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Visible light-induced selective hydrobromodifluoromethylation of alkenes with dibromodifluoromethane

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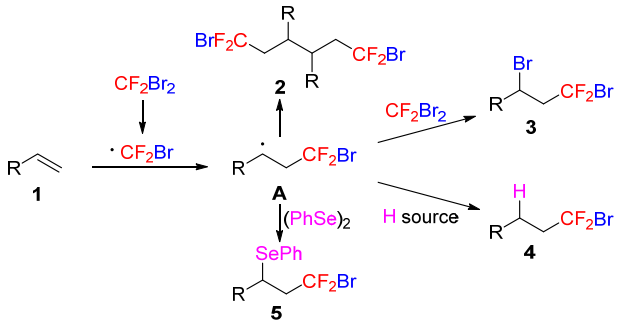
A visible light-induced selective hydrobromodifluoromethylation of alkenes using CF_2Br_2 was developed. This transformation proceeded smoothly in the presence of catalytic Eosin Y at room temperature to give various hydrobromodifluoromethylated compounds with broad functional group tolerance.

Introduction

The myriad applications of fluorinated compounds have stimulated the development of novel methods for the introduction of fluorine atom and fluorinated groups into organic molecules.[1] While strategies for trifluoromethylation have been extensively developed,[2] the methods for the preparation of other fluoroalkylated compounds are relatively underdeveloped despite their potential importance in many research fields. Bromodifluoromethylated compounds are well known as good candidates for the formation of halogen bonding[3] and important intermediates of the preparation of valuable fluorinated compounds.[4] The known methods for the preparation of these compounds were divided into indirect and direct approaches. The indirect approaches, such as bromination of *gem*-difluoromethylenated precursors[5] and *gem*-difluoroalkenes[6] as well as transformation from CF_2Br-containing building blocks,[7] require long synthetic sequences. Recently, the direct approaches involving the electrophilic bromodifluoromethylating reagents have been developed by Magnier,[8a] Shibata,[8b,c] and Xiao.[8d] Furthermore, Hu and co-workers reported a novel formal nucleophilic bromodifluoromethylation of carbonyl compounds via the bromination of in-situ generated sulfinate intermediates from the Julia-Kocienski reactions of difluoromethyl 2-pyridyl sulfone.[9a] Very recently, Dilman accomplished the nucleophilic bromodifluoromethylation of aldehydes[9b] and iminium ions[9c] with (bromodifluoromethyl)trimethylsilane in the presence of excess of bromide ion. Besides these methods, the addition of dibromodifluoromethane (CF_2Br_2) to alkenes provides a convenient access to a series of bromodifluoromethylated compounds.[10-13] As shown in Scheme 1, the single electron transfer (SET) from a radical initiator to CF_2Br_2 generates CF_2Br radical, which is added to alkenes **1** to form radical intermediate **A**. The intermediate **A** may undergo different reaction processes to give compounds **2**-**5**. The dimerization reaction of intermediate **A** produced compound **2**.[10] Bromine and hydrogen abstraction of intermediate **A** from CF_2Br_2 and a hydrogen donor gave compounds **3**[11] and **4**[12] respectively. In the presence of other radical trap agents such as diphenyl diselenide, intermediate **A** was transformed into the selenobromodifluorometylated product **5**.[13] Because the atom transfer radical addition (ATRA) for the formation of product **3** is a preferred process,[11] the selective formation of hydrobromodifluoromethylated compound **4** is particularly challenging.



Scheme 1 The addition of CF_2Br_2 to alkenes.

To the best of our knowledge, only two reactions of the direct hydrobromodifluoromethylation of alkenes with CF_2Br_2 appeared. Hu reported the hydrobromodifluoromethylation of electron-deficient alkenes initiated by a $CrCl_3$/Fe bimetal redox system (Scheme 2a).[12a] Wu and co-workers disclosed that the Zn-induced addition of CF_2Br_2 to cyclohexene yielded the hydrobromodifluoromethylated product in low yield along with byproducts (Scheme 2b).[12b] Both of these methods suffered from narrow substrate scope. Recently, visible light photoredox catalysis has emerged as an efficient and eco-friendly tool in organic synthesis[14] and has been applied in the fluoroalkylation of organic compounds.[15,16] As part of our on-

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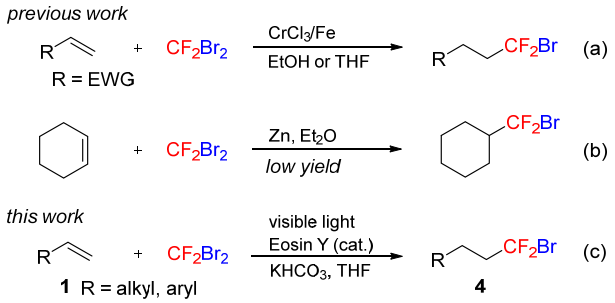
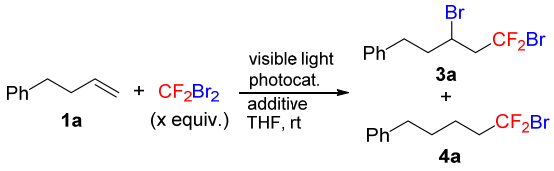


Scheme 2 Hydrobromodifluoromethylation of alkenes.

Table 1. Optimization of reaction conditions[a]



Entry	Photocat.(mol%)	X	Additive	Yield (**4a**/**3a**, %)[b]
1[c]	*fac*-Ir(ppy)$_3$ (3)	4	—	0/97
2	*fac*-Ir(ppy)$_3$ (3)	4	—	48/46
3	Ru(bpy)$_3$Cl$_2$·6H$_2$O (3)	4	—	10/9
4	Ru(bpy)$_3$(PF$_6$)$_2$ (2)	4	—	15/8
5	Methylene Blue (3)	4	—	33/8
6	Eosin Y (3)	4	—	54/6
7	Eosin Y (5)	4	—	57/trace
8[d]	Eosin Y (5)	4+2	—	81/trace
9[e]	Eosin Y (5)	4+2	Et$_3$N	86/trace
10[e]	Eosin Y (5)	4+2	KHCO$_3$	87/trace
11[e]	—	4+2	KHCO$_3$	0/0
12[e,f]	Eosin Y (5)	4+2	KHCO$_3$	0/0

[a]Reaction conditions: **1a** (0.1 mmol), CF_2Br_2 (x equiv), photocat., additive (0.1 mmol), THF (3.0 mL), visible light, rt, under N_2, 10 h. [b]Yields determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard. [c]The reaction was performed in MeOH (3.0 mL). [d]A second portion of CF_2Br_2 (2 equiv) was added after 5 h. [e]A second portion of CF_2Br_2 (2 equiv) and additive (0.1 mmol) was added after 5 h. [f]No light.

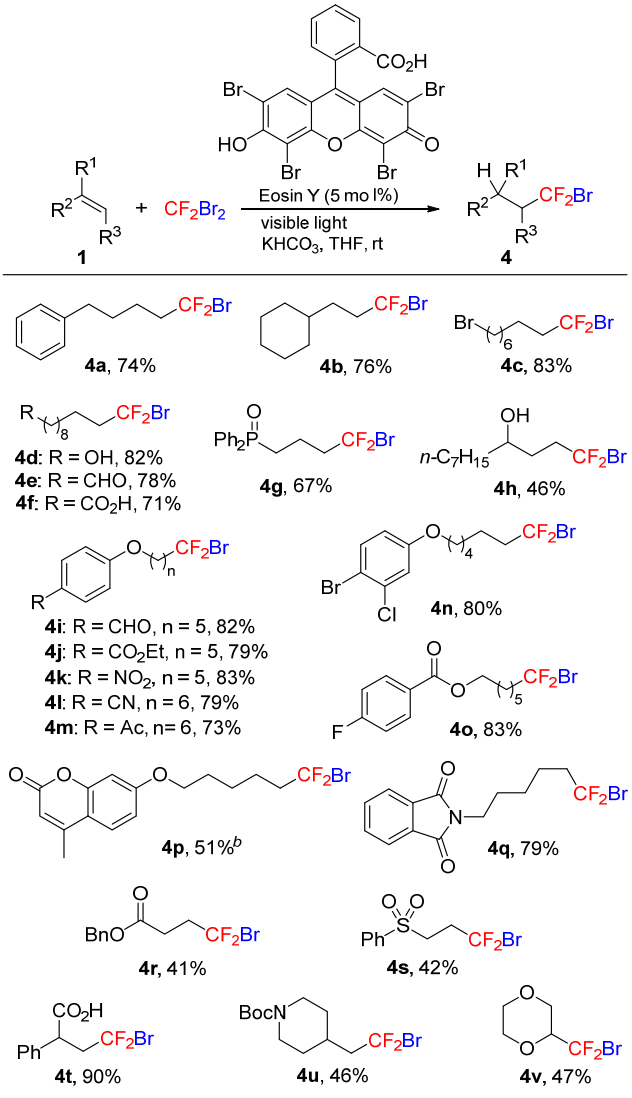
going research on photocatalytic fluoroalkylation reactions,[17] herein we disclose the selective hydrobromodifluoromethylation of alkenes with CF_2Br_2 through visible light photoredox catalysis (Scheme 2c).

Results and discussion

Optimization of the reaction conditions was explored using 4-phenyl-1-butene (**1a**) as the substrate (Table 1). The reaction catalyzed by *fac*-Ir(ppy)$_3$ in MeOH mainly led to the atom transfer radical addition (ATRA) product **3a** (entry 1). When the reaction was performed in THF, a mixture of **3a** and **4a** was generated (entry 2). Various solvents, including toluene, CH_2Cl_2, Et_2O, dioxane, CH_3CN, DMF, and DMSO, were also investigated. However, no higher yield was gained by altering the solvent. Then different photocatalysts were screened (entries 3-6). Among them, Eosin Y[18] was superior to other photocatalysts, giving the desired product **4a** in 54% yield (entry 6). The yield of **4a** was slightly improved to 57% by increasing the amount of photocatalyst (entry 7). The GC-MS analysis of the reaction mixture indicated that the substrate **1a** was only partly converted, while the ^{19}F NMR showed that CF_2Br_2 was totally consumed. Consequently, compound **4a** was formed in 81% yield when another portion of CF_2Br_2 was added (entry 8). Finally, the addition of additives, including Et$_3$N and KHCO$_3$, led to a further improvement of the yield (entries 9 and 10). Control experiments showed that both the photocatalyst and visible light were indispensable for this transformation (entries 11 and 12).

With the optimized reaction conditions in hand (Table 1, entry 10), we next investigated the substrate scope of this photocatalytic reaction. A variety of monosubstituted and disubstituted alkenes could be transformed into the corresponding hydrobromodifluoromethylated products in

Table 2. Substrate scope of photocatalytic hydrobromodifluoromethylation of alkenes[a]

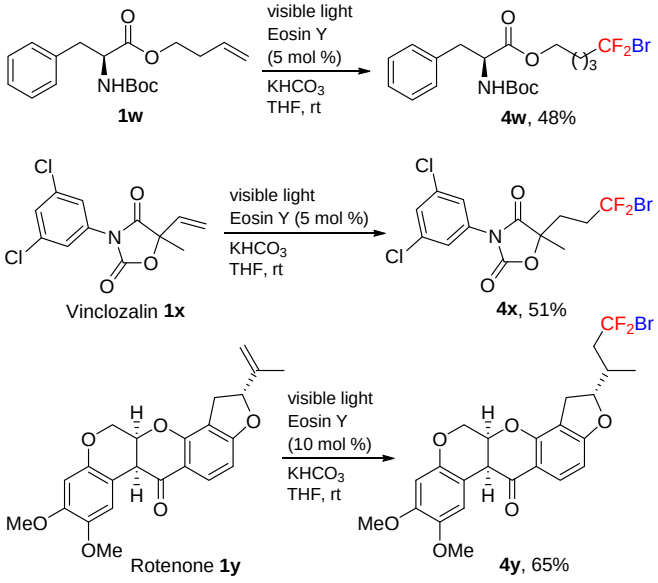


[a]Reaction conditions: **1** (0.5 mmol), CF_2Br_2 (3.0 mmol), Eosin Y (0.025 mmol), KHCO$_3$ (0.5 mmol), THF (15.0 mL), visible light, rt, under N_2, 10 h, isolated yields. [b]Eosin Y (0.05 mmol).

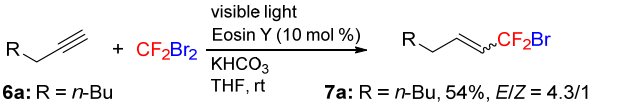
moderate to excellent yields (Table 2). A wide range of functional groups were tolerated, including alkyl and allylic alcohols, aldehydes, ketones, carboxylic acids, esters, nitriles, amides, nitro groups, phosphie oxides, ethers, sulfones, and halides. Substrates bearing fluoro, chloro, and bromo substitutents on the arene rings were also compatible. Heterocyclic substrates, **1p** and **1q**, were smoothly converted into the desired products. α,ß-Unsaturated ester **1r** and α,ß-unsaturated sulfone **1s** exhibited moderate reactivity in this transformation. It was noteworthy that the photocatalytic protocol presented herein was also easily extended to branched terminal and internal alkenes **1t**-**v**. However, styrenes were not suitable substrates for this transformation.

Remarkably, this facile protocol allowed the direct hydrobromodifluoromethylation of natural product analogues, such as L-phenylalanine derivative **1w** (Scheme 3). The complex compounds such as Vinclozalin **1x** and Rotenone **1y** were also examined, affording the corresponding hydrobromodifluoromethylated products **4x** and **4y** in moderate yields, respectively. These results showed that this photocatalytic protocol might be applicable to "late-stage hydrobromodifluoromethylation" of natural products and drugs.

The hydrobromodifluoromethylation of alkynes was also successful (Scheme 4). Reactions of alkynes **6a**-**d** with CF_2Br_2 in the presence of Eosin Y (10 mol %) and $KHCO_3$ under visible light irradiation provided a mixture of the *E* and *Z* alkenyl-CF_2Br compounds **7a**-**d** in moderate yields.[19]



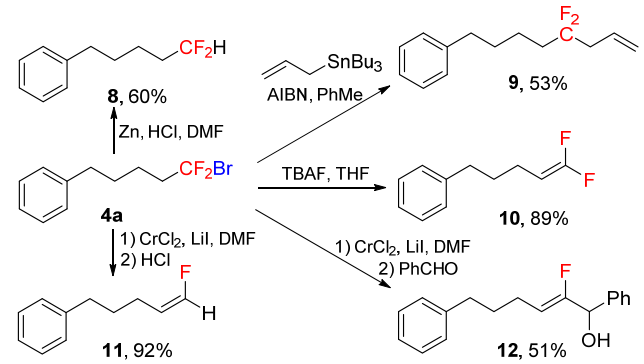
Scheme 3 Hydrobromodifluoromethylation of compounds **1w**-**y**.



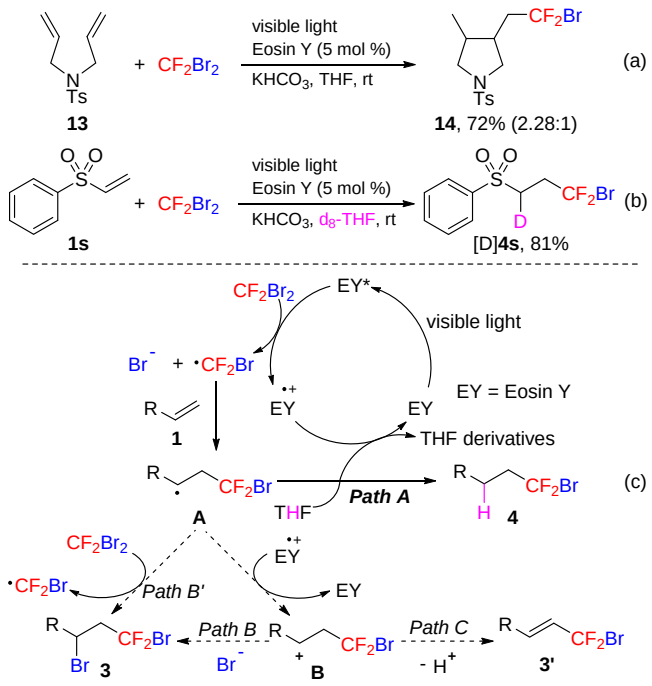
6a: R = *n*-Bu
6b: R = Bn
6c: R = *c*-hex
6d: R = $(CH_2)_4OH$

7a: R = *n*-Bu, 54%, *E*/*Z* = 4.3/1
7b: R = Bn, 55%, *E*/*Z* = 3.2/1
7c: R = *c*-hex, 53%, *E*/*Z* = 2.4/1
7d: R = $(CH_2)_4OH$, 54%, *E*/*Z* = 4.2/1

Scheme 4 Hydrobromodifluoromethylation of alkynes.



Scheme 5 Hydrobromodifluoromethylation of alkynes.



Scheme 6 Mechanistic investigations.

The bromodifluoromethylated compounds are important intermediates for the preparation of other fluorinated compounds. As shown in Scheme 5, compound **4a** underwent several transformations to give products **8**-**12**. Reduction of **4a** with Zn/HCl in DMF yielded difluoromethylated product **8**.[20] The reaction of **4a** with allyltributyltin in the presence of a catalytic amount of AIBN afforded *gem*-difluoromethylenated product **9**.[21] The *gem*-difluoroalkene **10** could be conveniently obtained by the elimination reaction using TBAF as the base.[22] Treatment of **4a** with $CrCl_2$ generated the nucleophilic α-fluorovinylchromium intermediate,[23] which subsequently reacted with HCl or PhCHO to give (*Z*)-fluoroalkene **11** and (*Z*)-ß-fluoroallylic alcohol **12** respectively in high stereoselectivities.

To gain insight into the reaction mechanism, a radical clock **13** was submitted to the standard reaction conditions (Scheme 6a). The cyclized bromodifluoromethylated product **14** was formed in 72% yield (2.28:1 dr). This result revealed that the CF_2Br radical was involved in this visible light-induced hydrobromodifluoromethylation of alkenes. The reaction of **1s** with CF_2Br_2 in d_8-THF exclusively gave the deuterated product

[D]**4s** in 81% yield, which indicated that THF served as the hydrogen atom source (Scheme 6b). What was more, Stern-Volmer studies showed that CF_2Br_2 exhibited significant fluorescence quenching of Eosin Y* (see the Supporting Information). This result suggested that electron transfer occurred from Eosin Y* to CF_2Br_2 first. On the basis of these experimental results and the literature reports,[18] a plausible mechanism for the hydrobromodifluoromethylation was depicted in Scheme 6c. Intially, the excitation of Eosin Y with visible light produced the excited state Eosin Y*. Then a single electron transfer (SET) from Eosin Y* to CF_2Br_2 generated the CF_2Br radical, which was subsequently added to alkenes **1** for the formation of radical intermediate **A**. Finally, intermediate **A** abstracted hydrogen from THF to give the desired hydrobromodifluoromethylated product **4** (Path A).[15m]

The byproduct **3** might be formed via two different routes from intermediate **A**: either by oxidation to cation **B** followed by nucleophilic trapping (Path B) or by propagation (Path B'). From this proposed mechanism, we can explain that why Eosin Y is selected for this transformation. Its high reduction potential (–1.60 V vs SCE) facilitates the generation of CF_2Br radical and its low oxidation potential (0.72 V vs SCE) avoids the oxidation to cation **B**.[24] Furthermore, cation **B** might undergo elimination of the proton to give alkenes **3'** (Path C). This process would make the reaction mixture acidic, which needs a base to neutralize the reaction system. That is why the addition of $KHCO_3$ benefits for this reaction.

Conclusions

In conclusion, we have developed a photocatalytic hydrobromodifluoromethylation of unactivated alkenes with CF_2Br_2 in the presence of Eosin Y at room temperature. The mild reaction conditions allow the tolerance of a wide range of functional groups. This protocol could also be extended to alkyne substrates. Furthermore, the application of the bromodifluoromethylated products in organic synthesis has been demonstrated by the transformations of compound **4a** into other fluorinated compounds.

Experimental

General information

^{1}H NMR (TMS as the internal standard) and ^{19}F NMR spectra ($CFCl_3$ as the outside standard and low field is positive) were recorded on a 400 MHz spectrometer. ^{13}C NMR was recorded on 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Substrates **1a**-**h**, **1r**-**v**, **1x**, **1y**, **6a**-**d**, and **13** were purchased from commercial sources and used as received. Substrates **1i**-**q**[25] and **1w**[26] were prepared according to literature procedures. Unless otherwise noted, all reagents were obtained commercially and used without further purification.

General procedures for hydrobromodifluoromethylation of alkenes and alkynes

A 25 mL Schlenk flask equipped with a rubber septum and a magnetic stir bar was charged with Eosin Y (16.2 mg, 0.025 mmol, 5 mol%), substrates (0.5 mmol, 1.0 equiv.). Then a solution of CF_2Br_2 (420 mg, 4.0 equiv., 2.0 mmol) in THF (10 mL, 2.0 mol/L) was added to the reaction flask by a syringe. The flask was sealed with 3M vinyl electrical tape, then the mixture was degassed three times by the freeze-pump-thaw procedure. The flask was placed at a distance of 2 cm from the blue LEDs (λ = 460-470 nm).[27] The mixture was stirred under nitrogen atmosphere and irradiated by blue LEDs for 5 h. After cooled in ice-water bath, then $KHCO_3$ (50 mg, 1.0 equiv., 0.5 mmol) and the second portion of CF_2Br_2 (210 mg, 2.0 equiv., 1.0 mmol) in THF (5 mL, 2.0 mol/L) were added to the reaction mixture. Then the mixture was degassed and irradiated by blue LEDs for another 5 h. After the reaction was complete, the reaction mixture was concentrated under vacuum and the crude product was purified by column chromatography on silica gel to give the product.

(3,5-Dibromo-5,5-difluoropentyl)benzene (3a). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32-7.28 (m, 2H), 7.23-7.20 (m, 3H), 4.21-4.15 (m, 1H), 3.17-3.04 (m, 1H), 3.02-2.89 (m, 2H), 2.81-2.73 (m, 1H), 2.28-2.19 (m, 1H), 2.12-2.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 140.1, 128.6, 128.5, 126.4, 120.4 (t, *J* = 305.2 Hz), 52.7 (t, *J* = 21.5 Hz), 46.2 (t, *J* = 2.6 Hz), 39.9, 33.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -42.2- (-43.2) (m, 2F); IR (thin film) ν 3063, 3028, 2928, 1603, 1497, 1454, 1196, 1112, 926, 748, 699, 543 cm^{-1}; MS (EI): *m/z* (%) 344 ([M+4]$^+$, 11.0), 342 ([M+2]$^+$, 11.0), 340 ([M]$^+$, 12.3), 91 (100); HRMS Calculated for $C_{11}H_{12}Br_2F_2$: 339.9274; Found: 339.9278.

(5-Bromo-5,5-difluoropentyl)benzene (4a). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.31 (t, *J* = 7.2 Hz, 2H), 7.24-7.18 (m, 3H), 2.67 (t, *J* = 7.0 Hz, 2H), 2.44-2.33 (m, 2H), 1.74-1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.7, 128.5, 128.4, 126.0, 123.1 (t, *J* = 303.4 Hz), 44.2 (t, *J* = 21.2 Hz), 35.5, 30.3, 23.6 (t, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.4 (t, *J* = 13.5 Hz, 2F); IR (thin film) ν 3027, 2943, 2860, 1497, 1454, 1195, 1103, 947, 909, 747, 699 cm^{-1}; MS (EI): *m/z* (%) 264 ([M+2]$^+$, 11.0), 262 ([M]$^+$, 12.3), 91 (100); HRMS Calculated for $C_{11}H_{13}BrF_2$: 262.0169; Found: 262.0173.

(3-Bromo-3,3-difluoropropyl)cyclohexane (4b). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.39-2.28 (m, 2H), 1.72-1.68 (m, 4H), 1.53-1.45 (m, 2H), 1.31-1.09 (m, 5H), 0.96-0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 123.6 (t, *J* = 303.4 Hz), 42.0 (t, *J* = 20.8 Hz), 36.7, 33.0, 31.2 (t, *J* = 2.6 Hz), 26.4, 26.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.4 (t, *J* = 13.7 Hz, 2F); IR (thin film) ν 2924, 2853, 1457, 1377, 923 cm^{-1}; MS (EI): *m/z* (%) 240 ([M]$^+$, 0.24), 161 (50.8), 83 (100); HRMS Calculated for $C_9H_{15}BrF_2$: 240.0325; Found: 240.0319.

1,9-Dibromo-1,1-difluorononane (4c). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.39 (t, *J* = 6.8 Hz, 2H), 2.37-2.27 (m, 2H), 1.88-1.81 (m, 2H), 1.61-1.56 (m, 2H), 1.44-1.33 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 123.2 (t, *J* = 303.8 Hz), 44.2 (t, *J* = 21.2 Hz), 33.9, 32.7, 29.0, 28.5, 28.3, 28.0, 23.9 (t, *J* = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.4 (t, *J* = 13.5 Hz,

2F); IR (thin film) ν 2934, 2857, 1465, 1198, 1106, 910, 635cm^{-1}; MS (EI): *m/z* (%) 243 ([M+2]$^+$, 6.7), 241 (M$^+$, 6.8), 161 (100), 119 (53.9); HRMS Calculated for $C_9H_{16}BrF_2$: 241.0403; Found: 241.0400.

11-Bromo-11,11-difluoroundecan-1-ol (4d). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.62 (t, *J* = 6.6 Hz, 2H), 2.37-2.26 (m, 2H), 1.62-1.51 (m, 4H), 1.36-1.28 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 123.3 (t, *J* = 303.8 Hz), 63.0, 44.3 (t, *J* = 21.2 Hz), 32.8, 29.5, 29.4, 29.3, 29.2, 28.4, 25.7, 23.9 (t, *J* = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.3 (t, *J* = 14.3 Hz, 2F); IR (thin film) ν 3349(w) 2928, 2856, 1466, 1198, 1086, 911cm^{-1}; MS (EI): *m/z* (%) 268 ([M-18]$^+$, 2.61), 133 (35.6), 69 (97.0), 55 (100); HRMS Calculated for $C_{11}H_{19}BrF_2$ [M-H_2O]: 268.0638; Found: 268.0634.

12-Bromo-12,12-difluorododecanal (4e). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.75 (t, *J* = 1.8 Hz, 1H), 2.41 (dt, *J* = 7.4, 2.0 Hz, 2H), 2.37-2.26 (m, 2H), 1.63-1.56 (m, 4H), 1.36-1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 202.9, 123.3 (t, *J* = 303.7 Hz), 44.3 (t, *J* = 21.1 Hz), 43.9, 29.29, 29.26, 29.2, 29.1, 28.4, 23.9 (t, *J* = 2.9 Hz), 22.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.3 (t, *J* = 13.7 Hz, 2F); IR (thin film) ν 2928, 2856, 1710, 1199, 911cm^{-1}; MS (EI): *m/z* (%) 280 ([M-18]$^+$, 15.4), 254 (72.7), 95 (92.0), 55 (100); HRMS Calculated for $C_{12}H_{21}BrF_2O$: 298.0744; Found: 298.0750.

12-Bromo-12,12-difluorododecanoic acid (4f). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.37-2.27 (m, 4H), 1.66-1.55 (m, 4H), 1.36-1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.7, 123.3 (t, *J* = 303.8 Hz), 44.3 (t, *J* = 21.2 Hz), 34.0, 29.7, 29.29, 29.27, 29.2, 29.0, 28.4, 24.6, 23.9 (t, *J* = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.3 (t, *J* = 14.3 Hz, 2F); IR (thin film) ν 3050, 2926, 2855, 1710, 1200, 911cm^{-1}; MS (EI): *m/z* (%) 314 ([M]$^+$, 2.0), 254 (6.3), 73 (73.6), 60 (100); HRMS Calculated for $C_{12}H_{21}BrF_2O_2$: 314.0693; Found: 314.0692.

(4-Bromo-4,4-difluorobutyl)diphenylphosphine oxide (4g). White solid, m.p. 80-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75-7.70 (m, 4H), 7.54-7.45 (m, 6H), 2.55-2.44 (m, 2H), 2.35-2.29 (m, 2H), 2.00-1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 132.4 (d, *J* = 98.5 Hz), 132.0 (d, *J* = 2.2 Hz), 130.7 (d, *J* = 8.7 Hz), 128.8 (d, *J* = 11.6 Hz), 122.3 (t, *J* = 302.2 Hz), 44.7 (td, *J* = 21.5, 13.1 Hz), 28.6 (d, *J* = 71.5 Hz), 16.8 (q, *J* = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.7 (t, *J* = 13.5 Hz, 2F); ^{31}P NMR (162 MHz, $CDCl_3$) δ ppm 31.5 (s, 1P); IR (thin film) ν 3056, 2941, 1438, 1186, 1120, 914, 718, 695, 543, 509 cm^{-1}; MS (EI): *m/z* (%) 355 ([M+2]$^+$, 0.39), 353 ([M]$^+$, 0.29), 293 (100), 201 (51.7); HRMS Calculated for $C_{16}H_{16}BrF_2OP$: 353.0118; Found: 353.0101.

1-Bromo-1,1-difluoroundecan-4-ol (4h). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.64 (s, 1H), 2.67-2.52 (m, 1H), 2.47-2.32 (m, 1H), 1.83-1.75 (m, 1H), 1.70-1.60 (m, 1H), 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 123.2 (t, *J* = 303.4 Hz), 70.5, 40.8 (t, *J* = 21.5 Hz), 37.7, 31.8, 31.4 (t, *J* = 3.0 Hz), 29.5, 29.2, 25.6, 22.6, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.0-(-44.0) (m, 2F); IR (thin film) ν 3357, 2929, 2857, 1466, 1204, 1071, 988, 919 cm^{-1}; MS (EI): *m/z* (%) 268 ([M-18]$^+$, 2.24), 169 (62.4), 167 (62.7) 129 (83.6), 69 (100); HRMS Calculated for $C_{11}H_{19}BrF_2$ [M-H_2O]: 268.0638; Found: 268.0641.

4-((6-Bromo-6,6-difluorohexyl)oxy)benzaldehyde (4i). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.85 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 2.42-2.31 (m, 2H), 1.87-1.80 (m, 2H) , 1.72-1.65 (m, 2H), 1.59-1.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 190.8, 164.0, 132.0, 129.9, 123.0 (t, *J* = 303.4 Hz), 114.7, 67.9, 44.1 (t, *J* = 21.2 Hz), 28.7, 25.0, 23.7 (t, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.5 (t, *J* = 13.5 Hz, 2F); IR (thin film) ν 2946, 1689, 1602, 1257, 1160, 909, 832 cm^{-1}; MS (EI): *m/z* (%) 322 ([M+2]$^+$, 18.6), 320 ([M]$^+$, 19.2), 193 (5.9), 121 (100); HRMS Calculated for $C_{13}H_{15}BrF_2O_2$: 320.0223; Found: 320.0222.

Ethyl 4-((6-bromo-6,6-difluorohexyl)oxy)benzoate (4j). White solid, m.p. 38-40 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.97 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.00 (t, *J* = 6.2 Hz, 2H), 2.42-2.31 (m, 2H), 1.85-1.76 (m, 2H), 1.72-1.64 (m, 2H), 1.60-1.51 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.4, 162.7, 131.6, 123.0 (t, *J* = 303.4 Hz), 122.9, 114.0, 67.6, 60.6, 44.2 (t, *J* = 21.5 Hz), 28.8, 25.1, 23.7 (t, *J* = 3.0 Hz), 14.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.5 (t, *J* = 13.5 Hz, 2F); IR (thin film) ν 2945, 2872, 1712, 1606, 1277, 1253, 1168, 1103 cm^{-1}; MS (EI): *m/z* (%) 366 ([M+2]$^+$, 19.3),364 (M$^+$, 18.8), 139 (84.2), 121 (100); HRMS Calculated for $C_{15}H_{19}BrF_2O_3$: 364.0486; Found: 364.0484.

1-((6-Bromo-6,6-difluorohexyl)oxy)-4-nitrobenzene (4k). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, *J* = 8.8, 2.0 Hz, 2H), 6.92 (dd, *J* = 9.6, 2.4 Hz, 2H), 4.04 (td, *J* = 6.2, 2.4 Hz, 2H), 4.43-2.32 (m, 2H), 1.88-1.81 (m, 2H), 1.72-1.65 (m, 2H), 1.60-1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.0, 141.5, 126.0, 122.9 (t, *J* = 303.4 Hz), 114.4, 68.3, 44.1 (t, *J* = 21.2 Hz), 28.7, 25.0, 23.7 (t, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.5 (t, *J* = 14.3 Hz, 2F); IR (thin film) ν 3113, 2947, 1594, 1342, 1264, 1112, 910, 860, 753 cm^{-1}; MS (EI): *m/z* (%) 337 (M$^+$, 22.3), 238 (12.8), 139 (100); HRMS Calculated for $C_{12}H_{14}BrF_2NO_3$: 337.0125; Found: 337.0121.

4-((7-Bromo-7,7-difluoroheptyl)oxy)benzonitrile (4l). White solid, m.p. 43-45 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55 (d, *J* = 9.2 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 2.39-2.28 (m, 2H), 1.84-1.77 (m, 2H), 1.67-1.60 (m, 2H), 1.51-1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.4, 134.0, 123.1 (t, *J* = 303.4 Hz), 119.3, 115.2, 103.8, 68.1, 44.1(t, *J* = 21.2 Hz), 28.7, 28.1, 25.7, 23.8 (t, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.5 (t, *J* = 13.7 Hz, 2F); IR (thin film) ν 2944, 2869, 2225, 1606, 1509, 1302, 1259, 1172, 835, 578 cm^{-1}; MS (EI): *m/z* (%) 333 ([M+2]$^+$, 14.2), 331 (M$^+$, 14.3), 238 (6.3), 119 (100); HRMS Calculated for $C_{14}H_{16}BrF_2NO$: 331.0383; Found: 331.0378.

1-(4-((6-Bromo-6,6-difluorohexyl)oxy)phenyl)ethanone (4m). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (dd, *J* = 8.8, 2.4 Hz, 2H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 2H), 4.00 (t, *J* = 6.0 Hz, 2H), 2.52 (s, 3H), 2.39-2.27 (m, 2H), 1.84-1.76 (m, 2H), 1.67-1.60 (m, 2H), 1.51-1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 196.7, 163.0, 130.6, 130.3, 123.1 (t, *J* = 303.4 Hz), 114.1, 67.9, 44.2 (t, *J* = 21.2 Hz), 28.8, 28.1, 26.3, 25.7, 23.8 (t, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.4 (t, *J* = 13.5 Hz, 2F); IR (thin film) ν 2943, 2869, 1677, 1601, 1256, 1172, 835, 591cm^{-1}; MS (EI): *m/z* (%) 333 ([M-CH_3]$^+$, 10.4), 269 (7.0), 121

(100); HRMS Calculated for $C_{14}H_{16}BrF_2O_2$: 333.0302; Found: 333.0305.

1-bromo-4-((7-bromo-7,7-difluoroheptyl)oxy)-2-chlorobenzene (4n). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.47 (d, *J* = 2.4 Hz, 1H), 7.28 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 3.98 (t, *J* = 6.4 Hz, 2H), 2.40-2.29 (m, 2H), 1.86-1.79 (m, 2H), 1.68-1.60 (m, 2H), 1.56-1.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 153.9, 132.7, 130.5, 124.1, 123.1 (t, *J* = 303.4 Hz), 114.5, 112.4, 69.2, 44.2 (t, *J* = 21.2 Hz), 28.7, 28.1, 25.7, 23.8 (t, *J* = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.4 (t, *J* = 13.7 Hz, 2F); IR (thin film) ν 2942, 2862, 1582, 1485, 1467, 1289, 1265, 1249, 1086, 1062, 910, 802, 638 cm^{-1}; MS (EI): *m/z* (%) 422 ([M+4]$^+$, 5.1), 420([M+2]$^+$, 7.7), 418(M$^+$, 3.9), 208 (100), 206 (74.2); HRMS Calculated for $C_{13}H_{15}Br_2ClFO$: 417.9146; Found: 417.9147.

7-Bromo-7,7-difluoroheptyl-4-fluorobenzoate (4o). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04-8.01 (m, 2H), 7.08 (t, *J* = 8.8 Hz, 2H), 4.28 (t, *J* = 6.4 Hz, 2H), 2.37-2.27 (m, 2H), 1.79-1.71 (m, 2H), 1.66-1.58 (m, 2H), 1.47-1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.7 (d, *J* = 252.3 Hz), 132.1 (d, *J* = 8.7 Hz), 126.6 (d, *J* = 2.9 Hz), 123.1 (t, *J* = 303.4 Hz), 115.5 (d, *J* = 21.9 Hz), 64.9, 44.2 (t, *J* = 21.2 Hz), 28.5, 28.1, 25.7, 23.9 (t, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.5 (t, *J* = 14.3 Hz, 2F), -105.9 (m, 1F); IR (thin film) ν 2943, 2862, 1720, 1604, 1508, 1276, 1113, 930, 768, 608 cm^{-1}; MS (EI): *m/z* (%) 352 (M$^+$, 0.78), 141 (77.6), 123 (100); HRMS Calculated for $C_{14}H_{16}BrF_3O_2$: 352.0286; Found: 352.0288.

7-((6-Bromo-6,6-difluorohexyl)oxy)-4-methyl-2*H*-chromen-2-one (4p). Red liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.45 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.74 (s, 1H), 6.08 (s, 1H), 3.99 (t, *J* = 6.2 Hz, 2H), 2.41-2.31 (m, 5H), 1.86-1.79 (m, 2H), 1.71-1.63 (m, 2H), 1.58-1.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.0, 161.3, 155.3, 152.6, 125.6, 123.0 (t, *J* = 303.0 Hz), 113.5, 112.5, 111.9, 101.4, 68.1, 44.1 (t, *J* = 21.2 Hz), 28.6, 25.0, 23.7 (t, *J* = 3.3 Hz), 18.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.5 (t, *J* = 13.7 Hz, 2F); IR (thin film) ν 2946, 1728, 1614, 1200, 1147, 1071, 910, 849 cm^{-1}; MS (EI): *m/z* (%) 376 ([M+2]$^+$, 19.9), 374 (M$^+$, 21.7), 176 (86.1), 148 (100); HRMS Calculated for $C_{16}H_{17}BrF_2O_3$: 374.0329; Found: 374.0327.

2-(6-Bromo-6,6-difluorohexyl)isoindoline-1,3-dione (4q). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82-7.80 (m, 2H), 7.70-7.67 (m, 2H), 3.67 (t, *J* = 7.2 Hz, 2H), 2.36-2.25 (m, 2H), 1.72-1.59 (m, 4H) , 1.44-1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.4, 134.0, 132.1, 123.2, 122.9 (t, *J* = 303.4 Hz), 44.1 (t, *J* = 21.2 Hz), 37.6, 28.2, 25.7, 23.5 (t, *J* = 3.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.6 (t, *J* = 13.5 Hz, 2F); IR (thin film) ν 2944, 1773, 1713, 1397, 1056, 915, 720 cm^{-1}; MS (EI): *m/z* (%) 347 ([M+2]$^+$, 13.8), 345 ([M]$^+$, 13.6), 266 (19.1), 160 (100); HRMS Calculated for $C_{14}H_{14}BrF_2NO_2$: 345.0176; Found: 345.0178.

Benzyl 4-bromo-4,4-difluorobutanoate (4r). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.36 (s, 5H), 5.15 (s, 2H), 2.80-2.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.6, 135.4, 128.7, 128.5, 128.4, 121.6 (t, *J* = 303.0 Hz), 67.0, 39.5 (t, *J* = 22.6 Hz), 29.0 (t, *J* = 3.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -45.0 (t, *J* = 13.0 Hz, 2F); IR (thin film) ν 3032, 2958, 1740, 1172, 1104, 920, 698 cm^{-1}; MS (EI): *m/z* (%) 294 ([M+2]$^+$, 11.5), 292 ([M]$^+$, 11.6), 199 (20.3), 108 (90.4), 91 (100); HRMS Calculated for $C_{11}H_{11}BrF_2O_2$: 291.9910; Found: 291.9913.

((3-Bromo-3,3-difluoropropyl)sulfonyl)benzene (4s). White solid, m.p. 78-79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91 (d, *J* = 6.8 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 2H), 3.35-3.31 (m, 2H), 2.85-2.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.2, 134.5, 129.7, 128.1, 119.7 (t, *J* = 303.7 Hz), 50.9 (t, *J* = 3.0 Hz), 37.8 (t, *J* = 24.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -45.2 (t, *J* = 13.0 Hz, 2F); IR (thin film) ν 3053, 2992, 2915, 1448, 1311, 1291, 1146, 1097, 909, 746, 687, 530 cm^{-1}; MS (EI): *m/z* (%) 298 (M$^+$, 4.21), 219 (40.3), 77 (100); HRMS Calculated for $C_9H_9BrF_2O_2S$: 297.9475; Found: 297.9480.

4-Bromo-4,4-difluoro-2-phenylbutanoic acid (4t). White solid, m.p. 64-66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.9 (s, 1H), 7.38-7.30 (m, 5H), 4.01-3.98 (m, 1H), 3.48-3.35 (m, 1H), 2.84-2.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 178.1, 136.3, 129.2, 128.4, 127.8, 120.8 (t, *J* = 304.1 Hz), 47.0 (t, *J* = 21.1 Hz), 46.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.4-(-44.8) (m, 2F); IR (thin film) ν 3034, 2917, 1714, 1216, 1099, 933, 697 cm^{-1}; MS (EI): *m/z* (%) 280 ([M+2]$^+$, 63.5), 278 ([M]$^+$, 64.4), 199 (20.3), 171 (100), 169 (92.4); HRMS Calculated for $C_{10}H_9BrF_2O_2$: 277.9754; Found: 277.9757.

***Tert*-butyl 4-(2-bromo-2,2-difluoroethyl)piperidine-1-carboxylate (4u).** Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.06 (s, 2H), 2.70 (t, *J* = 12.2 Hz, 2H), 2.31 (td, *J* = 15.2, 6.4 Hz, 2H), 1.94-1.84 (m, 1H), 1.76 (d, *J* = 13.2 Hz, 2H), 1.43 (s, 9H), 1.25-1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.7, 122.4 (t, *J* = 304.9 Hz), 79.5, 50.4 (t, *J* = 20.5 Hz), 43.6, 32.6 (t, *J* = 1.9 Hz), 31.9, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -40.9-(-41.1) (m, 2F); IR (thin film) ν 2976, 2926, 1694, 1423, 1173, 965, 915 cm^{-1}; MS (EI): *m/z* (%) 329 ([M+2]$^+$, 2.70), 327 ([M]$^+$, 2.73), 192 (29.1), 57 (100); HRMS Calculated for $C_{12}H_{20}BrF_2NO_2$: 327.0645; Found: 327.0641.

2-(Bromodifluoromethyl)-1,4-dioxane (4v). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.01-3.91 (m, 3H), 3.81 (td, *J* = 11.4, 2.8 Hz, 1H), 3.75-3.71 (m, 1H), 3.66 (dd, *J* = 12.0, 2.8 Hz, 1H), 3.63-3.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 120.1 (t, *J* = 304.8 Hz), 78.0 (t, *J* = 25.2 Hz), 66.9, 66.1, 65.8 (t, *J* = 2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -56.5-(-58.6) (m, 2F); IR (thin film) ν 2975, 2921, 2866, 1726, 1453, 1121, 1048, 951, 902, 793, 698 cm^{-1}; MS (EI): *m/z* (%) 218 ([M+2]$^+$, 25.0), 216 ([M]$^+$, 24.7), 87 (100), 77 (51.1); HRMS Calculated for $C_5H_7BrF_2O_2$: 215.9597; Found: 215.9605.

(*S*)-5-Bromo-5,5-difluoropentyl-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoate (4w). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30-7.21 (m, 3H), 7.12 (d, *J* = 6.8 Hz, 2H), 4.96 (d, *J* = 8.4 Hz, 1H), 4.55 (q, *J* = 6.8 Hz, 1H), 4.13-4.03 (m, 2H), 3.05 (d, *J* = 6.4 Hz, 2H), 2.37-2.26 (m, 2H), 1.68-1.54 (m, 4H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.0, 155.1, 136.0, 129.3, 128.6, 127.1, 122.7 (t, *J* = 303.0 Hz), 78.0, 64.5, 54.5, 43.7 (t, *J* = 21.5 Hz), 38.6, 28.3, 27.3, 20.6 (t, *J* = 3.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -43.7 (t, *J* = 13.7 Hz, 2F); IR (thin film) ν 3062, 2926, 2854, 2787, 1658, 1598, 1322, 1127, 988, 761 cm^{-1}; MS (EI): *m/z* (%) 449 (M$^+$, 0.15), 332 (38.1), 57 (100); HRMS Calculated for $C_{19}H_{26}BrF_2NO_4$: 449.1013; Found: 449.1010.

5-(3-Bromo-3,3-difluoropropyl)-3-(3,5-dichlorophenyl)-5-methyloxazolidine-2,4-dione (4x). White solid, m.p. 119-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44-7.42 (m, 3H), 2.66-2.54 (m, 1H), 2.49-2.35 (m, 1H), 2.31-2.23 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.7, 151.8, 135.7, 132.3, 129.3, 123.7, 120.9 (t, *J* = 303.4 Hz), 84.0, 38.2 (t, *J* = 23.4 Hz), 31.2 (t, *J* = 3.3 Hz), 22.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -44.4-(-45.4) (m, 2F); IR (thin film) ν 3092, 2917, 1821, 1748, 1578, 1452, 1391, 1180, 923, 807 cm^{-1}; MS (EI): *m/z* (%) 419 ([M+4]$^+$, 16.5), 417 ([M+2]$^+$, 39.2), 415 (M$^+$, 25.3), 264 (100); HRMS Calculated for $C_{13}H_{10}BrCl_2F_2NO_3$: 414.9189; Found: 414.9192.

(2*R*,6a*S*,12a*S*)-2-((*R*)-4-Bromo-4,4-difluorobutan-2-yl)-8,9-dimethoxy-1,2,12,12a-tetrahydrochromeno[3,4-*b*]furo[2,3-*h*]chromen-6(6a*H*)-one (4y). Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82 (d, *J* = 8.4 Hz, 1H), 6.74 (s, 1H), 6.46-6.43 (m, 2H), 4.92 (s, 1H), 4.85-4.58 (m, 2H), 4.17 (d, *J* = 12.4 Hz, 3H), 3.83 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.26-3.18 (m, 1H), 2.89-2.83 (m, 1H), 2.77-2.57 (m, 1H), 2.40-2.19 (m, 2H), 1.12-1.07 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 118.91, 118.89, 167.3, 167.0, 157.93, 157.90, 149.6, 147.4, 143.9, 130.10, 130.08, 122.6 (t, *J* = 303.5 Hz), 122.5 (t, *J* = 304.1 Hz), 113.42, 113.38, 112.8, 112.7, 110.4, 104.9, 104.8, 101.0, 88.1, 87.5, 72.3, 66.2, 56.3, 55.9, 46.7 (t, *J* = 20.8 Hz), 46.3 (t, *J* = 20.8 Hz), 44.6, 35.15, 35.13, 34.5, 29.8, 29.1, 15.6, 14.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -39.3-(-43.0) (m, 2F); IR (thin film) ν 2973, 2932, 2857, 1674, 1610, 1513, 1458, 1349, 816 cm^{-1}; MS (EI): *m/z* (%) 526 ([M+2]$^+$, 3.76), 524 (M$^+$, 3.79), 445 (1.77), 192 (100), 177 (15.2); HRMS Calculated for $C_{24}H_{23}BrF_2O_6$: 524.0646; Found: 526.0644.

1-Bromo-1,1-difluorooct-2-ene (7a). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.25-6.17 (m, 1H), 5.89-5.71 (m, 1H), 2.33-2.10 (m, 2H), 1.43 (p, *J* = 7.3 Hz, 2H), 1.35-1.25 (m, 4H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.6 (t, *J* = 5.8 Hz, *Z*), 137.2 (t, *J* = 7.0 Hz, *E*), 126.7 (t, *J* = 23.0 Hz, *E*), 126.2 (t, *J* = 25.2 Hz, *Z*), 117.2 (t, *J* = 299.0 Hz, *E*), 117.0 (t, *J* = 300.8 Hz, *Z*), 31.3 (*Z*), 31.2 (*E*), 31.1 (*E*), 28.4 (*Z*), 28.1 (t, *J* = 1.8 Hz, *Z*), 27.7 (*E*), 22.3 (*E*, *Z*), 13.9 (*E*, *Z*); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -38.4 (d, *J* = 10.9 Hz, 2F, *Z*), -43.8 (d, *J* = 9.4 Hz, 2F, *E*); IR (thin film) ν 2922, 2851, 1735, 1465, 1026 cm^{-1}; MS (EI): *m/z* (%) 227 ([M+2]$^+$, 37.5), 225 (M$^+$, 39.5), 145 (100), 103 (90.5); HRMS Calculated for $C_8H_{12}BrF_2$: 225.0090; Found: 225.0085.

(5-Bromo-5,5-difluoropent-3-en-1-yl)benzene (7b). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.35-7.18 (m, 5H), 6.31-6.24 (m, 1H), 5.94-5.76 (m, 1H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.72-2.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 140.7 (*Z*), 140.5 (*E*), 138.0 (t, *J* = 5.9 Hz, *Z*), 136.0 (t, *J* = 7.3 Hz, *E*), 128.58 (*E*), 128.56 (*Z*), 128.5 (*Z*), 128.4 (*E*), 127.4 (t, *J* = 23.3 Hz, *E*), 126.9 (t, *J* = 24.8 Hz, *Z*), 117.0 (t, *J* = 299.4 Hz, *E*), 116.8 (t, *J* = 300.8 Hz, *Z*), 34.8 (*Z*), 34.4 (*E*), 32.9 (*E*), 29.8 (*Z*); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -38.8 (d, *J* = 12.4 Hz, 2F, *Z*), -44.1 (d, *J* = 10.9 Hz, 2F, *E*); IR (thin film) ν 3028, 2928, 1667, 1497, 1454, 1230, 1103, 1076, 922, 746, 698 cm^{-1}; MS (EI): *m/z* (%) 262 ([M+2]$^+$, 1.42), 260 (M$^+$, 1.68), 181 (22.2), 91 (100); HRMS Calculated for $C_{11}H_{11}BrF_2$: 262.0012; Found: 262.0014.

(4-Bromo-4,4-difluorobut-2-en-1-yl)cyclohexane (7c). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.22-6.14 (m, 1H), 5.89-5.73 (m, 1H), 2.24-2.20 (m, 1H), 2.04-1.99 (m, 1H), 1.71-1.62 (m, 5H), 1.42-1.34 (m, 1H), 1.28-1.10 (m, 3H), 1.00-0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.4 (t, *J* = 5.8 Hz, *Z*), 135.9 (t, *J* = 7.3 Hz, *E*), 127.7 (t, *J* = 23.0 Hz, *E*), 126.7 (t, *J* = 24.4 Hz, *Z*), 117.0 (t, *J* = 299.4 Hz, *E*, *Z*), 39.1 (*E*), 37.9 (*Z*), 37.3 (*E*), 35.7 (*Z*), 33.0 (*E*, *Z*), 26.3 (*E*, *Z*), 26.22 (*Z*), 26.16 (*E*); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -38.2 (d, *J* = 12.4 Hz, 2F, *Z*), -43.8 (d, *J* = 9.4 Hz, 2F, *E*); IR (thin film) ν 2924, 2853, 1741, 1449, 1171, 922 cm^{-1}; MS (EI): *m/z* (%) 173 ([M-Br]$^+$, 11.0), 90 (49.7), 83 (100); HRMS Calculated for $C_{10}H_{15}BrF_2$: 252.0325; Found: 252.0320.

8-Bromo-8,8-difluorooct-6-en-1-ol (7d). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.23-6.17 (m, 1H), 5.90-5.72 (m, 1H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.37-2.12 (m, 2H), 1.61-1.54 (m, 3H), 1.51-1.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.1 (t, *J* = 5.9 Hz, *Z*), 136.8 (t, *J* = 7.3 Hz, *E*), 126.9 (t, *J* = 23.0 Hz, *E*), 126.5 (t, *J* = 23.7 Hz, *Z*), 117.1 (t, *J* = 299.0 Hz, *E*), 116.9 (t, *J* = 301.2 Hz, *Z*), 62.8 (*Z*), 62.7 (*E*), 32.4 (*E*), 32.2 (*Z*), 31.1 (*E*), 28.5 (*Z*), 28.2 (*Z*), 27.8 (*E*), 25.2 (*E*), 24.9 (*Z*); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -38.5 (d, *J* = 12.4 Hz, 2F, *Z*), -43.8 (d, *J* = 8.3 Hz, 2F, *E*); IR (thin film) ν 3310 (w), 2936, 2862, 1668, 1230, 1075, 921, 737, 634 cm^{-1}; MS (EI): *m/z* (%) 163 ([M-Br]$^+$, 2.32), 145 (19.6), 103 (100); HRMS Calculated for $C_8H_{11}BrF_2$ [M-H_2O]: 224.0012; Found: 224.0013.

3-(2-Bromo-2,2-difluoroethyl)-4-methyl-1-tosylpyrrolidine (14). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.66-3.32 (m, 2H), 3.06-2.74 (m, 2H), 2.59-1.71 (m, 7H), 0.73 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 143.65, 143.61, 133.9, 133.7, 129.8, 127.5, 127.4, 121.9 (t, *J* = 303.7 Hz), 121.6 (t, *J* = 303.4 Hz), 54.4, 53.8, 53.1 (t, *J* = 2.2 Hz), 50.4, 46.4 (t, *J* = 21.9 Hz), 42.9 (t, *J* = 21.9 Hz), 41.40, 41.38, 38.6, 37.4 (t, *J* = 2.2 Hz), 35.3, 21.5, 15.6, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -42.1-(-44.8) (m, 2F); IR (thin film) ν 2959, 2929, 1598, 1346, 1222, 1094, 1051, 929, 665, 592, 548 cm^{-1}; MS (EI): *m/z* (%) 383 ([M+2]$^+$, 31.4), 381 (M$^+$, 31.7), 228 (97.1), 226 (100), 91 (95.8); HRMS Calculated for $C_{14}H_{18}BrF_2NO_2S$: 381.0210; Found: 381.0208.

[2-D]-((3-Bromo-3,3-difluoropropyl)sulfonyl)benzene ([D]4S). White solid, m.p. 85-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91 (d, *J* = 6.8 Hz, 2H), 7.71-7.68 (m, 1H), 7.61-7.58 (m, 2H), 3.31-3.29 (m, 1H), 2.84-2.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.2, 134.5, 129.7, 128.1, 119.7 (t, *J* = 303.4 Hz), 50.9-50.4 (m), 37.8 (t, *J* = 24.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -45.2 (t, *J* = 12.2 Hz, 2F); IR (thin film) ν 3059, 1448, 1308, 1254, 1088, 1021, 734, 527 cm^{-1}; MS (EI): *m/z* (%) 301 ([M+2]$^+$, 10.2), 299 (M$^+$, 10.2), 220 (78.7), 77 (100); HRMS Calculated for $C_9H_8DBrF_2O_2S$: 298.9537; Found: 298.9541.

(5,5-Difluoropentyl)benzene (8). A mixture of **4a** (0.2 mmol, 52.4 mg, 1.0 equiv), activated zinc powder (1.0 mmol, 65 mg, 5.0 equiv) and 0.1 mL HCl (2M in water) in 2 mL DMF was stirred at 60 °C for 20 h and monitored by TLC. After the mixture was cooled to room temperature, saturated NaCl aqueous solution (10 mL) was added. Then the mixture was extracted with diethyl ether (3×5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (hexane) to afford compound **8**

(colorless liquid, 22.3 mg, 60 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30-7.11 (m, 5H), 5.78 (tt, *J* = 57.0, 4.6 Hz, 1H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.91-1.77 (m, 2H), 1.72-1.64 (m, 2H), 1.53-1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.0, 128.4, 125.9, 117.4 (t, *J* = 237.4 Hz), 35.7, 34.0 (t, *J* = 20.4 Hz), 30.9, 21.8 (t, *J* = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -115.8 (dt, *J* = 57.2, 17.7 Hz, 2F).

(5,5-Difluorooct-7-en-1-yl)benzene (9). To a mixture of **4a** (0.2 mmol, 52.4 mg, 1.0 equiv) and allytributyltin (1.0 mL, 9.8 mmol) in toluene (1 mL) was added catalytic amount of AIBN several times at 90 °C under argon atmosphere. After 2 h, saturated KF aq. and AcOEt (10 mL) was added to the reaction mixture and stirred at room temperature for 1 h. The organic layer was filtered and dried over anhydrous $MgSO_4$, then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane) to afford the desired product **9** (colorless liquid, 24.2 mg 53 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.82-5.72 (m, 1H), 5.19 (d, *J* = 4.0 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.57 (td, *J* = 16.4, 7.2 Hz, 2H), 1.89-1.76 (m, 2H), 1.68-1.61 (m, 2H), 1.55-1.49 (m, 2H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.2, 129.8, 128.4, 128.3, 125.8, 124.2 (t, *J* = 239.9 Hz), 120.0, 41.2 (t, *J* = 25.9 Hz), 35.8 (t, *J* = 25.2 Hz), 35.7, 31.1, 21.8 (t, *J* = 4.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -97.2 (m, *J* = 17.4 Hz, 2F); IR (thin film) ν 3084, 3027, 2932, 2859, 1646, 1496, 1454, 987, 925, 876, 746, 698 cm^{-1}; MS (EI): *m/z* (%) 224 ($[M]^+$, 53.7), 117 (26.7), 91 (100); HRMS Calculated for $C_{14}H_{18}F_2$: 224.1377; Found: 224.1380.

(5,5-Difluorooct-7-en-1-yl)benzene (10). Compound **4a** (0.2 mmol, 52.4 mg, 1.0 equiv) was added to a solution of TBAF (0.6 mmol, 1.0 equiv) in dry THF (1 mL) at room temperature under argon atmosphere. After 2 h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane) to afford the desired product **10** (colorless liquid, 32.4 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 (t, *J* = 7.4 Hz, 2H), 7.25-7.17 (m, 3H), 4.16 (dtd, *J* = 25.6, 7.8, 2.4 Hz, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.05-2.00 (m, 2H), 1.75-1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.4 (dd, *J* = 285.1, 282.9 Hz), 141.9, 128.42, 128.38, 125.9, 77.7 (t, *J* = 21.2 Hz), 35.1, 31.3 (t, *J* = 2.6 Hz), 21.8 (d, *J* = 4.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -89.2 (d, *J* = 47.8 Hz, 1F), -91.5 (dd, *J* = 47.8, 25.6 Hz, 1F).

(*Z*)-(5-Fluoropent-4-en-1-yl)benzene (11). A mixture of **4a** (0.2 mmol, 52.4 mg, 1.0 equiv), $CrCl_2$ (1.2 mmol, 74.2 mg, 6.0 equiv) and LiI (0.1 mmol, 13.4 mg, 0.5 equiv) in DMF (1 mL) was stirred at room temperature under an argon atmosphere for 4 h. Then HCl solution (2M, 1 mL) was added and the mixture was extracted with diethyl ether (3×5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane) to afford the desired product **11** (colorless liquid, 30.2 mg, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30-7.15 (m, 5H), 6.49 (ddt, *J* = 85.6, 4.4, 1.6 Hz, 1H), 4.77 (dtd, *J* = 43.2, 7.4, 4.8 Hz, 1H), 2.66 (t, *J* = 10.2 Hz, 2H), 2.20-2.11 (m, 2H), 1.77-1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 147.9 (d, *J* = 255.2 Hz), 142.2, 128.5, 128.3, 125.8, 110.6 (d, *J* = 5.1 Hz), 35.4, 31.0, 22.4 (d, *J* = 5.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -130.6 (dd, *J* = 85.7, 42.1 Hz, 1F); IR (thin film) ν 3027, 2927, 2859, 1672, 1496, 1454, 1030, 744, 699 cm^{-1}; MS (EI): *m/z* (%) 164 (M^+, 47.9), 117 (26.0), 91 (100); HRMS Calculated for $C_{11}H_{13}F$: 164.1001; Found: 164.0997.

(*Z*)-2-Fluoro-1,6-diphenylhex-2-en-1-ol (12). Benzaldehyde (0.4 mmol, 42.4 mg, 2.0 equiv) was added dropwise to a mixture of **4a** (0.2 mmol, 52.4 mg, 1.0 equiv), $CrCl_2$ (1.2 mmol, 74.2 mg, 6.0 equiv) and LiI (0.1 mmol, 13.4 mg, 0.5 equiv) in DMF (1 mL) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature for 4 h. Then H_2O (10 mL) was added and the mixture was extracted with diethyl ether (3×5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane:EtOAc = 5:1) to afford the desired product **12** (colorless liquid, 27.5 mg, 51 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44-7.25 (m, 7H), 7.20-7.16 (m, 3H), 5.20 (dd, *J* = 12.8, 4.0 Hz, 1H), 4.16 (dt, *J* = 37.2, 7.6 Hz, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.22-2.14 (m, 3H), 1.75-1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.8 (d, *J* = 254.5 Hz), 142.2, 139.7, 128.6, 128.5, 128.3, 126.7, 125.8, 107.3 (d, *J* = 13.9 Hz), 72.8 (d, *J* = 32.1 Hz), 35.5, 30.9, 23.1 (d, *J* = 4.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -122.7 (dd, *J* = 36.5, 12.0 Hz, 1F); IR (thin film) ν 3389 (w), 3027, 2929, 2859, 1707, 1603, 1495, 1453, 1016, 747, 699 cm^{-1}; MS (EI): *m/z* (%) 270 (M^+, 30.1), 107 (100), 91 (92.0); HRMS Calculated for $C_{18}H_{19}FO_4$: 270.1420; Found: 270.1423.

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27 We would like to thank one of the referees for the comment that green irradiation should be used for exciting Eosin Y. Indeed, the green LEDs (λ = 510-525 nm) were better than blue LEDs (λ = 460-470 nm) for this reaction, affording products **4** in slightly higher yields.