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A Nickel(II) Chloride and Tetrahydroxydiboron Cocatalyzed Facile Synthesis of Benzo[*b*]azepines with an Appended Fluorinated Side Chain

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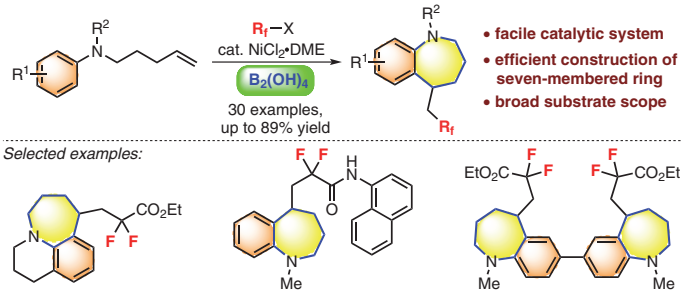

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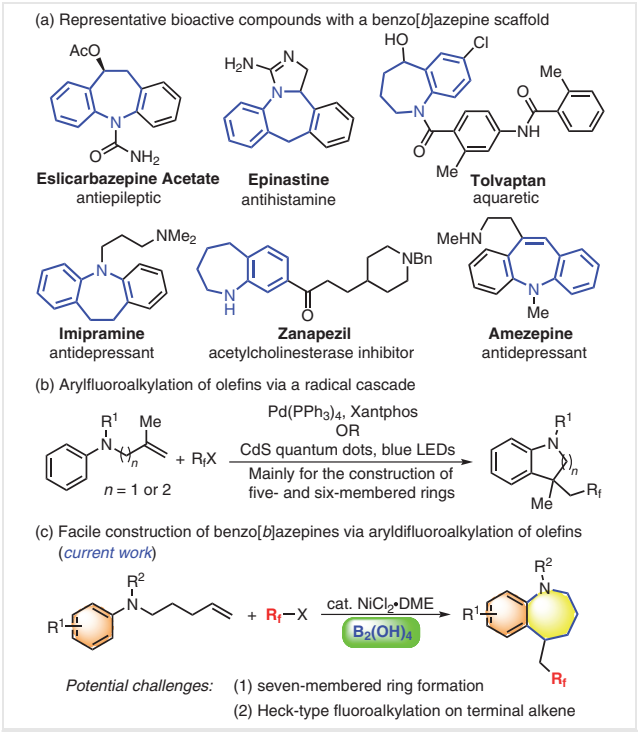
Abstract A novel nickel-catalyzed chemoselective cascade reaction strategy towards the synthesis of benzo[*b*]azepines was developed. The method is characterized by simple and mild conditions, low cost, and a wide range of substrates. This method enabled the facile and efficient synthesis of a series of 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine analogues with an appended fluorinated side chain.

Key words tetrahydroxydiboron, ethyl bromodifluoroacetate, nickel catalyst, radical cascade, benzo[*b*]azepines

Benzo[*b*]azepines have a wide range of applications in biology and medicine as a biologically significant benzoheterocyclic structure. Biologically active compounds containing this structural unit have been reported, including eslicarbazepine acetate, epinastine, tolvaptan, imipramine, zanapezil, and so on, some of which are used as antiepileptic, antihistamine, aquaretic, and antidepressant agents (Scheme 1a).[1–5] Meanwhile, recent studies have shown that the introduction of fluorine atoms into the molecular structure of drugs can effectively improve the metabolic stability, bioavailability, and protein–ligand interaction of drug molecules.[6–9] Therefore, the introduction of fluorine-containing groups into a parent structure to improve drug performance has become a common strategy and the design and synthesis of fluorine-containing compounds is a hot topic of current research.[10–12] Compared with normal tetrahydrobenzo[*b*]azepines, their fluorinated analogues might exhibit more excellent bioactivities and drug performances. However, the synthesis of fluorinated tetrahydrobenzo[*b*]azepines still poses a major challenge to synthetic chemists, which can be attributed to the practical construction of the seven-membered ring and the introduction of fluorinated groups. The current methods for constructing a seven-membered ring mainly include cycloaddition, ring extension resulting from the rearrangement of aryl azides, aziridines, or nitrones, derivatization of unsaturated bonds with bifunctional precursors, and radical tandem cyclization/addition reactions.[13–18] The ubiquitous presence of heteroatom-containing seven-membered rings in natural compounds has led to the development of novel synthetic methods for seven-membered rings especially those containing at least one heteroatom so various natural compounds and potential bioactive compounds could be conveniently accessed. The synthesis of tetrahydrobenzo[*b*]azepines has been realized through the intramolecular Heck reaction[19] or various transition-metal-catalyzed tandem reactions.[20–23] However, the synthesis of tetrahydrobenzo[*b*]azepines with a fluorinated pendant is just beginning.[24]

In the past years, five- or six-membered azaheterocycles with fluoroalkyl pendants have been successfully constructed through the radical cascade reaction of fluoroalkylated halides with unactivated olefins.[25–30] For example, Cheng's group[31] reported their study on palladium-catalyzed arylperfluorinated alkylation of unactivated olefins to construct dihydroindole-type heterocyclic products in 2017. Then Feng's group[24] reported their work on photocatalyzed aryldifluoroalkylation of unactivated olefins to construct dihydroindole and tetrahydroquinoline-type products in 2019, which also yielded the only benzazepine example, albeit in 42% yield (Scheme 1b). Until the present, the synthesis of fluoroalkyl-appended benzazepines has been only scarcely reported. Therefore, it is necessary to develop a facile and practical synthetic strategy for the efficient construction of benzazepine heptacycles.

Our group has been exploiting ethyl bromodifluoroacetate as a universal difluoroalkylation reagent for the synthesis of various difluoroalkylated products. We have successfully developed an efficient copper–amine system for

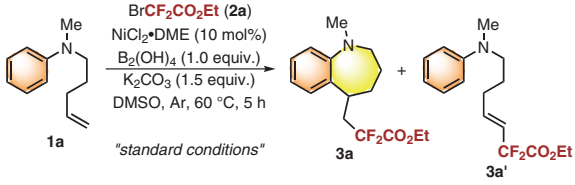


Scheme 1 Benzo[*b*]azepine drugs and arylfluoroalkylation of olefins

initiating difluoroalkyl radicals, and have successfully applied this system to a series of cascade reactions.[32–36] Our recent work has revealed a novel strategy for the initiation of difluoroalkyl radicals by tetrahydroxydiboron, which has been successfully applied to the synthesis of a series of izidine analogues via a radical cascade reaction of ethyl bromodifluoroacetate with indoles bearing an *N*-tethered unactivated olefin.[37,38] Here we hoped to further apply this strategy to the reaction of anilines bearing an *N*-tethered unactivated olefin and fluoroalkylated halides, which will provide a facile construction of fluoroalkyl-appended tetrahydrobenzo[*b*]azepines (Scheme 1c).

Initially, the reaction was carried out with *N*-methyl-*N*-(pent-4-en-1-yl)aniline (**1a**) as a substrate and ethyl bromodifluoroacetate (**2a**) as a fluorine source in the presence of $NiCl_2$·DME (10 mmol%), $B_2(OH)_4$ (1.0 equiv), and K_2CO_3 (1.5 equiv) in dimethyl sulfoxide (DMSO) under an argon atmosphere at 60 °C. It was exciting that the expected product **3a** was observed with a yield of 88% after 5 hours, accompanied by 8% of the Heck-type byproduct **3a′** (Table 1, entry 1). In the absence of nickel catalyst, tetrahydroxydiboron, or base, neither cyclic compound **3a** nor byproduct **3a′** can be afforded and substrate **1a** remained (entry 2), indicating that these reaction parameters are all essential for the reaction to proceed successfully. Then, we examined the effect of the nickel catalyst on the reaction. When $NiCl_2$·DPPE was used instead of $NiCl_2$·DME, a similar result was obtained with 82% yield of **3a** and 9% yield of **3a′**; however, in the presence of $NiCl_2(PPh_3)_2$, the yield of cyclic product dropped significantly (entries 3 and 4). With $Ni(acac)_2$ as the catalyst, the yield of cyclic product **3a** decreased significantly while the yield of byproduct **3a′** increased obviously (entry 5). Subsequently, when we tried to reduce the amount of $B_2(OH)_4$ to a substoichiometric amount, the yield of cyclic product **3a** slightly decreased and the yield of **3a′** slightly increased (entry 6). When $B_2(OH)_4$ was replaced with B_2pin_2 or zinc powder, no reaction occurred, indicating that the role of $B_2(OH)_4$ is beyond radical initiator through homolytic B–B cleavage and reductant (entries 7 and 8). Excellent yields were also obtained when CsF was used instead of K_2CO_3, while the yields decreased considerably when strong inorganic bases such as KOH or the organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used (entries 9–11). When *N*,*N*-dimethylformamide (DMF), 1,4-dioxane, or *N*-methyl-2-pyrrolidone (NMP) was used as a solvent, the target product yield de-

Table 1 Optimization of the Reaction Conditions[a]



Entry	Variation from the standard conditions	Yield (%)[b]	
		3a	**3a′**
1	none	88	8
2[c]	w/o $NiCl_2$·DME, w/o $B_2(OH)_4$, or w/o K_2CO_3	n.d.	n.d.
3	$NiCl_2$·DPPE instead of $NiCl_2$·DME	82	9
4	$NiCl_2(PPh_3)_2$ instead of $NiCl_2$·DME	45	9
5	$Ni(acac)_2$ instead of $NiCl_2$·DME	43	31
6	0.5 equivalents of $B_2(OH)_4$	75	20
7[c]	B_2pin_2 instead of $B_2(OH)_4$	n.d.	n.d.
8[c]	Zn instead of $B_2(OH)_4$	n.d.	n.d.
9	CsF instead of K_2CO_3	85	15
10	KOH instead of K_2CO_3	54	n.d.
11	DBU instead of K_2CO_3	21	16
12	DMF instead of DMSO	62	38
13	1,4-dioxane instead of DMSO	66	13
14	NMP instead of DMSO	68	15

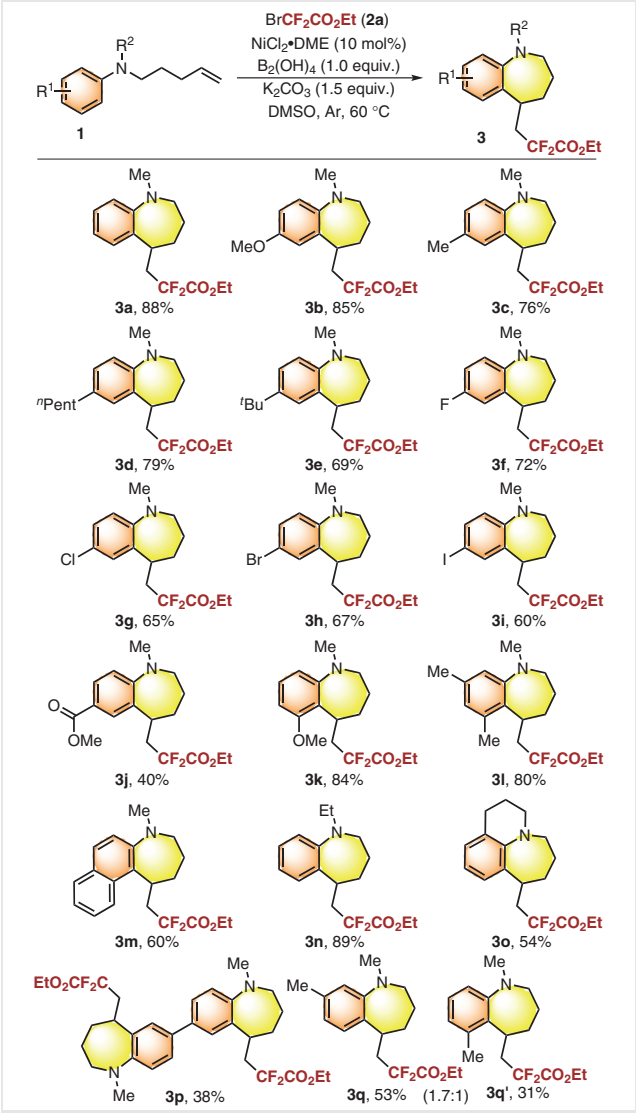
[a] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), **2a** (0.30 mmol, 1.5 equiv), $NiCl_2$·DME (0.02 mmol, 10 mol%), $B_2(OH)_4$ (0.20 mmol, 1.0 equiv), K_2CO_3 (0.30 mmol, 1.5 equiv), DMSO (1.0 mL), argon atmosphere, 60 °C, 5 h.
[b] Yields were determined by GC analysis with mesitylene as the internal standard. n.d.: not detected.
[c] **1a** was not consumed.

creased obviously (entries 12–14). Based on the above screening results, the conditions shown in entry 1 were selected as the optimal conditions.

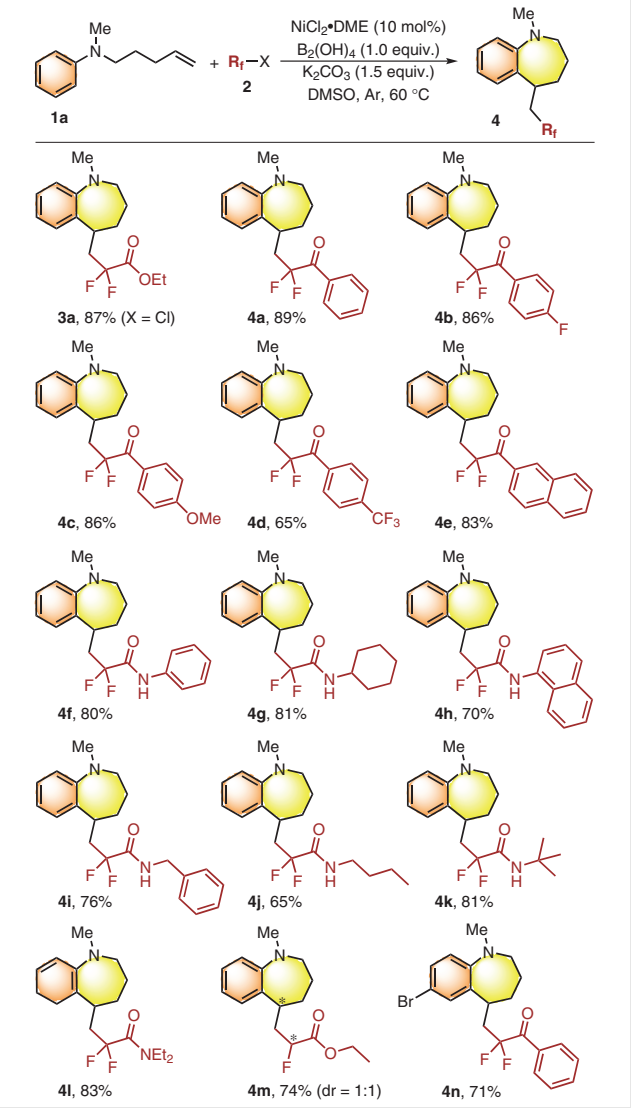
Then, we examined the scope of substrates under the optimal reaction conditions. Firstly, *N*-methyl-*N*-(pent-4-en-1-yl)aniline substrates with different substituents attached to the benzene ring were investigated. As depicted in Scheme 2, the target products were obtained in moderate to excellent yields when the *para*-position of the benzene ring was modified with either an electron-donating or an electron-withdrawing substituent (**3a**–**3j**). When the *meta*-position of the benzene ring has a methoxy group, the sterically hindered product **3k** can be obtained with excellent regioselectivity and yield. We speculate that the coordination of oxygen to nickel might play a key role in overcoming the site hindrance effect. The result of the reaction of the *m*-methyl-substituted substrate, which gives 1,2,4-trisubstituted product **3q** and 1,2,3-trisubstituted product **3q′** in 84% yield with a 1.7:1 ratio, supports our speculation. When the 3- and 5-positions of the benzene ring are substituted by methyl groups, heptacycle **3l** can also be constructed in a yield of 80%. When *N*-methyl-*N*-(pent-4-en-1-yl)naphthalen-2-amine (**1m**) was used instead of **1a**, the corresponding target product **3m** could also be obtained in good yield. Excellent yield was also obtained when the methyl substituent on the nitrogen atom was replaced by other alkyl groups such as ethyl (**3n**). Surprisingly, when 1-(pent-4-en-1-yl)-1,2,3,4-tetrahydroquinoline (**1o**) was used as the substrate, a tricyclic structure, product **3o**, which is difficult to synthesize by other strategies, was obtained in a moderate yield. A structurally symmetrical product containing two seven-membered rings (**3p**) can be obtained when there are two reaction sites in the substrate.

Then, different fluorine sources were applied to the reaction and the results are summarized in Scheme 3. Ethyl chlorodifluoroacetate also gave the target product **3a** in excellent yield. Also, various bromodifluoroacetophenones with an electron-donating or electron-withdrawing substituent attached to the benzene ring and bromodifluoroacetonaphthone could give the corresponding products in good to excellent yields (**4a**–**4e**). When bromodifluoroacetamides were used as fluorine sources, the corresponding target products could be obtained in good to excellent yields (**4f**–**4l**). In the case of ethyl bromofluoroacetate as fluorine source, the target product **4m** was also obtained with a good yield. In addition, a halogen group is compatible in the process (**4n**).

In order to elucidate the possible mechanism of the reaction, several control experiments were carried out. When TEMPO or 1,1-diphenylethylene was added, respectively, to the reaction mixture under the standard conditions, neither the target product **3a** nor the byproduct **3a′** was formed. Instead, 21% yield of TEMPO–CF_2CO_2Et adduct (**5**) was obtained (Scheme 4a), and 38% yield of a mixture of **6** and **7** was obtained (Scheme 4b), suggesting that the reaction undergoes a free-radical pathway. Meanwhile, we speculated that activation of the benzene ring by the amine group plays an important role in the cyclization process. When *N*-(pent-4-en-1-yl)-*N*-phenylacetamide (**1r**) was used as a substrate instead of **1a**, no expected cyclization product was obtained and the bromodifluoroalkylation product **8** of the terminal olefin was obtained in 66% yield. We also found that increasing the basicity of the reaction system facilitated the formation of Heck-type product **8′**. When we added triethylamine or DBU to the reactions of *N*-acetylated substrate **1r**, the formation of Heck-type product was observed in both cases (Scheme 4c). We also used 4-pentenyl phenyl ether (**1s**) as a substrate, which also gave



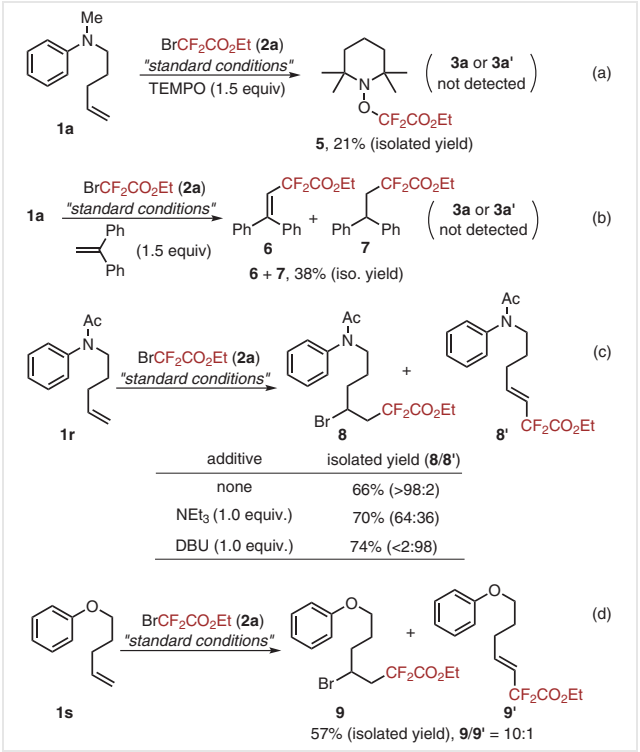
Scheme 2 Substrate scope of aryls. *Reagents and conditions*: **1** (1.0 mmol, 1.0 equiv), **2a** (1.5 mmol, 1.5 equiv), $NiCl_2$·DME (0.1 mmol, 10 mol%), $B_2(OH)_4$ (1.0 mmol, 1.0 equiv), K_2CO_3 (1.5 mmol, 1.5 equiv), DMSO (5.0 mL), argon atmosphere, 60 °C, 5 h.



Scheme 3 Substrate scope of halides. *Reagents and conditions*: **1a** (1.0 mmol, 1.0 equiv), **2** (1.5 mmol, 1.5 equiv), $NiCl_2$·DME (0.1 mmol, 10 mol%), $B_2(OH)_4$ (1.0 mmol, 1.0 equiv), K_2CO_3 (1.5 mmol, 1.5 equiv), DMSO (5.0 mL), argon atmosphere, 60 °C, 5–10 h.

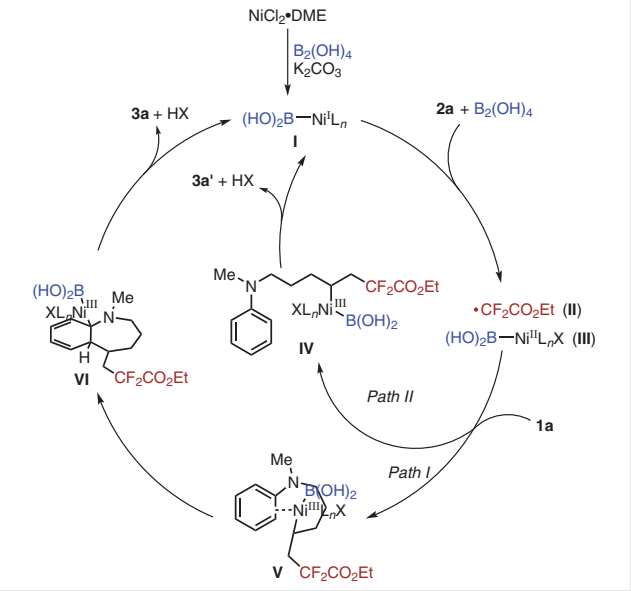
the alkene bromodifluoroalkylation product **9** with a small amount of Heck-type product **9′** (**9**/**9′** = 10:1 by ^{1}H NMR) in 57% yield (Scheme 4d). Accordingly, in the absence of the amine moiety, only linear bromodifluoroalkylation of alkenes or Heck-type products were obtained. Therefore, we believe that the amine moiety can increase the electron density on the benzene ring and favor the cyclization.

Based on the above control experiments, we propose a possible reaction pathway as shown in Scheme 5. Firstly, the reaction of $NiCl_2$ and $B_2(OH)_4$ in the presence of base generates $(HO)_2B–Ni^{I}L_n$ (**I**), which further reacts with **2a** to form $^{\bullet}CF_2CO_2Et$ (**II**) and $(HO)_2B–Ni^{II}L_nBr$ (**III**). Subsequently, attack of **II** on the terminal olefin affords a new alkyl radical. The alkyl radical can combine with the free **III** to give intermediate **IV**, which has two possible conversion pathways. Direct β-H elimination from **IV** affords the byproduct **3a′**. Meanwhile, coordination of the benzene ring with Ni (intermediate **V**) renders the alkyl radical spatially advantageous to attack the benzene ring to form a C–Ni bond and give intermediate **VI**, which then undergoes β-H elimination to give the target product **3a** and completes the cycle by reductive elimination.



Scheme 4 Mechanistic studies. *Standard conditions*: $NiCl_2$·DME (0.1 mmol, 10 mol%), $B_2(OH)_4$ (1.0 mmol, 1.0 equiv), K_2CO_3 (1.5 mmol, 1.5 equiv), DMSO (5.0 mL), argon atmosphere, 60 °C, 5 h.

In conclusion, a novel strategy for the direct construction of tetrahydrobenzo[*b*]azepines has been developed which features simple starting materials, an easily accessed Ni–B catalyst, a simple cascade reaction, and no need of ligands. By this method, a variety of benzazepine heptacyclic products have been conveniently synthesized, including a tricyclic compound with high strain and a compound with two tetrahydrobenzo[*b*]azepine structural units. This method provides an alternative to the existing cascade reaction of fluoroalkylated halides with unactivated olefins for the construction of multiple benzoheterocycles. This strategy demonstrates the unique ability of tetrahydroxydiboron to initiate free radicals and further exploration of its practical value in organic synthesis is still ongoing in this group.



Scheme 5 Proposed reaction mechanism

All experiments were conducted under argon atmosphere. DMF, DMSO, DMAc, NMP, THF, DCE, DCM, 1,4-dioxane, and acetonitrile were dried and distilled by the standard methods. Other commercially available reagents were purchased and used without further purification, unless otherwise stated. Flash chromatographic separations were carried out on 200–300 mesh silica gel. Reactions were monitored by TLC and GC analysis of reaction aliquots. GC analysis was performed on an Agilent 7890 gas chromatograph using an HP-5 capillary column (30 m × 0.32 mm, 0.5 μm film) with appropriate hydrocarbons as internal standards. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in deuterated solvent on a Bruker Avance III or JNM-ECZ600R spectrometer and calibrated using residual undeuterated solvent ($CDCl_3$ at 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in hertz (Hz). High-resolution mass spectrometry (HRMS) was recorded on a Waters G2-XS QTOF mass analyzer with electrospray ionization (ESI).

Tetrahydrobenzo[*b*]azepines 3 and 4; General Procedure

To a 25-mL Schlenk tube were added $NiCl_2$·DME (22.2 mg, 0.1 mmol), K_2CO_3 [207.3 mg, 1.5 mmol (for products **3a–3o**, **3q**); 2.5 mmol (for product **3p**)], and $B_2(OH)_4$ [89.6 mg, 1.0 mmol (for products **3a–3o**, **3q**); 2.0 mmol (for product **3p**)] under argon atmosphere. DMSO (5.0 mL), aniline **1** [e.g., *N*-methyl-*N*-(pent-4-en-1-yl)aniline (**1a**; 175.3 mg, 1.0 mmol)] and halide **2** {e.g., ethyl bromodifluoroacetate [**2a**; 192.3 μL, 1.5 mmol (for products **3a–3o**, **3q**); 2.5 mmol (for product **3p**)]}, which were synthesized as previously reported,[39–44] were added subsequently. The reaction mixture was stirred at 60 °C (oil bath) for 5 h. After completion by TLC detection, the reaction was cooled to room temperature and quenched with water and EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified with silica gel chromatography (petroleum ether/EtOAc, 50:1–10:1 v/v) to afford the pure products **3** and **4**.

Ethyl 2,2-Difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanoate (3a)

Light-yellow liquid; yield: 260.3 mg (88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, *J* = 7.5 Hz, 1 H), 7.04 (d, *J* = 7.2 Hz, 1 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 6.87 (t, *J* = 7.2 Hz, 1 H), 4.11–3.90 (m, 2 H), 3.37–3.24 (m, 1 H), 3.04–2.87 (m, 2 H), 2.84 (s, 3 H), 2.77 (t, *J* = 11.6 Hz, 1 H), 2.49–2.34 (m, 1 H), 1.92–1.79 (m, 1 H), 1.79–1.69 (m, 2 H), 1.66–1.57 (m, 1 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 33.4 Hz), 151.8, 135.5, 129.4, 127.5, 121.4, 117.1, 116.8 (t, *J* = 251.0 Hz), 62.7, 56.9, 42.7, 38.3, 36.6 (t, *J* = 22.3 Hz), 30.8, 25.4, 13.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –100.29 (d, *J* = 257.6 Hz, 1 F), –107.16 (d, *J* = 257.5 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}F_2NO_2^+$: 298.1619; found: 298.1618.

Ethyl 2,2-Difluoro-3-(7-methoxy-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanoate (3b)

Light-yellow liquid; yield: 277.2 mg (85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (d, *J* = 8.7 Hz, 1 H), 6.70 (dd, *J* = 8.7, 3.0 Hz, 1 H), 6.63 (d, *J* = 3.0 Hz, 1 H), 4.12–3.92 (m, 2 H), 3.76 (s, 3 H), 3.31–3.20 (m, 1 H), 3.02–2.83 (m, 2 H), 2.79 (s, 3 H), 2.73–2.62 (m, 1 H), 2.51–2.35 (m, 1 H), 1.88–1.70 (m, 3 H), 1.63–1.53 (m, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 33.1 Hz), 154.3, 145.3, 137.2, 117.8, 116.8 (t, *J* = 250.9 Hz), 115.5, 111.6, 62.7, 57.0, 55.5, 42.9, 38.4, 36.6 (t, *J* = 22.4 Hz), 30.8, 25.6, 13.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –100.36 (d, *J* = 257.2 Hz, 1 F), –107.03 (d, *J* = 257.2 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}F_2NO_3^+$: 328.1724; found: 328.1728.

Ethyl 3-(1,7-Dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-2,2-difluoropropanoate (3c)[24]

Colorless liquid; yield: 237.5 mg (76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 7.8 Hz, 1 H), 6.84 (d, *J* = 9.7 Hz, 2 H), 4.10–3.91 (m, 2 H), 3.25 (p, *J* = 6.0 Hz, 1 H), 3.03–2.85 (m, 2 H), 2.82 (s, 3 H), 2.71 (t, *J* = 11.9 Hz, 1 H), 2.51–2.38 (m, 1 H), 2.27 (s, 3 H), 1.93–1.68 (m, 3 H), 1.60 (d, *J* = 13.1 Hz, 1 H), 1.23 (t, *J* = 7.0 Hz, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 33.2 Hz), 149.5, 135.6, 130.6, 130.3, 127.8, 117.0, 116.8 (t, *J* = 250.9 Hz), 62.6, 57.0, 42.8, 38.4, 36.6 (t, *J* = 22.2 Hz), 30.8, 25.5, 20.7, 13.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –100.21 (d, *J* = 257.4 Hz, 1 F), –107.21 (d, *J* = 257.5 Hz, 1 F).

Ethyl 2,2-Difluoro-3-(1-methyl-7-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanoate (3d)

Colorless liquid; yield: 288.4 mg (79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 7.8 Hz, 1 H), 6.89–6.81 (m, 2 H), 4.11–3.90 (m, 2 H), 3.32–3.21 (m, 1 H), 3.01–2.86 (m, 2 H), 2.82 (s, 3 H), 2.72 (t, *J* = 11.4 Hz, 1 H), 2.53–2.48 (m, 2 H), 2.46–2.38 (m, 1 H), 1.94–1.69 (m, 3 H), 1.65–1.53 (m, 3 H), 1.36–1.25 (m, 4 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 33.1 Hz), 149.6, 135.9, 135.6, 129.7, 127.0, 116.85, 116.85 (t, *J* = 250.8 Hz), 62.6, 57.0, 42.9, 38.5, 36.6 (t, *J* = 22.3 Hz), 35.3, 31.8, 31.5, 30.9, 25.6, 22.7, 14.2, 14.0.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.60 (d, *J* = 257.4 Hz, 1 F), –106.98 (d, *J* = 257.5 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{32}F_2NO_2^+$: 368.2401; found: 368.2408.

Ethyl 3-(7-(*tert*-Butyl)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-2,2-difluoropropanoate (3e)

Colorless liquid; yield: 243.5 mg (69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.15 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.04 (s, 1 H), 6.87 (d, *J* = 8.3 Hz, 1 H), 4.12–3.85 (m, 2 H), 3.27 (s, 1 H), 3.03–2.85 (m, 2 H), 2.82 (s, 3 H), 2.71 (t, *J* = 11.5 Hz, 1 H), 2.53–2.40 (m, 1 H), 1.95–1.56 (m, 4 H), 1.30 (s, 9 H), 1.20 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 32.8 Hz), 149.4, 144.0, 135.2, 127.0, 123.9, 116.9 (t, *J* = 253.1 Hz), 116.5, 62.6, 57.0, 43.0, 39.2, 36.5 (t, *J* = 22.0 Hz), 34.1, 31.6, 30.9, 25.6, 14.0.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.6 (d, *J* = 257.5 Hz, 1 F), –107.0 (d, *J* = 257.8 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{30}F_2NO_2^+$: 354.2245; found: 354.2251.

Ethyl 2,2-Difluoro-3-(7-fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanoate (3f)

Light-yellow liquid; yield: 225.8 mg (72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86–6.83 (m, 2 H), 6.77 (d, *J* = 9.0 Hz, 1 H), 4.13–4.03 (m, 2 H), 3.27 (p, *J* = 6.2 Hz, 1 H), 2.95–2.84 (m, 2 H), 2.80 (s, 3 H), 2.77–2.69 (m, 1 H), 2.48–2.34 (m, 1 H), 1.82–1.68 (m, 3 H), 1.63–1.56 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 32.9 Hz), 157.9 (d, *J* = 239.7 Hz), 147.8, 137.7 (d, *J* = 6.5 Hz), 118.1 (d, *J* = 8.0 Hz), 116.6 (t, *J* = 251.5 Hz), 115.9 (d, *J* = 22.6 Hz), 113.3 (d, *J* = 21.4 Hz), 62.8, 56.7, 42.9, 37.8, 36.6 (t, *J* = 22.5 Hz), 30.6, 25.4, 13.9.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.96 (d, *J* = 258.1 Hz, 1 F), –106.76 (d, *J* = 258.4 Hz, 1 F), –123.10 (s, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}F_3NO_2^+$: 316.1524; found: 316.1529.

Ethyl 3-(7-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-2,2-difluoropropanoate (3g)

Light-yellow liquid; yield: 216.3 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (dd, *J* = 8.5, 2.6 Hz, 1 H), 7.00 (d, *J* = 2.6 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 4.08 (q, *J* = 6.8 Hz, 2 H), 3.26 (p, *J* = 5.9 Hz, 1 H), 3.01–2.85 (m, 2 H), 2.81 (s, 3 H), 2.79–2.71 (m, 1 H), 2.46–2.33 (m, 1 H), 1.87–1.67 (m, 3 H), 1.61 (d, *J* = 12.8 Hz, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 32.8 Hz), 150.3, 137.2, 129.0, 127.1, 126.2, 118.5, 116.6 (t, *J* = 251.7 Hz), 62.9, 56.7, 42.7, 37.9, 36.5 (t, *J* = 22.6 Hz), 30.6, 25.1, 14.0.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.59 (d, *J* = 258.2 Hz, 1 F), –107.06 (d, *J* = 258.2 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}ClF_2NO_2^+$: 332.1229; found: 332.1234.

Ethyl 3-(7-Bromo-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-2,2-difluoropropanoate (3h)

Yellow liquid; yield: 250.2 mg (67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.07 (d, *J* = 2.0 Hz, 1 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 4.01 (q, *J* = 7.0 Hz, 2 H), 3.18 (p, *J* = 5.3 Hz, 1 H), 2.95–2.76 (m, 2 H), 2.73 (s, 3 H), 2.72–2.63 (m, 1 H), 2.38–2.25 (m, 1 H), 1.78–1.60 (m, 3 H), 1.59–1.50 (m, 1 H), 1.19 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 32.8 Hz), 150.8, 137.6, 131.8, 130.1, 119.0, 116.6 (t, *J* = 251.6 Hz), 113.8, 62.9, 56.6, 42.6, 37.9, 36.4 (t, *J* = 22.8 Hz), 30.5, 25.1, 14.0.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.55 (d, *J* = 258.1 Hz, 1 F), –107.05 (d, *J* = 258.4 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}BrF_2NO_2^+$: 376.0724; found: 376.0728.

Ethyl 2,2-Difluoro-3-(7-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanoate (3i)

Colorless liquid; yield: 252.7 mg (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.4 Hz, 1 H), 7.32 (s, 1 H), 6.67 (d, *J* = 8.4 Hz, 1 H), 4.09 (q, *J* = 6.8 Hz, 2 H), 3.23 (p, *J* = 5.5 Hz, 1 H), 3.02–2.93 (m, 1 H), 2.91–2.81 (m, 1 H), 2.80 (s, 3 H), 2.79–2.72 (m, 1 H), 2.45–2.32 (m, 1 H), 1.89–1.68 (m, 3 H), 1.66–1.53 (m, 1 H), 1.27 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 32.9 Hz), 151.5, 138.0, 137.6, 136.2, 119.5, 116.6 (t, *J* = 251.8 Hz), 108.1, 62.9, 56.6, 42.5, 37.9, 36.4 (t, *J* = 22.8 Hz), 30.5, 25.1, 14.0.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.52 (d, *J* = 258.4 Hz, 1 F), –107.09 (d, *J* = 258.6 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}F_2INO_2^+$: 424.0585; found: 424.0593.

Methyl 5-(3-Ethoxy-2,2-difluoro-3-oxopropyl)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-7-carboxylate (3j)

Yellow oil; yield: 140.3 mg (40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 8.4, 1.9 Hz, 1 H), 7.72–7.69 (m, 1 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 3.87 (s, 3 H), 3.42–3.36 (m, 1 H), 3.09–3.04 (m, 1 H), 3.02–2.93 (m, 1 H), 2.89 (s, 3 H), 2.83–2.68 (m, 1 H), 2.52–2.39 (m, 1 H), 1.83–1.75 (m, 2 H), 1.74–1.67 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 167.3, 164.3 (t, *J* = 33.0 Hz), 155.5, 134.2, 130.1, 129.5, 122.3, 116.62, 116.57 (t, *J* = 253.8 Hz), 62.9, 56.4, 51.9, 42.4, 37.3, 36.9 (t, *J* = 22.6 Hz), 30.5, 24.7, 13.9.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –101.16 (d, *J* = 258.2 Hz, 1 F), –106.62 (d, *J* = 258.1 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{23}F_2NNaO_4^+$: 378.1493; found: 378.1496.

Ethyl 2,2-Difluoro-3-(6-methoxy-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanoate (3k)

Yellow liquid; yield: 274.7 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (t, *J* = 8.2 Hz, 1 H), 6.59 (d, *J* = 8.1 Hz, 1 H), 6.51 (d, *J* = 8.1 Hz, 1 H), 4.12–4.01 (m, 2 H), 3.96–3.86 (m, 1 H), 3.78 (s, 3 H), 3.10–3.05 (m, 1 H), 2.99–2.85 (m, 1 H), 2.84 (s, 3 H), 2.62 (t, *J* = 11.7 Hz, 1 H), 2.47–2.34 (m, 1 H), 2.04–1.95 (m, 1 H), 1.91–1.83 (m, 1 H), 1.62–1.52 (m, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 32.6 Hz), 157.7, 154.1, 127.4, 123.8, 117.1 (t, *J* = 250.5 Hz), 110.0, 104.8, 62.5, 57.4, 56.0, 43.1, 35.8 (t, *J* = 22.5 Hz), 29.7, 27.7, 25.4, 14.0.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.0 (d, *J* = 257.8 Hz, 1 F), –106.8 (d, *J* = 257.7 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{24}F_2NO_3^+$: 328.1724; found: 328.1730.

Ethyl 2,2-Difluoro-3-(1,6,8-trimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanoate (3l)

Colorless liquid; yield: 259.3 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (s, 1 H), 6.63 (s, 1 H), 4.02–3.82 (m, 2 H), 3.65–3.58 (m, 1 H), 3.20–3.03 (m, 2 H), 2.84 (s, 3 H), 2.61–2.53 (m, 1 H), 2.52–2.38 (m, 1 H), 2.31 (s, 3 H), 2.26 (s, 3 H), 2.05–1.95 (m, 1 H), 1.91–1.81 (m, 1 H), 1.57 (t, *J* = 13.1 Hz, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 34.1 Hz), 152.9, 136.8, 136.2, 131.3, 125.3, 117.1 (t, *J* = 250.5 Hz), 116.3, 62.6, 57.3, 43.0, 35.8 (t, *J* = 22.2 Hz), 32.0 (dd, *J* = 6.4, 2.1 Hz), 29.9, 25.3, 21.2, 21.0, 13.8.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –99.61 (d, *J* = 256.5 Hz, 1 F), –107.61 (d, *J* = 256.5 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{26}F_2NO_2^+$: 326.1932; found: 326.1937.

Ethyl 2,2-Difluoro-3-(5-methyl-2,3,4,5-tetrahydro-1*H*-naphtho-[2,1-*b*]azepin-1-yl)propanoate (3m)

Light-yellow liquid; yield: 209.1 mg (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.7 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.8 Hz, 1 H), 7.49 (t, *J* = 7.3 Hz, 1 H), 7.38–7.30 (m, 2 H), 4.32 (s, 1 H), 3.86–3.63 (m, 2 H), 3.22–3.14 (m, 1 H), 3.14–3.03 (m, 1 H), 3.00 (s, 3 H), 2.72–2.58 (m, 2 H), 2.14–1.97 (m, 2 H), 1.71 (t, *J* = 12.7 Hz, 1 H), 1.66–1.57 (m, 1 H), 1.04 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 32.8 Hz), 149.7, 132.7, 130.2, 128.6, 128.5, 128.0, 126.4, 123.4, 123.0, 118.8, 117.1 (t, *J* = 251.4 Hz), 62.5, 56.8, 42.6, 36.1 (t, *J* = 22.4 Hz), 30.6 (dd, *J* = 5.8, 2.6 Hz), 29.3, 25.2, 13.7.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –99.69 (d, *J* = 256.9 Hz, 1 F), –107.21 (d, *J* = 256.9 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{24}F_2NO_2^+$: 348.1775; found: 348.1773.

Ethyl 3-(1-Ethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-2,2-difluoropropanoate (3n)

Yellow liquid; yield: 276.9 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dt, *J* = 7.9, 1.6 Hz, 1 H), 7.06–7.03 (dd, *J* = 7.4, 1.6 Hz, 1 H), 6.93 (d, *J* = 7.9 Hz, 1 H), 6.87 (t, *J* = 7.4 Hz, 1 H), 4.11–3.94 (m, 2 H), 3.31–3.26 (m, 1 H), 3.24–3.17 (m, 1 H), 3.12–3.03 (m, 2 H), 3.01–2.88 (m, 1 H), 2.69 (t, *J* = 11.8 Hz, 1 H), 2.51–2.39 (m, 1 H), 1.84–1.71 (m, 3 H), 1.67–1.58 (m, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.20 (t, *J* = 7.0 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 33.6 Hz), 151.5, 136.5, 129.5, 127.4, 121.6, 118.5, 116.9 (t, *J* = 251.1 Hz), 62.6, 54.0, 48.0, 38.3, 36.7 (t, *J* = 22.5 Hz), 31.1, 26.0, 14.2, 13.9.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.60 (d, *J* = 256.9 Hz, 1 F), –106.90 (d, *J* = 257.1 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{24}F_2NO_2^+$: 312.1775; found: 312.1778.

Ethyl 2,2-Difluoro-3-(2,3,5,6,7,8-hexahydro-1*H*-azepino[3,2,1-*ij*]quinolin-8-yl)propanoate (3o)

Yellow oil; yield: 175.3 mg (54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (d, *J* = 7.4 Hz, 1 H), 6.86 (d, *J* = 7.2 Hz, 1 H), 6.77 (t, *J* = 7.4 Hz, 1 H), 4.10–3.93 (m, 2 H), 3.31–3.19 (m,1 H), 3.17–3.12 (m, 2 H), 3.04–2.97 (m, 1 H), 2.97–2.86 (m, 2 H), 2.81–2.74 (m, 2 H), 2.52–2.35 (m, 1 H), 1.94–1.78 (m, 2 H), 1.79–1.59 (m, 4 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 32.8 Hz), 147.8, 135.7, 128.4, 128.2, 127.3, 120.9, 116.9 (t, *J* = 251.0 Hz), 62.7, 57.2, 54.1, 38.6, 36.4 (t, *J* = 22.4 Hz), 30.8, 28.4, 25.7, 19.1, 14.0.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.30 (d, *J* = 257.0 Hz, 1 F), –107.19 (d, *J* = 256.8 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}F_2NO_2^+$: 324.1775; found: 324.1778.

Diethyl 3,3′-(1,1′-Dimethyl-2,2′,3,3′,4,4′,5,5′-octahydro-1*H*,1′*H*-[7,7′-bibenzo[*b*]azepine]-5,5′-diyl)bis(2,2-difluoropropanoate) (3p)

Yellow oil; yield: 224.1 mg (38%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (dt, *J* = 8.2, 2.3 Hz, 2 H), 7.22–7.20 (m, 2 H), 6.97 (d, *J* = 8.3 Hz, 2 H), 4.06–3.85 (m, 4 H), 3.41–3.30 (m, 2 H), 3.06–2.90 (m, 4 H), 2.87 (s, 6 H), 2.83–2.74 (m, 2 H), 2.54–2.36 (m, 2 H), 1.94–1.84 (m, 2 H), 1.82–1.72 (m, 4 H), 1.67–1.59 (m, 2 H), 1.15 (dt, *J* = 7.1, 1.3 Hz, 6 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 32.9 Hz), 150.7, 150.6, 135.7, 134.1, 134.0, 128.0, 125.5, 125.5, 117.4, 116.9 (t, *J* = 250.9 Hz), 62.8, 57.0, 42.9, 38.6, 36.6 (t, *J* = 22.4 Hz), 31.0, 29.8 ('grease'), 25.4, 13.9.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.02 (d, *J* = 257.1 Hz, 1 F), –100.05 (d, *J* = 257.1 Hz, 1 F), –107.29 (d, *J* = 256.2 Hz, 1 F), –107.34 (d, *J* = 257.5 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{41}F_4N_2O_4^+$: 593.3002; found: 593.3013.

Ethyl 3-(1,8-Dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-2,2-difluoropropanoate (3q)

Light-yellow liquid; yield: 163.7 mg (53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 7.5 Hz, 1 H), 6.74 (s, 1 H), 6.68 (d, *J* = 7.5 Hz, 1 H), 4.09–3.91 (m, 2 H), 3.26 (p, *J* = 6.0 Hz, 1 H), 3.00–2.95 (m, 1 H), 2.94–2.85 (m, 1 H), 2.83 (s, 3 H), 2.78–2.69 (m, 1 H), 2.47–2.34 (m, 1 H), 2.29 (s, 3 H), 1.90–1.81 (m, 1 H), 1.77–1.65 (m, 2 H), 1.65–1.54 (m, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 32.8 Hz), 151.7, 137.0, 132.6, 129.4, 122.0, 117.9, 116.9 (t, *J* = 252.9 Hz), 62.7, 57.0, 42.7, 38.1, 36.7 (t, *J* = 21.8 Hz), 31.0, 29.8, 25.5, 21.4, 13.9.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ = –100.4 (d, *J* = 257.3 Hz, 1 F), –107.2 (d, *J* = 257.3 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{24}F_2NO_2^+$: 312.1775; found: 312.1778.

Ethyl 3-(1,6-Dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-2,2-difluoropropanoate (3q′)

Light-yellow liquid; yield: 97.6 mg (31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (t, *J* = 7.7 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.77 (d, *J* = 7.4 Hz, 1 H), 4.00–3.78 (m, 2 H), 3.66–3.61 (m, 1 H), 3.25–3.01 (m, 2 H), 2.83 (s, 3 H), 2.58–2.52 (m, 1 H), 2.51–2.38 (m, 1 H), 2.33 (s, 3 H), 2.07–1.93 (m, 1 H), 1.91–1.83 (m, 1 H), 1.62–1.51 (m, 2 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 32.2 Hz), 152.9, 137.0, 134.4, 126.9, 124.6, 117.1 (dd, *J* = 253.5, 247.8 Hz), 115.6, 62.7, 57.3, 43.0, 35.7 (t, *J* = 22.1 Hz), 32.3 (dd, *J* = 6.4, 2.2 Hz), 29.8, 25.3, 21.1, 13.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –99.7 (d, *J* = 256.7 Hz, 1 F), –107.6 (d, *J* = 256.7 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}F_2NO_2^+$: 312.1775; found: 312.1779.

2,2-Difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-1-phenylpropan-1-one (4a)

Yellow oil; yield: 293.5 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 7.9, 1.2 Hz, 1 H), 7.73–7.60 (m, 1 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.40 (d, *J* = 7.9 Hz, 1 H), 7.32–7.25 (m, 2 H), 6.80–6.73 (m, 3 H), 3.42 (t, *J* = 7.2 Hz, 2 H), 3.31 (p, *J* = 6.1 Hz, 1 H), 2.98 (s, 3 H), 2.76–2.59 (m, 1 H), 2.56–2.41 (m, 1 H), 2.01–1.89 (m, 1 H), 1.89–1.77 (m, 2 H), 1.76–1.64 (m, 1 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 185.4 (t, *J* = 25.7 Hz), 149.3, 146.5, 135.3, 129.8 (t, *J* = 1.9 Hz), 129.3, 129.0, 128.0, 127.6, 116.4, 113.5 (t, *J* = 249.1 Hz), 112.4, 52.6, 38.5, 36.3 (t, *J* = 22.3 Hz), 35.7 (dd, *J* = 5.3, 4.0 Hz), 32.7, 24.0.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –104.71 (d, *J* = 277.5 Hz, 1 F), –106.33 (d, *J* = 277.5 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}F_2NO^+$: 330.1669; found: 330.1677.

2,2-Difluoro-1-(4-fluorophenyl)-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propan-1-one (4b)

Yellow oil; yield: 299.7 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 8.7, 6.0 Hz, 1 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 7.17–7.10 (m, 1 H), 7.07 (dd, *J* = 9.7, 2.1 Hz, 1 H), 6.81–6.68 (m, 3 H), 3.46–3.39 (m, 2 H), 3.33–3.24 (m, 1 H), 2.98 (s, 3 H), 2.74–2.59 (m, 1 H), 2.53–2.37 (m, 1 H), 1.98–1.89 (m, 1 H), 1.89–1.76 (m, 2 H), 1.75–1.64 (m, 1 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 184.0 (t, *J* = 25.8 Hz), 167.0 (d, *J* = 258.7 Hz), 149.8 (d, *J* = 8.9 Hz), 149.3, 132.3 (d, *J* = 10.1 Hz), 129.4, 126.5, 116.6, 115.7 (d, *J* = 22.3 Hz), 114.6 (d, *J* = 22.4 Hz), 113.3 (t, *J* = 249.2 Hz), 112.4, 52.6, 38.5, 36.2 (t, *J* = 22.0 Hz), 35.6, 32.29, 32.27, 23.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –100.34 (s, 1 F), –105.56 (d, *J* = 278.0 Hz, 1 F), –106.70 (d, *J* = 278.1 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}F_3NO^+$: 348.1575; found: 348.1577.

2,2-Difluoro-1-(4-methoxyphenyl)-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propan-1-one (4c)

Yellow oil; yield: 308.1 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.8 Hz, 1 H), 7.31–7.20 (m, 2 H), 6.92 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.79 (d, *J* = 2.0 Hz, 1 H), 6.78–6.68 (m, 3 H), 3.87 (s, 3 H), 3.40 (t, *J* = 7.0 Hz, 2 H), 3.26–3.17 (m, 1 H), 2.97 (s, 3 H), 2.68–2.53 (m, 1 H), 2.51–2.37 (m, 1 H), 1.93–1.76 (m, 3 H), 1.74–1.60 (m, 1 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 183.9 (t, *J* = 25.4 Hz), 165.2, 149.3, 149.2, 129.3, 123.1, 116.3, 114.0, 113.6 (t, *J* = 248.5 Hz), 112.4, 112.3, 55.7, 52.6, 38.5, 36.3 (t, *J* = 21.8 Hz), 35.8 (dd, *J* = 5.3, 4.0 Hz), 32.5, 24.0.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –104.35 (d, *J* = 278.1 Hz, 1 F), –105.81 (d, *J* = 278.2 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{24}F_2NO_2^+$: 360.1775; found: 360.1777.

2,2-Difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-1-(4-(trifluoromethyl)phenyl)propan-1-one (4d)

Yellow oil; yield: 256.4 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.2 Hz, 1 H), 7.72–7.60 (m, 2 H), 7.32–7.11 (m, 2 H), 6.75–6.67 (m, 3 H), 3.43–3.37 (m, 2 H), 3.36–3.29 (m, 1 H), 2.94 (s, 3 H), 2.74–2.59 (m, 1 H), 2.54–2.39 (m, 1 H), 1.97–1.71 (m, 3 H), 1.74–1.62 (m, 1 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 184.7 (t, *J* = 25.9 Hz), 149.3, 147.1, 136.4 (q, *J* = 32.9 Hz), 132.3, 129.8, 129.4, 125.1, 124.5 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 274.4 Hz), 116.7, 113.3 (t, *J* = 247.0 Hz), 112.5, 110.8, 52.6, 38.5, 36.1 (t, *J* = 21.4 Hz), 35.8, 32.5, 23.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –63.37 (s, 3 F), –105.68 (d, *J* = 278.6 Hz, 1 F), –106.97 (d, *J* = 278.6 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}F_5NO^+$: 398.1543; found: 398.1547.

2,2-Difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-1-(naphthalen-2-yl)propan-1-one (4e)

Yellow oil; yield: 315.4 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.7 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 7.87 (d, *J* = 8.6 Hz, 1 H), 7.79 (d, *J* = 8.7 Hz, 1 H), 7.68–7.62 (m, 1 H), 7.62–7.56 (m, 1 H), 7.29–7.18 (m, 2 H), 6.74–6.67 (m, 3 H), 3.88–3.82 (m, 1 H), 3.41–3.25 (m, 2 H), 2.97–2.86 (m, 1 H), 2.91 (s, 3 H), 2.62–2.43 (m, 1 H), 2.10–1.97 (m, 1 H), 1.91–1.76 (m, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 185.6 (t, *J* = 25.5 Hz), 149.3, 147.41, 147.40, 136.8, 130.1, 129.5, 129.43, 129.38, 129.38, 128.6, 127.7, 126.9, 124.9, 123.2, 116.6, 113.0 (t, *J* = 248.7 Hz), 112.5, 52.3, 38.5, 34.0 (t, *J* = 21.0 Hz), 33.5, 33.3, 25.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –98.38 (d, *J* = 285.5 Hz, 1 F), –102.82 (d, *J* = 285.5 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{24}F_2NO^+$: 380.1826; found: 380.1832.

2,2-Difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-*N*-phenylpropanamide (4f)

Colorless oil; yield: 274.2 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 7.49 (d, *J* = 7.6 Hz, 2 H), 7.35 (t, *J* = 7.9 Hz, 2 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 7.15–7.10 (m, 1 H), 7.08 (d, *J* = 7.5 Hz, 1 H), 6.93 (d, *J* = 7.9 Hz, 1 H), 6.89–6.79 (m, 1 H), 3.44–3.35 (m, 1 H), 3.18–2.97 (m, 2 H), 2.85 (s, 3 H), 2.83–2.73 (m, 1 H), 2.66–2.48 (m, 1 H), 1.97–1.83 (m, 1 H), 1.83–1.72 (m, 2 H), 1.69–1.55 (m, 1 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 162.3 (t, *J* = 28.8 Hz), 151.8, 136.2, 135.6, 129.2, 129.1, 127.5, 125.4, 121.3, 120.2, 118.8 (t, *J* = 255.2 Hz), 117.2, 56.8, 42.6, 38.5, 35.6 (t, *J* = 22.4 Hz), 30.7, 25.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –102.09 (d, *J* = 252.5 Hz, 1 F), –104.68 (d, *J* = 252.5 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}F_2N_2O^+$: 345.1778; found: 345.1781.

N-Cyclohexyl-2,2-difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanamide (4g)

Colorless oil; yield: 283.3 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.12 (m, 1 H), 7.05 (dd, *J* = 7.5, 1.7 Hz, 1 H), 6.93 (d, *J* = 8.1 Hz, 1 H), 6.91–6.83 (m, 1 H), 6.12 (s, 1 H), 3.77–3.64 (m, 1 H), 3.33 (p, *J* = 6.4 Hz, 1 H), 3.00–2.90 (m, 1 H), 2.83 (s, 3 H), 2.83–2.73 (m, 1 H), 2.65–2.46 (m, 1 H), 1.97–1.80 (m, 3 H), 1.81–1.67 (m, 5 H), 1.67–1.54 (m, 2 H), 1.44–1.29 (m, 2 H), 1.23–1.08 (m, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 163.5 (t, *J* = 28.6 Hz), 151.5, 136.1, 128.7, 127.2, 121.3, 118.8 (t, *J* = 253.8 Hz), 117.1, 56.7, 48.5, 42.5, 37.8, 35.9 (t, *J* = 22.4 Hz), 32.73, 32.67, 30.7, 25.4, 25.3, 24.8.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –104.03 (s, 1 F), –104.04 (s, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}F_2N_2O^+$: 351.2248; found: 351.2253.

2,2-Difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-*N*-(naphthalen-1-yl)propanamide (4h)

Light-red oil; yield: 274.2 mg (70%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.29 (s, 1 H), 7.93 (d, *J* = 7.5 Hz, 1 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 7.74 (t, *J* = 8.9 Hz, 2 H), 7.60–7.49 (m, 2 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.13 (t, *J* = 7.7 Hz, 2 H), 6.95 (d, *J* = 7.8 Hz, 1 H), 6.83 (t, *J* = 7.3 Hz, 1 H), 3.51–3.45 (m, 1 H), 3.18–3.06 (m, 1 H), 3.03–2.98 (m, 1 H), 2.86 (s, 3 H), 2.85–2.79 (m, 1 H), 2.74–2.62 (m, 1 H), 1.95–1.86 (m, 1 H), 1.84–1.78 (m, 2 H), 1.67–1.61 (m, 1 H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 162.9 (t, *J* = 28.8 Hz), 151.7, 135.8, 134.1, 130.6, 129.0, 127.5, 126.8, 126.7, 126.6, 126.3, 125.7, 121.5, 120.5, 120.2, 119.2 (t, *J* = 254.1 Hz), 117.3, 56.8, 42.6, 38.3, 35.8 (t, *J* = 22.0 Hz), 30.8, 25.4.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –101.68 (dt, *J* = 253.7, 18.4 Hz, 1 F), –103.43 (dt, *J* = 253.7, 16.4 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{25}F_2N_2O^+$: 395.1935; found: 395.1942.

N-Benzyl-2,2-difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanamide (4i)

Colorless liquid; yield: 273.5 mg (76%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 2 H), 7.33–7.30 (m, 1 H), 7.27–7.25 (m, 2 H), 7.18 (td, *J* = 7.9, 1.7 Hz, 1 H), 7.03 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.95 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.86 (td, *J* = 7.4, 1.2 Hz, 1 H), 6.48 (s, 1 H), 4.44 (dd, *J* = 14.7, 6.1 Hz, 1 H), 4.27 (dd, *J* = 14.7, 5.4 Hz, 1 H), 3.34 (p, *J* = 5.7 Hz, 1 H), 3.00–2.88 (m, 2 H), 2.84 (s, 3 H), 2.82–2.76 (m, 1 H), 2.60–2.50 (m, 1 H), 1.89–1.79 (m, 1 H), 1.76–1.71 (m, 2 H), 1.63–1.57 (m, 1 H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 29.0 Hz), 151.7, 137.0, 135.9, 128.9, 128.04, 128.01, 127.38, 127.37, 121.3, 118.8 (t, *J* = 252.9 Hz), 117.1, 56.7, 43.6, 42.6, 38.1, 35.8 (t, *J* = 22.5 Hz), 30.7, 25.3.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –102.36 (dt, *J* = 253.7, 17.9 Hz, 1 F), –105.19 (dt, *J* = 254.2, 18.0 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}F_2N_2O^+$: 359.1935; found: 359.1938.

N-Butyl-2,2-difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanamide (4j)

Colorless liquid; yield: 211.5 mg (65%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.18–7.14 (m, 1 H), 7.05 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.93 (dd, *J* = 8.0, 0.9 Hz, 1 H), 6.89–6.85 (m, 1 H), 6.20 (s, 1 H), 3.35–3.30 (m, 1 H), 3.27–3.20 (m, 1 H), 3.17–3.11 (m, 1 H), 2.98–2.94 (m, 1 H), 2.91–2.84 (m, 1 H), 2.83 (s, 3 H), 2.82–2.77 (m, 1 H), 2.57–2.45 (m, 1 H), 1.86–1.79 (m, 1 H), 1.75–1.70 (m, 2 H), 1.62–1.56 (m, 1 H), 1.51–1.44 (m, 2 H), 1.37–1.30 (m, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 164.5 (t, *J* = 28.5 Hz), 151.6, 136.0, 128.8, 127.3, 121.2, 118.8 (t, *J* = 252.9 Hz), 117.1, 56.7, 42.5, 39.3, 38.0, 35.8 (t, *J* = 22.2 Hz), 31.2, 30.7, 25.3, 20.0, 13.8.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –102.83 (dt, *J* = 252.5, 18.9 Hz, 1 F), –105.13 (dt, *J* = 252.5, 17.5 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{27}F_2N_2O^+$: 325.2091; found: 325.2097.

N-(*tert*-Butyl)-2,2-difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanamide (4k)

Colorless liquid; yield: 261.9 mg (81%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.19–7.15 (m, 1 H), 7.07 (dd, *J* = 7.5, 1.4 Hz, 1 H), 6.93 (dd, *J* = 8.0, 0.9 Hz, 1 H), 6.90–6.85 (m, 1 H), 6.03 (s, 1 H), 3.34 (p, *J* = 6.6 Hz, 1 H), 2.95 (dt, *J* = 12.5, 4.3 Hz, 1 H), 2.83 (s, 3 H), 2.82–2.69 (m, 2 H), 2.62–2.51 (m, 1 H), 1.87–1.78 (m, 1 H), 1.77–1.68 (m, 2 H), 1.63–1.57 (m, 1 H), 1.36 (s, 9 H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 163.6 (t, *J* = 27.7 Hz), 151.5, 136.3, 128.7, 127.3, 121.3, 118.6 (t, *J* = 253.7 Hz), 117.1, 56.7, 51.8, 42.5, 37.8, 35.8 (t, *J* = 22.7 Hz), 30.7, 28.4, 25.3.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –103.10 (dt, *J* = 251.1, 17.0 Hz, 1 F), –103.65 (dt, *J* = 251.0, 18.8 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{27}F_2N_2O^+$: 325.2091; found: 325.2095.

N,N-Diethyl-2,2-difluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanamide (4l)

Colorless oil; yield: 267.8 mg (83%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.17–7.14 (m, 1 H), 7.10 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.92 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.89–6.86 (m, 1 H), 3.46–3.39 (m, 3 H), 3.38–3.29 (m, 2 H), 2.97–2.93 (m, 1 H), 2.85–2.81 (m, 4 H), 2.80–2.70 (m, 1 H), 2.68–2.57 (m, 1 H), 1.88–1.80 (m, 1 H), 1.78–1.73 (m, 2 H), 1.64–1.59 (m, 1 H), 1.16–1.11 (m, 6 H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 163.4 (t, *J* = 29.5 Hz), 151.5, 137.1, 129.0, 127.1, 121.4, 120.0 (t, *J* = 254.2 Hz), 117.0, 56.8, 42.6, 42.0 (t, *J* = 6.0 Hz), 41.7, 37.7, 37.0 (t, *J* = 22.3 Hz), 30.9, 25.5, 14.4, 12.5.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –98.73 (d, *J* = 19.6 Hz, 1 F), –98.80 (d, *J* = 21.0 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{27}F_2N_2O^+$: 325.2091; found: 325.2099.

Ethyl 2-Fluoro-3-(1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)propanoate (4m)

Light-yellow liquid; yield: 205.7 mg (74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = (isomer 1) = 7.18 (q, *J* = 7.9 Hz, 1 H), 7.11–7.05 (m, 1 H), 6.98–6.87 (m, 2 H), 4.93 (ddd, *J* = 49.2, 7.8, 4.9 Hz, 1 H), 4.23–4.09 (m, 2 H), 3.34–3.25 (m, 1 H), 3.02–2.91 (m, 1 H), 2.90–2.79 (m, 1 H), 2.85 (s, 3 H), 2.79-2.62 (m, 1 H), 2.51–2.29 (m, 1 H), 1.85–1.72 (m, 2 H), 1.71–1.58 (m, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H);

δ (isomer 2) = 7.18 (q, *J* = 7.8 Hz, 1 H), 7.11–7.05 (m, 1 H), 6.98–6.87 (m, 2 H), 4.54 (ddd, *J* = 49.8, 10.7, 2.6 Hz, 1 H), 4.23–4.09 (m, 2 H), 3.34–3.25 (m, 1 H), 3.02–2.91 (m, 1 H), 2.90–2.79 (m, 1 H), 2.84 (s, 3 H), 2.51–2.29 (m, 1 H), 2.06–1.92 (m, 1 H), 1.85–1.72 (m, 2 H), 1.71–1.58 (m, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ (isomer 1) = 170.8 (d, *J* = 23.6 Hz), 151.7, 136.2, 129.5, 127.3, 121.4, 117.3, 88.1 (d, *J* = 183.5 Hz), 61.5, 56.9, 42.6, 40.0, 35.1 (d, *J* = 20.3 Hz), 30.9, 25.6, 14.2; δ (isomer 2) = 170.3 (d, *J* = 23.6 Hz), 151.5, 134.8, 128.7, 127.2, 121.3, 117.1, 87.9 (d, *J* = 183.5 Hz), 61.4, 56.7, 42.6, 38.6, 35.0 (d, *J* = 20.3 Hz), 29.5, 25.5, 14.2.

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = –192.3 (s, 1 F, isomer 1), –192.4 (s, 1 F, isomer 2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{23}FNO_2^+$: 280.1713; found: 280.1715.

3-(7-Bromo-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-2,2-difluoro-1-phenylpropan-1-one (4n)

Yellow oil; yield: 288.4 mg (71%).

^1H NMR (600 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.9 Hz, 1 H), 7.55–7.49 (m, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.24 (d, *J* = 7.8 Hz, 1 H), 7.20–7.15 (m, 2 H), 6.45 (d, *J* = 9.0 Hz, 2 H), 3.24 (t, *J* = 7.2 Hz, 2 H), 3.19–3.12 (m, 1 H), 2.81 (s, 3 H), 2.57–2.46 (m, 1 H), 2.39–2.28 (m, 1 H), 1.81–1.75 (m, 1 H), 1.74–1.61 (m, 2 H), 1.57–1.49 (m, 1 H).

$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 185.4 (t, *J* = 25.7 Hz), 148.2, 146.4, 135.3, 131.9, 129.8, 129.0, 127.9, 127.7, 113.9, 113.5 (t, *J* = 249.0 Hz), 108.2, 52.6, 38.6, 36.2 (t, *J* = 21.6 Hz), 35.7, 32.7, 23.9.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –104.46 (ddd, *J* = 277.8, 22.3, 8.4 Hz, 1 F), –106.09 (ddd, *J* = 277.9, 20.3, 9.4 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{20}BrF_2NNaO^+$: 430.0589; found: 430.0592.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References

(1) Puig-Antich, J.; Perel, J. M.; Lupatkin, W.; Chambers, W. J.; Tabrizi, M. A.; King, J.; Goetz, R.; Davies, M.; Stiller, R. L. *Arch. Gen. Psychiatry* **1987**, *44*, 81.
(2) Sallee, F. R.; Pollock, B. G. *Clin. Pharmacokinet.* **1990**, *18*, 346.
(3) Yamamoto, Y.; Ishihara, Y.; Kuntz, I. D. *J. Med. Chem.* **1994**, *37*, 3141.
(4) Jiang, Y.-R.; Yang, Y.-Y.; Chen, Y.-L.; Liang, Z.-J. *Curr. Comput.-Aided Drug Des.* **2013**, *9*, 385.
(5) Yempala, T.; Babu, T.; Gibson, D.; Cassels, B. K. *Synth. Commun.* **2019**, *50*, 438.
(6) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
(7) Heidelberger, C.; Chaudhuri, N. K.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, R. J. *Nature* **1957**, *179*, 663.
(8) Wong, D. T.; Horng, J. S.; Bymaster, F. P.; Hauser, K. L.; Molloy, B. B. *Life Sci.* **1974**, *15*, 471.
(9) Robertson, J. F. R.; Come, S. E.; Jones, S. E.; Beex, L.; Kaufmann, M.; Makris, A.; Nortier, J. W. R.; Possinger, K.; Rutqvist, L.-E. *Eur. J. Cancer* **2005**, *41*, 346.
(10) Carvalho, M. F.; Oliveira, R. S. *Crit. Rev. Biotechnol.* **2017**, *37*, 880.
(11) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
(12) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.
(13) Hassner, A.; D'Costa, R.; McPhail, A. T.; Butler, W. *Tetrahedron Lett.* **1981**, *22*, 3691.
(14) Chen, W.-Y.; Gilman, N. W. *J. Heterocycl. Chem.* **1983**, *20*, 663.
(15) Scheiner, P. *J. Org. Chem.* **1967**, *32*, 2628.
(16) Tamura, S. Y.; Goldman, E. A.; Bergum, P. W.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2573.
(17) Li, D.; Park, Y.; Yang, J. *Org. Lett.* **2018**, *20*, 7526.
(18) Clark, A. J.; Jones, K.; McCarthy, C.; Storey, J. M. D. *Tetrahedron Lett.* **1991**, *32*, 2829.
(19) Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, A. J. P.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1545.
(20) Qadir, M.; Priestley, R. E.; Rising, T. W. D. F.; Gelbrich, T.; Coles, S. J.; Hursthouse, M. B.; Sheldrake, P. W.; Whittall, N.; Hii, K. K. *Tetrahedron Lett.* **2003**, *44*, 3675.
(21) Suh, C. W.; Kwon, S. J.; Kim, D. Y. *Org. Lett.* **2017**, *19*, 1334.
(22) Waldmann, H.; Eberhardt, L.; Wittstein, K.; Kumar, K. *Chem. Commun.* **2010**, *46*, 4622.
(23) Wang, R.; Jin, R.-X.; Qin, Z.-Y.; Bian, K.-J.; Wang, X.-S. *Chem. Commun.* **2017**, *53*, 12229.
(24) Hu, J.; Pu, T.-J.; Xu, Z.-W.; Xu, W.-Y.; Feng, Y.-S. *Adv. Synth. Catal.* **2019**, *361*, 708.
(25) Liu, L.; Aguilera, M. C.; Lee, W.; Youshaw, C. R.; Neidig, M. L.; Gutierrez, O. *Science* **2021**, *374*, 432.
(26) Li, C.; Xue, L.; Zhou, J.; Zhao, Y.; Han, G.; Hou, J.; Song, Y.; Liu, Y. *Org. Lett.* **2020**, *22*, 3291.
(27) Meng, Z.; Zhang, X.; Shi, M. *Org. Chem. Front.* **2021**, *8*, 3796.
(28) Qu, C.; Xu, P.; Ma, W.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2015**, *51*, 13508.
(29) Xiao, Q.; Lu, M.; Deng, Y.; Jian, J.-X.; Tong, Q.-X.; Zhong, J.-J. *Org. Lett.* **2021**, *23*, 9303.
(30) Zhuang, X.; Shi, X.; Zhu, R.; Sun, B.; Su, W.; Jin, C. *Org. Chem. Front.* **2021**, *8*, 736.
(31) Zheng, J.; Chen, P.; Yuan, Y.; Cheng, J. *J. Org. Chem.* **2017**, *82*, 5790.
(32) Chen, H.; Wang, X.; Guo, M.; Zhao, W.; Tang, X.; Wang, G. *Org. Chem. Front.* **2017**, *4*, 2403.
(33) Wang, X.; Li, M.; Yang, Y.; Guo, M.; Tang, X.; Wang, G. *Adv. Synth. Catal.* **2018**, *360*, 2151.
(34) Wang, X.; Liu, J.; Yu, Z.; Guo, M.; Tang, X.; Wang, G. *Org. Lett.* **2018**, *20*, 6516.
(35) Yang, Y.; Yuan, F.; Ren, X.; Wang, G.; Zhao, W.; Tang, X.; Guo, M. *J. Org. Chem.* **2019**, *84*, 4507.
(36) Yuan, F.; Zhou, S.; Yang, Y.; Guo, M.; Tang, X.; Wang, G. *Org. Chem. Front.* **2018**, *5*, 3306.
(37) Sun, Z.-Y.; Zhou, S.; Yang, K.; Guo, M.; Zhao, W.; Tang, X.; Wang, G. *Org. Lett.* **2020**, *22*, 6214.

(38) Yang, Z.; Chen, L.; Sun, Q.; Guo, M.; Wang, G.; Zhao, W.; Tang, X. *J. Org. Chem.* **2022**, *87*, 3788.
(39) Leishner, T.; Suarez, L. A.; Spannenberg, A.; Junge, K.; Nova, A.; Beller, M. *Chem. Sci.* **2019**, *10*, 10566.
(40) Cerichelli, G.; Luchetti, L. *Tetrahedron* **1993**, *49*, 10733.
(41) Perumal, G.; Kandasamy, M.; Ganesan, B.; Govindan, K.; Sathya, H.; Hung, M.-Y.; Senadi, G. C.; Wu, Y.-C.; Lin, W.-Y. *Tetrahedron* **2021**, *80*, 131891.
(42) Zhao, Y.; Ge, S. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116133.
(43) Fujita, T.; Morioka, R.; Arita, T.; Ichikawa, J. *Chem. Commun.* **2018**, *54*, 12938.
(44) Xu, P.; Wang, G.; Zhu, Y.; Li, W.; Cheng, Y.; Li, S.; Zhu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 2939.