

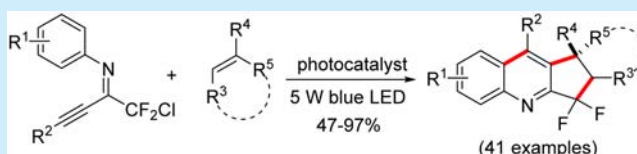
Synthesis of *Gem*-Difluorinated Fused Quinolines via Visible Light-Mediated Cascade Radical Cyclization

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S Supporting Information

ABSTRACT: A facile synthesis of *gem*-difluorinated fused quinolines via visible light-mediated cascade radical cyclization between functionalized difluoromethyl chlorides and alkenes was developed. Various highly functionalized fused quinolines were assembled in moderate to good yields under very mild reaction conditions. The reaction extends the applications of chlorodifluoroacetic acid as the *gem*-difluoromethylenated building block by simple derivatization, especially in the synthesis of *gem*-difluorinated fused heterocyclic rings, which are difficult to access with existing methods.



The difluoromethylene group (CF_2) plays an important role in medicinal chemistry because it can functionalize as a bioisostere of a carbonyl group or an oxygen atom and would have significant effects on the chemical and biochemical properties of bioactive compounds.¹ Therefore, the development of new methodologies for selective incorporation of the difluoromethylene motif into organic molecules is of great importance.^{2,3} Fused quinolines are common structural units present in various natural products and many synthetic therapeutic agents.⁴ For example, quinolinohopane **1** occurs in substantial quantities in biodegraded crude oils.^{4f} Fused tetracyclic quinoline **2** is a mixed DNA-intercalating topo I/II inhibitor, which shows broad spectrum activity against solid tumors.^{4g} Quinoline-based compounds **3** represent a novel class of calcitonin gene-related peptide receptor antagonists (Figure 1).^{4b} Although various synthetic strategies have been

promoting selective radical reactions.⁵ In particular, since the pioneering work of Stephenson, who demonstrated $\text{BrCF}_2\text{CO}_2\text{Et}$ could serve as a CF_2 radical precursor using visible light photocatalysis,⁶ a series of studies involving the radical difluoroalkylation of aromatic rings,⁷ alkenes,⁸ alkynes,⁹ isocyanides,¹⁰ and hydrazones¹¹ were reported. Although $\text{BrCF}_2\text{CO}_2\text{Et}$ is a commonly used difluoroalkylation reagent because of its availability, it is still desirable to develop a new type of CF_2 building block that contains more functional groups, and these groups themselves can participate in the reactions to construct complex molecules.

N-Aryl chlorodifluoromethyl alkynyl ketimines **5** are versatile nitrogen-containing building blocks that could be readily prepared in good yields by the reaction of $\text{ClF}_2\text{CO}_2\text{H}$, CCl_4 , and anilines¹² followed by a Sonogashira coupling of the resulted imidoyl chlorides **4** with terminal alkynes (Scheme 1).¹³ Although this type of compounds has been widely used

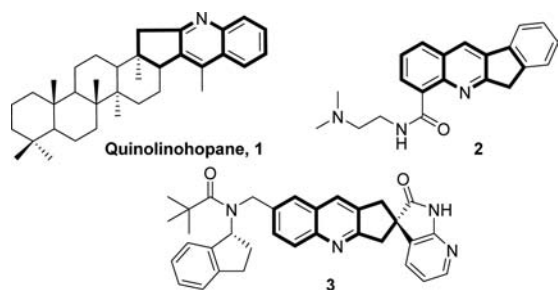
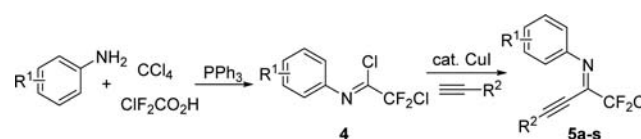


Figure 1. Selected examples of fused quinoline-based bioactive compounds.

devised for the synthesis of fused quinolines, methods leading to the *gem*-difluorinated substrates are rather limited. If a difluoromethylene group ($-\text{CF}_2-$) would be combined with fused quinolines, it might result in further advances in the pharmacological applications.

Recently, visible light photoredox catalysis has been demonstrated as an environmentally friendly method for

Scheme 1. Synthesis of Substrates **5**

for the synthesis of *N*-heterocycles, methods involving the cleavage of sp^3 C–Cl bond are rare.¹⁴ We envisioned that the strong sp^3 C–Cl bond of compound **5** could be activated by the imine and two F groups, which might be single-electron reduced by the photocatalyst to generate the highly functionalized difluoromethyl radicals. To combine the advantages of visible light photocatalysis, the availability of **5**, and cascade radical chemistry for synthesis of complex natural products,¹⁵ we chose to functionalize alkenes in a sequence of free-radical

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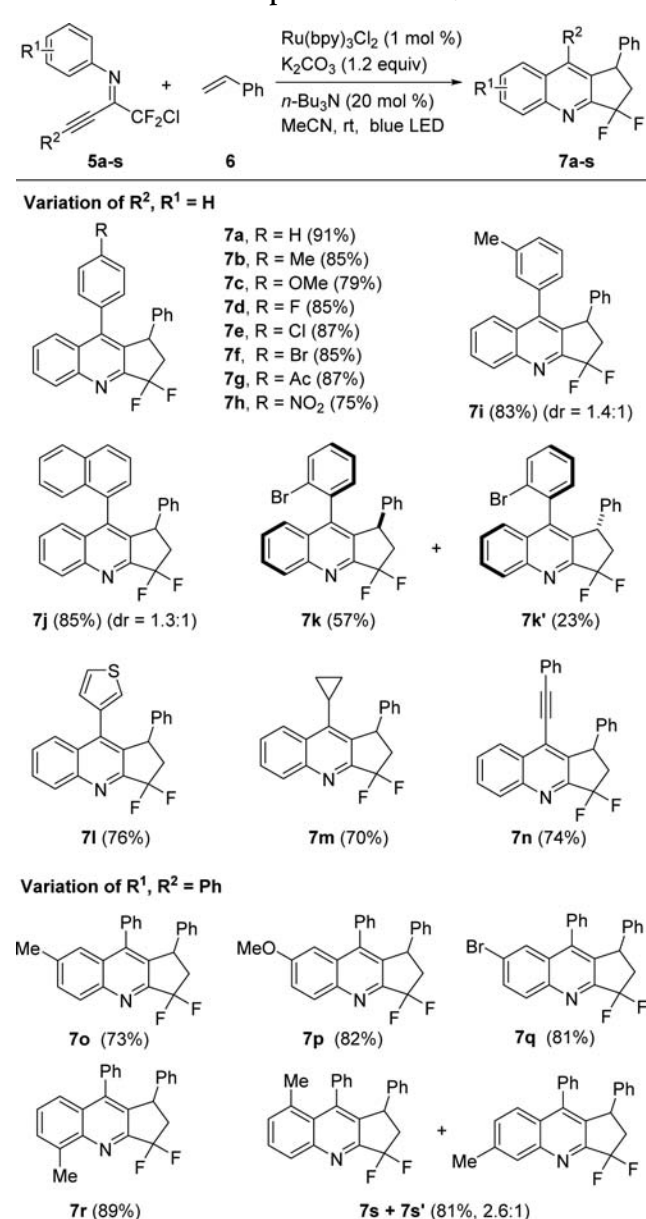
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reactions.⁸ This sequence allows the facile synthesis of *gem*-difluorinated fused quinolines in good yields with the formation of three C–C bonds in one catalytic cycle.

We started our investigation with the reaction between alkynyl ketimine **5a** ($R^1 = \text{H}$, $R^2 = \text{Ph}$) and styrene **6**. After some experiments, we found the desired cyclopenta-fused quinoline **7a** was obtained in 91% yield by utilizing the reductive quenching cycle of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ with *n*-Bu₃N (0.2 equiv) as the electron donor and K_2CO_3 (1.2 equiv) as the base (see Table S1, [Supporting Information](#)). With the optimized conditions in hand, we examined the generality of this reaction by employing a variety of alkynyl ketimines **5** to react with styrene **6**. We first examined the substituent effect on the benzene ring connected to the C–C triple bond. As shown in [Scheme 2](#), both electron-withdrawing groups and electron-donating groups on the *para*-position were well-tolerated and afforded the corresponding products **7a–h** in 75–91% yields. When a methyl group was introduced to the *meta*-position of phenyl ring, the desired fused quinoline **7i** was isolated in 83% yield. In addition to the one tertiary carbon center, this compound has a chiral biaryl axis. Thus, 1.4:1 diastereoselectivity was observed with respect to the two types of stereogenic elements. Similarly, the reactions provided 4-(1-naphthyl)quinoline **7j** in 85% yield with 1.3:1 dr. When the R^2 group was 2-bromophenyl, two separable diastereomers **7k** and **7k'** were obtained in yields of 57% and 23%. We were delighted to find that substrates derived from 3-ethynylthiophene or cyclopropylacetylene also smoothly underwent reaction with styrene **6**, affording the corresponding quinolines **7l** and **7m** in yields of 76% and 70%, respectively. Notably, 4-alkynyl-substituted fused quinoline **7n** could be assembled via this cascade radical cyclization by using a substrate bearing a 1,3-butadiyne motif. For the substrates bearing a substituent (methyl, methoxy, and bromo) on the aromatic ring attached to the nitrogen atom, the reactions led to the fused quinolines **7o–q** in good yields. In previous reports, the annulation of vinyl radical usually encounters regioselectivity problem owing to the *ipso*-cyclization and the rearrangement through the C–N bond cleavage in the spirocyclohexadienyl radical.¹⁶ In this reaction, the rigid structure of the five-membered ring might disfavor the *ipso*-addition, leading to the fused quinolines with high regioselectivity.¹⁷ The reaction also worked smoothly when only one *ortho*-hydrogen atom was available in substrate **5r**. When two nonequivalent *ortho*-hydrogen atoms were available, a mixture of two inseparable isomers **7s** and **7s'** was obtained in a ratio of 2.6:1.

Next, the reactions of substrate **5a** with various alkenes **8** were examined. As shown in [Scheme 3](#), *p*-, *m*-, and *o*-methyl-substituted styrenes all worked well in the present system to give the fused quinolines **9a–c** in good to excellent yields. The reaction was found to tolerate various functional groups such as methoxy, halide (F, Cl, Br), and cyano at the *para*-position of styrene. Furthermore, vinyl ester **8i**, enamide **8j**, acrylate **8k**, and vinylcyclohexane **8l** were examined and proved to be compatible as well. Notably, allylic alcohol was also a suitable substrate for the reaction, affording the fused quinoline **9m** without a need for hydroxyl group protection. To further demonstrate the generality of present protocol, 1,1- and 1,2-disubstituted alkenes were also tested. We were delighted to find that 1,1-diphenylethylene smoothly underwent reaction with **5a** to give product **9n** in 49% yield. In the case of 2,3-dimethyl-1,3-butenyne **8o**, only one C–C double bond was functionalized. It is worth noting that the reaction of **5a** with

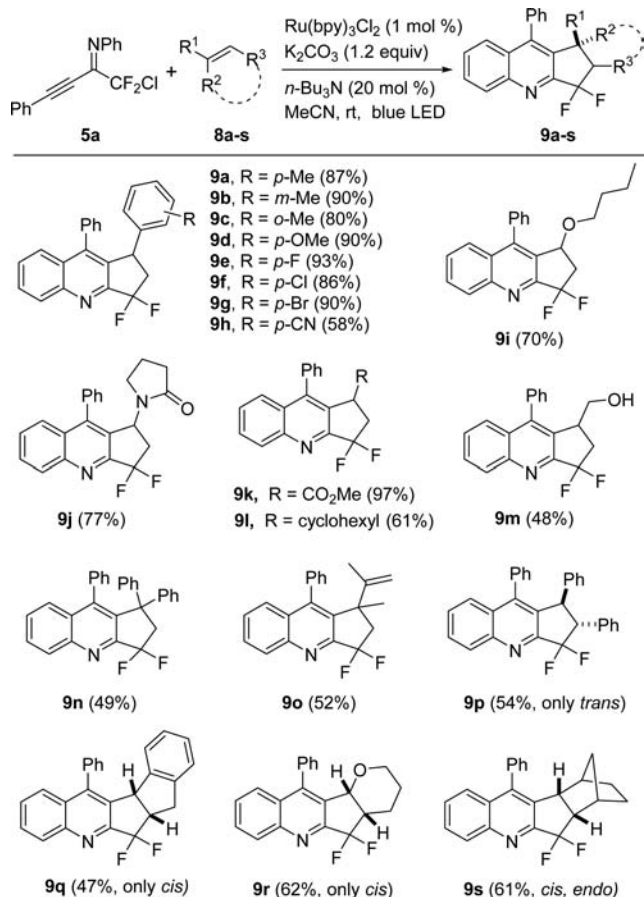
Scheme 2. Reaction Scope of Substrates **5a,b**



^aReaction conditions: $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (1 mol %), **5a–s** (0.2 mmol), styrene **6** (1.2 equiv), *n*-Bu₃N (20 mol %), and K_2CO_3 (1.2 equiv) in 1 mL of MeCN, irradiated with a 5 W blue LED under N₂ at room temperature for 10 h. ^bIsolated yields.

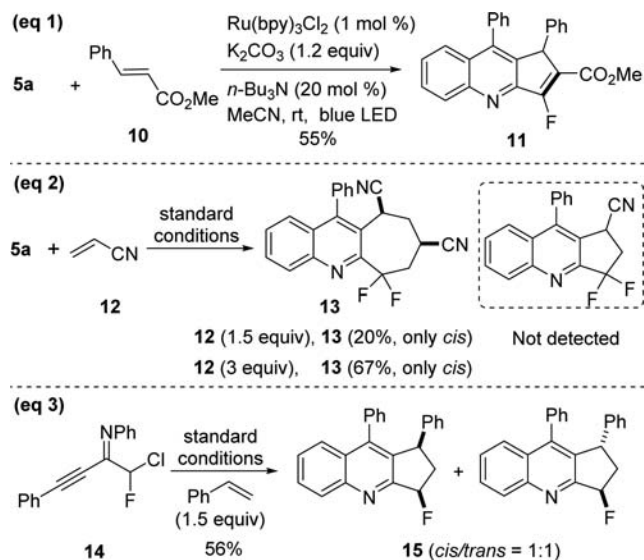
1,2-diphenylalkene afforded *trans*-isomer of **9p** as the sole product, while *cis*-isomers were formed when indene **8q** and dihydropyran **8r** were tested. In addition, the radical cyclization of **5a** with norbornene afforded the *endo*-fused quinoline **9s** in 61% yield. The configurations of **9p–s** were confirmed by their NOESY spectra.

Interestingly, a monofluorinated product **11** was isolated in a yield of 55% when methyl cinnamate **10** was used as the substrate. This product might be generated from the desired *gem*-difluorinated cyclopenta-fused quinoline, followed by the elimination of HF in the presence of the base ([Scheme 4](#), eq 1). Another interesting example is the visible light-mediated radical reaction between **5a** and acrylonitrile **12**. Instead of the desired cyclopenta-fused quinoline, a cyclohepta-fused quinoline **13** with *cis*-configuration was obtained in 20% yield, which was

Scheme 3. Reaction Scope of Alkenes^{a,b}

^aAll the reactions were carried out under the conditions as described in Scheme 2. For 9n–s, 2.5 equiv of alkenes was used. ^bIsolated yields.

Scheme 4. Synthesis of Monofluorinated Fused Quinolines and Gem-Difluorinated Cyclohepta-Fused Quinoline

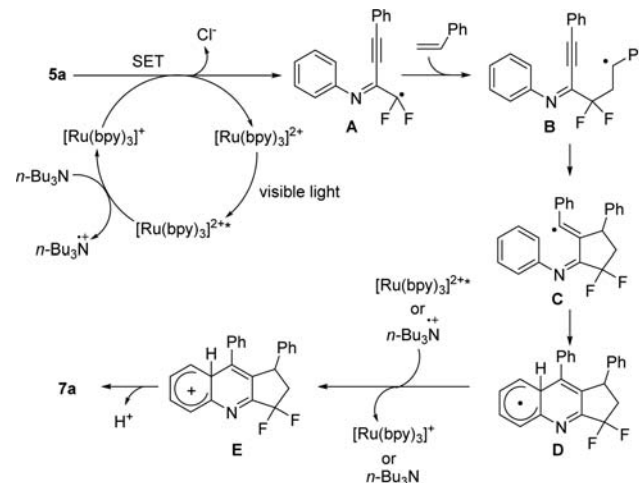


further improved to 67% when 3 equiv of acrylonitrile was used (Scheme 4, eq 2). This outcome is mainly caused by the delocalization of the cyanoalkyl radical, which increases the stability and provides the opportunity for its addition to another molecular of acrylonitrile.¹⁸ For comparison, we

reexamined the reaction of 5a and methyl acrylate. Although methyl acrylate is also an electron-deficient alkene, no seven-membered ring-fused quinoline was detected even after its amount was increased to 4 equiv. Finally, we examined the reaction of styrene and chloromonofluoromethyl substrate 14, which could be easily prepared from chlorofluoroacetic acid in two steps. Separable *cis*- and *trans*-isomers of fused quinoline 15 were obtained in a total yield of 56% with poor diastereoselectivity (Scheme 4, eq 3).

On the basis of our previous report on visible light-mediated radical cyclization of trifluoroacetimidoyl chlorides with alkynes,^{16a} a plausible mechanism for the formation of 7a is proposed (Scheme 5). Photoexcitation of $[\text{Ru}(\text{bpy})_3]^{2+}$ by

Scheme 5. Plausible Mechanism



visible light generates excited $[\text{Ru}(\text{bpy})_3]^{2+*}$, which undergoes one-electron reduction by $n\text{-Bu}_3\text{N}$ to give $[\text{Ru}(\text{bpy})_3]^+$. Single-electron transfer (SET) from $[\text{Ru}(\text{bpy})_3]^+$ to 5a leads to difluoromethyl radical A with concomitant regeneration of the photocatalyst. Radical addition of A to styrene forms radical B, which is trapped by the C–C triple bond intramolecularly to give vinyl radical C. Aromatic substitution of the resulting vinyl radical forms intermediate D, followed by one-electron transfer back to either the photoexcited catalyst or the radical cation of $n\text{-Bu}_3\text{N}$ to provide cyclohexadienyl cation E. Finally, deprotonation of E with the aid of inorganic base leads to the desired fused quinoline 7a.

In conclusion, we have developed a mild and efficient method for the synthesis of *gem*-difluorinated fused quinolines via visible light mediated cascade radical cyclization. A variety of highly functionalized fused quinolines were assembled with broad substrate scope and good functional group tolerance. The reaction extends the applications of chlorodifluoroacetic acid as the *gem*-difluoromethylenated building block by simple derivatization, especially in the synthesis of *gem*-difluorinated fused heterocyclic rings, which are difficult to access by existing methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00119.

Experimental details, characterization data, and NMR spectra of all new products (PDF)

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Notes

The authors declare no competing financial interest.

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