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Enantioselective Synthesis of 3,3-Difluoropyrrolidin-4-ol, a Valuable Building Block in Medicinal Chemistry

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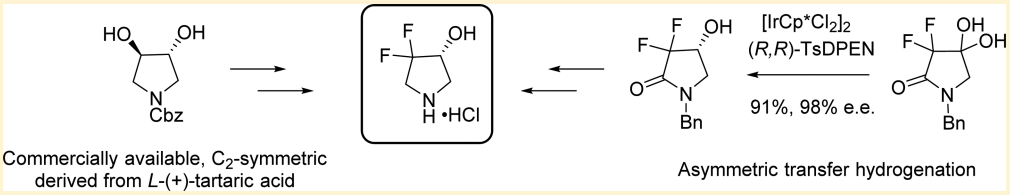
Supporting Information



ABSTRACT: In this paper, we report for the first time two enantioselective routes to 4,4-difluoropyrrolidin-3-ol, a valuable building block in medicinal chemistry. In the first route, we took advantage of the C_2 symmetry of (3*R*,4*R*)-3,4-dihydroxypyrrolidine in which the desired chirality was derived from the chiral pool (L-(+)-tartaric acid). In the second route, we efficiently assembled the pyrrolidine ring in the presence of a *gem*-difluoro moiety to avoid using potentially hazardous deoxofluorinating reagents and subsequently introduced the chirality by a stereoselective iridium−diamine-catalyzed asymmetric transfer hydrogenation reaction.

Fluorine plays an increasingly important role in drug design and development.[1−5] In particular, the introduction of a *gem*-difluoro moiety into a molecule could modulate the pK_a of proximal functional groups,[6] influence compound lipophilicity,[7] alter molecular conformation,[8] induce multiple interactions with protein residues,[9] and significantly improve metabolic stability and pharmacokinetic properties.[10] Several marketed drugs (notable examples include gemcitabine, a nucleoside analogue widely used as chemotherapy for cancer,[11] maraviroc, a CCR5 inhibitor for the treatment of HIV[12]), and numerous drug candidates (e.g., PF-00734200, a DPP4 inhibitor that progressed to phase 3 for the treatment of type 2 diabetes[13]) have incorporated a *gem*-difluoro moiety in their molecular structures (Figure 1). To enhance the general utility of this functionality, there remains a need for efficient methods to synthesize *gem*-difluorinated building blocks for medicinal chemistry.[14−16]

As part of a recent discovery program, we were interested in enantioselective synthesis of (*R*)-4,4-difluoropyrrolidin-3-ol (**1**)

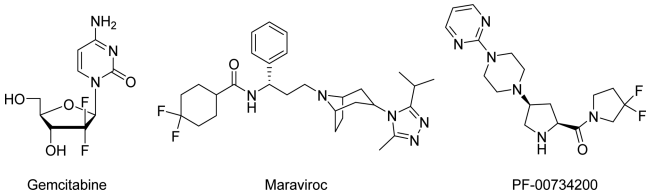


Figure 1. *gem*-Difluoro-containing pharmaceuticals.

as a key building block in our SAR development. To the best of our knowledge, there has been no enantioselective synthesis reported for this class of compounds. Our initial route started from the commercially available, C_2-symmetric (*R*,*R*)-diol **2** which could be derived from L-(+)-tartaric acid.[17]

Monoprotection of diol **2** was achieved by slow addition of lithium diisopropylamide (LDA, 1.0 equiv) to a solution of diol **2** in 2-methyltetrahydrofuran, which led to immediate precipitation of the monolithium alkoxide salt from the solution, preventing further deprotonation. This lithium salt was subsequently alkylated with benzyl bromide to provide the monobenzylated product **3** in 50% yield. Oxidization of the free alcohol with Dess−Martin periodinane yielded the corresponding ketone,[18] which underwent deoxo-fluorination with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) to afford difluoropyrrolidine **4** in 48% yield.[19] Analysis of compound **4** with chiral HPLC indicated no detectable decrease in enantiopurity. Finally, full deprotection by palladium hydroxide catalyzed hydrogenation in the presence of hydrochloric acid gave (*R*)-4,4-difluoropyrrolidin-3-ol hydrochloride **1** in quantitative yield.

Although the route above in Scheme 1 was short and efficient, it necessitated the use of a deoxo-fluorinating reagent which is expensive and has safety concerns for large-scale synthesis. Therefore, we decided to further develop an

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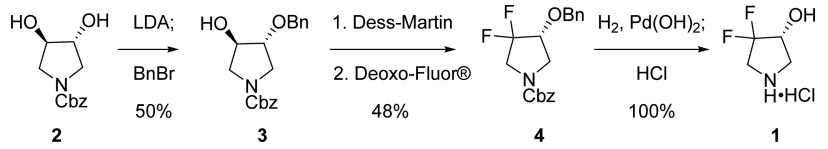
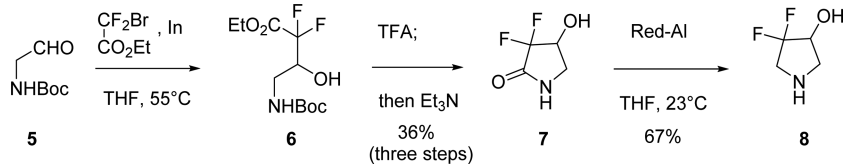
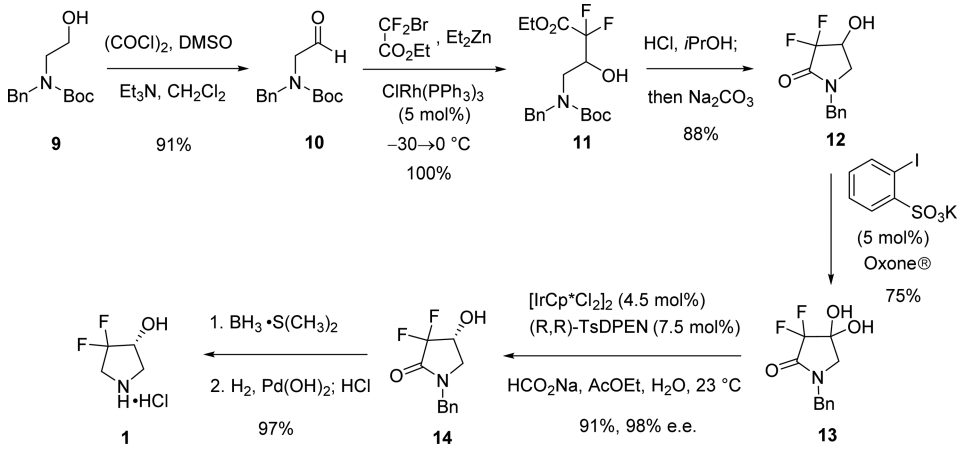
Scheme 1. Synthesis of (*R*)-4,4-Difluoropyrrolidin-3-ol 1 from (*R*, *R*)-Diol 2



Scheme 2. Racemic Route to 4,4-Difluoropyrrolidin-3-ol



Scheme 3. Synthesis of (*R*)-4,4-Difluoropyrrolidin-3-ol 1 by Enantioselective Ketone Reduction



alternative route that circumvented these challenges. We envisioned assembling the pyrrolidine ring from a readily available *gem*-difluoride starting material and subsequently introducing the chiral center by asymmetric ketone reduction. In a model study, we developed a synthesis of racemic 4,4-difluoropyrrolidin-3-ol as shown in Scheme 2. Starting from readily available ethyl 2-bromo-2,2-difluoroacetates, indium-mediated Reformatsky reaction[20] with *N*-Boc-2-aminoacetaldehyde **5** provided alcohol **6**, which was used crude after aqueous workup. After deprotection with trifluoroacetic acid, the pyrrolidinone ring was formed upon treatment with triethylamine. Finally, pyrrolidinone **7** was reduced with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) to 4,4-difluoropyrrolidin-3-ol **8** in 67% yield.

Based on this short racemic route (Scheme 2), we further optimized the reaction conditions and developed an enantioselective synthesis of **1** as shown in Scheme 3. Swern oxidation of commercially available alcohol **9** provided aldehyde **10** in 91% yield.[21] It was found that an additional benzyl protecting group on the amine not only added a chromophore that was useful for purification of ensuring intermediates but also helped to improve the stability of aldehyde **10** (as compared to **5**, which slowly decomposes at room temperature) and led to higher yields in subsequent steps. Next, Reformatsky reaction between **10** and ethyl bromodifluoroacetate under Kumadaki's rhodium-catalyzed condition with 5 mol % of Wilkinson's catalyst gave alcohol **11** in quantitative yield upon extractive isolation.[22] *N*-Boc removal of crude **11** with hydrochloric acid in 2-propanol and lactam formation by stirring a biphasic mixture of crude amine in ethyl acetate and saturated aqueous sodium carbonate solution provided pyrrolidinone **12** in 88% yield. Subsequently, alcohol **12** was oxidized to the corresponding ketone using Ishihara's procedure with Oxone in the presence of catalytic amount of 2-iodoxybenzenesulfonic acid.[23] This ketone was found to exist in the hydrated form **13**.[14] In the key enantioselective ketone reduction step, after examining many possible conditions, we came to aqueous-phase asymmetric transfer hydrogenation with sodium formate as the reductant[24] and ultimately found Carreira's iridium-catalyzed conditions with (*R*,*R*)-TsDPEN (TsDPEN = *N*-(p-toluenesulfonyl)-1,2-diphenylethylenediamine) as the ligand gave the desired (*R*)-alcohol **14** in high yield (91%) and best enantioselectivity (98% ee).[25] Finally, pyrrolidinone **14** was reduced to amine by refluxing with borane dimethyl sulfide complex in tetrahydrofuran, and subsequent hydrogenolytic cleavage of the benzyl group catalyzed by palladium hydroxide in the presence of hydrochloric acid provided (*R*)-4,4-difluoropyrrolidin-3-ol **1** in excellent yields with no loss in chiral purity.

In summary, we have developed for the first time two enantioselective routes to (*R*)-4,4-difluoropyrrolidin-3-ol, a valuable building block in medicinal chemistry. Chirality was introduced either from the chiral pool (L-(+)-tartaric acid) or by using a highly stereoselective and high-yielding iridium diamine ((*R*,*R*)-TsDPEN) catalyzed asymmetric transfer hydrogenation. In the second route, we successfully avoided using potentially hazardous deoxofluorinating reagents and provided a practical route for future scale-up of this useful key

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J. Org. Chem. XXXX, XXX, XXX−XXX

intermediate. Given the (*S*,*S*)- stereoisomer of diol **2** and the (*S*,*S*)-stereoisomer of ligand TsDPEN were also readily available from commercial sources, these routes could be applied to access the (*S*)-isomer of 4,4-difluoropyrrolidin-3-ol as well.

EXPERIMENTAL SECTION

All commercial reagents were used without further purification. All solvents were reagent or HPLC grade. Flash chromatography was carried out using an automated system with prepacked silica columns. Yields refer to chromatographically and spectroscpically pure compounds. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on 400/500 MHz spectrometers at ambient temperature (^{1}H NMR, 400/500 MHz; ^{19}F NMR, 377/470 MHz; ^{13}C NMR, 75/100 MHz). High-resolution mass spectra were recorded using a time-of-flight mass spectrometer with an atmospheric pressure chemical ionization source. Chiral analysis was performed using either HPLC or supercritical fluid chromatography (SFC). The methods chosen were based upon their ability to obtain baseline separation of the racemic mixtures for the compounds of interest.

Benzyl (3*R*,4*R*)-3-(Benzyloxy)-4-hydroxypyrrolidine-1-carboxylate(3). To a solution of benzyl (3*R*,4*R*)-3,4-dihydroxypyrrolidine-1-carboxylate (1.00 g, 4.22 mmol) in 2-ethyltetrahydrofuran (20 mL) was added 2.0 M lithium diisopropylamide solution in tetrahydrofuran (2.11 mL, 4.22 mmol) dropwise. As the base was added, the lithium alkoxide salt precipitated. Once addition was completed, the reaction mixture was concentrated to dryness. The residue was dissolved in dimethylformamide (2 mL), and benzyl bromide (1.00 mL, 8.43 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. The crude material was purified by flash chromatography (25−100% ethyl acetate in hexanes) to afford benzyl (3*R*,4*R*)-3-(benzyloxy)-4-hydroxypyrrolidine-1-carboxylate **3** (690 mg, 50% yield) as off-white solid: $[\alpha]_D^{20}$ = +2.67 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.27 (m, 10H), 5.12 (s, 2H), 4.56 (dd, *J* = 13.1, 12.1 Hz, 2H), 4.29−4.33 (m, 1H), 3.92 (s, 1H), 4.56 (app td, *J* = 11.9, 4.0 Hz, 2H), 3.64−3.40 (m, 2H), 1.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 137.5, 136.7, 128.5, 128.4, 128.0, 127.9, 127.9, 127.7, 77.2, 71.4, 66.9, 52.1, 49.2; HRMS (ESI) calcd for $C_{19}H_{22}NO_4$ $[M + H]^+$ = 328.1549, found 328.1556.

Benzyl (*R*)-3-(Benzyloxy)-4-oxopyrrolidine-1-carboxylate (3a). To a solution of benzyl (3*R*,4*R*)-3-(benzyloxy)-4-hydroxypyrrolidine-1-carboxylate (350 mg, 1.07 mmol) in dichloromethane (5 mL) was added Dess−Martin periodinane (544 mg, 1.28 mmol). After 3 h, the reaction mixture was diluted with ethyl acetate, washed with a 1:1:1 mixture of saturated aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered, and concentrated to give benzyl (3*R*)-3-(benzyloxy)-4-oxo-pyrrolidine-1-carboxylate (348 mg, 100%) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.27 (m, 10H), 5.16 (s, 2H), 4.84 (d, *J* = 11.8 Hz, 1H), 4.67 (d, *J* = 11.8 Hz, 1H), 4.19−4.07 (m, 1H), 4.08 (t, *J* = 8.2 Hz, 1H), 3.95 (d, *J* = 18.7 Hz, 1H), 3.84 (d, *J* = 18.7 Hz, 1H), 3.57−3.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 154.8, 136.6, 136.1, 128.6, 128.6, 128.3, 128.2, 128.1, 77.3, 72.6, 67.5, 51.2, 48.3; HRMS (ESI) calcd for $C_{19}H_{20}NO_4$ $[M + H]^+$ = 326.1392, found 326.1387.

Benzyl (*R*)-4-(Benzyloxy)-3,3-difluoropyrrolidine-1-carboxylate (4). To a solution of crude benzyl (3*R*)-3-(benzyloxy)-4-oxopyrrolidine-1-carboxylate (348 mg, 1.07 mmol) in dichloromethane (20 mL) was added (bis(2-methoxyethyl)amino)sulfur trifluoride (480 mg, 2.17 mmol). After 18 h, the reaction mixture was quenched by cooling to 0 °C and slowly pouring into saturated aqueous $NaHCO_3$ solution, allowing for CO_2 evolution. The layers were separated; aqueous layer was extracted twice with dichloromethane. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash chromatography (20% MBTE in hexanes) to afford benzyl (4*R*)-4-(benzyloxy)-3,3-difluoropyrrolidine-1-carboxylate **4** (177 mg, 48% yield): mp 78.0−78.5 °C; $[\alpha]_D^{20}$ = +6.52 (*c* 0.5, $CHCl_3$). Chiral analysis indicated a 99.5 (t_R = 4.15 min): 0.5 (t_R = 3.78 min) ratio (99% e) with the other possible enantiomer determined by chiral HPLC (Chiralpak AD-H, 4.6 × 100 mm; 100% EtOH, 1.0 mL/min): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.27 (m, 10H), 5.14 (s, 2H), 4.80 (t, *J* = 10.9 Hz, 1H), 4.64 (t, *J* = 10.9 Hz, 1H), 4.01 (br. s., 1H), 3.82 (dd, *J* = 18.2, 8.2 Hz, 1H), 3.80−3.74 (m, 2H), 3.70 (ddd, *J* = 12.1, 5.5, 2.3 Hz, 1H), 3.60 (app t, *J* = 12.9 Hz, 1H); ^{19}F NMR (377 MHz, $CDCl_3$) −105.8 (dd, *J* = 245, 125 Hz), −122.1 (dd, *J* = 245, 214 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 136.8, 136.2, 128.6, 128.5, 128.2, 128.1, 127.9, 122.1 (dd, *J* = 220, 40 Hz), 76.4−75.9 (m), 72.7, 67.4, 50.8−49.9 (m), 49.7 (d, *J* = 7.2 Hz); HRMS (ESI) calcd for $C_{19}H_{19}F_2NNaO_3$ $[M + Na]^+$ = 370.1231, found 370.1228.

(*R*)-4,4-Difluoropyrrolidin-3-ol Hydrochloride (1). To a solution of (4*R*)-4-(benzyloxy)-3,3-difluoropyrrolidine-1-carboxylate **4** (177 mg, 0.51 mmol) in ethanol (4.0 mL) was added palladium hydroxide on carbon (35.4 mg, 0.051 mmol, 20 mass %). The vessel was then closed and purged with hydrogen. The reaction was set under hydrogen atmosphere (80 psi) and stirred at room temperature for 3 h. The reaction mixture was diluted with methanol and filtered. To the filtrate was added 1 N HCl in methanol. Solvents were removed under reduced pressure. The crude was triturated with 2-propanol/hexane (1:1) to provide (3*R*)-4,4-difluoropyrrolidin-3-ol hydrochloride **1** (81 mg, 0.51 mmol, in quantitative yield): $[\alpha]_D^{20}$ = −12.3 (*c* 1.0, H_2O); mp 180−181 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (2H, s), 6.60 (1H, s), 4.31 (1H, m), 3.7−3.5 (2H, m), 3.5−3.4 (1H, m), 3.21 (1H, dt, *J* = 12.5, 2.9 Hz); ^{19}F NMR (377 MHz, DMSO-d_6) −106.3 (d, *J* = 240 Hz), −120.58 (d, *J* = 238 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 126.2 (dd, *J* = 258, 246 Hz), 69.5 (dd, *J* = 30.8, 19.8 Hz), 49.5, 47.2 (t, *J* = 32.8 Hz); HRMS (ESI) calcd for $C_4H_8F_2NO$ $[M + H]^+$ = 124.0574, found 124.0571.

3,3-Difluoro-4-hydroxypyrrolidin-2-one (7). A mixture of *tert*-butyl *N*-(2-oxoethyl)carbamate (53.0 g, 333 mmol), indium powder (40.1 g, 350 mmol, 1.05 equiv), and ethyl bromodifluoroacetate (45.8 mL, 350 mmol, 1.05 equiv) in THF (800 mL) was heated to 55 °C for 16 h. After being cooled to ambient temperature, the mixture was quenched by the addition of satd aq NH_4Cl solution. Most solvents were removed under reduced pressure. The residue was diluted with 1 N aq HCl solution and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford ethyl 4-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-hydroxybutanoate **6** (70.0 g, 333 mmol) as a dark amber oil which was used without further purification.

The crude ethyl 4-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-hydroxybutanoate **6** (70.0 g, 333 mmol) was dissolved in 200 mL of DCM. Trifluoroacetic acid (126 mL, 1.66 mol, 5.00 equiv) was added. The mixture was stirred at ambient temperature for 2 h and concentrated under reduced pressure. The residue was dissolved in acetonitrile and concentrated to dryness. The crude intermediate (4-ethoxy-3,3-difluoro-2-hydroxy-4-oxobutyl)ammonium;2,2,2-trifluoroacetate was dissolved in 350 mL of acetonitrile. Triethylamine (234 mL, 1.66 mol, 5.00 equiv) was added. The mixture was stirred at ambient temperature for 16 h and then concentrated under reduced pressure. The residue was purified by flash chromatography (40% acetone in hexanes) to give 3,3-difluoro-4-hydroxypyrrolidin-2-one **7** (16.4 g, 120 mmol, 36% over three steps) as a yellow solid: mp 136−138 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 6.16 (d, *J* = 5.8 Hz, 1H), 4.33 (qd, *J* = 11.7, 5.9 Hz, 1H), 3.54−3.50 (m, 1H), 3.00 (dd, *J* = 10.0, 5.00 Hz, 1H); ^{19}F NMR (377 MHz, DMSO-d_6) δ −119.0 − −119.7 (d, *J* = 264.3 Hz), −125.5 − −126.2 (d, *J* = 264.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0 (t, *J* = 59.4 Hz), 113.5 (t, *J* = 506.2 Hz), 67.8 (q, *J* = 44.8 Hz), 44.5 (d, *J* = 8.1 Hz); HRMS (ESI) calcd for $C_4H_3F_2NNaO_2$ $[M + Na]^+$ = 160.0186, found 160.0183.

4,4-Difluoropyrrolidin-3-ol (8). 3,3-Difluoro-4-hydroxypyrrolidin-2-one **7** (0.700 g, 5.11 mmol) was dissolved in THF (20 mL). The mixture was purged with N_2 and cooled to 0 °C. Red-Al (60 mass %) in toluene (8.30 mL, 25.5 mmol, 5.00 equiv) was added dropwise. The mixture was stirred for 16 h while warming to ambient temperature. The mixture was cooled back to 0 °C and carefully quenched with solid $Na_2SO_4{\cdot}10H_2O$ until gas evolution ceased. Additional solid $Na_2SO_4{\cdot}10H_2O$ was added, and the mixture was

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J. Org. Chem. XXXX, XXX, XXX−XXX

stirred for 1 h and filtered over a pad of Celite. The cake was diluted with THF, stirred for 20 min, and filtered. This was repeated 2×. The combined filtrates were concentrated under reduced pressure. The crude material was purified by flash chromatography (0−10% methanol in dichloromethane) to afford 4,4-difluoropyrrolidin-3-ol **8** (0.420 g, 3.41 mmol, 67% yield) as light cream solid: mp 85.8−86.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14−4.11 (m, 1H), 3.36−3.16 (m, 3H), 3.00 (d, J = 12.5 Hz, 1H), 2.57−2.55 (bs, 2H); ^{19}F NMR (377 MHz, $CDCl_3$) δ −104.6 − −105.2 (d, J = 239.8 Hz), −121.0 to −121.6 (d, J = 239.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 126.9 (t, J = 508.4 Hz), 72.5 (dd, J = 50.6, 30.1 Hz), 52.7, 52.4 (d, J = 25.0 Hz); HRMS (ESI) calcd for $C_4H_8F_2NO$ $[M + H]^+$ = 124.05740, found 124.05739.

***tert*-Butyl *N*-Benzyl-*N*-(2-oxoethyl)carbamate (10).** To a solution of dimethyl sulfoxide (21.0 mL, 298.4 mmol) in dichloromethane (375 mL) at −78 °C was added dropwise 2 M oxalyl chloride solution in dichloromethane (74.6 mL, 149.2 mmol). The resulting solution was stirred at −78 °C for 20 min. To this mixture was then added a solution of *tert*-butyl *N*-benzyl-*N*-(2-hydroxyethyl)carbamate (25.0 g, 99.5 mmol) in dichloromethane (125 mL). The resulting solution was stirred at −78 °C for 2 h after the addition was completed. Then triethylamine (125 mL, 895.3 mmol) was added. Once the addition was completed, the reaction was allowed to slowly warm to 0 °C and allowed to stir at this temperature for 30 min. The reaction was quenched by addition of a 10% aq solution of citric acid. The resulting mixture was stirred for 15 min, and then the two phases were separated. The aqueous phase was extracted with additional dichloromethane. The combined organic phases were washed with 10% aq solution of citric acid, water, satd aq Na_2CO_3 solution, and brine, dried over Na_2SO_4, and filtered, and the solvents were removed under reduced pressure. The crude was absorbed on silica gel and purified by flash chromatography (0−50% ethyl acetate in hexanes). The fractions containing desired product were collected and evaporated to dryness to obtain *tert*-butyl *N*-benzyl-*N*-(2-oxoethyl)-carbamate **10** (23.6 g, 90.9 mmol, 91%) as a light yellow oil. The product showed two sets of peaks as equilibrium of rotamers: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.49 and 9.42 (2 s, 1 H), 7.40−7.16 (m, 5H), 4.55 (s, 1H), 4.50 (s, 1H), 3.93 (s, 1H), 3.78 (s, 1H), 1.49 and 1.47 (2 s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.8, 154.8 and 154.4, 136.3 and 136.1, 127.7, 127.1, 126.7, 126.5, 80.0, 55.4, 51.0 and 50.5, 27.3, and 27.2; HRMS (m/z) calcd for $C_{14}H_{19}NNaO_3$, $[M + Na]^+$ = 272.1263, found 272.1258.

Ethyl 4-[Benzyl(*tert*-butoxycarbonyl)amino]-2,2-difluoro-3-hydroxy-butanoate (11). To a suspension of chlorotris-(triphenylphosphine)rhodium(I) (4.50 g, 5.00 mmol) in acetonitrile (353 mL) were added *tert*-butyl *N*-benzyl-*N*-(2-oxoethyl)carbamate (25 g, 100.3 mmol) and ethyl 2-bromo-2,2-difluoroacetate (48.3 mL, 401.1 mmol). The resulting mixture was cooled to −30 °C, and diethylzinc (377 mL, 401 mmol, 1.0 M in hexane) was added to the mixture over a period of 45 min (no exotherm was observed). The reaction temperature was maintained between −30 and −20 °C during the addition. The reaction was then allowed to slowly warm from −20 to 0 °C and was kept at 0 °C for 30 min. The reaction was quenched (at 0 °C) by addition of a 20% aq citric acid solution and diluted with ethyl acetate. The resulting biphasic solution was stirred for 30 min. The two phases were separated, and the aqueous phase was extracted with additional ethyl acetate. The combined organic phases were washed with 20% aq citric acid solution, 2 N aq NaOH solution, satd NH_4Cl, and brine, dried over Na_2SO_4, and filtered, and the solvents were removed under reduced pressure. The crude was dried under high vacuum to afford crude ethyl 4-[benzyl(*tert*-butoxycarbonyl)-amino]-2,2-difluoro-3-hydroxy-butanoate **11** (37.4 g, 100 mmol, in quantitative yield) as a brown oil. This crude was used without further purification on the next step. A small amount of the sample was purified by flash chromatography (0−30% ethyl acetate in hexanes) to obtain pure product (a colorless oil) for analytical data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43−7.21 (5H, m), 4.86 (1H, broad s), 4.56 (1H, d, J = 15 Hz), 4.42 (1H, d, J = 16.5 Hz), 4.36 (2H, q, J = 7 Hz),4.26−4.15 (1H, m), 3.83 (1H, dd, J = 15, 9.5 Hz), 3.33 (1H, d, J = 15 Hz), 1.49 (9H, s), 1.37 (3H, t, J = 7 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ − 113.19 (d, J = 261.79 Hz), −125.08 (d, J = 262.26 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1 (t, J = 32.5 Hz), 157.4, 136.3, 127.7, 126.6, 126.3, 113.0 (t, J = 260.5 Hz), 80.6, 70.8 (t, J = 27.8 Hz), 62.0, 51.5, 46.4, 27.3, 12.9; HRMS (m/z) calcd for $C_{18}H_{25}F_2NNaO_5$ $[M + Na]^+$ = 396.1598, found 396.1603.

1-Benzyl-3,3-difluoro-4-hydroxypyrrolidin-2-one (12). Crude ethyl 4-[benzyl(*tert*-butoxycarbonyl)amino]-2,2-difluoro-3-hydroxybutanoate (35.2 g, 94.3 mmol) was dissolved in 2-propanol (53 mL) and was added to a solution of hydrochloric acid (176 mL, 4.99 M in 2-propanol) at room temperature. The resulting solution was stirred for 1 h at room temperature. The solvents were then evaporated to dryness. The resulting solid was cooled to 0 °C and suspended in ethyl acetate (300 mL). Saturated aq Na_2CO_3 (200 mL) was added, and the resulting biphasic mixture was vigorously stirred (keeping the pH > 9) for 40 min at 0 °C. The two phases were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness to give the desired product together with triphenylphosphine oxide. The crude was dissolved in ethyl acetate and passed through a silica gel pad (eluent: 100% ethyl acetate) to obtain 1-benzyl-3,3-difluoro-4-hydroxy-pyrrolidin-2-one (18.6 g, 82 mmol, 88%) as a light brown solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.39−7.30 (3H, m), 7.23 (2H, d, J = 7.2 Hz), 6.22 (1H, d, J = 5.7 Hz), 4.57 (1H, d, J = 14.8 Hz), 4.38 (1H, d, J = 14.8 Hz), 4.43−4.33 (1H, m), 3.56 (1H, dd, J = 10.4, 6.7 Hz), 3.04 (1H, dd, J = 10.4, 4.4 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ −116.61 (d, J = 274.0 Hz), −126.95 (d, J = 273.5 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.4 (t, J = 30.4 Hz), 134.6, 128.2, 127.25, 127.21, 115.37 (dd, J = 254.9, 250.9 Hz), 65.5 (dd, J = 27.3, 17.5 Hz), 48.6 (d, J = 6.0 Hz), 45.6; HRMS (m/z) calcd for $C_{11}H_{11}F_2NNaO_2$ $[M + Na]^+$ = 250.0656, found 250.0648.

1-Benzyl-3,3-difluoro-4,4-dihydroxypyrrolidine-2-one (13). To a solution of 1-benzyl-3,3-difluoro-4-hydroxypyrrolidin-2-one (1.00 g, 4.40 mmol) in acetonitrile (20 mL) were added potassium 2-iodo-5-methylbenzenesulfonate (75 mg, 0.20 mmol) and potassium peroxymonosulfate (2.65 g, 8.80 mmol). The resulting mixture was heated to reflux at 90 °C for 16 h. The reaction was diluted with ethyl acetate, and the precipitated solid was filtered through a Celite pad and washed with ethyl acetate. The filtrate was passed to a separatory funnel and washed with satd aq $Na_2S_2O_3$ solution, satd aq $NaHCO_3$ solution, and brine. The organic phase was separated, dried over Na_2SO_4, and filtered, and the solvents were removed under reduced pressure. The crude was purified by flash chromatography (0 to 60% hexanes in acetone) to afford 1-benzyl-3,3-difluoro-4,4-dihydroxypyrrolidine-2-one **13** (740 mg, 3.30 mmol, 75%) as a white solid: mp 128−129 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.43−7.30 (3H, m), 7.23 (2H, d, J = 7.3 Hz), 7.17 (2H, s), 4.49 (2H, s), 3.29 (2H, s); ^{19}F NMR (DMSO-d_6, 470 MHz) δ −126.9 (s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.8 (t, J = 29.7 Hz), 134.6, 128.2, 127.14, 127.10, 112.2 (t, J = 256.8 Hz), 91.0 (t, J = 20.8 Hz), 54.4, 45.2; HRMS (m/z) calcd for $C_{11}H_{12}F_2NO_3$, $[M + H]^+$ = 244.0785, found 244.0786.

(4*R*)-1-Benzyl-3,3-difluoro-4-hydroxypyrrolidin-2-one (14). A mixture of (1*R*,2*R*)-(−)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (0.20 g, 0.50 mmol) and dichloro-(pentanemethylcyclopentadienyl)iridium(III) dimer (0.22 g, 0.30 mmol) in ethyl acetate (15 mL) and water (60 mL) was vigorously stirred at 40 °C under nitrogen for 30 min. The resulting bright orange mixture was cooled to room temperature. Sodium formate (18.0 g, 270 mmol) was added, and the reaction mixture turned black. After 10 min, the reaction mixture turned yellow-orange. 1-Benzyl-3,3-difluoro-4,4-dihydroxypyrrolidine-2-one (1.50 g, 6.70 mmol) was then added in one portion. The mixture turned purple and then back to yellow-orange again. After 30 min, the reaction mixture was diluted with ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, and filtered, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography (0−60% hexanes in acetone to afford (4*R*)-1-benzyl-3,3-difluoro-4-hydroxypyrrolidin-2-one **14** (1.40 g, 6.10 mmol, 91%) as a light brown solid in a 99 (t_R = 0.86 min): 1 (t_R = 0.78 min) ratio with the other possible enantiomer

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J. Org. Chem. XXXX, XXX, XXX−XXX

(98% ee) determined by chiral SFC (Chiralpak ID, 4.6 × 100 mm, 5 μm; 15−55% *i*PrOH in CO_2, 4 mL/min): $[\alpha]_D^{20}$ = +10.7 (*c* 1.0, EtOH); mp 71.3−71.6 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.35 (3H, m), 7.26−7.25 (2H, m), 4.56 (2H, s), 4.42−4.37 (1H, m), 3.55 (1H, dd, *J* = 10.7, 6.1 Hz), 3.18 (1H, ddd, *J* = 11, 3.5, 1.5 Hz), 2.68−2.61 (1H, broad s); ^{19}F NMR ($CDCl_3$, 470 MHz) δ − 116.64 (d, *J* = 273.5 Hz), −127.04 (d, *J* = 273.5 Hz);^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.5 (t, *J* = 30.7 Hz), 133.0, 128.0, 127.3, 127.2, 114.2 (t, *J* = 256.7 Hz), 66.2 (dd, *J* = 29.3, 18.7 Hz), 48.25 (d, *J* = 4.1 Hz), 46.2; HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{11}H_{11}F_2NNaO_2$ 250.0656, found 250.0650.

(3*R*)-1-Benzyl-4,4-difluoropyrrolidin-3-ol (14a). To a solution of (4*R*)-1-benzyl-3,3-difluoro-4-hydroxypyrrolidin-2-one **14** (1.00 g, 4.40 mmol) in tetrahydrofuran (10 mL) was added borane dimethyl sulfide complex (1.35 mL, 13.2 mmol) and the mixture stirred at room temperature for 20 min. The reaction mixture was then heated. After 3 h, the reaction was quenched by slow addition of ethanol (10 mL, CAUTION: gas generation) at 0 °C. The mixture was then refluxed overnight. The solvents were removed under reduced pressure. The crude was dissolved in 1 M hydrogen chloride methanol solution (20 mL) and 20% weight/weight activated carbon. The slurry was stirred for 1 h at room temperature and filtered over a membrane of polypropane (0.45 μm). The active carbon was then washed with MeOH. The solvents were removed under reduced pressure, and the solid was further dried under high vacuum to give (3*R*)-1-benzyl-4,4-difluoropyrrolidin-3-ol hydrochloride (920 mg, 4.31 mmol, 98% yield) as a white solid. A fraction of the HCl salt was liberated to generate the analytical data: mp 69.8−71.1 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.31 (5H, m), 4.24−4.22 (1H, m), 3.67 (2H,ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB}= 12.8 Hz), 3.09 (1H, dd, *J* = 10.5, 6 Hz), 3.04−2.91 (2H, m), 2.64 (1H, ddd, *J* = 10.1, 4.8, 2.5 Hz), 2.30 (1H, d, *J* = 5.2 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ − 100.53 (d, *J* = 236.4 Hz), −113.53 (d, *J* = 236.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.1, 128.9, 128.6, 127.6, 126.0 (t, *J* = 254.7 Hz), 73.35 (dd, *J* = 31.6, 18.9 Hz), 59.7, 59.6 (t, *J* = 28.4 Hz), 59.4 (d, *J* = 4.6 Hz); HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{11}H_{14}F_2NO$ 214.1043, found 214.1041.

(3*R*)-4,4-Difluoropyrrolidin-3-ol Hydrochloride (1). To a solution of (3*R*)-1-benzyl-4,4-difluoropyrrolidin-3-ol hydrochloride (1100 mg, 4.40 mmol) in ethanol (11 mL) was added palladium hydroxide on carbon (310 mg, 0.44 mmol, 20 mass %). The vessel was then closed and purged with hydrogen. The reaction was set under hydrogen atmosphere (80 psi) and allowed to stir at room temperature for 3 h. The reaction mixture was diluted with methanol and filtered, and the solvent was removed under reduced pressure. The crude was triturated with 2-propanol/hexane (1:1), filtered, dried, and collected. The solid was further dried under high vacuum overnight to obtain (3*R*)-4,4-difluoropyrrolidin-3-ol hydrochloride **1** (703 mg, 4.38 mmol, 99%): $[\alpha]_D^{20}$ = −12.0 (*c* 1.0, H_2O). All of the other analytical data were identical to previous analyses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00305.

^{1}H, ^{13}C, and ^{19}F NMR spectra for reported compounds and HPLC chromatograms for compounds **4** and **14** (PDF)

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Notes

The authors declare no competing financial interest.

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J. Org. Chem. XXXX, XXX, XXX−XXX