3g** was obtained as a colorless solid (219 mg, 76%), after column chromatography (AcOEt/hexane = 1:9). mp 75–77.0 °C; $[\alpha]_D^{25}$ −82 (c 1.00 in $CHCl_3$); IR (KBr) cm^{-1} 1770; δ_H ($CDCl_3$, 600 MHz) 2.39 (3H, s), 3.90 (1H, dd, *J* 14.9, 1.9 Hz), 4.68 (1H, dd, *J* 7.3, 2.1 Hz), 4.94 (1H, d, *J* 14.9 Hz), 7.11–7.13 (4H, m), 7.23 (2H, d, *J* 7.8 Hz), 7.32–7.34 (3H, m); δ_C ($CDCl_3$, 150 MHz) 21.3, 44.1 (m), 67.8 (dd, *J* 26, 24 Hz), 120.6 (dd, *J* 292, 290 Hz), 126.9, 128.0, 128.4, 128.6, 129.0, 129.8, 133.5, 139.9, 161.0 (m); δ_F ($CDCl_3$, 90 MHz) −58.8 (1F, d, *J* 224 Hz), −52.2 (1F, dd, *J* 224, 7 Hz); m/z (EI) 287.1118 (M^+. $C_{17}H_{15}F_2NO$ requires 287.1122). The ee was determined to be 91% by HPLC (Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 9:1, 1.0 mL/min, 254 nm, major 6.8 min and minor 6.2 min).

(*R*)-1-Benzyl-3,3-difluoro-4-(4-methoxyphenyl)azetidin-2-one 3h. The titled product **3h** was obtained as a colorless solid (208 mg, 68%), after column chromatography (AcOEt/hexane = 1:9). mp 120.0–121.0 °C; $[\alpha]_D^{25}$ −94 (c 1.00 in $CHCl_3$); IR (KBr) cm^{-1} 1771; δ_H ($CDCl_3$, 600 MHz) 3.83 (3H, s), 3.90 (1H, dd, *J* 14.9, 2.0 Hz), 4.67 (1H, dd, *J* 7.3, 2.2 Hz), 4.91 (1H, d, *J* 14.9 Hz), 6.94 (2H, d, *J* 8.6 Hz), 7.11–7.13 (2H, m), 7.15 (2H, d, *J* 8.6 Hz), 7.32–7.33 (3H, m); δ_C ($CDCl_3$, 150 MHz) 44.0 (m), 55.4, 67.7 (dd, *J* 26, 24 Hz), 114.5, 120.6 (dd, *J* 292, 290 Hz), 121.7, 128.4, 128.6, 129.0, 129.5, 133.5, 160.8, 160.9 (m); δ_F ($CDCl_3$, 90 MHz) −59.2 (1F, d, *J* 224 Hz), −52.1 (1F, dd, *J* 224, 7 Hz); *m/z* (EI) 303.1073 (M^+. $C_{17}H_{15}F_2NO_2$ requires 303.1071). The ee was determined to be 86% by HPLC (Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 9:1, 0.7 mL/min, 254 nm, major 15.4 min and minor 13.3 min).

Synthesis of the (*S*)-isomer of difluoro-β-lactam 3a.[19d] (−)-Menthyl bromodifluoroacetate (1.5 mmol, 403 mg) was added to a solution of benzylidenbenzylamine (0.5 mmol) and $RhCl(PPh_3)_3$ (0.005 mmol, 4.6 mg) in THF (4 mL) at ambient temperature. Then the mixture was cooled to −10 °C, and 1.0 M Et_2Zn in hexane (1.5 mmol, 1.5 mL) was slowly added to the mixture at −10 °C. The whole mixture was stirred at −10 °C for 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$, and was filtered through a Celite pad. The filtrate was extracted with AcOEt, and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt/hexane) to afford the corresponding α,α-difluoro-β-lactam **3a**.

(*S*)-1-Benzyl-3,3-difluoro-4-phenylazetidin-2-one 3a. The titled product **3a** was obtained as a colorless liquid (66 mg, 48%), after column chromatography (AcOEt/hexane = 1:9). $[\alpha]_D^{25}$ +65.1 (c 1.09 in $CHCl_3$); δ_H ($CDCl_3$, 400 MHz) 3.94 (1H, dd, *J* 14.8, 2.1 Hz), 4.72 (1H, dd, *J* 7.2, 2.2 Hz), 4.95 (1H, d, *J* 14.8 Hz), 7.11–7.14 (2H, m), 7.22–7.24 (2H, m), 7.32–7.33 (3H, m), 7.41–7.44 (3H, m); δ_F ($CDCl_3$, 90 MHz) −58.9 (1F, d, *J* 224 Hz), −51.8 (1F, dd, *J* 224, 7 Hz). The ee was determined to be 89% by HPLC (Daicel CHIRALPAK AD-H, hexane/*i*PrOH = 9:1, 0.7 mL/min, 254 nm, major 9.0 min and minor 10.2 min).

Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: Copies of ^1H NMR, ^{13}C NMR spectra and HPLC chromatograms. See DOI: 10.1039/c000000x/

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