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Visible-Light-Induced External Radical-Triggered Annulation To Access CF_2-Containing Benzoxepine Derivatives

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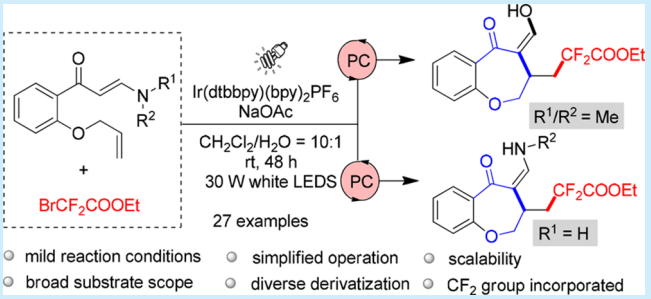
Supporting Information

ABSTRACT: A facile and diversified synthesis of functionalized CF_2-containing benzoxepine derivatives via photoredox catalysis was achieved in this work. This novel protocol features broad substrate scope, mild reaction conditions, operational simplicity, easy scale-up, and versatile derivatization, which would facilitate its practical and broad applications in the construction of valuable and synthetically challenging heterocycles.



Benzoxepines and their derivatives, as representative seven-membered cyclic ethers, are widely encountered structural motifs in many natural products and pharmaceuticals[1] (Figure 1)

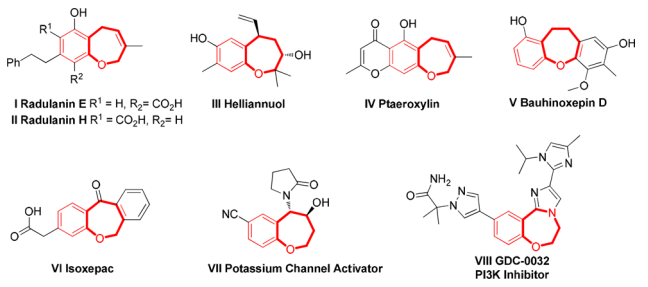


Figure 1. Representative examples of important molecules containing a benzoxepine core skeleton.

with a variety of physiological and biological activities. Thus, development of efficient strategies to easily assemble this significant scaffold has received considerable attention.

Unlike five- and six-membered cyclic ethers, the construction of seven-membered ethers may be more problematic due to unfavorable entropic penalties and transannular interactions associated with their formation.[2] While challenging, the synthesis of benzoxepines has attracted intensive efforts to answer the needs of synthetic and medicinal chemistry. Generally, two major strategies accessing benzoxepines, intermolecular and intramolecular modes, predominately contributed to the progress of the methodology. A variety of transition-metal-catalyzed intermolecular $[m + n]$-cyclizations have been developed to construct this important heterocycle.[3] Very recently, the groups of Jiang,[3g] Ren,[3h] and Meng[3i] reported base-mediated [4 + 3]-annulation. Alternatively, various intramolecular annulations emerged to rapidly install functionalized benzoxepines,[4] which primarily relied on the metal-mediated cyclizations, such as palladium,[4a] rhodium,[4d] osmium,[4e] gold,[4f] and silver.[4g] Despite these impressive advances, in view of step-economy and green and sustainable chemistry, pursuing new annulation pathways accessing such valuable ring systems with higher bond-forming efficiency under mild conditions is of continued interest.

Radical-triggered cascade reactions serve as ideal strategies in the synthesis of heterocyclic scaffolds, owing to multiple bonds which can be formed under a single set of reaction conditions. In recent years, photoredox catalysis has experienced a resurgence in interest as a powerful synthetic tool for effectively promoting radical-involved transformations.[5] Particularly, the visible-light-induced radical addition cascade annulation has demonstrated its synthetic utility in the construction of various ring systems[6] but has rarely been extended to the assembly of a seven-membered cyclic system, especially benzoxepine. In a recent report describing photoredox catalytic cyclization of enaminones promoted by fluorinated radicals to synthesize fluorinated chromones,[7] we demonstrated that the C=C double bond in the enaminone motif showed an advantageous reactivity in the radical addition. Concurrently, the amino group acted as an excellent reductive quencher to regenerate the corresponding photocatalyst and drive the progress of the photocatalytic reaction while avoiding the need of adding stoichiometric reductants. We envisioned that merging an enaminone moiety with other functionality by rational design would provide a versatile photocatalytic platform in the assembly of challenging ring systems. Following this rationale, we intentionally preinstalled an enaminone moiety and olefin unit in the substrate

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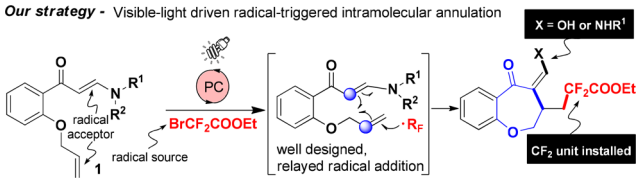
and thus designed novel precursors (*E*)-1-(2-(allyloxy)phenyl)-3-(substituted amino)prop-2-en-1-ones **1** that can be readily synthesized from *o*-hydroxyacetophenones (Scheme 1).

Scheme 1. Strategy Accessing Seven-Membered Cyclic Ethers

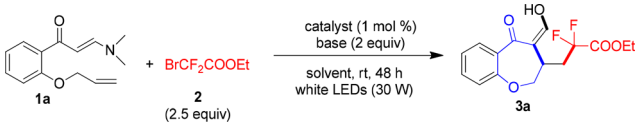


It was commonly accepted that the chemical and physical properties of heterocycles could be readily altered upon introduction of fluorinated functional groups, which is beneficial for modulating their biological activities.[8] Given the recent success on the difunctionalization of alkenes[9] and the significance of difluorinated analogues in medicinal chemistry, 2-bromo-2,2-difluoroacetic acid ethyl ester ($BrCF_2COOEt$)[10] could be considered an ideal fluorinated radical source. As part of our continued interest in the photoredox catalysis,[7,11] we reasoned that simultaneous assembly of benzoxepines and installment of the CF_2 unit can be easily realized under photocatalytic conditions (Scheme 1). We, herein, report a visible-light-driven external radical-triggered intramolecular annulation to efficiently assemble CF_2-bearing benzoxepines, which would surely enrich the library of diverse fluorine-containing seven-membered heterocycles.

We commenced our exploration with the reaction of (*E*)-1-(2-(allyloxy)phenyl)-3-(dimethylamino)prop-2-*en*-1-one (**1a**) with $BrCF_2COOEt$ (**2**) under irradiation of white LEDs (30 W) (Table 1). Catalyst screening demonstrated that Ir(dtbbpy)$(bpy)_2PF_6$ was the premium choice, whereas eosin Y and rhodamine B were ineffective in this reaction (Table 1, entries 1−5). Noticeably, it was found that the enamine group was unexpectedly hydrolyzed, giving benzoxepine **3a** bearing a 1,3-dicarbonyl functional group as the corresponding enol. Conceivably, the resulting 1,3-dicarbonyl moiety offers broader synthetic opportunities for further derivatization of the resulting benzoxepines. Subsequently, several bases were also evaluated in the reaction, of which NaOAc provided the highest yield (Table 1, entries 6−10). In addition, various solvents were also screened (Table 1, entries 11−16), and CH_2Cl_2 was the optimal choice with a slightly improved yield (42%, Table 1, entry 14). Further increasing the amount of the catalyst did not improve the chemical yield (Table 1, entry 17). Because water is necessary for this transformation, 0.4 mL of H_2O (CH_2Cl_2/H_2O = 10:1) was added to this system, and desired product **3a** was obtained in 57% yield. However, adding more water led to a slightly decreased yield. To gain mechanistic insight into the reaction, several control experiments were carried out. The desired product could not be obtained in the absence of photocatalyst or light (Table 1, entries 20 and 21), revealing that this transformation is a photocatalytic process. When TEMPO, as a radical inhibitor, was added into the reaction, no desired product was detected (Table 1, entry 22). This result indicates that a radical pathway may be involved in this transformation.

To evaluate the substrate scope of this approach, various (*E*)-1-(2-(allyloxy)phenyl)-3-(dimethylamino)prop-2-*en*-1-ones **1** were prepared and subjected to the optimized reaction conditions. As summarized in Scheme 2, the substitution patterns on the phenyl moiety were first modulated and

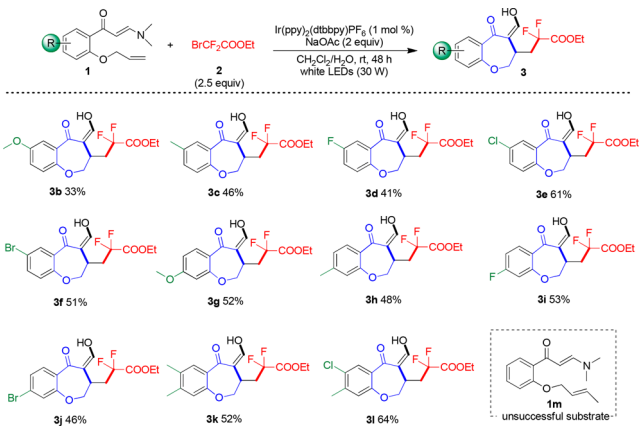
Table 1. Investigation of Reaction Conditions[a]



entry	catalyst	solvent	base	yield[b] (%)
1	eosin Y	acetone	NaOAc	trace
2	rhodamine B	acetone	NaOAc	trace
3	Ir(dtbbpy)$(bpy)_2PF_6$	acetone	NaOAc	30
4	$Ir(ppy)_3$	acetone	NaOAc	18
5	$Ru(bpy)_3PF_6$	acetone	NaOAc	12
6	Ir(dtbbpy)$(bpy)_2PF_6$	acetone		15
7	Ir(dtbbpy)$(bpy)_2PF_6$	acetone	Me_3N	18
8	Ir(dtbbpy)$(bpy)_2PF_6$	acetone	DBU	trace
9	Ir(dtbbpy)$(bpy)_2PF_6$	acetone	K_2CO_3	trace
10	Ir(dtbbpy)$(bpy)_2PF_6$	acetone	KH_2PO_4	<10
11	Ir(dtbbpy)$(bpy)_2PF_6$	MeCN	NaOAc	22
12	Ir(dtbbpy)$(bpy)_2PF_6$	THF	NaOAc	14
13	Ir(dtbbpy)$(bpy)_2PF_6$	DCE	NaOAc	34
14	Ir(dtbbpy)$(bpy)_2PF_6$	CH_2Cl_2	NaOAc	42
15	Ir(dtbbpy)$(bpy)_2PF_6$	DMF	NaOAc	trace
16	Ir(dtbbpy)$(bpy)_2PF_6$	MeOH	NaOAc	
17	Ir(dtbbpy)$(bpy)_2PF_6$	CH_2Cl_2	NaOAc	40[c]
18	**Ir(dtbbpy)$(bpy)_2PF_6$**	**CH_2Cl_2**	**NaOAc**	**57**[d]
19	Ir(dtbbpy)$(bpy)_2PF_6$	CH_2Cl_2	NaOAc	52[e]
20		CH_2Cl_2	NaOAc	[d,f]
21	Ir(dtbbpy)$(bpy)_2PF_6$	CH_2Cl_2	NaOAc	[d,g]
22	Ir(dtbbpy)$(bpy)_2PF_6$	CH_2Cl_2	NaOAc	[d,h]

[a]Reaction conditions: **1a** (0.4 mmol), $BrCF_2COOEt$ (**2**) (2.5 equiv), base (2 equiv), catalyst (1 mol %), solvent (4 mL), irradiation with white LEDs (30 W), rt, 48 h. [b]Isolated yields. [c]5 mol % of catalyst was used. [d]0.4 mL of water was added. [e]1 mL of water was added. [f]Without catalyst. [g]Without light. [h]3 equiv of TEMPO was added.

Scheme 2. Substrate Scope for the Synthesis of CF_2-Bearing Benzoxepines[a]



[a]Reaction conditions: **1** (0.4 mmol, 1 equiv), **2** (1.0 mmol, 2.5 equiv), NaOAc (0.8 mmol, 2 equiv), Ir(dtbbpy)$(bpy)_2PF_6$ (1 mol %), CH_2Cl_2/H_2O (4 mL/0.4 mL), irradiation with white LEDs (30 W), rt, 48 h, isolated yields.

evaluated, which were generally tolerated well in this protocol. Specifically, for the substituent at the *para*-position of the phenol group in the substrate, the presence of a methoxy group evidently undermined the yield while other substituents consistently provided moderate to good yields (Scheme 2, **3b**−**3f**). The electronic feature of substituents at the *meta*-position of the

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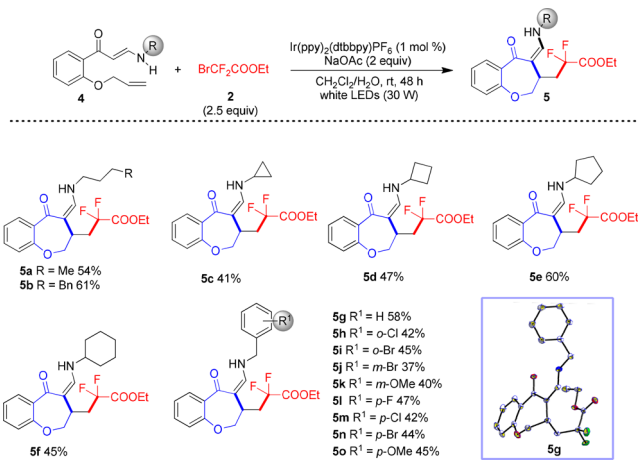
phenol moiety slightly affected the efficacy of this reaction, and thus comparable chemical yields were secured (Scheme 2, **3g**–**3j**). Disubstituted products **3k** and **3i** were also successfully prepared in moderate yields. It is noteworthy that the preparation of the corresponding products bearing Cl or Br would facilitate the expansion to a wider variety of functionalized benzoxepines through subsequent cross-coupling reactions. In contrast to the unsubstituted olefin substrate, the Me-substituted counterpart **1m** was unable to proceed in the cyclization.

Encouraged by the above results, we next turned our attention to the effects of N-substituents (as illustrated in Scheme 3).

Scheme 3. Variation of Enaminone for the Synthesis of CF_2-Bearing Benzoxepines[a]

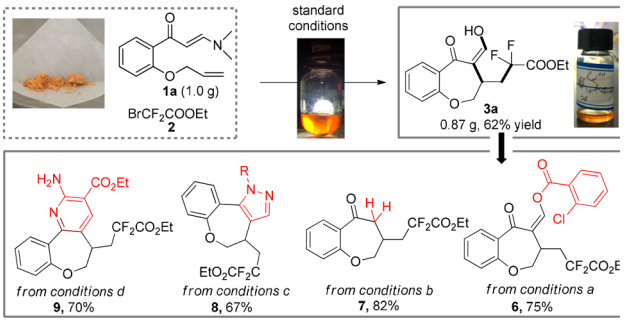


[a]Reaction conditions: **4** (0.4 mmol, 1 equiv), $BrCF_2COOEt$ (**2**) (1.0 mmol, 2.5 equiv), NaOAc (0.8 mmol, 2 equiv), $Ir(dtbbpy)(bpy)_2PF_6$ (1 mol %), CH_2Cl_2/H_2O (4 mL/0.4 mL), irradiation with white LEDs (30 W), rt, 48 h, isolated yields.

Differently, under the standard conditions, *N*-monosubstituted substrates **4** gave the corresponding benzoxepines **5** with the amino groups remaining, even in the presence of water. Presumably, the final deamination step was significantly hindered by the inherently inert leaving capability of primary amino groups in substrate **4**. Given the fact that amino groups widely encountered structural fragments in many pharmaceuticals, modification of the amino group further diversifies the structural features of benzoxepines. As water seemed unnecessary in this transformation, we attempted to remove water from the reaction system, but a decreased yield was obtained. Both acyclic and cyclic substituents on amines were well tolerated in the reaction. Similar yields were achieved for the acyclic substrates (Scheme 3, **5a** and **5b**). For those bearing cyclic substituents, the five-membered analogue gave a relatively higher yield (Scheme 3, **5c**–**5f**). Meanwhile, diversely substituted benzylamines were also tolerated (Scheme 3, **5g**–**5o**). Finally, the structure of **5g** was confirmed by X-ray crystallographic analysis.

Noticing the mildness of the reaction conditions, we exploited the practicality and scalability of this protocol. Thus, the title reaction for enaminones **1a** was performed at gram scale under the standard reaction conditions, which proceeded smoothly to give the corresponding product **3a** in 62% yield without any loss of efficiency. As expected, benzoxepine **3** can be readily transformed into other interesting derivatives owing to the presence of 1,3-dicarbonyl functional groups (Scheme 4). First, esterification of **3a** by acyl chloride was achieved easily to furnish

Scheme 4. Scale-Up and Synthetic Utility of This Reaction[a]

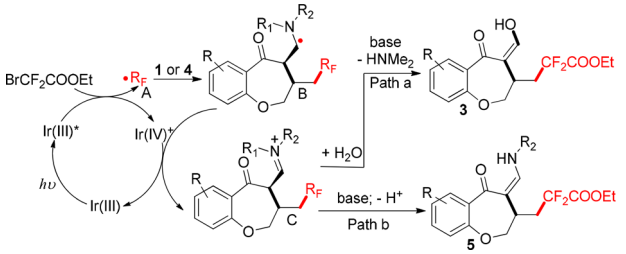


[a]Reaction conditions (all of the reactions were not optimized): (a) Et_3N, 2-chlorobenzoyl chloride, CH_2Cl_2, rt; (b) NaOAc, EtOH, reflux; (c) 4-chlorophenylhydrazine hydrochloride, EtOH, reflux for 30 min then NaOAc; (d) ethyl 2-amidinoacetate hydrochloride, NaOAc, EtOH, rt.

ester **6** in 75% yield. Interestingly, deformylation was observed when treating **3a** with NaOAc in EtOH under reflux, leading to the deformylated derivative **7**. Fused tricyclic analogues **8** and **9** could be effectively assembled by treating **3a** with 4-chlorophenylhydrazine hydrochloride and ethyl 2-amidinoacetate hydrochloride, respectively.[12] Notably, such fused tricyclic benzoxepine analogues exhibited attractive anticancer activity in the previous studies.[1e,f] Thus, the operational ease and diversity for the derivatization of the as-prepared products could greatly broaden the versatility for this protocol in drug discovery.

On the basis of the obtained results in Table 1, a plausible mechanism is proposed in Scheme 5. Initially, the excited state

Scheme 5. Plausible Mechanism



$[Ir(dtbbpy)(bpy)_2PF_6]^*$ was generated under visible-light irradiation, which was further oxidized by $BrCF_2COOEt$ to generate $[Ir(IV)(dtbbpy)(bpy)_2PF_6]^+$ complex and R_F radical species **A**. Subsequently, the R_F radical attacked the propenyl group of substrate **1** or **4** chemoselectively to generate a sequential radical addition cascade process, giving radical intermediate **B**. It was then quickly oxidized by $[Ir(IV)(dtbbpy)(bpy)_2PF_6]^+$ to form iminium intermediate **C** with the concurrent regeneration of $[Ir(dtbbpy)(bpy)_2PF_6]$. The resulting iminium ion **C** was quickly hydrolyzed by water to furnish the final product **3** (path a). In the case of the monosubstituted iminium ion, the deprotonation followed by tautomerization would ultimately provide the corresponding enamine **5** (path b).

In conclusion, we successfully developed a facile and diversified protocol accessing a range of CF_2-containing benzoxepines via visible-light photoredox catalysis under mild conditions. Moreover, the scalability of the reaction and versatility of the transformations for the obtained benzoxepines would greatly broaden the practical applications of the developed protocol in drug discovery. The design and application of

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photocatalytic radical-triggered cascade annulation reactions in the construction of other valuable heterocycles are currently underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00131.

General experimental information and copies of ^{1}H and ^{13}C NMR of new compounds (PDF)

Accession Codes

CCDC 1815308 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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