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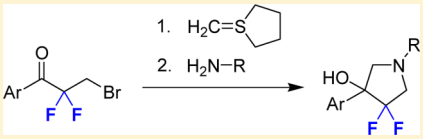
Synthesis of *gem*-Difluorinated Hydroxypyrrolidines

Oleg V. Fedorov, Marina I. Struchkova, and Alexander D. Dilman*

N. D. Zelinsky Institute of Organic Chemistry, 119991 Moscow, Leninsky prosp. 47, Russian Federation

Supporting Information

ABSTRACT: A method for the synthesis of 3-hydroxy-4,4-difluoropyrrolidines from α,α-difluoro-β-bromoketones is described. The reaction involves methylenation of the carbonyl group with tetrahydrothiophenium ylide followed by coupling with primary amines.

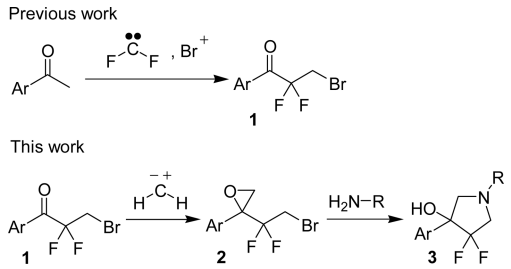


Compounds bearing a fluorinated fragment find wide applications in medicinal chemistry, since introduction of fluorine may favorably affect the biological properties of prospective drugs.[1] For example, the difluoromethylene unit can behave as bioisostere of ethereal oxygen[2] and can incur conformational changes.[3] Furthermore, when close to nitrogen or oxygen, two fluorine atoms notably modify the basicity and hydrogen bonding characteristics of amines[4] and alcohols.[5]

gem-Difluorinated pyrrolidines have been considered as valuable building blocks[6] and as target compounds[7] in medicinal research. They are typically synthesized either from acyclic precursors[8] or by deoxofluorination reaction from corresponding ketones.[9] Cycloaddition pathways have also been proposed.[10]

Recently, we demonstrated that α,α-difluoro-β-bromoketones **1** can be prepared in one convenient step from methyl ketones via a halogenative difluorohomologation process[11] (Scheme 1). These ketones were used as 1,3-dielectrophiles in

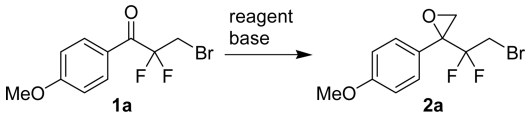
Scheme 1. Preparation and Use of Ketones 1



reactions with hydrazines, Grignard reagents, and nitro compounds furnishing various heterocycles.[11a,12] Herein we report that ketones **1** can be transformed into *gem*-difluorinated pyrrolidines **3** through the intermediacy of epoxides **2**.

At the beginning, we used the conventional Corey–Chaykovsky methylenation reaction using trimethylsulfoxonium iodide,[13] which has previously been applied to reactions with trifluoromethyl ketones.[14] *p*-Methoxyphenyl-substituted ketone **1a** was selected as a model substrate, and its methylenation was evaluated (Table 1). Conventional methylenation conditions using trimethylsulfoxonium iodide or triflate in combination with various bases provided epoxide **2a**

Table 1. Methylenation of Ketone 1a



reagent[a]	base (equiv)	solv	temp	yield of **2a**, %[b]
Me_3SO I (1.2)	NaH (1.4)	DMSO	−10 °C to rt	39
Me_3SO I (1.7)	*t*-BuOK (1.5)	DMSO	−10 °C to rt	50
Me_3SO OTf (1.7)	*t*-BuOK (1.5)	DMSO	−10 °C to rt	27
Me_3SO I (1.2)	DBU (1.2)	MeCN	60 °C	51
$MeTHT^+$ OTf^- (1.1)	LiHMDS (1.5)	THF	−78 °C to rt	66
$MeTHT^+$ OTf^- (1.1)	LDA (1.2)	THF	−78 °C to rt	69
$MeTHT^+$ OTf^- (1.1)	BuLi (1.1)	THF	−78 °C to rt	71

[a]$MeTHT^+$ OTf^- was generated from MeOTf and tetrahydrothiophene. [b]Isolated yield.

in moderate yields (entries 1–4). In these experiments, we noted that the order of addition is important, and ylide should be generated first followed by addition of the ketone. Otherwise, a byproduct was observed by GC-MS measurements, tentatively assigned as bromofluoroenone, presumably originating from base-mediated hydrogen fluoride elimination from the starting ketone. Then, we turned our attention to methylenation with sulfonium ylides. In the literature, it was mentioned that the iodide counterion in conventional sulfonium salt Me_3SI may cause nucleophilic demethylation of intermediate sulfonium species thus leading to the formation of $MeSCH_2$–addition products.[15] Therefore, we decided to focus on a sulfonium salt generated from tetrahydrothiophene (THT) and methyl triflate.[16] This salt was deprotonated at −78 °C followed by addition of the ketone. Use of *n*-butyl lithium as a base provided the best results, and epoxide **2a** was isolated in 71% yield. Under the optimized conditions a series of

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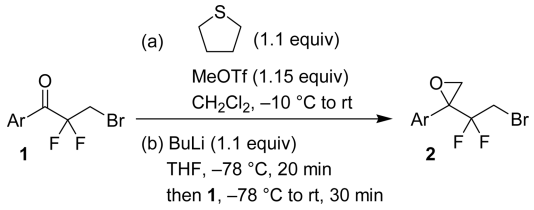
bromoketones **1b−e** were converted into corresponding epoxides in good yields (Table 2).

Table 2. Synthesis of Epoxides 2



Ar	1	2	yield of 2, %[a]
Ph	**1b**	**2b**	65
4-BrC_6H_4	**1c**	**2c**	89
4-ClC_6H_4	**1d**	**2d**	72
2-naphthyl	**1e**	**2e**	91

[a]Isolated yield.

Compounds **2** were involved in coupling with primary amines (Table 3). The reaction smoothly proceeded at elevated temperatures in dimethylformamide in the presence of potassium carbonate. A slight excess of amine (1.5 equiv) was needed for complete conversion of the starting epoxide. Products **3** were formed cleanly, and no byproducts were observed in crude material. The reaction proved to be quite general, and good yields of difluorinated pyrrolidines were achieved. Various nucleophiles were used, involving linear, branched, and sterically hindered amines.

Since reaction of epoxides **2** with amines is quite clean, we evaluated a one-pot protocol starting from a bromoketone. Thus, when ketone **1a** was methylenated with tetrahydrothiophenium ylide followed by a change of solvent and addition of allylamine, target product **3a** was isolated in 56% yield.

Concerning the mechanism of pyrrolidine formation, substrates **2** have two electrophilic sites: epoxide and C−Br bond. In an attempt to determine the site which is attacked first by an amine nucleophile, the reaction was performed at lower temperature (40 °C). However, even at low conversions of starting bromoepoxide, only the pyrrolidine product was detected (GCMS control). This experiment suggests that the formation of the pyrrolidine cycle proceeds faster than the reaction of bromoepoxide with the amine. It is likely that two fluorine atoms deactivate alkyl bromide toward intermolecular nucleophilic attack, whereas intramolecular displacement of bromine furnishing the five-membered ring could be quite facile.

In summary, an efficient two-step method for the synthesis of *gem*-difluorinated hydroxypyrrolidines is described. The use of ylide derived from tetrahydrothiophene is important for success in carbonyl group methylenation. The coupling of intermediate bromoepoxides with amines is not sensitive to the nature of the amine thereby leading to diverse *N*-substituted pyrrolidines.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an argon atmosphere. Dimethylformamide (DMF) was distilled under vacuum from CaH_2 and stored over MS 4A. Dichloromethane was distilled from CaH_2 prior to use. Tetrahydrofuran was distilled from lithium aluminum hydride. High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and a time-of-flight (TOF) mass analyzer.[17] The measurements were done in a positive ion mode (interface capillary voltage −4500 V) or in a negative ion mode (3200 V); mass range from *m*/*z* 50 to *m*/*z* 3000. Column chromatography was carried out employing silica gel (230−400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or aq. $KMnO_4$ solution. Starting compounds **1a−d**[10] and **1e**[11] were obtained according to literature procedures.

Preparation of Epoxides 2a−e (General Procedure 1). In a Schlenk tube, methyl triflate (126 μL, 1.15 mmol, 1.15 equiv) was added dropwise by a syringe to a solution of tetrahydrothiophene (97 μL, 1.1 mmol, 1.1 equiv) in dichloromethane (1 mL) at −10 °C. The mixture was allowed to warm to room temperature over 40 min. Then, all volatiles were evaporated under vacuum, the tube was filled with argon followed by addition of THF (1 mL). The mixture was cooled to −78 °C, and a solution of *n*-BuLi (500 μL of 2.2 M solution, 1.1 mmol, 1.1 equiv) was added dropwise, and the mixture was stirred for 20 min at −78 °C. A solution of ketone **1a−e** (1 mmol, 1 equiv) in THF (0.5 mL) was added. The mixture was stirred for 20 min at −78 °C and then was allowed to warm to room temperature over 30 min. For the workup, all volatiles were evaporated under vacuum, and the residue was washed with hexane (3 × 5 mL). The combined hexane layers were filtered through a thin layer of silica gel and concentrated under vacuum, and the residue was purified by flash chromatography on silica gel.

2-(2-Bromo-1,1-difluoroethyl)-2-(4-methoxyphenyl)oxirane ***(2a)***. Yield 209 mg (71%). Colorless oil. R_f 0.25 (hexane/EtOAc, 6/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.47 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H), 3.64−3.37 (m, 3H), 2.88 (ddd, *J* = 5.4, 3.2, 1.1 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 160.5, 129.4, 125.2, 117.9 (dd, *J* = 249.8, 247.3 Hz), 114.1, 59.4 (dd, *J* = 32.1, 27.0 Hz), 55.5, 51.3 (dd, *J* = 5.8, 2.4 Hz), 29.7 (t, *J* = 30.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −108.2 (ddd, *J* = 249.5, 18.0, 11.7 Hz), −110.9 (ddd, *J* = 249.5, 16.9, 8.7 Hz). Anal. calcd for $C_{11}H_{11}BrF_2O_2$ (293.11): C, 45.08; H, 3.78. Found: C, 45.11; H, 3.63.

2-(2-Bromo-1,1-difluoroethyl)-2-phenyloxirane ***(2b)***. Yield 172 mg (65%). Colorless oil. R_f 0.31 (hexane/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.67−7.54 (m, 2H), 7.48−7.36 (m, 3H), 3.68−3.41 (m, 3H), 2.89 (ddd, *J* = 5.3, 2.8, 1.0 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 133.1 (d, *J* = 2.3 Hz), 129.3, 128.6, 127.8, 117.7 (dd, *J* = 249.8, 247.0 Hz), 59.6 (dd, *J* = 32.1, 26.8 Hz), 50.1 (dd, *J* = 5.7, 2.3 Hz), 29.6 (t, *J* = 30.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −107.4 (ddd, *J* = 249.8, 18.8, 10.6 Hz), −110.5 (ddd, *J* = 249.8, 18.0, 8.0 Hz). Anal. calcd for $C_{10}H_9BrF_2O$ (263.08): C, 45.65; H, 3.45. Found: C, 45.69; H, 3.43.

2-(2-Bromo-1,1-difluoroethyl)-2-(4-bromophenyl)oxirane ***(2c)***. Yield 306 mg (89%). Colorless oil. R_f 0.34 (hexane/EtOAc, 6/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.54 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 3.65−3.33 (m, 3H), 2.86 (dd, *J* = 4.9, 2.7 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 132.3 (d, *J* = 2.0 Hz), 132.0, 129.6, 123.9, 117.7 (dd, *J* = 264.2, 234.6 Hz), 59.4 (dd, *J* = 33.3, 26.5 Hz), 51.3 (dd, *J* = 6.1, 2.1 Hz), 29.3 (t, *J* = 30.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −106.8 (ddd, *J* = 252.0, 18.0, 11.1 Hz), −110.5 (ddd, *J* = 252.0, 17.3, 9.8 Hz). Anal. calcd for $C_{10}H_8Br_2F_2O$ (341.98): C, 35.12; H, 2.36. Found: C, 35.21; H, 2.40.

2-(2-Bromo-1,1-difluoroethyl)-2-(4-chlorophenyl)oxirane ***(2d)***. Yield 215 mg (72%). Colorless oil. R_f 0.28 (hexane/EtOAc, 7/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.50 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 3.67−3.33 (m, 2H), 2.87 (dd, *J* = 5.5, 3.1 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 135.6, 131.7 (d, *J* = 2.2 Hz), 129.3 (d, *J* = 1.3 Hz), 129.1, 117.7 (dd, *J* = 250.3, 246.8 Hz), 59.3 (dd, *J* = 32.6, 27.1 Hz), 51.3 (dd, *J* = 6.0, 2.3 Hz), 29.3 (dd, *J* = 31.2, 30.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −106.8 (ddd, *J* = 251.4, 18.1, 10.9 Hz), −110.1 (ddd, *J* = 251.4, 17.2, 8.8 Hz). Anal. calcd for $C_{10}H_8BrClF_2O$ (297.52): C, 40.37; H, 2.71. Found: C, 40.41; H, 2.58.

2-(2-Bromo-1,1-difluoroethyl)-2-(naphthalen-2-yl)oxirane ***(2e)***. Yield 284 mg (91%). Colorless oil. R_f 0.28 (hexane/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.18 (s, 1H), 8.03−7.87 (m, 3H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.69−7.55 (m, 2H), 3.81−3.48 (m, 3H), 3.03 (dd, *J* = 4.8, 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 133.4, 132.7, 130.4 (d, *J* = 1.9 Hz), 128.4, 128.1, 127.7, 127.4, 126.9, 126.6,

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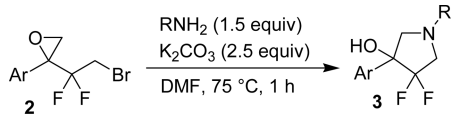
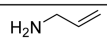
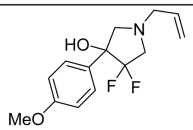
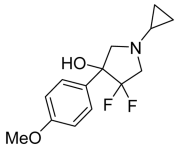
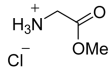
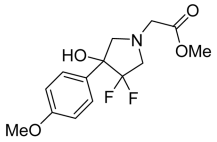
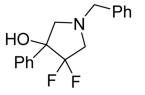
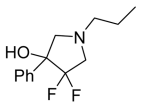
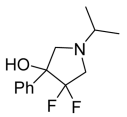
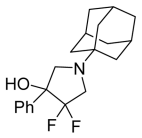
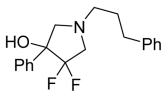
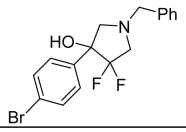
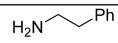
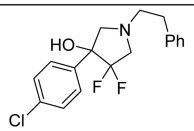
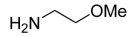
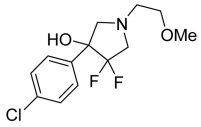
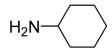
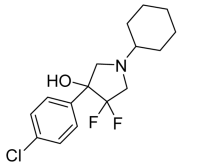
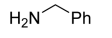
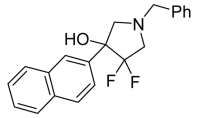
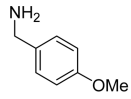
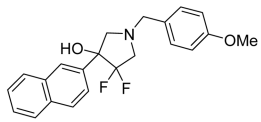
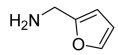
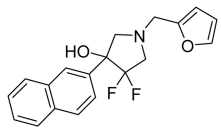
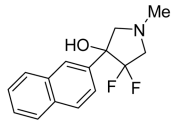
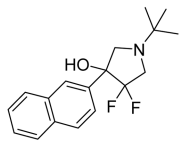
Table 3. Synthesis of Pyrrolidines 3



Substrates		Product		Yield of 3, %[a]
2a			**3a**	89
			**3b**	83
			**3c**	51
2b			**3d**	95
			**3e**	84
			**3f**	81
			**3g**	90
			**3h**	83
2c			**3i**	81
2d			**3j**	87
			**3k**	85
			**3l**	80
2e			**3m**	90
			**3n**	85
			**3o**	98
			**3p**	81
			**3q**	96

[a]Isolated yield.

124.7 (d, J = 1.5 Hz), 117.8 (dd, J = 250.0, 247.1 Hz), 59.7 (dd, J = 32.2, 26.8 Hz), 51.1 (dd, J = 5.9, 2.1 Hz), 29.7 (t, J = 30.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −106.5 (dm, J = 249.7 Hz), −109.8 (dm, J = 249.7 Hz). Anal. calcd for $C_{14}H_{11}BrF_2O$ (313.14): C, 53.70; H, 3.54. Found: C, 53.79; H, 3.56.

Synthesis of Pyrrolidines 3 (General Procedure 2). The reaction tube with a screw cap was charged with epoxide **2** (0.5 mmol, 1 equiv), amine (0.75 mmol, 1.5 equiv), potassium carbonate (173 mg, 1.25 mmol, 2.5 equiv), and DMF (0.5 mL), and the mixture was stirred at 75 °C for 1 h. The mixture was cooled to room temperature, water (4 mL) was added, and the aqueous phase was extracted with ethyl acetate (3 × 4 mL). The combined organic layers were filtered through Na_2SO_4 and concentrated under vacuum, and the residue was purified by flash chromatography on silica gel.

1-Allyl-4,4-difluoro-3-(4-methoxyphenyl)pyrrolidin-3-ol (***3a***). Yield 120 mg (89%). White crystals. Mp 56−57 °C. R_f 0.30 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.46 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.89 (ddt, J = 16.7, 10.1, 6.4 Hz, 1H), 5.33−5.10 (m, 2H), 3.81 (s, 3H), 3.63−3.19 (m, 4H), 3.18−3.12 (m, 2H), 2.91 (ddd, J = 22.5, 11.7, 7.2 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 159.7, 134.3, 128.2, 128.1, 126.3 (dd, J = 263.7, 253.9 Hz), 118.4, 113.7, 79.3 (dd, J = 26.3, 19.7 Hz), 62.7 (d, J = 2.3 Hz), 59.4 (t, J = 28.4 Hz), 58.6, 55.3. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −98.2 (dt, J = 230.9, 22.5 Hz), −119.5 (dm, J = 230.9 Hz). HRMS (ESI): calcd for $C_{14}H_{18}F_2NO_2$ [M + H] 270.1300; found 270.1296.

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*1-Cyclopropyl-4,4-difluoro-3-(4-methoxyphenyl)pyrrolidin-3-ol (**3b**).* Yield 112 mg (83%). Colorless oil. R_f 0.26 (hexane/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.45 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 3.81 (s, J = 23.1 Hz, 2H), 3.53 (dt, J = 20.2, 11.5 Hz, 1H), 3.41−3.00 (m, 2H), 2.06−1.87 (m, 1H), 0.61−0.38 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 159.7, 128.1, 126.4 (dd, J = 263.8, 254.0 Hz), 113.7, 79.3 (dd, J = 26.4, 19.5 Hz), 62.8 (d, J = 2.1 Hz), 59.6 (t, J = 27.9 Hz), 55.3, 35.6, 6.1, 6.0. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −98.7 (dt, J = 230.8, 21.2 Hz), −120.1 (d, J = 230.8 Hz). HRMS (ESI): calcd for $C_{14}H_{18}F_2NO_2$ [M + H] 270.1300; found 270.1299.

*Methyl 2-[3,3-Difluoro-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidin-1-yl]acetate (**3c**).* A modified General Procedure 2 was used: methyl glycine hydrochloride (157 mg, 1.25 mmol, 2.5 equiv), potassium carbonate (242 mg, 1.75 mmol, 3.5 equiv), reaction time 3 h. Yield 77 mg (51%). White crystals. Mp 76−77 °C. R_f 0.34 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.48 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.71−3.44 (m, 5H), 3.31−3.13 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 171.3, 159.7, 128.2, 127.8, 126.4 (dd, J = 262.6, 253.4 Hz), 113.7, 79.2 (dd, J = 26.3, 19.7 Hz), 62.3, 57.9 (t, J = 28.6 Hz), 55.4, 54.5, 52.0. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −101.5 (dt, J = 231.7, 21.3 Hz), −122.7 (d, J = 231.7 Hz). HRMS (ESI): calcd for $C_{14}H_{18}F_2NO_4$ [M + H] 302.1198; found 302.1200.

*1-Benzyl-4,4-difluoro-3-phenylpyrrolidin-3-ol (**3d**).* Yield 138 mg (95%). Yellow oil. R_f 0.35 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.61−7.49 (m, 2H), 7.47−7.28 (m, 8H), 3.88−3.75 (m, 2H), 3.45 (dt, J = 17.5, 11.7 Hz, 1H), 3.42 (broad s, 1H), 3.24 (dd, J = 10.2, 3.3 Hz, 1H), 3.16 (dd, J = 10.2, 3.5 Hz, 1H), 2.96 (ddd, J = 22.3, 11.7, 7.9 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 137.3, 136.0, 128.8, 128.7, 128.5, 128.3, 127.8, 126.9, 126.3 (dd, J = 263.7, 254.9 Hz), 79.7 (dd, J = 26.2, 19.6 Hz), 63.1 (d, J = 1.7 Hz), 59.9 (t, J = 28.6 Hz), 59.9. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −97.9 (dt, J = 231.2, 22.3 Hz), −118.2 (dt, J = 231.2, 7.9 Hz). HRMS (ESI): calcd for $C_{17}H_{18}F_2NO$ [M + H] 290.1351; found 290.1354.

*4,4-Difluoro-3-phenyl-1-propylpyrrolidin-3-ol (**3e**).* Yield 101 mg (84%). Colorless oil. R_f 0.27 (hexane/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.56 (d, J = 7.0 Hz, 2H), 7.45−7.31 (m, 3H), 3.63 (br s, 1H), 3.49 (dt, J = 18.1, 11.7 Hz, 1H), 3.20−3.11 (m, 1H), 2.88 (ddd, J = 22.9, 11.7, 7.7 Hz, 1H), 2.68−2.47 (m, 1H), 1.64−1.46 (m, 1H), 0.97 (t, J = 7.4 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 136.0, 128.5, 128.2, 126.8 (d, J = 1.6 Hz), 126.3 (dd, J = 263.7, 254.4 Hz), 79.5 (dd, J = 26.3, 19.5 Hz), 63.2 (d, J = 2.4 Hz), 60.1 (t, J = 28.2 Hz), 57.7, 21.2, 11.8. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −97.8 (dt, J = 231.0, 22.9 Hz), −118.7 (dt, J = 231.0, 7.7 Hz). HRMS (ESI): calcd for $C_{13}H_{18}F_2NO$ [M + H] 242.1351; found 242.1358.

*4,4-Difluoro-1-isopropyl-3-phenylpyrrolidin-3-ol (**3f**).* Yield 98 mg (81%). White crystals. Mp 29−30 °C. R_f 0.26 (hexane/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.57 (d, J = 6.7 Hz, 2H), 7.48−7.30 (m, 3H), 3.72 (br s, 1H), 3.50 (dt, J = 19.3, 11.6 Hz, 1H), 3.14−3.29 (m, 2H), 2.98 (ddd, J = 23.4, 11.6, 6.9 Hz, 1H), 2.73 (sept, J = 6.2 Hz, 1H), 1.13 (dd, J = 5.9, 3.1 Hz, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 136.0, 128.4, 128.2, 126.9 (d, J = 1.5 Hz), 126.3 (dd, J = 263.6, 253.6 Hz), 79.1 (dd, J = 26.3, 19.5 Hz), 60.2 (d, J = 2.5 Hz), 57.6 (t, J = 28.4 Hz), 53.6, 20.5 (d, J = 1.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −97.9 (dt, J = 230.8, 23.4 Hz), −119.3 (dt, J = 230.8, 6.9 Hz). HRMS (ESI): calcd for $C_{13}H_{18}F_2NO$ [M + H] 242.1351; found 242.1358.

*1-(1-Adamantyl)-4,4-difluoro-3-phenylpyrrolidin-3-ol (**3g**).* A modified workup was used: the reaction mixture was filtered from precipitate, and the precipitate was washed with water and ethyl acetate (3 × 5 mL). Then, a combined biphasic mixture was extracted with methyl *tert*-butyl ether (4 × 5 mL). The combined organic layers were filtered through Na_2SO_4 and evaporated to give a crystalline white substance. The crude product was washed with cold hexane (5 × 5 mL) and a cold hexane/methyl *tert*-butyl ether mixture (1/1, 2 × 5 mL) to give 150 mg (yield 90%) of compound **3g** as a white powder. Mp 107−108 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.57 (d, J = 7.0 Hz, 2H), 7.51−7.30 (m, 3H), 3.66 (br s, 1H), 3.50−3.04 (m, 4H), 2.13 (s, 3H), 1.94−1.49 (m, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 135.9, 128.5, 128.2, 127.0 (d, J = 1.6 Hz), 126.3 (dd, J = 263.6, 253.2 Hz), 78.6 (dd, J = 26.3, 19.4 Hz), 54.1 (d, J = 2.5 Hz), 52.9, 51.5 (dd, J = 29.2, 27.9 Hz), 38.9, 36.8, 29.4. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −99.5 (dt, J = 228.6, 22.4 Hz), −120.9 (dm, J = 228.6 Hz). HRMS (ESI): calcd for $C_{20}H_{26}F_2NO$ [M + H] 334.1977; found 334.1972.

*4,4-Difluoro-3-phenyl-1-(3-phenylpropyl)pyrrolidin-3-ol (**3h**).* Yield 131 mg (83%). Colorless oil. R_f 0.24 (hexane/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.63−7.51 (m, 2H), 7.47−7.28 (m, 5H), 7.28−7.16 (m, 3H), 3.49 (s, 2H), 3.49 (dt, J = 18.5, 11.6 Hz, 2H), 3.23−3.11 (m, 2H), 2.90 (ddd, J = 22.7, 11.6, 7.5 Hz, 1H), 2.77−2.55 (m, 4H), 1.95−1.83 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 141.7, 136.0, 128.5, 128.5, 128.5, 128.3, 126.8, 126.2 (dd, J = 263.9, 254.4 Hz), 126.1, 79.5 (dd, J = 26.3, 19.5 Hz), 63.2 (d, J = 2.3 Hz), 59.9 (t, J = 28.3 Hz), 55.2, 33.5, 29.5. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −97.9 (dt, J = 231.1, 22.7 Hz), −118.7 (dm, J = 231.1 Hz). HRMS (ESI): calcd for $C_{19}H_{22}F_2NO$ [M + H] 318.1664; found 318.1663.

*1-Benzyl-3-(4-bromophenyl)-4,4-difluoropyrrolidin-3-ol (**3i**).* Yield 150 mg (81%). White crystals. Mp 65−66 °C. R_f 0.31 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.58−7.46 (m, 2H), 7.46−7.39 (m, 2H), 7.39−7.28 (m, 5H), 3.86−3.71 (m, 2H), 3.52−3.30 (m, 2H), 3.17 (dd, J = 10.1, 3.1 Hz, 1H), 3.09 (dd, J = 10.1, 3.3 Hz, 1H), 2.96 (ddd, J = 21.9, 11.6, 8.3 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 137.1, 135.1, 131.4, 128.8, 128.7, 128.7 (d, J = 1.5 Hz), 127.8, 126.0 (dd, J = 263.8, 255.3 Hz), 122.8, 79.4 (dd, J = 25.9, 19.7 Hz), 63.1 (d, J = 1.6 Hz), 59.8 (t, J = 28.6 Hz), 59.7. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −98.0 (dt, J = 231.5, 21.9 Hz), −117.7 (dt, J = 231.5, 9.1 Hz). HRMS (ESI): calcd for $C_{17}H_{17}BrF_2NO$ [M + H] 368.0456, 370.0436; found 368.0455, 370.0436.

*3-(4-Chlorophenyl)-4,4-difluoro-1-phenethylpyrrolidin-3-ol (**3j**).* Yield 147 mg (87%). White crystals. Mp 105−106 °C. R_f 0.30 (hexane/EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.43 (d, J = 8.4 Hz, 2H), 7.35−7.24 (m, 4H), 7.24−7.13 (m, 3H), 3.60−3.30 (m, 2H), 3.19−3.03 (m, 2H), 3.02−2.70 (m, 5H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 139.5, 134.5, 134.5, 128.7, 128.4, 128.4, 128.4, 126.5, 126.0 (dd, J = 263.7, 255.0 Hz), 79.2 (dd, J = 25.9, 19.7 Hz), 63.2 (d, J = 1.7 Hz), 59.9 (t, J = 28.4 Hz), 57.0, 34.6. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −98.3 (dt, J = 231.2, 19.8 Hz), −118.1 (dt, J = 231.2, 9.4 Hz). HRMS (ESI): calcd for $C_{18}H_{19}ClF_2NO$ [M + H] 338.1118; found 338.1116.

*3-(4-Chlorophenyl)-4,4-difluoro-1-(2-methoxyethyl)pyrrolidin-3-ol (**3k**).* Yield 124 mg (85%). Colorless oil. R_f 0.26 (hexane/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.48 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 3.76 (br s, 1H), 3.63−3.43 (m, 3H), 3.34 (s, 3H), 3.27−3.12 (m, 2H), 2.98 (ddd, J = 22.5, 11.7, 7.5 Hz, 1H), 2.89−2.73 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 134.5, 134.5, 128.4, 128.4, 126.2 (dd, J = 263.8, 254.2 Hz), 79.1 (dd, J = 26.1, 19.7 Hz), 71.1, 63.6 (d, J = 2.2 Hz), 60.2 (t, J = 28.4 Hz), 59.0, 54.8. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −98.4 (dt, J = 231.4, 22.5 Hz), −119.3 (dt, J = 231.4, 10.6 Hz). HRMS (ESI): calcd for $C_{13}H_{17}ClF_2NO_2$ [M + H] 292.0910; found 292.0909.

*3-(4-Chlorophenyl)-1-cyclohexyl-4,4-difluoropyrrolidin-3-ol (**3l**).* Yield 127 mg (80%). White crystals. Mp 104−105 °C. R_f 0.31 (hexane/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.50 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 3.70 (br s, 1H), 3.48 (dt, J = 18.5, 11.8 Hz, 1H), 3.23−3.08 (m, 2H), 2.97 (ddd, J = 23.6, 11.8, 7.4 Hz, 1H), 2.35 (s, 1H), 1.97−1.69 (m, 4H), 1.64 (s, 1H), 1.41−1.14 (m, 5H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 134.5, 128.4 (d, J = 1.9 Hz), 128.4, 126.0 (dd, J = 263.6, 253.7 Hz), 78.7 (dd, J = 26.1, 19.7 Hz), 61.7, 60.0 (d, J = 2.2 Hz), 57.6 (t, J = 28.3 Hz), 30.9, 30.7, 26.0, 24.7 (d, J = 1.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −98.0 (dt, J = 230.6, 23.6 Hz), −119.3 (dt, J = 230.6, 7.4 Hz). HRMS (ESI): calcd for $C_{16}H_{21}ClF_2NO$ [M + H] 316.1274; found 316.1270.

*1-Benzyl-4,4-difluoro-3-(naphthalen-2-yl)pyrrolidin-3-ol (**3m**).* Yield 152 mg (90%). Orange oil. R_f 0.36 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.00 (s, 1H), 7.96−7.77 (m, 3H), 7.67 (d, J = 8.5 Hz, 1H), 7.59−7.45 (m, 2H), 7.45−7.28 (m, 5H), 3.98−3.77 (m, 2H), 3.64−3.15 (m, 4H), 3.15−2.86 (m, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 137.3, 133.5, 133.3, 133.0, 128.9, 128.8, 128.5, 127.9, 127.8, 127.7, 126.5, 126.4 (dd, J = 263.8, 255.1 Hz), 126.3, 126.1, 124.7 (d, J = 2.0 Hz), 79.9 (dd, J = 26.1, 19.6 Hz), 63.3 (d, J = 2.1 Hz), 60.1 (t, J = 28.6 Hz), 59.9. ^{19}F NMR (282 MHz, $CDCl_3$), δ:

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−97.9 (dt, J = 231.3, 19.4 Hz), −117.5 (d, J = 231.3 Hz). HRMS (ESI): calcd for $C_{21}H_{20}F_2NO$ [M + H] 340.1507; found 340.1517.

*4,4-Difluoro-1-(4-methoxybenzyl)-3-(naphthalen-2-yl)pyrrolidin-3-ol (**3n**).* Yield 157 mg (85%). White crystals. Mp. 111−112 °C. R_f 0.39 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.01 (s, 1H), 7.93−7.79 (m, 3H), 7.67 (d, J = 8.6 Hz, 1H), 7.54−7.44 (m, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 3.82 (s, 3H), 3.83−3.69 (m, 2H), 3.58−3.37 (m, 2H), 3.33 (dd, J = 10.1, 3.1 Hz, 1H), 3.21 (dd, J = 10.1, 3.5 Hz, 1H), 2.98 (ddd, J = 22.0, 11.6, 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 159.4, 133.6, 133.3, 133.1, 130.1, 129.3, 128.5, 127.9, 127.7, 126.5, 126.4 (dd, J = 262.5, 257.5 Hz), 126.3, 126.1, 124.7, 114.2, 79.9 (dd, J = 26.2, 19.4 Hz), 63.2, 59.9 (t, J = 28.7 Hz), 59.2, 55.4. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −97.7 (dt, J = 231.3, 22.0 Hz), −117.4 (dt, J = 231.3, 8.2 Hz). HRMS (ESI): calcd for $C_{22}H_{22}F_2NO_2$ [M + H] 370.1619; found 370.1603.

*4,4-Difluoro-1-(furan-2-ylmethyl)-3-(naphthalen-2-yl)pyrrolidin-3-ol (**3o**).* Yield 162 mg (98%). Colorless oil. R_f 0.30 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.02 (s, 1H), 7.93−7.80 (m, 3H), 7.67 (d, J = 8.7 Hz, 1H), 7.56−7.46 (m, 2H), 7.43 (s, 1H), 6.40−6.33 (m, 1H), 6.29 (d, J = 3.1 Hz, 1H), 3.83−3.93 (m, 2H), 3.63 (br s, 1H), 3.61−3.46 (m, 1H), 3.44 (dd, J = 10.3, 3.2 Hz, 1H), 3.26 (dd, J = 10.3, 3.5 Hz, 1H), 3.11 (ddd, J = 21.9, 11.6, 7.5 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 151.0, 142.6, 133.5, 133.3, 133.0, 128.5, 127.9, 127.7, 126.5, 126.4 (dd, J = 264.2, 254.4 Hz), 126.3, 126.1, 124.7, 110.4, 109.0, 79.9 (dd, J = 26.1, 19.5 Hz), 62.6, 59.0 (t, J = 28.7 Hz), 50.9. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −98.3 (dt, J = 231.5, 21.9 Hz), −118.3 (d, J = 231.5 Hz). HRMS (ESI): calcd for $C_{19}H_{18}F_2NO_2$ [M + H] 330.1300; found 330.1294.

*4,4-Difluoro-1-methyl-3-(naphthalen-2-yl)pyrrolidin-3-ol (**3p**).* Yield 106 mg (81%). White crystals. Mp 156−157 °C. R_f 0.29 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.00 (s, 1H), 7.94−7.79 (m, 3H), 7.65 (d, J = 8.6 Hz, 1H), 7.55−7.44 (m, 2H), 3.71−3.40 (m, 1H), 3.52 (dt, J = 17.1, 11.6 Hz, 1H), 3.31 (dd, J = 10.1, 3.1 Hz, 1H), 3.21 (dd, J = 10.1, 3.4 Hz, 1H), 2.91 (ddd, J = 22.0, 11.6, 8.3 Hz, 1H), 2.53 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 133.5, 133.3, 133.0, 128.5, 128.0, 127.7, 126.8 (dd, J = 264.0, 255.0 Hz), 126.6, 126.3, 126.1, 124.7, 80.5 (dd, J = 26.3, 19.4 Hz), 65.6 (d, J = 2.2 Hz), 62.1 (t, J = 28.2 Hz), 42.2. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −97.6 (dt, J = 231.8, 22.0 Hz), −117.64 (dt, J = 231.8, 7.8 Hz). HRMS (ESI): calcd for $C_{15}H_{16}F_2NO$ [M + H] 264.1194; found 264.1188.

*1-(tert-Butyl)-4,4-difluoro-3-(naphthalen-2-yl)pyrrolidin-3-ol (**3q**).* Yield 146 mg (96%). White crystals. Mp 75−76 °C. R_f 0.34 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.07 (s, 1H), 8.00−7.81 (m, 3H), 7.71 (d, J = 8.7 Hz, 1H), 7.55−7.42 (m, 2H), 3.75 (br s, 1H), 3.54−3.35 (m, 2H), 3.28−3.07 (m, 2H), 1.19 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 133.4, 133.3, 133.0, 128.5, 127.9, 127.7, 126.6 (dd, J = 263.7, 253.5 Hz), 126.5, 126.2, 124.7 (d, J = 1.8 Hz), 79.2 (dd, J = 26.1, 19.5 Hz), 56.2 (d, J = 2.3 Hz), 53.5 (t, J = 28.6), 52.6, 25.8. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −99.1 (dt, J = 229.6, 21.6 Hz), −119.8 (dm, J = 229.6 Hz). HRMS (ESI): calcd for $C_{18}H_{22}F_2NO$ [M + H] 306.1664; found 306.1664.

*One-Pot Synthesis of Compound **3a**.* In a Schlenk tube, methyl triflate (252 μL, 2.3 mmol) was added dropwise by a syringe to a solution of tetrahydrothiophene (194 μL, 2.2 mmol) in dichloromethane (2 mL) at −10 °C. The mixture was allowed to warm to room temperature over 40 min. Then, all volatiles were evaporated under vacuum, and the tube was filled with argon followed by addition of THF (2 mL). The mixture was cooled to −78 °C, a solution of *n*-BuLi (1.0 mL of 2.2 M solution, 2.2 mmol) was added dropwise, and the mixture was stirred for 20 min at −78 °C. A solution of ketone **1a** (558 mg, 2 mmol) in THF (1 mL) was added. The mixture was stirred for 20 min at −78 °C and then was allowed to warm to room temperature over 30 min. The solvent was evaporated under vacuum. The residue was dissolved in DMF (2 mL) followed by addition of allylamine (171 mg, 3 mmol) and potassium carbonate (552 mg, 4 mmol), and the mixture was stirred at 75 °C for 1 h. The mixture was cooled to room temperature, water (8 mL) was added, and the aqueous phase was extracted with ethyl acetate (3 × 8 mL). The combined organic layers were filtered through Na_2SO_4 and concentrated under vacuum, and the residue was purified by flash chromatography on silica gel affording 300 mg (56% yield) of compound **3a**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03033.

Copies of NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: adil25@mail.ru.

ORCID

Alexander D. Dilman: 0000-0001-8048-7223

Notes

The authors declare no competing financial interest.

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