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Nickel-Catalysed Radical Tandem Cyclisation/Arylation: Practical Synthesis of 4-Benzyl-3,3-Difluoro-γ-Lactams

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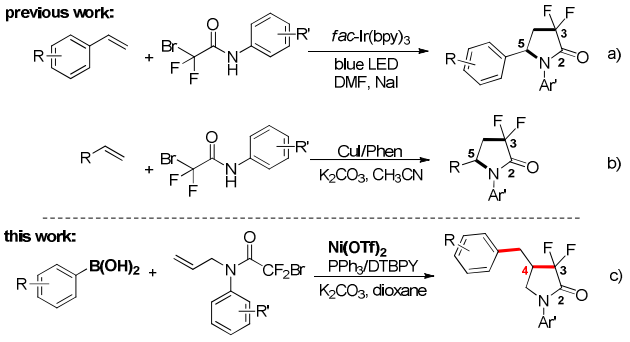
Enabled by nickel catalysis, a practical access to synthesis of 4-benzyl-3,3-difluoro-γ-lactams has been developed via radical tandem cyclisation/arylation. This method features nickel catalyst, high reaction efficiency, good substrate tolerance and scope. This protocol proceeds through an intramolecular radical addition to form a primary alkyl radical followed by intermolecular Suzuki-type coupling.

Introduction

Fluorine-containing molecules are of particular interest in the fields of biomedicine, agriculture, and material sciences.[1] Thus, the development of novel and high efficient methods for the selective introduction of fluorinated moieties such as F, CF_2 and CF_3 into organic molecules has received much attention in the past few years.[2] Conceptually, introduction of a difluoromethylene group (CF_2) into some heterocycles could lead to the discovery of some interesting bioactive molecules.[3] In addition, pyrrolidinone structures are also very important in many bioactive molecules.[4] Pyrrolidinones containing difluoromethylene moiety may have more attractive properties in drug discovery.[5] Consequently, it is a desirable task to explore new catalytic strategy to construct fluorinated pyrrolidinones. In 2012, Chen developed a synthesis of 3,3-difuloro-γ-lactam via radical addition of *N*-aryl halofluoroacetamide to alkyl substituted alkenes.[6] Recently, highly efficient synthesis for 3,3-Difluoro-γ-lactams have been achieved in the presence of an iridium photocatalyst (Scheme 1a) or copper catalyst (Scheme 1b).[7] Very recently, Wang et al also reported a Cu-catalysed aminodifluoroalkylation of alkenes for the synthesis of 3,3-Difluoro-γ-lactams which is similar with the work shown in Scheme 1b.[8] However, the target of all the works is to develop the synthesis of 5-substituted-3,3-Difluoro-γ-lactams. As a part of our program of



Scheme 1 The synthesis of 3,3-difluoropyrrolidin-2-ones.

radical cyclisation and difluoroalkylation,[9] herein, we describe the successful development of the Ni(II)-catalysed radical tandem cyclisation/arylation for the synthesis of 4-substituted-3,3-difluoro-γ-lactams (Scheme 1c).

Up to now, Pd[10b-c,e,f] and Ni-catalysed[10d,g,j]difluoroalkylations and visible-light photoredox[10h] reaction have emerged as a powerful tool for the construction of Ar–CF_2R bond efficiently. As inexpensive catalyst, nickel has proved to be very effective for cross-couplings, especially for Suzuki–Miyaura and Negishi reactions in the past 20 years.[11] In recent years, the scope of nickel-catalysed cross-coupling reactions has expanded far beyond simple bi-aryl synthesis and are rapidly growing,[12] in which, considerable efforts have been dedicated towards expanding the scope of coupling partners. Despite the advances, nickel-catalysed an efficient cascade reaction which involves alkenes by a radical pathway to the diverse molecules containing difluoromethylene group is highly attractive.

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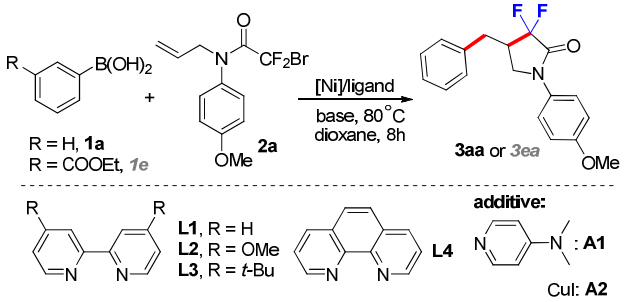
Results and discussion

Table 1 Optimization of reaction conditions[a]

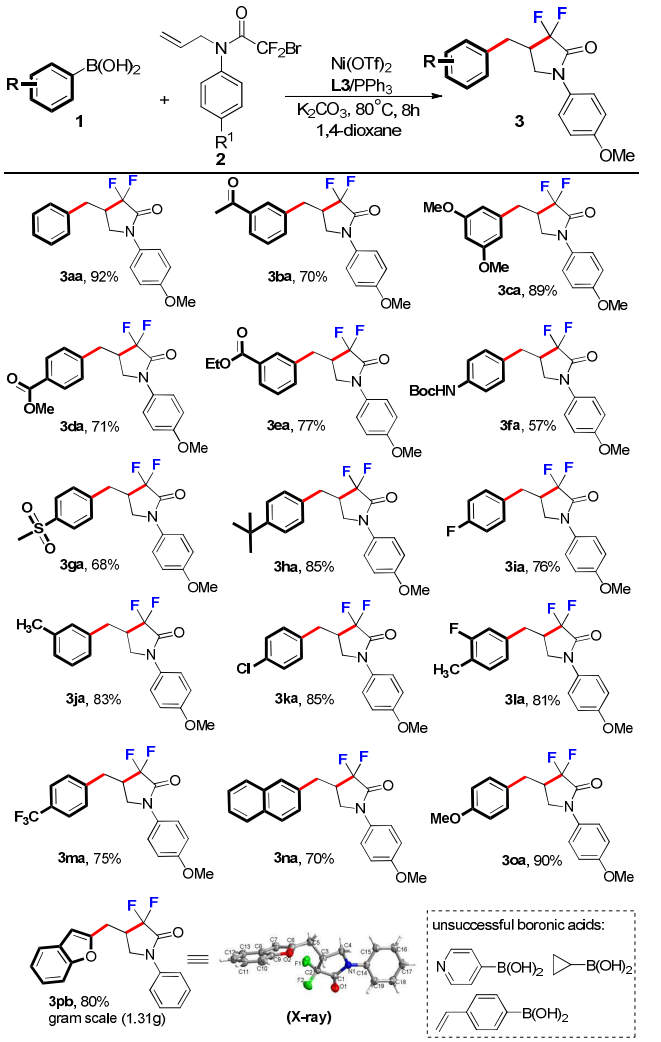


Entry	[Ni] (mol %)	Ligand (mol %)	Base (eq)	Yield[b](%)
1	$Ni(NO_3)_2$•$6H_2O$ (5)	**L1**(5)	K_2CO_3 (3)	33
2	$Ni(NO_3)_2$•$6H_2O$ (5)	**L2**(5)	K_2CO_3 (3)	51
3	$Ni(NO_3)_2$•$6H_2O$ (5)	**L3**(5)	K_2CO_3 (3)	55(*0*)[c]
4	$Ni(NO_3)_2$•$6H_2O$ (5)	**L4**(5)	K_2CO_3 (3)	trace
5	$NiCl_2$•DME (5)	**L2**(5)	K_2CO_3 (3)	32
6	$NiCl_2$•DME (5)	**L3**(5)	K_2CO_3 (3)	36
7	$NiCl_2$•DME (5)	**L3**(5)/**A1**(5)	K_2CO_3 (3)	40(*16*)[c]
8	$NiCl_2$•DME (5)	**L3**(5)/**A2**(5)	K_2CO_3 (3)	32
9	$Ni(acac)_2$ (5)	**L3**(5)	K_2CO_3 (3)	0
10	$Ni(OAc)_2$•$4H_2O$ (5)	**L3**(5)	K_2CO_3 (3)	0
11	$Ni(OTf)_2$ (5)	**L3**(5)	K_2CO_3 (3)	68(*37*)[c]
12	$Ni(OTf)_2$ (5)	**L3**(5)/PPh_3(5)	K_2CO_3 (3)	79(*56*)[c]
13	$Ni(OTf)_2$ (5)	**L3**(5)/PPh_3(10)	K_2CO_3 (3)	83
14	$Ni(OTf)_2$ (7.5)	**L3**(7.5)/PPh_3(15)	K_2CO_3 (3)	88
15[d]	$Ni(OTf)_2$ (7.5)	**L3**(7.5)/PPh_3(15)	K_2CO_3 (3)	92(*77*)[c]
16[d,e]	$Ni(OTf)_2$ (7.5)	**L3**(7.5)/PPh_3(15)	K_2CO_3 (3)	27

[a]Reaction conditions: **1a** or **1e** (0.75 mmol, 1.5 equiv), **2a** (0.5 mmol), Ni catalyst (5-7.5 mol%), Ligand (5-15 mol %), 1,4-dioxane (3.0 mL), under N_2 atmosphere, 80℃, 8 h.[b] Isolated yield. [c]The yield in bracket is product **3ea'**s. [d]**1a** or **1e** (1.0 mmol), **2a** (0.5 mmol).[e] Under air.

Initially, we set out to examine the feasibility of the radical cascade process using *N*-allyl-2-bromo-2,2-difluoro-*N*-(4-methoxyphenyl)acetamide (**2a**) and phenylboronic acid (**1a**) as substrates. Selected optimization results are summarized in Table 1 (see Table S1 in SI). We first examined low-cost $Ni(NO_3)_2$•$6H_2O$ as catalyst by using K_2CO_3 as base (entries 1-4). Screening the ligands from **L1** to **L4**, the best result was obtained when **L3** was chosen as ligand (Table 1, entry 3). However, it failed to furnish any of the desired product when electron-poor 3-(ethoxycarbonyl)-phenylboronic acid (**1e**) and **2a** were put in the cascade process under the same condition (entry 3). Thus, the central challenge was to improve Ni's catalytic performance in the use of less reactive arylboronic acids. When $NiCl_2$•DME was selected as catalyst, the similar results were obtained even if some additives (**A1** or **A2**) were used (entries 5-8). Other nickel complexes such as $Ni(acac)_2$ and $Ni(OAc)_2$ were found to be not effective (entries 9-10). However, when the $Ni(OTf)_2$ was tested, it showed higher catalytic efficiency, giving products **3aa** and **3ea** in 68% and 37% isolated yields respectively (entry 11). To our delight, significant improvements were achieved when 5 mol% PPh_3 was added and the products **3aa** and **3ea** were obtained in 79% and 56% respectively (entry 12). The product yield could be increased to 88% when 7.5mol %

Table 2 Scope of Arylboronic acids 1[a,b]



[a]Reaction conditions: 1 (1.0 mmol), **2a** or **2b** (0.5 mmol), K_2CO_3 (3.0 equiv), $Ni(OTf)_2$ (7.5 mol %), **L3** (7.5 mol %) and PPh_3 (15 mol %) in 1,4-dioxane (3.0 mL) at 80 ℃ for 8 h.[b] Isolated yield.

$Ni(OTf)_2$ and 15 mol % PPh_3 were used as catalyst system (entry 14). Furthermore, excellent yield (92%) for **3aa** and good yield (77%) for **3ea** could be obtained when the ratio of **1a** (**1e**) to **2a** was 2:1 (entry 15).

With the optimized conditions in hand, we then investigated the scope of arylboronic acids in this reaction (Table 2). Arylboronic acids bearing various substituents, including electron-donating (**3c**, **3f**, **3m**, **3o**) and electron-withdrawing (**3b**, **3d-e**, **3g-i**) performed well in the cascade process. Compared with the electron-rich

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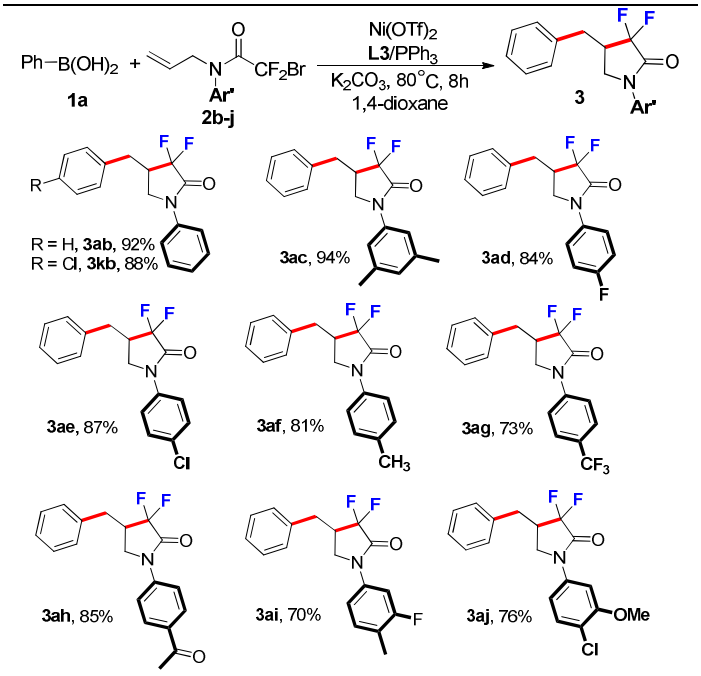
arylboronic acids, those electron-poor analogues showed lower reactivity obviously. Many versatile functional groups, such as ketone, ester and sulphone were all tolerated under the reaction conditions (**3ba**, **3da**, **3ea** and **3ga**). Moreover, Boc-protected amine group was also compatible in this reaction, which provided possibility of further functionalization (**3fa**). Pleasingly, aromatic heterocyclic benzofuran-2-ylboronic acid could also perform well in this transformation and the desired product **3pb** was obtained in 80% yield even in gram-scale (5 mmol). The structure of product **3pb** was clearly confirmed by single crystal X-ray crystallographic analysis, which signified the cascade process was 5-*exo*-*trig* cyclisation (Table 2). It is noteworthy that alkyl boronic acid is not suitable for the current reaction. A possible reason is that it is more difficult for coordination and insertion with nickel catalyst. Furthermore arylboronic acids containing double bond and nitrogen are not compatible in this transformation (Table 2). Unfortunately, some *ortho*-substituted aryl boronic acids are not efficient coupling partners in this reaction (see details in ESI).

Subsequently, the scope of *N*-substituted groups in substrate **2** was evaluated and found to proceed smoothly in all the cases (Table 3). The nickel-catalysed cascade reaction between *N*-phenylacetamide **2b** and boronic acid **1a** proceeded efficiently to afford **3ab** in 92% yield. Good result was also obtained when **2b** reacted with **1k**, providing **3kb** in 80% yield (Table 3).

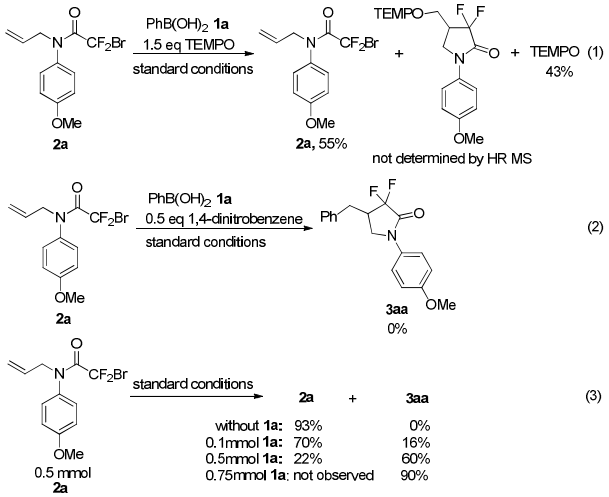
Table 3. Scope of Substrate **2**.[a]



Reaction conditions: **1a** (1.0 mmol), **2b-j** (0.5 mmol), K_2CO_3 (3.0 equiv), $Ni(OTf)_2$ (7.5 mol %), **L3** (7.5 mol %) and PPh_3 (15 mol %) in 1,4-dioxane (3.0 mL) at 80 ℃ for 8 h.

When *N*-(3,5-dimethylphenyl)-acetamide **2c** was tested under the current conditions, excellent yield (94%) for **3ac** was achieved. Electron-withdrawing groups such as CF_3, F and acetyl on the *N*-substituted phenyl ring were well tolerated and have no influence on product yield. In addition, no obvious changes were found when the substituents on *N*-substituted phenyl ring were electron-donating groups such as CH_3 and OMe, good yields were also obtained (**3ac**, **3af** and **3aj**). However, the transformation failed to furnish any of the desired products when the *N*-substituted groups were alkyl or allyl analogues (see Scheme S1 and S3 in ESI). The reason for this result is not clear at present.

In order to acquire further insight into the transformation mechanism, the standard reaction was performed in the presence of 1.5 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a radical scavenger. To our surprise, the reaction did not proceed at all and the substrate **2a** was recovered in 55% yield (eq 1). The reason may be TEMPO deactivates the nickel catalyst at the beginning of the reaction. Addition of the ET scavenger 1,4-dinitrobenzene also shut down the reaction completely (eq 2). The above studies may support a SET pathway in the cascade process to a certain extent and suggest that a radical mechanism may be involved in the catalytic cycle. However, the substrate **2a** could not undergo the cyclisation and was recovered in 93% yield in the absence of phenylboronic acid which implied arylboronic acids play an important role in the transformation (eq 3). As shown in eq 3, it seems that only Ni catalyst does not initiate the reaction and arylboronic acid may play a role like activating agent.



Based on the above studies and previous works,[10] a primary plausible mechanism for the nickel-catalysed tandem cyclisation-arylation is described in Scheme 2. Initially, the LNi(I)X complex **A** with **1** were translated into species **B**.[10j] Then the Ni(I) complex **B** could initiate the generation of radical **D** from **2** through single electron transfer (SET), leading Ni(II) intermediate **C** in the meanwhile. The radical intermediate **D** forms radical **E** rapidly via 5-*exo*-*trig* cyclisation. After an oxidative radical addition, the **E** and **C** were transferred into Ni(III) complex **F**. Subsequently, **F** is transformed to the final product **3aa**, which undergoes reductive elimination of the nickel catalyst and regenerates species **A**.

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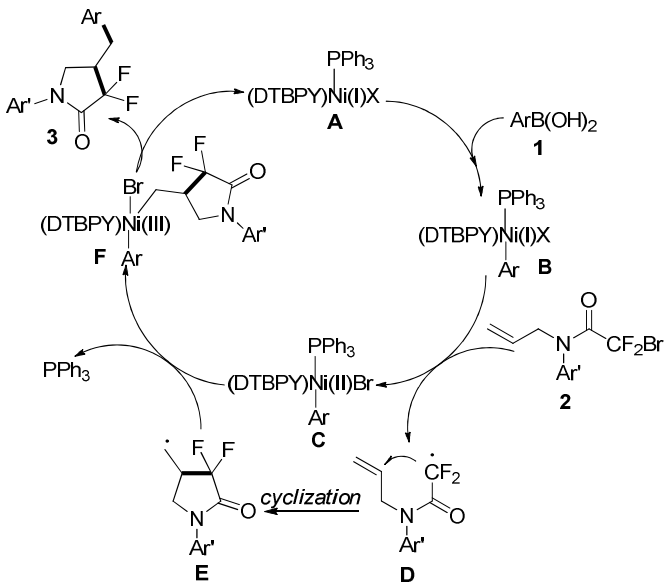

Scheme 2 Proposed mechanism for the reaction

Conclusions

In summary, we have disclosed a high efficient synthesis of γ-lactams via inexpensive nickel-catalysed intramolecular radical cyclisation followed by intermolecular arylation of *N*-allyl-2-bromo-2,2-difluoro-*N*-arylacetamides with arylboronic acids, which provides a simple and straightforward route to various 4-benzyl-3,3-difluoropyrrolidin-2-ones. Further applications of this method to more wide substrates and the study of mechanism are ongoing in our laboratory.

Experimental section

General Procedure for the Radical Tandem Cyclisation-Arylation: The synthesis of 4-benzyl-3,3-difluoro-1-(4-methoxyphenyl)pyrrolidin-2-one (**3aa**). To a 25 mL of Schlenck tube were added phenylboronic acid **1a** (1.0 mmol, 0.122g, 2.0 equiv), **2a** (0.5 mmol, 0.16g), $Ni(OTf)_2$ (7.5 mmol %, 13 mg), DTBPy (7.5 mmol %, 10 mg), PPh_3 (15 mmol %, 19.6 mg) under air, followed by K_2CO_3 (1.5 mmol, 3.0 equiv). The mixture was then evacuated and backfilled with N_2 (3 times), dioxane (3 mL) were added subsequently. The tube was put into a preheated oil bath (80 ^oC). After stirring for 8 h, the reaction mixture was cooled to room temperature and was evaporated under reduced pressure. The residue was extracted with EtOAc (15 ml x 2) and then dried by Na_2SO_4. After removing EtOAc, the residue was purified with silica gel chromatography to give product **3aa** in 92% yield.White solid; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 12.0 Hz, 2H), 7.30-7.36 (m, 2H), 7.26-7.30 (m, 3H), 6.93 (dd, *J* = 8.0, 4.0 Hz, 2H), 3.82 (s, 3H), 3.69 (t, *J* = 8.0 Hz, 1H), 3.60 (t, *J* = 8.0 Hz, 1H), 3.30 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.95-2.99 (m, 1H), 2.79-2.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.13 (t), 157.67, 136.96, 129.92, 128.97, 128.73, 127.10, 121.73, 114.95 (t, *J* = 257 Hz), 114.18, 55.48, 48.54, 41.67 (t, *J* = 21 Hz), 31.53; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.44 (d, *J* = 266.96 Hz), -117.03 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{18}H_{18}F_2NO_2$ $[M+H]^+$: 318.1300; found: 318.1308.

4-(3-acetylbenzyl)-3,3-difluoro-1-(4-methoxyphenyl)pyrrolidin-2-one(3ba) White solid; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 4H), 6.92 (d, *J* = 8.0 Hz, 2H), 3.81 (s, 3H), 3.72 (t, *J* = 8.0 Hz, 1H), 3.59 (t, *J* = 8.0 Hz, 1H), 3.33 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.97-3.02 (m, 1H), 2.88-2.94 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.90, 161.93 (t), 157.72, 137.72, 133.48, 129.27, 128.22, 127.37, 121.75, 117.35 (t, *J* = 247 Hz), 114.32, 55.49, 48.49, 41.30 (t, *J* = 21 Hz), 31.45, 26.71; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.13 (d, *J* = 266.96 Hz), -116.60 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{20}H_{20}F_2NO_3$ $[M+H]^+$: 360.1406; found: 360.1411.

4-(3,5-dimethoxybenzyl)-3,3-difluoro-1-(4-ethoxyphenyl)pyrrolidin-2-one(3ca) Pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.40 (s, 3H), 3.82 (s, 9H), 3.71 (t, *J* = 8.0 Hz, 1H), 3.57 (t, *J* = 8.0 Hz, 1H), 3.24 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.91-2.96 (m, 1H), 2.70-2.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.79, 161.20, 157.67, 139.24, 130.97, 121.75, 117.37 (t, *J* = 244 Hz), 114.29, 106.81, 98.63, 55.50, 48.53, 41.51 (t, *J* = 21 Hz), 31.77; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.44 (d, *J* = 366.96 Hz), -116.97 (d, *J* = 366.96 Hz); HRMS (ESI) calcd for $C_{20}H_{22}F_2NO_4$ $[M+H]^+$: 378.1511; found: 378.1514.

methyl-4-((4,4-difluoro-1-(4-methoxyphenyl)-5-oxopyrrolidin-3-yl)methyl)benzoate(3da) white solid; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.0 Hz, 2.0Hz), 7.50 (d, *J* = 8.0 Hz, 2.0Hz), 7.36 (d, *J* = 8.0 Hz, 2.0Hz), 6.92 (d, *J* = 8.0 Hz, 2.0Hz), 3.94 (s, 3H), 3.81 (s, 3H), 3.72 (t, *J* = 8.0 Hz, 1H), 3.59 (t, *J* = 8.0 Hz, 1H), 3.34 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.94-2.98 (m, 1H), 2.86-2.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.72, 161.89 (t), 157.72, 142.28, 130.85, 130.25, 129.18, 128.81, 121.69, 117.14 (t, *J* = 255 Hz), 114.32, 55.49, 52.18, 48.43 (d), 41.40 (t, *J* = 21 Hz), 31.57; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.24 (d, *J* = 266.96 Hz), -116.68 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{20}H_{20}F_2NO_4$ $[M+H]^+$: 376.1355, found: 376.1355.

ethyl-3-((4,4-difluoro-1-(4-methoxyphenyl)-5-oxopyrrolidin-3-yl)methyl)benzoate(3ea) white solid; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95-7.99 (m, 2H), 7.44-7.50 (m, 4H), 6.91 (d, *J* = 8.0 Hz), 4.43 (q, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 3.69 (t, *J* = 8.0 Hz, 1H), 3.59 (t, *J* = 8.0 Hz, 1H), 3.33 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.94-3.00 (m, 1H), 2.86-2.92 (m, 1H), 1.42 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.31, 162.29 (t), 157.70, 137.32, 133.22, 130.88, 129.65, 129.04, 128.34, 121.75, 117.45 (t, *J* = 233 Hz), 114.30, 61.18, 55.48, 48.47 (d), 41.51 (t, *J* = 21 Hz), 31.33, 14.34; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.28 (d, *J* = 266.96 Hz), -116.67 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{21}H_{22}F_2NO_4$ $[M+H]^+$: 390.1511, found: 390.1515.

tert-butyl(4-((4,4-difluoro-1-(4-methoxyphenyl)-5-oxopyrrolidin-3-yl)methyl)phenyl)carbamate(3fa) white solid; ^1H NMR (400

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MHz, $CDCl_3$) δ: 7.51 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.58 (s, 1H), 3.81 (s, 3H), 3.69 (t, *J* = 8.0 Hz, 1H), 3.56 (t, *J* = 8.0 Hz, 1H), 3.24 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.85-2.93 (m, 1H), 2.72-2.78 (m, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.16 (t), 157.64, 152.83, 137.42, 131.33, 130.98, 129.24, 121.69, 119.86, 117.55 (t, *J* = 231 Hz), 114.29, 80.64, 55.49, 48.49, 41.70 (t, *J* = 21 Hz), 30.82, 28.34; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.26 (d, *J* = 266.96 Hz), -116.99 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{23}H_{27}F_2N_2O_4$ $[M+H]^+$: 433.1933, found: 433.1930.

3,3-difluoro-1-(4-methoxyphenyl)-4-(4-(methylsulfonyl)benzyl)pyrrolidin-2-one(3ga) Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 4H), 6.93 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 3.75 (t, *J* = 8.0 Hz, 1H), 3.58 (t, *J* = 8.0 Hz, 1H), 3.36 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.08 (s, 3H), 2.93-3.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.69 (t), 157.79, 143.51, 139.53, 130.71, 129.81, 128.07, 121.71, 117.24 (t, *J* = 248 Hz), 114.36, 55.51, 48.38, 44.48, 41.26 (t, *J* = 21 Hz), 31.59; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -108.85 (d, *J* = 266.96 Hz), -116.31 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{19}H_{20}F_2NO_4S$ $[M+H]^+$: 396.1076, found: 396.1080.

4-(4-(tert-butyl)benzyl)-3,3-difluoro-1-(4-methoxyphenyl)pyrolidin-2-one(3ha) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 3.72 (t, *J* = 8.0 Hz, 1H), 3.56 (t, *J* = 8.0 Hz, 1H), 3.28 (dd, *J* = 16.0, 12.0 Hz, 1H), 2.91-2.99 (m, 1H), 2.76-2.82 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.20 (t), 157.67, 150.03, 133.80, 131.04, 128.39, 125.86, 121.80, 117.60 (t, *J* = 235 Hz), 114.29, 55.49, 48.65, 41.46 (t, *J* = 21 Hz), 34.49, 31.35; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.31 (d, *J* = 266.96 Hz), -117.16 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{22}H_{26}F_2NO_2$ $[M+H]^+$: 374.1926; found: 374.1923.

3,3-difluoro-4-(4-fluorobenzyl)-1-(4-methoxyphenyl)pyrrolidin-2-one(3ia) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, *J* = 8.0 Hz, 2H), 7.22-7.23 (m, 2H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.91-6.94 (m, 2H), 3.82 (s, 3H), 3.71 (t, *J* = 8.0 Hz, 1H), 3.56 (t, *J* = 8.0 Hz, 1H), 3.25 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.87-2.95 (m, 1H), 2.78-2.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.14 (d, *J* = 244 Hz), 162.02 (t), 157.71, 132.64, 130.92, 130.19, 121.71, 117.40 (t, *J* = 243 Hz), 115.72, 114.32, 55.49, 48.47, 41.53 (t, *J* = 21 Hz), 30.80; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.14 (d, *J* = 266.96 Hz), -115.54, -116.90 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{18}H_{17}F_3NO_2$ $[M+H]^+$: 336.1206, found: 336.1211.

3,3-difluoro-1-(4-methoxyphenyl)-4-(3-methylbenzyl)pyrrolidin-2-one(3ja) pale white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 8.0 Hz, 2H), 7.24-7.28 (m, 1H), 7.05-7.10 (m, 3H), 6.94 (d, *J* = 12.0 Hz, 2H), 3.82 (s, 3H), 3.69 (t, *J* = 8.0 Hz, 1H), 3.57 (t, *J* = 8.0 Hz, 1H), 3.28 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.91-2.98 (m, 1H), 2.74-2.80 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.19, 157.65, 138.68, 136.87, 131.01, 129.48, 128.84, 127.84, 125.70, 121.75, 117.48 (t, *J* = 242 Hz), 55.50, 48.59, 41.69 (t, *J* = 21 Hz), 31.42, 21.42; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.48 (d, *J* = 266.96 Hz), -117.07 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{19}H_{20}F_2NO_2$ $[M+H]^+$: 332.1457, found: 332.1460.

4-(4-chlorobenzyl)-3,3-difluoro-1-(4-methoxyphenyl)pyrrolidin-2-one(3ka) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0, 4.0 Hz, 2H), 3.82 (s, 3H), 3.73 (t, *J* = 8.0 Hz, 1H), 3.57 (t, *J* = 8.0 Hz, 1H), 3.27 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.88-2.95 (m, 1H), 2.78-2.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.95 (t), 157.71, 135.39, 133.03, 130.87, 130.08, 129.13, 121.70, 119.87 (t, *J* = 269 Hz), 114.33, 55.51, 48.43, 41.58 (t, *J* = 21 Hz), 30.97; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.07 (d, *J* = 266.96 Hz), -116.78 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{18}H_{17}ClF_2NO_2$ $[M+H]^+$: 352.0910, found: 352.0915.

3,3-difluoro-4-(3-fluoro-4-methylbenzyl)-1-(4-methoxyphenyl)pyrrolidin-2-one(3la) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 12 Hz, 2.0Hz), 7.17 (t, *J* = 8.0 Hz, 1H), 6.91-6.95 (m, 4H), 3.82 (s, 3H), 3.71 (t, *J* = 12 Hz, 1H), 3.58 (t, *J* = 12 Hz, 1H), 3.25 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.87-2.93 (m, 1H), 2.75-2.81 (m, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.63, 162.03 (t, *J* = 32 Hz), 160.19, 157.69, 136.5(d), 131.96, 130.93, 124.11, 123.51, 121.72, 117.26 (t, *J* = 252 Hz), 115.35(d), 114.31, 55.49, 48.47, 41.54 (t, *J* = 21 Hz), 30.97(d), 14.22(d); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.26 (d, *J* = 266.96 Hz), -116.74, -116.86 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{19}H_{19}F_3NO_2$ $[M+H]^+$: 350.1362, found: 350.1366.

3,3-difluoro-1-(4-methoxyphenyl)-4-(4-(trifluoromethyl)benzyl)pyrrolidin-2-one(3ma) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 3.73 (t, *J* = 8.0 Hz, 1H), 3.62 (t, *J* = 8.0 Hz, 1H), 3.34 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.88-2.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.79 (t), 157.76, 141.07, 130.79, 129.13, 125.88 (d, *J* = 4.0 Hz), 121.72, 117.18 (t, *J* = 274 Hz), 114.35, 55.50, 48.41, 41.24 (t, *J* = 20 Hz), 31.47; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.53, -109.15 (d, *J* = 266.96 Hz), -116.66 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{19}H_{17}F_5NO_2$ $[M+H]^+$: 386.1174; found: 386.1172.

3,3-difluoro-1-(4-methoxyphenyl)-4-(naphthalen-2-ylmethyl)pyrrolidin-2-one(3na) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83-7.88 (m, 3H), 7.72 (s, 1H), 7.50-7.52 (m, 4H), 7.41 (d, *J* = 12 Hz, 1H), 6.92 (d, *J* = 12 Hz, 2H), 3.81 (s, 3H), 3.59-3.70 (m, 2H), 3.48 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.06-3.11 (m, 1H), 2.98-3.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.13 (t), 157.65, 134.38, 133.55, 132.45, 130.98, 128.82, 127.75, 127.53, 127.37, 126.49, 125.97, 121.68, 117.31 (t, J = 214 Hz), 114.29, 55.49, 48.55, 41.59 (t, *J* = 21 Hz), 31.70; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.29 (d, *J* = 266.96 Hz), -116.82 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{22}H_{20}F_2NO_2$ $[M+H]^+$: 368.1457, found: 368.1455.

3,3-difluoro-4-(4-methoxybenzyl)-1-(4-methoxyphenyl)pyrrolidin-2-one(3oa) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.93 (t, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 3.69 (t, *J* = 8.0 Hz, 1H), 3.58 (t,

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J = 8.0 Hz, 1H), 3.25 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.85-2.94 (m, 1H), 2.73-2.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.19 (t), 158.65, 157.64, 131.02, 129.71, 128.82, 121.70, 121.61, 117.58 (t, *J* = 244 Hz), 114.34, 114.29, 55.50 (d, *J* = 20 Hz), 48.53, 41.85 (t, *J* = 20 Hz), 30.65; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.25 (d, *J* = 266.96 Hz), -117.07 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{19}H_{20}F_2NO_3$ $[M+H]^+$: 348.1406, found: 348.1406.

4-(benzofuran-2-ylmethyl)-3,3-difluoro-1-phenylpyrrolidin-2-one(3pb) pure crystal; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.40-7.47 (m, 3H), 7.24-7.32 (m, 3H), 6.60 (s, 1H), 3.96 (t, *J* = 8.0 Hz, 1H), 3.76 (t, *J* = 8.0 Hz, 1H), 3.43 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.15-3.22 (m, 1H), 3.05-3.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.02 (t), 154.96, 153.69, 137.80, 129.22, 128.33, 126.29, 124.14, 123.01, 120.76, 120.01, 117.17 (t, *J* = 241 Hz), 111.01, 104.54, 48.28 (d), 38.94 (t, *J* = 21 Hz), 24.89; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -110.64 (d, *J* = 266.96 Hz), -118.80 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{19}H_{16}F_2NO_2$ $[M+H]^+$: 328.1144, found: 328.1141.

4-(4-chlorobenzyl)-3,3-difluoro-1-phenylpyrrolidin-2-one(3kb) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.21-7.28 (m, 3H), 3.76 (t, *J* = 8.0 Hz, 1H), 3.59 (t, *J* = 8.0 Hz, 1H), 3.28 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.89-2.97 (m, 1H), 2.79-2.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.25 (t), 137.81, 135.32, 133.07, 130.08, 129.21, 129.15, 126.26, 119.96, 117.18 (t, *J* = 249 Hz), 48.04, 41.32 (t, *J* = 21 Hz), 30.92; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.17 (d, *J* = 266.96 Hz), -117.49 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{17}H_{15}ClF_2NO$ $[M+H]^+$: 322.0805, found: 322.0801.

4-benzyl-3,3-difluoro-1-phenylpyrrolidin-2-one(3ab) pure crystal; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 8.0 Hz, 2H), 7.33-7.41 (m, 4H), 7.23-7.29 (m, 4H), 3.74 (t, *J* = 8.0 Hz, 1H), 3.62 (t, *J* = 8.0 Hz, 1H), 3.32 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.92-3.01 (m, 1H), 2.80-2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.87 (t), 137.91, 136.89, 129.17, 129.01, 128.72, 127.15, 126.18, 119.99, 117.33 (t, *J* = 21 Hz), 48.16 (d), 41.65 (t, *J* = 21 Hz), 31.48 (d); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.57 (d, *J* = 266.96 Hz), -117.24 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{17}H_{16}F_2NO$ $[M+H]^+$: 288.1194, found: 288.1192.

4-benzyl-1-(3,5-dimethylphenyl)-3,3-difluoropyrrolidin-2-one(3ac) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (t, *J* = 8.0 Hz, 2H), 7.27-7.33 (m, 3H), 7.21 (s, 2H), 6.90 (s, 1H), 3.74 (t, *J* = 8.0 Hz, 1H), 3.61 (t, *J* = 8.0 Hz, 1H), 3.32 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.90-3.00 (m, 1H), 2.79-2.85 (m, 1H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.68 (t), 138.93, 137.76, 136.98, 128.99, 128.74, 128.01, 127.10, 118.00, 117.42 (t, *J* = 245 Hz), 48.44, 41.68 (t, *J* = 21 Hz), 31.55, 21.43; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.50 (d, *J* = 266.96 Hz), -117.29 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{19}H_{20}F_2NO$ $[M+H]^+$: 316.1507, found: 316.1504.

4-benzyl-3,3-difluoro-1-(4-fluorophenyl)pyrrolidin-2-one(3ad) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (q, *J* = 4.0 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.27-7.31 (m, 3H), 7.12 (t, *J* = 8.0 Hz, 2H), 3.71 (t, *J* = 8.0 Hz, 1H), 3.60 (t, *J* = 8.0 Hz, 1H), 3.32 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.91-3.04 (m, 1H), 2.80-2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.36 (t), 161.6 (d, *J* = 245 Hz), 136.78, 133.97, 129.03, 128.72, 127.19, 121.90, 117.30 (t, *J* = 249 Hz), 116.09, 115.87, 48.40, 41.42 (t, *J* = 21 Hz), 31.44; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.63 (d, *J* = 266.96 Hz), -115.10, -117.14 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{17}H_{15}F_3NO$ $[M+H]^+$: 306.1100, found: 306.1108.

4-benzyl-1-(4-chlorophenyl)-3,3-difluoropyrrolidin-2-one(3ae) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 8.0 Hz, 2H), 7.31-7.40 (m, 5H), 7.28 (d, *J* = 8.0 Hz, 2H), 3.71 (t, *J* = 8.0 Hz, 1H), 3.59 (t, *J* = 8.0 Hz, 1H), 3.32 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.92-2.98 (m, 1H), 2.80-2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.44 (t), 136.70, 136.45, 131.44, 129.23, 129.05, 128.71, 127.22, 117.13 (t, *J* = 241 Hz), 48.05 (d), 41.55 (t, *J* = 21 Hz), 31.42 (d); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -111.20 (d, *J* = 266.96 Hz), -118.70 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{17}H_{15}ClF_2NO$ $[M+H]^+$: 322.0805, found: 322.0800.

4-benzyl-3,3-difluoro-1-(p-tolyl)pyrrolidin-2-one(3af) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.27-7.33 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 3.74 (t, *J* = 8.0 Hz, 1H), 3.61 (t, *J* = 8.0 Hz, 1H), 3.32 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.89-3.02 (m, 1H), 2.79-2.85 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.49 (t), 136.95, 136.07, 135.40, 129.68, 128.99, 128.73, 127.12, 119.98, 114.92 (t, *J* = 252 Hz), 48.26, 41.66 (t, *J* = 21 Hz), 31.52, 20.96; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -111.00 (d, *J* = 266.96 Hz), -118.73 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{18}H_{18}F_2NO$ $[M+H]^+$: 302.1351, found: 302.1357.

4-benzyl-3,3-difluoro-1-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one(3ag) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.28-7.34 (m, 3H), 3.78 (t, *J* = 8.0 Hz, 1H), 3.64 (t, *J* = 8.0 Hz, 1H), 3.33 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.94-3.09 (m, 1H), 2.82-2.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.79 (t), 140.79, 136.59, 129.07, 128.70, 127.27, 126.37 (q), 116.96 (t, J = 244 Hz), 47.88, 41.30 (t, *J* = 21 Hz), 31.36; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.46, -109.87 (d, *J* = 266.96 Hz), -117.29 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{18}H_{15}F_5NO$ $[M+H]^+$: 356.1068, found: 356.1065.

1-(4-acetylphenyl)-4-benzyl-3,3-difluoropyrrolidin-2-one(3ah) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.27-7.33 (m, 3H), 3.79 (t, *J* = 8.0 Hz, 1H), 3.65 (t, *J* = 8.0 Hz, 1H), 3.32 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.92-3.03 (m, 1H), 2.81-2.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.80, 163.11 (t), 141.75, 141.76, 136.61, 134.26, 129.52, 129.07, 128.71, 127.25, 119.12, 117.04 (t, *J* = 249 Hz), 47.86, 41.26 (t, *J* = 21 Hz), 31.37, 26.55; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.82 (d, *J* = 266.96 Hz), -117.17 (d, *J* = 266.96 Hz); HRMS (ESI) calcd for $C_{19}H_{18}F_2NO_2$ $[M+H]^+$: 330.1300, found: 330.1308.

4-benzyl-3,3-difluoro-1-(3-fluoro-4-methylphenyl)pyrrolidin-2-one(3ai) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17-7.46 (m,

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8H), 3.71 (t, J = 8.0 Hz, 1H), 3.57 (t, J = 8.0 Hz, 1H), 3.30 (dd, J = 12.0, 4.0 Hz, 1H), 2.91-2.99 (m, 1H), 2.79-2.85 (m, 1H), 2.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.79 (t), 162.24 (d, J = 243 Hz), 136.93, 131.62, 129.03, 128.71, 127.19, 122.81, 117.25 (t, J = 248 Hz), 114.82, 107.36, 107.07, 48.08, 41.31 (t, J = 21 Hz), 31.45, 14.19; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -111.15 (d, J = 266.96 Hz), -115.99, -118.66 (d, J = 266.96 Hz); HRMS (ESI) calcd for $C_{18}H_{17}F_3NO$ $[M+H]^+$: 320.1257, found: 320.1253.

4-benzyl-1-(4-chloro-3-methoxyphenyl)-3,3-difluoropyrrolidin-2-one(3aj) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (s, 1H), 7.27-7.33 (m, 6H), 6.78 (d, J = 8.0 Hz, 1H), 3.93 (s, 3H), 3.74 (t, J = 8.0 Hz, 1H), 3.59 (t, J = 8.0 Hz, 1H), 3.32 (dd, J = 16.0, 4.0 Hz, 1H), 2.91-2.98 (m, 1H), 2.80-2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.55 (t), 155.30, 137.63, 136.69, 130.06, 129.05, 128.71, 127.22, 119.82, 117.29 (t, J = 236 Hz), 111.36, 104.81, 56.30, 48.19, 41.27 (t, J = 21 Hz), 31.44; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.48 (d, J = 266.96 Hz), -117.48 (d, J = 266.96 Hz); HRMS (ESI) calcd for $C_{18}H_{17}ClF_2NO_2$ $[M+H]^+$: 352.0910, found: 352.0913.

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