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Synthesis of Small 3-Fluoro- and 3,3-Difluoropyrrolidines Using Azomethine Ylide Chemistry

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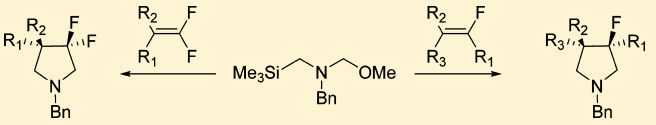
Supporting Information

ABSTRACT: Here, we report accessing small 3-fluoropyrrolidines and 3,3-difluoropyrrolidines through a 1,3-dipolar cycloaddition with a simple azomethine ylide and a variety of vinyl fluorides and vinyl difluorides. We demonstrate that vinyl fluorides within α,β-unsaturated, styrenyl and even enol ether systems can participate in the cycloaddition reaction. The vinyl fluorides are relatively easy to synthesize through a variety of methods, making the 3-fluoropyrrolidines very accessible.

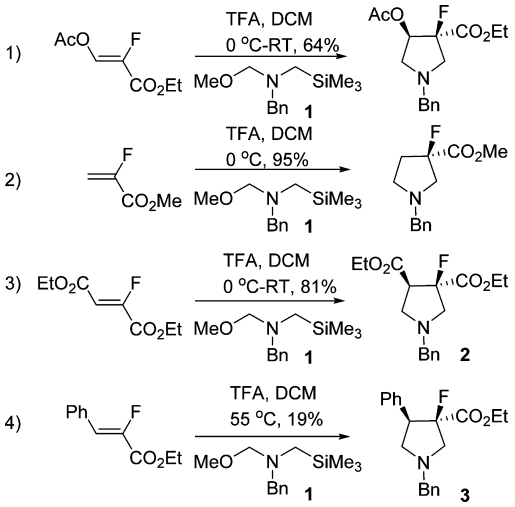


Replacing a hydrogen atom for a fluorine atom is very advantageous in medicinal chemistry and can have dramatic effects on enzyme binding, absorption, distribution, and metabolic profile of a compound while having minimal changes in size.[1] Because of pK_a changes, placement of a fluorine atom beta or gamma to a basic nitrogen has major effects on the lipophilicity and thereby the permeability, solubility, efflux, and safety profile of a compound.[2] For these reasons, efficient and scalable syntheses of small fluorinated aliphatic amines benefit drug discovery programs.

The most common way to synthesize fluoropyrrolidines and *gem*-difluoropyrrolidines is through deoxofluorination of the respective precursor pyrrolidinol or pyrrolidinone.[3] This approach often forms the corresponding vinyl fluoride as a side product, which can make purification difficult.[3b,c] Furthermore, there are limited cases reporting the synthesis of 4-substituted 3,3-difluoropyrrolidines in this manner, most likely due to steric hindrance.[4] The synthesis of 4-substituted 3,3-difluoropyrrolidnes usually proceeds through a carbonyl reduction of the lactam or imide precursor.[5] This approach requires building the difluorolactam or difluoroimide in a multistep sequence. There are numerous examples of generating 3,4-substituted pyrrolidines by reacting an electron-deficient alkene with azomethine ylides.[6] The ability to control the relative stereochemistry provided by the dipolarophile geometry through a concerted cycloaddition reaction is an attractive aspect to forming substituted pyrrolidines in this manner. However, there are only a few examples in the literature of using this reaction to generate simple fluoropyrrolidines[7] and almost none to generate *gem*-difluoropyrrolidines[8] despite the fact that vinyl fluorides should be reasonable substrates for the dipolar cycloaddition. We demonstrate, herein, that easily accessible vinyl fluorides and vinyl difluorides within α,β-unsaturated, styrenyl and even enol ether systems can undergo the cycloaddition reaction to give pharmaceutically relevant fluoropyrrolidines and further the scope of dipolarophiles used in the cycloaddition reaction.

To our knowledge, there are only two reported examples (Scheme 1, lines 1 and 2) of reacting a fluoroacrylate with the simple azomethine ylide precursor, *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl) methanamine (**1**).[7] These results suggest that any fluoroacrylate should be amenable to the

Scheme 1. Fluoroacrylates



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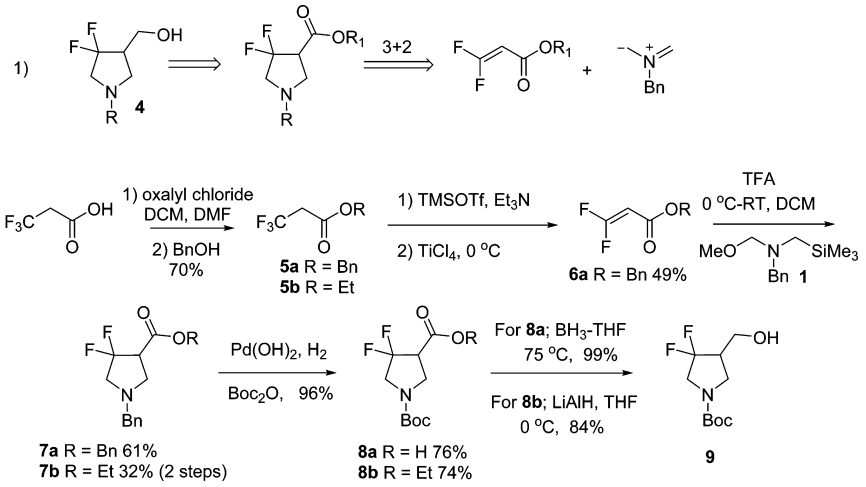
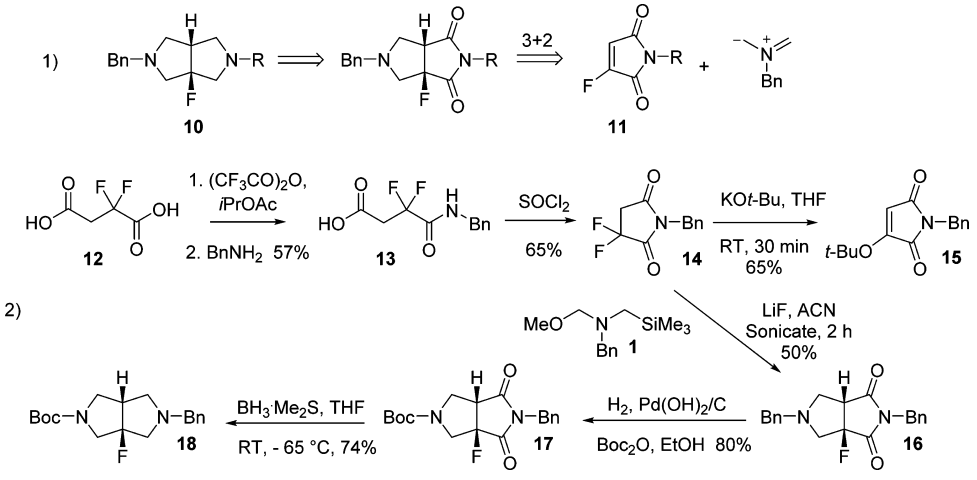
Scheme 2. Difluoroacrylate



Scheme 3. 3α-Fluoro-octahydropyrrolo[3,4-*c*]pyrrole



cycloaddition reaction. In our hands, we've used similar dipolarophiles such as diethylfluoro fumarate[9] (Scheme 1, line 3) and ethyl (*Z*)-2-fluoro-3-phenyl acrylate[10] (Scheme 1, line 4) to generate the corresponding fluoropyrrolidines **2**[11] and **3**, respectively. The challenge arises in synthesizing the desired fluoroacrylate.

To the best of our knowledge, there are no reports describing the use of simple difluoroacrylate esters in the 3 + 2 cycloaddition shown in Scheme 2 (line 1). We envisioned that the resulting 3,3-difluoropyrrolidine would allow access to an *N*-protected 4-hydroxymethyl-3,3-difluoropyrrolidine **4**. Starting with 3,3,3-trifluoropropionic acid (Scheme 2, line 2), the benzyl ester **5a** is made in 70% yield via the acid chloride. We found the method published by Shimada et al. to be a reliable process to generate the difluoroacrylate benzyl ester.[12] Treatment of benzyl ester **5a** with trimethylsilyl triflate generates the trimethylsilyl enol ether, which is then exposed to titanium tetrachloride effecting the elimination and creating the difluoroacrylate benzyl ester **6a** in 49% yield. Subjecting difluoroacrylate **6a** to the azomethine precursor, **1**, in dichloromethane with a catalytic amount of trifluoroacetic acid reveals the desired benzyl protected 4,4-difluoropyrrolidine-3-carboxylate benzyl ester **7a** in a modest 61% yield. A similar sequence can be applied to the commercially available 3,3,3-trifluoropropionic ethyl ester **5b** to generate 4,4-difluoropyrrolidine-3-carboxylate ethyl ester **7b** in 32% yield over the two steps.[13] The pyrrolidines **7a** and **7b** are fairly sensitive to base and can readily eliminate to unwanted pyrrole compounds. However, benzyl deprotection and pyrrolidine reprotection with a Boc group can be done in excellent yield using standard hydrogenolysis in the presence of Boc anhydride. For compound **7a**, this leads to the difluoropyrrolidine acid **8a**, which is reduced to the desired Boc-protected 3,3-difluoro-4-(hydroxymethyl)pyrrolidine **9** in 99% yield using borane−THF complex. For compound **7b**, hydrogenolysis leaves the ethyl ester intact (**8b**), which can be reduced to pyrrolidine **9** using lithium aluminum hydride in 84% yield.

One of the more elaborate systems we desired is 3α-fluoro-octahydropyrrolo[3,4-*c*]pyrrole (**10**) with orthogonal protecting groups (Scheme 3, line 1). We envisioned we could utilize 3-fluoromaleimide (**11**) in the 1,3-dipolar cycloaddition reaction. A very scalable synthesis of 3,3-difluoropyrrolidine published by Xu et al. proceeds through 3,3-difluoroimide (**14**).[5c] We speculated that a controlled HF elimination of 3,3-difluoroimide would generate the desired 3-fluoromaleimide. Following this route, 3,3-difluoroimide is made from 2,2-difluorosuccinic acid (**15**) in two steps (Scheme 3, line 2). Initial attempts to perform the selective HF elimination using potassium *t*-butoxide generated 3-*t*-butoxymaleimide (**15**) in 65% yield. Presumably, the desired elimination occurs;

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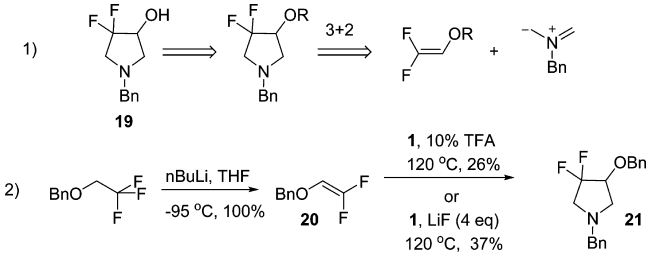
however, *t*-butoxide performs a subsequent Michael addition and eliminates fluoride ion. If this is true, we reasoned that we could trap the intermediate 3-fluoromaleimide with azomethine ylide if we can concomitantly promote the elimination and generation of the azomethine ylide using lithium fluoride. Treatment of a mixture containing 3,3-difluoroimide (**14**) and azomethine ylide precursor (**1**) in acetonitrile with lithium fluoride reveals the desired 3α-fluoro-tetraydropyrrolo imide system (**16**) in good yield. The benzyl group on the pyrrolidine can be selectively exchanged for a Boc group via hydrogenolysis conditions. The cyclic imide is reduced to the pyrrolidine using borane-dimethylsulfide to give our desired orthogonally protected 3α-fluoro-octahydropyrrolo[3,4-*c*]pyrrole (**18**) in excellent yield. Starting from 2,2-difluorosuccinic acid, a five-step sequence generates the complex [3.3.0] system in 11% overall yield.

In another instance, synthesis of 4,4-difluoropyrrolidin-3-ol (**19**), a close variant of the pyrrolidine (**9**), was desired. To utilize the 3 + 2 cycloaddition would require reacting the azomethine ylide with a difluoroenol ether (Scheme 4, line 1).

Scheme 4. Benzyl Difluoroenol Ether

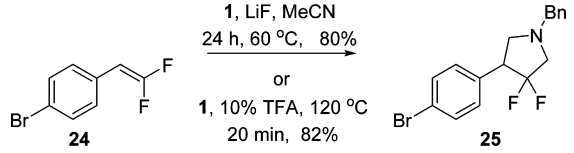


Simple difluoroenol ethers are commonly made by eliminating HF from protected trifluoroethanol.[14] Synthesis of benzyl difluoroenol ether (**20**) is done by treating trifluoroethylbenzyl ether with butyl lithium in THF (Scheme 4, line 2). Subjecting benzyl difluoroenol ether (**20**) to the azomethine ylide precursor (**1**) under TFA conditions yielded the desired difluoropyrrolidine (**21**) in 26%. Using lithium fluoride conditions to generate the azomethine ylide gave a modest improvement in yield.

We hypothesized that a more electron-deficient difluoroenol ether would improve the yield of the 3 + 2 reaction. To that end, we synthesized the tosyl difluoroenol ether (**22**) using the same HF elimination route (Scheme 5). Treatment of tosyl-protected trifluoroethanol with butyl lithium in THF generates the desired difluoroenol ether (**22**) in excellent yield. Reacting this material with the azomethine ylide precursor under TFA condition reveals the desired difluoropyrrolidine (**23**) in greater than 90% yield. This reaction works extremely well and can be carried out on 10 g scale. By comparison, using lithium fluoride conditions to generate the azomethine ylide only gave a 60% yield of the difluoropyrrolidine (**23**). The tosyl group is removed to reveal the difluoropyrroldinol (**19**) by treating compound **23** with magnesium metal in methanol or refluxing with Super-Hydride in THF.

While doing this work, we could only find one report of a difluorostyrenyl compound used in a 1,3-dipolar cycloaddition with an azomethine ylide.[8] The patent reports reacting *p*-bromo-(2,2-difluorovinyl)benzene (**24**) with lithium fluoride and the azomethine ylide precursor **1**, but gave no yield for the reaction. Under modified reaction conditions using 3 equiv of LiF and 4 equiv of azomethine precursor (**1**) in acetonitrile at 60 °C generates the desired difluoropyrrolidne (**25**) in 80% yield (Scheme 6). Running the reaction at 120 °C using 10% TFA instead of LiF generates the desired product in 82% yield.

Scheme 6. *p*-Bromodifluorostyrene



We tested a number of 2,2-difluorostyrenes synthesized using the difluoromethylsulfonyl-2-pyridine reagent developed by Hu and co-workers[15] and reacting with various benzaldehydes, as shown in Scheme 7. As shown in Table 1, having electron-

Scheme 7. Difluorostyrenes

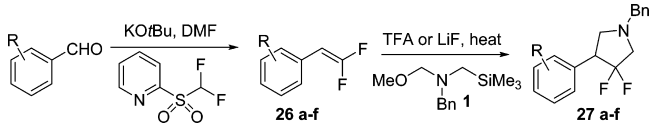
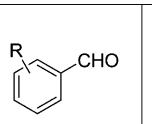
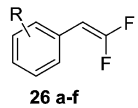
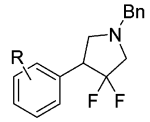
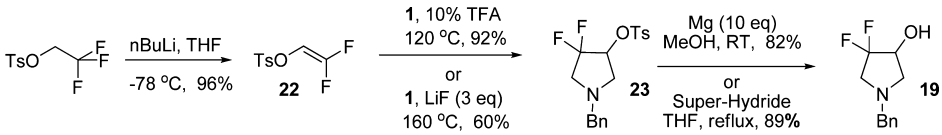


Table 1. Difluorostyrenes and 3,3-Difluoro-4-phenyl Pyrroldines

Entry		 26 a-f	 27 a-f
a	R = 2,4-diCl	78%	(LiF) 89%
b	R = 2,5-diCl	36%	(LiF) 84%
c	R = 3-NO_2	25%	(LiF) 76%, (TFA) 80%
d	R = 4-Me	48%	(LiF) 13%[a]
e	R = 4-MeO	86%	(LiF) 41%
f	R = 4-*t*Bu	61%	(LiF) 67%

[a]Low yield is due to the volatility of **26d**.

Scheme 5. Tosyl Difluoroenol Ether



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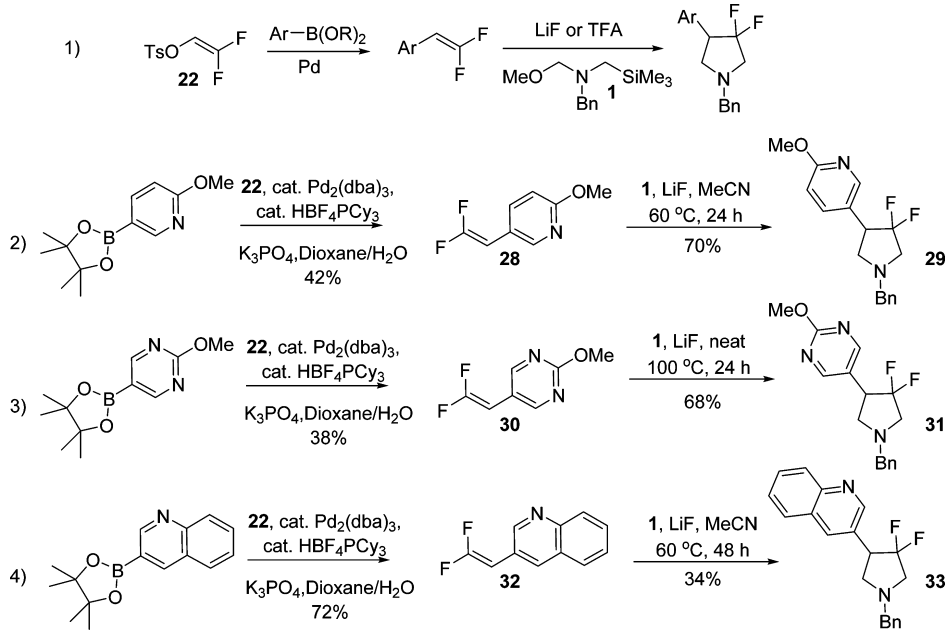
Scheme 8. Heterocyclic Difluorostyrenes



deficient groups on the benzene ring gives higher yields in the 3 + 2 cycloaddition reaction. The low yield in the *p*-tolyl system (entry d) is due to the difficulty in isolating the volatile *p*-methyl-(2,2-difluorovinyl)benzene. In general, all the difluorostyrenes participate in the cycloaddition reaction to give their respective *gem*-difluoropyrrolidines in moderate to good yields.

Another approach to making difluorostyrene compounds was shown by Gøgsig et. al.[16] utilizing the difluoroenol ether (**22**) previously described in a Suzuki coupling. We explored using this method to make heterocyclic difluorostyrenes and subjecting them to the 3 + 2 cycloaddition reaction (Scheme 8, line 1). Using the same coupling conditions, 2.5 mol % $Pd_2(dba)_3$ catalyst with 5 mol % HBF_4PCy_3 ligand and potassium phosphate base in a dioxane/water mixture gives moderate yields of the heterocyclic difluorostyrenes (Scheme 8, lines 2−4). Subjecting these to the LiF activating conditions to generate the azomethine ylide gives moderate to good yields of the desired *gem*-difluoropyrrolidines. In the case of the methoxypyrimidine (line 3), higher equivalents of LiF and azomethine ylide are needed to push the reaction. This route demonstrates the ease of accessing 4,4-difluoro-3-heteroaryl pyrrolidines starting from heteroaryl boronates and boronic acids.

In summary, we have shown that a variety of vinyl fluorides and vinyl difluorides can participate in a 1,3-dipolar cycloaddition with a simple azomethine ylide to generate novel 3-fluoropyrrolidines and 3,3-difluoropyrrolidines. The vinyl fluorides and vinyl difluorides can exist as α,β-unsaturated, styrenyl and even enol ether moieties. These can be readily prepared through a variety of methods, which gives easy and efficient access to structurally diverse fluoropyrrolidines.

EXPERIMENTAL SECTION

Silica gel chromatography purification was usually performed on Biotage or ISCO systems using prepacked cartridges. All ^{13}C NMR data reported are ^{1}H decoupled. All ^{19}F NMR data are ^{13}C decoupled. HRMS data were collected using a TOF method with an Atmospheric Pressure Chemical Ionization source.

Diethyl (3*R*,4*S*)-1-Benzyl-3-fluoropyrrolidine-3,4-dicarboxylate (2). To a colorless solution of diethyl but-2-ynedioate (5.0 g, 29.4 mmol) in DMF (450 mL) was added the solution of CsF (13.5 g, 88.1 mmol) and KHF_2 (3.24 g, 41.1 mmol) in H_2O (240 mL) slowly. The mixture was stirred at 80 °C for 3 h. The dark mixture was quenched with H_2O and extracted with Et_2O (200 mL × 3). The organic layers were washed with H_2O (100 mL) and brine (100 mL). The organic layers were dried over $MgSO_4$ and filtered. The organic layers were concentrated by flushing with N_2 through the organic layers overnight. The organic layers were concentrated in vacuum to give diethyl 2-fluorofumarate (2.36 g, 60.1%) as a yellow oil. ^{1}H NMR show roughly a 9:1 ratio of Z:E isomers. ^{1}H NMR (Z-isomer) (400 MHz, $CDCl_3$) δ ppm 6.30−6.38 (m, 1H), 4.24−4.37(m, 4H), 1.57−1.25 (m, 6H). This mixture of diethyl 2-fluorofumarate (2.34 g, 12.3 mmol) was diluted with dichloromethane (30 mL). To this was added *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (2.92 g, 12.3 mmol), and the mixture was cooled to 0 °C. To this mixture was added TFA (0.095 mL, 1.23 mmol), and the reaction was stirred at 0 °C for 30 min. The reaction mixture was then stirred at 25 °C for 48 h. The mixture was concentrated to give the crude product (6.35 g) as an orange residue. Silica gel chromatography (5:95 EtOAc:Heptanes) gave the desired product **2** as a clear oil (3.25 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.45−7.17 (m, 5H), 4.32 (q, J = 7.1 Hz, 2H), 4.26−4.09 (m, 2H), 3.84−3.63 (m, 3H), 3.39−3.25 (m, 1H), 3.16 (dd, J = 2.2, 8.8 Hz, 2H), 3.04−2.88 (m, 1H), 1.38−1.31 (m, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 169.3 (d, J = 27.1 Hz, 1C), 167.7 (d, J = 5.1 Hz, 1C), 138.0, 128.7 (s, 2C), 128.4 (s, 2C), 127.3, 99.1 (d, J = 198.8 Hz, 1C), 63.4 (d, J = 24.2 Hz, 1C), 62.3, 61.2, 59.8, 53.1, 52.2 (d, J = 22.0 Hz, 1C), 14.1, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −164.74 (s, 1 F); HRMS calculated for $C_{17}H_{22}FNO_4$ 323.1533, found 323.1537.

Ethyl (3*R*,4*R*)-1-Benzyl-3-fluoro-4-phenylpyrrolidine-3-carboxylate (3). To a mixture of acid-washed Zn (5.61 g, 85.7 mmol), CuCl (849 mg, 8.57 mmol), and 15 g of 4 Å molecular sieves in 125 mL of THF were added benzaldehyde (3.64 g, 34.3 mmol) and acetic anhydride (3.5 g, 34.3 mmol). The reaction was heated at 50 °C for 5 min under N_2. To this reaction mixture was added ethyl 2,2-dichloro-2-fluoroacetate (5 g, 28.57 mmol). The mixture was stirred at 80 °C for 16 h under N_2. The mixture was filtered through Celite and concentrated to give the crude product (23.4 g) as a yellow oil, which was purified by silica gel column chromatography (EtOAc in petroleum ether from 0% to 5%) to give ethyl (*Z*)-2-fluoro-3-phenyl acrylate (8.05 g, 145%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$)

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δ ppm 7.70−7.59 (m, 2H), 7.47−7.33 (m, 3H), 7.01−6.84 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H). To a solution of ethyl (Z)-2-fluoro-3-phenyl acrylate (6.85 g, 35.27 mmol) and N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (31.4 g, 106 mmol) in dichloromethane (150 mL) was added TFA (18 mL) at 0 °C. The mixture was stirred at 55 °C for 16 h. The mixture was concentrated to give the crude product (27 g), which was purified by prep-HPLC to give compound 3 (2.21 g, 19.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25−7.47 (m, 10 H), 4.26 (q, J = 7.09 Hz, 2 H), 3.84−3.99 (m, 1 H), 3.77−3.92 (m, 2 H), 3.49−3.63 (m, 1 H), 3.24−3.33 (m, 1 H), 3.14 (t, J = 9.40 Hz, 1 H), 3.08 (q, J = 12.30 Hz, 1 H), 1.28 (t, J = 7.09 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.1 (d, J = 27.9 Hz, 1C), 138.5, 134.7 (d, J = 3.1 Hz, 1C), 129.2 (d, J = 1.5 Hz, 2C), 128.7 (s, 2C), 128.4 (s, 2C), 128.3 (s, 2C), 127.5, 127.3, 99.9 (d, J = 199.5 Hz, 1C), 63.9 (d, J = 24.6 Hz, 1C), 62.0, 60.3, 57.8, 52.5 (d, J = 20.2 Hz, 1C), 14.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −161.11 (br. s., 1F); HRMS calculated for $C_{20}H_{22}FNO_2$ 327.1635, found 327.1638.

Benzyl 3,3,3-Trifluoropropanoate (5a). To a solution of 3,3,3-trifluoropropionic acid (1.76 g, 13.7 mmol) in dichloromethane (12.00 mL) was added oxalyl chloride (20 mmol, 1.80 mL), followed by DMF (0.10 mL). Gas evolution was observed while stirring was continued at rt for 2 h. Benzyl alcohol (1.78 g, 16.5 mmol, 1.70 mL) was added, and the reaction was heated to 60 °C for 3 h. The reaction was cooled to rt and then quenched with saturated $NaHCO_3$ solution (20 mL) and extracted with DCM (2 × 15 mL). The combined extracts were washed with brine (20 mL) and then dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by column chromatography using a 0−50% DCM/heptane gradient to give 2.11 g (70%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.46−7.31 (m, 5H), 5.23 (s, 2H), 3.23 (q, J = 10.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 163.9 (q, J = 4.2 Hz, 1C), 134.8, 128.6 (s, 2C), 128.6 (s, 1C), 128.3 (s, 2C), 122.0(q, J = 276.6 Hz, 1C), 67.4 (s, 1C), 39.6 (q, J = 30.8 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −63.42 (s, 3F).

Benzyl 3,3-Difluoroacrylate (6a). To a solution of benzyl 3,3,3-trifluoropropanoate (490 mg, 2.25 mmol) in DCM (10 mL) was added triethylamine (0.273 g, 2.70 mmol, 0.38 mL), followed by dropwise addition of trimethylsilyl triflate (0.611 g, 2.70 mmol, 0.499 mL). The pale yellow solution was stirred at rt for 18 h and then cooled in an ice bath. Titanium(IV) chloride (0.225 mmol, 0.225 mL, 1.0 M) was added, and the reaction turned deep red and then brown. The reaction was taken out of the ice bath, stirred at rt for 12 h, recooled in the ice bath, and then quenched with water. The layers were separated, and the organic phase was washed with brine (5 mL) and then dried ($MgSO_4$), filtered, and concentrated. The crude concentrate was purified by column chromatography using a 0−50% DCM/heptane gradient. 286 mg (49% by NMR) was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37−7.41 (m, 5H), 5.21 (s, 2H), 4.99−5.09 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 162.8 (dd, J = 7.7, 17.2 Hz, 1C), 162.1 (dd, J = 298.9, 312.1 Hz, 1C), 135.5 (s, 1C), 128.6 (s, 2C), 128.4 (s, 1C), 128.3 (s, 2C), 77.1 (dd, J = 8.1, 30.1 Hz, 1C), 66.6 (s,1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −63.28 (d, J = 18.3 Hz, 1F), −68.83 (d, J = 18.3 Hz, 1F).

Benzyl 1-Benzyl-4,4-difluoropyrrolidine-3-carboxylate (7a). To a solution of benzyl 3,3-difluoroacrylate (195 mg, 0.98 mmol) and N-(methoxymethyl)-N-(trimethylsilylmethyl)-benzylamine (2.2 mmol, 0.550 mL) in DCM (1.2 mL) was added slowly trifluoroacetic acid (22.5 mg, 0.197 mmol, 0.02 mL) at rt. Upon addition, an exotherm was observed with vigorous bubbling. The reaction was stirred at rt for 1 h and then quenched with saturated $NaHCO_3$ solution (15 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were washed with brine (15 mL) and then dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by column chromatography using a 0−40% EtOAc/heptane gradient. 200 mg (61%) was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34−7.40 (m, 5H), 7.28−7.33 (m, 5H), 5.22 (s, 2H), 3.61−3.75 (m, 2H), 3.37−3.53 (m, 1H), 3.17−3.27 (m, 1H), 3.13 (t, J = 8.80 Hz, 1H), 2.94−3.04 (m, 1H), 2.80 (ddd, J = 10.94, 14.15, 16.96 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 167.4 (br. s., 1C), 137.2 (br. s., 1C), 135.4, 128.7 (s, 2C), 128.5 (s, 2C), 128.5 (s, 2C), 128.3, 128.2 (s, 2C), 127.5, 127.2 (dd, J = 252.4, 256.8 Hz, 1C), 67.1, 61.3 (t, J = 27.9 Hz, 1C), 59.4, 54.1 (d, J = 3.7 Hz, 1C), 51.7 (dd, J = 22.7, 24.9 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −91.12 (d, J = 231.2 Hz, 1F), −100.43 (d, J = 231.2 Hz, 1F); HRMS calculated for $C_{19}H_{19}F_2NO_2$ 331.1384, found 332.1389.

Ethyl 1-Benzyl-4,4-difluoropyrrolidine-3-carboxylate (7b). To a microwave vial containing a solution of commercially available ethyl 3,3,3-trifluoropropanoate (1.0 g, 6.41 mmol) in $CDCl_3$ (10 mL) was added triethylamine (0.78 mg, 7.69 mmol), followed by dropwise addition of trimethylsilyl triflate (1.74 g, 7.69 mmol). Upon addition, the clear solution changes to an orange color. After 1.5 h, the reaction was cooled in an ice bath, and then titanium(IV) chloride (0.961 mL, 1.0 M in DCM) was added. The orange solution changes to a deep black-red color. The ice bath was removed, and the reaction was stirred at rt for 1 h and then recooled in an ice bath. The reaction was quenched with water (10 mL), the layers separated, and then the organic phase was dried ($MgSO_4$) and filtered. The resulting solution was cooled in an ice bath and N-(methoxymethyl)-N-(trimethylsilylmethyl)-benzylamine (2.32 g, 9.4 mmol, 2.50 mL) was added, followed by trifluoroacetic acid (100 mg, 1 mmol, 0.1 mL). The reaction was stirred in the ice bath for 1 h, warmed to rt, and stirred for 2 h and then quenched with saturated $NaHCO_3$ solution. The layers were separated, and the organic phase was dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by column chromatography using a 0−40% EtOAc/heptane gradient to provide 543.0 mg (32%, 2 steps) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.36−7.31 (m, 4H), 7.30−7.25 (m, 1H), 4.37−4.13 (m, 2H), 3.77−3.57 (m, 2H), 3.46−3.31 (m, 1H), 3.21 (dt, J = 8.6, 11.8 Hz, 1H), 3.12 (t, J = 8.8 Hz, 1H), 3.02−2.93 (m, 1H), 2.77 (ddd, J = 11.0, 14.4, 17.0 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 167.5 (dd, J = 2.6, 4.0 Hz, 1C), 137.3, 128.6 (s, 2C), 128.4 (s, 2C), 127.4, 127.7 (dd, J = 252.0, 256.4 Hz, 1C), 61.4, 61.8−60.9 (m, 1C), 59.4, 54.1 (d, J = 3.7 Hz, 1C), 51.7 (dd, J = 22.0, 24.9 Hz, 1C), 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −91.15 (d, J = 231.2 Hz, 1F), −101.02 (d, J = 233.5 Hz, 1F); HRMS calculated for $C_{14}H_{17}F_2NO_2$ 269.1227, found 269.123.

1-(*tert*-Butoxycarbonyl)-4,4-difluoropyrrolidine-3-carboxylic Acid (8a). To a nitrogen-purged solution of 1-benzyl-4,4-difluoropyrrolidine-3-carboxylic acid (93 mg, 0.28 mmol) in EtOH (3 mL) was added 20% palladium hydroxide on carbon (7.2 mg, 0.05 mmol), followed by di-*tert*-butyl-dicarbonate (88 mg, 0.40 mmol). The reaction was evacuated and backfilled with H_2 three times and then run under a hydrogen atmosphere (balloon) for 66 h. The crude reaction was filtered through a bed of Celite and then rinsed with dichloromethane (15 mL) and methanol (15 mL). The filtrate was concentrated to give 71 mg (99%) as a clear oil. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.44 (s, 9 H) 3.55−3.77 (m, 5 H); ^{13}C NMR (101 MHz, at 80 °C in DMSO-d_6) δ ppm 167.3 (br. s., 1C), 152.8, 129.2−120.1 (m, 1C), 79.3, 52.1 (t, J = 30.8 Hz, 1C), 48.4 (t, J = 22.0 Hz, 1C), 45.6 (br. s., 1C), 27.7 (s, 3C); ^{19}F NMR (376 MHz, at 80 °C in DMSO-d_6) δ ppm −106.34 (s, 1F), −106.96 (s, 1F); HRMS calculated for $C_{10}H_{15}F_2NO_4$ 251.0969, found 251.0958.

1-(*tert*-Butyl) 3-Ethyl 4,4-Difluoropyrrolidine-1,3-dicarboxylate (8b). To a nitrogen-purged solution of ethyl 1-benzyl-4,4-difluoropyrrolidine-3-carboxylate (543.0 mg, 2.02 mmol) in ethyl alcohol (13.4 mL) was added 20% palladium hydroxide on carbon (55.0 mg, 0.39 mmol), followed by di-*tert*-butyl-dicarbonate (528 mg, 2.42 mmol). The reaction was evacuated and backfilled with H_2 three times and then stirred under a hydrogen atmosphere (balloon) for 18 h. The crude reaction was filtered through a bed of Celite and then rinsed with DCM (15 mL) and MeOH (15 mL). The filtrated was concentrated and purified by column chromatography using a 0−60% EtOAc/heptane gradient to give 415 mg (74%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.35−4.18 (m, 2H), 3.93−3.69 (m, 4H), 3.38 (br. s., 1H), 1.48 (s, 9H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.8 (br. s., 1C), 153.7, 80.6, 61.8, 53.4−51.9 (m, 1C), 50.6−48.9 (m, 1C), 46.5−45.5 (m, 1C), 28.3 (s, 3C), 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −100.55 (dd, J = 235.8, 604.3 Hz, 1F), −108.15 (dd, J = 162.5, 235.8 Hz, 1F); HRMS calculated for $C_{12}H_{19}F_2NO_4$ 279.1282, found 279.1292.

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***tert*-Butyl 3,3-Difluoro-4-(hydroxymethyl)pyrrolidine-1-carboxylate (9).** From **8a**: To a capped microwave vial containing 1-(*tert*-butoxycarbonyl)-4,4-difluoropyrrolidine-3-carboxylic acid (714 mg, 2.84 mmol) was added BH_3−THF (5.68 mL, 5.68 mmol, 1 M) at rt. The reaction was heated to 75 °C for 15 min, cooled to rt, carefully quenched with saturated NH_4Cl solution, and then diluted with EtOAc. The layers were separated, and the organic phase was dried ($MgSO_4$), filtered, and concentrated to give 674 mg (99%) as a clear oil. From **8b**: To a cooled (ice bath) solution of 1-(*tert*-butyl) 3-ethyl 4,4-difluoropyrrolidine-1,3-dicarboxylate (358 mg, 1.28 mmol) in tetrahydrofuran (4.27 mL) was added lithium aluminum hydride (1.41 mL, 1.0 M in THF). After 5 min, the reaction was carefully quenched with Rochelle's salt (satd, 10 mL) and then extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine (20 mL) and then dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by column chromatography using 0−50% EtOAc/heptane gradient to provide 255 mg (84%) as a clear oil. ^{1}H NMR (400 MHz, at 80 °C in DMSO-d_6) δ ppm 4.65 (br. s., 1H), 3.74−3.57 (m, 4H), 3.52 (t, J = 7.5 Hz, 1H), 3.30 (dd, J = 7.0, 11.0 Hz, 1H), 2.66 (tq, J = 7.0, 13.7 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, at 80 °C in DMSO-d_6) δ ppm 153.0 (s, 1 C), 126.8 (t, J = 249.8 Hz, 1 C), 78.9 (s, 1 C), 56.9 (dd, J = 7.0, 3.3 Hz, 1 C), 52.3 (t, J = 31.5 Hz, 1 C), 46.6 (br. s., 1 C), 45.5 (t, J = 20.2 Hz, 1 C), 27.7 (s, 3 C); ^{19}F NMR (376 MHz, at 100 °C in DMSO-d_6) δ ppm −113.07 (d, J = 233.46 Hz, 1 F), −99.95 (d, J = 233.46 Hz, 1 F); HRMS calculated for $C_{10}H_{17}F_2NO_3$ 237.1176, found 237.1182.

1-Benzyl-3-*tert*-butoxy-1*H*-pyrrole-2,5-dione (15). To a solution of 1-benzyl-3,3-difluoropyrrolidine-2,5-dione (**14**) (80 mg, 0.36 mmol) in THF (1.2 mL) was added KO*t*Bu (0.71 mL, 0.71 mmol, 1 M in THF). The solution turned immediately dark brown. After stirring for 1 h, the reaction mixture was quenched with AcOH to pH 4, diluted with H_2O (15 mL), extracted with EtOAc (2 × 15 mL), washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography and eluted with 2−25% EtOAc/heptane gradient to obtain compound **15** as an oil (66 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.12−7.32 (m, 5 H) 5.27 (s, 1 H) 4.56 (s, 2 H) 1.42 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.8 (s, 1 C) 166.6 (s, 1 C) 155.9 (s, 1 C) 136.4 (s, 1 C) 128.5 (s, 2 C) 128.4 (s, 2 C) 127.6 (s, 1 C) 97.3 (s, 1 C) 84.1 (s, 1 C) 41.1 (s, 1 C) 27.1 (s, 3 C); HRMS calculated for $C_{15}H_{17}NO_3$ 259.1205, found 259.1213.

2,5-Dibenzyl-3a-fluorotetrahydropyrrolo[3,4-*c*]pyrrole-1,3-(2*H*,3a*H*)-dione (16). To a solution of compound **15** (200 mg, 2.66 mmol) in MeTHF (2.22 mL) was added LiF (57.7 mg, 2.22 mmol), and the mixture was sonicated for 2 h. *N*-(Methoxymethyl)-*N*-(trimethylsilylmethyl)-benzylamine (0.400 mL, 1.39 mmol) and additional LiF (37 mg, 1.43 mmol) were added, and sonication continued for 18 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography eluting with 2−10% EtOAc/heptane gradient to obtain the desired compound **16** as a clear oil (152 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32−7.42 (m, 5 H) 7.23−7.31 (m, 3 H) 7.06−7.15 (m, 2 H) 4.70−4.84 (m, 2 H) 3.56−3.68 (m, 2 H) 3.53 (dd, J = 10.21, 2.75 Hz, 1 H) 3.34 (d, J = 9.54 Hz, 1 H) 3.21 (dd, J = 18.89, 6.91 Hz, 1 H) 2.75 (dd, J = 9.54, 7.09 Hz, 1 H) 2.60−2.70 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 174.6 (d, J = 7.3 Hz, 1 C) 172.4−173.4 (m, 1 C) 136.9 (s, 1 C) 134.9 (s, 1 C) 128.7 (s, 2 C) 128.4 (s, 2 C) 128.2 (s, 2 C) 128.1 (s, 2 C) 128.0 (s, 1 C) 127.4 (s, 1 C) 96.4−100.9 (m, 1 C) 59.7−60.5 (m, 1 C) 58.1 (s, 1 C) 54.8 (d, J = 1.5 Hz, 1 C) 49.7 (d, J = 18.3 Hz, 1 C) 42.7 (s, 1 C); ^{19}F NMR (377 MHz, $CDCl_3$) δ ppm −104.15 (s, 1 F); HRMS calculated for $C_{20}H_{19}FN_2O_2$ 338.1431, found 338.1431.

***tert*-Butyl 5-Benzyl-3a-fluoro-4,6-dioxohexahydropyrrolo-[3,4-*c*]pyrrole-2(1*H*)-carboxylate (17).** To a nitrogen-purged solution of compound **16** (270 mg, 0.798 mmol) in EtOH (8 mL) were added 20% $Pd(OH)_2$/C (60 mg) and Boc anhydride (209 mg, 0.957 mmol, 1.20 equiv). The reaction was evacuated and backfilled with H_2 (balloon) three times. The reaction mixture was stirred for 3 h under H_2. The $Pd(OH)_2$/C was removed by filtration. The filtrate was concentrated under reduced pressure and purified by column chromatography eluting with 2−20% EtOAc/heptane to obtain the desired compound **17** as a white solid (244 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29−7.37 (m, 5 H) 4.70 (s, 2 H) 3.97−4.19 (m, 2 H) 3.62−3.80 (m, 2 H) 3.34−3.47 (m, 1 H) 1.43 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 172.8 (d, J = 8.8 Hz, 1 C) 171.0−171.9 (m, 1 C) 153.3 (s, 1 C) 134.6 (s, 1 C) 128.8 (s, 2 C) 128.5 (s, 2 C) 128.3 (s, 1 C) 96.6−99.9 (m, 1 C) 81.1 (s, 1 C) 52.8−54.0 (m, 1 C) 50.4 (br. s., 1 C) 46.5 (s, 1 C) 43.1 (s, 1 C) 28.2 (s, 3 C); ^{19}F NMR (377 MHz, $CDCl_3$) δ ppm −104.15 (s, 1 F); HRMS calculated for $C_{18}H_{21}FN_2O_4$ 348.1485, found 348.1475.

***tert*-Butyl 5-Benzyl-3a-fluorohexahydropyrrolo[3,4-*c*]-pyrrole-2(1*H*)-carboxylate (18).** Compound **17** (212 mg, 0.609 mmol) was dissolved in THF (6 mL), and borane dimethyl sulfide complex (0.231 mL, 2.43 mmol) was added. The reaction mixture was heated to 55 °C for 2.5 h. The reaction was then cooled to 0−5 °C (ice water bath), quenched with MeOH (6 mL), concentrated under reduced pressure, and then dried under high vacuum. The borane-amine crude adduct was diluted with MeOH (6 mL), and under N_2, 20% $Pd(OH)_2$/C (60 mg) was added. The reaction mixture was stirred for 18 h. The $Pd(OH)_2$/C was removed by filtration, and the filtrate was concentrated. The crude product was purified by column chromatography, eluting with a 2−20% EtOAc/heptane gradient to obtain the desired product **18** as a clear oil (106 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28−7.32 (m, 4 H) 7.18−7.25 (m, 1 H) 3.65−3.89 (m, 2 H) 3.49−3.64 (m, 3 H) 3.18 (dd, J = 11.19, 4.46 Hz, 1 H) 2.63−2.95 (m, 4 H) 2.37 (br. s., 1 H) 1.44 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.1 (s, 1 C) 138.1 (s, 1 C) 128.5 (s, 2 C) 128.3 (s, 3 C) 127.1 (s, 1 C) 79.7 (s, 1 C) 62.3−63.6 (m, 1 C) 59.2 (s, 1 C) 58.6 (d, J = 3.7 Hz, 1 C) 55.9 (br. s., 1 C) 50.5 (br. s., 1 C) 47.5 (br. s., 1 C) 28.4 (s, 3 C); ^{19}F NMR (377 MHz, $CDCl_3$) δ ppm −147.75 (br. s., 1 F); HRMS calculated for $C_{18}H_{25}FN_2O_2$ 320.1900, found 320.1903.

1-Benzyl-4-(benzyloxy)-3,3-difluoropyrrolidine (21). *Method A (TFA).* The a solution of the (((2,2-difluorovinyl)oxy)methyl)-benzene **20** (1.0 g, 5.877 mmol) and *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (5.58 g, 23.5 mmol) was stirred in the preheated heating block at 130 °C for 5 min. TFA (58.3 uL, 0.588 mmol) was added dropwise (white smoke evolved upon addition). The mixture was heated at 130 °C for 30 min. The reaction was concentrated to an orange oil and purified by column chromatography using a 0−15% EtOAc/heptane gradient, leading to the desired product as a colorless oil (469 mg, 26%).

Method B (LiF). To a solution of the (((2,2-difluorovinyl)oxy)-methyl)benzene **20** (100 mg, 0.59 mmol) in ACN (1.18 mL, 0.5 M) were added LiF (61 mg, 2.35 mmol) and *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (601 uL, 2.35 mmol). The mixture was stirred in a preheating heating block at 130 °C for 4 h. The reaction was concentrated to an orange oil and purified by column chromatography (EtOAc/heptane, 0−15%), leading to the desired product as a colorless oil (65 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32−7.08 (m, 10H), 4.71 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 4.02−3.88 (m, 1H), 3.58−3.42 (m, 2H), 3.14−2.98 (m, 2H), 2.67 (dt, J = 11.2, 16.4 Hz, 1H), 2.45−2.36 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 137.3 (s, 1 C), 137.2 (s, 1 C), 128.8 (s, 2 C), 128.5 (s, 2 C), 128.4 (s, 2 C), 128.0 (s, 2 C), 128.0 (s, 1 C), 127.5 (s, 1 C), 126.4 (dd, J = 245.8, 242.1 Hz, 1 C), 79.0 (dd, J = 30.1, 16.9 Hz, 1C), 72.8 (d, J = 2.9 Hz, 1 C), 60.3 (t, J = 28.2 Hz, 1 C), 59.8 (s, 1 C), 57.7 (d, J = 5.9 Hz, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −95.29 (d, J = 254.8 Hz, 1F), −112.33 (d, J = 253.4 Hz, 1F); HRMS calculated for $C_{18}H_{19}F_2NO$ 303.1435, found 303.1446.

1-Benzyl-4,4-difluoropyrrolidin-3-yl 4-Methylbenzene-sulfonate (23). *Method A (TFA).* The mixture of 2,2-difluorovinyl 4-methylbenzenesulfonate **22** (5.528 g, 23.6 mmol) and *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (22.4 g, 94.4 mmol) was heated in an oil bath (preheated to 130 °C) for 5 min; then, TFA (182 uL, 2.36 mmol) was added dropwise slowly. A couple of minutes after the TFA was added, the reaction mixture reacted vigorously. Smoke and volatile material were generated, and the reaction turned

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dark. After 20 min, LCMS indicated that the reaction was complete. The volatiles were evaporated, and the residue was purified by column chromatography with 15−20% EtOAc/heptane gradient to obtain an oil (8.0 g, 92%).

Method B (LiF). To a solution of 2,2-difluorovinyl 4-methylbenzenesulfonate **22** (45.0 mg, 0.192 mmol) and *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (197 uL, 0.769 mmol) was added LiF (15.0 mg, 0.576 mmol), and the mixture was stirred at 160 °C for 4 h. The reaction was dissolved in EtOAc and washed with 10 mL of water. The aqueous layer was extracted with EtOAc (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography using a 0−40% EtOAc/heptane gradient to obtain an oil (42.6 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.83 (d, J = 8.3 Hz, 2H), 7.41−7.22 (m, 7H), 4.91−4.76 (m, 1H), 3.70−3.52 (m, 2H), 3.23 (dd, J = 6.7, 10.4 Hz, 1H), 3.08 (ddd, J = 7.5, 11.2, 14.4 Hz, 1H), 2.79 (dt, J = 11.2, 15.7 Hz, 1H), 2.72−2.63 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 145.3 (s, 1 C), 136.5 (s, 1 C), 132.9 (s, 1 C), 129.9 (s, 2 C), 128.6 (s, 2 C), 128.5 (s, 2 C), 128.0 (s, 2 C), 127.6 (s, 1 C), 123.8 (dd, J = 260.2, 252.8 Hz, 1 C), 77.9 (dd, J = 34.5, 16.9 Hz, 1 C), 59.2 (s, 1 C), 59.5 (dd, J = 28.6, 28.0 Hz, 1 C), 56.7 (d, J = 5.1 Hz, 1 C), 21.7 (s, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −98.45 (d, J = 239.8 Hz, 1F), −109.41 (d, J = 239.8 Hz, 1F); HRMS calculated for $C_{18}H_{19}F_2NO_3S$ 367.1054, found 367.1051.

1-Benzyl-4,4-difluoropyrrolidin-3-ol (19). *Method A.* Magnesium (small turnings, 5.29 g, 218 mmol) was added to the solution of 1-benzyl-4,4-difluoropyrrolidin-3-yl 4-methylbenzenesulfonate **23** (8.0 g, 21.77 mmol) in MeOH (78 mL, 0.28 M), and the mixture was stirred at room temperature for 1 h. (The reaction became exothermic and a solid foam formed.) The reaction mixture was cooled in a water bath, and cold water was added. Concentrated HCl was added to dissolve the solids, and the mixture was extracted with EtOAc three times. The aqueous layer still contained product and, therefore, was adjusted to pH 6−7 by adding solid KOH. The mixture was then extracted with EtOAc three times again. The organic layers were combined, dried over Na_2SO_4, concentrated, and purified by column chromatography with a 20% EtOAc/heptane through 10% MeOH/EtOAc gradient to obtain 3.83 g of a brown oil (3.83 g, 82%)

Method B. To a solution of 1-benzyl-4,4-difluoropyrrolidin-3-yl 4-methylbenzenesulfonate **23** (811 mg, 2.21 mmol) in THF (11 mL, 0.1 M) was added Super Hydride (8.83 mL, 8.83 mmol, 1 M) at room temperature. The mixture turned to light yellow and was then heated at reflux overnight. The reaction was then cooled to room temperature. To the reaction mixture was added 8 mL of sat. aq. NH_4Cl, and it was extracted with EtOAc twice. The combined organic layer was carefully washed with 1 N HCl. The aqueous layer was adjusted to ph 7−8 with solid $NaHCO_3$ and then extracted by EtOAc three times, dried over Na_2SO_4, and concentrated. The crude material was purified by column chromatography using a 0−40% EtOAc/Heptane gradient to give a yellow oil (417 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39−7.22 (m, 5H), 4.29−4.17 (m, 1H), 3.73−3.60 (m, 2H), 3.13−3.04 (m, 1H), 3.04−2.88 (m, 2H), 2.63 (ddd, J = 2.4, 4.9, 10.2 Hz, 1H), 2.37 (br. s., 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 137.0 (s, 1 C), 128.8 (s, 2 C), 128.5 (s, 2 C), 127.6 (s, 1 C), 125.9 (t, J = 253.5 Hz, 1 C), 73.3 (dd, J = 31.9, 19.8 Hz, 1 C), 59.7 (s, 1 C), 59.6 (t, J = 28.1 Hz, 1 C), 59.3 (d, J = 4.4 Hz, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −100.56 (d, J = 223.4 Hz, 1F), −113.56 (d, J = 237.1 Hz, 1F); HRMS calculated for $C_{11}H_{13}F_2NO$ 213.0965, found 231.0975.

Compounds 26a−f. Compounds **26a−f** were prepared according to literature methods.[15] Analytical data for compounds **26a** and **26c−f** match those in the literature. 1,4-Dichloro-2-(2,2-difluorovinyl)-benzene (**26b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.32 Hz, 1H), 7.33 (d, J = 8.56 Hz, 1H), 7.18 (dd, J = 2.45, 8.56 Hz, 1H), 5.58−5.73 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.9 (dd, J = 264.8, 300.0 Hz, 1C), 132.9, 131.3−131.0 (m, 1C), 130.6, 130.2 (dd, J = 6.2, 7.7 Hz, 1C), 128.7 (dd, J = 1.5, 10.3 Hz, 1C), 128.4, 78.6 (ddd, J = 11.0, 13.2, 21.3 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.01−79.55 (m, 1F), −80.81−80.25 (m, 1F).

General Procedure Using LiF and Difluoro Styrenes Using 1-Bromo-4-(2,2-dfluorovinyl)benzene as an Example: 1-Benzyl-4-(4-bromophenyl)-3,3-difluoropyrrolidine (25). In a 2 dram vial with a Teflon cap charged with a stir bar were added 1-bromo-4-(2,2-difluorovinyl)benzene (**24**) (150 mg, 0.685 mmol), *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (488 mg, 2.05 mmol, 0.526 mL), and acetonitrile (1.37 mL, 0.5 M). To this solution was added LiF (71.1 mg, 2.74 mmol), and the mixture was stirred at 60 °C for 6 h on an aluminum block. LCMS shows complete conversion. The resulting mixture was concentrated in vacuo and purified by silica gel chromatography (0−10% EtOAc/Heptane) to afford **25** as a clear oil (192 mg, 80% y). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38−7.47 (m, 2H), 7.25−7.35 (m, 5H), 7.15 (d, J = 8.44 Hz, 2H), 3.63−3.73 (m, 2H), 3.48−3.62 (m, 1H), 3.14−3.31 (m, 2H), 2.86−2.97 (m, 1H), 2.75−2.86 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 137.6 (s, 1 C), 133.7 (d, J = 3.7 Hz, 1C), 131.5 (s, 2 C), 130.6 (s, 2 C), 128.7 (s, 2 C), 128.5 (s, 2 C), 127.5 (s, 1 C), 127.9 (dd, J = 252.4, 253.8 Hz, 1C), 121.6 (s, 1 C), 62.0 (dd, J = 24.9, 27.9 Hz, 1C), 59.9 (s, 1 C), 58.0 (d, J = 5.9 Hz, 1C), 51.6 (dd, J = 22.0, 24.9 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −93.36 (d, J = 228.9 Hz, 1F), −98.90 (d, J = 231.6 Hz, 1F); HRMS calculated for $C_{17}H_{16}BrF_2N$ 351.0434, found 351.0431.

1-Benzyl-4-(2,4-dichlorophenyl)-3,3-difluoropyrrolidine (27a). Similar reaction conditions to make compound **25** were used to make **27a** in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 1.1, 8.4 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.35−7.21 (m, 6H), 4.28−4.13 (m, 1H), 3.78−3.64 (m, 2H), 3.16−3.01 (m, 3H), 2.89 (dd, J = 6.7, 9.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 137.5 (s, 1 C), 135.8 (s, 1 C), 133.8 (s, 1 C), 132.2 (t, J = 2.7 Hz, 1 C), 130.8 (d, J = 2.0 Hz, 1 C), 129.2 (s, 1 C), 128.7 (s, 2 C), 128.6 (s, 2 C), 127.6 (s, 1 C), 127.1 (s, 1 C), 128.1 (t, J = 253.8 Hz, 1 C), 62.0 (t, J = 29.0 Hz, 1 C), 59.9 (s, 1 C), 58.5 (d, J = 5.1 Hz, 1 C), 47.4 (dd, J = 26.0, 20.7 Hz, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.25 (d, J = 228.9 Hz, 1F), −98.42 (d, J = 230.2 Hz, 1F); HRMS calculated for $C_{17}H_{15}Cl_2F_2N$ 341.055, found 341.0558.

1-Benzyl-4-(2,5-dichlorophenyl)-3,3-difluoropyrrolidine (27b). Similar reaction conditions to make compound **25** were used to make **27b** in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 1.34 Hz, 1H), 7.36−7.41 (m, 4H), 7.28−7.35 (m, 2H), 7.20 (dd, J = 2.57, 8.56 Hz, 1H), 4.14−4.30 (m, 1H), 3.63−3.84 (m, 2H), 3.05−3.20 (m, 3H), 2.93 (dd, J = 6.24, 9.54 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 138.6 (s, 1 C), 136.4−136.8 (m, 1 C), 134.6 (s, 1 C), 133.8 (s, 1 C), 131.6 (s, 1 C), 131.1 (d, J = 2.2 Hz, 1 C), 129.9 (s, 2 C), 129.8 (s, 1 C), 129.8 (s, 2 C), 128.7 (s, 1 C), 129.3 (t, J = 253.8 Hz, 1 C), 62.5−63.9 (m, 1 C), 60.9 (s, 1 C), 59.5 (d, J = 5.1 Hz, 1 C), 48.5−49.5 (m, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.91 to −88.61 (m, 1F), −102.24 to −96.34 (m, 1F); HRMS calculated for $C_{17}H_{15}Cl_2F_2N$ 342.0622, found 342.0631.

1-Benzyl-3,3-difluoro-4-(3-nitrophenyl)pyrrolidine (27c). Similar reaction conditions to make compound **25** were used to make **27c** in 76% yield using LiF (Method B), and it also was made using TFA (Method A): In a scintillation vial, a mixture of 1-(2,2-difluorovinyl)-3-nitrobenzene **26c** (40 mg, 0.22 mmol) and *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (0.221 mL, 0.864 mmol) was heated at 120 °C in an oil bath for 5 min. TFA (3 uL, 0.043 mmol) was added, and the mixture was heated for 30 min. LCMS showed the product formed and the starting material mostly consumed. The reaction was cooled to room temperature and purified by column chromatography using a 20% EtOAc/heptane gradient to afford a colorless oil (55 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.26 (s, 1 H) 8.17 (dd, J = 8.19, 1.35 Hz, 1 H) 7.66 (d, J = 7.70 Hz, 1 H) 7.52 (t, J = 7.95 Hz, 1 H) 7.34−7.42 (m, 4 H) 7.28−7.33 (m, 1 H) 3.69−3.82 (m, 3 H) 3.22−3.34 (m, 2 H) 3.05 (dt, J = 18.43, 11.02 Hz, 1 H) 2.95 (t, J = 8.74 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 148.3 (s, 1 C), 137.3 (s, 1 C), 137.1 (s, 1 C), 135.3 (s, 1 C), 129.2 (s, 1 C), 128.7 (s, 2 C), 128.6 (s, 2 C), 127.8 (t, J = 253.1 Hz, 1 C), 127.6 (s, 1 C), 123.8 (s, 1 C), 122.6 (s, 1 C), 61.8 (t, J = 29.3 Hz, 1 C), 59.8 (s, 1 C), 57.8 (d, J = 5.1 Hz, 1 C), 51.7 (td, J = 22.0, 2.9 Hz, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −92.84 (d, J = 231.61

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Hz, 1 F) −98.16 (d, J = 230.25 Hz, 1 F); HRMS calculated for $C_{17}H_{16}F_2N_2O_2$ 318.1180, found 318.1182.

1-Benzyl-3,3-difluoro-4-(*p*-tolyl)pyrrolidine (27d). Similar reaction conditions to make compound **25** were used to make **27d** in 13% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.97−7.26 (m, 9 H) 3.54−3.65 (m, 2 H) 3.42−3.54 (m, 1 H) 3.08−3.27 (m, 2 H) 2.69−2.84 (m, 2 H) 2.21 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 139.3 (s, 1 C) 138.8 (s, 1 C) 133.0 (d, J = 2.9 Hz, 1 C) 130.6 (s, 1 C) 130.5 (s, 1 C) 130.3 (s, 1 C) 130.1 (s, 1 C) 129.7 (t, J = 251.6 Hz, 1 C) 129.0 (s, 1 C) 63.6 (t, J = 29.3 Hz, 1 C) 61.7 (s, 1 C) 59.8 (d, J = 5.9 Hz, 1 C) 53.3 (dd, J = 21.3, 2.2 Hz, 1 C) 22.7 (s, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −93.37 (d, J = 228.88 Hz, 1 F) −99.25 (d, J = 228.88 Hz, 1 F); HRMS calculated for $C_{18}H_{19}F_2N$ 287.1486, found 287.1496.

1-Benzyl-3,3-difluoro-4-(4-methoxyphenyl)pyrrolidine (27e). Similar reaction conditions to make compound **25** were used to make **27e** in 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.06 (m, 7H), 6.80 (d, J = 8.7 Hz, 2H), 3.72 (s, 3H), 3.69−3.58 (m, 2H), 3.58−3.45 (m, 1H), 3.32−3.09 (m, 2H), 2.88−2.65 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.74 (d, J = 233.0 Hz, 1F), −99.33 (d, J = 228.9 Hz, 1F); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 160.3 (s, 1 C), 139.1 (s, 1 C), 131.3 (s, 2 C), 130.0 (s, 2 C), 129.8 (s, 2 C), 128.7 (s, 1 C), 127.9 (d, J = 3.5 Hz, 1 C), 129.4 (t, J = 245.6 Hz, 1 C), 115.1 (s, 2 C), 63.4 (t, J = 29.2 Hz, 1 C), 61.4 (s, 1 C), 59.7 (d, J = 6.2 Hz, 1 C), 56.6 (s, 1 C), 52.7 (dd, J = 24.4, 21.5 Hz, 1 C); HRMS calculated for $C_{18}H_{19}F_2NO$ 303.1435, found 303.1421.

1-Benzyl-4-(4-(*tert*-butyl)phenyl)-3,3-difluoropyrrolidine (27f). Similar reaction conditions to make compound **25** were used to make **27f** in 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.43 (m, 7H), 7.24 (d, J = 8.19 Hz, 2H), 3.66−3.82 (m, 2H), 3.54−3.66 (m, 1H), 3.20−3.39 (m, 2H), 2.81−2.99 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 151.5 (s, 1 C), 139.0 (s, 1 C), 132.6 (d, J = 3.7 Hz, 1 C), 129.9 (s, 4 C), 129.6 (s, 2 C), 128.5 (s, 1 C), 129.6 (t, J = 252.4 Hz, 1 C), 126.4 (s, 2 C), 62.8−63.9 (m, 1 C), 61.3 (s, 1 C), 59.5 (d, J = 5.9 Hz, 1 C), 52.4−53.3 (m, 1 C), 35.6 (s, 1 C), 32.5 (s, 3 C); HRMS calculated for $C_{21}H_{25}F_2N$ 330.2028, found 330.2036.

5-(1-Benzyl-4,4-difluoropyrrolidin-3-yl)-2-methoxypyridine (29). Similar reaction conditions to make compound **25** were used to make **29** in 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 2.20 Hz, 1H), 7.56 (d, J = 8.68 Hz, 1H), 7.28−7.39 (m, 5H), 6.72 (d, J = 8.56 Hz, 1H), 3.92 (s, 3H), 3.65−3.78 (m, 2H), 3.49−3.62 (m, 1H), 3.18−3.34 (m, 2H), 2.93 (td, J = 11.32, 18.80 Hz, 1H), 2.79 (t, J = 9.11 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (s, 1C), 146.9 (s, 1C), 139.1 (s, 1C), 137.6 (s, 1C), 128.6 (s, 2C), 128.5 (s, 2C), 127.5 (s, 1C), 127.9 (dd, J = 249.4, 252.4 Hz, 1C), 123.2 (d, J = 3.7 Hz, 1C), 110.6 (s, 1C), 61.9 (dd, J = 27.1, 29.3 Hz, 1C), 59.9 (s, 1C), 58.2 (d, J = 5.9 Hz, 1C), 53.4 (s, 1C), 49.2 (dd, J = 22.7, 30.8 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.95 (d, J = 227.5 Hz, 1F), −98.90 (d, J = 228.9 Hz, 1F); HRMS calculated for $C_{17}H_{18}F_2N_2O$ 304.1387, found 304.1395.

5-(1-Benzyl-4,4-difluoropyrrolidin-3-yl)-2-methoxypyrimidine (31). To a reaction vial was added 5-(2,2-difluorovinyl)-2-methoxypyrimidine **30** (50.0 mg, 0.29 mmol), followed by *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (0.446 mL, 1.74 mmol). Then, LiF (60 mg, 2.32 mmol) was added and the reaction was stirred at 120 °C for 5 h. LCMS and TLC showed that the starting material was consumed. The reaction was diluted with water and EtOAc. The aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organics were washed with brine, dried over $MgSO_4$, and then filtered and concentrated. The resultant was purified by column chromatography using a 0−100% EtOAc/heptane gradient to obtain a clear oil (60 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 2H), 7.39−7.33 (m, 4H), 7.33−7.28 (m, 1H), 4.02 (s, 3H), 3.79−3.66 (m, 2H), 3.62−3.45 (m, 1H), 3.31−3.15 (m, 2H), 3.02 (td, J = 11.1, 18.4 Hz, 1H), 2.83 (t, J = 8.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 165.3 (s, 1 C), 159.4 (s, 2 C), 137.3 (s, 1 C), 128.6 (s, 2 C), 128.6 (s, 2 C), 127.6 (s, 1 C), 127.7 (dd, J = 258.2, 250.2 Hz, 1 C), 122.0 (d, J = 2.2 Hz, 1 C), 61.7 (t, J = 29.0 Hz, 1 C), 59.7 (s, 1 C), 57.8 (d, J = 5.1 Hz, 1 C), 55.0 (s, 1 C), 47.4 (dd, J = 25.7, 22.0 Hz, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.76 (d, J = 230.25 Hz, 1F), −97.99 (d, J = 230.25 Hz, 1F); HRMS calculated for $C_{16}H_{17}F_2N_3O$ 305.1340, found 305.1343.

3-(1-Benzyl-4,4-difluoropyrrolidin-3-yl)quinolone (33). Similar reaction conditions to make compound **25** were used to make **33** in 34% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 2.90−2.96 (m, 1 H), 2.97−3.03 (m, 1 H), 3.17−3.23 (m, 1 H), 3.23−3.28 (m, 1 H), 3.63−3.72 (m, 2 H), 3.72−3.80 (m, 1 H) 7.19−7.23 (m, 1 H), 7.26−7.30 (m, 2 H), 7.29−7.33 (m, 2 H), 7.47 (t, J = 7.43 Hz, 1 H), 7.62 (t, J = 7.24 Hz, 1 H), 7.72 (d, J = 7.89 Hz, 1 H), 8.00 (s, 1 H), 8.02 (d, J = 8.44 Hz, 1 H), 8.81 (br. s., 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 151.3 (s, 1 C), 147.5 (s, 1 C), 137.5 (s, 1 C), 135.7 (s, 1 C), 129.5 (s, 1 C), 129.2 (s, 1 C), 128.7 (s, 2 C), 128.5 (s, 2 C), 127.95−127.99 (m, 1 C), 127.71−127.76 (m, 1 C), 127.67 (s, 1 C), 127.5 (s, 1 C), 126.8 (s, 1 C), 127.2 (dd, J = 252.0, 249.8 Hz, 1 C), 62.0 (t, J = 28.61 Hz, 1 C), 59.9 (s, 1 C), 58.0 (d, J = 5.5 Hz, 1 C), 50.1 (dd, J = 25.3, 22.0 Hz, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.90 (d, J = 228.9 Hz, 1F), −98.02 (d, J = 228.9 Hz, 1F); HRMS calculated for $C_{20}H_{18}F_2N_2$ 324.1438, found 324.1441.

5-(2,2-Difluorovinyl)-2-methoxypyridine (28). In a microwave vial were added 2,2-difluorovinyl 4-methylbenzenesulfonate (400 mg, 1.71 mmol), 2-methoxypyridine-5-boronic acid pinacol ester (703 mg, 2.99 mmol), and dioxane (8.54 mL, 0.2 M). The system was purged with N_2. $Pd_2(dba)_3$ (39 mg, 0.043 mmol) was added, followed by a solution of tricyclohexylphosphine tetrafluoroborate (31 mg, 0.85 mmol) in water (2 mL). The system was purged again with N_2, and the vial was sealed and stirred for 100 °C for 18 h. The reaction was cooled to room temperature. Water and EtOAc (20 mL each) were added, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organics were combined and dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography (0−20% EtOAc/Heptanes) to afford 5-(2,2-difluorovinyl)-2-methoxypyridine (122 mg, 42% yield). Analytical data match those in the literature.[16]

5-(2,2-Difluorovinyl)-2-methoxypyrimidine (30). Followed similar procedures to make compound **28** using 2-methoxypyrimidine-5-boronic acid pinacol ester, compound **30** was obtained in 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 2H), 5.41−5.01 (m, 1H), 4.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 164.4 (t, J = 2.2 Hz, 1 C), 157.6 (dd, J = 6.6, 3.5 Hz, 2 C), 156.5 (dd, J = 297.3, 290.6 Hz, 1 C), 118.5 (dd, J = 6.6, 6.5 Hz, 1 C), 76.0 (dd, J = 32.1, 16.2 Hz, 1 C), 55.0 (s, 1 C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.47 (d, J = 28.6 Hz, 1F), −82.11 (d, J = 28.6 Hz, 1F); HRMS calculated for $C_7H_6F_2N_2O$ 172.0448, found 172.0445.

3-(2,2-Difluorovinyl)quinolone (32). Followed similar procedures to make compound **28** using quinoline-3-boronic acid pinacol ester, compound **32** was obtained in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 1.8 Hz, 1H), 8.21−8.00 (m, 2H), 7.80 (d, J = 8.2 Hz, 1H), 7.71 (ddd, J = 1.3, 7.0, 8.4 Hz, 1H), 7.63−7.49 (m, 1H), 5.56−5.39 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5−159.2 (m, 1C), 158.0−156.6 (m, 1C), 154.5−153.5 (m, 1C), 149.9 (dd, J = 2.9, 5.1 Hz, 1C), 146.9 (s, 1C), 133.4 (dd, J = 3.7, 8.1 Hz, 1C), 129.4 (d, J = 1.0 Hz, 1C), 128.0−127.6 (m, 1C), 127.2 (s, 1C), 124.0−123.5 (m, 1C), 80.0−79.2 (m, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.70 (d, J = 27.2 Hz, 1F), −81.03 (d, J = 25.9 Hz, 1F); HRMS calculated for $C_{11}H_7F_2N$ 191.0547, found 191.0539.

■ ASSOCIATED CONTENT

Supporting Information

Experimental methods of HRMS and NMR spectra for compounds listed in the Experimental Section. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00853.

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Notes

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