Visible light-induced selective hydrobromodifluoromethylation of alkenes with dibromodifluoromethane†

Qing-Yu Lin,a Xiu-Hua Xua and Feng-Ling Qings,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 fluoride 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,7 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 bromodifluoromethylolation of aldehydes9b 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,13 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 CF2Br2 have been reported. Hu reported the hydrobromodifluoromethylation of electron-deficient alkenes initiated by a CrCl3/Fe bimetal redox system (Scheme 2a).12a Wu and co-workers disclosed that the Zn-induced addition of CF2Br2 to cyclo-

† Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data for all new compounds. See DOI: 10.1039/c5ob01302j
hexene yielded the hydrobromodifluoromethylated product in low yield along with byproducts (Scheme 2b).12,13 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 synthesis14 and has been applied in the fluoroalkylation of organic compounds.15,16 As part of our ongoing research on photocatalytic fluoroalkylation reactions,17 herein we disclose the selective hydrobromodifluoromethylation of alkenes with CF$_2$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 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$_2$Cl$_2$, Et$_2$O, dioxane, CH$_3$CN, 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 CF$_2$Br$_2$ was totally consumed. Consequently, compound 4a was formed in 81% yield when another portion of CF$_2$Br$_2$ 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 moderate to excellent yields (Table 2). A wide range of functional groups were tolerated, including alkylic 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. $\alpha,\beta$-Unsaturated ester 1r and $\alpha,\beta$-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$_2$Br$_2$ in the presence of eosin Y (10 mol%) and KHCO$_3$ under visible light irradiation provided a mixture of the E and Z alkylidene-CF$_2$Br 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.
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-difluoromethylated 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 \(\alpha\)-fluoro-vinylchromium intermediate,\(^{23}\) which subsequently reacted with HCl or PhCHO to give \((Z)\)-fluoroalkene 11 and \((Z)\)-\(\beta\)-fluoro-allylic 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 CF\(_2\)Br radical was involved in this visible light-induced hydrobromodifluoromethylation of alkenes. The reaction of 1s with CF\(_2\)Br\(_2\) 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 is more, Stern–Volmer studies showed that CF\(_2\)Br\(_2\) exhibited significant fluorescence quenching of eosin Y* (see the ESI†). This result suggested that electron transfer occurred from eosin Y* to CF\(_2\)Br\(_2\) 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

### Table 2: Substrate scope of photocatalytic hydrobromodifluoromethylation of alkenes

<table>
<thead>
<tr>
<th>Reaction conditions: 1 (0.5 mmol), CF(_2)Br(_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).</th>
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<tbody>
<tr>
<td>4a, 74%</td>
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<tr>
<td>4b, 76%</td>
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<tr>
<td>4c, 83%</td>
</tr>
<tr>
<td>4d: R = OH, 82%</td>
</tr>
<tr>
<td>4e: R = CHO, 78%</td>
</tr>
<tr>
<td>4f: R = CO(_2)H, 71%</td>
</tr>
<tr>
<td>4g, 67%</td>
</tr>
<tr>
<td>4h, 46%</td>
</tr>
<tr>
<td>4i: R = CHO, n = 5, 82%</td>
</tr>
<tr>
<td>4j: R = CO(_2)Et, n = 5, 79%</td>
</tr>
<tr>
<td>4k: R = NO(_2), n = 5, 83%</td>
</tr>
<tr>
<td>4l: R = CN, n = 6, 79%</td>
</tr>
<tr>
<td>4m: R = Ac, n = 6, 73%</td>
</tr>
<tr>
<td>4n, 80%</td>
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<tr>
<td>4o, 83%</td>
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<tr>
<td>4p, 51%</td>
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<tr>
<td>4q, 79%</td>
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<tr>
<td>4r, 41%</td>
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<tr>
<td>4s, 42%</td>
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<tr>
<td>4t, 90%</td>
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<tr>
<td>4u, 46%</td>
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<tr>
<td>4v, 47%</td>
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</table>

\(^{a}\) Reaction conditions: 1 (0.5 mmol), CF\(_2\)Br\(_2\) (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).
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 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–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%) and substrates (0.5 mmol, 1.0 equiv.). Then a solution of CF$_2$Br$_2$ (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 (λ = 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, KHCO$_3$ (50 mg, 1.0 equiv., 0.5 mmol) and the second portion of CF$_2$Br$_2$ (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. $^1$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 (t, 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$_2$F$_2$: 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 = 7.0 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,

Conclusions

In conclusion, we have developed a photocatalytic hydrobromodifluoromethylation of unactivated alkenes with CF$_2$Br$_2$ 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.
1-Bromo-4,4-bis-(chloromethyl)benzene (5c). Colorless liquid. 1H NMR (400 MHz, CDCl3) δ ppm 7.40 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H) 4.04 (t, J = 6.2 Hz, 2H), 2.42–2.31 (m, 2H), 1.72–1.65 (m, 2H), 1.59–1.53 (m, 2H), 1.53–1.45 (m, 2H), 1.31–1.09 (m, 5H), 0.96–0.86 (m, 2H); 13C NMR (100 MHz, CDCl3) δ ppm 155.7 (s, 3H), 137.2, 127.7, 125.5, 120.2, 118.9, 116.2, 114.1, 113.7, 109.8, 95.2, 46.6, 40.6, 33.9, 33.8, 29.2, 29.1, 19.3 (m, 2H), 22.1; 3F NMR (376 MHz, CDCl3) δ ppm −43.3 (t, J = 13.5 Hz, 2F); IR (thin film) ν 2937, 2825, 2856, 2856, 1710, 1199, 1191 cm−1; MS (EI): m/z (%) 286 (M−18)2, 269 (M−27)3, 251 (M−36)3, 233 (M−45)3, 215 (M−54)3, 197 (M−63)3, 179 (M−81)3, 161 (M−90)3, 143 (M−108)3, 125 (M−117)3, 107 (M−126)3, 89 (M−144)3, 71 (M−162)3, 53 (M−180)3, 35 (M−202)3, 17 (M−324)3; HRMS calculated for C15H13Cl2F2: 286.0608; found: 286.0600.

4-((2-Bromo-6,6-difluorohexyl)oxy)benzaldehyde (6i). Colorless solid. 1H NMR (400 MHz, CDCl3) δ ppm 9.90 (d, J = 8.8 Hz, 2H), 8.06 (dd, 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); 13C 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 (m, 2H), 28.7, 25.0, 23.7 (t, J = 3.0 Hz); 13F NMR (376 MHz, CDCl3) δ ppm −43.5 (t, J = 13.5 Hz, 2F); IR (thin film) ν 2937, 2825, 2856, 2856, 1710, 1199, 1191 cm−1; MS (EI): m/z (%) 268 (M−18)2, 250 (M−26)3, 232 (M−34)3, 214 (M−42)3, 196 (M−50)3, 178 (M−68)3, 160 (M−86)3, 142 (M−104)3, 124 (M−122)3, 106 (M−140)3, 88 (M−158)3, 70 (M−176)3, 52 (M−194)3, 34 (M−212)3, 16 (M−334)3; HRMS calculated for C15H13BrF2O2: 268.0638; found: 268.0641.

4,4′-(Diethylidinitramino)biphenyl (4h). White solid. m.p. 88–90 °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); IR (thin film) ν 3056, 2941, 1438, 1186, 1120, 718, 695, 543, 509 cm−1; MS (EI): m/z (%) 355 ([M + 2]3, [M]3, [M−1]2, [M−2]3, 0.29), 293 (100), 201 (51.7); HRMS calculated for C24H20BrF2N2O2: 353.0118; found: 353.0101.
753 cm$^{-1}$; MS (EI): m/z (%) 337 (M$^+$, 22.3), 238 (12.8), 139 (100); HRMS calculated for C$_{12}$H$_{14}$BrF$_2$NO$_2$: 337.0125; found: 337.0121.

4-(7-Bromo-7-difluoroheptyloxy)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, 86.1, 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 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$_{14}$H$_{17}$BrF$_2$O$_3$: 374.0329; found: 374.0327.

2-(6-Bromo-6-difluoroethyl)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 = 13.7 Hz, 2F); IR (thin film) ν 2944, 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$_{10}$H$_{16}$BrF$_2$O$_3$: 345.0176; found: 345.0178.

Benzyl 4-bromo-4,4-difluorobutanoate (4t). 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$_{10}$H$_{11}$BrF$_2$O$_2$: 291.9910; found: 291.9913.

((3-Bromo-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$^+$], 42.1), 219 (40.3), 77 (100); HRMS calculated for C$_{10}$H$_{11}$BrF$_2$O$_2$: 297.9475; found: 297.9480.

Benzyl 4,4-difluoro-2-propionate 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$_{10}$F$_2$O$_2$: 277.9754; found: 277.9757.

tert-Butyl 4-(2-bromo-2,2-difluoroethyl)pipеридине-1-carboxy-late (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; 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 C₁₉H₂₀BrF₂NO₄: 527.0645; found: 527.0644.

2-(Bromodifluoromethyl)-1,4-dioxane (4v). Colorless liquid. 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); ¹³C NMR (376 MHz, CDCl₃) δ ppm −56.5(−58.6) (m, 2F); IR (thin film) ν 2975, 2921, 2866, 1726, 1453, 1121, 1048, 951, 903, 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 C₁₉H₂₀BrF₂O₂: 315.9597; found: 315.9605.

(S)-5-Bromo-5,5-difluoropentyl-2-(tert-butoxycarbonyl)aminooxazolidine-2,4-dione (4w). Colorless liquid. δ ppm 3.18 (m, 1H), 1.51 (m, 3H), 2.12 (m, 2H), 1.61 (m, 2H), 2.89–2.83 (m, 1H), 2.77–2.57 (m, 1H), 2.40–2.19 (m, 2H), 1.12–1.07 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 111.91, 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, 53.9, 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; ¹¹B 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 C₂₄H₂₃BrF₂O₄Cl: 524.0646; found: 524.0644.

1-Bromo-1-difluorooct-2-ene (7a). Colorless liquid. δ ppm 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, 53.9, 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; ¹¹B 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 C₂₄H₂₃BrF₂O₄Cl: 524.0646; found: 524.0644.

(S)-5-Bromo-5,5-difluoropentyl-2,2-difluoroethyl-4-methyl-1-oxoisoxazoline (20). Colorless liquid. ¹¹B NMR (400 MHz, CDCl₃) δ ppm 3.40(−3.40) (m, 2F); IR (thin film) ν 2973, 2932, 2857, 1674, 1610, 1513, 1458, 1349, 816 cm⁻¹; MS (EI): m/z (%) 163 [(M + Br⁻), 2.32], 145 (19.6), 103 (100); HRMS calculated for C₁₉H₁₉BrF₂: 224.0012; found: 224.0013.

2-(Bromodifluoromethyl)-4-methyl-1-tosylpyridoline (14). Colorless liquid. ¹¹B NMR (400 MHz, CDCl₃) δ ppm 7.69
1.53 δ (d, J = 7.2 Hz, 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, 125.9, 125.2 (m, 2H), 119.7 (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, 925, 692, 548 cm−1; MS (EI): m/z (%) 383 ([M + 2]+, 31.4), 381 (M+, 31.7), 228 (97.1), 226 (100); 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, 2F), 37.8 (t, J = 24.1 Hz); 19F NMR (376 MHz, CDCl3) δ ppm −45.2 (t, J = 12.2 Hz, 2F); IR (thin film) ν 3059, 1448, 1304, 1254, 1088, 1021, 734, 527 cm−1; MS (EI): m/z (%) 383 ([M + 2]+, 10.2), 299 (M+, 10.2), 220 (78.7), 77 (100); HRMS calculated for C15H16BrF2NO2S: 393.0357; found: 393.0352.

(5,5-Difluorooct-7-en-1-yl)benzene (10). 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 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 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 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 (dd, 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); 13C 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), 53.1, 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 (d, J = 47.8, 25.6 Hz, 1F).

(2)-[Fluorophen-4-ene-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 (ddt, J = 43.2, 7.4, 4.8 Hz, 1H), 2.66 (t, J = 10.2 Hz, 2H), 2.20–2.11 (m, 1H), 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) 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 C11H12F2: 164.1001; found: 164.0997.

(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). 1H NMR (400 MHz, CDCl3) δ ppm 7.49–7.25 (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); 13C NMR (100 MHz, CDCl3) δ ppm 158.8
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Notes and references


19 The ratios of E/Z isomers of compounds 7a-d were determined by the $^{19}$F 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.


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.