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Qing-Yu Lin, a Xiu-Hua Xua and Feng-Ling Qing*a,b

A visible light-induced selective hydrobromodifluoromethylation of alkenes using CF₂Br₂ 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 the 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 bonding³ and important intermediates for 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 precursors⁵ and gem-difluoroalkenes⁶ as well as transformation from CF₂Br-containing building blocks, require long synthetic sequences. Recently, 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 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 ions9c with (bromodifluoromethyl)trimethylsilane in the presence of an excess of bromide ions. Besides

these methods, the addition of dibromodifluoromethane (CF₂Br₂) to alkenes provides convenient access to a series of bromodifluoromethylated compounds. 10-13 As shown in Scheme 1, single electron transfer (SET) from a radical initiator to CF2Br2 generates the CF2Br 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 CF₂Br₂ and a hydrogen donor gave compounds 3¹¹ and 4¹² respectively. In the presence of other radical trap agents such as diphenyl diselenide, intermediate A was transformed into the selenobromodifluoromethylated 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.

To the best of our knowledge, only two reactions of the direct hydrobromodifluoromethylation of alkenes with CF_2Br_2 have been reported. 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 cyclo-

Scheme 1 The addition of CF₂Br₂ to alkenes.

^aKey Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai 200032, China. E-mail: flq@mail.sioc.ac.cn

^bCollege of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, China

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previous work

$$R = EWG$$
 $+ CF_2Br_2$
 $+$

Scheme 2 Hydrobromodifluoromethylation of alkenes

hexene yielded the hydrobromodifluoromethylated product in low yield along with byproducts (Scheme 2b). Both these methods suffered from a narrow substrate scope. Recently, visible light photoredox catalysis has emerged as an efficient and eco-friendly tool in organic synthesis and has been applied in the fluoroalkylation of organic compounds. As part of our ongoing research on photocatalytic fluoroalkylation reactions, herein we disclose the selective hydrobromodifluoromethylation of alkenes with $\mathrm{CF}_2\mathrm{Br}_2$ 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

Table 1 Optimization of reaction conditions

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	$Ru(bpy)_3Cl_2\cdot 6H_2O(3)$	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_3N	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 ¹⁹F 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.

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, CH₂Cl₂, Et₂O, dioxane, CH₃CN, 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 Y¹⁸ 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 the 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 CF₂Br₂ was totally consumed. Consequently, compound 4a was formed in 81% yield when another portion of CF₂Br₂ was added (entry 8). Finally, the addition of additives, including Et₃N and KHCO₃, 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 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, phosphine oxides, ethers, sulfones, and halides. Substrates bearing fluoro, chloro, and bromo substituents on the arene rings were also compatible. Heterocyclic substrates, 1p and 1q, were smoothly converted into the desired products. α,β -Unsaturated ester 1r and α,β -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 vinclozolin **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 KHCO₃ under visible light irradiation provided a mixture of the E and Z alkenyl- CF_2Br compounds 7a-d in moderate yields. ¹⁹

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

Table 2 Substrate scope of photocatalytic hydrobromodifluoromethylation of alkenes^a

^a Reaction conditions: 1 (0.5 mmol), CF₂Br₂ (3.0 mmol), eosin Y (0.025 mmol), KHCO₃ (0.5 mmol), THF (15.0 mL), visible light, rt, under N₂, 10 h, isolated yields. ^b Eosin Y (0.05 mmol).

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 CrCl₂ generated the nucleophilic α-fluorovinylchromium intermediate,23 which subsequently reacted with HCl or PhCHO to give (Z)-fluoroalkene 11 and (Z)- β -fluoroallylic alcohol 12 respectively in high stereoselectivities.

To gain insight into the reaction mechanism, a radical clock 13 was subjected 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 CF2Br radical was involved in this visible lightinduced hydrobromodifluoromethylation of alkenes. The reac-

Scheme 3 Hydrobromodifluoromethylation of compounds 1w-y.

Scheme 4 Hydrobromodifluoromethylation of alkynes.

Scheme 5 Hydrobromodifluoromethylation of alkynes.

tion of 1s with CF2Br2 in d8-THF exclusively gave the deuterated product [D]4s in 81% yield, which indicated that THF served as the hydrogen atom source (Scheme 6b). What is more, Stern-Volmer studies showed that CF2Br2 exhibited significant fluorescence quenching of eosin Y* (see the ESI†). This result suggested that electron transfer occurred from eosin Y* to CF2Br2 first. On the basis of these experimental results and the literature reports, 18 a plausible mechanism for the hydrobromodifluoromethylation is depicted in Scheme 6c. Initially, the excitation of eosin Y with visible light produced

$$\begin{array}{c} \text{visible light} \\ \text{Eosin Y (5 mol \%)} \\ \text{Ts} \\ \textbf{13} \\ \text{Visible light} \\ \text{Eosin Y (5 mol \%)} \\ \text{HCO}_3, \text{THF, rt} \\ \textbf{1s} \\ \text{CF}_2\text{Br}_2 \\ \text{Visible light} \\ \text{Eosin Y (5 mol \%)} \\ \text{KHCO}_3, d_8\text{-THF, rt} \\ \text{Is} \\ \text{CF}_2\text{Br}_2 \\ \text{Visible light} \\ \text{EY} \\ \text{CF}_2\text{Br} \\ \text{CF}_2\text{Br$$

Scheme 6 Mechanistic investigations.

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 why eosin Y is selected for this transformation. Its high reduction potential (-1.60 V vs. SCE) facilitates the generation of the CF₂Br 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 KHCO₃ benefits 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 $\bf 4a$ into other fluorinated compounds.

Experimental

General information

¹H NMR (TMS as the internal standard) and ¹⁹F NMR spectra (CFCl₃ as the outside standard and low field is positive) were recorded on a 400 MHz spectrometer. ¹³C NMR was recorded on a 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–q²⁵ and 1w²⁶ 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%) and substrates (0.5 mmol, 1.0 equiv.). Then a solution of CF₂Br₂ (420 mg, 4.0 equiv., 2.0 mmol) in THF (10 mL, 2.0 mol L⁻¹) was added to the reaction flask by using a syringe. The flask was sealed with 3M vinyl electrical tape, and 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 ($\lambda = 460-470$ nm).²⁷ The mixture was stirred under a nitrogen atmosphere and irradiated by blue LEDs for 5 h. After cooling in an ice-water bath, KHCO₃ (50 mg, 1.0 equiv., 0.5 mmol) and the second portion of CF₂Br₂ (210 mg, 2.0 equiv., 1.0 mmol) in THF (5 mL, 2.0 mol L^{-1}) 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. ^1H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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 $\text{C}_{11}\text{H}_{12}\text{Br}_2\text{F}_2$: 339.9274; found: 339.9278.

(5-Bromo-5,5-difluoropentyl)benzene (4a). Colorless liquid.
¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₁H₁₃BrF₂: 262.0169; found: 262.0173.

(3-Bromo-3,3-difluoropropyl)cyclohexane (4b). Colorless liquid. ${}^{1}H$ NMR (400 MHz, CDCl₃) 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, CDCl₃) δ ppm 123.6 (t, J = 303.4 Hz), 42.0 (t, J = 20.8 Hz), 36.7, 33.0, 31.2 (t, J = 20.8 Hz)2.6 Hz), 26.4, 26.1; 19 F NMR (376 MHz, CDCl₃) 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 C₉H₁₅BrF₂: 240.0325; found: 240,0319.

1,9-Dibromo-1,1-difluorononane (4c). Colorless ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -43.4 (t, J = 13.5 Hz, 2F); IR (thin film) ν 2934, 2857, 1465, 1198, 1106, 910, 635 cm⁻¹; MS (EI): m/z (%) 243 ([M + 2]⁺, 6.7), 241 (M⁺, 6.8), 161 (100), 119 (53.9); HRMS calculated for C₉H₁₆BrF₂: 241.0403; found: 241.0400.

11-Bromo-11,11-difluoroundecan-1-ol (4d). Colorless liquid. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -43.3 (t, J =14.3 Hz, 2F); IR (thin film) ν 3349 (w) 2928, 2856, 1466, 1198, 1086, 911 cm⁻¹; MS (EI): m/z (%) 268 ([M - 18]⁺, 2.61), 133 (35.6), 69 (97.0), 55 (100); HRMS calculated for C₁₁H₁₉BrF₂ $[M - H_2O]$: 268.0638; found: 268.0634.

12-Bromo-12,12-difluorododecanal (4e). Colorless liquid. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -43.3 (t, J = 13.7 Hz, 2F); IR (thin film) ν 2928, 2856, 1710, 1199, 911 cm⁻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, CDCl₃) δ ppm 2.37–2.27 (m, 4H), 1.66-1.55 (m, 4H), 1.36-1.24 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -43.3 (t, J = 14.3Hz, 2F); IR (thin film) ν 3050, 2926, 2855, 1710, 1200, 911 cm⁻¹; MS (EI): m/z (%) 314 ([M]⁺, 2.0), 254 (6.3), 73 (73.6), 60 (100); HRMS calculated for C₁₂H₂₁BrF₂O₂: 314.0693; found:

(4-Bromo-4,4-difluorobutyl)diphenylphosphine oxide (4g). White solid, m.p. 80–83 °C. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -43.7 (t, J =13.5 Hz, 2F); ³¹P NMR (162 MHz, CDCl₃) 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 C₁₆H₁₆BrF₂OP: 353.0118; found: 353.0101.

1-Bromo-1,1-difluoroundecan-4-ol (4h). Colorless liquid. 1 H NMR (400 MHz, CDCl₃) 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, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, 4H), 1.30-1.25 (m, 9H), 0.87 (t, I = 1.47-1.40 (m, I =7.0 Hz, 3H); 13 C NMR (100 MHz, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) 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. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₃H₁₅BrF₂O₂: 320.0223; found: 320.0222.

Ethyl 4-((6-bromo-6,6-difluorohexyl)oxy)benzoate (4j). White solid, m.p. 38-40 °C. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₅H₁₉BrF₂O₃: 364.0486; found: 364.0484.

1-((6-Bromo-6,6-difluorohexyl)oxy)-4-nitrobenzene (4k). Colorless liquid. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ¹³F NMR (376 MHz, CDCl₃) 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 C₁₄H₁₆BrF₂NO: 331.0383; found: 331.0378.

1-(4-((6-Bromo-6,6-difluorohexyl)oxy)phenyl)ethanone (4m). Colorless liquid. 1 H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) δ ppm –43.4 (t, J = 13.5 Hz, 2F); IR (thin film) ν 2943, 2869, 1677, 1601, 1256, 1172, 835, 591 cm $^{-1}$; MS (EI): m/z (%) 333 ([M – CH₃] $^{+}$, 10.4), 269 (7.0), 121 (100); HRMS calculated for C₁₄H₁₆BrF₂O₂: 333.0302; found: 333.0305.

1-Bromo-4-((7-bromo-7,7-difluoroheptyl)oxy)-2-chlorobenzene (4n). Colorless liquid. 1 H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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 C₁₃H₁₅Br₂ClFO: 417.9146; found: 417.9147.

7-Bromo-7,7-difluoroheptyl-4-fluorobenzoate (4o). Colorless liquid. 1 H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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 $C_{16}H_{17}BrF_{2}O_{3}$: 374.0329; found: 374.0327.

2-(6-Bromo-6,6-difluorohexyl)isoindoline-1,3-dione (4q). Colorless liquid. 1 H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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 C₁₄H₁₄BrF₂NO₂: 345.0176; found: 345.0178.

Benzyl 4-bromo-4,4-difluorobutanoate (4r). Colorless liquid.
¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 (s, 5H), 5.15 (s, 2H), 2.80–2.67 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₁H₁₁BrF₂O₂: 291.9910; found: 291.9913.

((3-Bromo-3,3-difluoropropyl)sulfonyl)benzene (4s). White solid, m.p. 78–79 °C. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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 C₉H₉BrF₂O₂S: 297.9475; found: 297.9480.

4-Bromo-4,4-difluoro-2-phenylbutanoic acid (4t). White solid, m.p. 64–66 °C. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₂H₂₀BrF₂NO₂: 327.0645; found: 327.0641.

2-(Bromodifluoromethyl)-1,4-dioxane (4v). Colorless liquid. 1 H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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 C₅H₇BrF₂O₂: 215.9597; found: 215.9605.

(S)-5-Bromo-5,5-difluoropentyl-2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (4w). Colorless liquid. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₉H₂₆BrF₂NO₄: 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. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₃H₁₀BrCl₂F₂NO₃: 414.9189; found: 414.9192.

(2R,6aS,12aS)-2-((R)-4-Bromo-4,4-difluorobutan-2-yl)-8,9dimethoxy-1,2,12,12a-tetrahydrochromeno[3,4-b]furo[2,3-h]chromen-6(6aH)-one (4y). Yellow liquid. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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 = 20.8Hz), 44.6, 35.15, 35.13, 34.5, 29.8, 29.1, 15.6, 14.2; ¹⁹F NMR (376 MHz, CDCl₃) 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 C₂₄H₂₃BrF₂O₆: 524.0646; found: 526.0644.

1-Bromo-1,1-difluorooct-2-ene (7a). Colorless liquid. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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 C₈H₁₂BrF₂: 225.0090; found: 225.0085.

(5-Bromo-5,5-difluoropent-3-en-1-yl)benzene (7b). Colorless liquid. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₁H₁₁BrF₂: 262.0012; found: 262.0014.

(4-Bromo-4,4-difluorobut-2-en-1-yl)cyclohexane (7c). Colorless liquid. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -38.2 (d, J = 12.4Hz, 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. ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) δ ppm 139.1 (t, J = 5.9 Hz, Z), 136.8 (t, J = 7.3 Hz, E), 126.9 (t, J = 1.023.0 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); ¹⁹F NMR (376 MHz, CDCl₃) 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. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₄H₁₈BrF₂NO₂S: 381.0210; found: 381.0208.

[2-D]-((3-bromo-3,3-difluoropropyl)sulfonyl)benzene ([D]4S). White solid, m.p. 85–87 °C. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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); ¹°F NMR (376 MHz, CDCl₃) 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 C₉H₈DBrF₂O₂S: 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 (2 M 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 MgSO4 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). ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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 allyltributyltin (1.0 mL, 9.8 mmol) in toluene (1 mL) was added catalytic amounts of AIBN several times at 90 °C under an 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 MgSO4, 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, CDCl₃) 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 = 12.0 Hz, 1H) 16.4, 7.2 Hz, 2H), 1.89-1.76 (m, 2H), 1.68-1.61 (m, 2H), 1.55–1.49 (m, 2H); $^{13}\mathrm{C}$ 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);

¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₄H₁₈F₂: 224.1377; found: 224.1380.

(5,5-Difluorooct-7-en-1-vl)benzene (10). Compound (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 an 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%). ¹H NMR (400 MHz, CDCl₃) 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, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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.), CrCl₂ (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 (2 M, 1 mL) was added and the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over anhydrous MgSO4 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%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.30–7.15 (m, 5H), 6.49 (ddt, J = 85.6, 4.4, 1.6 Hz, 1H, 4.77 (dtd, <math>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);¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -130.6 (dd, J = 85.7, 42.1 Hz, 1F; IR (thin film) $\nu 3027, 2927, 2859, 1672,$ 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.), CrCl₂ (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 an argon atmosphere. The reaction mixture was stirred at room temperature for 4 h. Then H₂O (10 mL) was added and the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over anhydrous MgSO4 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, CDCl₃) 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 = 12.8) 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, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) 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 C₁₈H₁₉FO₄: 270.1420; found: 270.1423.

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Notes and references

- 1 (a) M. Cametti, B. Crousse, P. Metrangolo, R. Milani and G. Resnati, Chem. Soc. Rev., 2012, 41, 31; (b) Y. Li, Acc. Chem. Res., 2012, 45, 723; (c) R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, Chem. Soc. Rev., 2011, 40, 3496; (d) W. K. Hagmann, J. Med. Chem., 2008, 51, 4359; (e) D. O'Hagan, Chem. Soc. Rev., 2008, 37, 308; (f) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, Chem. Soc. Rev., 2008, 37, 320; (g) K. Muller, C. Faeh and F. Diederich, Science, 2007, 317, 1881.
- 2 (a) X. Yang, T. Wu, R. J. Phipps and F. D. Toste, Chem. Rev., 2015, **115**, 826; (b) X.-H. Xu, K. Matsuzaki and N. Shibata, Chem. Rev., 2015, 115, 731; (c) C. Ni, M. Hu and J. Hu, Chem. Rev., 2015, 115, 765; (d) X. Liu, C. Xu, M. Wang and Q. Liu, Chem. Rev., 2015, 115, 683; (e) B. Lantaño, M. R. Torviso, S. M. Bonesi, S. Barata-Vallejo and Coord. Chem. 2015, Postigo, Rev.,(f) J. Charpentier, N. Früh and A. Togni, Chem. Rev., 2015, 115, 650; (g) C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, Chem. Rev., 2015, 115, 1847; (h) N. Santschi and R. Gilmour, Angew. Chem., Int. Ed., 2014, 53, 11414; (i) E. Merino and C. Nevado, Chem. Soc. Rev., 2014, 43, 6598; (j) L. Chu and F.-L. Qing, Acc. Chem. Res., 2014, 47, 1513; (k) D. L. Browne, Angew. Chem., Int. Ed., 2014, 53, 1482; (l) T. Liang, C. N. Neumann and T. Ritter, Angew. Chem., Int. Ed., 2013, 52, 8214.
- 3 (a) S. Z. Zhu, C. H. Xing, W. Xu, G. F. Jin and Z. T. Li, Cryst. Growth Des., 2004, 4, 53; (b) P. Cardillo, E. Corradi, A. Lunghi, S. V. Meille, M. T. Messina, P. Metrangolo and G. Resnati, Tetrahedron, 2000, 56, 5535; (c) E. Corradi, S. V. Meille, M. T. Messina, P. Metrangolo and G. Resnati, Tetrahedron Lett., 1999, 40, 7519; (d) A. Farina, S. V. Meille, M. T. Messina, P. Metrangolo, G. Resnati and G. Vecchio, Angew. Chem., Int. Ed., 1999, 38, 2433.
- 4 (a) Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, J. Am. Chem. Soc., 2014, 136, 1230; (b) B. Gao, Y. Zhao, M. Hu, C. Ni and J. Hu, Chem. - Eur. J., 2014, 20, 7803; (c) S. Ou, M. Jiang and J.-T. Liu, Tetrahedron, 2013, 69, 10820;

- (d) H. Martinez, A. Rebeyrol, T. B. Nelms and W. R. Dolbier Jr., J. Fluorine Chem., 2012, 135, 167.
- 5 (a) T.-P. Yang, Q. Li, J.-H. Lin and J.-C. Xiao, Chem. Commun., 2014, 50, 1077; (b) V. V. Levin, A. A. Zemtsov, M. I. Struchkova and A. D. Dilman, Org. Lett., 2013, 15, 917; (c) K. M. Borys, M. D. Korzyński and Z. Ochal, Tetrahedron Lett., 2012, 53, 6606; (d) A. Suzuki, M. Mae, H. Amii and K. Uneyama, J. Org. Chem., 2004, 69, 5132.
- 6 (a) C. Ehm, F. A. Akkerman and D. Lentz, J. Fluorine Chem., 2010, 131, 1173; (b) T. B. Nguyen, A. Martel, R. Dhal and G. Dujardin, Synlett, 2009, 2492; (c) Y. Guo, K. Fujiwara, H. Amii and K. Uneyama, J. Org. Chem., 2007, 72, 8523; (d) S. Higashiya, W. J. Chung, D. S. Lim, S. C. Ngo, W. H. Kelly IV, P. J. Toscano and J. T. Welch, J. Org. Chem., 2004, 69, 6323.
- 7 (a) M.-C. Belhomme, D. Dru, H.-Y. Xiong, D. Cahard, T. Besset, T. Poisson and X. Pannecoucke, Synthesis, 2014, 1859; (b) H. Jiang, S. Yuan, Y. Cai, W. Wan, S. Zhu and J. Hao, J. Fluorine Chem., 2012, 133, 167; (c) H. Jiang, L. Sun, S. Yuan, W. Lu, W. Wan, S. Zhu and J. Hao, Tetrahedron, 2012, **68**, 2858; (d) S. N. Tverdomed, J. Kolanowski, E. Lork and G.-V. Röschenthaler, Tetrahedron, 2011, 67, 3887.
- 8 (a) B. Pégot, C. Urban, P. Diter and E. Magnier, Eur. J. Org. Chem., 2013, 7800; (b) G. Liu, X. Wang, X. Lu, X.-H. Xu, E. Tokunaga and N. Shibata, ChemistryOpen, 2012, 1, 227; (c) G. Liu, S. Mori, X. Wang, S. Noritake, E. Tokunaga and N. Shibata, New J. Chem., 2012, 36, 1769; (d) C.-P. Zhang, H.-P. Cao, Z.-L. Wang, C.-T. Zhang, Q.-Y. Chen and J.-C. Xiao, Synlett, 2010, 1089.
- 9 (a) Y. Zhao, B. Gao and J. Hu, J. Am. Chem. Soc., 2012, 134, 5790; (b) M. D. Kosobokov, V. V. Levin, M. I. Struchkova and A. D. Dilman, Org. Lett., 2014, 16, 3784; (c) A. V. Tsymbal, M. D. Kosobokov, V. V. Levin, M. I. Struchkova and A. D. Dilman, J. Org. Chem., 2014, 79, 7831.
- 10 J. Ignatowska and W. Dmowski, J. Fluorine Chem., 2007, 128, 997.
- 11 (a) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner and C. R. J. Stephenson, J. Am. Chem. Soc., 2012, 134, 8875; (b) X.-C. Guo and Q.-Y. Chen, J. Fluorine Chem., 1998, 88, 63; (c) F.-H. Wu, B.-N. Huang, L. Lu and W.-Y. Huang, J. Fluorine Chem., 1996, 80, 91; (d) C.-M. Hu and J. Chen, J. Fluorine Chem., 1994, 69, 79; (e) J. Gonzalez, C. J. Foti and Elsheimer, J. Org. Chem., 1991, **56**, (f) S. Elsheimer, D. K. Slattery, M. Michael, J. Weeks and K. Topoleski, J. Org. Chem., 1989, 54, 3992.
- 12 (a) C.-M. Hu and J. Chen, J. Chem. Soc., Chem. Commun., 1993, 72; (b) S.-H. Wu, W.-Z. Liu and X.-K. Jiang, J. Org. Chem., 1994, 59, 854.
- 13 H. Asai and K. Uneyama, Chem. Lett., 1995, 24, 1123.
- 14 (a) D. A. Nicewicz and T. M. Nguyen, ACS Catal., 2014, 4, 355; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, Chem. Rev., 2013, 113, 5322; (c) J. Xuan and W.-J. Xiao, Angew. Chem., Int. Ed., 2012, 51, 6828; (d) J. M. R. Narayanam and C. R. J. Stephenson, Chem. Soc. Rev., 2011, 40, 102; (e) T. P. Yoon, M. A. Ischay and J. Du, Nat. Chem., 2010, 2, 527.

- 15 (a) P. Xu, A. Abdukader, K. Hu, Y. Cheng and C. Zhu, Chem. Commun., 2014, 50, 2308; (b) J. Xie, X. Yuan, A. Abdukader, C. Zhu and J. Ma, Org. Lett., 2014, 16, 1768; (c) S. H. Oh, Y. R. Malpani, N. Ha, Y.-S. Jung and S. B. Han, Org. Lett., 2014, 16, 1310; (d) T. Koike and M. Akita, Top. Catal., 2014, 57, 967; (e) N. Iqbal, J. Jung, S. Park and E. J. Cho, Angew. Chem., Int. Ed., 2014, 53, 539; (f) G. Dagousset, A. Carboni, E. Magnier and G. Masson, Org. Lett., 2014, 16, 4340; (g) Y. Cheng, X. Yuan, H. Jiang, R. Wang, J. Ma, Y. Zhang and S. Yu, Adv. Synth. Catal., 2014, 356, 2859; (h) D. Cantillo, O. de Frutos, J. A. Rincón, C. Mateos and C. O. Kappe, Org. Lett., 2014, 16, 896; (i) Y. Yasu, T. Koike and M. Akita, Chem. Commun., 2013, 49, 2037; (j) Y. Yasu, T. Koike and M. Akita, Org. Lett., 2013, 15, 2136; (k) D. J. Wilger, N. J. Gesmundo and D. A. Nicewicz, Chem. Sci., 2013, 4, 3160; (1) E. Kim, S. Choi, H. Kim and E. J. Cho, Chem. - Eur. J., 2013, 19, 6209; (m) S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, Wheelhouse, G. Rassias, M. Médebielle V. Gouverneur, J. Am. Chem. Soc., 2013, 135, 2505; (n) Y. Yasu, T. Koike and M. Akita, Angew. Chem., Int. Ed., 2012, 51, 9567; (o) N. Iqbal, S. Choi, E. Ko and E. J. Cho, Tetrahedron Lett., 2012, 53, 2005; (p) Y. Ye and M. S. Sanford, J. Am. Chem. Soc., 2012, 134, 9034; (q) D. A. Nagib and D. W. C. MacMillan, *Nature*, 2011, 480, 224; (r) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, J. Am. Chem. Soc., 2009, 131, 10875.
- 16 (a) X.-J. Tang and W. R. Dolbier, Angew. Chem., Int. Ed., 2015, 54, 4246; (b) C. Yu, N. Iqbal, S. Park and E. J. Cho, Chem. Commun., 2014, 50, 12884; (c) W. Li, X. Zhu, H. Mao, Z. Tang, Y. Cheng and C. Zhu, Chem. Commun., 2014, 50, 7521; (d) L. Wang, X.-J. Wei, W.-L. Jia, J.-J. Zhong, L.-Z. Wu and Q. Liu, Org. Lett., 2014, 16, 5842; (e) X. Sun and S. Yu, Org. Lett., 2014, 16, 2938; (f) Y.-M. Su, Y. Hou, F. Yin,

- Y.-M. Xu, Y. Li, X. Zheng and X.-S. Wang, *Org. Lett.*, 2014, **16**, 2958; (*g*) J. Jung, E. Kim, Y. You and E. J. Cho, *Adv. Synth. Catal.*, 2014, **356**, 2741; (*h*) M. Rueda-Becerril, O. Mahé, M. Drouin, M. B. Majewski, J. G. West, M. O. Wolf, G. M. Sammis and J.-F. Paquin, *J. Am. Chem. Soc.*, 2014, **136**, 2637.
- 17 (a) Q.-Y. Lin, X.-H. Xu and F.-L. Qing, J. Org. Chem., 2014, 79, 10434; (b) Q. Lin, L. Chu and F.-L. Qing, Chin. J. Chem., 2013, 31, 885.
- 18 D. P. Hari and B. Konig, Chem. Commun., 2014, 50, 6688.
- 19 The ratios of *E/Z* isomers of compounds **7a-d** were determined by the ¹⁹F NMR of isolated products. The *E* isomers were assigned according to a recent literature: Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 1230.
- 20 S. Peng, F.-L. Qing, Y.-Q. Li and C.-M. Hu, *J. Org. Chem.*, 2000, **65**, 694.
- 21 A. Suzuki, M. Mae, H. Amii and K. Uneyama, J. Org. Chem., 2004, 69, 5132.
- 22 P. Tarrant and E. C. Stump, J. Org. Chem., 1964, 29, 1198.
- 23 T. Nihei, S. Yokotani, T. Ishihara and T. Konno, *Chem. Commun.*, 2014, 50, 1543.
- 24 For the oxidation and reduction potentials of typical photocatalysts, see: M. Reckenthäler and A. G. Griesbeck, *Adv. Synth. Catal.*, 2013, 355, 2727.
- 25 B. H. Lipshutz, S. Ghorai and W. W. Y. Leong, *J. Org. Chem.*, 2009, 74, 2854.
- 26 J. E. Enholm, T. Low, D. Cooper and I. Ghivirija, *Tetrahedron*, 2012, **68**, 6920.
- 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 ($\lambda = 510-525$ nm) were better than blue LEDs ($\lambda = 460-470$ nm) for this reaction, affording products 4 in slightly higher yields.