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# Photoredox radical/polar crossover enables C–H *gem*-difunctionalization of 1,3-benzodioxoles for the synthesis of monofluorocyclohexenes†

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A photocatalytic C–H *gem*-difunctionalization of 1,3-benzodioxoles with two different alkenes for the synthesis of highly functionalized monofluorocyclohexenes is described. Using 4CzIPN as the photocatalyst, the direct single electron oxidation of 1,3-benzodioxoles allows their defluorinative coupling with  $\alpha$ -trifluoromethyl alkenes to produce *gem*-difluoroalkenes in a redox-neutral radical polar crossover manifold. The C–H bond of the resultant  $\gamma,\gamma$ -difluoroallylated 1,3-benzodioxoles was further functionalized *via* radical addition to electron-deficient alkenes using a more oxidizing iridium photocatalyst. The capture of *in situ* generated carbanions by an electrophilic *gem*-difluoromethylene carbon and consecutive  $\beta$ -fluoride elimination afford monofluorocyclohexenes. The synergistic combination of multiple termination pathways of carbanions enables rapid incorporation of molecular complexity *via* stitching simple and readily accessible starting materials together.

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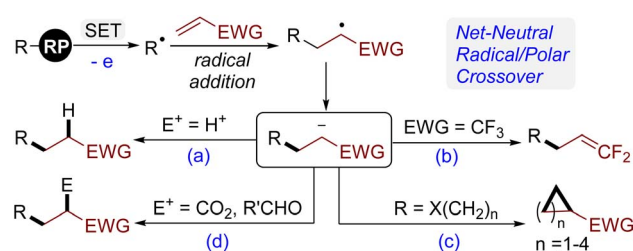
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## Introduction

Owing to the easy generation of diverse radical intermediates under mild conditions, visible-light photoredox catalysis has emerged as a powerful tool for organic synthesis.<sup>1</sup> One of notable features of photoredox catalysis is its inherent ability to crossover from a radical to a polar pathway during the overall catalytic process, which has resulted in a wide array of novel synthetic methodologies, especially in the field of alkene functionalization.<sup>2</sup> The carbon-centered radicals generated upon Giese-type radical addition to electron-deficient alkenes are readily single electron reduced to the corresponding carbanions.<sup>3</sup> Although direct protonation is the most common pathway to terminate these carbanions (Scheme 1a), other processes have been developed in the last few years, including: (1) elimination of a neighbouring leaving group;<sup>4</sup> when carbanions have  $\beta$ -substituted leaving groups, they tend to form a C=C double bond *via* E1cB-type elimination. In this context, our group<sup>5</sup> and Molander<sup>6</sup> have reported photocatalytic defluorinative coupling reactions of radical precursors and  $\alpha$ -trifluoromethyl alkenes for the synthesis of diverse *gem*-difluoroalkenes (Scheme 1b). (2) Ring closure reactions;<sup>7</sup> when the leaving groups are present at the distal position of carbanions, the intramolecular S<sub>N</sub>2 reaction would produce cyclic products (Scheme 1c). Although the formation of cyclopropanes *via* 3-*exo-tet* cyclization is often effective,<sup>7a</sup> the construction of

other-membered rings is still considered to be challenging.<sup>7d</sup> (3) Trapping by a carbon-based electrophile;<sup>8</sup> the capture of carbanions by electrophiles rather than a proton, such as CO<sub>2</sub> and aldehydes, is a synthetically useful pathway to introduce a functional group into the molecules (Scheme 1d). Undoubtedly, the synergistic combination of multiple termination pathways of carbanions can rapidly increase molecular complexity through stitching structural fragments together. For such a purpose, it is crucial to find a radical precursor, which allows the generation of radicals at least twice and the subsequent radical addition to different alkenes in a controllable manner.<sup>9</sup>

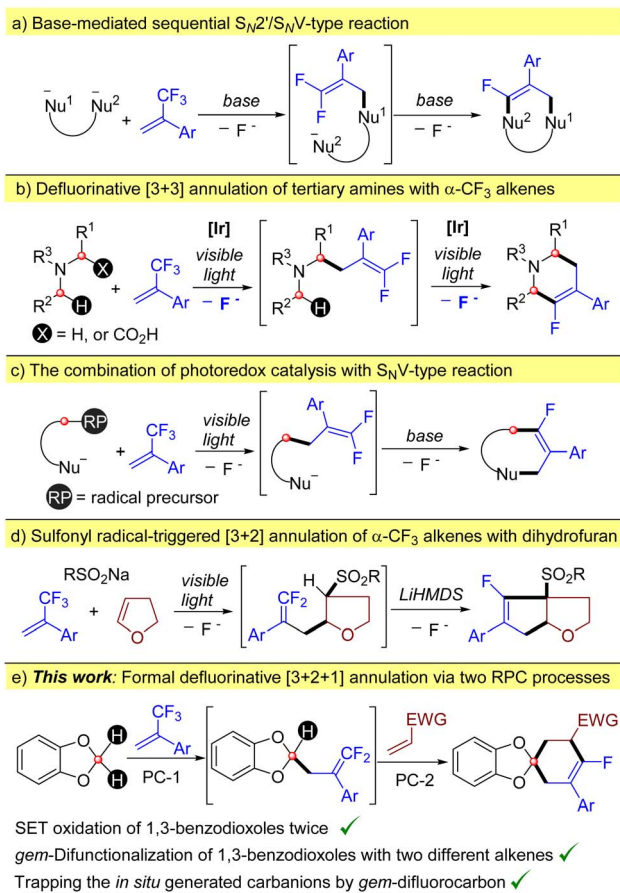
The dual C–F bond cleavage of  $\alpha$ -trifluoromethyl alkenes has been demonstrated as a valuable alternative to the existing C–F bond formation protocols for the construction of monofluorinated carbo- or heterocyclic frameworks.<sup>10</sup> Typically, it is accomplished by means of the classical base-mediated sequential S<sub>N</sub>2/S<sub>N</sub>V reactions of binucleophiles with trifluoromethyl alkenes (Scheme 2a).<sup>11</sup> To distinguish the reactivity of two nucleophilic sites, a fine control on the reaction



Scheme 1 Termination pathways of carbanions.

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Scheme 2 Cyclization via dual C–F bond cleavage of  $\alpha$ -CF<sub>3</sub> alkenes.

conditions is always necessary. Taking advantage of readily formed  $\alpha$ -amino alkyl radicals by photoredox catalysis, we have previously reported the visible light-mediated [3 + 3] annulation of tertiary amines with  $\alpha$ -trifluoromethyl alkenes. When the alkyl groups of tertiary amines are different, an additional carboxylic group was installed to control the regioselectivity (Scheme 2b).<sup>12</sup> Through the combination of photoredox catalysis and the intramolecular base-mediated  $S_NV$  reaction, the defluorinative annulations of trifluoromethyl alkenes with radical precursors bearing a nucleophilic site have been developed, allowing the dual C–F bond cleavage of a CF<sub>3</sub> group in a more controllable manner (Scheme 2c).<sup>13</sup> To extend such a strategy to substrates without a nucleophilic site,<sup>14</sup> our group recently reported a photocatalytic sulfonyl radical-triggered [3 + 2] annulation of  $\alpha$ -CF<sub>3</sub> alkenes with dihydrofuran (Scheme 2d).<sup>15</sup> Due to the electron-deficient nature of the sulfonyl group, *gem*-difluoroalkenes generated by this three-component reaction can further undergo the  $S_NV$  reaction to give fused pentenes in the presence of LiHMDS. However, the strong basic conditions of the  $S_NV$  reaction not only limit the functional group tolerance but also suffer from some chemoselectivity issues because bases are potential nucleophiles to undergo the  $S_NV$  reaction with *gem*-difluoroalkenes.<sup>16</sup> Therefore, milder alternatives are highly sought after.

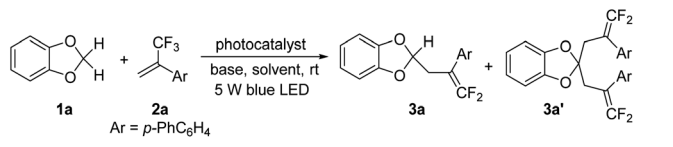
Herein, we report the synergistic combination of multiple termination pathways of carbanions for the synthesis of spiro monofluorinated cyclohexenes *via* a formal defluorinative [3 + 2 + 1] annulation of 1,3-benzodioxoles,  $\alpha$ -trifluoromethyl alkenes and electron-deficient alkenes (Scheme 2e). 1,3-Benzodioxole served as a biradical precursor, which allows the step-by-step radical addition to  $\alpha$ -CF<sub>3</sub> alkenes and electron-deficient alkenes in a net RPC manner. The carbanions *in situ* generated in the second addition process can be trapped by the *gem*-difluoroalkenes intramolecularly to close the ring before they are protonated. Notably, although the radical addition of 1,3-benzodioxole to alkenes has been extensively studied, the 1,3-benzodioxole-2-yl radicals involved in all these reactions are generated *via* the hydrogen-atom transfer (HAT) pathway in the presence of various HAT catalysts,<sup>17</sup> such as (*n*Bu<sub>4</sub>N)<sub>4</sub>[W<sub>10</sub>O<sub>32</sub>] (TBADT),<sup>17a-c</sup> (*n*-Bu<sub>4</sub>N)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>,<sup>17d</sup> and quinuclidine,<sup>17e</sup> thus usually providing Giese-type alkylation products. To the best of our knowledge, the direct photochemical SET oxidation of 1,3-benzodioxoles and their 2-substituted analogues is hitherto not reported.

## Results and discussion

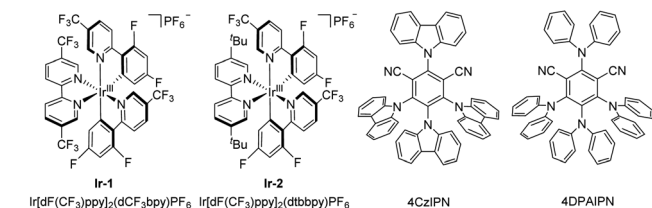
Initially, the reaction conditions for the defluorinative mono- $\gamma,\gamma$ -difluoroallylation of 1,3-benzodioxole **1a** with  $\alpha$ -trifluoromethyl-(*p*-phenyl)styrene **2a** were optimized. Using a 1 : 1 ratio of **1a** and **2a** with Ir[dFCF<sub>3</sub>ppy]<sub>2</sub>(dCF<sub>3</sub>bpy)PF<sub>6</sub> (**Ir-1**) as the photocatalyst and 2,4,6-collidine as the base, the reaction gave a mixture of mono and dual  $\gamma,\gamma$ -difluoroallylation products **3a** and **3a'** in the yields of 51% and 14%, respectively (Table 1, entry 1). The yields of **3a** and **3a'** varied when the reaction was performed in other solvents, such as CH<sub>2</sub>Cl<sub>2</sub>, DMF, THF and MeOH; but the total yields were lower than that in MeCN (Table 1, entries 2–5). On switching the ratio of **1a** and **2a** from 1 : 1 to 1 : 2, the reaction afforded dual functionalization product **3a'** in 90% yield and **3a** was consumed completely (Table 1, entry 6). Other photocatalysts such as Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> (**Ir-2**) and 4DPAIPN were found to be essentially ineffective (Table 1, entries 7 and 8). To our delight, **3a** could be obtained as the major product with 4CzIPN as the photocatalyst, even using excess amounts of **2a** (Table 1, entries 9 and 10). The reaction afforded 29% yield of **3a** without **3a'** when the ratio of **1a** and **2a** was 2 : 1 (Table 1, entry 11). However, the defluorinative coupling of **3a** with the unconsumed **1a** would form monofluorinated alkene **3a''** as the side product (see Scheme S1 in the ESI†). We found that the reaction provided the best yield of **3a** after 13 h of irradiation as monitored by TLC (Table 1, entry 12). Further inspection of the conditions revealed that this reaction cannot proceed when Cs<sub>2</sub>CO<sub>3</sub>, DABCO and DBU were employed as the bases (Table 1, entries 13–15). LiOH is an effective base for the reaction; but it is no better than 2,4,6-collidine (Table 1, entry 16). The control experiments indicated that no product was observed in the absence of either light or the catalyst (Table 1, entries 17 and 18).

Having established the optimal reaction conditions (Table 1, entry 12), we next explored the scope of the mono-*gem*-difluoroallylation of 1,3-benzodioxoles with a variety of  $\alpha$ -CF<sub>3</sub> alkenes



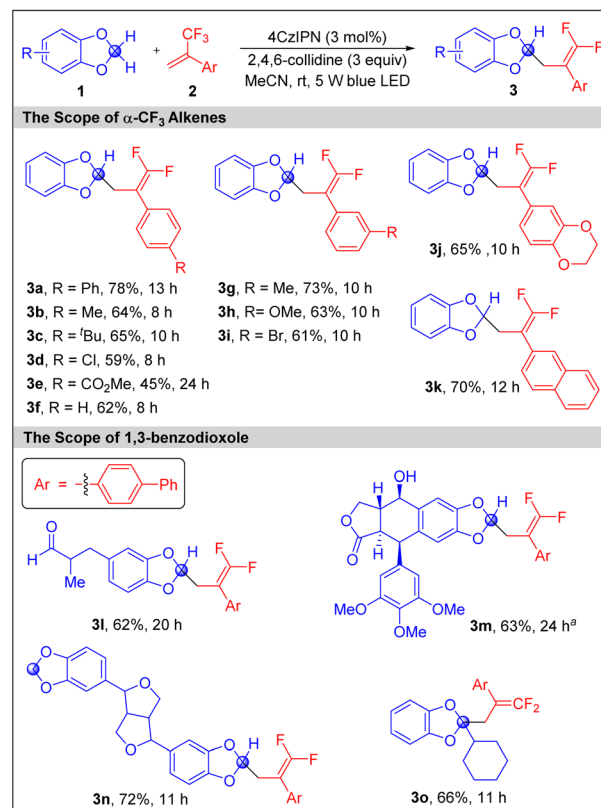
**Table 1** Photocatalytic defluorinative  $\gamma,\gamma$ -difluoroallylation of 1,3-benzodioxole **1a** with **2a**<sup>a,b</sup>


Entry	PC	1a : 2a	Solvent	Base	3a (%)	3a' (%)
1	<b>Ir-1</b>	1 : 1	MeCN	Collidine	51	14
2	<b>Ir-1</b>	1 : 1	CH <sub>2</sub> Cl <sub>2</sub>	Collidine	38	16
3	<b>Ir-1</b>	1 : 1	DMF	Collidine	45	10
4	<b>Ir-1</b>	1 : 1	THF	Collidine	42	12
5	<b>Ir-1</b>	1 : 1	MeOH	Collidine	14	6
6	<b>Ir-1</b>	1 : 2	MeCN	Collidine	0	90
7	<b>Ir-2</b>	1 : 1	MeCN	Collidine	0	0
8	4DPAIPN	1 : 1	MeCN	Collidine	0	0
9	4CzIPN	1 : 1	MeCN	Collidine	56	2
10	4CzIPN	1 : 2	MeCN	Collidine	71	5
11 <sup>c</sup>	4CzIPN	2 : 1	MeCN	Collidine	29	0
12 <sup>d</sup>	4CzIPN	2 : 1	MeCN	Collidine	81	0
13	4CzIPN	2 : 1	MeCN	Cs <sub>2</sub> CO <sub>3</sub>	0	0
14	4CzIPN	2 : 1	MeCN	DABCO	0	0
15	4CzIPN	2 : 1	MeCN	DBU	5	0
16	4CzIPN	2 : 1	MeCN	LiOH	27	0
17 <sup>e</sup>	4CzIPN	2 : 1	MeCN	Collidine	0	0
18	None	2 : 1	MeCN	Collidine	0	0



<sup>a</sup> All the reactions were carried out at the 0.2 mmol scale using **1a**, **2a**, photocatalyst (2.5 mol%) and base (3 equiv) under the irradiation of a 5 W blue LED at room temperature for 24 h. <sup>b</sup> Yield was determined by <sup>19</sup>F NMR using 4-bromotrifluorobenzene as an internal standard. <sup>c</sup> Mono-fluorinated alkene **3a''** by the reaction of **3a** and **1a** was isolated in 43% yield. <sup>d</sup> Reaction time: 13 h. <sup>e</sup> In the dark.

(Scheme 3). The reactions of **1a** with  $\alpha$ -CF<sub>3</sub> styrenes bearing an electron-donating group on the phenyl ring, such as *p*-Me (**3b**), *p*-<sup>t</sup>Bu (**3c**), *m*-Me (**3g**), and *m*-OMe (**3h**) occurred smoothly. The installation of an electron-withdrawing chloro or ester group at the *para*-position of  $\alpha$ -CF<sub>3</sub> styrene slightly disfavoured the reactions, affording **3d** and **3e** in moderate yields.  $\alpha$ -CF<sub>3</sub> (*meta*-bromo)styrene (**3i**) has similar efficiency as that without a substituent (**3f**).  $\alpha$ -CF<sub>3</sub> alkenes substituted by 3,4-ethylenedioxyphenyl (**3j**) and 2-naphthyl (**3k**) were also suitable substrates. Next, **2a** was used to examine the scope of 1,3-benzodioxoles. We were delighted to find that 1,3-benzodioxoles bearing an aldehyde (**3l**) or a free alcohol (**3m**) motif underwent reactions with **2a** smoothly, while these sensitive functional groups remained intact. In the case of **3n**, only one of two symmetric 1,3-benzodioxole units was mono-functionalized. The reaction of **2a** with 2-cyclohexyl 1,3-benzodioxole

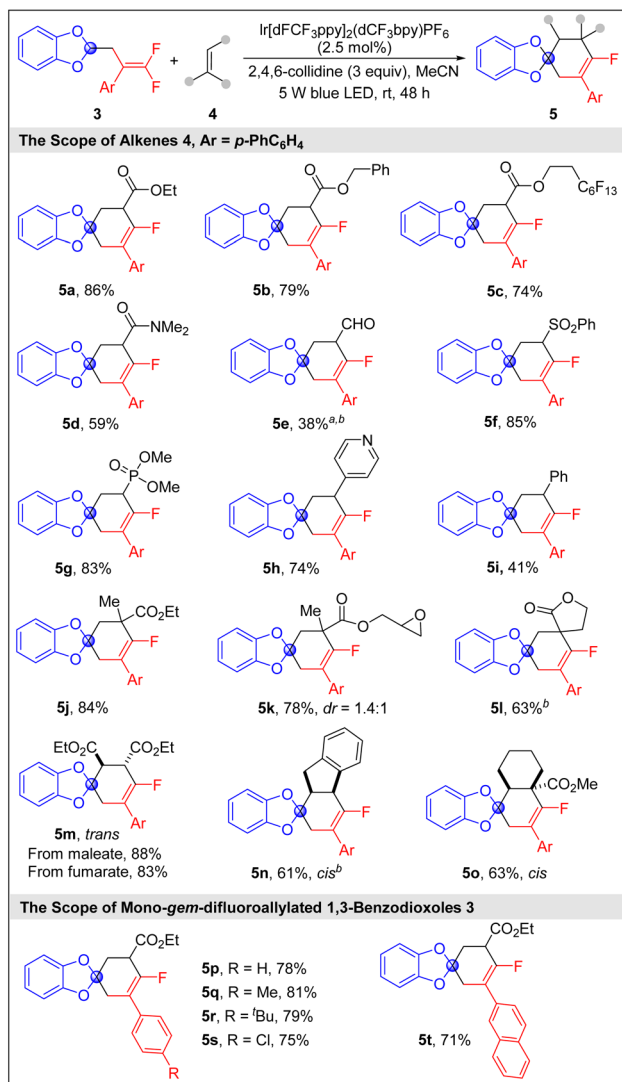


**Scheme 3** Mono- $\gamma,\gamma$ -difluoroallylation of 1,3-benzodioxoles. Reaction conditions: 1,3-benzodioxole **1** (0.4 mmol),  $\alpha$ -CF<sub>3</sub> alkene **2** (0.2 mmol), 4CzIPN (2.5 mol%) and 2,4,6-collidine (3 equiv) under the irradiation of a 5 W blue LED at r.t. Isolated yields. <sup>a</sup>Ir-1 was used as the photocatalyst.

produced **3o** in 66% yield, indicating that the interference of an alkyl group at the 2-position was weak.

With various mono- $\gamma,\gamma$ -difluoroallylated 1,3-benzodioxoles in hand, we then examined their reactions with alkenes for the construction of monofluorocyclohexenes *via* another C-F bond cleavage process. Because Ir[dFCF<sub>3</sub>ppy]<sub>2</sub>(dCF<sub>3</sub>bpy)PF<sub>6</sub> (**Ir-1**) showed better catalytic ability than 4CzIPN for the dual functionalization of 1,3-benzodioxole **1a**, this photocatalyst was used for the reactions of mono- $\gamma,\gamma$ -difluoroallylated 1,3-benzodioxoles **3** with alkenes **4** (Scheme 4). We were delighted to find that the reaction of **3a** and ethyl acrylate (**4a**) provided the anticipated monofluorinated cyclohexene **5a** in 86% yield. Alkenes **4** with benzyl (**5b**) and (2-perfluorohexanyl)ethyl (**5c**) also provided cyclized products in good yields. *N,N*-dimethyl acrylamide was also a suitable alkene for the reaction (**5d**). Using acrolein as the radical acceptor, the desired monofluorinated cyclohexene **5e** was obtained only in 38% yield, while direct protonation product **5e'** was isolated in the yield of 40%. Alkenes monosubstituted by other electron-withdrawing groups (EWGs), such as sulfonyl (**5f**), phosphoryl (**5g**), and 4-pyridinyl (**5h**) were found to be viable. It is noteworthy that the substrates were not limited to electron-deficient alkenes, as exemplified by the reaction of **3a** with styrene to form **5i**. To further demonstrate the generality of this protocol, 1,1- and 1,2-



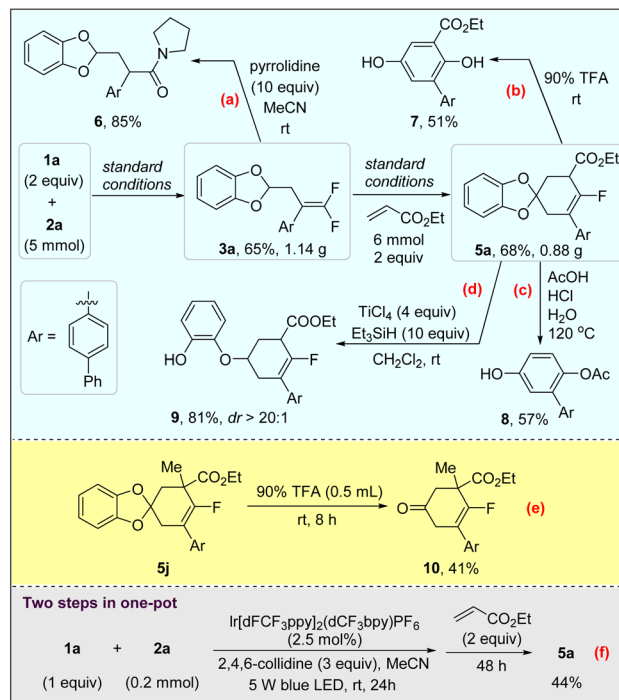


Scheme 4 Synthesis of monofluorinated cyclohexenes *via* photocatalytic defluorinative reactions of **3** with various alkenes **4**. Reaction conditions: mono-*gem*-difluoroallylated 1,3-benzodioxole **3** (0.2 mmol), alkene **4** (0.4 mmol), Ir[dFCF<sub>3</sub>ppy]<sub>2</sub>(dCF<sub>3</sub>bpy)PF<sub>6</sub> (2.5 mol%) and 2,4,6-collidine (3 equiv) under the irradiation of a 5 W blue LED at r.t. for 48 h. Isolated yields. <sup>a</sup>Alkylation but direct protonation product **5e** was isolated in 40% yield. <sup>b</sup>Reaction time: 72 h.

disubstituted alkenes were tested.  $\alpha$ -Methyl acrylates underwent reactions with **3a** to give products in good yields (**5j**, **5k**). An epoxide in the ester motif of **5k** can survive under the present weak basic conditions. Due to the chiral carbon in the epoxide, **5k** was obtained as a 1.4 : 1 mixture of two diastereomers. Spiro product **5l** was constructed in 63% yield by the reaction of **3a** and  $\alpha$ -methylene- $\gamma$ -butyrolactone. When diethyl maleate (*cis*-1,2-substituted alkene) and diethyl fumarate (*trans*-1,2-substituted alkene) were employed as the alkenes, **5m** was obtained with the *trans*-configuration in both cases, as determined by the H–H cosy spectra. In contrast, the reaction of indene and **3a** delivered the *cis*-isomer of **5n** in 61% yield. Remarkably, a fused bicycle bearing a bridgehead quaternary carbon (**5o**) was constructed from tri-substituted alkene methyl 1-cyclohexene-1-

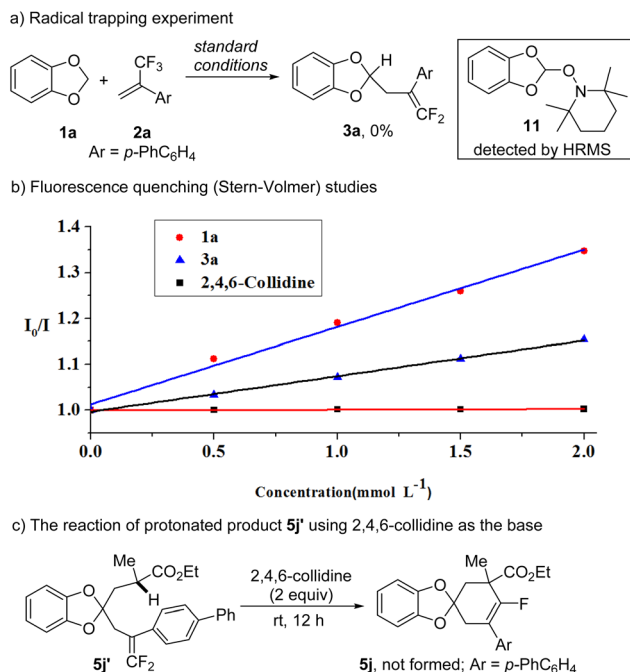
carboxylate in 63% yield with excellent stereoselectivity. The cyclization was found to not be significantly affected by the substituent on the phenyl ring attached to the C=CF<sub>2</sub> unit, providing monofluorinated cyclohexenes **5p–t** in 71–81% yields.

To demonstrate the practicality of this method, **3a** and **5a** were prepared in the gram-scale under standard conditions and their synthetic applications were demonstrated. As shown in Scheme 5a, treatment of mono- $\gamma,\gamma$ -difluoroallylated 1,3-benzodioxole **3a** with pyrrolidine (10 equiv) in MeCN at room temperature afforded amide **6** in 85% yield without any other additives.<sup>18</sup> The oxygen of the carbonyl group might have come from the trace amount of water in the solvent. The catechol protecting group of **5a** can be readily removed in 0.5 mL of 90% v/v aqueous trifluoroacetic acid (TFA) solution at room temperature.<sup>19</sup> However, the deprotected cyclohexenone tends to undergo aromatization followed by aromatic nucleophilic substitution (S<sub>N</sub>Ar) with the aid of an electron-withdrawing ester group, affording 1,4-diphenol **7** in 51% yield eventually (Scheme 5b).<sup>20</sup> The hydrolysis of the cyclic acetal structure of **5a** in aqueous AcOH/HCl solution at 120 °C led to the mono-acetyl substituted 1,4-diphenol **8** with the removal of the ester group.<sup>21</sup> In this case, an acetate ion rather than H<sub>2</sub>O acted as the nucleophile to react with the Csp<sup>2</sup>–F bond, while another hydroxyl group generated by the deprotection and tautomerization of carbonyl remained intact (Scheme 5c). The reduction of **5a** with Et<sub>3</sub>SiH can cleave one C–O bond of a cyclic acetal motif, providing ether **9** in 81% yield with >20 : 1 dr selectivity (Scheme 5d).<sup>22</sup> The deprotection of **5j** using the same conditions as described in Scheme 5b released the carbonyl group successfully, which afforded mono-fluorinated 3-cyclohex-1-one



Scheme 5 Gram scale reaction, synthetic applications of the products, and one-pot reaction.

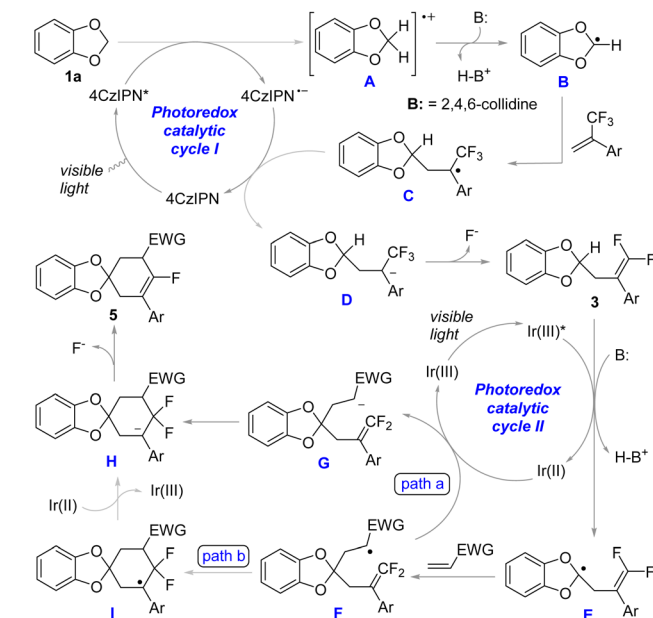




Scheme 6 Mechanistic studies.

10 in 41% yield (Scheme 5e). We also examined the synthesis of 5a *via* two steps in one-pot without the isolation of 3a. To our delight, 5a was isolated in 44% yield under slightly modified conditions (Scheme 5f). One-step reaction by mixing 1a, 2a and 4a together led to a complex mixture, despite the formation of 5a which could be detected by <sup>19</sup>F NMR in 17% yield.

Preliminary mechanistic studies were carried out to probe the possible reaction pathway. When 2,2,6,6-tetramethylpiperidinoxyl (TEMPO) was added to the reaction of 1a and 2a under standard conditions (Table 1, entry 12), the formation of 3a was completely suppressed and an 1,3-benzodioxol-2-yl-TEMPO adduct 11 was detected by HRMS (Scheme 6a), suggesting the generation of a 1,3-benzodioxol-2-yl radical. The luminescence quenching experiments demonstrated that both 1a and 3a displayed luminescence quenching of the excited Ir-1 photocatalyst. By comparing the rates of the slope (Scheme 6b), we found that the quenching ability of 3a was lower than that of 1a, which provides the opportunity of dual functionalization of the CH<sub>2</sub> group with two different alkenes. The cyclic voltammetry experiments (Fig. S3 in the ESI<sup>†</sup>) indicated that 3a has a higher oxidative potential ( $E_{1/2} = +1.53$  V vs. SCE) than 1a ( $E_{1/2} = +1.16$  V vs. SCE).<sup>23</sup> Therefore, Ir-1 with stronger oxidative ability ( $E_{1/2}(\text{PC}^*/\text{PC}^-) = +1.68$  V vs. SCE)<sup>24</sup> produced dual *gem*-difluoroallylation 3a' efficiently, while 4CzIPN ( $E_{1/2}(\text{PC}^*/\text{PC}^-) = +1.35$  V vs. SCE)<sup>25</sup> can restrain the further functionalization of 3a. A decrease in Ir-1\* luminescence was not observed by adding 2,4,6-collidine, indicating that this reagent acted as a base only. In the gram scale reaction for the synthesis of 5j, 7% yield of protonated product 5j<sup>+</sup> was isolated. When 5j<sup>+</sup> was treated with 2,4,6-collidine, no cyclized product 5j can be detected (Scheme 6c). With  $pK_{\text{aH}} 15.00$ ,<sup>26</sup> 2,4,6-collidine is not strong enough to



Scheme 7 A plausible mechanism.

deprotonate the  $\alpha$ -hydrogen of an electron-withdrawing group, for example, the C–H bond  $\alpha$  to an ester group with a  $pK_{\text{a}}$  of around 25.<sup>27</sup> Therefore, a carbanion was generated *in situ* during the photoredox catalytic processes rather than deprotonation by a base.

On the basis of the above results, a plausible mechanism for this two-step formal [3 + 2 + 1] defluorinative annulation is proposed in Scheme 7. The single electron oxidation of 1,3-benzodioxole by the excited photocatalyst 4CzIPN\* produces radical cation A. In the presence of a base, the deprotonation of A generates 1,3-benzodioxol-2-yl radical B, which undergoes addition to the  $\alpha$ -CF<sub>3</sub> alkene to give radical C. The reduction of C by 4CzIPN<sup>•-</sup> forms  $\alpha$ -CF<sub>3</sub> carbanion D and regenerates the photocatalyst in its ground state.  $\beta$ -Fluoride elimination of D leads to mono-*gem*-difluoroallylated 1,3-benzodioxole 3. In the second photoredox catalytic cycle, carbanion G was generated with an Ir complex as the photocatalyst *via* similar processes for the formation of D. Due to the high electron deficiency on *gem*-difluoromethylene carbon, the *in situ* generated carbanion can be trapped by *gem*-difluoroalkene intramolecularly to give H (path a). Alternatively, intramolecular radical addition to *gem*-difluoroalkene followed by SET reduction is also a possible route to form H (path b). However, the presence of a single EWG imparts electrophilic characteristics to alkyl radicals, which disfavours their addition to the high electron deficient *gem*-difluoromethylene carbon.<sup>28</sup> In contrast, alkyl radicals adjacent to an EWG are readily converted to carbanions through SET reduction.<sup>3a</sup> The observation of the direct protonation products, such as 5e' and 5j' indicated the formation of carbanion G. Therefore, path b is less likely for ring closure. Finally, monofluorocyclohexene 5 was produced *via* the  $\beta$ -fluoride elimination of intermediate H.



## Conclusions

In conclusion, we report that a photoredox radical/polar cross-over enables *gem*-difunctionalization of 1,3-benzodioxoles with two different alkenes. The key 1,3-benzodioxol-2-yl radicals were produced by direct single electron oxidation rather than hydrogen atom abstraction. The photocatalytic defluorinative coupling of 1,3-benzodioxoles with  $\alpha$ -trifluoromethyl alkenes cleaves the first C–F bond, while the second C–F bond cleavage was achieved *via* the annulation of the resultant  $\gamma,\gamma$ -difluoroallylated 1,3-benzodioxoles and electron-deficient alkenes. A functionalized monofluorocyclohexene framework was constructed in a formal [3 + 2 + 1] annulation process. Since  $\alpha$ -trifluoromethyl alkenes were readily prepared from bulk industrial chemical 2-bromo-3,3,3-trifluoropropene (BTP), we wish that this dual C–F bond cleavage protocol can be a valuable alternative to the existing C–F bond formation reactions for the synthesis of interesting fluorinated compounds.<sup>29</sup>

## Data availability

The data underlying this study are available in the ESI.†

## Author contributions

J. T. discovered the reaction, performed the experiments and analysed the data. L. Z. conceived and directed the project. L. Z. prepared the manuscript while J. T prepared the ESI.† All authors discussed the experimental results and commented on the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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