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硼自由基促进的三氟乙酰胺选择性脱单氟和双氟氘代反应

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摘要 氘代单氟烷基和二氟烷基化合物在医学和生物学研究中受到了越来越多的关注. 从可广泛获得的三氟甲基化合物出发, 可控地切断一个或两个碳-氟键并氘代是制备这类分子的一种有效方法, 但是脱氟过程中化学选择性地控制仍具挑战. 报道了一种通过自旋中心转移实现的三氟乙酰胺选择性脱单氟和双氟氘化反应. 首先, 氘代 4-二甲氨基吡啶-硼自由基(DMAP-BD_2•)加成到羰基氧上, 然后发生自旋中心转移引发碳-氟键断裂, 生成的二氟烷基自由基经过氘原子转移, 能以良好的收率和氘代率得到氘代二氟烷基产物. 增加 4-二甲氨基吡啶-硼烷的用量可以选择性切断两个 C—F 键, 从而高效地制备氘代单氟烷基化合物.

关键词 路易斯碱-硼自由基; 碳-氟键断裂; 脱氟氘化; 自旋中心转移

Selective Mono- and Di-deuterodefluorination of Trifluoroacetamides Promoted by Boryl Radicals

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Abstract Deuterated mono- and difluoroalkyl groups have attracted increasing attention in medicinal and biological studies. Controllable snipping one or two fluorine atoms from widely accessible trifluoromethyl groups followed by deuteration is an attractive method to access these molecules, whereas this has been hindered by the challenges associated with the chemoselectivity control during the defluoriantion process. Herein, a strategy for chemoselective deuterodefluorination reaction of trifluoro- and difluoroalkylacetamides via spin-center shifts is reported. The reaction starts with the attack of a deuterated 4-dimethylaminopyridine-boryl radical (DMAP-BD_2•) to the amide oxygen atom, followed by a spin-center shift process to trigger the C—F bond scission. The resulting *α*,*α*-difluorocarbonyl radicals undergo deuterium atom transfer to afford the CF_2D-products in high yields and high levels of D-incorporation. Notably, increasing the amount of DMAP-BD_3 enables the selective cleavage of the two C—F bonds, leading to CFD_2-products in good yields meanwhile maintaining good levels of D-incorporation.

Keywords Lewis base-boryl radical; C—F bond cleavage; deuterodefluorination; spin-center shift

1 Introduction

Organofluorine compounds are widely applied in pharmaceutics, pesticide science, and material science.[1-3] For example, the mono- and difluoroalkyl groups show distinctive value in medical and biological fields for their unique biochemistry properties.[4-6] Meanwhile, deuterium has been used for isotope labeling in drug discovery and functional materials research,[7-8] and deuteration modification is a common method for improving drug pharmacokinetics.[9] Combined with these two benefits, installing deuterated fluoroalkyl groups to biomolecules shows great potential in medicinal chemistry. Direct deuterodefluorination via C—F bond cleavage of readily prepared tri- or difluoroalkyl groups is a feasible pathway for achieving deuterated mono- and difluoroalkyl groups. However, the chemoselective deuterodefluorination of these fluoroalkyl groups has been a challenge due to the high bond dissociation energy of the C—F bonds as well as the issue of over-defluorination.[10-11]

In 2016, Lalic *et al.*[12] reported one example of Pd/Cu-cocatalyzed mono-deuterodefluorination of trifluoromethylarene, where ^{t}BuOD was used as the D source. (Scheme 1, a). Using magnesium powder as reductant and

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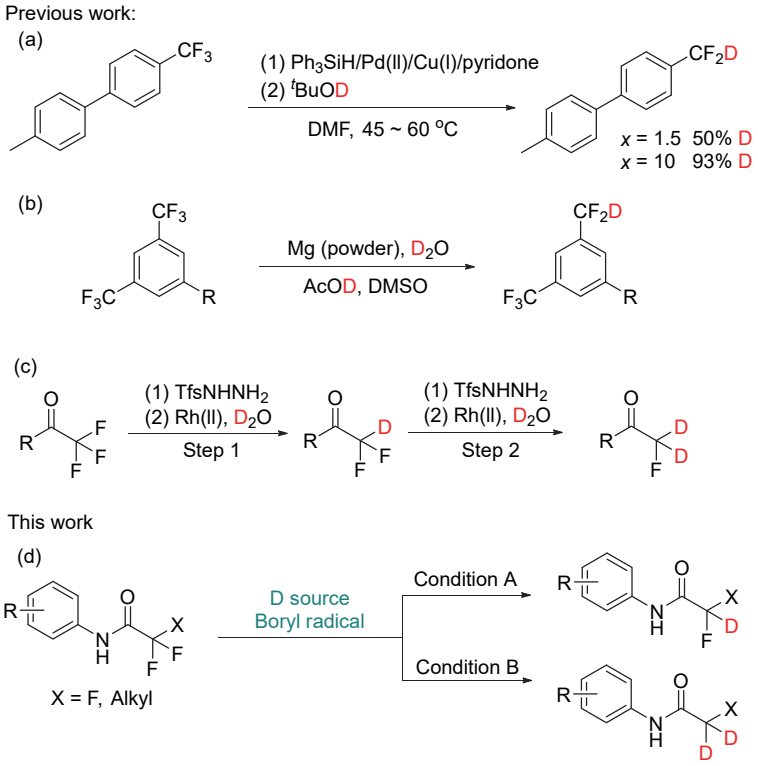
D_2O/AcOD as the D source, Prakash *et al.*[13] also described an example to access a CF_2D-substituted aryl product (Scheme 1, b). Very recently, Bi *et al.*[14] disclosed an elegant carbene strategy to realize the progressive deuterodefluorination of fluoroalkyl ketones under rhodium catalysis (Scheme 1, c). The ketones were first transformed to hydrazones, which were then converted to Rh-carbene intermediates. The nucleophilic attack of D_2O followed by fluoride elimination yielded enol intermediates, and [1,3]-D shift took place to give CF_2D products. The repeat of this sequence using these CF_2D compounds as the starting materials could form CFD_2 ketones. Despite these advances, the direct and selective displacement of one or two C—F bonds of CF_3 groups with D atoms still remains a challenging task. Recently, our group[15a] developed a boryl radical-promoted sequential C—F bond functionalizations of trifluoroacetamides and trifluoroacetates, in which one or two C—F bonds were selectively reduced. Based on this finding, we envisioned that using deuterated 4-dimethylaminopyridine (DMAP)-BD_3 as the D source would selectively give CF_2D- and CFD_2-handled amides and esters (Scheme 1, d).

2 Results and discussion

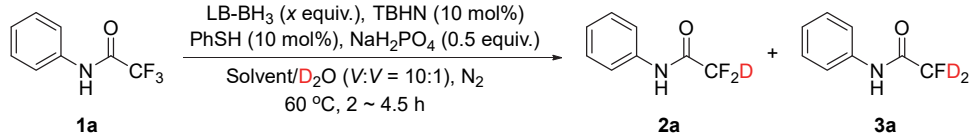
We commenced our study by investigating monodeuterodefluorination of 2,2,2-trifluoro-*N*-phenylacetamide (**1a**). It has been reported that PhSH could be transformed to PhSD in the existence of large amount of D_2O.[16] Based on our previous work,[15] reaction of **1a** with DMAP-BH_3 in MeCN/D_2O (V∶V=10∶1) at 60 ℃ was conducted. However, the product 2,2-difluoro-*N*-phenylacetamide-2-*d* (**2a**) only had 3% deuterium incorporation (Table 1, Entry 1). It was supposed that the difluoromethyl radical could undergo hydrogen atom transfer (HAT) with DMAP-BH_3, which led to the low deuterium incorporation. We then DMAP-BD_3 and subjected it to the same reaction. As expected, **2a** was obtained in 73% yield and 90% deuterium incorporation with only trace amount of dideuterodefluorination product **3a** (Table 1, Entry 2). When D_2O was absent, HAT of the difluoromethyl radical from the initially added PhSH without H/D exchange resulted in the decrease of deuterium incorporation level (Table 1, Entry 3). When thiophenol was absent, inferior yield was obtained. It is indicated that the difluoromethyl radical could abstract the deuterium atom from DMAP-BD_3, but with lower efficiency (Table 1, Entry 4). Thiol could serve as polar-reversal catalyst to accelerate the deuterium atom transfer (DAT) process.[17] Hereafter, we turned our attention to dideuterodefluorination of trifluoroacetamide. In sight of the previous results, the amount of DMAP-BD_3 was increased to 3.0 equiv., and 2-fluoro-*N*-phenylacetamide-2,2-d_2 (**3a**) was furnished in 42% yield (Table 1, Entry 5). Switching the solvent to 1,4-dioxane led to increased yield (Table 1, Entry 6). When the amount of NaH_2PO_4 was increased to 1 equiv., **3a** was furnished in 71% yield and 85% deuterium incorporation (Table 1, Entry 7).

With the optimized conditions in hand, the substrate scope of mono- and di-deuterodefluorination of trifluoroacetamides was examined (Table 2). A gram-scale synthesis for **2a** was accomplished in 69% yield and 90% deuterium



Scheme 1 Deuterodefluorination reactions

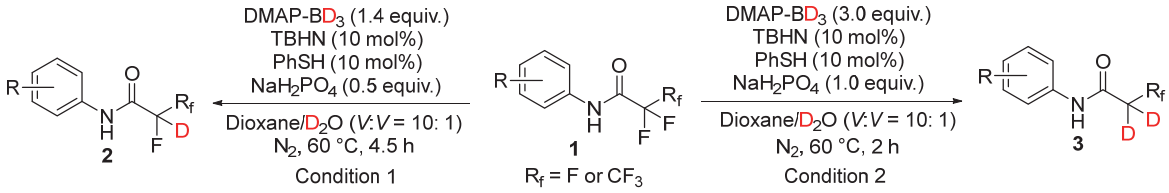
Table 1 Optimization of deuterodefluorination reaction of trifluoroacetamide **1a**[a]

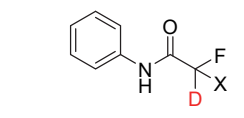


Entry	LB-BH$_3$ (x)	Solvent	Yield[b]/% of **2a** (deuterium incorporation/%)	Yield[b]/% of **3a** (deuterium incorporation/%)
1	DMAP-BH$_3$ (1.5)	MeCN	55 (3)	Not detected
2	DMAP-BD$_3$ (1.4)	MeCN	73[c] (90)	Trace
3[d]	DMAP-BD$_3$ (1.4)	MeCN	64 (80)	Trace
4[e]	DMAP-BD$_3$ (1.4)	MeCN	36 (82)	Not detected
5	DMAP-BD$_3$ (3.0)	MeCN	11 (90)	42 (88)
6	DMAP-BD$_3$ (3.0)	1,4-Dioxane	Trace	55 (88)
7[f]	DMAP-BD$_3$ (3.0)	1,4-Dioxane	Trace	71[c] (85)

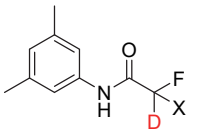
[a] Reaction conditions: **1a** (0.3 mmol), LB-BH$_3$ (x equiv.), TBHN (0.03 mmol), PhSH (0.03 mmol), NaH_2PO_4 (0.5 equiv.) in solvent (3 mL) and D_2O (0.3 mL) at 60 ℃ under nitrogen. [b] Yield based on ^{19}F NMR analysis of the crude product with $PhCF_3$ as an internal standard. [c] Isolated yield. [d] Without D_2O. [e] Without PhSH. [f] 1.0 equiv. of NaH_2PO_4 was used.

Table 2 Substrate scope of deuterodefluorination of trifluoroacetamides[a]

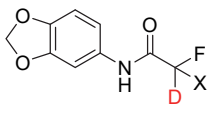




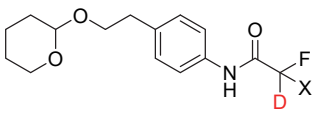
X = F, **2a**: 73% (90% D), 69% (90% D)[b]
X = D, **3a**: 71% (85% D)



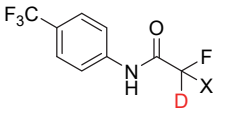
X = F, **2b**: 76% (90% D)
X = D, **3b**: 66% (87% D)



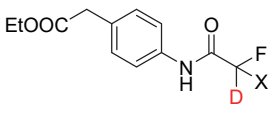
X = F, **2c**: 71% (88% D)
X = D, **3c**: 59% (86% D)



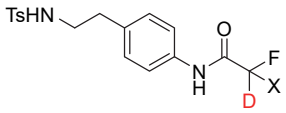
X = F, **2d**: 75% (90% D)
X = D, **3d**: 74% (87% D)



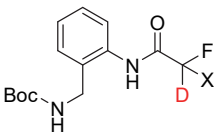
X = F, **2e**: 49% (90% D)
X = D, **3e**: 43% (85% D)



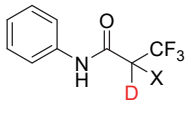
X = F, **2f**: 68% (90% D)
X = D, **3f**: 73% (87% D)



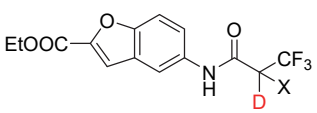
X = F, **2g**: 64% (90% D)
X = D, **3g**: 68% (87% D)



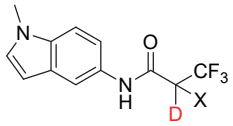
X = F, **2h**: 59% (89% D)
X = D, **3h**: 76% (83% D)



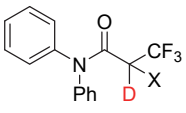
X = F, **2i**: 66% (91% D)
X = D, **3i**: 85% (92% D)



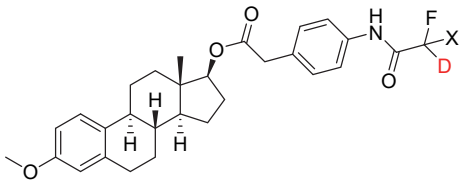
X = F, **2j**: 26% (92% D)



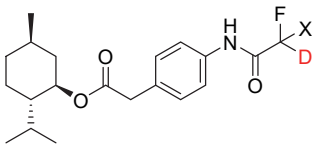
X = F, **2k**: 74% (91% D)



X = F, **2l**: 50% (94% D)



X = F, **2m**: 62% (85% D)
X = D, **3m**: 63% (83% D)



X = F, **2n**: 71% (89% D)
X = D, **3n**: 78% (86% D)

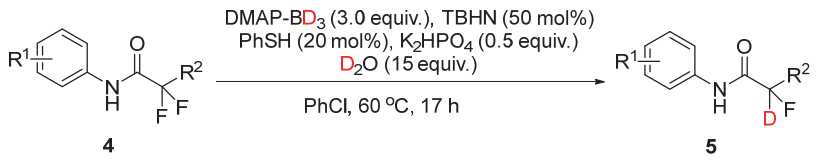
[a] Condition 1: **1** (0.3 mmol), DMAP-BD$_3$ (1.4 equiv.), TBHN (10 mol%), PhSH (10 mol%), NaH_2PO_4 (0.5 equiv.) in CH_3CN (3 mL) and D_2O (0.3 mL) at 60 ℃ for 4.5 h under nitrogen; Condition 2: **1** (0.3 mmol), DMAP-BD$_3$ (3.0 equiv.), TBHN (10 mol%), PhSH (10 mol%), NaH_2PO_4 (1.0 equiv.) in dioxane (3 mL) and D_2O (0.3 mL) at 60 ℃ for 2 h under nitrogen. Isolated yields after chromatography are given. [b] A gram-scale synthesis.

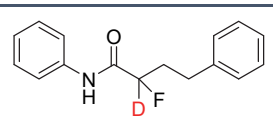
incorporation. Both reactions show broad substrate scope. Aryl ring bearing a wide range of functional groups, including electron-donating groups (**1b**～**1d**) and electron-withdrawing groups (**1e**), could be converted to mono- and di-deuterodefluorinated product with moderate to good yields and high deuterium incorporation. Notably, substrates substituted with protected amine containing a N—H (**1g**, **1h**) were tolerated without diminish in deuterium incorporation. Pentafluoro-propanamide substrates (**1i**～**1l**) were proved to be feasible for the reaction, in which cases only the C—F bond on the CF_2 was functionalized, whereas the CF_3 remained intact. Heterocycles, such as benzofuran **1k** and indole **1l** were tolerated in the monodeuterodefluorination reaction. Installation of deuterated mono- and di-fluoroacetyl groups to *β*-estradiol (**1m**) and (+)-menthol (**1n**) was successful, and both protocols gave good yields and deuterium incorporation.

Next, the monodeuterodefluorination of difluoroalkylacetamides was explored (Table 3). After further screening of reaction conditions, we found that the combination of DMAP-BD_3 (3.0 equiv.), di-*tert*-butyl hyponitrite (TBHN) (50 mol%), PhSH (20 mol%), K_2HPO_4 (0.5 equiv.), and D_2O (15 equiv.) in PhCl (0.1 mol/L) at 60 ℃ afforded monodeuterodefluorination product **5a** in 66% yield and 80% deuterium incorporation. Then the substrate scope was investigated. Several *N*-aryl-4-phenylbutanamide substrates bearing various functional groups (**4b**～**4f**) on both benzene rings were tested, and all of these cases gave moderate to good yields and fine deuterium incorporation. The 4,4-diphenyl substrate **4g** was also found to be effective, afforded the product in 63% yield and 80% deuterium incorporation. The reductions of substrates containing (cyclo)alkyl chain and ether moiety (**4h**～**4m**) were achieved, giving moderate to good yields and good deuterium incorporation level. Finally, the modification of *β*-estradiol derivative also worked well, giving product **5n** in 66% yield and 83% deuterium incorporation.

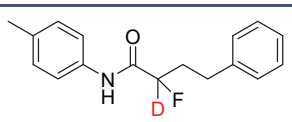
Based on our previous work,[15] a plausible reaction mechanism was depicted (Scheme 2). DMAP-BD_2• radical was generated through deuterium atom abstraction in the presence of radical initiator. Then addition of DMAP-BD_2• to the carbonyl oxygen of the amide substrate **1** or **4** gave the intermediate **Int-1**. After that, spin-center shift occurred with the elimination of a fluoride ion.[18] The resulting **Int-2** underwent deuterium atom transfer with PhSD and hydrolyzed to furnish the mono-defluorodeuterated product **2** or **5**. The generated thiyl radical in turn abstracts a deuterium atom from DMAP-BD_3 to regenerate

Table 3 Substrate scope of monodeuterodefluorination of difluoroalkylaceticamides[a]

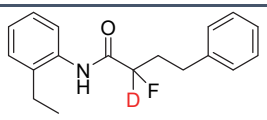




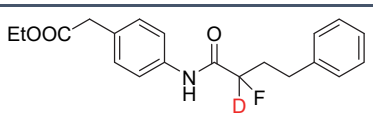
5a: 66% (80% D)



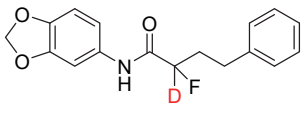
5b: 69% (81% D)



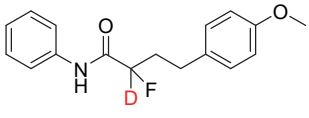
5c: 57% (81% D)



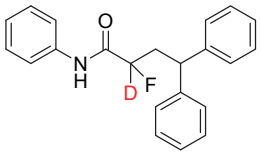
5d: 47% (73% D)



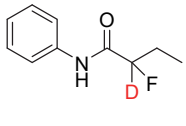
5e: 55% (81% D)



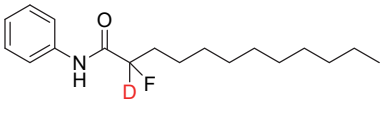
5f: 77% (81% D)



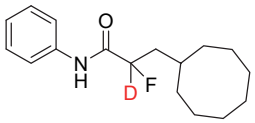
5g: 63% (80% D)



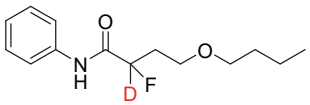
5h: 76% (81% D)



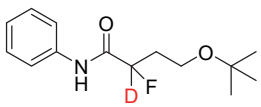
5i: 60% (82% D)



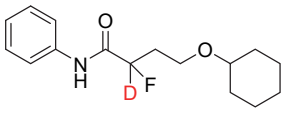
5j: 55% (80% D)



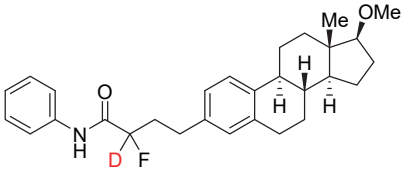
5k: 70% (83% D)



5l: 56% (82% D)

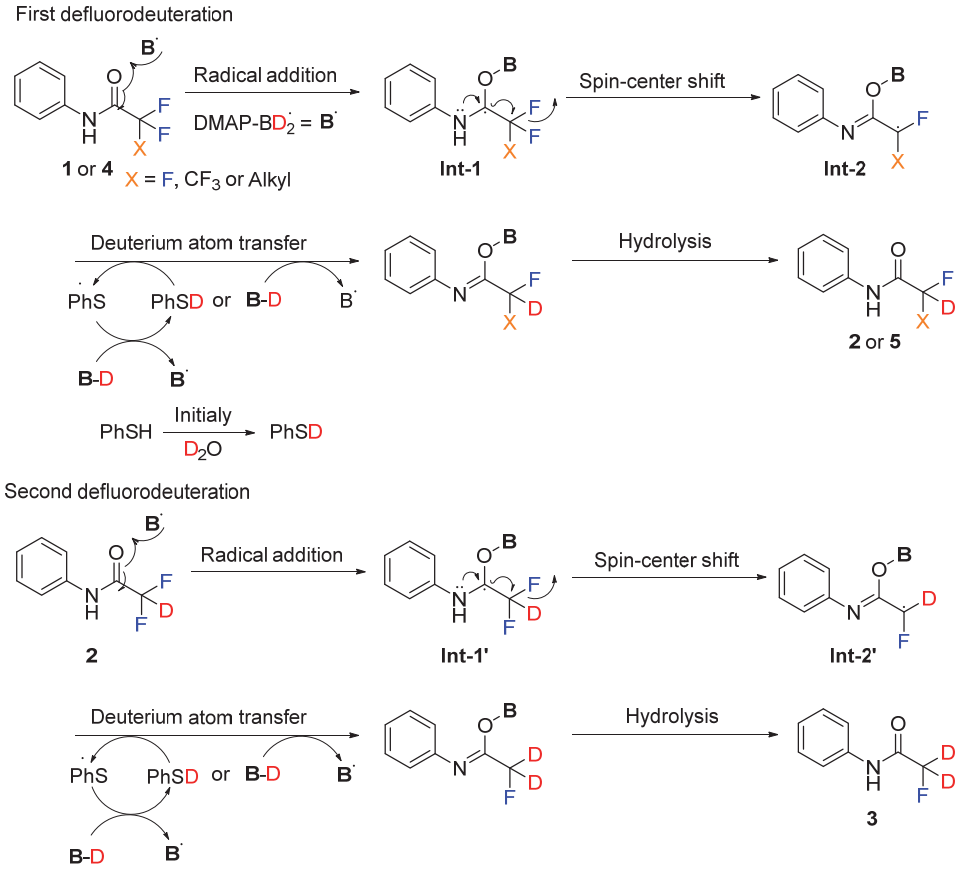


5m: 72% (80% D)



5n: 66% (83% D)

[a] Reaction condition: **4** (0.1～0.3 mmol), DMAP-BD_3 (3 equiv.), TBHN (50 mol%), PhSH (20 mol%), K_2HPO_4 (0.5 equiv.), D_2O (15 equiv.) in PhCl (1～3 mL) at 60 ℃ for 17 h under nitrogen. Isolated yields after chromatography are given.



Scheme 2 A plausible reaction mechanism

the boryl radical and PhSD, thereby propagating the radical chain process. Deuterium atom transfer from DMAP-BD_3 to **Int-2** also happened albeit with lower efficiency. When further amounts of DMAP-BD_3 was added, the second spin-center shift (SCS) occurred to provide didefluorodeuterated product **3**. Based on our previous studies, we supposed that the chemoselectivity was based on the decreasing radical addition reactivity of DMAP-BD_2• to carbonyl oxygen of deuterodefluorinated product.[15a]

3 Conclusions

In conclusion, the controllable mono- and di-deuterodefluorination reactions of trifluoroacetamides and difluoroalkylacetamides were developed. With slight modification of reaction conditions, mono- and di-defluorodeuterated products could be obtained in good yields and high levels of deuterium incorporation. The reaction features mild reaction conditions, a broad substrate scope, and good chemoselectivity. The mechanism involves the attack of a DMAP-BD_2• to the carbonyl oxygen, followed by a spin-center shift process and deuterium atom transfer.

4 Experimental section

4.1 General experimental information

Unless otherwise noted, all reactions were performed under nitrogen atmosphere using flame-dried glassware. Acetonitrile was dried over 4Å molecular sieve. Tetrahydrofuran (THF) was distilled over CaH_2. All reagents were purchased from commercial sources and were used directly without further purification or prepared as described in the literature. ^{1}H NMR (400 MHz, 500 MHz), ^{19}F NMR (376 MHz, 470 MHz), ^{13}C NMR (100 MHz, 125 MHz) spectra were recorded on a Bruker Avance 400 spectrometer and a Bruker Avance 500 spectrometer in $CDCl_3$ and MeOD. The percentage of D content was based on a decrease in the integral of the ^{1}H NMR signals of CF_2D or CFD_2 groups, as compared to the integral of the corresponding CF_2H or CFH_2 signals in the hydrodefluorination products. For CFD_2 groups, the percentage of D content was based on the integral of the ^{19}F NMR signals of CFD_2 and a half of CFDH groups in the proportion of the integral of CFD_2, CFDH and CFH_2 groups. High-resolution mass spectra (HRMS) were obtained with a Water XEVO G2 Q-Tof (Waters Corporation). Melting points were recorded on a WRS-1C melting point apparatus and uncorrected. Commercially available reagents were purchased from Energy Chemical, J & K Scientific, Adamas-beta, and Sigma-Aldrich Co., Inc.

4.2 Synthesis of DMAP-BD_3

To a solution of 4-dimethylaminopyridine (1.0 equiv.), sodium bicarbonate (3 equiv.) and sodium borodeuteride (1.5 equiv.) in anhydrous tetrahydrofuran (THF) (5.7 mL

for 5 mmol DMAP) under nitrogen, wet THF (totally 1.9 mL for 5 mmol DMAP, with 14.4% D_2O) was added dropwise. After addition, the mixture was stirred at room temperature for 4 h. The reaction mixture was then filtered with celite and sodium sulfate, washed with THF and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate/dichloromethane, V∶V∶V=6∶3∶1) to obtain the DMAP-BD_3 in 99% yield and 97% deuterium incorporation.

4-Dimethylaminopyridine trideuterioborane (DMAP-BD_3): White solid, m.p. 172～178 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (d, J=7.2 Hz, 2H), 6.49 (d, J=7.2 Hz, 2H), 3.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.55 (s), 146.74 (s), 106.31 (s), 39.43 (s); ^{11}B NMR (128 MHz, $CDCl_3$) δ: −14.31 (s); ESI-HRMS calcd for $C_7H_{10}D_3BN_2Na$ $(M+Na)^+$ 162.1252, found 162.1252.

4.3 Monodeuterodefluorination reaction of trifluoroacetamides

4.3.1 Typical procedure

To a N_2 flushed, oven-dried 10 mL sealed tube with a magnetic stir bar, 2,2,2-trifluoro-*N*-phenylacetamide (**1a**) (56.5 mg, 0.299 mmol), DMAP-BD_3 (58.1 mg, 0.419 mmol, 1.4 equiv.), TBHN (5.2 mg, 0.030 mmol, 0.1 equiv.), PhSH (3.1 μL, 0.030 mmol, 0.1 equiv.), NaH_2PO_4 (17.9 mg, 0.15 mmol, 0.5 equiv.), 3 mL of MeCN and 0.3 mL of D_2O were added, then the tube was sealed and the reaction mixture was stirred for 4.5 h under 60 ℃. The reaction was quenched with water, then the reaction mixture was extracted with ethyl acetate. The organic phase was combined and washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, V∶V=15∶1) to give a white solid **2a** (37.6 mg) in 73% yield and 90% deuterium incorporation. Compounds **2b**～**2n** were prepared using the same procedure.

4.3.2 Gram-scale synthesis

To a 250 mL flame-dried two-neck round-bottom flask under nitrogen, 2,2,2-trifluoro-*N*-phenylacetamide (**1a**) (1.91 g, 10.08 mmol), DMAP-BD_3 (1.96 g, 14.11 mmol, 1.4 equiv.), TBHN (0.18 g, 1.01 mmol, 0.1 equiv.), PhSH (104 μL, 1.01 mmol, 0.1 equiv.), NaH_2PO_4 (0.60 g, 5.04 mmol, 0.5 equiv.), 100 mL of MeCN and 10 mL of D_2O were added, then the reaction mixture was stirred for 4.5 h under 60 ℃ under nitrogen atmosphere. After cooling to room temperature, the reaction was quenched with water and extracted with ethyl acetate. The organic phase was combined and washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, V∶V=15∶1) to give a white solid **2a** (1.19 g) in 69% yield and 90% deuterium incorporation.

2,2-Difluoro-*N*-phenylacetamide-2-*d* (**2a**): White solid, m.p. 62～67 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.91 (br s, 1H), 7.58 (d, J=7.6 Hz, 2H), 7.39 (dd, J=8.0, 8.0 Hz, 2H), 7.22 (t, J=7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.25 (t, J=24.5 Hz), 135.62 (s), 129.28 (s), 125.84 (s), 120.28 (s), 180.22 (tt, J=249.88, 28.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −126.19 (t, J=8.5 Hz); ESI-HRMS calcd for $C_8H_7DF_2NO$ $(M+H)^+$ 173.0631, found 173.0627.

N-(3,5-Dimethylphenyl)-2,2-difluoroacetamide-2-*d* (**2b**): 76% yield, 90% deuterium incorporation. White solid, m.p. 118～123 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (br s, 1H), 7.19 (s, 2H), 6.84 (s, 1H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.27 (t, J=24.0 Hz), 138.99 (s), 135.44 (s), 127.49 (s), 118.07 (s), 108.20 (tt, J=251.3, 29.4 Hz), 21.22 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −126.18 (t, J=7.52 Hz); ESI-HRMS calcd for $C_{10}H_{11}DF_2NO$ $(M+H)^+$ 201.0944, found 201.0948.

N-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoroacetamide-2-*d* (**2c**): 71% yield, 88% deuterium incorporation. White solid, m.p. 105～109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (br s, 1H), 7.23 (d, J=2.0 Hz, 1H), 6.89 (dd, J=8.4, 2.0 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 5.98 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.22 (t, J=24.3 Hz), 147.97 (s), 145.40 (s), 129.65 (s), 113.84 (s), 108.19 (tt, J=250.9, 29.1 Hz), 108.18 (s), 102.90 (s), 101.53 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −126.28 (t, J=8.3 Hz); ESI-HRMS calcd for $C_9H_7DF_2NO_3$ $(M+H)^+$ 217.0530, found 217.0533.

2,2-Difluoro-*N*-(4-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)-ethyl)phenyl)acetamide-2-*d* (**2d**): 75% yield, 90% deuterium incorporation. White solid, m.p. 64～69 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (br s, 1H), 7.49 (d, J=8.4 Hz, 2H), 7.23 (d, J=8.4 Hz, 2H), 4.62～4.55 (m, 1H), 3.93 (dt, J=9.6, 7.2 Hz, 1H), 3.75 (ddd, J=11.2, 8.4, 3.2 Hz, 1H), 3.62～3.56 (m, 1H), 3.48～3.42 (m, 1H), 2.89 (t, J=7.2 Hz, 2H), 1.84～1.76 (m, 1H), 1.72～1.65 (m, 1H), 1.59～1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.30 (t, J=24.3 Hz), 136.80 (s), 133.82 (s), 129.59 (s), 120.31 (s), 108.14 (tt, J=252, 32.3 Hz) 98.69 (s), 67.97 (s), 62.13 (s), 35.66 (s), 30.52 (s), 25.30 (s), 19.37 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −126.21 (t, J=7.9 Hz); ESI-HRMS calcd for $C_{15}H_{18}DF_2NO_3Na$ $(M+Na)^+$ 323.1288, found 323.1287.

2,2-Difluoro-*N*-(4-(trifluoromethyl)phenyl)acetamide-2-*d* (**2e**): 49% yield, 90% deuterium incorporation. White solid, m.p. 135～138 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (br s, 1H), 7.73 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.52 (t, J=25.1 Hz), 138.65 (s), 127.71 (d, J=33.4 Hz), 126.56 (q, J=3.7 Hz), 123.75 (d, J=270.2 Hz), 120.04 (s), 108.02 (t, J=29.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −62.39 (s), −126.34 (t, J=8.5 Hz); ESI-HRMS calcd for $C_9H_5DF_5NO$ $(M+H)^+$ 241.0505, found 241.0497.

Ethyl 2-(4-(2,2-difluoroacetamido-2-*d*)phenyl)acetate (**2f**): 68% yield, 90% deuterium incorporation. White solid, m.p. 97～100 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (br s, 1H), 7.49 (d, J=8.4 Hz, 2H), 7.24 (d, J=8.4 Hz, 2H), 4.16 (q, J=7.2 Hz, 2H), 3.60 (s, 2H), 1.26 (t, J=7.2 Hz,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.68 (s), 160.38 (t, J=24.8 Hz), 134.78 (s), 131.37 (s), 129.93 (s), 120.49 (s), 108.13 (tt, J=205.4, 29.2 Hz), 61.01 (s), 40.65 (s), 14.05 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −126.34 (t, J=7.9 Hz); ESI-HRMS calcd for $C_{12}H_{12}DF_2NO_3Na$ $(M+Na)^+$ 281.0818, found 281.0823.

2,2-Difluoro-*N*-(4-(2-((4-methylphenyl)sulfonamido)-ethyl)phenyl)acetamide-2-*d* (**2g**): 64% yield, 90% deuterium incorporation. White solid, m.p. 153～155 ℃; ^{1}H NMR (400 MHz, MeOD) δ: 7.66 (d, J=8.4 Hz, 2H), 7.50 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.4, 2H), 7.21 (d, J=8.4 Hz, 2H), 3.05 (t, J=7.2 Hz, 2H), 2.70 (t, J=7.2 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ: 162.92 (s), 144.62 (s), 138.98 (s), 137.28 (s), 136.65 (s), 130.56 (d, J=36.7 Hz), 128.06 (s), 128.06 (s), 121.98 (s), 110.07 (tt, J=248.5, 57.9 Hz), 45.55 (s), 36.50 (s), 21.48 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −126.15 (t, J=29.7 Hz); ESI-HRMS calcd for $C_{17}H_{18}DF_2N_2O_3S$ $(M+H)^+$ 370.1142, found 370.1139.

tert-Butyl (2-(2,2-difluoroacetamido-2-*d*)benzyl)carbamate (**2h**): 59% yield and 89% deuterium incorporation. White solid, m.p. 115～121 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.50 (br s, 1H), 8.01 (d, J=8.4 Hz, 1H), 7.33 (td, J=8.4, 1.6 Hz, 1H), 7.22 (dd, J=8.4, 1.6 Hz, 1H), 7.16 (td, J=8.4, 1.6 Hz, 1H), 5.33 (br s, 1H), 4.22 (d, J=6.8 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.31 (t, J=25.6 Hz), 157.32 (s), 134.51 (s), 130.58 (s), 130.16 (s), 128.72 (s), 125.86 (s), 123.61 (s), 108.17 (tt, J=249.5, 32.8 Hz), 80.76 (s), 41.18 (s), 28.15 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −126.00 (t, J=8.3 Hz); ESI-HRMS calcd for $C_{14}H_{17}DF_2N_2O_3Na$ $(M+Na)^+$ 324.1240, found 324.1248.

2,3,3,3-Tetrafluoro-*N*-phenylpropanamide-2-*d* (**2i**): 77% yield and 91% deuterium incorporation. White solid, m.p. 84～90 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (br s, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.39 (dd, J=8.0, 7.5 Hz, 2H), 7.22 (t, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.85 (d, J=17.5 Hz), 135.64 (s), 129.25 (s), 125.88 (s), 122.03～121.78 (m), 120.31 (s), 119.23～118.97 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −75.80 (d, J=11.0 Hz, 3F), −200.56～−200.69 (m, 1F); ESI-HRMS calcd for $C_9H_7DF_4NO$ $(M+H)^+$ 223.0605, found 223.0608.

Ethyl 5-(2,3,3,3-tetrafluoropropanamido-2-*d*)benzofuran-2-carboxylate (**2j**): 26% yield, 92% deuterium incorporation. White solid, m.p. 141～146 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (br s, 1H), 8.12 (d, J=2.0 Hz, 1H), 7.58 (d, J=9.2 Hz, 1H), 7.50 (d, J=1.2 Hz, 1H), 7.45 (dd, J=9.2, 1.2 Hz, 1H), 4.45 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.30 (s), 153.16 (s), 146.95 (s), 131.73 (s), 127.48 (s), 120.97 (s), 114.65 (s), 113.66 (s), 112.87 (s), 61.73 (s), 14.26 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −75.77 (d, J=10.9 Hz, 3F), −200.76～−200.92 (m, 1F); ESI-HRMS calcd for $C_{14}H_{10}DF_4NO_4$ $(M+H)^+$ 335.0760, found 335.0766.

2,3,3,3-Tetrafluoro-*N*-(1-methyl-indol-5-yl)propanamide-2-*d* (**2k**): 74% yield, 91% deuterium incorporation. White solid, m.p. 146～152 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (br s, 1H), 7.88 (s, 1H), 7.29 (d, J=1.2 Hz, 2H), 7.08 (d, J=3.2 Hz, 1H), 6.47 (d, J=3.2 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.68 (d, J=17.8 Hz), 134.78 (s), 130.15 (s), 128.46 (s), 127.81 (s), 115.67 (s), 113.28 (s), 109.55 (s), 101.23 (s), 32.95 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −75.80 (d, J=10.9 Hz, 3F), −200.53～−200.66 (m, 1F); ESI-HRMS calcd for $C_{12}H_{10}DF_4N_2O$ $(M+H)^+$ 276.0865, found 276.0869.

2,3,3,3-Tetrafluoro-*N*,*N*-diphenylpropanamide-2-*d* (**2l**): 50% yield, 94% deuterium incorporation. colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47～7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.94 (d, J=21.3 Hz), 141.35 (s), 140.49 (s), 130.39 (s), 129.23 (s), 128.38 (s), 127.21 (s), 125.85 (s), 119.37 (td, J=281.1, 26.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −75.19 (d, J=13.9 Hz, 3F), −201.02～−201.13 (m, 1F); ESI-HRMS calcd for $C_{15}H_{11}DF_4NO$ $(M+H)^+$ 299.0912, found 299.0915.

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl 2-(4-(2,2-difluoroacetamido-2-*d*)phenyl)acetate (**2m**): 62% yield, 85% deuterium incorporation, *dr*=1∶1. White solid, m.p. 173～177 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (br s, 1H), 7.53 (d, J=8.8 Hz, 2H), 7.27 (d, J=8.4 Hz, 2H), 7.18 (d, J=8.8 Hz, 1H), 6.70 (dd, J=8.8, 2.8 Hz, 1H), 6.62 (d, J=2.8 Hz, 1H), 4.69 (dd, J=8.8, 8.4 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 2H), 2.86～2.82 (m, 2H), 2.27～2.15 (m, 3H), 1.88～1.69 (m, 3H), 1.53～1.21 (m, 8H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.51 (s), 160.28 (t, J=24.9 Hz), 157.36 (s), 137.79 (s), 134.70 (s), 132.35 (s), 131.69 (s), 129.98 (s), 126.25 (s), 120.35 (s), 113.71 (s), 111.40 (s), 108.15 (tt, J=293.2, 31.3 Hz), 83.26 (s), 55.10 (s), 49.62 (s), 43.65 (s), 42.93 (s), 40.98 (s), 38.44 (s), 36.79 (s), 29.67 (s), 27.44 (s), 27.12 (s), 26.09 (s), 23.16 (s), 11.98 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −126.12 (t, J=8.3 Hz); ESI-HRMS calcd for $C_{29}H_{32}DF_2NO_4Na$ $(M+Na)^+$ 521.2333, found 521.2335.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(4-(2,2-difluoroacetamido-2-*d*)phenyl) acetate (**2n**): 71% yield and 89% deuterium incorporation, *dr*=1∶1. White solid, m.p. 99～103 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (br s, 1H), 7.50 (d, J=8.4 Hz, 2H), 7.24 (d, J=8.4 Hz, 2H), 4.68 (td, J=10.8, 4.4 Hz, 1H), 3.58 (s, 2H), 2.01～1.89 (m, 2H), 1.80～1.73 (m, 1H), 1.68～1.64 (m, 2H), 1.50～1.41 (m, 1H), 1.40～1.33 (m, 1H), 1.08～0.91 (m, 3H), 0.87 (dd, J=12.0, 6.8 Hz, 6H), 0.70 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.19 (s), 160.34 (t, J=24.6 Hz), 134.74 (s), 131.62 (s), 129.86 (s), 120.40 (s), 108.15 (tt, J=252.5, 31.0 Hz), 74.92 (s), 46.89 (s), 41.06 (s), 40.66 (s), 34.10 (s), 31.28 (s), 26.12 (s), 23.31 (s), 21.91 (s), 20.61 (s), 16.16 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −126.17 (t, J=8.3 Hz); ESI-HRMS calcd for $C_{20}H_{26}DF_2NO_3Na$ $(M+Na)^+$ 391.1914, found 391.1911.

4.4 Monodeuterodefluorination reaction of trifluoroacetamides

To a N_2 flushed, oven-dried 10 mL sealed tube with a magnetic stir bar, 2,2,2-trifluoro-*N*-phenylacetamide (**1a**)

(58.1 mg, 0.307 mmol), DMAP-BD_3 (128.31 mg, 0.923 mmol, 3 equiv.), TBHN (5.0 mg, 0.029 mmol, 0.1 equiv.), PhSH (3.2 μL, 0.031 mmol, 0.1 equiv.), NaH_2PO_4 (37.0 mg, 0.308 mmol, 1 equiv.), 3 mL of 1,4-dioxane, 0.3 mL of D_2O were added, then the tube was sealed and the reaction mixture was stirred for 2 h under 60 ℃. The reaction was quenched with water, then the reaction mixture was extracted with ethyl acetate. The organic phase was combined and washed with brine, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, V∶V=6∶1) to give a white solid **3a** (33.9 mg) in 71% yield and 85% deuterium incorporation. Compounds **3b**～**3n** were prepared using the same procedure.

2-Fluoro-*N*-phenylacetamide-2,2-d_2 (**3a**): White solid, m.p. 87～92 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (br s, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.35 (dd, J=8.0, 7.6 Hz, 2H), 7.16 (t, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.45 (d, J=16.5 Hz), 136.35 (s), 129.14 (s), 125.12 (s), 120.05 (s), 79.70 (dt, J=215.6, 24.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −223.16 (d, J=6 Hz); ESI-HRMS calcd for $C_8H_6D_2FNONa$ $(M+Na)^+$ 178.0608, found 178.0619.

N-(3,5-Dimethylphenyl)-2-fluoroacetamide-2,2-d_2 (**3b**): 66% yield, 87% deuterium incorporation. White solid, m.p. 119～122 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (br s, 1H), 7.20 (s, 2H), 6.80 (s, 1H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.33 (d, J=16.2 Hz), 138.82 (s), 136.17 (s), 126.78 (s), 117.78 (s), 79.82 (dt, J=185.5, 23.7 Hz), 21.26 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −222.99～−223.06 (m); ESI-HRMS calcd for $C_{10}H_{11}D_2FNO$ $(M+H)^+$ 184.1101, found 184.1103.

N-(Benzo[*d*][1,3]dioxol-5-yl)-2-fluoroacetamide-2,2-d_2 (**3c**): 59% yield and 86% deuterium incorporation. White solid, m.p. 131～137 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (br s, 1H), 7.26 (s, 1H), 6.86 (d, J=8.4 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.29 (d, J=16.3 Hz), 147.87 (s), 144.85 (s), 130.49 (s), 113.43 (s), 108.10 (s), 102.85 (s), 101.36 (s), 79.80 (dtd, J=192.5, 30.8, 7.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −223.47～−223.56 (m); ESI-HRMS calcd for $C_9H_7D_2FNO_3$ $(M+H)^+$ 200.0687, found 200.0689.

2-Fluoro-*N*-(4-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-phenyl)acetamide-2,2-d_2 (**3d**): 74% yield, 87% deuterium incorporation. White solid, m.p. 83～88 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (br s, 1H), 7.48 (d, J=8.8 Hz, 2H), 7.23 (d, J=8.8 Hz, 2H), 4.60～4.58 (m, 1H), 3.96～3.90 (m, 1H), 3.75 (ddd, J=11.2, 8.4, 3.2 Hz, 1H), 3.59 (dt, J=9.6, 7.2 Hz, 1H), 3.48～3.43 (m, 1H), 2.89 (t, J=6.8 Hz, 2H), 1.84～1.76 (m, 1H), 1.73～1.66 (m, 1H), 1.61～1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.33 (d, J=16.1Hz), 136.09 (s), 134.48 (s), 129.57 (s), 120.02 (s), 98.65 (s), 79.81 (dt, J=185.9, 25.3 Hz), 68.05 (s), 62.11 (s), 35.70 (s), 30.57 (s), 25.36 (s), 19.41 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −223.17～−223.22 (m); ESI-HRMS calcd for $C_{15}H_{18}D_2FNO_3Na$ $(M+Na)^+$ 306.1445, found 306.1446.

2-Fluoro-*N*-(4-(trifluoromethyl)phenyl)acetamide-2,2-d_2 (**3e**): 43% yield, 85% deuterium incorporation. White solid, m.p. 139～143 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (br s, 1H), 7.72 (d, J=8.4 Hz, 2H), 7.62 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.77 (d, J=16.4 Hz), 139.41 (s), 126.73 (q, J=32.8 Hz), 126.41 (q, J=3.6 Hz), 123.89 (q, J=269.9 Hz), 119.68 (s), 79.77 (dt, J=186.1, 23.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.25 (s, 3F), −223.40～−223.48 (m, 1F); ESI-HRMS calcd for $C_9H_5D_2F_4NO$ $(M+H)^+$ 224.0662, found 224.0654.

Ethyl 2-(4-(2-fluoroacetamido-2,2-d_2)phenyl)acetate (**3f**): 73% yield, 87% deuterium incorporation. White solid, m.p. 101～106 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (br s, 1H), 7.53 (d, J=8.4 Hz, 2H), 7.27 (d, J=8.4 Hz, 2H), 4.15 (q, J=7.2 Hz, 2H), 3.59 (s, 2H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.44 (s), 165.45 (d, J=16.3 Hz), 135.35 (s), 130.82 (s), 129.88 (s), 120.18 (s), 79.77 (dt, J=185.9, 23.5 Hz), 60.86 (s), 40.71 (s), 14.07 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −223.27～−223.33 (m); ESI-HRMS calcd for $C_{12}H_{12}D_2FNO_3Na$ $(M+Na)^+$ 264.0975, found 264.0979.

2-Fluoro-*N*-(4-(2-((4-methylphenyl)sulfonamido)ethyl)-phenyl)acetamide-2,2-d_2 (**3g**): 68% yield, 87% deuterium incorporation. White solid, m.p. 146～152 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (br s, 1H), 7.70 (d, J=8.0 Hz, 2H), 7.47 (d, J=8.4 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 7.07 (d, J=8.4 Hz, 2H), 4.49 (t, J=6.0 Hz, 1H), 3.19 (dd, J=13.2, 6.8 Hz, 2H), 2.75 (t, J=6.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.48 (d J=16.4 Hz), 143.48 (s), 136.77 (s), 135.05 (s), 134.55 (s), 129.44 (s), 127.04 (s), 120.46 (s), 44.12 (s), 35.23 (s), 21.51 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −223.24～−223.26 (m); ESI-HRMS calcd for $C_{17}H_{18}D_2FN_2O_3S$ $(M+H)^+$ 353.1299, found 353.1292.

tert-Butyl (2-(2-fluoroacetamido-2,2-d_2)benzyl)carbamate (**3h**): 76% yield, 83% deuterium incorporation. White solid, m.p. 142～146 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.62 (br s, 1H), 7.89 (d, J=7.6 Hz, 1H), 7.31 (dd, J=7.6, 7.6 Hz, 1H), 7.23 (dd, J=7.6, 1.2 Hz, 1H), 7.14 (dd, J=7.6, 7.6 Hz, 1H), 5.26 (br s, 1H), 4.22 (d, J=6.4 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.57 (d, J=17.7 Hz), 156.61 (s), 134.74 (s), 130.23 (s), 128.58 (s), 125.61 (s), 124.10 (s), 80.30 (s),79.81 (dt, J=185.2, 23.5 Hz), 41.31 (s), 28.21 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −225.14 (s); ESI-HRMS calcd for $C_{14}H_{17}D_2FN_2O_3Na$ $(M+Na)^+$ 307.1397, found 307.1398.

3,3,3-Trifluoro-*N*-phenylpropanamide-2-d_2 (**3i**): 85% yield, 92% deuterium incorporation. White solid, m.p. 122～127 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (br s, 1H), 7.48 (d, J=7.6 Hz, 2H), 7.33 (dd, J=7.6, 7.6 Hz, 2H), 7.16 (t, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.03 (s), 136.76 (s), 129.09 (s), 125.34 (s), 123.94 (d, J=281 Hz), 120.49 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.03 (s); ESI-HRMS calcd for $C_9H_7D_2F_3NO$ $(M+H)^+$ 206.0756, found 206.0757.

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Methoxy-13-methyl-7,8,9,11,12,

13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl 2-(4-(2-fluoroacetamido-2,2-d_2)phenyl)acetate (**3m**): 63% yield, 83% deuterium incorporation, *dr*=1∶1. White solid, m.p. 129～134 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (br s, 1H), 7.54 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=8.4 Hz, 2H), 7.18 (d, *J*=8.4 Hz, 1H), 6.70 (d, *J*=8.0 Hz, 1H), 6.62 (s, 1H), 4.69 (t, *J*=8.4 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 2H), 2.84～2.83 (m, 2H), 2.27～2.18 (m, 2H), 1.88～1.69 (m, 3H), 1.53～1.18 (m, 5H), 0.87～0.86 (m, 2H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.44 (s), 165.38 (d, *J*=16.3 Hz), 157.38 (s), 137.82 (s), 135.31 (s), 132.39 (s), 131.11 (s), 129.96 (s), 126.29 (s), 120.05 (s), 113.71 (s), 111.42 (s), 83.16 (s), 55.14 (s), 49.66 (s), 43.69 (s), 42.96 (s), 41.06 (s), 38.47 (s), 36.82 (s), 29.71 (s), 27.47 (s), 27.16 (s), 26.12 (s), 23.20 (s), 12.00 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: －223.15 (s); ESI-HRMS calcd for $(M+Na)^+$ $C_{29}H_{32}D_2FNO_4Na$ 504.2490, found 504.2486.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(4-(2-fluoroacetamido-2,2-d_2)phenyl) acetate (**3n**): 78% yield, 86% deuterium incorporation, *dr*=1∶1. White solid, m.p. 79～84 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (br s, 1H), 7.53 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=8.4 Hz, 2H), 4.67 (td, *J*=11.2, 4.4 Hz, 1H), 3.58 (s, 2H), 1.95 (dd, *J*=6.8, 4.8 Hz, 1H), 1.79～1.72 (m, 1H), 1.68～1.62 (m, 2H), 1.50～1.42 (m, 1H), 1.39～1.32 (m, 1H), 1.08～0.93 (m, 2H), 0.86 (dd, *J*=14.4, 6.4 Hz, 6H), 0.69 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.97 (s), 165.34 (d, *J*=16.3 Hz), 135.31 (s), 131.18 (s), 129.90 (s), 120.07 (s), 79.73 (dq, *J*=186.1, 23.4 Hz), 74.74 (s), 46.92 (s), 41.15 (s), 40.69 (s), 34.31 (s), 31.31 (s), 26.10 (s), 23.31 (s), 21.97 (s), 20.68 (s), 16.19 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: －223.14 ～ －223.18 (m); ESI-HRMS calcd for $C_{20}H_{26}D_2FNO_3Na$ $(M+Na)^+$ 374.2071, found 374.2074.

4.5 Monodeuterodefluorination reaction of difluoroalkylacetamides

To a N_2 flushed, oven-dried 10 mL sealed tube with a magnetic stir bar, 2,2-difluoro-*N*,4-diphenylbutanamide (**4a**) (55 mg, 0.200 mmol), DMAP-BD_3 (83.3 mg, 0.599 mmol, 3 equiv.), TBHN (17.5 mg, 0.100 mmol, 0.5 equiv.), PhSH (4.1 μL, 0.040 mmol, 0.2 equiv.), K_2HPO_4 (17.4 mg, 0.100 mmol, 0.5 equiv.), D_2O (55 μL, 3.025 mmmol, 15 equiv.) and 2 mL of PhCl were added, then the tube was sealed and the reaction mixture was stirred for 17 h under 60 ℃. The reaction was quenched with water, then the reaction mixture was extracted with ethyl acetate. The organic phase was combined and washed with brine, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, *V*∶*V*=30∶1) to give a white solid **5a** (34.1 mg) in 66% yield and 80% deuterium incorporation. Compounds **5b**～**5n** were prepared using the same procedure.

2-Fluoro-*N*,4-diphenylbutanamide-2-*d* (**5a**): White solid, m.p. 137～143 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (br s, 1H), 7.56 (d, *J*=7.6 Hz, 2H), 7.35 (t, *J*=8.0 Hz, 2H), 7.30 (dd, *J*=10.0, 4.8 Hz, 2H), 7.22 (dd, *J*=7.6, 2.4 Hz, 3H), 7.16 (t, *J*=7.6 Hz, 1H), 2.94～2.75 (m, 2H), 2.51～2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.81 (d, *J*=17.9 Hz), 133.14 (s), 129.58 (s), 122.10 (s), 121.53 (s), 121.49 (s), 119.28 (s), 117.96 (s), 112.97 (s), 84.21 (d, *J*=186.6 Hz), 26.87 (d, *J*=19.8 Hz), 23.53 (t, *J*=3.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: －189.30～－189.49 (m); ESI-HRMS calcd for $C_{16}H_{16}DFNO$ $(M+H)^+$ 259.1351, found 259.1351.

2-Fluoro-4-phenyl-*N*-(*p*-tolyl)butanamide-2-*d* (**5b**): 69% yield, 81% deuterium incorporation. White solid, m.p. 70～76 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (br s, 1H), 7.43 (d, *J*=8.5 Hz, 2H), 7.29 (t, *J*=7.5 Hz, 2H), 7.25～7.19 (m, 3H), 7.14 (d, *J*=8.0 Hz, 2H), 2.89～2.78 (m, 2H), 2.44～2.18 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.65 (d, *J*=17.7 Hz), 140.20 (s), 134.64 (s), 134.03 (s), 129.57 (s), 128.49 (s), 126.25 (s), 120.03 (s), 91.24 (d, *J*=186.7 Hz), 33.88 (d, *J*=19.9 Hz), 30.53 (d, *J*=2.9 Hz), 20.87 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ: －189.38 (t, *J*=7.1 Hz); ESI-HRMS calcd for $C_{17}H_{18}DFNO$ $(M+H)^+$ 273.1508, found 273.1508.

N-(2-Ethylphenyl)-2-fluoro-4-phenylbutanamide-2-*d* (**5c**): 57% yield, 81% deuterium incorporation. White solid, m.p. 44～47 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.88 (d, *J*=8.0 Hz, 1H), 7.30 (t, *J*=7.5 Hz, 2H), 7.24～7.22 (m, 5H), 7.16 (t, *J*=7.5 Hz, 1H), 2.91～2.80 (m, 2H), 2.63 (q, *J*=7.5 Hz, 2H), 2.47～2.35 (m, 1H), 2.32～2.21 (m, 1H), 1.25 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.93 (d, *J*=17.7 Hz), 140.17 (s), 134.74 (s), 133.77 (s), 128.71 (s), 128.55 (s), 128.51 (s), 126.80 (s), 126.29 (s), 125.86 (s), 123.03 (s), 91.52 (d, *J*=186.0 Hz), 34.01 (d, *J*=19.8 Hz), 30.53 (d, *J*=3.0 Hz), 24.24 (s), 13.86 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ: －189.49 (t, *J*=7.1 Hz); ESI-HRMS calcd for $C_{18}H_{20}DFNO$ $(M+H)^+$ 287.1664, found 287.1657.

Ethyl 2-(4-(2-fluoro-4-phenylbutanamido-2-*d*)phenyl)-acetate (**5d**): 47% yield, 73% deuterium incorporation. White solid, m.p. 55～58 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J*=6.0 Hz, 1H), 7.52 (d, *J*=8.4 Hz, 2H), 7.32～7.21 (m, 7H), 4.14 (q, *J*=7.2 Hz, 2H), 3.58～3.57 (m, 2H), 2.88～2.77 (m, 2H), 2.46～2.17 (m, 2H), 1.24 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.44 (s), 167.77 (d, *J*=18.0 Hz), 140.12 (s), 135.56 (s), 130.73 (d, *J*=3.5 Hz), 129.91 (d, *J*=1.6 Hz), 128.50 (d, *J*=4.2 Hz), 126.27 (s), 120.09 (s), 91.18 (d, *J*=186.6 Hz), 60.88 (s), 40.79 (s), 33.85 (d, *J*=19.8 Hz), 30.51 (t, *J*=3.0 Hz), 14.13 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: －189.40～－189.56 (m); ESI-HRMS calcd for $C_{21}H_{23}DFNO_3Na$ $(M+Na)^+$ 381.1695, found 381.1700.

N-(Benzo[*d*][1,3]dioxol-5-yl)-2-fluoro-4-phenylbutanamide-2-*d* (**5e**): 55% yield, 81% deuterium incorporation. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J*=5.2 Hz, 1H), 7.30 (t, *J*=7.6 Hz, 2H), 7.23 (t, *J*=7.6 Hz, 4H), 6.84 (dd, *J*=8.4, 2.0 Hz, 1H), 6.75 (d, *J*=8.4 Hz, 1H), 5.95 (s, 2H), 2.89～2.76 (m, 2H), 2.45～2.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.08 (d, *J*=17.9 Hz), 147.85 (s), 144.71 (s), 140.14 (s), 130.75 (s), 128.51 (s), 128.48 (s), 126.26 (s), 113.26 (s), 108.09 (s), 102.73

(s), 101.34 (s), 91.19 (d, J=186.4 Hz), 33.85 (d, J=19.8 Hz), 30.50 (d, J=3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −189.63～−189.77 (m); ESI-HRMS calcd for $C_{17}H_{16}DFNO_3$ $(M+H)^+$ 303.1250, found 303.1256.

2-Fluoro-4-(4-methoxyphenyl)-*N*-phenylbutanamide-2-*d* (**5f**): 77% yield, 81% deuterium incorporation. White solid, m.p. 77～82 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, J=5.0 Hz, 1H), 7.55 (d, J=8.0 Hz, 2H), 7.34 (t, J=8.0 Hz, 2H), 7.14 (dd, J=11.5, 8.0 Hz, 3H), 6.83 (d, J=8.5 Hz, 2H), 3.76 (s, 3H), 2.83～2.69 (m, 2H), 2.40～2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.87 (d, J=18.0 Hz), 158.01 (s), 136.59 (s), 132.09 (s), 129.40 (s), 129.04 (s), 124.89 (s), 119.94 (s), 113.88 (s), 91.14 (d, J=186.5 Hz), 55.17 (s), 34.02 (d, J=19.8 Hz), 29.56 (d, J=3.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −189.48 (t, J=7.1 Hz); ESI-HRMS calcd for $C_{17}H_{18}DFNO_2$ $(M+H)^+$ 289.1457, found 289.1457.

2-Fluoro-*N*,4,4-triphenylbutanamide-2-*d* (**5g**): 63% yield, 80% deuterium incorporation. White solid, m.p. 155～158 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (d, J=5.0 Hz, 1H), 7.52 (d, J=7.5 Hz, 2H), 7.35～7.28 (m, 10H), 7.17～7.13 (m, 3H), 4.31 (dd, J=11.0, 4.5 Hz, 1H), 2.98～2.85 (m, 1H), 2.53 (td, J=15.5, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.93 (d, J=17.7 Hz), 143.76 (s), 142.28 (s), 136.57 (s), 129.07 (s), 128.82 (s), 128.58 (s), 128.17 (s), 127.59 (s), 126.81 (s), 126.52 (s), 124.93 (s), 90.21 (d, J=186.5 Hz), 46.46 (d, J=2.2 Hz), 38.10 (d, J=19.7 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −189.40～−189.48 (m); ESI-HRMS calcd for $C_{22}H_{18}DFNO$ $(M+H)^+$ 335.1664, found 335.1663.

2-Fluoro-*N*-phenylbutanamide-2-*d* (**5h**): 76% yield and 81% deuterium incorporation. White solid, m.p. 61～66 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (br s, 1H), 7.58 (d, J=7.5 Hz, 2H), 7.35 (dd, J=7.5, 7.5 Hz, 2H), 7.16 (t, J=7.5 Hz, 1H), 2.17～1.91 (m, 2H), 1.07 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.94 (d, J=18.0 Hz), 136.64 (s), 129.07 (s), 124.88 (s), 119.94 (s), 92.95 (d, J=186.0 Hz), 25.55 (d, J=20.3 Hz), 8.53 (d, J=3.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −190.54～−190.73 (m); ESI-HRMS calcd for $C_{10}H_{12}DFNO$ $(M+H)^+$ 183.1038, found 183.1035.

2-Fluoro-*N*-phenyldodecanamide-2-*d* (**5i**): 60% yield, 82% deuterium incorporation. White solid, m.p. 78～82 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, J=5.6 Hz, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.35 (dd, J=8.0, 7.6 Hz, 2H), 7.16 (t, J=7.6 Hz, 1H), 2.13～1.85 (m, 2H), 1.54～1.47 (m, 2H), 1.35～1.26 (m, 14H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.15 (d, J=18.0 Hz), 136.68 (s), 129.09 (s), 124.88 (s), 119.92 (s), 92.22 (d, J=185.8 Hz), 32.29 (d, J=19.9 Hz), 31.87(s), 29.51 (d, J=4.5 Hz), 29.31 (d, J=5.9 Hz), 29.13 (s), 24.33 (d, J=2.5 Hz), 22.66 (s), 14.10 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −188.53～−188.68 (m); ESI-HRMS calcd for $C_{18}H_{28}DFNO$ $(M+H)^+$ 295.2290, found 295.2289.

3-Cyclooctyl-2-fluoro-*N*-phenylpropanamide-2-*d* (**5j**): 55% yield, 80% deuterium incorporation. White solid, m.p. 91～95 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J=5.6 Hz, 1H), 7.57 (dd, J=8.4, 1.2 Hz, 2H), 7.35 (dd, J=7.6, 8.4 Hz, 2H), 7.15 (t, J=7.6 Hz, 1H), 2.05～1.26 (m, 17H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.59 (d, J=17.9 Hz), 136.73 (s), 129.07 (s), 124.83 (s), 119.90 (s), 91.06 (d, J=185.8 Hz), 40.32 (d, J=19.5 Hz), 33.26 (s), 32.84 (s), 30.58 (s), 27.24 (s), 27.16 (s), 26.09 (s), 25.18 (s), 25.01 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −187.07～−187.23 (m); ESI-HRMS calcd for $C_{17}H_{24}DFNO$ $(M+H)^+$ 279.1977, found 279.1974.

4-Butoxy-2-fluoro-*N*-phenylbutanamide-2-*d* (**5k**): 70% yield, 83% deuterium incorporation. White solid, m.p. 44～48 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (br s, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.35 (dd, J=8.0, 7.5 Hz, 2H), 7.07 (t, J=7.5 Hz, 1H), 3.65～3.58 (m, 2H), 3.47～3.40 (m, 2H), 2.43～2.31 (m, 1H), 2.19～2.09 (m, 1H), 1.55～1.49 (m, 2H), 1.38～1.30 (m, 2H), 0.88 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.04 (d, J=17.9 Hz), 136.73 (s), 129.06 (s), 124.82 (s), 119.85 (s), 89.43 (d, J=186.2 Hz), 70.81 (s), 65.33 (s), 32.43 (d, J=19.8 Hz), 31.69 (s), 19.27 (s), 13.85 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −190.28～−190.44 (m); ESI-HRMS calcd for $C_{14}H_{19}DFNO_2Na$ $(M+Na)^+$ 277.1433, found 277.1432.

4-(*tert*-Butoxy)-2-fluoro-*N*-phenylbutanamide-2-*d* (**5l**): 56% yield, 82% deuterium incorporation. White solid, m.p. 42～46 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00 (br s, 1H), 7.58 (d, J=8.0 Hz, 2H), 7.35 (dd, J=8.0, 7.5 Hz, 2H), 7.15 (t, J=7.5 Hz, 1H), 3.60～3.52 (m, 2H), 2.37～2.25 (m, 1H), 2.17～2.06 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.21 (d, J=18.1 Hz), 136.80 (s), 129.08 (s), 124.76 (s), 119.83 (s), 89.45 (d, J=185.8 Hz), 73.00 (s), 56.25 (d, J=3.7 Hz), 33.32 (d, J=19.5 Hz), 27.41 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −190.60～−190.71 (m); ESI-HRMS calcd for $C_{14}H_{19}DFNO_2Na$ $(M+Na)^+$ 277.1433, found 277.1433.

4-(Cyclohexyloxy)-2-fluoro-*N*-phenylbutanamide-2-*d* (**5m**): 72% yield, 80% deuterium incorporation. White solid, m.p. 74～78 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.03 (d, J=4.0 Hz, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.34 (dd, J=8.0, 7.5 Hz, 2H), 7.14 (t, J=7.5 Hz, 1H), 3.69～3.61 (m, 2H), 3.27～3.23 (m, 1H), 2.41～2.29 (m, 1H), 2.17～2.07 (m, 1H), 1.86 (m, 2H) 1.71 (d, J=6.0 Hz, 2H), 1.52-1.50 (m, 1H), 1.30～1.17 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.07 (d, J=18.1 Hz), 136.75 (s), 129.04 (s), 124.78 (s), 119.85 (s), 89.46 (d, J=185.9 Hz), 77.54 (s), 62.30 (s), 32.93 (d, J=19.7 Hz), 32.18 (s), 31.97 (s), 25.73 (s), 23.96 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −190.14～−190.34 (m); ESI-HRMS calcd for $C_{16}H_{21}DFNO_2Na$ $(M+Na)^+$ 303.1590, found 303.1582.

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl 2-(4-(2-fluoro-4-phenylbutanamido-2-*d*)phenyl) acetate (**5n**): 66% yield, 83% deuterium incorporation, *dr*=1∶1. Colorless oil. 1H NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, J=6.5 Hz, 1H), 7.57 (d, J=7.5 Hz, 2H), 7.36 (dd, J=8.5, 7.5 Hz, 2H), 7.23 (d, J=8.0 Hz, 1H), 7.16 (t, J=7.5 Hz, 1H), 7.01 (d, J=8.0 Hz, 1H), 6.95 (s, 1H), 3.39 (s, 3H),

3.34～3.31 (m, 1H), 2.86～2.73 (m, 4H), 2.42～2.19 (m, 4H), 2.11～2.04 (m, 2H), 1.90～1.87 (m, 1H), 1.74～1.67 (m, 1H), 1.57～1.18 (m, 7H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.86 (d, J=17.8 Hz), 138.34 (s), 137.24 (s), 136.81 (s), 136.62 (s), 129.07 (s), 125.75 (s), 125.51 (s), 124.90 (s), 119.93 (s), 91.27 (d, J=186.6 Hz), 90.73 (s), 57.86 (s), 50.34 (s), 44.19 (s), 43.16 (s), 38.36 (s), 38.02 (s), 33.82 (d, J=20.0 Hz), 29.91 (d, J=3.0 Hz), 29.46 (s), 27.71 (s), 27.15 (s), 26.20 (s), 23.00 (s), 11.50 (s); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −189.39～−189.51 (m); ESI-HRMS calcd for $C_{29}H_{36}DFNO_2$ $(M+H)^+$ 451.2866, found 451.2860.

Supporting Information NMR spectra of reported new compounds. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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