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Facile synthesis of fluorovinyl-containing lactams via ring-closing metathesis of *N*-substituted 2-fluoroallylamides

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ABSTRACT

A cost-efficient method for the preparation of a series of *N*-substituted 2-fluoroallylamines and their application in the synthesis of fluoroalkene-containing lactams are described. *N*-substituted 2-fluoroallylamine could be readily synthesized from methyl 2-fluoroacrylate via aminolysis and subsequently selective reduction of the amide group. These amines were further converted into the corresponding amides with diverse acids bearing a terminal double bond. The Ring-Closing Metathesis (RCM) of the resulting amides led to the formation fluorovinyl-containing lactams in good yields.

1. Introduction

Fluorinated molecules have a wide range of applications in almost all areas of science.[1] Of particular relevance is the emergence of fluoroolefins, which have appeared as peptidomimetics, bioactive compounds, and materials.[2] In the medicinal chemistry field, monofluorovinyl group has been described as an isopolar and isosteric mimic of an amide group with increased lipophilicity, membrane permeability and rigidity.[3] Recently such fragments have been incorporated in a variety of antiviral, antibacterial, antidiabetic and anticancer agents (Fig. 1),[4] indicating its importance in drug discovery. It is also extensively utilized as starting material in such synthetic reactions as Diels–Alder reaction, cyclopropanation, polymerization to introduce fluorine atom in the final products.[5]

Nowadays, several methods have been developed for preparing the monofluoroalkenes via direct fluorination of olefin group or fluorine-containing fragment implanting strategies.[6] Nevertheless, most of those methods have some limitations, such as a narrow range of substrates, poor functional group tolerance, requirement of expensive fluorine-containing reagents, or formation of inseparable *E*/*Z* isomers.

The ring-closing metathesis (RCM) is a well-known and powerful reaction for the preparation of cyclic alkenes owing to its broad substrate and functional group tolerability, and high regioselectivity of the formed double bond.[6] However, fluoroalkenes have scarcely been studied in RCM, because there are two inherent defects to hinder subsequent turnover in the catalytic transformation: slow phosphine dissociation to form the ruthenium mono-fluorocarbene complex and abnormal stability of the complex.[7] Recently, a pioneering breakthrough in the challenging RCM reaction of monofluoroolefins has been achieved by Brown and coworkers,[8] and subsequently others have also reported the successful RCM reactions with some specific monofluorovinyl derivatives.[9] Therefore, further exploration with diverse monofluorovinyl substrates in RCM remains desirable. Due to their potential utilities in constrained pseudopeptides and bioactive heterocycles,[10] herein we describe an efficient preparation of fluorovinyl-containing lactams from 2-fluoroallylamine derivatives via RCM reaction.

2. Results and discussion

Retrosynthetic analysis indicates that fluorolactams **6** would be prepared from the 2-fluoroallylamides **5**, which could in turn come

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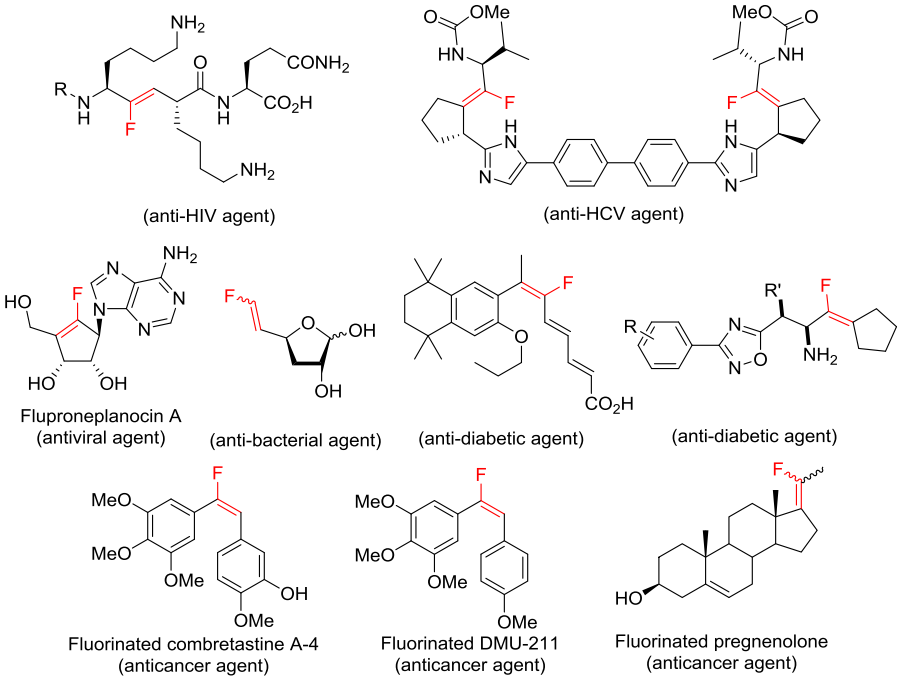
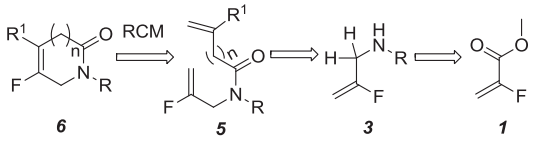


Fig. 1. Monofluorovinyl fragments in bioactive compounds.

from the 2-fluoroallylamines **3** through amide formation (Scheme 1). Although **3** could be directly obtained through N-alkylation between the corresponding amines and expensive 2-fluoroallyl chloride, it is more attractive to develop a cost-efficient method for preparation of **3** from the cheap methyl 2-fluoroacrylate through aminolysis reaction and subsequently selective reduction of amides.



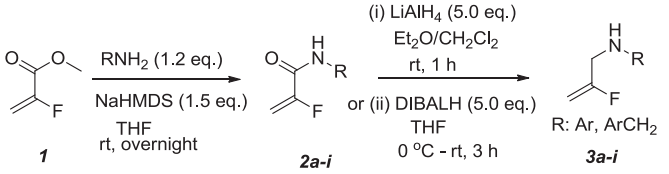
Scheme 1. The approach to fluorovinyl-containing lactams.

As shown in Table 1, the aminolysis reaction of methyl 2-fluoroacrylate with 4-methoxybenzyl amine was initially tested under basic conditions. It was noticed that weaker bases such as K_2CO_3, Et_3N, EtONa, or *t*-BuOK could hardly initiate the aminolysis in the presence of a slight excess amount of the amine. After screening a number of bases, we found that 1.5 equiv of NaHMDS could promote the reaction and give the desired amide **2a** in 64% yield. Thus, a variety of amines were subjected to this condition and could smoothly react with methyl 2-fluoroacrylate, providing the amides **2a**–**i** in moderate to good yields (Table 1).

Compared with 4-methoxybenzyl amine, the benzyl amines with an electron-neutral or withdrawing group on the phenyl ring resulted in slightly lower yields in the aminolysis reaction (**2b**–**2d**, ~55%), however, when aryl amines were used, the yields of aminolysis were greatly improved. All of the aryl amines, regardless of electron-donating or withdrawing substituents on the benzene ring, afforded the desired *N*-aryl 2-fluoroacrylamides in good to excellent yields (**2e**–**2i**, 67–85%).

Subsequently, the selective reduction of the amide group in **2a** was attempted with $LiAlH_4$. Due to the poor solubility of **2a** in ether or THF, thus a solution of **2a** in CH_2Cl_2 was added dropwise to the suspension of $LiAlH_4$ in Et_2O at rt and the selective reduction was rapidly completed. In comparison, decreasing the temperature or the amount of the reducing reagent resulted in a sluggish reaction. In addition, despite the high conversion, the isolated yield was unfortunately low (**3a**, 32%), mainly due to the product adsorption on aluminum salt. On the other hand, the aryl amide (**2e** or **2g**) was subjected to the same condition, the significant amount of the olefin-reduction product was observed. Finally, DIBALH was found as a more suitable reducing reagent for this selective transformation (**3a** 52%, **3e** 54%), and other amides could also be reduced into 2-fluoroallyl amines in acceptable yields (**3b**–**3i**, ~50%), as shown in Table 1.

Table 1
The isolated yields of *N*-substituted 2-fluoroacrylamides (**2**) and *N*-substituted 2-fluoroallyl amines (**3**)

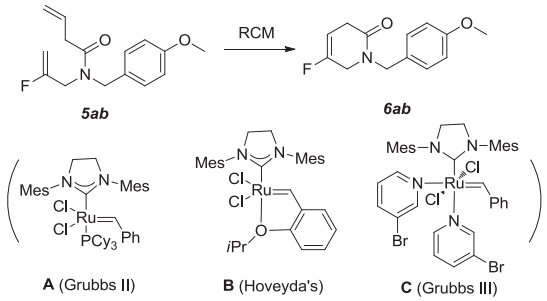


Entry	R	Yield	
		2 (%)	**3** (%)[a]
1	4-MeO–$C_6H_4CH_2$	**2a**, 64	**3a**, 52 (32[b])
2	$C_6H_5CH_2$	**2b**, 54	**3b**, 54
3	4-CF_3–$C_6H_4CH_2$	**2c**, 56	**3c**, 53
4	4-Br–$C_6H_4CH_2$	**2d**, 55	**3d**, 63
5	C_6H_5	**2e**, 75	**3e**, 54
6	4-MeO–C_6H_4	**2f**, 70	**3f**, 56
7	4-CF_3–C_6H_4	**2g**, 85	**3g**, 48
8	3-Br–C_6H_4	**2h**, 75	**3h**, 48
9	2-CH_3–C_6H_4	**2i**, 67	**3i**, 54

[a] The isolated yield is obtained by reduction with DIBALH unless otherwise noted.
[b] Reduction with $LiAlH_4$ (4.0 equiv).

With a set of 2-fluoroallyl amines in hand, further acylation was performed under the routine condition, aiming at preparing a series of precursors for RCM reaction. The various acids (**4a**–**4e**) tagged with the terminal double bond involving different electronic properties and distances, were converted into acyl chlorides in situ with $(COCl)_2$ in the presence of a catalytic amount of DMF. Then the acyl chlorides were trapped with the amines (**3a**–**3i**) to give the corresponding amides (**5aa**–**5fe**) in satisfactory yields (61–89%), as described in Table 2.

Table 2
Optimized conditions of RCM reaction with **5ab**[a]



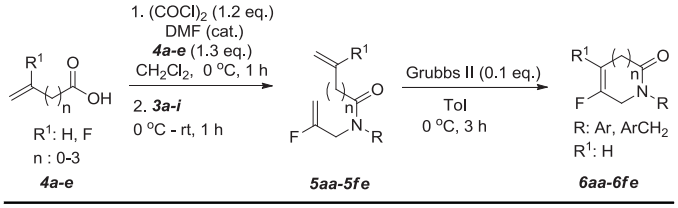
Entry	Cat. (eq.)	Solv.	Temp (°C)	Yield (%)[b]
1	A (0.30)	CH_2Cl_2	Reflux	8
2	A (0.10)	THF	Reflux	5
3	A (0.10)	Tol	Reflux	38
4	A (0.10)	Tol	80	36
5	A (0.10)	Tol	100	73
6	A (0.20)	Tol	100	67
7	A (0.30)	Tol	100	69
8	A (0.05)	Tol	100	48
9	A (0.10)	Tol	100	16[c]
10	A (0.10)	Tol	100	60[d]
11	B (0.10)	Tol	100	46
12	C (0.10)	Tol	100	58

[a] Reactions were run for 1 h at the shown temperature after the solution of **5a** (0.5 mmol) in the suitable solvent (0.01 M) had been treated by the catalyst, unless otherwise noted;
[b] The isolated yields;
[c] The reaction concentration was at 0.10 M;
[d] The reaction concentration was at 0.005 M.

Next, the RCM reaction was carried out on compound **5ab** with catalyst A (Table 2), which was reported to catalyze an efficient RCM reaction.[8,9] The initial attempt failed to produce the desired **6ab** in refluxing CH_2Cl_2 with 0.1 or 0.3 equiv of catalyst A, although a negligible yield was obtained overnight (Entry 1).[8] When the reaction was conducted in refluxing THF, similar result was obtained (Entries 2) (see Table 3). However, in refluxing toluene,[9a,b,e] the RCM reaction yield was increased (Entries 3). Extension of reaction time did not improve the yield, and no reaction was detected at the temperature below 80 °C (Entries 4). These results suggested that the catalyst could promote the RCM reaction at a higher temperature while it might be easily decomposed at that temperature. To keep the catalyst's activity and life span, a solution of the catalyst in toluene was added to the diene solution slowly via a syringe pump over 1 h at 100 °C, and reaction mixture was continued to stir for 1 h. The reaction yield was greatly improved and **6ab** could be obtained in 73% yield (Entries 5).

Subsequently, the catalyst loading and the reaction concentration were further evaluated. No improvement was observed with higher amount of catalyst (0.3 equiv) as compared to a lower one (0.1 equiv), but less amount of catalyst apparently led to a lower yield (Entries 6, 7, 8). On the other hand, reaction concentration also affected the reaction yields. Reaction concentration at 0.01 M appeared to be a better choice than the concentration at 0.005 M (Entries 9, 10). In addition, catalyst B or C, bearing a non-phosphine ligand moiety, often has a superior performance in the case of cross-metathesis with 1-haloethylene or 1,2-dihaloethylene,[11] but they did not enhance the catalytic activity for this transformation (Entries 11, 12).

Table 3
The acylation of 2-fluoroallyl amines and the subsequent RCM reaction



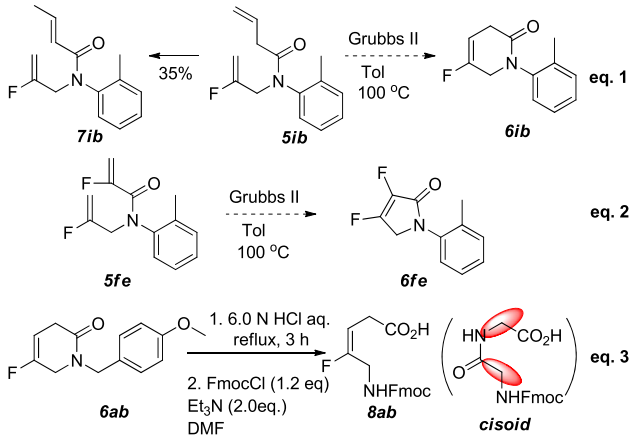
Entry	R	R^1	n	Yield[a]	
				5 (%)	**6** (%)
1	4-MeO–$C_6H_4CH_2$	H	0	**5aa**, 61	**6aa**, 70
2	4-MeO–$C_6H_4CH_2$	H	1	**5ab**, 76	**6ab**, 73
3	4-MeO–$C_6H_4CH_2$	H	2	**5ac**, 73	**6aa**, 48
4	4-MeO–$C_6H_4CH_2$	H	3	**5ad**, 79	**6ad**, 0
5	$C_6H_5CH_2$	H	1	**5bb**, 82	**6bb**, 84
6	4-CF_3–$C_6H_4CH_2$	H	1	**5cb**, 89	**6cb**, 81
7	4-Br–$C_6H_4CH_2$	H	1	**5db**, 86	**6db**, 60
8	C_6H_5	H	1	**5eb**, 83	**6ef**, 83
9	4-MeO–C_6H_4	H	1	**5fb**, 82	**6fb**, 81
10	4-CF_3–C_6H_4	H	1	**5gb**, 86	**6gb**, 35
12	2-CH_3–C_6H_4	H	1	**5ib**, 78	**6ib**, 0[b]
13	4-MeO–C_6H_4	F	0	**5fe**, 76	**6fe**, NR[c]

[a] The isolated yields;
[b] **7ib** could be isolated instead of **6ib**;
[c] No reaction.

With the optimized condition in hand, our attention was turned to **5aa**, and the five-membered ring product (**6aa)** could smoothly be obtained in 70% yield, similar to the case of the six-membered ring (**6ab**). It has been reported the formation of the five-[8,9b,d] or seven-[9b,d,e] membered ring appeared troublesome in the literature. The RCM reaction could still continue to form the seven-membered ring albeit in a lower yield (**6ac**, 48%). However, our reaction condition failed to provide the eight-membered ring (**8ad**, 0%).

As expected, the electronic effect on the benzene ring of *N*-benzyl substituted substrates hardly had an effect on the formation of the six-membered ring, and similar yields were obtained from 60% to 84% (**6ab**, **6bb**, **6cb**, **6db**).

After that, *N*-aryl substituted amides were next examined (**5eb**, **5fb**, **5gb**, **5hb**, **5ib**). To our best knowledge, this type of substrates have never been studied in RCM reaction. The results indicated that the reaction could tolerate diverse functional groups regardless of their *meta* or *para* position on the benzene ring, and smoothly produced the desired *N*-aryl fluorovinyl-containing lactams in moderate to good yields (**6eb**, **6fb**, **6gb**, **6hb**). However, the withdrawing electronic group on benzene ring evidently had a detrimental effect on the metathesis reaction. To our surprise, the substrate (**5ib**) bearing *ortho* methyl on the benzene ring did not undergo the RCM reaction, instead, it was partially transformed into the corresponding α,β-unsaturated amide (**7ib**) through 1,3-*H* shift, suggesting that the *ortho* methyl might hinder the cyclization (shown in eq. 1).



Although metathesis cyclization between one fluoroalkene and the other terminal non-fluorinated alkene went smoothly to provide 5–7 membered lactams, the metathesis between two terminal fluoroalkene partners (**5fe**) failed to provide the desired product (**6fe**) (eq. 2).

Finally, the application of the fluorovinyl-containing lactams was demonstrated in a stereo-selective synthesis of an important building block in the conformation-constrained fluoropseudopeptides, Fmoc-Gly-Ψ[(*E*)CF=CH]-Gly-OH, *cisoid* mimic of Fmoc-Gly-Gly-OH (eq. 3), which was previously available via poorly stereo-selective method.[2a,d] Thus, **6ab** was first hydrolyzed in refluxing hydrochloride aqueous solution (6.0 N) for 3 h to afford the corresponding amino acid hydrochloride, and subsequently reacted with Fmoc chloride under basic conditions, giving rise to the *cisoid* mimic **8ab** in 76% yield.

3. Conclusion

In conclusion, a cost-efficient method for preparation of a series of 2-fluoroallylamines from methyl 2-fluoroacrylate has been developed through aminolysis and subsequently selective reduction. Through acylation reaction with diverse acids tagged with terminal olefin moiety, the 2-fluoroallylamines could be transformed into the corresponding precursors for RCM reaction. The RCM reaction with these precursors led to fluorovinyl-containing lactams bearing five-, six- and seven-membered rings, but the reaction between two terminal fluoroalkene partners might be a more challenging task.

4. Experimental section

4.1. General methods and materials

Solvents were distilled from the appropriate drying agents before use. All the reagents were purchased from Acros, Alfa Aesar, and National Chemical Reagent Group Co. Ltd., P. R. China and used as received. The progress of the reactions was monitored by TLC (silica-coated glass plates) and visualized under UV light, and by using iodine or phosphomolybdic acid. Flash column chromatography was performed on silica gel (300–400 mesh). Melting points were measured on a SGW X-4 microscopy melting point apparatus without correction. NMR samples were recorded in $CDCl_3$ on 400 MHz spectrometers. Chemical shifts (δ) are reported in ppm using TMS (δ=0.0) as an internal standard. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR and ^{19}F NMR spectra were recorded on a 150 MHz or 376 MHz spectrometer, respectively. HRMS spectra were recorded on Finnigan-Mat-95 mass spectrometer, equipped with ESI source. Infrared (IR) spectra were recorded neat on KBr tablets with frequencies expressed in cm^{-1}.

4.2. Synthetic procedures and characterization data

*4.2.1. General procedure for the synthesis of N-substituted α-fluoroacrylamides (**2a**–**i**).* A solution of 2.0 M NaHMDS in THF (7.5 mL, 15.0 mmol) was added to the solution of RNH_2 (1.2 equiv) in THF (25 mL) at 0 °C under Ar atmosphere. The reaction solution was then stirred for 30 min at room temperature, after that, methyl 2-fluoroacrylate (0.91 mL, 10.0 mmol) was added dropwise at 0 °C. The resulting solution was then warmed to room temperature and stirred for overnight. After quenched with saturated NH_4Cl aqueous solution, the mixture was extracted with EtOAc (2×100 mL), and the combined organic layers were washed with brine (20 mL) and dried over $NaSO_4$. After filtration and concentration, the residue was purified by column chromatography, and the isolated yields were shown in Table 1.

*4.2.1.1. 2-Fluoro-N-(4-methoxybenzyl)-acrylamide (**2a**).* Eluent solvent: petroleum ether/ethyl acetate=2/1. White solid, mp 94–95 °C. IR (neat): ν 3258, 2916, 2848, 1640, 1541, 1514, 1371, 1323, 1251, 1177, 988, 827 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J=7.5 Hz, 2H, ArH), 6.88 (d, J=7.5 Hz, 2H, ArH), 6.51 (brs, 1H, NH), 5.72 (dd, J=47.8, 1.6 Hz, 1H, CH_2=CF), 5.13 (dd, J=15.3, 1.6 Hz, 1H, CH_2=CF), 4.46 (d, J=5.6 Hz, 2H, CH_2Ar), 3.80 (d, J=0.5 Hz, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.3 (d, J=28.8 Hz), 159.2, 156.2 (d, J=267.8 Hz), 129.3, 114.1, 99.1 (d, J=15.5 Hz), 55.2, 42.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −121.6 (ddd, $J_{H-F(trans)}$=47.8 Hz, $J_{H-F(cis)}$=15.3 Hz, J=1.9 Hz). HRMS (ESI) *m/z*: calcd for $C_{11}H_{13}FNO_2^+$ $[M+H]^+$ 210.0925, found: 210.0926.

*4.2.1.2. 2-Fluoro-N-benzylacrylamide (**2b**).* Eluent solvent: petroleum ether/ethyl acetate=5/1. White solid, mp 57–58 °C. IR (neat): ν 3319, 2918, 2849, 1649, 1536, 1497, 1357, 1319, 1208, 1186, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.22 (m, 5H, ArH), 6.60 (brs, 1H, NH), 5.74 (dd, J=48.0, 3.2 Hz, 1H, CH_2=CF), 5.15 (dd, J=15.3, 3.2 Hz, 1H, CH_2=CF), 4.54 (d, J=5.8 Hz, 2H, CH_2Ph). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.8 (d, J=31 Hz), 155.6 (d, J=270 Hz), 137.3, 128.8, 127.9, 127.8, 99.1 (d, J=15 Hz), 43.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.6 (dd, $J_{H-F(trans)}$=48.0 Hz, $J_{H-F(cis)}$=15.2 Hz). HRMS (ESI) *m/z*: calcd for $C_{10}H_{11}FNO^+$ $[M+H]^+$ 180.0819, found 180.0818.

*4.2.1.3. 2-Fluoro-N-(4-(trifluoromethyl)benzyl)acrylamide (**2c**).* Eluent solvent: petroleum ether/ethyl acetate=8/1. White solid, mp 100–100 °C. IR (neat): ν 3324, 2917, 2849, 1664, 1540, 1333, 1190, 1166, 920, 899 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ7.60 (d, J=8.0 Hz, 2H, ArH), 7.40 (d, J=8.0 Hz, 2H, ArH), 6.70 (brs, 1H, NH), 5.74 (dd, J=47.4, 3.2 Hz, 1H, CH_2=CF), 5.18 (dd, J=15.0, 3.2 Hz, 1H, CH_2=CF), 4.59 (d, J=6.0 Hz, 2H, CH_2Ar). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0 (d, J=31.2 Hz), 155.4 (d, J=268 Hz), 140.7, 129.6 (q, J=32.2 Hz), 127.3, 125.1 (q, J=3.3 Hz), 123.6 (q, J=270 Hz), 98.9 (d, J=14.7 Hz), 42.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.10 (s, 3F), −121.8 (dd, $J_{H-F(trans)}$=47.4 Hz, $J_{H-F(cis)}$=15.0 Hz, 1F). HRMS (ESI) *m/z*: calcd for $C_{11}H_{10}F_4NO^+$ $[M+H]^+$ 248.0693, found 248.0693.

*4.2.1.4. 2-Fluoro-N-(4-bromobenzyl) acrylamide (**2d**).* Eluent solvent: petroleum ether/ethyl acetate=5/1. White solid, mp 108–109 °C. IR (neat): ν 3329, 2918, 2849, 1650, 1537, 1316, 1207, 1186, 920, 895 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.30 (m, 2H, ArH), 7.20–7.10 (m, 2H, ArH), 6.65 (brs, 1H, NH), 5.33 (dd, J=48.0, 2.2 Hz, 1H, CH_2=CF), 4.76 (dd, J=15.6, 2.1 Hz, 1H, CH_2=CF), 4.08 (m, 2H, CH_2Ar). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.9 (d, J=31.0 Hz), 155.4

(d, J=268 Hz), 135.7, 131.3, 128.9, 121.1, 98.8 (d, J=14.7 Hz), 42.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.7 (ddd, $J_{H-F(trans)}$=47.7 Hz, $J_{H-F(cis)}$=15.4 Hz, J=2.2 Hz). HRMS (ESI) m/z: calcd for $C_{10}H_{10}BrFNO^+$ $[M+H]^+$ 257.9924, found 257.9928.

*4.2.1.5. 2-Fluoro-N-phenylacrylamide (**2e**).* Eluent solvent: petroleum ether/ethyl acetate=20/1. White solid, mp 57–58 °C. IR (neat): ν 3349, 2917, 1682, 1661, 1530, 1445, 1329, 1164, 888, 747, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (brs, 1H, NH), 7.59 (d, J=8.0 Hz, 2H, ArH), 7.37 (m, 2H, ArH), 7.22 (t, J=7.6 Hz, 1H, ArH), 5.81 (dd, J=47.9, 3.3 Hz, 1H, CH_2=CF), 5.26 (dd, J=15.4, 3.3 Hz, 1H, CH_2=CF). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6 (d, J=31.0 Hz), 155.8 (d, J=268 Hz), 135.9, 128.5, 124.6, 119.6, 99.3 (d, J=15.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.1 (ddd, $J_{H-F(trans)}$=47.9 Hz, $J_{H-F(cis)}$=15.4 Hz, J=5.1 Hz). HRMS (ESI) m/z: calcd for $C_9H_9FNO^+$ $[M+H]^+$ 166.0663, found 166.0662.

*4.2.1.6. 2-Fluoro-N-(4-methoxyphenyl)acrylamide (**2f**).* Eluent solvent: petroleum ether/ethyl acetate=8/1. White solid, mp 128–109 °C. IR (neat): ν 3438, 3339, 2962, 1680, 1655, 1528, 1414, 1031, 901, 822, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (brs, 1H, NH), 7.49 (d, J=9.0 Hz, 2H, ArH), 6.87 (d, J=9.0 Hz, 2H, ArH), 5.79 (dd, J=47.9, 3.3 Hz, 1H, CH_2=CF), 5.21 (dd, J=15.4, 3.3 Hz, 1H, CH_2=CF), 3.79 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.5 (d, J=34.8 Hz), 154.8 (d, J=270 Hz), 128.9, 121.4, 113.6, 98.9 (d, J=15.0 Hz), 54.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.1 (ddd, $J_{H-F(trans)}$=47.9 Hz, $J_{H-F(cis)}$=15.4 Hz, J=4.9 Hz). HRMS (ESI) m/z: calcd for $C_{10}H_{11}FNO_2^+$ $[M+H]^+$ 196.0768, found 196.0770.

*4.2.1.7. 2-Fluoro-N-(4-trifluoromethylphenyl)acrylamide (**2g**).* Eluent solvent: petroleum ether/ethyl acetate=8/1. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (brs, 1H, NH), 7.73 (d, J=8.4 Hz, 2H, ArH), 6.87 (d, J=8.4 Hz, 2H, ArH), 5.85 (dd, J=47.6, 3.6 Hz, 1H, CH_2=CF), 5.21 (dd, J=15.2, 3.6 Hz, 1H, CH_2=CF). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.5 (d, J=30.0 Hz), 155.8 (d, J=270 Hz), 139.6, 127.1 (q, J=32.7 Hz), 126.4 (q, J=3.4 Hz), 123.9 (q, J=270 Hz), 119.9, 100.7 (d, J=15.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.3 (dd, $J_{H-F(trans)}$=47.9 Hz, $J_{H-F(cis)}$=15.2 Hz, 1F), −62.7 (s, 3F). HRMS (ESI) m/z: calcd for $C_{10}H_{11}FNO_2^+$ $[M+H]^+$ 196.0768, found 196.0770.

*4.2.1.8. 2-Fluoro-N-(3-bromophenyl)acrylamide (**2h**).* Recrystallization: dichloromethane/ethyl acetate=5/30. White solid, mp 93–94 °C. IR (neat): ν 3438, 3304, 2917, 1682, 1661, 1592, 1536, 1425, 1162, 776, 681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (brs, 1H, NH), 7.86 (d, J=2.1 Hz, 1H, ArH), 7.21 (d, J=8.1 Hz, 1H, ArH), 6.96 (m, 2H, ArH), 5.79 (dd, J=47.8, 3.4 Hz, 1H, CH_2=CF), 5.27 (dd, J=16.1, 3.4 Hz, 1H, CH_2=CF). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6 (d, J=29.7 Hz), 155.1 (d, J=270 Hz), 137.1, 129.8, 127.6, 122.5, 122.1, 118.0, 99.8 (d, J=14.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.4 (ddd, $J_{H-F(trans)}$=47.8 Hz, $J_{H-F(cis)}$=16.3 Hz, J=5.3 Hz). HRMS (ESI) m/z: calcd for $C_9H_8BrFNO^+$ $[M+H]^+$ 243.9768, found 243.9774.

*4.2.1.9. 2-Fluoro-N-(o-tolyl)acrylamide (**2i**).* Eluent solvent: petroleum ether/ethyl acetate=20/1. White solid, mp 60–61 °C. IR (neat): ν 3443, 3294, 2927, 1687, 1659, 1590, 1530, 1458, 1318, 933, 897, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J=8.0 Hz, 1H, ArH), 7.84 (brs, 1H, NH), 7.30–7.13 (m, 3H, ArH), 5.83 (dd, J=48.1, 3.2 Hz, 1H, CH_2=CF), 5.26 (dd, J=15.4, 3.2 Hz, 1H, CH_2=CF), 2.29 (s, 3H, ArCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6 (d, J=29.3 Hz), 155.7 (d, J=270 Hz), 133.8, 129.9, 128.3, 126.3, 125.1, 122.1, 99.2 (d, J=15.0 Hz), 16.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.2 (dd, $J_{H-F(trans)}$=48.2 Hz, $J_{H-F(cis)}$=15.6 Hz). HRMS (ESI) m/z: calcd for $C_{10}H_{11}FNO^+$ $[M+H]^+$ 180.0819, found 180.0821.

*4.2.2. General procedure for the synthesis of N-substituted 2-fluoroallyl amines (**3a**–**i**).* A solution of 1.0 M DIBALH in THF (40 mL, 40 mmol) was added dropwise to the solution of compound **2a**–**i** (8.0 mmol) in dichloromethane (80 mL) within 20 min at 0 °C under Ar atmosphere. The reaction solution was then warmed to room temperature and stirred for overnight. After quenched with saturated NH_4Cl aqueous solution (50 mL), the mixture was filtered, and the filtrate was then extracted with EtOAc (3×100 mL), washed with brine (100 mL) and dried over $NaSO_4$. After filtration and concentration. The residue was purified by column chromatography, and the isolated yields were shown in Table 1.

*4.2.2.1. 2-Fluoro-N-(4-methoxybenzyl)-prop-2-en-1-amine (**3a**).* Eluent solvent: dichloromethane/acetone=200/1. Colorless oil. IR (neat): ν 3409, 2955, 2917, 1677, 1662, 1513, 1464, 1247, 1176, 1036, 847 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.7 Hz, 2H, ArH), 6.87 (d, J=8.7 Hz, 2H, ArH), 4.70 (dd, J=17.4, 2.8 Hz, 1H, CH_2=CF), 4.45 (dd, J=49.6, 2.8 Hz, 1H, CH_2=CF), 3.80 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2Ar), 3.32 (d, J=14.3 Hz, 2H, CH_2NH), 1.60 (brs, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.9 (d, J=260 Hz), 158.6, 131.6, 129.3, 113.7, 91.4 (d, J=10.0 Hz), 55.2, 51.7, 48.4 (d, J=30.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.4 (ddt, $J_{H-F(trans)}$=49.7 Hz, $J_{H-F(cis)}$=17.4 Hz, J=14.3 Hz). HRMS (ESI) m/z: calcd for $C_{11}H_{14}FNONa^+$ $[M+Na]^+$ 218.0952, found 218.0953.

*4.2.2.2. 2-Fluoro-N-benzyl-prop-2-en-1-amine (**3b**).* Eluent solvent: Petroleum ether/ethyl acetate=2/1. Colorless oil. IR (neat): ν 3338, 3028, 2918, 2846, 1677, 1495, 1454, 1196, 1119, 932, 738, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H, ArH), 4.70 (dd, J=17.1, 2.8 Hz, 1H, CH_2=CF), 4.46 (dd, J=49.7, 2.8 Hz, 1H, CH_2=CF), 3.82 (s, 2H, CH_2Ph), 3.34 (d, J=14.3 Hz, 2H, CH_2NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3 (d, J=257 Hz), 139.1, 127.8, 127.5, 126.5, 90.8 (d, J=18.4 Hz), 51.8, 48.1 (d, J=30.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.5 (ddt, $J_{H-F(trans)}$=49.7 Hz, $J_{H-F(cis)}$=17.1 Hz, J=14.3 Hz). HRMS (ESI) m/z: calcd for $C_{10}H_{13}FN^+$ $[M+H]^+$ 166.1027, found 166.1024.

*4.2.2.3. 2-Fluoro-N-(4-(trifluoromethyl)benzyl)-prop-2-en-1-amine (**3c**).* Eluent solvent: dichloromethane. Colorless oil. IR (neat): ν 3423, 2955, 2921, 2849, 1677, 1620, 1326, 1164, 1126, 1019, 850 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J=8.0 Hz, 2H, ArH), 7.46 (d, J=7.9 Hz, 2H, ArH), 4.71 (dd, J=17.0, 2.9 Hz, 1H, CH_2=CF), 4.45 (dd, J=49.5, 2.9 Hz, 1H, CH_2=CF), 3.87 (s, 2H, CH_2Ar), 3.33 (d, J=14.5 Hz, 2H,CH_2NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.6 (d, J=257 Hz), 143.2, 128.8 (q, J=32.4 Hz), 127.7, 124.7 (q, J=4.0 Hz), 123.6 (q, J=270 Hz), 91.1 (d, J=18.4 Hz), 51.1, 48.1 (d, J=30.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8 (s, 3F), −100.0 (ddt, $J_{H-F(trans)}$=49.5 Hz, $J_{H-F(cis)}$=17.0 Hz, J=14.5 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{11}H_{12}F_4N^+$ $[M+H]^+$ 234.0900, found 234.0905.

*4.2.2.4. 2-Fluoro-N-(4-bromobenzyl)-acrylamide (**3d**).* Eluent solvent: petroleum ether/ethyl acetate=10/1. Colorless oil. IR (neat): ν 3338, 2919, 2836, 1677, 1487, 1461, 1197, 1120, 1070, 1011, 932, 855, 799 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J=8.0 Hz, 2H, ArH), 7.22 (d, J=8.0 Hz, 2H, ArH), 4.69 (d, J=17.0 Hz, 1H, CH_2=CF), 4.44 (d, J=49.7 Hz, 1H, CH_2=CF), 3.77 (s, 2H, CH_2Ph), 3.31 (d, J=14.6 Hz, 2H, CH_2NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0 (d, J=257 Hz), 138.1, 130.9, 129.3, 120.3, 91.0 (d, J=18.5 Hz), 51.0, 48.0 (d, J=30.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0 (s, 3F), −103.5 (ddt, $J_{H-F(trans)}$=49.6 Hz, $J_{H-F(cis)}$=17.0 Hz, J=14.6 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{10}H_{12}BrFN^+$ $[M+H]^+$ 244.0132, found 244.0127.

*4.2.2.5. 2-Fluoroallyl-N-aniline (**3e**).* Eluent solvent: petroleum ether/ethyl acetate=50/1. Colorless oil. IR (neat): ν 3338, 2919, 2836, 1677, 1487, 1461, 1197, 1120, 1070, 1011, 932, 855, 799 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.20 (m, 2H, ArH), 6.77 (m, 1H, ArH), 6.69–6.62 (m, 2H, ArH), 4.71 (dd, J=17.3, 3.2 Hz, 1H, CH_2=CF), 4.54 (dd, J=49.5, 3.2 Hz, 1H, CH_2=CF), 3.90 (brs, NH), 3.88 (d, J=8.3 Hz,

2H, CH_2NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5 (d, J=258 Hz), 146.4, 128.6, 117.6, 112.5, 90.4 (d, J=17.3 Hz), 43.7 (d, J=34.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.5 (ddt, $J_{H-F(trans)}$=49.5 Hz, $J_{H-F(cis)}$=17.3 Hz, J=8.3 Hz). HRMS (ESI) *m/z*: calcd for $C_9H_{11}FN^+$ $[M+H]^+$ 152.0870, found 152.0869.

4.2.2.6. 2-Fluoroallyl-N-4-methoxyaniline (***3f***). Eluent solvent: petroleum ether/dichloromethane/ethyl acetate=45/10/1. Colorless oil. IR (neat): ν 3410, 2934, 2834, 1680, 1514, 1464, 1441, 1236, 1201, 1180, 1036, 932, 855, 820 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89–6.71 (m, 2H, ArH), 6.63 (m, 2H, ArH), 4.70 (dd, J=17.3, 2.7 Hz, 1H, CH_2=CF), 4.52 (dd, J=49.7 Hz, 2.7, 1H, CH_2=CF), 3.82 (d, J=8.9 Hz, 2H, CH_2NH), 3.76 (s, 3H, OCH_3), 3.70–3.50 (brs, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7 (d, J=258 Hz), 152.1, 140.6, 114.1 (d, J=48.8 Hz), 90.4 (d, J=17.7 Hz), 55.1, 44.7 (d, J=34.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.2 (ddt, $J_{H-F(trans)}$=49.7, $J_{H-F(cis)}$=17.3, J=8.9 Hz). HRMS (ESI) *m/z*: calcd for $C_{10}H_{13}FNO^+$ $[M+H]^+$ 182.0976, found 182.0972.

4.2.2.7. 2-Fluoroallyl-4-(trifluoromethyl)-N-aniline (***3g***). Eluent solvent: petroleum ether/ethyl acetate=65/1. Colorless oil. IR (neat): ν 3410, 1617, 1528, 1328, 1187, 1162, 1065, 829 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J=8.6 Hz, 2H, ArH), 6.65 (d, J=8.6 Hz, 2H, ArH), 4.70 (dd, J=16.8, 3.2 Hz, 1H, CH_2=CF), 4.52 (dd, J=49.2, 3.2 Hz, 1H, CH_2=CF), 4.29 (brs, 1H, NH), 3.89 (d, J=8.0 Hz, 2H, CH_2NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.3 (d, J=258 Hz), 148.9, 126.7 (q, J=3.4 Hz), 124.1 (q, J=269 Hz), 119.3 (q, J=32.5 Hz), 111.6, 91.6 (d, J=17.2 Hz), 44.7 (d, J=34.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.7 (s, 3F), 104.2 (ddt, $J_{H-F(trans)}$=49.2, $J_{H-F(cis)}$=16.8, J=8.0 Hz, 1F). HRMS (ESI) *m/z*: calcd for $C_{10}H_{10}F_4N^+$ $[M+H]^+$ 220.0749, found 220.0735.

4.2.2.8. 2-Fluoroally-3-bromo-N-aniline (***3h***). Eluent solvent: petroleum ether/acetone=50:1. Colorless oil. IR (neat): ν 3426, 2923, 1681, 1596, 1575, 1505, 1482, 1203, 987, 852, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–6.90 (m, 1H, ArH), 6.80–6.75 (m, 1H, ArH), 6.70–6.60 (m, 1H, ArH), 6.55 (dd, J=8.2, 2.1 Hz, 1H, ArH), 4.72 (dd, J=17.2, 3.3 Hz, 1H, CH_2=CF), 4.52 (dd, J=49.3, 3.3 Hz, 1H, CH_2=CF), 4.03 (brs, 1H, NH), 3.93–3.72 (m, 2H,CH_2NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7 (d, J=258 Hz), 147.7, 129.9, 122.6, 120.4, 115.1, 111.2, 90.8 (d, J=17.1 Hz), 43.48 (d, J=35.0 Hz) ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.0 to −103.5.0 (m). HRMS (ESI) *m/z*: calcd for $C_9H_{10}BrFN^+$ $[M+H]^+$ 229.9975, found 229.9979.

4.2.2.9. 2-Fluoroallyl-N-2-methylaniline (***3i***). Eluent solvent: petroleum ether: Acetone=200:1. Colorless oil. IR (neat): ν 3311, 3061, 1657, 1537, 1441, 1314, 1206, 1184, 1045, 920, 893, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.00 (m, 2H, ArH), 6.80–6.50 (m, 2H, ArH), 4.73 (dd, J=17.2, 3.2 Hz, 1H, CH_2=CF), 4.55 (dd, J=49.6, 3.2 Hz, 1H, CH_2=CF), 4.02 (brs, 1H, NH), 3.94 (d, J=8.3 Hz, 2H, CH_2NH), 2.20 (s, 3H, ArCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6 (d, J=257 Hz), 144.4, 129.6, 126.5, 121.7, 117.2, 109.6, 90.4 (d, J=17.3 Hz), 43.70 (d, J=34.8 Hz), 16.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.4 (ddt, $J_{H-F(trans)}$=49.6 Hz, $J_{H-F(cis)}$=17.2 Hz, J=8.3 Hz). HRMS (ESI) *m/z*: calcd for $C_{10}H_{13}FN^+$ $[M+H]^+$ 166.1027, found 166.1028.

4.2.3. General procedure for the acylation of 2-fluoroallyl amines (***5aa***–***5fe***). Oxalyl dichloride (1.56 mmol, 0.14 mL) was added to the solution of the tested acid (1.72 mmol) in CH_2Cl_2 (5 mL) and DMF (a drop, about 0.05 mL) at 0 °C under Ar atmosphere within 10 min. After the solution was stirred for 3 h at the room temperature, a solution of **3a**–**i** (1.32 mmol) in dichloromethane (8.0 mL) was added at 0 °C. The reaction solution was then warmed to room temperature and stirred for overnight. After quenched with saturated $NaHCO_3$ aqueous solution, the mixture was extracted with EtOAc (2×15 mL), and the combined organic layers were washed with brine (20 mL) and dried over $NaSO_4$. After filtration and concentration, the residue was purified by column chromatography to give the acylated product with two rotamers, and the isolated yields were shown in Table 2.

4.2.3.1. 2-Fluoroallyl-N-(4-(trifluoromethyl)-N-phenyl-acrylamide (***5aa***). Eluent solvent: petroleum ether/ethyl acetate=1/1. Colorless oil. IR (neat): ν 2933, 1651, 1613, 1513, 1441, 1284, 1205, 1176, 1033, 847 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J=8.8 Hz, 1H, ArH, one rotamer), 7.08 (d, J=8.4 Hz, 1H, ArH, the other rotamer), 6.87 (d, J=8.8 Hz, 1H, ArH, one rotamer), 6.84 (d, J=8.4 Hz, 2H, ArH, the other rotamer), 6.55–6.51 (m, 1H), 6.48–6.38 (m, 1H), 5.78–5.68 (m, 1H), 4.83–4.67 (m, 1H), 4.61 (m, 1H), 4.59 (m, 1H), 4.52–4.48 (m, 0.5H), 4.40–4.36 (m, 0.5H). 4.13 (d, J=12.8 Hz, 1H), 3.89 (d, J=8.8 Hz, 1H), 3.78 (s, 1.5H), 3.77 (s, 1.5H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 161.2 (d, J=258 Hz, one rotamer), 160.7 (d, J=258 Hz, one rotamer), 159.2, 159.0, 129.8, 129.5, 129.1, 128.8, 127.9, 127.7, 127.3, 127.2, 114.3, 114.0, 93.0 (d, J=17.3 Hz, one rotamer), 92.4 (d, J=17.2 Hz, one rotamer), 55.3, 50.0, 47.8, 46.3, 45.0 (d, J=32.0 Hz, one rotamer). ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.0 to −103.3 (m), δ −104.0 to −104.3 (m). HRMS (ESI) *m/z*: calcd for $C_{14}H_{17}FNO_2^+$ $[M+H]^+$ 250.1238, found 250.1239.

4.2.3.2. 2-Fluoroallyl-N-(4-methoxybenzyl)-N-but-3-enamide (***5ab***). Eluent solvent: petroleum ether/ethyl acetate=1/1. Colorless oil. IR (neat): ν 2955, 2923, 2850, 1651, 1612, 1513, 1456, 1247, 1174, 1033, 930, 847 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J=8.4 Hz, 1H, ArH, one rotamer), 7.09 (d, J=8.4 Hz, 1H, ArH, the other rotamer), 6.87 (d, J=8.4 Hz, 1H, ArH, the other rotamer), 6.84 (d, J=8.4 Hz, 1H, ArH, one rotamer), 6.09–5.90 (m, 1H), 5.21–5.16 (m, 1H), 5.21–5.16 (m, 1H), 4.83–4.67 (m, 1H), 4.56 (s, 1H), 4.52 (s, 1H), 4.51–4.33 (m, 1H), 4.08 (d, J=14.4 Hz, 1H), 3.84 (d, J=8.4 Hz, 1H), 3.80 (s, 1.5H), 3.79 (s, 1.5H), 3.25–3.20 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 171.5, 161.4 (d, J=261 Hz, one rotamer), 161 (d, J=260 Hz, the other rotamer), 159.5, 159.3, 131.6, 131.5, 130.0, 129.2, 128.0, 127.9, 118.3, 118.2, 114.6, 114.2, 93.2 (d, J=18.1 Hz), 92.8 (d, J=18.1 Hz), 55.6, 55.5, 50.3, 47.6, 46.5 (d, J=34.8 Hz), 44.8 (d, J=35.4 Hz), 38.9, 38.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.1 to −103.5 (m), −104.0 to −104.3 (m). HRMS (ESI) *m/z*: calcd for $C_{15}H_{19}FNO_2^+$ $[M+H]^+$ 264.1394, found 264.1395.

4.2.3.3. 2-Fluoroallyl-N-(4-methoxybenzyl)-N-pent-4-enamide (***5ac***). Eluent solvent: petroleum ether/ethyl acetate=2/1. Colorless oil. IR (neat): ν 3443, 2955, 2923, 2850, 1651, 1612, 1513, 1456, 1247, 1174, 1033, 930, 847 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.16 (d, J=8.4 Hz, 1H, ArH, one rotamer), 7.07 (d, J=8.4 Hz, 1H, ArH, the other rotamer), 6.88 (d, J=8.4 Hz, 1H, ArH, the other rotamer), 6.84 (d, J=8.4 Hz, 1H, ArH, one rotamer), 5.92–5.77 (m, 1H), 5.10–5.03 (m, 1H), 5.01–4.96 (m, 1H), 4.81–4.67 (m, 1H), 4.57 (s, 1H), 4.53 (s, 1H), 4.49–4.33 (m, 1H), 4.08 (d, J=13.6 Hz, 1H), 3.84 (d, J=8.8 Hz, 1H), 3.80 (s, 1.5H), 3.78 (s, 1.5H), 2.53–2.40 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 172.5, 161.4 (d, J=260 Hz, one rotamer), 160.8 (d, J=260 Hz, the other rotamer), 159.1, 159.0, 137.3, 137.2, 129.7, 129.0, 127.9, 127.6, 115.4, 115.3, 114.3, 114.0, 93.8 (d, J=17.5 Hz), 92.8 (d, J=17.1 Hz), 55.3, 55.2, 49.9, 47.3, 46.2 (d, J=33.4 Hz), 44.7 (d, J=32.0 Hz), 32.5, 32.2, 29.2, 29.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −103.3 to −103.6 (m), −104.1 to −104.4 (m). HRMS (ESI) *m/z*: calcd for $C_{16}H_{21}FNO_2^+$ $[M+H]^+$ 278.1151, found 278.1156.

4.2.3.4. 2-Fluoroallyl-N-benzyl-N-hex-5-enamide (***5ad***). Eluent solvent: petroleum ether/ethyl acetate=5/1. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J=8.4 Hz, 1H, ArH, one rotamer), 7.07 (d, J=8.4 Hz, 1H, ArH, the other rotamer), 6.88 (d, J=8.4 Hz, 1H, ArH, one rotamer), 6.84 (d, J=8.4 Hz, 1H, ArH, the other rotamer), 5.92–5.77 (m, 1H), 5.10–4.96 (m, 2H), 4.81–4.67 (m, 1H), 4.57 (s, 1H), 4.53 (s, 1H), 4.49–4.33 (m, 1H), 4.08 (d, J=13.6 Hz, 1H), 3.84 (d, J=8.8 Hz, 1H), 3.80 (s, 1.5H), 3.78 (s, 1.5H), 2.53–2.40 (m, 2H),

2.30–2.00 (m, 2H), 1.90–1.70 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ173.3, 173.1, 162.0 (d, *J*=260 Hz, one rotamer), 160.8 (d, *J*=260 Hz, the other rotamer), 159.1, 159.0, 138.1, 138.0, 129.7, 129.2, 128.1, 127.7, 115.4, 115.2, 114.3, 114.0, 92.7 (d, *J*=17.5 Hz), 92.3 (d, *J*=17.1 Hz), 55.3, 55.2, 50.0, 47.3, 46.2 (d, *J*=33.4 Hz), 44.7 (d, *J*=32.0 Hz), 33.2, 33.1, 32.4, 32.1, 24.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −103.3 to −103.6 (m), −104.1 to −104.4 (m). HRMS (ESI) *m/z*: calcd for $C_{17}H_{23}FNO_2^+$ $[M+H]^+$ 292.1707, found 292.1709.

*4.2.3.5. 2-Fluoroallyl-N-benzyl-N-but-3-enamide (**5bb**).* Eluent solvent: petroleum ether/ethyl acetate=5/1. Colorless oil. IR (neat): ν 3065, 3030, 2982, 2930, 1651, 1495, 1445, 1202, 932, 848, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.03 (m, 5H, ArH), 6.10–5.50 (m, 1H), 5.50–5.10 (m, 2H), 4.80–4.60 (m, 1H), 4.60–4.50 (m, 2H), 4.50–4.40 (m, 1H), 4.12 (d, *J*=13.8 Hz, 1H), 3.87 (d, *J*=9.1 Hz, 1H), 3.23–3.10 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 170.7, 160.7 (d, *J*=259 Hz, one rotamer), 159.3 (d, *J*=259 Hz, the other rotamer), 136.3, 135.5, 130.7, 128.4, 128.1, 127.7, 127.2, 127.0, 125.7, 117.5, 92.3 (d, *J*=17.6 Hz), 92.2 (d, *J*=17.4 Hz), 50.0, 47.4, 45.9 (d, *J*=34.2 Hz), 44.4 (d, *J*=31.7 Hz), 37.9, 37.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.0 to −104.0 (m), −104.0 to −106.0 (m). HRMS (ESI) *m/z*: calcd for $C_{14}H_{17}FNO^+$ $[M+H]^+$ 234.1289, found 234.1291.

*4.2.3.6. 2-Fluoroallyl-N-(4-(trifluoromethyl)phenyl-N-but-3-enamide (**5cb**).* Eluent solvent: petroleum ether/dichloromethane/ethyl acetate=35/15/1. Colorless oil. IR (neat): ν 2925, 1656, 1413, 1326, 1165, 1125, 1067, 934, 849 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J*=8.0 Hz, 1H, ArH, one rotamer), 7.57 (d, *J*=8.0 Hz, 1H, ArH, the other rotamer), 7.35 (d, *J*=8.0 Hz, 1H, ArH, the other rotamer), 7.29 (d, *J*=8.0 Hz, 1H, ArH, one rotamer), 6.10–5.80 (m, 1H), 5.38–5.00 (m, 2H), 4.82–4.70 (m, 2H), 4.70–4.60 (m, 2H), 4.45–4.25 (m, 1H), 4.12 (d, *J*=14.4 Hz, 1H), 3.89 (d, *J*=9.2 Hz, 1H), 3.26 (d, 6.5 Hz, 1H), 3.17 (d, 6.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 160.6 (d, *J*=259 Hz, one rotamer), 159.8 (d, *J*=259 Hz, the other rotamer), 140.3, 139.7, 130.4, 130.2, 129.0 (q, *J*=32.3 Hz), 127.8, 125.9, 125.4, 125.0 (q, *J*=3.1 Hz), 123.4 (q, *J*=270 Hz, one rotamer), 117.7, 117.6, 92.9 (d, *J*=17.7 Hz), 92.5(d, *J*=17.5 Hz), 49.7, 47.2, 46.5 (d, *J*=33.6 Hz), 44.6 (d, *J*=30.9 Hz), 37.9, 37.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.9 to −63.0 (m, 3F), −103 to −105 (m, 1F). HRMS (ESI) *m/z*: calcd for $C_{15}H_{15}F_4NONa^+$ $[M+Na]^+$ 324.0982, found 324.0986.

*4.2.3.7. 2-Fluoroallyl-N-(4-bromobenzyl)-N-but-3-enamide (**5db**).* Eluent solvent: petroleum ether/dichloromethane/ethyl acetate=30/10/4. Colorless oil. IR (neat): ν 3491, 3080, 3022, 2981, 2932, 1651, 1592, 1488, 1445, 1403, 1220, 1071, 1011, 932, 848, 794 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.39 (m, 2H, ArH), 7.08 (m, 2H, ArH), 6.06–5.90 (m, 1H), 5.23–5.06 (m, 2H), 4.80–4.60 (m, 1H), 4.50–4.40 (m, 2H), 4.40–4.20 (m, 1H), 4.12 (d, *J*=14.0, 1H), 3.85 (d, *J*=9.5 Hz, 1H), 3.24–3.20 (m, 1H), 3.19–3.15 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 160.3 (d, *J*=259 Hz), 159.9 (d, *J*=259 Hz), 135.4, 134.5, 131.5, 131.1, 130.5, 130.4, 129.4, 127.4, 121.1, 120.9, 117.6, 92.7 (d, *J*=17.7 Hz), 92.3 (d, *J*=17.3 Hz), 49.5, 46.9, 46.2 (d, *J*=34.0 Hz), 44.4 (d, *J*=31.5 Hz), 37.8, 37.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.0 to −103.0 (m), −103.0 to −106.0 (m). HRMS (ESI) *m/z*: calcd for $C_{14}H_{16}BrFNO^+$ $[M+H]^+$ 312.0394, found 312.0395.

*4.2.3.8. 2-Fluoroallyl-N-phenyl-N-but-3-enamide (**5eb**).* Eluent solvent: petroleum ether/ethyl acetate=10/1. White solid, mp 66–67 °C. IR (neat): ν 3497, 3079, 2981, 2933, 1667, 1596, 1495, 1423, 1393, 1195, 933, 848, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.06 (m, 5H, ArH), 5.89–5.70 (m, 1H), 5.07–4.90 (m, 1H), 4.90–4.70 (m, 1H), 4.65–4.50 (m, 1H), 4.50–4.20 (m, 3H), 2.87–2.70 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 160.4 (d, *J*=259 Hz), 141.1, 130.9, 129.0, 127.8, 127.7, 117.3, 93.0 (d, *J*=17.8 Hz), 48.6 (d, *J*=30.7 Hz), 38.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.0 to −104.0 (m). HRMS (ESI) *m/z*: calcd for $C_{13}H_{15}FNO^+$ $[M+H]^+$ 220.1132, found 220.1134.

*4.2.3.9. 2-Fluoroallyl-N-(4-methoxyphenyl)-N-but-3-enamide (**5fb**).* Eluent solvent: petroleum ether/ethyl acetate=10/1. Colorless oil. IR (neat): ν 3078, 2935, 2839, 1665, 1512, 1249, 1195, 1025, 841 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J*=8.8 Hz, 2H, ArH), 6.90 (d, *J*=8.8 Hz, 2H, ArH), 5.84 (m, 1H, C*H*=CH_2), 5.05 (dd, *J*=10.2, 1.6 Hz, 1H, CH=C*H*$_2$), 4.92 (dd, *J*=17.1, 1.6 Hz, 1H, CH=C*H*$_2$), 4.63 (dd, $J_{H-F(cis)}$=16.2 Hz, *J*=3.1 Hz, 1H, CF=C*H*$_2$), 4.37 (d, *J*=15.6 Hz, 2H, C*H*$_2$NAr), 4.35 (dd, $J_{H-F(trans)}$=48.1 Hz, *J*=3.1 Hz, 1H, CF=C*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 2.85 (m, 2H, C*H*$_2$CO). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 161.4 (d, *J*=259 Hz), 158.7, 133.7, 131.0, 128.7, 117.1, 114.1, 93.0 (d, *J*=17.9 Hz), 54.8, 48.7 (d, *J*=30.4 Hz), 38.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.0 to −104.0 (m). HRMS (ESI) *m/z*: calcd for $C_{14}H_{16}FNO_2Na^+$ $[M+Na]^+$ 272.1057, found 272.1064.

*4.2.3.10. 2-Fluoroallyl-N-(4-(trifluoromethyl)phenyl-N-but-3-enamide (**5gb**).* Eluent solvent: petroleum ether/ethyl acetate=10/1. Colorless oil. IR (neat): ν 3082, 2932, 1674, 1614, 1423, 1381, 1326, 1169, 1128, 1107, 852 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J*=8.2 Hz, 2H, ArH), 7.37 (d, *J*=8.2 Hz, 2H, ArH), 5.90–5.70 (m, 1H, C*H*=CH_2), 5.11 (d, $J_{H-H(cis)}$=10.1 Hz, 1H, CH=C*H*$_2$), 4.97 (d, $J_{H-H(trans)}$=17.2 Hz, 1H, CH=C*H*$_2$), 4.69 (dd, $J_{H-F(cis)}$=16.1 Hz, *J*=3.1 Hz, 1H, CF=C*H*$_2$), 4.45 (dd, $J_{H-F(trans)}$=47.6 Hz, *J*=3.1 Hz, 1H, CF=C*H*$_2$), 4.40 (d, *J*=15.2 Hz, 2H, C*H*$_2$NAr), 2.89 (d, *J*=6.7 Hz, 2H, C*H*$_2$CO). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 160.9 (d, *J*=276 Hz), 145.0, 131.1, 130.7 (q, *J*=32.7 Hz), 128.9, 127.0, 123.7 (q, *J*=270 Hz), 118.4, 94.3 (d, *J*=17.7 Hz), 49.3 (d, *J*=30.5 Hz), 39.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.9 (s, 3F), −103.2 (ddt, $J_{H-F(trans)}$=47.6 Hz, $J_{H-F(cis)}$=16.1 Hz, *J*=15.2 Hz, 1F). HRMS (ESI) *m/z*: calcd for $C_{13}H_{14}F_4NO$ $[M+H]^+$ 288.1006, found 288.1006.

*4.2.3.11. 2-Fluoroallyl-N-(3-bromophenyl)-N-but-3-enamide (**5hb**).* Eluent solvent: petroleum ether/ethyl acetate=10/1. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J*=8.0 Hz, 1H, ArH), 7.40 (s, 1H, ArH), 7.32 (m, 1H, ArH), 7.18 (d, *J*=8.4 Hz, 1H, ArH), 6.00–5.80 (m, 1H, C*H*=CH_2), 5.11 (d, *J*=10.1 Hz, 1H, CH=C*H*$_2$), 4.97 (d, *J*=17.2 Hz, 1H, CH=C*H*$_2$), 4.69 (dd, $J_{H-F(cis)}$=16.1, 3.1 Hz, 1H, CF=C*H*$_2$), 4.41 (dd, $J_{H-F(trans)}$=47.6 Hz, *J*=3.1 Hz, 1H, CF=C*H*$_2$), 4.40 (d, *J*=15.6 Hz, 2H, C*H*$_2$NAr), 2.89 (d, *J*=6.7 Hz, 2H, C*H*$_2$CO). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 160.9 (d, *J*=259 Hz), 142.3, 131.1, 130.9, 130.5, 130.3, 126.5, 122.3, 117.6, 93.4 (d, *J*=17.7 Hz), 48.6 (d, *J*=30.5 Hz), 38.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.0 to −103.0 (m). HRMS (ESI) *m/z*: calcd for $C_{13}H_{14}BrFNONa^+$ $[M+Na]^+$ 320.0057, found 320.0059.

*4.2.3.12. 2-Fluoroallyl-N-(o-tolyl)-N-but-3-enamide (**5ib**).* Eluent solvent: petroleum ether/ethyl acetate=10/1. White solid, mp 60–61 °C. IR (neat): ν 3424, 2919, 2849, 1666, 1492, 1393, 1378, 1187, 935, 848, 730 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.01 (m, 4H, ArH), 5.89 (m, 1H, C*H*=CH_2), 5.06–5.0 (m, 1H, CH=C*H*$_2$), 4.97–4.73 (m, 2H, CH=C*H*$_2$, C*H*$_2$NAr), 4.65 (dd, $J_{H-F(cis)}$=16.0 Hz, *J*=3.0 Hz, 1H, CFC*H*$_2$), 4.38 (dd, $J_{H-F(trans)}$=47.9 Hz, *J*=3.0 Hz, 1H, CFC*H*$_2$), 3.82 (dd, *J*=18.6, 15.0 Hz, 1H, C*H*$_2$NAr), 2.94–2.60 (m, 2H, C*H*$_2$CO), 2.22 (s, 3H, C*H*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 161.4 (d, *J*=259 Hz), 139.6, 135.2, 130.8, 130.7, 128.7, 128.2, 126.6, 117.3, 93.5 (d, *J*=17.9 Hz), 47.6 (d, *J*=30.1 Hz), 38.4, 16.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.5 to −102.0 (m). HRMS (ESI) *m/z*: calcd for $C_{14}H_{17}FNO^+$ $[M+H]^+$ 234.1289, found 234.1289.

*4.2.3.13. 2-Fluoro-N-(2-fluoroallyl)-N-(4-methoxyphenyl)-acrylamide (**5fe**).* Eluent solvent: petroleum ether/dichloromethane/ethyl acetate=15/4/1. Colorless oil. IR (neat): ν 3415, 2916, 2848, 1667, 1644, 1512, 1400, 1249, 1172, 934, 838, 769 cm^{-1}. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.13–7.11 (m, 2H, ArH), 6.89–6.86 (m, 2H, ArH), 5.26 (dd, $J_{H-F(trans)}$=45.6 Hz, J=3.2 Hz, 1H, COCFCH_2), 4.98 (dd, $J_{H-F(cis)}$=12.8 Hz, J=3.2 Hz, 1H, COCFCH_2), 4.70 (dd, $J_{H-F(cis)}$=16.0 Hz, J=3.2 Hz, 1H, CFCH_2), 4.43 (dd, $J_{H-F(trans)}$=48.0 Hz, J=3.2 Hz, 1H, CFCH_2), 4.42 (d, J=14.8 Hz, 1H, CH_2N), 3.80 (d, J=1.6 Hz, 3H, OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.1 (d, J=28.9 Hz), 159.8 (d, J=259 Hz), 158.5, 156.3 (d, J=271 Hz), 133.4, 127.4, 113.8, 100.5 (d, J=15.3 Hz), 93.5 (d, J=17.6 Hz), 54.8, 49.9 (d, J=30.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.8 to −103.0 (m), −105.9 to −106.1 (m). HRMS (ESI) *m/z*: calcd for $C_{13}H_{14}F_2NO_2^+$ $[M+H]^+$ 254.0987, found 254.0992.

*4.2.4. General procedure for the synthesis of compound (**6aa**–**6fe**).* A solution of Grubbs' II (0.145 g, 0.17 mmol) in Tol (40 mL) was added via a syringe pump over 1 h to a solution of compound **5ab**–**ib** (1.70 mmol) in Tol (150 mL) at 100 °C under Ar atmosphere. After that, the solution continued to stir for another 30 min at the same temperature. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, and the isolated yields were shown in Table 2.

*4.2.4.1. 4-Fluoro-1-(4-methoxybenzyl)-1H-pyrrol-2(5H)-one (**6aa**).* Eluent solvent: petroleum ether/ethyl acetate=2/1. White solid, mp 69–70 °C IR (neat): ν 3447, 2929, 2837, 1652, 1613, 1513, 1441, 1248, 1205, 1038, 933, 847, 819, 794 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=8.6 Hz, 2H, ArH), 6.97 (d, J=8.6 Hz, 2H, ArH), 5.62 (s, 1H, C*H*=CF), 4.63 (s, 2H, CH_2Ar), 3.93 (s, 2H, CH_2N), 3.89 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (d, J=291 Hz), 169.4 (d, J=15 Hz), 159.1, 129.4, 128.6, 114.2, 102.3, 55.3, 48.2 (d, J=25.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.6 (s). HRMS (ESI) *m/z*: calcd for $C_{12}H_{12}FNO_2Na^+$ [M+Na] 244.0744, found 244.0744.

*4.2.4.2. 5-Fluoro-1-(4-methoxybenzyl)-1,6-dihydropyridin-2(3H)-one (**6ab**).* Eluent solvent: petroleum ether/ethyl acetate=2/1. White solid, mp 73–74 °C IR (neat): ν 3442, 2955, 2923, 2850, 1651, 1513, 1456, 1247, 1198, 1174, 1038, 930, 847 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J=8.4 Hz, 2H, ArH), 6.86 (d, J=8.4 Hz, 2H, ArH), 5.25 (d, J=14.0 Hz, 1H, C*H*=CF), 4.57 (s, 2H, CH_2Ar), 3.83–3.81 (m, 2H, CH_2N), 3.79 (s, 3H, OCH_3), 3.11–3.00 (m, 2H, CH_2CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 159.2, 151.5 (d, J=250 Hz), 129.7, 127.8, 114.1, 97.7 (d, J=15.0 Hz), 55.2, 49.2, 45.7 (d, J=40.0 Hz), 29.9 (d, J=12.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −117.7 to −116.0 (m). HRMS (ESI) *m/z*: calcd for $C_{13}H_{15}FNO_2^+$ [M+H] 236.1081, found 236.1080.

*4.2.4.3. 6-Fluoro-1-(4-methoxybenzyl)-3,4-dihydro-1H-azepin-2(7H)-one (**6ac**).* Eluent solvent: petroleum ether/ethyl acetate=3/2. Colorless oil. IR (neat): ν 2920, 2849, 1652, 1611, 1513, 1473, 1246, 1110, 1032, 839, 815 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J=12 Hz, 2H, ArH), 6.85 (d, J=8.4 Hz, 2H, ArH), 5.43 (dt, J=20.4 Hz, J=4.0 Hz, 1H, C*H*=CF), 4.59 (s, 2H, CH_2Ar), 3.92 (d, J=12 Hz, 2H, CH_2N), 3.79 (s, 3H, OCH_3), 2.75–2.72 (t, J=6.0 Hz, 2H, CH_2CO), 2.43–2.40 (m, 2H, CH_2CH_2CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 159.0, 156.6 (d, J=252 Hz), 129.2, 128.7, 114.0, 106.0 (d, J=20 Hz), 55.2, 50.6, 46.4 (d, J=42 Hz), 33.7, 21.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −98.9 to −99.0 (m). HRMS (ESI) *m/z*: calcd for $C_{14}H_{17}FNO_2^+$ [M+H] 250.1238, found 250.1239.

*4.2.4.4. 5-Fluoro-1-benzyl-1,6-dihydropyridin-2(3H)-one (**6bb**).* Eluent solvent: petroleum ether/dichloromethane/ethyl acetate=10/5/2. White solid, mp 62–63 °C. IR (neat): ν 3462, 2920, 1650, 1489, 1453, 1252, 1181, 1064, 819, 710 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H, ArH), 5.29–5.24 (m, 1H, C*H*=CF), 4.63 (s, 2H, ArCH_2), 3.85–3.82 (m, 2H, CH_2N), 3.13–3.08 (m, 2H, CH_2CO). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 150.6 (d, J=250 Hz), 135.3, 128.2, 127.6, 127.2, 97.4 (d, J=14.8 Hz), 49.3, 45.3 (d, J=39.1 Hz), 29.2 (d, J=8.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.0 to −116.9 (m). HRMS (ESI) *m/z*: calcd for $C_{12}H_{13}FNO^+$ $[M+H]^+$ 206.0976, found 206.0974.

*4.2.4.5. 5-Fluoro-1-(4-(trifluoromethyl)benzyl)-1,6-dihydropyridin-2(3H)-one (**6cb**).* Eluent solvent: petroleum ether/ethyl acetate=5/3. White solid, mp 70–71 °C. IR (neat): ν 3453, 2924, 1651, 1620, 1489, 1419, 1325, 1169, 1124, 1066, 819 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J=8.0 Hz, 2H, ArH), 7.40 (d, J=8.0 Hz, 2H, ArH), 5.31 (d, J=16.0 Hz, 1H, C*H*=CF), 4.69 (s, 2H, CH_2Ar), 3.89–3.86 (m, 2H, CH_2N), 3.16–3.12 (m, 2H, CH_2CO). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 150.3 (d, J=250 Hz), 139.4, 129.6 (q, J=32.3 Hz), 127.7, 125.2–125.1 (q, J=3.8 Hz), 123.4 (q, J=270 Hz), 97.6 (d, J=15 Hz), 48.9, 45.7 (d, J=39.5 Hz), 29.1 (d, J=8.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.1 (s, 3F), −116.0 to −116.6 (m, 1F). HRMS (ESI) *m/z*: calcd for $C_{12}H_{10}F_4NO^+$ $[M+H]^+$ 260.0693, found 260.0695.

*4.2.4.6. 5-Fluoro-1-(4-bromobenzyl)-1,6-dihydropyridin-2(3H)-one (**6db**).* Eluent solvent: petroleum ether/ethyl acetate=5/2. White solid, mp 78–79 °C. IR (neat): ν 3455, 2920, 1649, 1488, 1181, 1070, 1012, 817 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J=7.6 Hz, 2H, ArH), 7.15 (d, J=8.0 Hz, 2H, ArH), 5.27 (d, J=12.4 Hz, 1H, C*H*=CF), 4.57 (s, 2H, CH_2Ar), 3.84–3.82 (m, 2H, CH_2N), 3.12–3.07 (m, 2H, CH_2CO). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 150.4 (d, J=250 Hz), 134.4, 131.3, 129.4, 121.2, 97.5 (d, J=14.9 Hz), 48.8, 45.4 (d, J=39.5 Hz), 29.2 (d, J=8.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.0 to −116.9 (m). HRMS (ESI) *m/z*: calcd for $C_{12}H_{12}BrFNO_2^+$ $[M+H]^+$ 284.0081, found 284.0083.

*4.2.4.7. 5-Fluoro-1-phenyl-1,6-dihydropyridin-2(3H)-one (**6eb**).* Eluent solvent: dichloromethane/ethyl acetate=30/1. White solid, mp 102–103 °C. IR (neat): ν 3421, 2917, 2849, 1645, 1595, 1441, 1368, 1277, 1174, 1140, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H, ArH), 7.35–7.26 (m, 3H, ArH), 5.40 (dt, J=14, 1.2 Hz, 1H, C*H*=CF), 4.33–4.31 (m, 2H, CH_2N), 3.25–3.20 (m, 2H, CH_2CO). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 150.8 (d, J=250 Hz), 140.8, 128.9, 127.0, 125.7, 97.6 (d, J=14.7 Hz), 49.4 (d, J=39.0 Hz), 29.7(d, J=8.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.0 to −118.1 (m). HRMS (ESI) *m/z*: calcd for $C_{11}H_{11}FNO^+$ $[M+H]^+$ 192.0819, found 192.0821.

*4.2.4.8. 5-Fluoro-1-(4-methoxyphenyl)-1,6-dihydropyridin-2(3H)-one (**6fb**).* Eluent solvent: petroleum ether/ethyl acetate=1/2. White solid, mp 138–139 °C. IR (neat): ν 3442, 2995, 2916, 1650, 1606, 1513, 1475, 1446, 1276, 1248, 1171, 1140, 1031, 821, 778 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.18 (m, 2H, ArH), 6.95–6.93 (m, 2H, ArH), 5.38 (d, J=13.6 Hz, 1H, C*H*=CF), 4.28–4.26 (m, 2H, CH_2N), 3.81 (s, 3H, OCH_3), 3.22–3.17 (m, 2H, CH_2CO). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 158.1, 150.8 (d, J=251 Hz), 133.6, 126.9, 114.2, 97.6 (d, J=15.0 Hz), 54.8, 49.8 (d, J=38.6 Hz), 29.6(d, J=8.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.9 to −117.3 (m). HRMS (ESI) *m/z*: calcd for $C_{12}H_{13}FNO_2^+$ $[M+H]^+$ 222.0925, found 222.0927.

*4.2.4.9. 5-Fluoro-1-(4-(trifluoromethyl)phenyl)-1,6-dihydro pyridin-2(3H)-one (**6gb**).* Eluent solvent: petroleum ether/ethyl acetate=15/1. White solid, mp 127–128 °C. IR (neat): ν 3441, 2954, 2917, 2849, 1648, 1610, 1442, 1324, 1277, 1165, 1116, 821, 783 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J=8.0 Hz, 2H, ArH), 7.45 (d, J=8.0 Hz, 2H, ArH), 5.42 (d, J=13.6 Hz, 1H, C*H*=CF), 4.35–4.33 (m, 2H, CH_2N), 3.25–3.21 (m, 2H, CH_2CO). ^{13}C NMR (150 MHz, $CDCl_3$)

δ 166.7, 151.2 (d, *J*=251 Hz), 144.6, 129.7 (q, *J*=32.7 Hz), 126.7 (q, *J*=3.5 Hz), 126.6, 123.9 (q, *J*=270 Hz), 98.4 (d, *J*=15.1 Hz), 49.6 (d, *J*=39.6 Hz), 30.5 (d, *J*=8.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.13 (s, 3F), −116.5 to −116.6 (m, 1F). HRMS (ESI) *m/z*: calcd for $C_{12}H_{10}F_4NO^+$ $[M+H]^+$ 261.0711, found 261.0711.

*4.2.4.10. 5-Fluoro-1-(3-bromophenyl)-1,6-dihydropyridin-2(3H)-one (**6hb**).* Eluent solvent: petroleum ether/ethyl acetate=5:2. White solid, mp 126–127 °C. IR (neat): ν 3414, 2955, 2918, 2849, 1663, 1580, 1573, 1476, 1362, 1259, 1178, 1143, 1028, 769 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H, ArH), 7.33–7.24 (m, 2H, ArH), 5.43–5.37 (dt, *J*=13.8, 1.4 Hz, 1H, C*H*=CF), 4.31–4.28 (m, 2H, CH_2N), 3.23–3.19 (m, 2H, CH_2CO). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 150.6 (d, *J*=251 Hz), 141.9, 130.1, 130.0, 128.9, 124.4, 122.1, 97.6 (d, *J*=14.8 Hz), 49.2 (d, *J*=39.3 Hz), 29.6 (d, *J*=8.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.7 to −116.8 (m). HRMS (ESI) *m/z*: calcd for $C_{11}H_{11}BrFNO^+$ $[M+H]^+$ 269.9924, found 269.9931.

*4.2.4.11. (E)-N-(2-Fluoroallyl)-N-(o-tolyl)but-2-enamide (**7ib**).* Eluent solvent: petroleum ether/ethyl acetate=10:1. White solid, mp 62–63 °C. IR (neat): ν 3484, 2924, 2852, 1669, 1633, 1492, 1445, 1375, 1206, 1188, 966, 935, 849, 729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H, ArH), 7.33–7.10 (m, 4H, ArH), 7.10–6.90 (m, 1H, MeC*H*=CH), 5.60–5.50 (dq, *J*=14.8, 1.4 Hz, 1H, MeCH=C*H*), 4.90–4.70 (dd, *J*=15.2, 15.2 Hz, 1H, CH_2N), 4.66 (dd, *J*=16.0, 3.2 Hz, 1H, CH_2=CF), 4.41 (dd, *J*=48, 3.2 Hz, 1H, CH_2=CF), 3.96 (dd, *J*=48, 3.2 Hz, 1H, CH_2N), 2.19 (s, 3H, $ArCH_3$), 1.72 (d, *J*=3.4 Hz, 3H, *Me*CH=CH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 160.8 (d, *J*=260 Hz), 142.2, 139.4, 135.7, 130.6, 128.6, 127.9, 126.5, 121.1, 93.3 (d, *J*=18 Hz), 47.7 (d, *J*=30 Hz), 17.4, 16.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.0 to −102.0 (m). HRMS (ESI) *m/z*: calcd for $C_{14}H_{16}FNONa^+$ $[M+H]^+$ 256.1108, found 256.1111.

*4.2.4.12. (E)-5-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-4-fluoropent-3-enoic acid (**8ab**).* **6ab** (0.235 g, 1.0 mmol) was added to a solution of 6 N HCl aqueous (10 mL), and the mixture was refluxed for 3 h and then concentrated under reduced pressure to dryness, giving a quantitative white solid, mp 52–53 °C. ^{1}H NMR (400 MHz, D_2O) δ 5.51 (dt, *J*=20, 8.0 Hz, 1H, CF=C*H*), 4.41 (d, *J*=20 Hz, 2H, CH_2CF), 3.04 (d, *J*=8.0 Hz, 2H, CH_2CO), MS (ESI) *m/z*: 143 $[M+H]^+$. The crude mixture was used in the next step without further purification.

Fmoc-Cl (0.310 g, 1.2 mmol) was added at 0 °C to a mixture of the amine hydrochloride (1.0 mmol) in THF and 10% Na_2CO_3 aqueous solution (10/10 mL) and the reaction mixture was stirred at 0 °C for 3 h and was then poured into ice-cooled HCl aqueous solution (1 N, 30 mL) and extracted with AcOEt (3×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography to afford **8ab** (0.269 g, 76%). Eluent solvent: petroleum ether/ethyl acetate=10:1. White solid, mp 123–124 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 3.23 (d, *J*=7.6 Hz, 2H, CH_2CO), 3.90–4.00 (m, 2H, OCH_2CH), 4.00–4.30 (m, 1 H, OCH_2CH), 4.30–4.40 (m, 2 H, CH_2CF), 5.35 (dt, *J*=19.6, 7.6 Hz, 1H, CF=C*H*), 6.90 (brs, 1 H, N*H*), 7.25–7.50 (m, 4 H, ArH), 7.60–7.80 (m, 2H, ArH), 7.64–7.66 (m, 2H, ArH); MS (ESI) *m/z*: 356.1 $[M+H]^+$. The data is consistent with the reported literature.[2d]

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.06.054.

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