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Synthesis of fluorine-containing bicyclo[4.1.1] octenes *via* photocatalyzed defluorinative (4 + 3) annulation of bicyclo[1.1.0]butanes with *gem*-difluoroalkenes†

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Although bicyclo[4.1.1] systems are privileged scaffolds in many natural products and drug molecules, efficient synthetic approaches to these systems remain underdeveloped. In this work, we disclose a photoredox-catalyzed defluorinative (4 + 3) annulation of bicyclo[1.1.0]butanes with *gem*-difluoroalkenes, which provides practical and straightforward access to the fluorine-containing bicyclo [4.1.1]octenes. Our protocol is characterized by mild conditions, broad substrate scope, excellent functional group tolerance and good to excellent yields. Notably, the ease and variety of product derivatizations further enrich the diversity and complexity of the fluorine-containing bicyclo[4.1.1] systems.

Introduction

In the realm of drug development, the concept of "escaping flatland" is gaining prominence, as sp^3-hybridized bioisosteres such as bicyclo[1.1.1]pentanes (BCPs), bicyclo[2.1.1]hexanes (BCHs), and bicyclo[3.1.1]heptanes (BCHeps) can improve the pharmacokinetic properties of drug candidates by replacing benzene rings. Additionally, Grygorenko has reported that bicyclo[*n*.1.1] bridged cycloalkane derivatives ($n > 3$) are potential bioisosteres of disubstituted benzene rings. Among these, the bicyclo[4.1.1] systems are particularly significant scaffolds found in natural products and drug molecules (Scheme 1a and 1b).[1] However, efficient synthetic strategies to access these scaffolds remain a challenge and are underdeveloped. Intramolecular cyclization represents an efficient strategy for the construction of bicyclic[4.1.1] systems (Scheme 1c). Oku and co-workers[2] reported the synthesis of oxa-bicyclo[4.1.1]octanes (oxa-BCOs) by thermally-driven [2 + 2] cycloaddition. Bach and co-workers[3] disclosed a photocatalyzed [2 + 2] cycloaddition to access these oxa-BCOs. Recently, Xu's group[4] reported a SmI_2-mediated reductive radical 1,6-addition strategy for constructing bicyclo[4.1.1]octane (BCO) scaffolds. Grygorenko and co-workers[1h] reported an intramolecular nucleophilic substitution strategy for the BCO backbones. However, the requirement for complex substrates and the lack of generality have limited the applicability of this monomolecular reaction strategy. Given the significance of bicyclo[4.1.1] systems, there is still an urgent and ongoing need to develop universal and rapid synthetic methods for obtaining complex BCOs.

Bicyclo[1.1.0]butanes (BCBs) are the smallest fused carbocycles, possessing a strain energy of 267 kJ mol^{-1}.[5] Consequently, they are highly reactive and valuable synthons in many chemical transformations that involve the release of ring strain.[6] Since Blanchard's pioneering work on the thermally induced [3 + 2] cycloaddition of BCBs with olefins, the cycloadditions of BCBs have garnered significant interests from chemists.[7] A variety of [3 + 2] and [3 + 3] cycloadditions of BCBs have been developed through visible light-mediated energy transfer,[8] visible light photoredox catalysis,[9] transition metal catalysis,[10] boron radical catalysis[11] and Lewis acid catalysis,[12] providing efficient strategies for the synthesis of bicyclo[2.1.1] and bicyclo[3.1.1] systems. However, there have been only a few reports on the construction of bicyclo[4.1.1] systems (Scheme 1d).[13] Waser and co-workers demonstrated a Lewis acid-catalyzed [4 + 3] cycloaddition of BCBs with dienol ethers to afford the BCOs.[13a] Feng and co-workers reported a Lewis acid-catalyzed [4 + 3] cycloaddition of BCBs with 3-benzylideneindoline-2-thiones to give the thia-BCOs.[13b] They also reported the palladium-catalyzed decarboxylative [4 + 3] cycloaddition of BCBs with 2-alkylidenetrimethylene carbonates to yield the oxa-BCOs.[13c] Biju and co-workers presented a Lewis acid-catalyzed (4 + 3) annulation of BCBs with *para*-quinone methides to give the oxa-BCOs.[13d] Despite these fascinating

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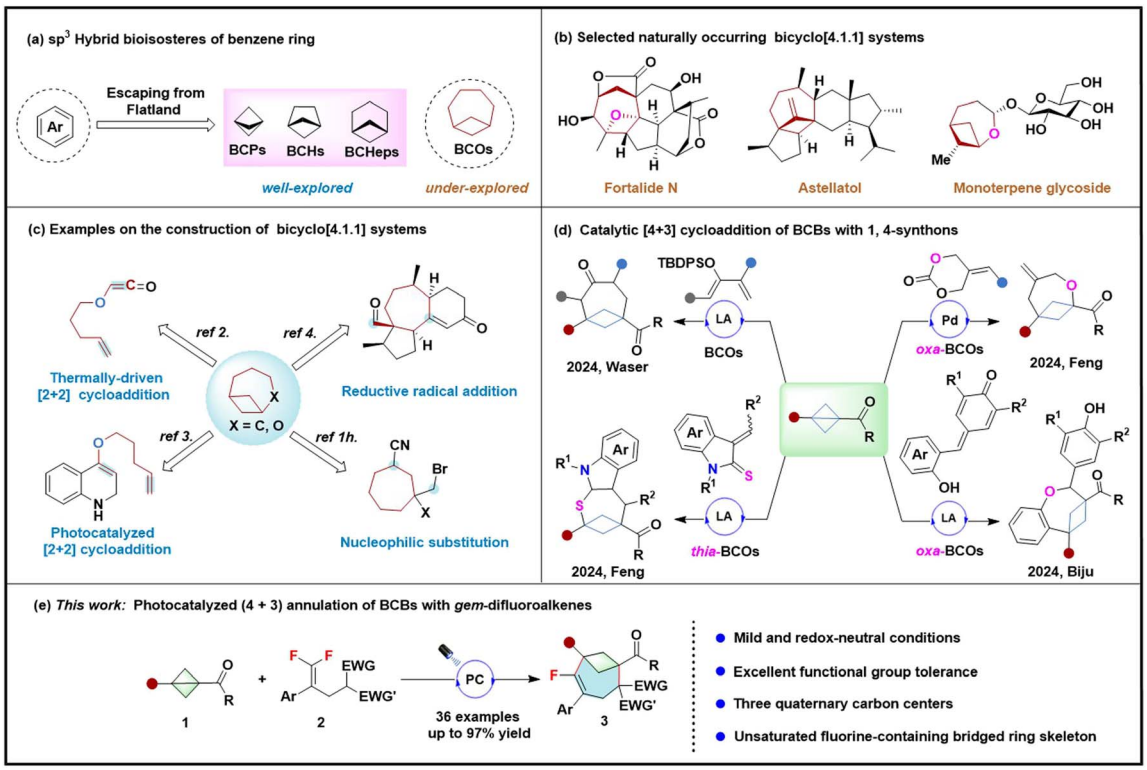
† Electronic supplementary information (ESI) available. CCDC 2382103 and 2382195. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4sc07243j



Scheme 1 Importance and synthetic strategies of the bicyclo[*n*.1.1] systems.

achievements, the synthesis of unsaturated bicyclo[4.1.1] octenes has never been reported. Therefore, there is a significant need to explore new catalytic systems and unsaturated π systems for the annulation reactions of BCBs, which could greatly enrich the structural diversity of bicyclo[*n*.1.1] systems.

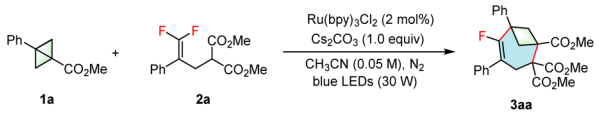
Due to the unique properties of the fluorine atom, organic fluorides represent an attractive class of candidates in the pharmaceutical, agrochemical and material sciences. It has been documented that 15–20% of the newly marketed drugs are organic fluorinated compounds.[14] Thus, the incorporation of the fluorine atom into the bridged ring skeletons is an important but challenging task. In this context, the groups of Ma and Mykhailiuk separately reported a [3 + 1] cycloaddition of BCBs with difluorocarbenes, providing an intriguing strategy for the synthesis of 2,2-difluorobicyclo[1.1.1]pentanes (BCPs).[15] However, the construction of the fluorinated bicyclo[*n*.1.1] alkanes ($n \geq 2$) remains undeveloped. *gem*-Difluoroalkenes, as readily accessible fluorine-containing building blocks, have shown excellent performance in the construction of complex fluorinated compounds.[16] We wonder whether *gem*-difluoroalkenes can serve as 4C synthons in the annulation reactions of BCBs to construct fluorine-containing bicyclo[4.1.1] systems (Scheme 1e). In this study, we report a visible light photoredox defluorinative (4 + 3) annulation of BCBs with *gem*-difluoroalkenes, which results in the formation of monofluorinated bicyclo[4.1.1]octenes. This protocol is characterized by readily available starting materials, mild reaction conditions and excellent functional group tolerance, providing a facile approach to the bicyclo[4.1.1]octenes featuring one fluorine atom and three quaternary carbon centers.

Results and discussion

Initially, BCB **1a** and *gem*-difluoroalkene **2a** were chosen as model substrates to determine the optimal reaction conditions (Table 1). Fortunately, the (4 + 3) annulation of **1a** with **2a** proceeded efficiently using $Ru(bpy)_3Cl_2$ as photocatalyst and Cs_2CO_3 as base in CH_3CN under 30 W blue LEDs irradiation for 12 h, yielding the desired monofluorinated bicyclo[4.1.1]octene **3aa** in 72% NMR yield (entry 1). Other organic and Ir-based photocatalysts were also tested for this transformation, with $Ru(bpy)_3Cl_2$ still being the best (entries 2 and 3). Solvent screening showed that CH_3CN was still the optimal solvent (entries 4 and 5). Screening of inorganic and organic bases showed that K_2CO_3 and K_3PO_4 were also effective, but both gave relatively lower yields than Cs_2CO_3 (entries 6 and 7). Satisfyingly, increasing the amount of **2a** and Cs_2CO_3 to 1.5 equiv. improved the yield of **3aa** to 80% (entry 8). Extending the reaction time from 12 h to 18 h further improved the yield of **3aa** up to 88% (entry 9). Reducing the catalyst loading to 1 mol% still gave a comparable yield of **3aa** (entry 10). Finally, control experiments indicated that the photocatalyst, base and visible light irradiation were all essential for this conversion (entry 11).

With the optimal conditions in hand, the generality and limitations of the BCBs **1** were first evaluated using the *gem*-difluoroalkene **2a** as a model substrate (Table 2). A variety of 1,3-disubstituted BCBs **1** bearing an ester group reacted efficiently

Table 1 Optimization of reaction conditions[a]

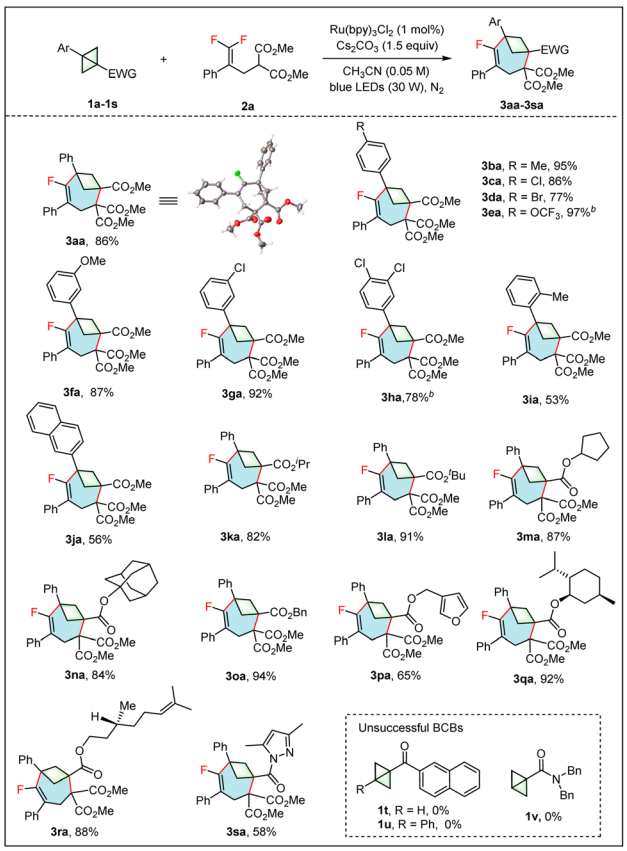


Entry	Variation from standard conditions	Yield
1	None	72
2	4CzIPN, $[Acr^+\text{-}Mes]ClO_4^-$	60, trace
3	$Ir[dF(CF_3)ppy_2(dtbbpy)]PF_6$	68
4	Acetone or DCE as solvent	58, 37
5	THF or toluene as solvent	36, 65
6	K_2CO_3 or K_3PO_4 as base	36, 34
7	Et_3N as base	Trace
8	1.5 equiv. of **2a** and Cs_2CO_3	80
9	18 h	88
10	1 mol% $Ru(bpy)_3Cl_2$	89 (86)[b]
11	No PC or no base or no *hv*	0

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.24 mmol, 1.2 equiv.), PC (2 mol%), Cs_2CO_3 (0.2 mmol, 1.0 equiv.), in CH_3CN (0.05 M), blue LEDs (30 W), rt, for 12 h, under N_2. Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield.

with *gem*-difluoroalkene **2a** to yield the desired fluorinated products **3aa–3pa** in good to excellent yields. Among these, the structure of **3aa** was further confirmed by single crystal X-ray diffraction. Meanwhile, we carried out a crystallographic analysis of the ORTEP diagram for **3aa** and provided the values of the geometrical parameters (r, θ, φ_1, φ_2) associated with the exit vectors. As noted by Grygorenko and coworkers,[1h] all these values fall within the β region of the exit vector plot, and therefore, can be considered as bioisosteres of *meta*-disubstituted benzene (Fig. 1). The electronic effect on the benzene ring didn't show any significant influence on the reaction efficiency. BCBs with electron-withdrawing or -donating groups at the *para*- and *meta*-positions of the benzene ring all reacted well to afford the desired products **3aa–3ha** in excellent yields. Functional groups, such as Br (**3da**) and OCF_3 (**3ea**) were fully compatible with this reaction. The BCB with an *ortho*-Me group on the benzene ring gave a relatively lower yield (**3ia**, 53% *vs.* **3ba**, 95%), probably due to steric hindrance. The 2-naphthyl substituted BCB **1j** also worked efficiently and gave a moderate yield of **3ja**. In addition to the methyl ester, BCBs containing various ester groups, including alkyl esters (**1k** and **1l**), cycloalkyl esters (**1m** and **1n**), benzyl ester (**1o**) and furan-2-ylmethyl ester (**1p**) all gave the corresponding products **3ka–3pa** in 65–94% yields. The steric hindrance of the ester group did not affect the reaction efficiency. Remarkably, the BCBs obtained from complex natural alcohols such as menthol and citronellol were also applicable to this reaction, giving products **3qa** and **3ra** in 92% and 88% yields, respectively. The BCB containing an amide group (**1s**) was also a viable substrate, giving the product **3sa** in 58% yield. Unfortunately, the substituted BCBs containing a carbonyl (**1t** and **1u**) or amide group (**1v**) did not yield the expected products.

Table 2 Scope of BCBs[a]



[a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.5 equiv.), $Ru(bpy)_3Cl_2$ (1 mol%), Cs_2CO_3 (0.3 mmol, 1.5 equiv.), CH_3CN (0.05 M), under N_2. Isolated yield. n. r. = no reaction. [b] Using $Ir[dF(CF_3)ppy_2(dtbbpy)]PF_6$ instead of $Ru(bpy)_3Cl_2$.

The scope of *gem*-difluoroalkenes **2** was then investigated using **1a** as a model substrate (Table 3). A number of aryl *gem*-difluoroalkenes containing electron-donating and -withdrawing groups on the benzene ring were well engaged in this annulation reaction, giving the desired products **3ab–3an** in good to excellent yields. Functional groups, such as OMe (**3ae** and **3ak**), TMS (**3af**), Br (**3ai**) and acetyl (**3al**) all survived well in this transformation, providing opportunities for further product

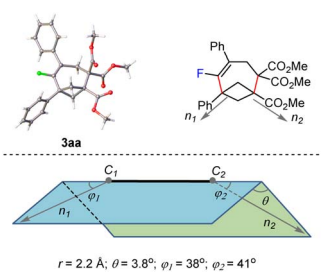
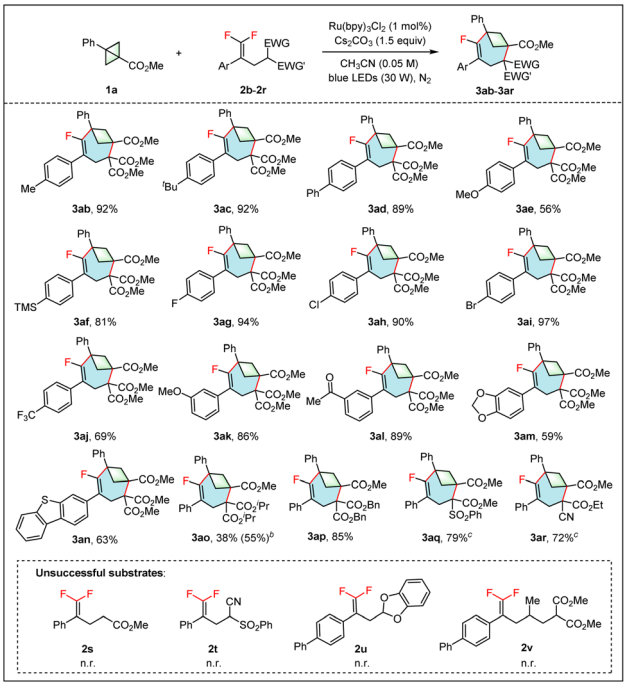


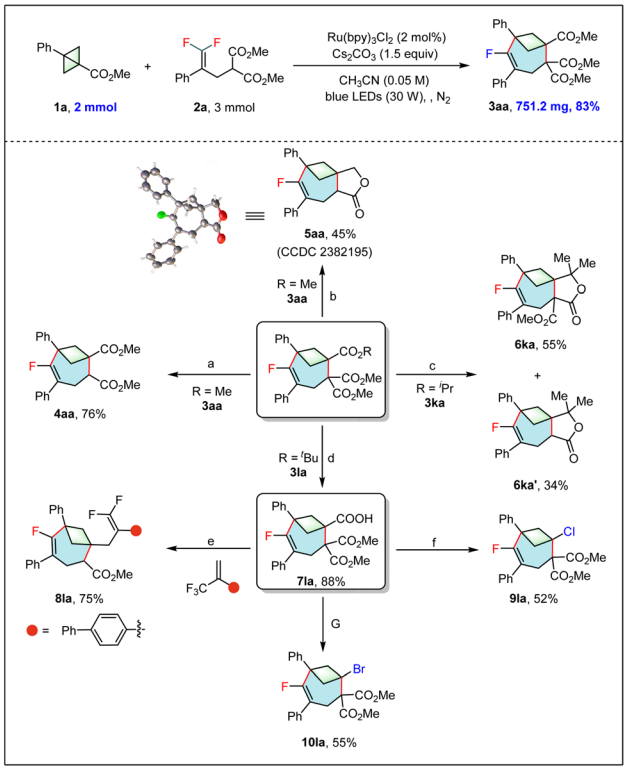
Fig. 1 The corresponding values of the geometrical parameters associated with the exit vectors n_1 and n_2 of **3aa**; geometrical definition of exit vectors and associated parameters.

Table 3 Scope of *gem*-difluoroalkenes[a]



[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.5 equiv.), $Ru(bpy)_3Cl_2$ (1 mol%), Cs_2CO_3 (0.3 mmol, 1.5 equiv.), CH_3CN (0.05 M), under N_2. Isolated yield. n. r. = no reaction. [b] Recovery of **1a** was given in parentheses. [c] Using K_2CO_3 instead of Cs_2CO_3.

Table 4 Scale-up synthesis and derivatizations[a]

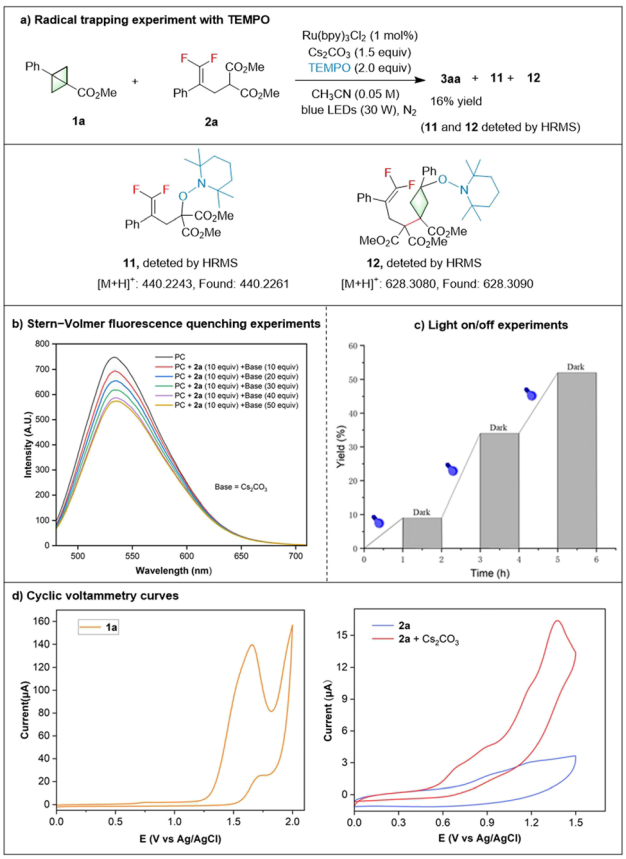


[a] Reaction conditions: (a) LiCl (1.0 equiv.), H_2O (1.0 equiv.), DMSO, 140 °C; (b) $LiAlH_4$ (5.0 equiv.), THF, 0 °C, then cyclohexanone (1.0 equiv.), PTSA (20 mol%), toluene, reflux; (c) MeMgBr (2.5 equiv.), THF, rt; (d) TFA (5.0 equiv.), DCM, rt; (e) 4CzIPN (2 mol%), Cs_2CO_3 (1.0 equiv.), DMSO, blue LEDs (30 W); (f) NCS (2.1 equiv.), $Fe(OAc)_2$ (10 mol%), 4,4′-dimethoxy-2,2′-bipyridine (10 mol%), 2,4,6-collidine (1.8 equiv.), CH_3CN, purple LEDs (390 nm); (g) NBS (2.1 equiv.), $Fe(OAc)_2$ (10 mol%), 4,4′-dimethoxy-2,2′-bipyridine (10 mol%), 2,4,6-collidine (1.8 equiv.), CH_3CN, purple LEDs (390 nm).

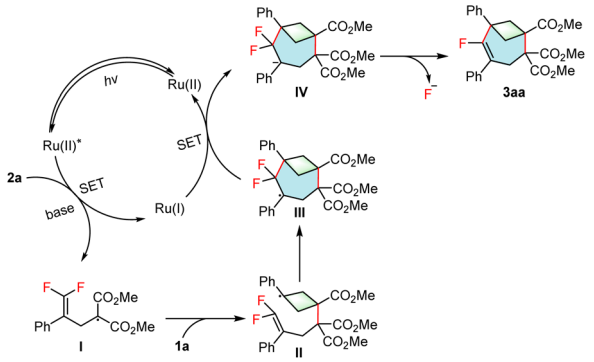
modification. The *gem*-difluoroalkene with a dibenzo[*b*,*d*]thiophen-3-yl group was also amenable, yielding the product **3an** in 63% yield. In addition, the *gem*-difluoroalkene with two isopropyl ester groups also worked, but gave the product **3ao** in only 38% yield due to the low conversion. Satisfactorily, the *gem*-difluoroalkene with two benzyl ester groups gave the target product **3ap** in 85% yield. As anticipated, the *gem*-difluoroalkene with one ester group (**2s**) didn't engage in this annulation reaction, probably due to the polarity mismatch. Replacement of one ester group with a sulfonyl (**2q**) or cyano (**2r**) group also successfully led to the corresponding products **3aq** and **3ar** in good yields. However, no reaction was observed when both ester groups were replaced by cyano and sulfonyl groups (**2t**). The *gem*-difluoroalkene with a 1,3-benzodioxole substituent (**2u**) also failed to undergo this (4 + 3) annulation reaction due to the polarity mismatch. Unfortunately, the *gem*-difluoroalkene **2v**, with an extended carbon chain, was incompatible with the reaction.

To demonstrate the potential application of this reaction, large-scale synthesis and derivatizations of products were carried out (Table 4). When the reaction was scaled up to 2.0 mmol, the monofluorinated bicyclo[4.1.1]octene **3aa** was obtained in 83% isolated yield. Treatment of **3aa** with LiCl and H_2O at 140 °C afforded the decarboxylated product **4aa** in 76% yield. Reduction of **3aa** with $LiAlH_4$ followed by treatment of the crude product with PTSA and cyclohexanone led to an unexpected product **5aa** in 45% yield. When **3ka** was treated with 2.5 equiv. of MeMgBr, two different lactones **6ka** and **6ka′** were formed in 55% and 34% yields respectively. The *tert*-butyl ester group in **3la** could be hydrolyzed using TFA to yield the product **7la** in an 88% yield. The acid **7la** could be reacted with α-CF_3 alkene under photoredox catalysis to give the *gem*-difluoroalkene **8la** in a 75% yield through a decarboxylation/radical addition/β-fluorine elimination cascade. Notably, the decarboxylative halogenations of **7la** could also be achieved *via* an iron-catalyzed LMCT strategy, leading to the formation of the chloride **9la** and bromide **10la** in yields of 52% and 55%, respectively.

To shed light on the mechanism of this annulation reaction, some control experiments were carried out (Scheme 2). Firstly, when 2.0 equiv. of TEMPO, a well-known radical scavenger, was added to the system, the model reaction was significantly inhibited, with the yield reduced from 89% to 16%. In addition, alkyl-TEMPO adducts **11** and **12** were detected by HRMS, indicating that the reaction proceeded *via* a radical pathway. A series of fluorescence quenching experiments were then carried out using 4CzIPN as the photosensitizer.[17] It was found that the



Scheme 2 Mechanism studies.



Scheme 3 Proposed mechanism.

4CzIPN* can be efficiently quenched by the anionic **2a**, suggesting that an excited state charge transfer occurred between the 4CzIPN* and the anionic **2a**. The light on/off experiments showed that continuous visible light irradiation was essential for this conversion. Finally, cyclic voltammetry (CV) experiments were conducted. BCB **1a** exhibited an oxidation peak at +1.4 V *versus* the saturated calomel electrode (SCE), which is considered beyond the reach of the $Ru(bpy)_3Cl_2$ excited state at +0.77 V *versus* SCE. The oxidation potential of compound **2a** was effectively lowered from 0.69 V to 0.56 V *versus* SCE in the presence of a base. These findings suggest that the oxidation of **2a** by the $Ru(bpy)_3Cl_2$ excited state is thermodynamically favorable.

Based on the above results, a plausible pathway is proposed in Scheme 3. First, the ground state Ru(II) is irradiated with visible light to form the excited state Ru(II)*. A SET event then occurs between the Ru(II)* and the deprotonated **2a** to form the electrophilic radical intermediate **I** and Ru(I). Intermediate **I** then undergoes regioselective addition to BCB **1a** to give the alkyl radical intermediate **II**. Intermediate **II** undergoes intramolecular radical addition to give the benzyl radical intermediate **III**, which is reduced by Ru(I) to give the carbanion intermediate **IV** and regenerate the Ru(II) species. Finally, β-fluorine elimination takes place to give the target product **3aa**.

Conclusions

In summary, we have developed a photoredox (4 + 3) annulation of bicyclo[1.1.0]butanes (BCBs) with *gem*-difluoroalkenes that provides a facile approach to the all-carbon bicyclo[4.1.1] octenes with one fluorine atom and three quaternary carbon centers. This protocol features readily available starting materials, mild conditions, excellent functional group tolerance and good to excellent yields. Remarkably, the ease of large-scale synthesis and derivatizations highlights its potential application in organic synthesis. The incorporation of fluorine atom may further modify the physicochemical properties of this all-carbon bicyclo[4.1.1] system and would be valuable for the development of new drugs.

Data availability

The authors confirm that the data supporting the findings of this study are available within the ESI.†

Author contributions

K. Z. performed all the experiments and prepared the manuscript and ESI.† Z. G. and Y. X. performed the preparation of raw materials. P. L., P. G., X.-H. D. and L.-N. G. directed this project and revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

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