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Visible Light Promoted Oxo-Difluoroalkylation of Alkenes with DMSO as the Oxidant

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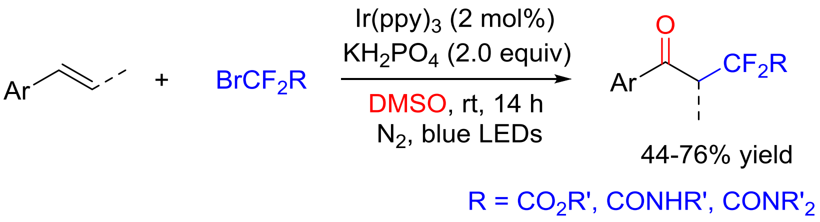


ABSTRACT

Visible light promoted oxo-difluoroalkylation (acetylation and acetamidation) of alkenes with DMSO as both the solvent and the oxidant was developed, affording the corresponding α, α-difluoro-γ-ketoacetates and acetamides in modest yields. Both terminal and internal alkenes worked well for the reaction. This reaction features simple starting materials, green oxidant, mild reaction condtions and highly functional products.

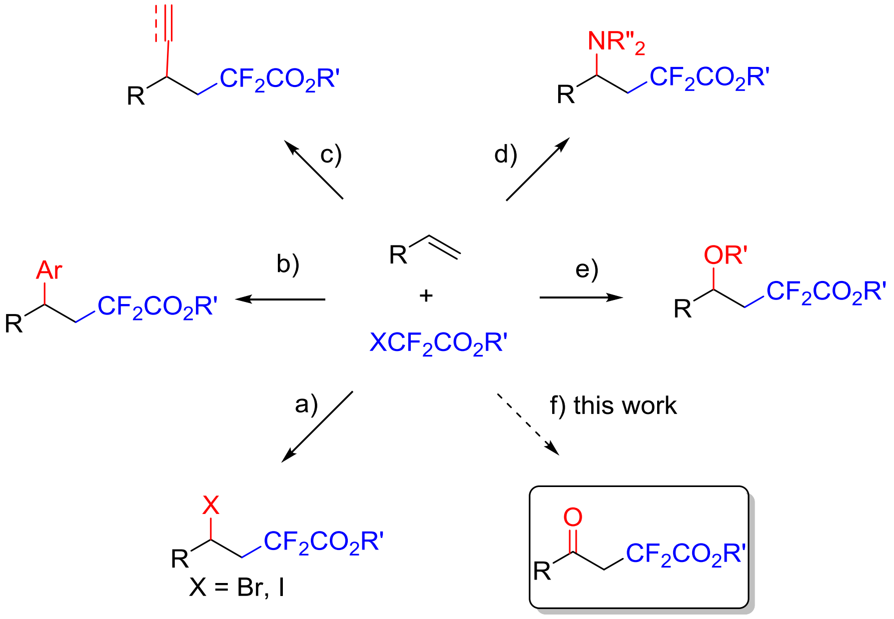
INTRODUCTION

Fluorinated organic compounds play an important role in pharmaceuticals, agrochemicals and materials.[1] As a bioisostere of oxygen and carbonyl group, incorporation of difluoromethyl into molecules can modulate the physical and chemical properties such as increasing the dipole moments and enhancing the acidity of adjacent group.[2] In particular, α,α-difluoroacetates (CF_2CO_2R) are of great interest for their presence in many bioactive compounds and as building blocks for further transformations.[3]

Alkene difunctionalization is powerful for the rapid synthesis of structurally diverse molecules from simple starting materials.[4] The metal-catalyzed difluoroacetylation of alkenes has been well established, including the difluoroacetylation with arylation,[5] oxylation,[6] thiolation[7] and halogenation reactions.[8] Meanwhile, the visible light promoted difluoroacetylation of alkenes emerged as a useful alternative for the synthesis of α, α-difluoroacetates (Scheme 1). In 2011, Stephenson *et al.* reported the pioneering photocatalyzed halo-difluoroacetylation of alkenes (reaction a).[9] Lately, the photocatalyzed difuoroacetylation of alkenes along with heteroarylation (reaction b),[10] alkenylation[11] and alkynylation[12] (reaction c), amination with bromodifluoroacetamide[13] or trimethylsilylazide[14] (reaction d), and oxygenation with carboxylic acid[15] or carbon dioxide[16] (reaction e) have been established.

Being an essential functional group, the synthesis of ketones from simple starting materials is one of the key transformations in organic reaction. Very recently, Glorius *et al.* and we independently reported a photocatalyzed synthesis of ketones from alkenes.[17] In this paper, we report the synthesis of α,α-difluoro-γ-ketoesters via the oxo-difluoroacetylation of alkenes (Scheme 1, reaction f). Although the synthesis of α,α-difluoro-γ-ketoesters from enol ether or acetate has been reported,[18] our work provides a highly valued method via the difunctionalization of simple alkenes using DMSO as the oxidant.

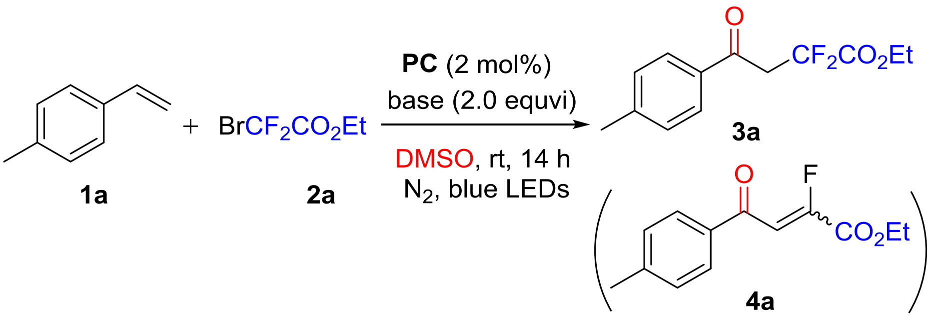
Scheme 1. Photocatalyzed difunctionalization of alkenes with difluoroacetylation



RESULTS AND DISCUSSION

Initially, the model reaction of 4-methylstyrene (**1a**) with $BrCF_2CO_2Et$ (**2a**) in the presence of base was carried out under photocatalysis using DMSO as both the oxidant and solvent (Table 1). Disappointedly, the reaction using $Ir(ppy)_3$ as the photocatalyst under the irradiation with blue LEDs in the presence of common organic (DBU, Et_3N) and inorganic bases (NaOAc and Cs_2CO_3) only gave trace desired α,α-difluoro-γ-ketoester **3a** (Table 1, entries 1-4). Interestingly, the reaction in the presence of K_3PO_4 gave α,β-unsaturated-α-fluoro-γ-ketoester **4a** in 61% yield (entry 5). Considering the possible elimination of hydrofluoride from compound **3a** to give **4a** under basic condition, we then explored weaker bases for the reaction. It was found that the reaction using K_2HPO_4 and KH_2PO_4 afforded the desired oxo-difluroroacetylation product **3a** in good yields without the formation of elimination product **4a** (entries 6 & 7). Variation of loading of the base did not give better results (entries 8 and 9). Screening of the photocatalysts showed that $[Ir(ppy)_2(dtbbpy)](PF_6)$ and 4CzIPN did not perform as well as $Ir(ppy)_3$ (entries 10 & 11).

Table 1. Optimization of conditions[a]



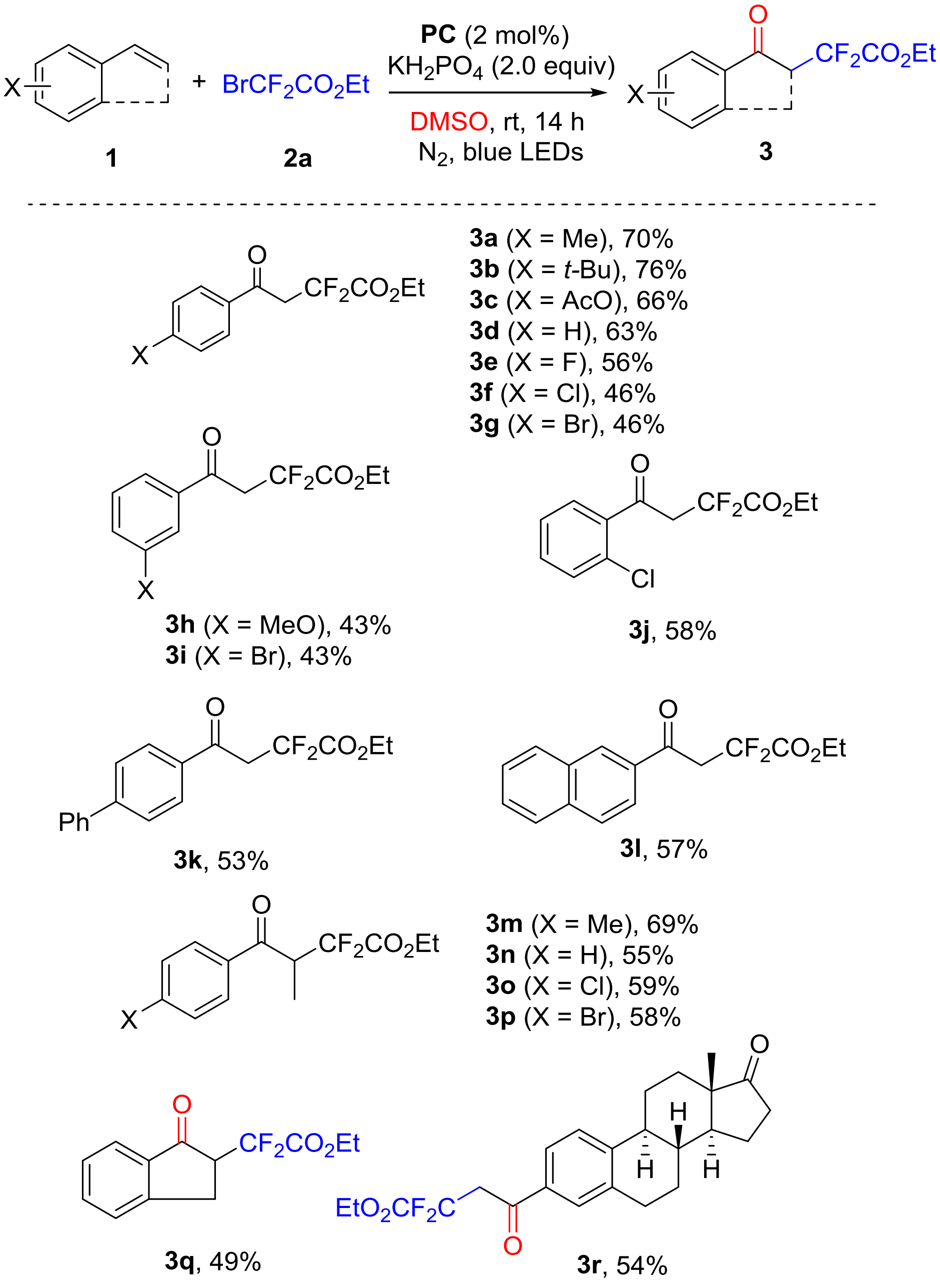
entry	PC (2 mol%)	base	**3a** (%)[b]	**4a** (%)[b]
1	*fac*-$Ir(ppy)_3$	DBU	trace	0
2	*fac*-$Ir(ppy)_3$	Et_3N	trace	0
3	*fac*-$Ir(ppy)_3$	NaOAc	trace	0

4	*fac*-Ir(ppy)$_3$	Cs_2CO_3	trace	0
5	*fac*-Ir(ppy)$_3$	K_3PO_4	trace	61
6	*fac*-Ir(ppy)$_3$	K_2HPO_4	61	0
7	*fac*-Ir(ppy)$_3$	KH_2PO_4	75^c	0
8	*fac*-Ir(ppy)$_3$	KH_2PO_4^{d}	66	0
9	*fac*-Ir(ppy)$_3$	KH_2PO_4^{e}	70	0
10	[Ir(ppy)$_2$(dtbbpy)] (PF$_6$)	KH_2PO_4	5	0
11	4CzIPN	KH_2PO_4	34	0

[a] General conditions: **1a** (0.3 mmol), **2** (0.45 mmol), PC (2.0 mol%), base (0.6 mmol), DMSO (2 mL), irradiation by 12 W blue LEDs at room temperature for 14h under nitrogen atmosphere. [b] Yields based on ^{19}F-NMR spectroscopy using benzotrifluoride as an internal standard. [c] 70% isolated yield. [d] KH_2PO_4 (1.5 equiv) was used. [e] KH_2PO_4 (3 equiv) was used. PC = photocatalyst.

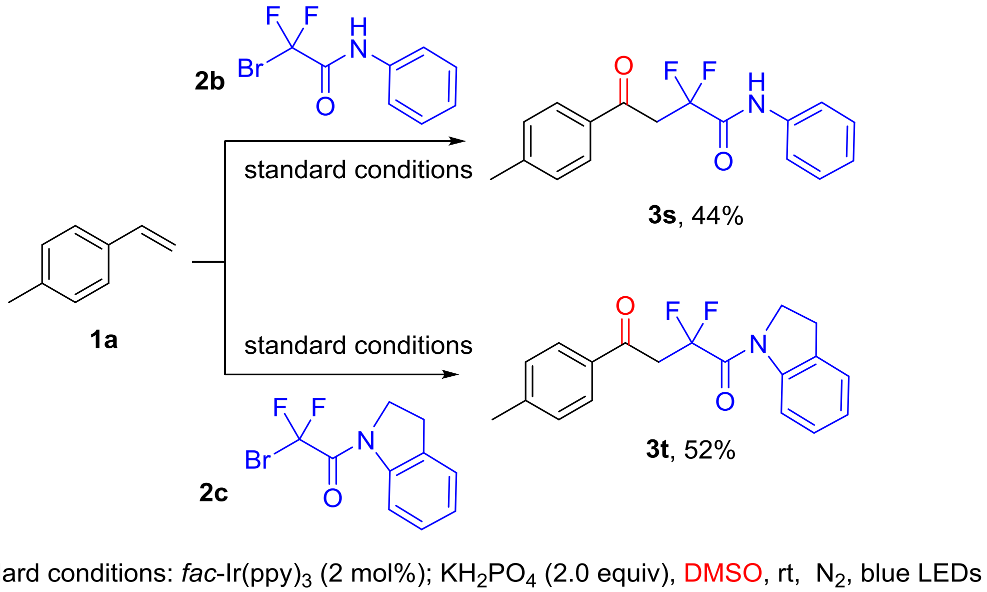
With the optimized reaction conditions in hand (Table 1, entry 7), a variety of alkenes were investigated for the reaction with ethyl bromodifluoroacetate (**2a**) (Scheme 2). It was found that styrenes with electron-donating groups (Ar = *p*-MeC$_6$H$_4$, *p*-*t*-BuC$_6$H$_4$, *p*-AcOC$_6$H$_4$) performed better than those with electron-withdrawing groups (Ar = *p*-FC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$), giving the α,α-difluoro-γ-ketoacetates (**3a**-**3g**) in moderate to good yields. Both *meta*- and *ortho*-substituents are tolerated to give the corresponding products (**3h**-**3j**) in moderate yields. It should be noted that some unidentified byproducts were formed along with the desired products for the reaction with moderate yields. In addition, both 4-vinyl-1,1’-biphenyl and 2-vinylnaphthalene worked well for the reaction (**3k**-**3l**). More importantly, the reaction of the internal alkenes went smoothly under the same conditions to give the β-substituted-α,α-difluoro-γ-ketoacetates (**3m**-**3p**) in good to high yields. Furthermore, the reaction of indene and estrone-derived alkenes afforded the corresponding oxo-difluoroacetylation products **3q** and **3r** in 49% and 54% yield, respectively. It should be noted that the reaction of styrenes with strong electron-withdrawing group such as 4-trifluoromethyl gave α,β-unsaturated-α-fluoro-γ-ketoester **4** via the elimination of hydrofluoride from the oxo-difluoroalkylaiton product, and the reaction of aliphatic alkenes failed under current reaction conditions.

Scheme 2. Reaction with ethyl bromodifluoroacetate

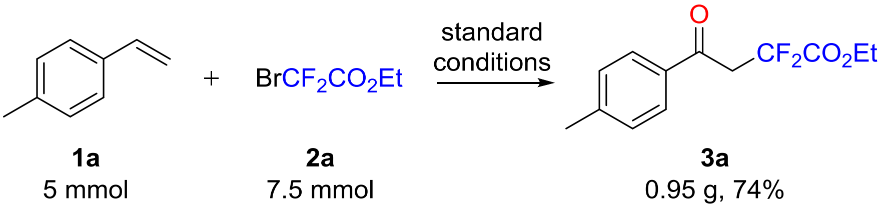


The reactions with difluoroacetamides were also investigated (Scheme 3). It was found that both aniline and indole-derived difluoroacetamides **2b** and **2c** worked well under the previous standard photocatalysis conditions, resulting in the desired oxo-difluoroacetamidation products **3s** and **3t** in moderate to good yields.

Scheme 3. Reaction with bromodifluoroacetamides



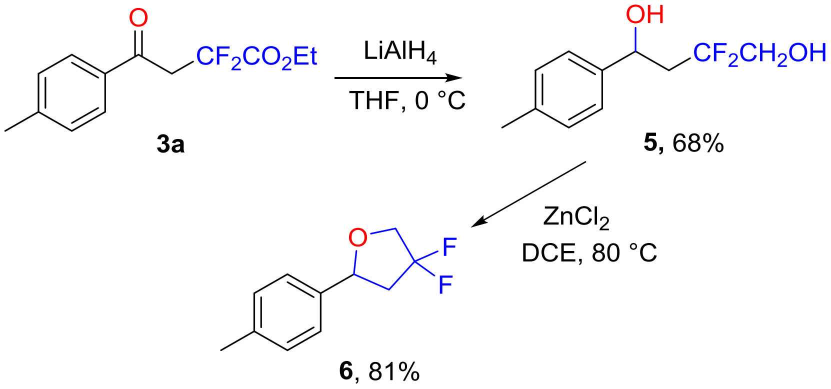
Scheme 4. Gram-scale reaction.



The reaction could be easily scaled up with 5 mmol of 4-methylstyrene under standard conditions, giving 0.95 g of the α,α-difluoro-γ-ketoacetate **3a** in 74% yield (Scheme 4).

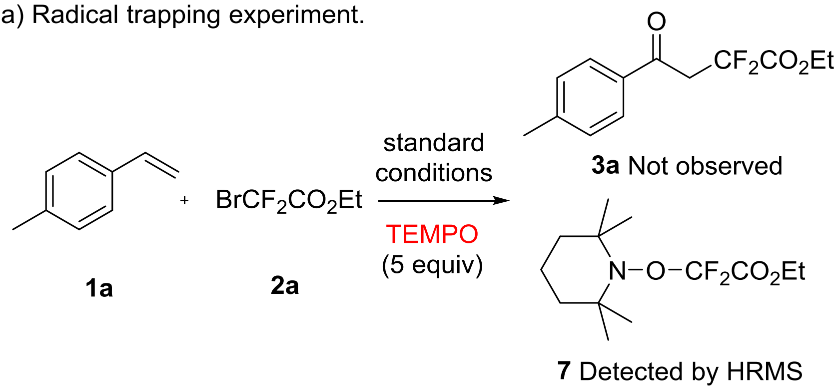
The multi-functional product affords many possible further chemical transformations (Scheme 5). For example, reduction of the α,α-difluoro-γ-ketoacetate **3a** by $LiAlH_4$ gave the corresponding 2,2-difluro-1,4-diol **5** in 68% yield. The difluorodiol could be cyclized *via* $ZnCl_2$ mediated dehydration to afford 4,4-difluoro-2-(*p*-tolyl)tetrahydrofuran **6** in high yield.

Scheme 5. Chemical transformations of 3a.

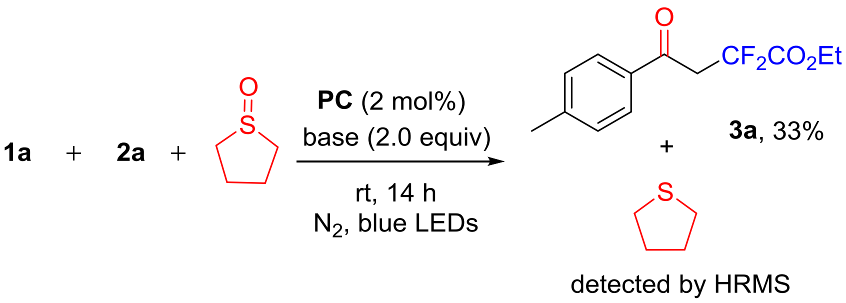


Scheme 6. Control experiments.

(a) Radical trapping experiment.



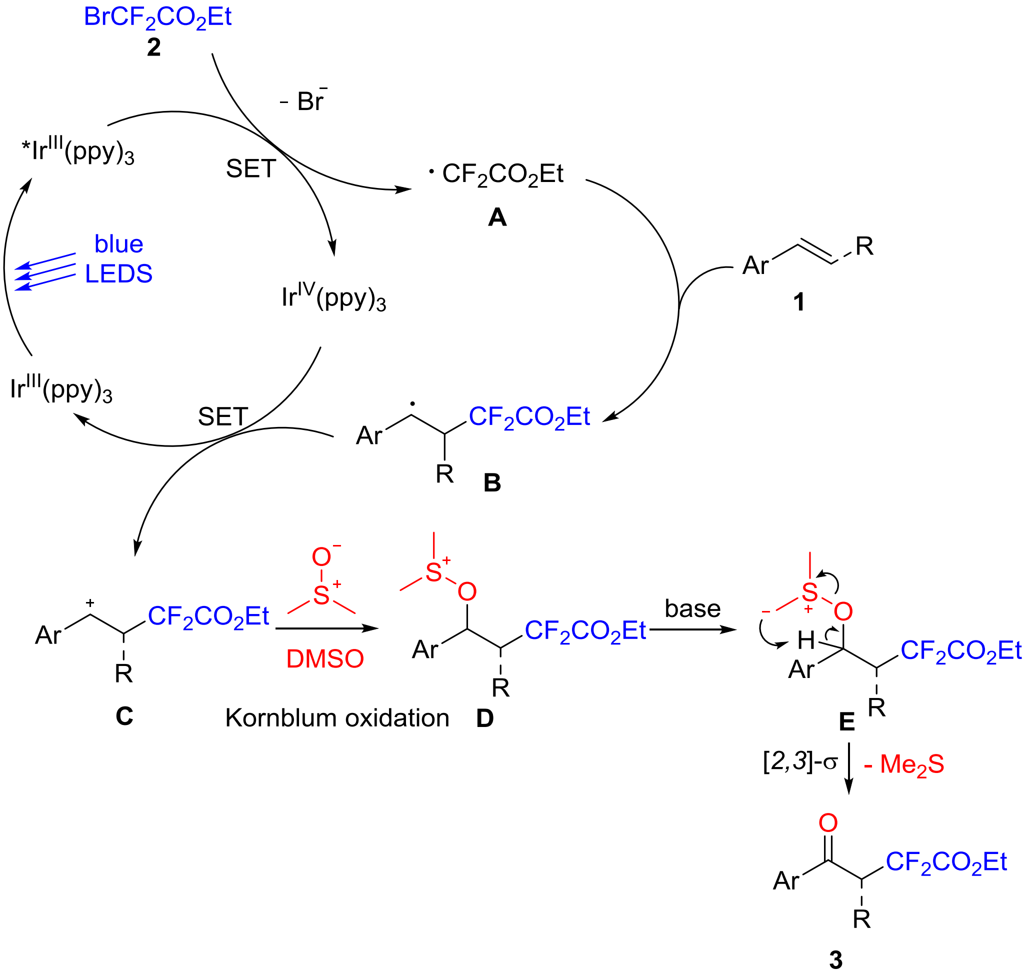
(b) Using tetrahydrothiophene 1-oxide instead of DMSO



The radical trapping experiment was conducted (Scheme 6, reaction a). When the reaction was carried out under the standard condition but with addition of 5.0 equiv of TEMPO as the radical scavenger, the formation of oxo-difluoroacetylation product **3a** was completely prohibited, while adduct **7** between TEMPO and difluoroacetate radical from **2a** was detected by HRMS (ESI). The experiment suggests a radical mechanism for the photocatalyzed reaction. To classify the oxidation of DMSO, the control experiment using tetrahydrothiophene 1-oxide instead of DMSO was conducted (Scheme 6, reaction b), which gave the desired oxo-difluoroalkylation prouduct **3a** in 33% and tetrahydrothiophene was detected by HRMS.

A plausible mechanism for the reaction is depicted in Scheme 7. Under the visible-light irradiation, the catalyst *fac*-Ir(ppy)$_3$ is excited and then reduces $BrCF_2CO_2Et$ (**2**) to produce radical intermediate **A** *via* the elimination of bromide.[9a] The addition of radical **A** to alkenes gives difluoroacetate radical species **B**, which is oxidized by Ir^{IV} to form the key carbocation intermediate **C** and regenerates the photocatalyst. The combination of carbocation intermediate **C** and DMSO affords the alkoxysulfonium intermediate **D**, which is fragmented in the presence of base *via* [*2*,*3*]-δ rearrangement to give the ketone **3**, a process similar to Kornblum oxidation.[19]

Scheme 7. Proposed mechanism.

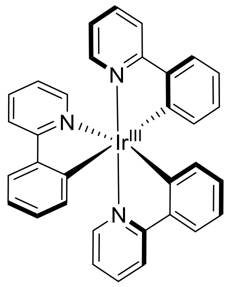


CONCLUSION

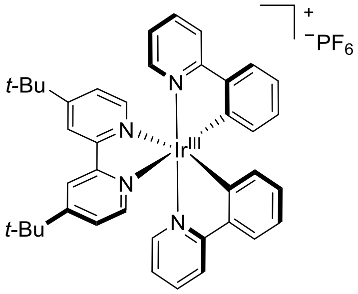
In summary, the visible light mediated oxo-difluoroalkylation of alkenes is developed, with ethyl 2-bromo-2,2-difluoroacetate and 2-bromo-2,2-difluoroacetamides as the difluoroalkyl radical source and DMSO as the oxidant. The corresponding α,α-difuoro-γ-ketoesters and amides were obtained in good yields. This reaction features simple starting materials, green oxidant, mild reaction condtion and highly functional products. Other related visible light mediated difunctionalization reactions of alkenes are underway in our laboratory.

EXPERIMENTAL SECTION

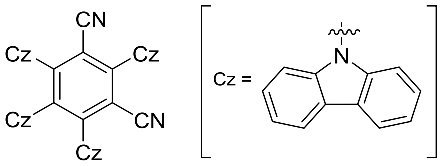
General Remarks. Unless otherwise indicated, all reactions were carried out under N_2 protection at room temperature with magnetic stirring in a Schlenk tube of normal borosilicate glass. Photocatalysts *fac*-Ir(ppy)$_3$,[20] [Ir(ppy)$_2$(dtbbpy)](PF$_6$)[4h] and 4-CzIPN[21] were prepared according to literatures. All ^{1}H NMR (400 and 500 MHz), ^{13}C NMR (100 and 125 MHz), and ^{19}F NMR (376 MHz) spectra were recorded on a Bruker Avance 400 and Bruker Avance 500 spectrometer in CDCl3, with tetramethylsilane as an internal standard and reported in parts per million (ppm, δ). 1H NMR spectroscopy splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Infrared spectra were recorded on a JASCO FT/IR-480 spectrophotometer and reported as wave number (cm^{-1}). Column chromatography was carried out on silica gel (200-300 mesh). HRMS were obtained on an ESI- Orbitrap mass analyzer , EI-TOF mass analyzer and ESI-ICR mass analyzer. Experiments upon visible-light irradiation were carried out using household blue LED lamps (JDY-THDGY, λmax = 455 nm, 18 × 1W). Irradiation occurred from the bottom of each vial at a distance of 3 cm.



fac-Ir(ppy)$_3$



[Ir(ppy)$_2$(dtbbpy]PF$_6$



4-CzIPN

Typical procedure for the oxo-difluoroalkylation (Schemes 2 and 3). To a 10 mL Schlenk-tube equipped with a rubber septum and magnetic stir bar was charged with styrene **1a** (35.4 mg, 0.3 mmol), ethyl 2-bromo-2,2-difluoroacetate **2a** (90.9 mg, 0.45 mmol), KH_2PO_4 (81.6 mg, 0.6 mmol) and Ir(ppy)$_3$ (3.9 mg, 2.0 mol%). The tube was evacuated and backfilled with N_2 for three times. DMSO (2.0 mL) was added with a syringe under nitrogen. The mixture was then irradiated by 12 W blue LEDs. After 14h, the reaction mixture was poured into a separatory funnel containing 20 mL of H_2O and 20 mL of DCM. The organic layer was collected and washed with H_2O (2×20 mL) and brine, successively, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (200-300 mesh) to afford the desired product **3a**.

ethyl 2,2-difluoro-4-oxo-4-(p-tolyl)butanoate (3a).

54 mg. 70% yield. Colorless oil. R_f = 0.35 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.88 (t, *J* = 13.5 Hz, 2H), 2.42 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H);

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 192.5 (t, *J* = 5.6 Hz), 163.3 (t, *J* = 31.3 Hz), 145.3, 133.2, 129.6, 128.3, 114.5 (t, *J* = 247.5 Hz), 63.0, 43.7 (t, *J* = 25 Hz), 21.7, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.4 (s, 2F); IR (KBr) 1778, 1687, 1607, 1091. Orbitrap-HRMS (ESI) calcd for $C_{13}H_{15}F_2O_3$ $[M+H]^+$ 257.0983, found 257.0985.

ethyl 4-(4-(tert-butyl)phenyl)-2,2-difluoro-4-oxobutanoate (3b).

68 mg. 76% yield. Oil. R_f = 0.45 (petroleum ether/ethyl acetate 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.89 (t, *J* = 13.6 Hz, 2H), 1.36 -1.34 (m, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.5 (t, *J* = 6.0 Hz), 163.3 (t, *J* = 31.0 Hz), 158.1, 133.1, 128.2, 125.9, 114.5 (t, *J* = 248.0 Hz), 63.0, 43.8 (t, *J* = 25 Hz), 35.3, 31.0, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.4 (s, 2F); IR (KBr) 1778, 1686, 1190, 1091. Orbitrap-HRMS (ESI) calcd for $C_{16}H_{21}F_2O_3$ $[M+H]^+$ 299.1453, found 299.1454.

ethyl 4-(4-acetoxyphenyl)-2,2-difluoro-4-oxobutanoate (3c).

59 mg. 66% yield. Colorless oil. R_f = 0.15 (petroleum ether/ethyl acetate 10:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.89 (t, *J* = 13.0 Hz, 2H), 2.33 (s), 1.36 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 191.7 (t, *J* = 6.3 Hz), 168.7, 163.2 (t, *J* = 31.3 Hz), 155.2, 133.1, 129.9, 122.2, 114.3 (t, *J* = 248.8 Hz), 63.1, 43.8 (t, *J* = 25.0 Hz), 21.3, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.3 (s, 2F); IR (KBr) 1760, 1688, 1600, 1190. Orbitrap-HRMS (APCI) calcd for $C_{14}H_{15}F_2O_5$

$[M+H]^+$ 301.0882, found 301.0884.

ethyl 2,2-difluoro-4-oxo-4-phenylbutanoate (3d).

46 mg. 63% yield. Colorless oil. R_f = 0.69 (petroleum ether/ethyl acetate 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.91 (t, *J* = 13.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.9 , 163.3 (t, *J* = 32.0 Hz), 135.6, 134.2, 128.9, 128.2, 114.4 (t, *J* = 248.0 Hz), 63.1, 43.8 (t, *J* = 25 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.4 (s, 2F); IR (KBr) 1776, 1689, 1192, 1092. Orbitrap-HRMS (ESI) calcd for $C_{12}H_{13}F_2O_3$ $[M+H]^+$ 243.0827, found 243.0829.

ethyl 2,2-difluoro-4-(4-fluorophenyl)-4-oxobutanoate (3e).

44 mg. 56% yield. Colorless oil. R_f = 0.39 (petroleum ether/ethyl acetate 10:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.16 (t, *J* = 8.8 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.87 (t, *J* = 13.5 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 191.4 (t, *J* = 6.3 Hz), 166.3 (d, *J* = 256.3 Hz), 163.2 (t, *J* = 31.3 Hz), 132.1, 130.9 (d, *J* = 10.0 Hz), 116.1 (d, *J* = 22.5 Hz), 114.3 (t, *J* = 248.8 Hz), 63.1, 43.7 (t, *J* = 25.0 Hz), 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.0 (s, 1F), -104.4 (s, 2F); IR (KBr) 1176, 1691, 1600, 1234. Orbitrap-HRMS (ESI) calcd for $C_{12}H_{12}F_3O_3$ $[M+H]^+$ 261.0733, found 261.0735.

ethyl 4-(4-chlorophenyl)-2,2-difluoro-4-oxobutanoate (3f).

38 mg. 46% yield. Colorless oil. R_f = 0.39 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.87 (t, *J* = 13.0 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.8 (t, *J* = 6.3 Hz), 163.2 (t, *J* = 31.3 Hz), 140.8, 133.9, 129.6, 129.3, 114.2 (t, *J* = 248.8 Hz), 63.1, 43.8 (t, *J* = 23.8 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.3 (s, 2F); IR (KBr) 1773, 1690, 1590, 1092. Orbitrap-HRMS (ESI) calcd for $C_{12}H_{12}F_2O_3Cl$ $[M+H]^+$ 277.0438, found 277.0439.

ethyl 4-(4-bromophenyl)-2,2-difluoro-4-oxobutanoate (3g).

44 mg. 46% yield. Colorless oil. R_f = 0.38 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78(d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.86 (t, *J* = 13.0 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.0 (t, *J* = 6.3 Hz), 163.2 (t, *J* = 31.3 Hz), 134.3, 132.3, 129.63, 129.59, 114.2 (t, *J* = 250.0 Hz), 63.2, 43.7 (t, *J* = 25.0 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.3 (s, 2F); IR (KBr) 1774, 1691, 1586, 1091. ICR-HRMS (ESI) calcd for $C_{12}H_{11}BrF_2O_3Na$ $[M+Na]^+$ 342.9752, found 342.9755.

ethyl 2,2-difluoro-4-(3-methoxyphenyl)-4-oxobutanoate (3h).

35 mg. 43% yield. Colorless oil. R_f = 0.29 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8 Hz, 1H), 7.44 (d, *J* = 1.5 Hz, 1H), 7.40 (t, *J* = 8 Hz, 1H), 7.17 – 7.15 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.88 (t, *J* = 13.5 Hz, 2H),

1.37 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 192.8 (t, *J* = 6.3 Hz), 163.3 (t, *J* = 31.3 Hz), 160.2, 136.9, 129.9, 120.84, 120.81,114.4 (t, *J* = 247.5 Hz), 112.1, 63.1, 55.5, 44.0 (t, *J* = 25.0 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5 (s, 2F); IR (KBr) 1776, 1689, 1266, 1092. Orbitrap-HRMS (ESI) calcd for $C_{13}H_{15}F_2O_4$ $[M+H]^+$ 273.0933, found 273.0934.

ethyl 4-(3-bromophenyl)-2,2-difluoro-4-oxobutanoate (3i).

41 mg. 43% yield. Colorless oil. R_f = 0.48 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 8.04 (m, 1H), 7.84 – 7.83 (m, 1H), 7.76 – 7.74 (m, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 4.38 (q, *J* = 7.5 Hz, 2H), 3.87 (t, *J* = 13.0 Hz, 2H), 1.36 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 191.7 (t, *J* = 5.0 Hz), 163.1 (t, *J* = 31.2 Hz), 137.2, 137.0, 131.2, 130.5, 126.7, 123.3, 114.1 (t, *J* = 250.0 Hz), 63.2, 43.9 (t, *J* = 25.0 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.3 (s, 2F); IR (KBr) 1776, 1693, 1191, 1092. ICR-HRMS (ESI) calcd for $C_{12}H_{11}BrF_2O_3Na$ $[M+Na]^+$ 342.9752, found 342.9753.

ethyl 4-(2-chlorophenyl)-2,2-difluoro-4-oxobutanoate (3j).

48 mg. 58% yield. Colorless oil. R_f = 0.48 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.0 Hz, 1H), 7.45 – 7.43 (m, 1H), 7.37 – 7.34 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.95 (t, *J* = 13.5 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 195.0 (t, *J* = 6.3 Hz),

163.1 (t, J = 31.3 Hz), 137.0, 133.1, 131.7, 130.9, 130.0, 127.2, 113.9 (t, J = 250.0 Hz), 63.1, 47.8 (t, J = 23.8 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.3 (s, 2F); IR (KBr) 1776, 1703, 1374, 1198. ICR-HRMS (ESI) calcd for $C_{12}H_{11}ClF_2O_3Na$ $[M+Na]^+$ 299.0257, found 299.0258.

4-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-oxobutanoate (3k).

51 mg. 53% yield. Colorless oil. R_f = 0.33 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.64 – 7.62 (m, 2H), 7.50 – 7.47 (m, 2H), 7.44 – 7.41 (m, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.95 (t, J = 13.5 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.5 (t, J = 6.3 Hz), 163.3 (t, J = 31.2 Hz), 146.9, 139.5, 134.3,129.0, 128.8, 128.6, 127.5, 127.3, 114.4 (t, J = 248.8 Hz), 63.1, 43.9 (t, J = 23.8 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.3 (s, 2F); IR (KBr) 1775, 1685, 1604, 1190. Orbitrap-HRMS (ESI) calcd for $C_{18}H_{17}F_2O_3$ $[M+H]^+$ 319.1140, found 319.1140.

ethyl 2,2-difluoro-4-(naphthalen-2-yl)-4-oxobutanoate (3l).

50 mg. 57% yield. Solid. m.p.= 43 - 44℃. R_f = 0.33 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.98 – 7.92 (m, 2H), 7.90 – 7.88 (m, 2H), 7.65 – 7.62 (m, 1H), 7.60 – 7.57 (m, 1H), 4.40 (q, J = 7.0 Hz, 2H), 4.05 (t, J = 13.0 Hz, 2H), 1.38 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 192.9 (t, J = 6.3 Hz), 163.4 (t, J = 31.3Hz), 136.0, 133.0, 132.4,

130.4, 129.7, 129.1, 128.9, 127.9, 127.2, 123.3, 114.5 (t, *J* = 248.8 Hz), 63.1, 43.9 (t, *J* = 23.8 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.3 (s, 2F); IR (KBr) 1773, 1685, 1188, 1090. Orbitrap-HRMS (ESI) calcd for $C_{16}H_{15}F_2O_3$ $[M+H]^+$ 293.0983, found 293.0985.

ethyl 2,2-difluoro-3-methyl-4-oxo-4-(p-tolyl)butanoate (3m).

56 mg. 69% yield. Colorless oil. R_f = 0.35 (petroleum ether/ethyl acetate 10:1)**;** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.32 – 4.26 (m, 3H), 2.42 (s, 3H), 1.46 (d, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 197.2 (d, *J* = 6.3 Hz), 163.5 (t, *J* = 32.5 Hz), 144.8, 132.8, 129.5, 128.7, 115.1 (dd, *J* = 247.5 Hz, 257.5 Hz), 62.9, 46.1 (dd, *J* = 21.3 Hz, 23.8 Hz), 21.7, 13.8, 11.5 (dd, *J* = 3.8 Hz, 5.0Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.6 (d, *J* = 270.7 Hz, 1F), -112.3 (d, *J* = 270.7 Hz, 1F); IR (KBr) 1774, 1683, 1235, 1120. Orbitrap-HRMS (ESI) calcd for $C_{14}H_{17}F_2O_3$ $[M+H]^+$ 271.1140, found 271.1142.

ethyl 2,2-difluoro-3-methyl-4-oxo-4-phenylbutanoate (3n).

42 mg. 55% yield. Colorless oil. R_f = 0.57 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 4.33 – 4.28 (m, 3H), 1.47 (d, *J* = 7.5 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 197.7 (d, *J* = 6.3 Hz), 163.5 (t, *J* = 31.3 Hz), 135.4, 133.8, 128.9, 128.6, 115.1 (dd, *J* = 247.5 Hz, 258.8 Hz),

63.0, 46.2 (dd, *J* = 22.5 Hz, 25.0 Hz), 13.8, 11.4 (dd, *J* = 3.8 Hz, 5.0Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.7 (d, *J* = 267.0 Hz, 1F), -112.4 (d, *J* = 270.7 Hz, 1F); IR (KBr) 1774, 1686, 1219, 1121. Orbitrap-HRMS (ESI) calcd for $C_{13}H_{15}F_2O_3$ $[M+H]^+$ 257.0983, found 257.0984.

ethyl 4-(4-chlorophenyl)-2,2-difluoro-3-methyl-4-oxobutanoate (3o).

51 mg. 59% yield. Colorless oil. R_f = 0.35 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 4.32 – 4.22 (m, 3H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 196.4 (d, *J* = 6.3 Hz), 163.4 (t, *J* = 31.3 Hz), 140.4, 130.0, 129.2, 115.0 (dd, *J* = 248.8 Hz, 258.8 Hz), 63.1, 46.0 (dd, *J* = 21.3 Hz, 23.8 Hz), 13.8, 11.3 (dd, *J* = 3.8 Hz, 5.0Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.8 (d, *J* = 270.7 Hz, 1F), -111.9 (d, *J* = 270.7 Hz, 1F); IR (KBr) 1774, 1687, 1589, 1093. Orbitrap-HRMS (ESI) calcd for $C_{13}H_{14}F_2O_3Cl$ $[M+H]^+$ 291.0594, found 291.0596.

ethyl 4-(4-bromophenyl)-2,2-difluoro-3-methyl-4-oxobutanoate (3p).

58 mg. 58% yield. Colorless oil. R_f = 0.45 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 4.33 – 4.21 (m, 3H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 196.6 (d, *J* = 5.0 Hz), 163.4 (t, *J* = 32.5 Hz), 134.1, 132.2, 130.1, 129.2, 115.0 (dd, *J* = 248.8 Hz, 258.8 Hz), 63.1, 46.0 (dd,

J = 22.5 Hz, 25.0 Hz), 13.8, 11.3 (dd, *J* = 3.8 Hz, 5.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.8 (d, *J* = 270.7 Hz, 1F), -111.9 (d, *J* = 270.7 Hz, 1F); IR (KBr) 1774, 1687, 1585, 1072. ICR-HRMS (ESI) calcd for $C_{13}H_{13}BrF_2O_3Na$ $[M+Na]^+$ 356.9908, found 356.9912.

ethyl 2,2-difluoro-2-(1-oxo-2,3-dihydro-1H-inden-2-yl)acetate (3q).

37 mg. 49% yield. Yellow oil. R_f = 0.29 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.27 (m, 1H), 4.42 (q, *J* = 7.0 Hz, 2H), 3.72 – 3.63 (m, 1H), 3.39 (d, *J* = 6.5 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 199.4 (d, *J* = 7.5 Hz), 163.0 (t, *J* = 32.5 Hz), 152.9, 136.0 (d, *J* = 3.8 Hz), 135.6, 128.0, 126.6, 124.4, 115.0 (dd, *J* = 250.0 Hz, 253.8 Hz), 63.3, 51.0 (t, *J* = 22.5 Hz), 26.8 (d, *J* = 2.5 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.9 (d, *J* = 267.0 Hz, 1F), -115.2 (d, *J* = 267.0 Hz, 1F); IR (KBr) 1774, 1723, 1294, 1067. Orbitrap-HRMS (ESI) calcd for $C_{13}H_{13}F_2O_3$ $[M+H]^+$ 255.0827, found 255.0828.

ethyl-2,2-difluoro-4-((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17- decahydro-6H-cyclopenta[a]phenanthren-3-yl)-4-oxobutanoate (3r).

68 mg. 54% yield. Colorless oil. R_f = 0.55 (petroleum ether/ethyl acetate 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.66 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 1H),

4.38 (q, *J* = 7.1 Hz 2H), 3.88 (t, *J* = 13.5 Hz, 2H), 2.98 – 2.97 (m, 2H), 2.51 – 2.49 (m, 1H), 2.37 – 2.33 (m, 1H), 2.20 – 2.11 (m, 1 H), 2.08 – 2.04 (m, 2H), 2.01 – 1.99 (m, 1H), 1.67 – 1.58 (m, 3H), 1.56 – 1.43 (m 4H), 1.36 (t, *J* = 7.2 Hz, 3H), 0.92 (s, 3H), 0.89 – 0.83 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 220.4, 192.7 (t, *J* = 6.3 Hz), 163.3 (t, *J* = 31.3 Hz,), 146.8, 137.4, 133.3, 128.8, 125.9, 125.6, 114.5 (t, *J* = 247.5 Hz), 63.0, 50.5, 47.9, 44.8, 43.8 (t, *J* = 23.8 Hz), 37.7, 35.8, 31.5, 29.3, 26.2, 25.5, 21.6, 13.9, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.4 (s, 2F); IR (KBr) 1738, 1684, 1195, 1091. Orbitrap-HRMS (ESI) calcd for $C_{24}H_{29}F_2O_4$ $[M+H]^+$ 419.2028, found 419.2029.

2,2-difluoro-4-oxo-N-phenyl-4-(p-tolyl)butanamide (3s).

40 mg. 44% yield. Solid. m.p.= 144 – 145 ^oC. R_f = 0.14 (petroleum ether/ethyl acetate 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (brs, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.19 (t, *J* = 7.2 Hz 1H), 4.00 (t, *J* = 14.0 Hz, 2H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 192.6 (t, *J* = 5.0 Hz), 161.7 (t, *J* = 26.3 Hz), 145.2, 136.3, 133.2, 129.6, 129.2, 128.3, 125.5, 120.4, 116.4 (t, *J* = 252.5 Hz), 42.9 (t, *J* = 25.0 Hz), 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.7 (s, 2F); IR (KBr) 1686, 1606, 1544, 1230. Orbitrap-HRMS (ESI) calcd for $C_{17}H_{16}NF_2O_2$ $[M+H]^+$ 304.1144, found 304.1144.

2,2-difluoro-1-(indolin-1-yl)-4-(p-tolyl)butane-1,4-dione (3t).

51 mg. 52% yield. Solid. m.p.= 66 - 67℃. R_f = 0.71 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.18 (m, 4H), 7.09 (t, *J* = 7.2 Hz, 1H), 4.46 (t, *J* = 8.0 Hz, 2H), 3.96 (t, *J* = 14.4 Hz, 2H), 3.24 (t, *J* = 8.0 Hz, 2H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 192.8 (t, *J* = 5 Hz), 160.9 (t, *J* = 28.8 Hz), 144.7, 142.7, 133.8, 131.7, 129.4, 128.4, 127.5, 125.1, 124.6, 118.4 (t, *J* = 255 Hz), 118.0, 47.9 (t, *J* = 8.8 Hz), 43.3 (t, *J* = 22.5 Hz), 28.7, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.0 (s, 2F); IR (KBr) 1670, 1483, 1430, 1230. Orbitrap-HRMS (ESI) calcd for $C_{19}H_{18}NF_2O_2$ $[M+H]^+$ 330.1300, found 330.1299.

Gram-scale reaction (Scheme 4). To a 100 mL Schlenk-tube equipped with a rubber septum and magnetic stir bar was charged with styrene **1a** (0.59 g, 5 mmol), ethyl 2-bromo-2,2-difluoroacetate **2a** (1.52 g, 7.5 mmol), KH_2PO_4 (1.36 g, 10 mmol) and Ir(ppy)$_3$ (66 mg, 2.0 mol%). The tube was evacuated and backfilled with N_2 for three times. DMSO (25mL) was added with a syringe under nitrogen. The mixture was then irradiated by 12 W blue LEDs. After 14 h, the reaction mixture was poured into a separatory funnel containing 50 mL of H_2O and 50 mL of DCM. The organic layer was collected and washed with H_2O (2×50 mL) and brine, successively, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (200-300 mesh) to afford 0.95 g (74%) of the desired product **3a.**

Chemical transformations of 3a (Scheme 5). To a solution of **3a** (0.128 g, 0.5 mmol) in THF (2 mL) was slowly added 1.5 mmol of $LiAlH_4$ in THF (1M, 1.5 mL) in 5 min at 0 ℃. The reaction mixture was further stirred for 1 h. The reaction mixture was quenched at 0 ℃ with several drops of H_2O and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to give diol **5** (73.0 mg, 68%) as white solid. m.p.= 66 – 67 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.96 (d, *J* = 10.5 Hz, 1H), 3.91 – 3.79 (m, 2H), 3.32 (s, 1H), 2.70 (s, 1H), 2.54 – 2.42 (m, 1H), 2.35 (s, 3H), 2.21 (q, *J* = 13.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 140.1, 138.1, 129.5, 125.6, 122.5 (t, *J* = 242.5 Hz), 69.3 (dd, *J* = 10.6, 2.2 Hz), 64.3 (t, *J* = 33.8 Hz), 43.4 (t, *J* = 25.0 Hz), 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.9 (d, *J* = 255.7 Hz, 1F), -107.2 (d, *J* = 255.7 Hz, 1F); IR (KBr) 3432, 1637, 1070, 553. TOF-HRMS (EI) calcd for $C_{11}H_{14}F_2O_2$ $[M]^+$ 216.0962, found 216.0965.

To a stirred solution of 3,3-difluoro-1-(*p*-tolyl)butane-1,4-diol **5** (43.2 mg, 0.2 mmol) in 1,2-dichloroethane (2 mL) at room temperature was added anhydrous zinc chloride (27.2 mg, 0.2 mmol) and the reaction mixture was stirred at 80 °C for 2.5 h. Then the reaction mixture was diluted with dichloromethane (5 mL), and washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$. The resulting residue was purified by silica gel flash column chromatography to give difluorotetrahedronfuran **6** (32 mg, 81%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.97 (dd, J = 9.6, 6.0 Hz, 1H), 4.16 (q, J = 11.2 Hz, 1H), 3.95 –3.85 (m, 1H), 2.69 – 2.58 (m, 1H), 2.35 – 2.21 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.1, 135.5, 129.1 (t, J = 249.0 Hz), 128.3, 124.9, 79.1 (t, J = 5.0 Hz), 72.6 (t, J = 31.0 Hz), 43.0 (t, J = 23.0 Hz), 20.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.9 (d, J = 233.1 Hz, 1F), -99.9 (d, J = 233.1 Hz, 1F). IR (KBr) 2926, 1370, 1066, 808. TOF-HRMS (EI) calcd for $C_{11}H_{12}F_2O$ $[M]^+$ 198.0856, found 198.0859.

Control experiments (Scheme 6). (Reaction a) To a 10 mL Schlenk-tube equipped with a rubber septum and magnetic stir bar was charged with styrene **1a** (35.4 mg, 0.3 mmol), ethyl 2-bromo-2,2-difluoroacetate **2a** (90.9 mg, 0.6 mmol), KH_2PO_4 (81.6 mg, 0.6 mmol), TEMPO (234 mg, 1.5 mmol) and $Ir(ppy)_3$ (3.9 mg, 2.0 mol%). The tube was evacuated and backfilled with N_2 for three times. DMSO (2.0 mL) was added with a syringe under nitrogen. The mixture was then irradiated by 12 W blue LEDs. After 12h, a drop of the reaction mixture (about 50 μL) was collected for Orbitrap-HRMS (ESI) analysis without further work-up. The adduct of TEMPO and difluoroacetate radical (**7**) was detected by HR-MS (ESI): calcd for $C_{17}H_{28}NO^+$ $[M+H]^+$ 280.17188, found 280.17188 (Figure S1), while the corresponding oxo-difluoroacetylation product **3a** was not detected.

(Reaction b) To a 10 mL Schlenk-tube equipped with a rubber septum and magnetic stir bar was charged with styrene **1a** (35.4 mg, 0.3 mmol), ethyl

2-bromo-2,2-difluoroacetate **2a** (90.9 mg, 0.45 mmol), KH_2PO_4 (81.6 mg, 0.6 mmol) and $Ir(ppy)_3$ (3.9 mg, 2.0 mol%). The tube was evacuated and backfilled with N_2 for three times. Tetrahydrothiophene 1-oxide (2.0 mL) was added with a syringe under nitrogen. The mixture was then irradiated by 12 W blue LEDs. After 12h, a drop of the reaction mixture (about 50 μL) was collected for Orbitrap-HRMS (ESI) analysis without further work-up. The tetrahydrothiophene was detected by HR-MS (APCI): calcd for $C_4H_9S^+$ $[M+H]^+$ 89.04195, found 89.04200. (Figure S2).

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXX.

HRMS spectra, copies of ^1H, ^{13}C and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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