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(Fluoro)alkylation of alkenes promoted by photolysis of alkylzirconocenes†

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Difluoroalkylated compounds have important applications in pharmaceutical, agrochemical, and materials science. However, efficient methods to construct the alkylCF_2–alkyl bond are very limited, and the site-selective introduction of a difluoromethylene (CF_2) group into an aliphatic chain at the desired position remains challenging. Here, we report an unprecedented example of alkylzirconocene promoted difluoroalkylation of alkyl- and silyl-alkenes with a variety of unactivated difluoroalkyl iodides and bromides under the irradiation of visible light without a catalyst. The resulting difluoroalkylated compounds can serve as versatile synthons in organic synthesis. The reaction can also be applied to activated difluoroalkyl, trifluoromethyl, perfluoroalkyl, monofluoroalkyl, and nonfluorinated alkyl halides, providing a general method to controllably access fluorinated compounds. Preliminary mechanistic studies reveal that a single electron transfer (SET) pathway induced by a Zr(III) species is involved in the reaction, in which the Zr(III) species is generated by the photolysis of alkylzirconocene with blue light.

Introduction

The site-selective introduction of fluorine atom(s) into organic molecules has important applications in medicinal chemistry, chemical biology, and materials science.[1] For instance, biologically active molecules containing a difluoromethylene (CF_2) moiety at the specific position exhibit improved bioactivities compared with their nonfluorinated counterparts, because the CF_2 can change the metabolic stability, conformation, acidity and polarity of the molecules.[2] Some important pharmaceuticals containing the CF_2 moiety have been discovered for the treatment of tumors and other deceases, such as gemcitabine,[3] vinflunine,[4] and lubiprostone[5] (Fig. 1A). To this end, efforts toward the development of efficient methods to access CF_2-containing molecules have been witnessed over the past decade.[6] However, most of these developed synthesis methods mainly focus on the preparation of difluoroalkylated arenes ($ArCF_2R$) with CF_2 at the benzylic position.[6a,7]

To date, efficient methods to site-selectively introduce CF_2 into an aliphatic chain remain limited. The traditional method to prepare difluoroalkylated compounds relies on the

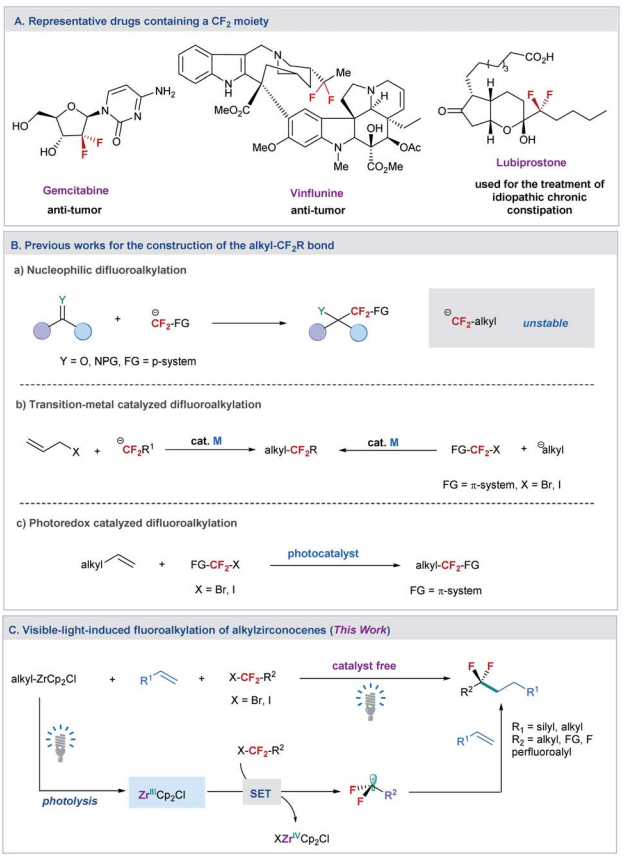

Fig. 1 Strategies for the difluoroalkylation and selected examples of pharmaceutical bearing CF_2 moieties. (A) Representative drugs containing a CF_2 moiety. (B) Previous works for the construction of the alkyl-CF_2R bond. (C) This work: visible-light-induced fluoroalkylation of alkylzirconocenes.

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deoxyfluorination of the carbonyl group with dialkylaminosulfur trifluorides, such as diethylaminosulfur trifluoride (DAST).[8] But the modest functional group tolerance of this method restricts its synthetic applications. Another common method to synthesize such a valuable fluorinated structure is based on the nucleophilic addition of difluoroalkylating reagents to aldehydes, ketones, and imines (Fig. 1B(a)).[6c,9] However, owing to the instability of nucleophilic difluoroalkylating reagents, usually a π-system adjacent to the CF_2 moiety, is needed to stabilize the difluoroalkyl anion,[10] making the method difficult in constructing the alkylCF_2–alkyl bond. Although nucleophilic substitution of aliphatic electrophiles with carbon nucleophiles is well known, the adoption of a similar strategy to react difluoroalkyl halides with aliphatic nucleophiles remains challenging and has not been reported yet.[11] In this context, transition-metal[12] or photo-redox[13] catalyzed difluoroalkylation reactions to construct the alkylCF_2-alkyl bond have been developed (Fig. 1B(b) and B(c)). These methods either need activated coupling partners, such as allylic substrates[12a] and π system functionalized difluoroalkyl halides[12b] (XCF_2-FG, FG = π system, transition-metal catalyzed process), or are difficult to be used in the reaction of aliphatic alkenes with XCF_2–alkyl (*e.g.* for the photoredox catalyzed process),[13c] thus restricting their widespread synthetic applications.

To overcome these limitations and meet the increasing demands of life and materials sciences, new methods that can extend the diversity of the difluoroalkylated structure with site-selective introduction of CF_2 into the aliphatic chain at the desired position are highly desired. Herein, we report an unprecedented example of catalyst free difluoroalkylation of silyl- and alkyl-alkenes with unactivated difluoroalkyl halides promoted by photolysis of alkylzirconocenes (Fig. 1C). The reaction can also be applied to π-functionalized difluoroalkyl, trifluoromethyl, perfluoroalkyl, monofluoroalkyl, and non-fluoroalkyl halides, providing a general method to access fluoroalkylated alkanes. Preliminary mechanistic studies reveal that a single electron transfer (SET) pathway induced by a Zr(III) species is involved in the reaction, in which the Zr(III) species is generated by the photolysis of alkylzirconocenes with visible light. This protocol paves a new way to construct the alkyl–fluoroalkyl bond by using readily available fluoroalkyl halides and aliphatic alkenes.

Results and discussion

Inspired by our nickel-catalyzed difluoroalkylation cross-coupling,[12b,c,14] we chose unactivated difluoroalkyl iodide **1a**[15] and alkylzirconocene **2a** as the model substrates (Table 1), in which alkylzirconocene can be readily prepared from the corresponding alkene **5** and Schwartz reagent ($HZrCp_2Cl$, **6**).[16] Directly adopting the nickel-catalyzed cross coupling failed to provide desired difluoroalkylated alkane **3a** (entry 1). In contrast, the irradiation of the nickel catalyzed reaction with a blue LED (12 W) generated product **3a** in 51% yield along with 27% yield of hydrodeiodinated by-product **4a** (entry 2).[17] The absence of the nickel catalyst could also provide a comparable yield (entry 3), and no reaction occurred without the blue LED

Table 1 Representative results for the optimization of the reaction conditions[a]

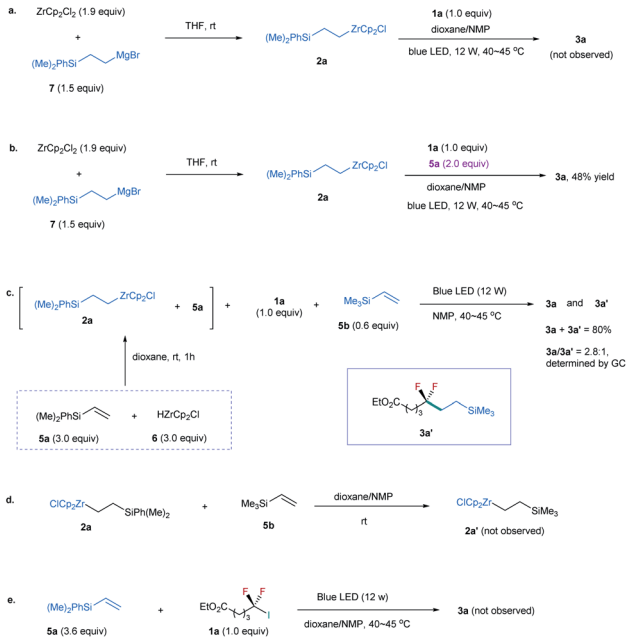
Entry	[Ni] (*x*)	Solvent	**3a**[b] (%)	**4a**[b] (%)
1[c]	$NiBr_2$·DME/bpy (10)	THF	0	5
2	$NiBr_2$·DME/bpy (10)	THF	51	27
3	None	THF	53	33
4[c]	None	THF	nd[e]	nd[e]
5[d]	None	NMP	81(62)	15

[a] Reaction conditions (unless otherwise specified): **1a** (1 equiv., 0.3 mmol), **5a** (0.72 mmol, 2.4 equiv.), **6** (0.6 mmol, 2.0 equiv.), solvent (2 mL), and 12 h. [b] The yield was determined by ^{19}F NMR using fluorobenzene as an internal standard, and the number given in parentheses is the isolated yield. [c] The reaction was conducted without the blue LED. [d] **5a** (1.08 mmol, 3.6 equiv.), **6** (0.9 mmol, 3.0 equiv.), and NMP (3 mL) were used. [e] nd, not detected.

(entry 4), demonstrating that blue light is essential in promoting the reaction. These mild conditions are quite different from the challenge S_N1 or S_N2 substitution of difluoroalkyl halides, because of the difficulty in forming a difluoroalkyl carbocation (S_N1) or the repulsion of the lone pairs of fluorine atoms to the carbon nucleophile (S_N2).[18] This difference implies a novel mechanism, which is discussed below. Encouraged by these results, we tested a series of reaction parameters (for details, see the ESI†), and found that the use of 3.0 equiv. of **2a** with NMP as the solvent could provide **3a** in 81% yield (62% isolated yield) (entry 5).

Because **2a** was derived from the reaction of **6** with excessive silylalkene **5a** (Table 1), this posed a question whether **5a**, instead of **2a**, is involved in the formation of **3a**. To identify the role of **2a**, we prepared **2a** by reaction of alkylmagnesium bromide **7** with $ZrCp_2Cl_2$ (Scheme 1a).[19] However, no **3a** was observed by reaction of **2a** with **1a** (Scheme 1a). In contrast, the addition of **5a** to the reaction could provide the desired product in 48% yield (Scheme 1b). These findings suggest that excessive silylalkene **5a** in the reaction is the substrate responsible for generating **3a** with **1a**. This deduction was further supported by the addition of another silylalkene **5b** to the reaction mixture of **1a**, **2a**, and **5a** under the irradiation of blue light, in which both difluoroalkylated products **3a** and **3a′** were formed (Scheme 1c). Since [Zr]-migration from alkylzirconocene to alkene cannot occur (Scheme 1d),[20] these results clearly demonstrate that the alkene is the substrate to react with difluoroalkyl halide. In addition, the reaction of alkene **5a** with **1a** in the absence of **2a** under the irradiation of a blue LED did not lead to **3a** (Scheme 1e), demonstrating that the alkylzirconocene is essential in promoting the reaction.

Based on the above results, we reoptimized the reaction conditions, and found that the use of 2.5 equiv. of **5a**, 1.2 equiv.

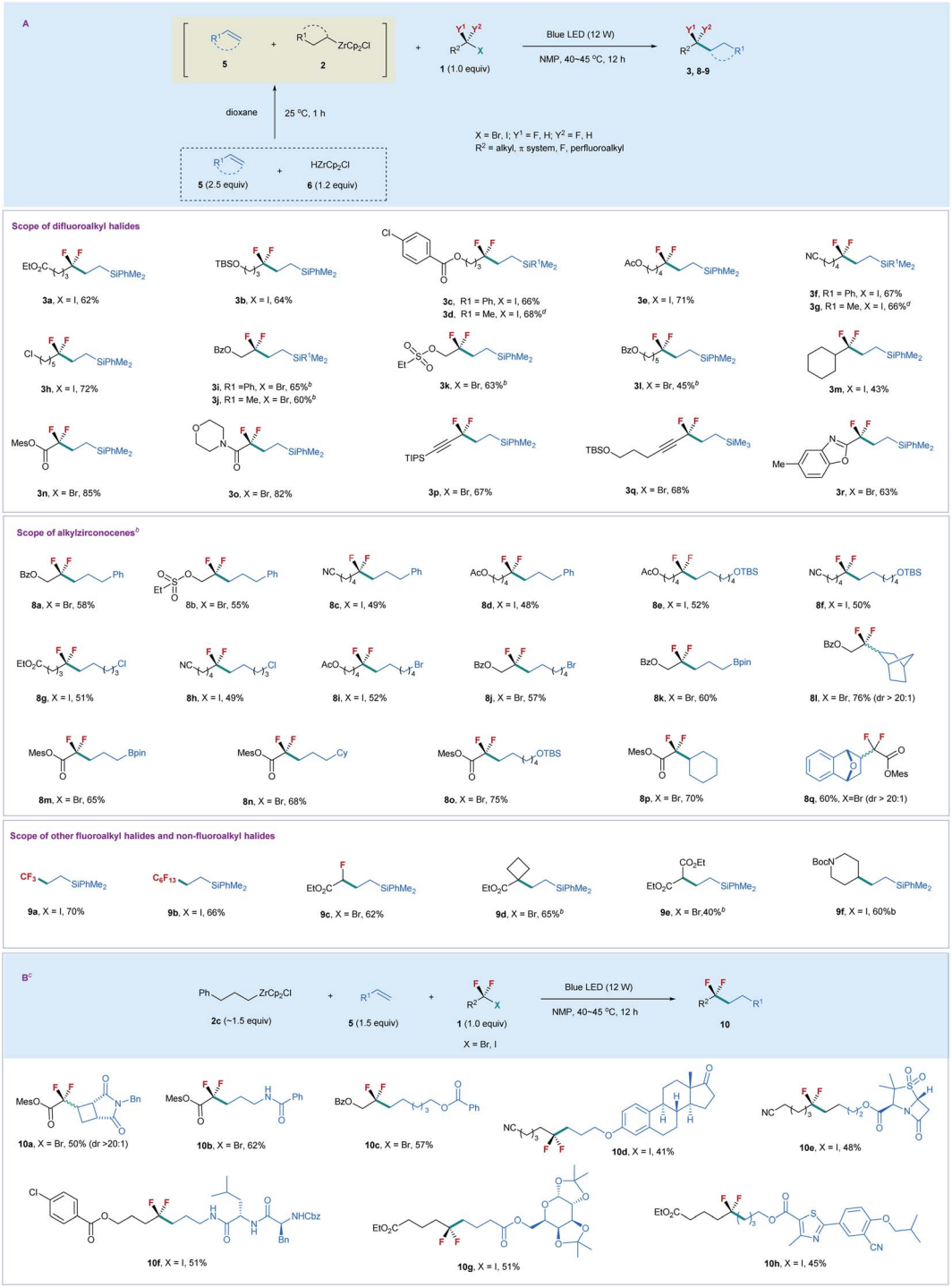


Scheme 1 Control experiments for the reaction. (a) Reaction of **2a** with **1a**. (b) Reaction of **2a** with **1a** and **5a**. (c) Reaction of **2a** with **1a** and **5a** in the presence of **5b**. (d) Reaction of **2a** with **5b**. (e) Reaction of **5a** with **1a** under irradiation of blue LED.

of **6**, and 1.0 equiv. of **1a** could provide **3a** in a comparable yield (80% determined by ^{19}F NMR and 62% isolated yield) (for details, see the ESI†). With the viable reaction conditions in hand, we examined the substrate scope of this process (Scheme 2A). Generally, the reaction of silylalkene **5a** with a series of unactivated difluoroalkyl iodides (ICF_2–alkyl) **1** furnished the corresponding products **3** efficiently. The chain length of **1** did not affect the reaction efficiency. Substrates **1** bearing a linear aliphatic chain from one to five carbons underwent the coupling smoothly (**3a–3k**). The reaction exhibited good functional group tolerance. A variety of important functional groups, such as ester, silyl ether, arylchloride, and nitrile, were compatible with the reaction conditions (**3a–3g**, **3i**, **3j**, and **3l**). Even alkylchloride- and sulphonate-containing substrates (**3h** and **3k**) were competent coupling partners, providing good opportunities for downstream derivatization. The reaction was not restricted to difluoroalkyl iodides, as unactivated difluoroalkyl bromides were also suitable substrates (**3i–3l**), with 3.5 equiv. of alkene and 1.8 equiv. of **6** needed. Replacing silylalkene **5a** with siylalkene **5b** led to comparable yields (**3d**, **3g**, and **3j**), suggesting that **5a** and **5b** possess similar reactivity. Notably, the steric difluoroalkyl iodide substituted with a cyclohexyl group was also applicable to the reaction (**3m**). In addition to XCF_2–alkyl (X = I, Br), the reaction of **5a** with functionalized difluoroalkyl bromides proceeded smoothly (**3n–3r**). Bromodifluoroacetate and bromodifluoroacetamide showed higher reactivity than those of XCF_2–alkyl, while *gem*-difluoropropargyl bromides and heteroaryl substituted difluoromethyl bromide provided comparable yields. The reaction is readily scalable, as demonstrated by the gram-scale synthesis of **3d** and **3g** without the erosion of the reaction efficiency. Chlorodifluoroacetate was also examined, but poor yield (19%) was obtained by reaction with **5a** and **2a**.

We next examined the substrate scope of alkenes **5**. The reaction of XCF_2–alkyl (X = I, Br) **1** with compounds **5** bearing a different chain length furnished the corresponding products smoothly (**8a–8k**). However, styrene was not applicable to the reaction. The successful production of **8i** and **8j** with alkyl bromide intact demonstrates that the alkyl bromides are less reactive than the difluoroalkyl iodides and bromides, due to the strong electron-withdrawing effect of the CF_2 group that enables the difluoroalkyl iodides and bromides to relatively more easily accept an electron than their nonfluorinated counterparts *via* a SET pathway. Most importantly, a boronate-containing substrate was also applicable to the reaction (**8k** and **8m**). Since boronate is a useful synthetic handle in organic synthesis, the resulting boronate-containing products should serve as a versatile building block for organic synthesis. Notably, the cyclic alkene did not affect the reaction efficiency, and norbornene provided compound **8l** in 76% yield. In addition, the reaction of difluoroacetate bromide with alkenes, including linear and cyclic alkenes, proceeded smoothly, and afforded the corresponding products **8m–8q** with high efficiency. The reaction can also be extended to trifluoromethyl, perfluoroalkyl, and monofluoroacetyl iodides and bromides, with moderate to good yields obtained (**9a–9c**). Remarkably, nonfluorinated alkyl halides were also applicable to the reaction. Tertiary alkyl bromide bearing an ester group (**9d**) and 2-bromomalonate (**9e**) underwent the coupling efficiently; even Boc-protected 4-iodopiperidine afforded **9f** in good yield, thus demonstrating the generality and advantage of this catalyst free, visible light induced process.

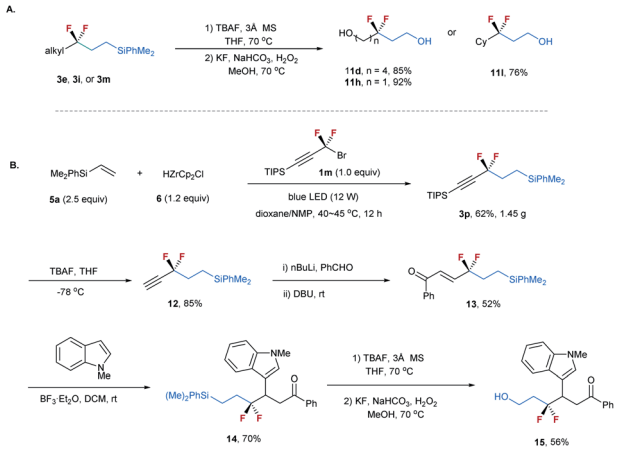
Given that the alkylzirconocene is essential in promoting the reaction, but is not the substrate for generating the desired product, we envisioned that alkylzirconocene may functionalize an initiator in the reaction. In this way, we can use a simple alkylzirconocene in combination with different alkenes and fluoroalkyl halides to construct alkylCF_2–alkyl bonds. Compared with the above synthetic procedure, this alternative process does not need the preparation of different alkylzirconocenes and enables fluoroalkylation of a variety of alkenes bearing different functional groups that are sensitive to $HZrCp_2Cl$, thus expanding the substrate scope of the current protocol. Accordingly, we prepared alkylzirconocene **2c** by reaction of allylbenzene with $HZrCp_2Cl$. As shown in Scheme 2B, the treatment of **2c** with bromodifluoroacetate and the cyclobutene derivative under the irradiation of blue light afforded product **10a** in 50% yield. Since a four-membered ring and difluoroacetyl are important structural motifs in medicinal chemistry,[21] compound **10a** would have applications in the synthesis of biologically active molecules. The terminal alkene bearing an amide proton was also applicable to the reaction, providing **10b** in good yield. In addition to bromodifluoroacetate, unactivated difluoroalkyl bromides and iodides were also competent coupling partners to react with a variety of complex molecule derived alkenes (**10c–10h**). Estone- and sulbactam-containing alkenes underwent the difluoroalkylation



Scheme 2 (A) Ikylzirconocene promoted fluoroalkylation of alkenes with (fluoro)alkyl halides under the irradiation of blue light. (B) Alkylzirconocene **2c** promoted fluoroalkylation of alkenes with difluoroalkyl halides under irradiation of blue light. [a] Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **5** (2.5 equiv.), **6** (1.2 equiv.), and NMP (3 mL). [b] **5** (3.5 equiv.) and **6** (1.8 equiv.) were used. [c] **2c** (~1.5 equiv.), **5** (1.5 equiv.), and **6** (2.0 equiv.), and NMP (3 mL) were used. [d] Gram scale synthesis.

reaction smoothly (**10d** and **10e**). Peptide and carbohydrate derivatives were also suitable substrates (**10f** and **10g**); even febuxostat bearing a heteroarene was also amenable to the reaction (**10h**). Thus, the current protocol represents a facile route for applications in medicinal chemistry.

To demonstrate the synthetic utility of this method, transformations of the resulting difluoroalkylated compounds were conducted (Scheme 3). The silyl group on compounds **3** can be readily converted into a hydroxyl. As shown in Scheme 3A, the treatment of compounds **3e**, **3i**, and **3m** with TBAF, followed by KF



Scheme 3 (A) Transformations of difluoroalkylated compounds **3e**, **3i** and **3m**. (B) Gram-scale synthesis of **3p** and its transformations.

and H_2O_2, afforded alcohols **11d**, **11h**, and **11l** with high efficiency.[22] Given the important applications of alcohols in organic synthesis and the unique properties of the CF_2 moiety, these CF_2-containing alcohols offer good opportunities in the synthesis of bioactive molecules. The resulting difluoroalkylated products can also serve as a useful building block for organic synthesis. As shown in Scheme 3B, the gram-scale synthesis of compound **3p** under standard reaction conditions proceeded smoothly. The selective deprotection of **3p** provided terminal alkyne **12** in 85% yield. The transformation of its carbon–carbon triple bond afforded α,β-unsaturated ketone **13** efficiently.[23] The reaction of **13** with N–Me indole in the presence of $BF_3 \cdot Et_2O$ afforded **14** in 70% yield, which was subsequently converted into alcohol **15** in 56% yield.

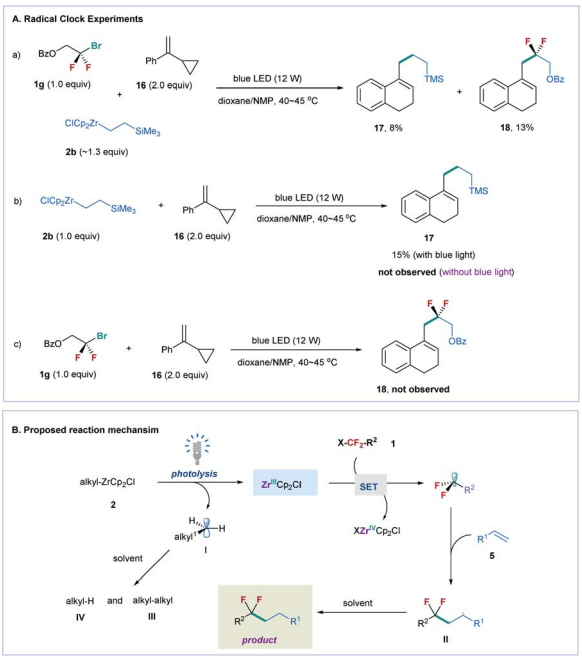


Fig. 2 Mechanistic studies and proposed reaction mechanism. (A) Radical clock experiments. (B) Proposed reaction mechanism.

To gain mechanistic insight into the reaction, we conducted several radical clock experiments with α-cyclopropylstyrene **16** as a probe (Fig. 2A).[24] When compound **16** was added to the reaction mixture of difluoroalkyl bromide **1g** and alkylzirconocene **2b**, two ring expanded products **17** (8% yield) and **18** (13% yield) were obtained under standard reaction conditions (Fig. 2A(a)). The treatment of **2b** with **16** under the irradiation of blue light also provided **17** in 15% yield, but no **17** was observed in the absence of blue light (Fig. 2A(b)). In addition, no **18** was provided when **1a** was treated with **16** under the irradiation of blue light (Fig. 2A(c)). These results suggest that visible light can induce alkylzirconocene **2b** to generate an alkyl radical; in the meanwhile, **2b** can also induce difluoroalkyl bromide to generate a difluoroalkyl radical under the irradiation of blue light. Because an alkyl radical (**I**) can be generated by photolysis of alkylzirconocene under the irradiation of blue light, we proposed that a Zr(III) species [$ZrCp_2Cl$] was formed simultaneously during this process, as illustrated in Fig. 2B.[25] The Zr(III) subsequently reacted with fluoroalkyl halide to produce a fluoroalkyl radical *via* a SET pathway. We also conducted light–dark experiments under standard reaction conditions (see the ESI†), and found that no reaction occurred in the dark, suggesting the essential role of blue light in promoting the reaction. This result demonstrates that a radical chain mechanism is unlikely involved in the reaction. After the fluoroalkyl radical was generated, we proposed that it directly reacted with the alkene to generate a new alkyl radical (**II**), which subsequently abstracted a proton from the solvent to produce the final product (Fig. 2B).[26] As for the radical (**I**) generated from alkylzirconocene, it can also be quenched by the solvent or undergo a homo-coupling reaction. This deduction was supported by the GC-MS analysis of the reaction, in which homo-coupling product **III** and a large amount of alkane **IV** were observed (for details, see Fig. S2†).

Conclusions

In conclusion, we have developed a general and catalyst-free method for the fluoroalkylation of alkenes promoted by photolysis of alkylzirconocenes. The reaction exhibits high functional group tolerance and broad substrate scope. A wide range of silyl- and alkyl-alkenes as well as fluoroalkyl halides, including difluoroalkyl, trifluoromethyl, perfluoroalkyl, and monofluoroalkyl bromides and iodides, were suitable substrates. In particular, the adaptability of the readily available unactivated difluoroalkyl halides and aliphatic alkenes to the reaction paves a new way for the construction of alkylCF_2–alkyl bonds. The reaction can also be applied to nonfluorinated alkyl halides, thus demonstrating the generality of this protocol further. Furthermore, the use of simple alkylzirconocene, instead of generating different alkylzirconocenes between $HZrCp_2Cl$ and a series of alkenes, significantly expands the substrate scope, including a variety of complex molecules that are sensitive to $HZrCp_2Cl$. The synthetic utility of this protocol has also been demonstrated by the transformations of

difluoroalkylated compounds, providing good opportunities in medicinal chemistry. Preliminary mechanistic studies reveal that a SET pathway induced by a Zr(III) species is involved in the reaction, in which the Zr(III) species is generated by the photolysis of alkylzirconocenes with blue light. This intriguing pathway may prompt great interest in using the photolysis of organozirconium for organic synthesis.

Data availability

The authors declare that all the data supporting the findings of this study are available within the paper and its ESI. For characterization data and all NMR spectra for all new compounds see ESI.†

Author contributions

X. Z. and X. R. conceived and designed the experiments. X. Z. directed the project. X. R. performed the experiments and mechanistic studies. X. G. and Q.-Q. M. prepared some starting materials and performed some reactions for the preparation of compounds **3** and **8–9**. X. Z. wrote the paper. S. Z. revised the paper. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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