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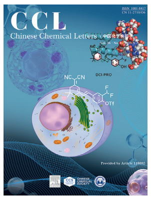

A general synthesis of *gem*–difluorobicyclo[2.1.1]hexanes

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ABSTRACT

Bridged bicyclic cores have been recognized as valuable bioisosteres of benzene ring, which are of great value in medicinal chemistry. However, the development of fluorinated bicyclic skeletons, which encompass two privileged elements widely acknowledged for fine tuning the working effect of target molecules, are far less common. Herein, we present a general and practical synthesis of *gem*–difluorobicyclo[2.1.1]hexanes (diF-BCHs) from readily available difluorinated hexa-1,5-dienes through energy transfer photocatalysis. By taking advantage of an efficient Cope rearrangement, the preparation of both constitutional isomers of diF-BCHs is readily achieved under identical conditions. The operational simplicity, mild conditions and wide scope further highlight the potential application of this protocol. Moreover, computational studies indicated a positive effect of fluorine atoms in lowering either the triplet or FMO energies of the hexa-1,5-diene substrates, thus promoting the present photoinduced [2 + 2] cycloaddition.

Bridged bicyclic cores have garnered exceptionally broad interests in recent years, largely because of the notation of “escape from flatland” that is prevailing in medicinal chemistry [1-5]. Therefore, the synthesis of bicyclic frameworks has evolved to a rapidly growing area in synthetic organic chemistry. For example, during the past few years, a wealth of studies have been directed toward the construction and application of bicyclo[1.1.1]pentanes (BCPs), which serve as 3D bioisosteres of *para*-substituted phenyl rings [6-10]. In contrast, the analogous bicyclo[2.1.1]hexanes (BCHs), which are bioisosteres of mono-substituted or ortho/meta-disubsituted benzene, received much less attention (Fig. 1A). In this context, intramolecular [2 + 2] cycloaddition of hexa-1,5-dienes is demonstrated to be an appealing strategy for the assembly of BCHs for decades. While efficient, UV light irradiation is always required in most reported examples, which more or less attenuates its broader applications [11-17]. Recently, Riggoti/Bach [18], Fessard/Salomé [19] and Walker [20] have took a massive stride forward in extending the applicability of this strategy by using visible light irradiation, however, a conjugated aryl group proved to be indispensable for substrate activation, thus engendering a much restricted flexibility of functionality at the bridgehead of BCHs (Fig. 1B, left equation). Alternatively, by leveraging the strain-release-driven cycloaddition of bicyclobutanes (BCBs), a straightforward synthesis of BCHs/(hetero)BCHs with much expanded structural diversity was successfully developed by the groups of Glorius [21-24], Brown [25], Leicht [26], Li [27], Procter [28], Wang [29], Deng [30], Feng [31] and Studer [32], particularly for those containing C2 and C3 substituents (Fig. 1B, right equation). Notwithstanding the impressive progress, conspicuous limitation with respect to structural diversity of BCHs is still of concern. Driven by the ever-increasing demand of structurally diversified BCHs in drug development, the continuing exploration of more general and practical synthetic protocols, especially those targeting BCHs beyond the reach of prior arts, is still highly sought after.

As a popular tactic in drug design, incorporation of fluorine atoms into the structure of drug candidates is routinely employed for improving binding affinity, metabolic stability and bioavailability [33-35]. However, the combination of fluorine substitution and bridged bicyclic framework, namely the fluorinated bicyclic structural motifs, remains essentially underexplored. We surmise that the main reason for this outcome may lie in the deficiency of effective synthetic protocols [36,37]. Taking consideration of the daunting challenge of peripheral decoration of bicyclic compound through site-selective C(sp^3)–H bond fluorination, resorting to use of fluorinated building blocks is anticipated to be more amenable. Nevertheless, appropriate fluorinated sub-

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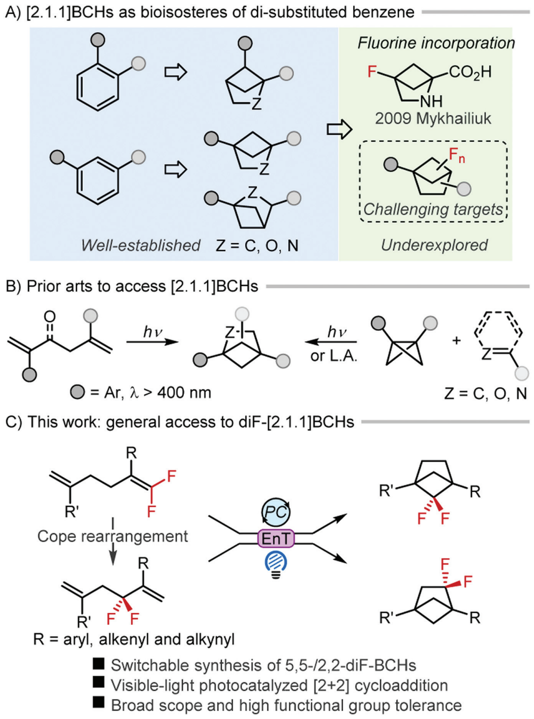
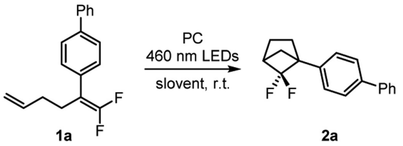


Fig. 1. State-of-arts for construction of bicyclo[2.1.1]hexanes.

Table 1
Optimization of reaction conditions.[a]



Entry	PC	Solvent	Yield (%)
1	Benzophenone	DMSO	ND
2	Thioxanthen-9-one	DMSO	ND
3	4CzIPN	DMSO	30
4	$Ir(ppy)_2(dtbpy)(PF_6)$	DMSO	ND
5	$Ir(dF(CF_3)ppy)_2(bpy)(PF_6)$	DMSO	99 (96)
6	*fac*-$[Ir(ppy)_3]$	DMSO	59
7	$Ru(bpy)_3Cl_2$	DMSO	NR
8	$Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$	DMSO	95
9	$Ir(dF(CF_3)ppy)_2(bpy)(PF_6)$	DCM	86
10	$Ir(dF(CF_3)ppy)_2(bpy)(PF_6)$	THF	10
11	$Ir(dF(CF_3)ppy)_2(bpy)(PF_6)$	1,4-Dioxane	Trace
12	$Ir(dF(CF_3)ppy)_2(bpy)(PF_6)$	MeOH	52
13	$Ir(dF(CF_3)ppy)_2(bpy)(PF_6)$	DMSO	99[b]
14	$Ir(dF(CF_3)ppy)_2(bpy)(PF_6)$	DMSO	99[c]

[a] Unless otherwise noted, the reactions were performed with **1a** (0.2 mmol) and PC (0.002 mmol) in solvent (0.3 mL) at room temperature under the irradiation of LEDs. Yields were determined by ^{19}F NMR with $PhOCF_3$ as internal standard. Isolated yield is indicated in the parentheses.

[b] 410 nm LEDs.

[c] 390 nm LEDs.

strate for this aim is not easily available, and the presence of fluorine atom often led to unpredictable influence to property and reactivity of the parent counterpart. For example, the photoredox reactivity of *gem*–difluoroalkene would complicate its involvement in cycloaddition reaction triggered by photoinduced triplet energy transfer [38-41]. Moreover, the different forms of fluorine substitution might necessitate contrasting reaction conditions for smooth transformation. To the best of our knowledge, only sporadic examples of fluorinated bicyclo[2.1.1]hexanes (F-BCHs) have been reported [42-45]. For instance, Mykhailiuk reported a synthesis of 1-fluorobicyclo[2.1.1]hexanecarboxylic acid from *mono*-fluoroalkene, however, only single example was demonstrated (Fig. 1A, right) [45]. In 2021, we reported an efficient synthesis of 1,1-difluorohexa-1,5-dienes through a S_N2' defluorinative allylation of trifluoromethylalkenes with allylsilanes, and a tandem process integrating ensuing Cope rearrangement, on the other hand, led to an expedient generation of 3,3-difluorohexa-1,5-dienes [46,47]. Inspired by these findings, we envisaged whether the readily available fluorinated hexa-1,5-dienes could be employed in the synthesis of F-BCHs. Herein, we would like to report our recent progress for the synthesis of 5,5-difluorobicyclo[2.1.1]hexanes (5,5-diF-BCHs) by photocatalysis. Moreover, isomeric 2,2-diF-BCHs could also be readily constructed by the same catalytic system from 3,3-difluorohexa-1,5-dienes deriving from Cope rearrangement of 1,1-difluorohexa-1,5-dienes, thus permitting a switchable synthesis of both constitutional isomers of diF-BCHs (Fig. 1C). Additionally, the applicability of dienyne and triene scaffolds allows more flexible derivatization of the resultant diF-BCHs. Being distinguished by the easy availability of starting materials, operational simplicity, mild reaction conditions and broad substrate scope, the present method provides an efficient synthetic tool for the construction of valuable diF-BCHs.

Our study commenced with examination of 1,1-difluorohexa-1,5-diene featuring 2-biphenyl substituent (**1a**), that is easily obtained by our reported γ-defluorinative allylation of trifluoromethylalkenes [46]. Initially, blue light with relatively low energy (λ = 460 nm) was selected as the light source, which was supposed to offer good compatibility of various functionalities. Then the photocatalysts were screened at ambient temperature in DMSO. While benzophenone and thioxanthen-9-one which are commonly used as triplet sensitizers were found ineffective, 4CzIPN furnished the desired product in 30% yield (Table 1, entries 1–3). Encouraged by this result, we further attempted the transition-metal based photocatalysts (entries 4–8), and $Ir(dF(CF_3)ppy)_2(bpy)(PF_6)$ was proved the optimal choice (entry 5). Subsequently, the solvent effect was evaluated. DCM displayed comparable reaction efficiency as DMSO, whereas THF, dioxane and methanol were less effective or invalid (entries 9–12). The reaction was revealed insensitive to the wavelength of light source. The light with wavelength ranging from 390 nm to 460 nm all offered excellent reaction efficiency (entries 13 and 14). Control experiments showed the photocatalyst and photoirradiation were both essential for the reaction.

Under the optimized conditions, the scope and limitations were investigated for the synthesis of 5,5-difluorobicyclo[2.1.1]hexanes (Fig. 2). The substrates bearing an aryl group conjugated with the *gem*–difluoroalkene moiety generally worked well. A wide spectrum of functional groups decorated on different positions of the phenyl ring were tolerated, such as alkoxyl (**2b-2e**), alkyl (**2f**), alkenyl (**2g**), halides (**2h-2j**), ester (**2k** and **2l**), amide (**2m**), trifluoromethyl (**2n**), and sulfonyl (**2o**). The structure of **2f** was unambiguously determined by X-ray crystallography. Remarkably, the styrene (**2g**) and arylbromide (**2j**) motifs which are potentially sensitive towards photosensitization were amenable, albeit with decreased yields. On the other hand, the synthesis of the arylsulfone containing 1,1-difluorohexa-1,5-diene was complicated by serious allylprotonation reaction, which was subjected to the photocatalyzed cycloaddition without further purification (see Supporting information for details). The telescoped procedure provided **2o** in 36% yield over two steps, and the modest yield was largely caused by the first step. Pi-conjugated systems, such as naphthyl (**2p** and **2q**) and 5-benzofuryl (**2r**) groups were demonstrated to be compatible with the reaction conditions. Moreover, the reactions with *O*- and *N*-containing heteroaromatic substitution, including benzofuran (**2s**), pyridine (**2t**) and quinoline (**2u**), afforded the desired products in good to excellent yields. Particularly noteworthy

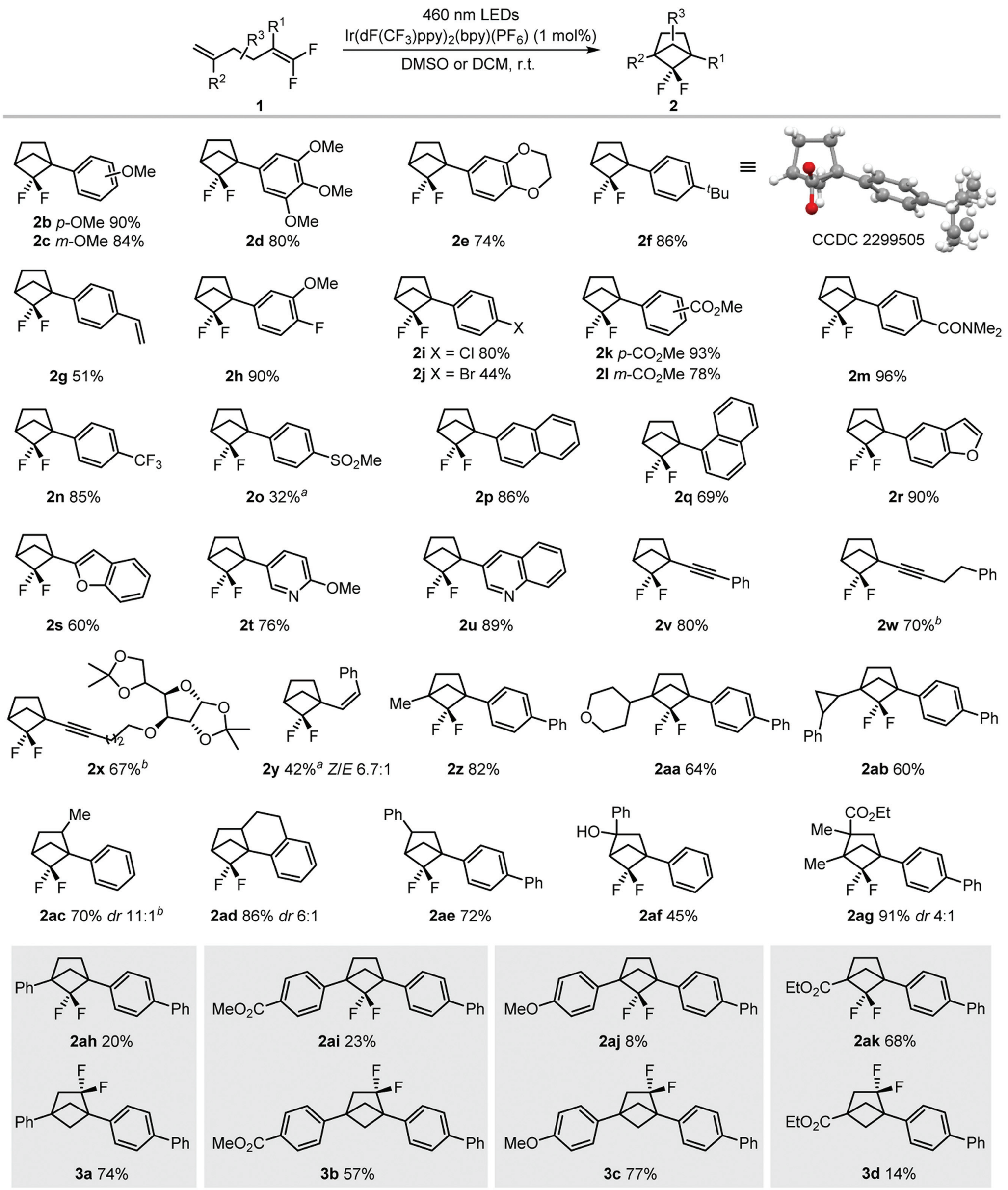


Fig. 2. Substrate scope for the synthesis of 5,5-difluorobicyclo[2.1.1]hexanes. Reaction conditions: **1** (0.2 mmol, 1.0 equiv.) and Ir(dF(CF_3)ppy)$_2$(bpy)(PF_6) (0.002 mmol, 1 mol%) in DMSO or DCM (0.3 mL) was irradiated under Blue LEDs (460 nm) at room temperature. [a]A telescoped procedure was used and overall yield of two steps was indicated. [b]Ir(dF(CF_3)ppy)$_2$(dtbbpy)(PF_6) was used instead of Ir(dF(CF_3)ppy)$_2$(bpy)(PF_6).

is feasibility of dienyne substrate which gave rise to alkynyl substituted diF-BCHs (**2v** and **2w**). The bridgehead substituted alkynyl group is poised for a broad array of further transformations. The mild reaction conditions render the approach useful for late-stage functionalizations as shown by the synthesis of diF-BCH tethered with a glucose motif (**2x**). The cycloaddition took place smoothly even with more challenging triene system (**2y**). As in the case of **2o**, a telescoped procedure was used because of the poor stability of the corresponding triene (**1y**), thereby providing the expected product in 42% yield over two steps (see Supporting information for details). In addition to C1-substituted diF-BCHs, this method also allows the incorporation of substituents at multi-position (C1, C3 and C4) by using readily accessible 1,1-difluorohexa-1,5-dienes. Bridgehead-disubstituted (C1, C4) diF-BCHs could be achieved from the substrates bearing aryl and alkyl substituents at 2- and 4-position, respectively (**2z**, **2aa**, and **2ab**). The generality of the method has also been examined through the synthesis of a series of poly-substituted scaffolds. DiF-BCH bearing substituents at 1,2-position (**2ac**) was achieved by this method in 70% yield with 11:1 diastereoselectivity. A fused tricyclic system was also applicable (**2ad**) despite the increased strain. Furthermore, the substituents including hydroxyl and ester groups, could be installed on the 1,3-, 1,3,3- and 1,2,2,4-position. It was shown 1,1-difluorohexa-1,5-dienes bearing two aromatic substituents at both 2- and 5-position yielded 5,5- and 2,2-positional regioisomers favoring 2,2-diF-BCHs in 94% overall yield (5,5-/2,2- = 1:3.7, **2ah** and **3a**). The formation CF_2-transposed product (**3a**-**3d**) was found to be relevant to the electronic property of R^2-substituent which is in conjugation with non-fluorinated alkene motif, and the yields of 2,2-diF-BCHs increased with a progressive enhancement of electron-donating ability of that substituent (**3b** *vs.* **3c**). Such a trend could be further corroborated by the replacement the 5-aryl group with an ester moiety, which afforded 2,2-diF-BCH in much lower ratio (5,5-/2,2- = 4.8:1, **2ak** and **3d**). Control experiments showed Cope rearrangement of the 1,1-difluorohexa-1,5-dienes of this type could occur at room temperature and be promoted by PC under photoirradiation

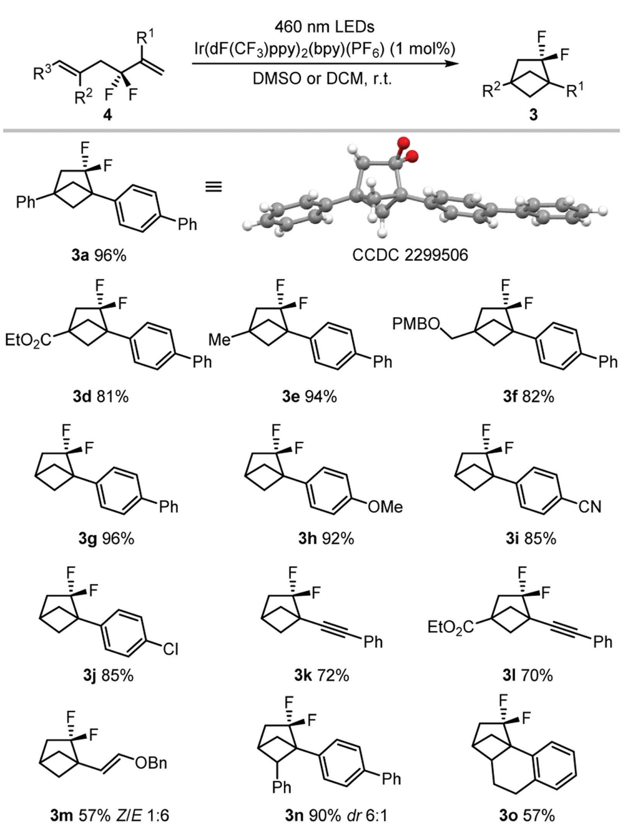


Fig. 3. Substrate scope for the synthesis of 2,2-difluorobicyclo[2.1.1]hexanes. Reaction conditions: **1** (0.2 mmol, 1.0 equiv.) and Ir(dF(CF$_3$)ppy)$_2$(bpy)(PF$_6$) (0.002 mmol, 1 mol%) in DMSO or DCM (0.3 mL) was irradiated under blue LEDs (460 nm) at room temperature.

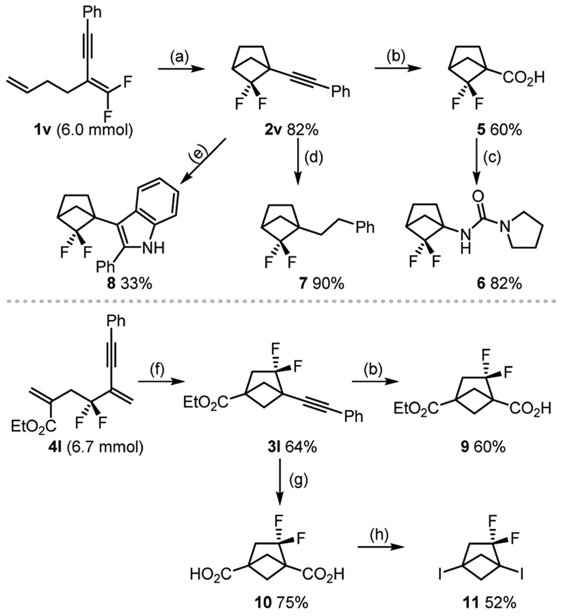


Fig. 4. Synthetic application of diF-BCHs. (a) Ir(dF(CF$_3$)ppy)$_2$(bpy)(PF$_6$) (0.5 mol%), blue LEDs (460 nm, 20 W), DMSO (6 mL), r.t. (b) RuO$_2$·H$_2$O (10 mol%), NaIO$_4$ (8.0 equiv.), MeCN/H$_2$O (15 mL, 3:2), r.t. (c) 1. Ph$_2$P(=O)N$_3$ (1.5 equiv.), Et$_3$N (1.4 equiv.), THF (2 mL), reflux; 2. pyrrolidine (3.0 equiv.), reflux. (d) Pd/C (10 wt%), H$_2$ (1 atm), EtOAc (1 mL). (e) **2v** (1.2 equiv.), Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%), 2-iodoaniline (1.0 equiv.), TABCl (1.0 equiv.), Na$_2$SO$_4$ (5.0 equiv.), DMF (2.0 mL), 95 °C. (f) Ir(dF(CF$_3$)ppy)$_2$(bpy)(PF$_6$) (0.5 mol%), blue LEDs (460 nm, 15 W), DMSO (8 mL), r.t. (g) 1. RuO$_2$·H$_2$O (10 mol%), NaIO$_4$ (8.0 equiv.), MeCN/H$_2$O (15 mL, 3:2), r.t.; 2. NaOH (5.0 equiv.), THF/H$_2$O (30 mL, 1:1). (h) 1. SOCl$_2$ (8.0 equiv.), DMF (cat.), DCM (20 mL), 40 °C; 2. 2-mercaptopyridine *N*-oxide (3.0 equiv.), CF$_3$CH$_2$I (10.0 equiv.), DMAP (7 mol%), DCM (60 mL), 40 °C.

(see Supporting information for details), thus providing structurally reorganized products.

Intrigued by the results to furnish 2,2-diF-[2.1.1]BCHs along with their 5,5-regioisomer, we sought to probe the synthesis of these scaffolds from 3,3-difluorohexa-1,5-dienes that are readily available through the defluorinative allylation of trifluoromethylalkenes developed by our group previously (Fig. 3) [47]. To our delight, the desired 2,2-diF-[2.1.1]BCH **3a** was obtained exclusively from the 3,3-difluorohexa-1,5-dienes under similar reaction conditions with excellent efficiency as well and the structure was confirmed by X-ray crystallography. The substituent at the bridgehead distal to the CF$_2$ could be changed to ester (**3d**), alkyl (**3e** and **3f**) groups without affecting the reaction efficiency, underscoring the potential for variation at the position. Then the generality of the aromatic substituents at 1-position was briefly surveyed. The reaction proceeded uniformly well irrespective of the nature of the arene substituent (**3g-3j**). CF$_2$ linked dienynes were still competent substrates in this reaction, providing both of the mono-substituted (**3k**) and 1,4-disubstituted 2,2-diF-BCH (**3l**) in excellent yields. The cycloaddition could be expanded to an analogous triene system successfully, giving an alkenyl substituted product **3m** in 57%. Considering the privileged utility of 1,5-disubstituted BCHs as the bioisostere of *ortho*-disubstituted arenes, we probed the viability of the 3,3-difluorohexa-1,5-diene bearing substituents at 2- and 6-position concomitantly, with which reaction proceeded in high efficiency with 6:1 diastereoselectivity (**3n**). In addition, a carbocycle-embedded substrate could participate into the reaction to furnish a tricyclic product **3o** in synthetically useful yield.

To showcase the synthetic application of the present method, some follow-up transformations of the diF-[2.1.1]BCHs were explored (Fig. 4). Given the synthetic versatility of alkynyl groups, 5,5-diF-BCH **2v** was chosen as the model compound, which was readily prepared on 6 mmol scale in 82% yield. Through a simple oxidation, a carboxylic acid **5** was obtained in 60% yield, and the following Curtius reaction delivered a diF-BCHs substituted urea **6** in 82% yield. Also, the hydrogenation catalyzed by Pd/C provided an alkyl substituted diF-BCHs **7** that is unable to be prepared by the direct [2 + 2] cycloaddition of the corresponding 5,5-difluorohexa-1,5-diene. We attempted the Larock's indole synthesis with the internal alkyne **2v**, by which an indole featuring a diF-BCH motif **8** was accessed successfully. Further demonstration of the synthetic potential of this method focused upon the elaboration of 2,2-diF-BCH **3l** that carries an alkynyl and an ester group at the C1 and C4 position, respectively. Initially, oxidation of the C−C triple bond led to the formation of a versatile synthon, *mono*-ester of 1,4-dicarboxylic acid **9**, in 60% yield. Meanwhile, the dicarboxylic acid **10** could be obtained in 75% by oxidation and basic work-up from **3l** The availability of carboxylic acids presents an opportunity to access halo-substituted diF-[2.1.1]BCHs. Following the reported method, diiodide **11** was prepared through a Barton ester in 52% yield.

Generally, a photoinduced triplet energy transfer and subsequent intramolecular [2 + 2] cycloaddition *via* a diradical intermediate is proposed for the formation of BCHs from 1,5-dienes [11-19]. Yet, despite the fact that *gem*–difluoroalkenes have been reported to engage in photocatalyzed cyclization reactions, the predominant scenarios rely on an intramolecular radical addition to the fluorinated alkene moiety [48,49], and the energy transfer associated transformation with *gem*–difluoroalkenes is rare [50]. To provide deeper insight into the reaction mechanism, density-functional theory (DFT) calculations were carried out (Fig. 5). Initially, the triplet energy (E_T) for **1a** was cal-

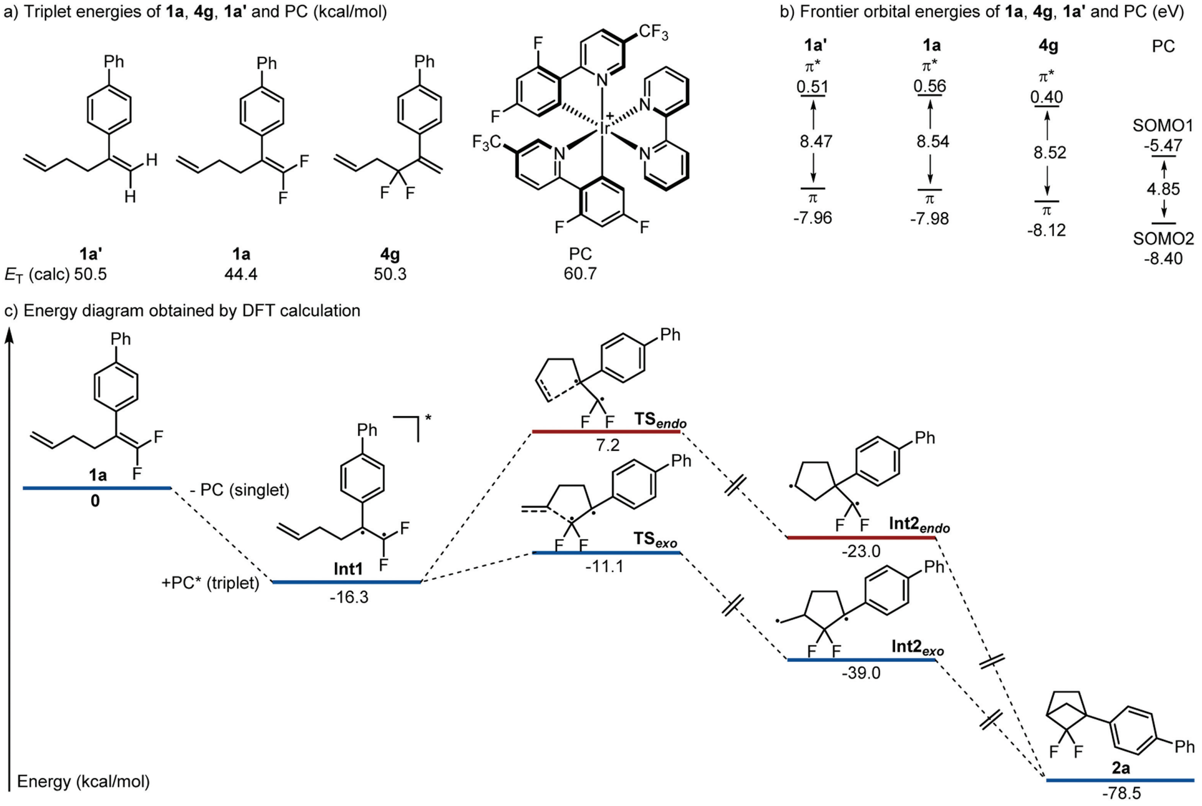


Fig. 5. Mechanistic investigations.

culated to be 44.4 kcal/mol (Fig. 5a), which matches with E_T of Ir(dF(CF$_3$)ppy)$_2$(bpy)(PF$_6$) (PC, 60.7 kcal/mol). Moreover, this value is significantly lower than the non-fluorinated analogue **1a'** (50.5 kcal/mol) and such a lowering of E_T has been suggested to be favorable for the energy transfer process [51,52]. In contrast, moving difluoride to the allylic position of hexa-1,5-diene (**4g**) led to only minimal change of the E_T (from 50.5 to 50.3 kcal/mol). On the other hand, the frontier molecular orbitals (FMOs) energy analysis suggested a positive influence of allylic fluorine that could be attributed to the decreased FMOs energies. Compared with **1a'**, the FMO energies of **4g** are closer to the SOMOs of **PC**, thus allowing enhanced efficiency of Dexter energy transfer (Fig. 5b) [53-56]. In addition, owing to the presence of fluorine atoms, particularly in the cases of 1,1-difluorohexa-1,5-dienes, two different reaction pathways, including 5-*exo* and 5-*endo*, could be conceived for the cyclization step. The 5-*exo* cyclization of diradical **Int1** requires overcoming a Gibbs energy barrier of 5.2 kcal/mol to yield the **Int2*exo***, whose formation is computed to be exergonic by 22.7 kcal/mol relative to **Int1**. In comparison, the Gibbs energy barrier for 5-*endo* cyclization of **Int1** to **Int2*endo*** is computed to be 23.5 kcal/mol, which is much higher than the 5-*exo* pathway (Fig. 5c). This is in agreement with the experimental result obtained from the 1,1-difluorohexa-1,5-diene bearing a cyclopropane substituent at 5-position, with which the three-member ring remained intact in the product **2ab**. Overall, the fluorine atoms were revealed as enabling substituents for the triplet energy transfer event. More importantly, the fluorine effects could be corroborated experimentally (Fig. 6). The non-fluorinated triene **12**, analogous to *gem*–difluorotriene **1y**, was prepared and subjected to standard conditions, but failed to give the target BCH product **13** and only complex mixture was observed. Meanwhile, diF-BCH **2y** was accomplished successfully. Such a comparison unequivocally demonstrated the critical role of fluorine in the [2 + 2] cycloaddition reaction, especially for the challenging substrate.

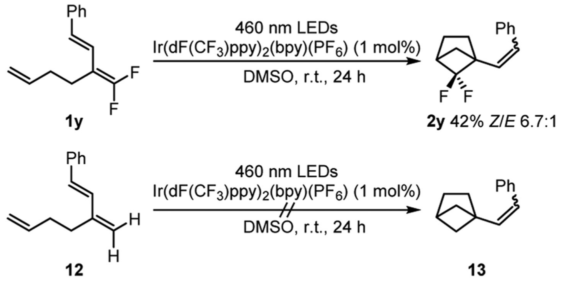


Fig. 6. Evaluation of fluorine effects.

In summary, we have successfully disclosed a general synthetic protocol for the expedient construction of *gem*–difluorobicyclo[2.1.1]hexanes, which represent a class of bicyclic compounds still remaining challenging to prepare. By exploiting visible-light photocatalyzed [2 + 2] cycloaddition, the readily available 1,1- and 3,3-difluorohexa-1,5-dienes by our reported methods allow the incorporation of fluorine atoms into BCH backbone at 2,2- and 5,5-positions with precise regiocontrol. Moreover, through the downstream elaboration of the resulting diF-BCHs, a variety of synthetically useful building blocks, including diF-BCH-substituted heterocycle, carboxylic acid, amine and halide could be accessed. In view of its broad scope and convenient operation, we envision that the protocol will find practical application in the drug discovery process and evoke new efforts for the forge of structurally diversified fluorinated bicyclic skeletons.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Mengyu Wu: Investigation. **Kewei Ren:** Validation. **Chengyu Zou:** Validation. **Jiacheng Chen:** Validation. **Rui Ma:** Validation. **Chuan Zhu:** Writing – original draft, Supervision, Conceptualization. **Chao Feng:** Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110213.

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