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Direct α-Monofluoroalkenylation of Heteroatomic Alkanes via a Combination of Photoredox Catalysis and Hydrogen-Atom-Transfer Catalysis

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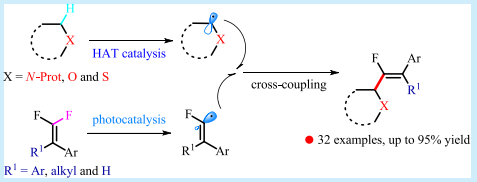
Supporting Information

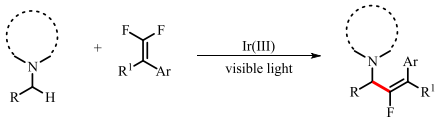
ABSTRACT: In this study, a new C(sp^3)−H monofluoroalkenylation reaction involving cooperative visible-light photoredox catalysis and hydrogen-atom-transfer catalysis to afford products generated by selective hydrogen abstraction and radical−radical cross-coupling was described. This mild, efficient reaction shows high regioselectivity for the α-carbon atoms of amines, ethers, and thioethers and thus allows the preparation of monofluoroalkenes bearing various substituents. The reaction was applied to two bioactive molecules, indicating its utility for late-stage monofluoroalkenylation of compounds with inert C(sp^3)−H bonds.



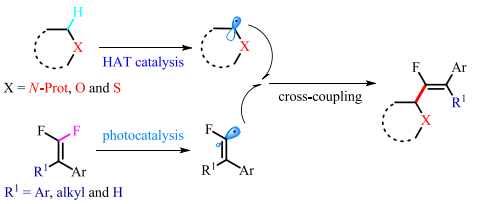
Organofluorinated molecules have recently been receiving increasing attention in various fields.[1] For example, fluoroalkenes have found many applications in materials science[2] and pharmaceutical chemistry,[3] owing to their synthetic utility and unique biological properties. Furthermore, these compounds are resistant to enzymatic degradation and are thus widely used as peptidomimetics.[3,4] Therefore, the development of new methods for the synthesis of fluoroalkenes has been progressing rapidly.[5] Recently, a series of mild, efficient methods for C(sp^2)−H bond monofluoroalkenylation by means of a transition-metal-catalyzed C−H activation strategy have been reported.[6] However, C(sp^3)−H bond monofluoroalkenylation remains a formidable challenge. Hashmi et al.[7] reported a catalytic visible-light-induced photoredox monofluoroalkenylation reaction of tertiary amines at an α-C(sp^3) to afford tetrasubstituted monofluoroalkenes (Scheme 1a). Nevertheless, because the reaction is suitable only for tertiary amines, its utility for the synthesis of drugs is severely limited. That leaves a large variety of bioactive molecules, such as secondary amines,[8] ethers,[9] and thioethers,[10] that are difficult to monofluoroalkenylate. Therefore, the development of methods for monofluoroalkenylation of inert C(sp^3)−H bonds would be desirable both for synthetic organic chemistry and for drug-discovery research.

Scheme 1. Monofluoroalkenylation of C(sp^3)−H Bonds

a) **Previous work**: tertiary amine monofluoroalkenylation by photoredox catalyst



b) **This work**: monofluoroalkenylation of unreactive C-H bonds by cooperative photoredox and HAT catalysis



Visible-light-induced photoredox catalysis through single-electron transfer (SET) pathways has recently emerged as a powerful synthetic tool.[11,12] Moreover, several studies showed that the merged of photoredox and transition-metal catalysis can successfully deliver many selective native-group functionalizations.[11f−h] Photoredox catalysis was recently used to address the issue of native C−H functionalization by introduce HAT strategy.[12] Combining HAT catalysis with photocatalysis, not only molecules with low oxidation potentials, such as olefins, imines, and heteroarenes, but also molecules with high oxidation potentials, such as secondary amines with easily removable protecting groups (e.g., *N*-Boc piperidine, $E_{1/2}^{ox}$ = +1.96 V vs SCE),[13] ethers (for THF and Et_2O, $E_{1/2}^{ox}$ > + 2.4 V vs SCE),[12a] and thioethers can be functionalized. Therefore, we set out to explore a cooperative pathway involving visible-light photoredox catalysis and HAT catalysis that would allow hydrogen abstraction from high-oxidation-potential molecules, so that compounds with inert C(sp^3)−H bonds could be monofluoroalkenylated (Scheme 1b).

We began our study by carrying out reactions of diphenyl *gem*-difluoroethylene (**1a**) and *N*-Boc-pyrrolidine (**2b**) with the goal of optimizing the reaction conditions (Table 1). First, we evaluated several photocatalysts: Ir[dF(CF$_3$)ppy]$_2$-

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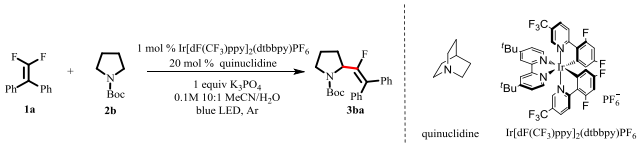
Table 1. Optimization of the Reaction Conditions[a]



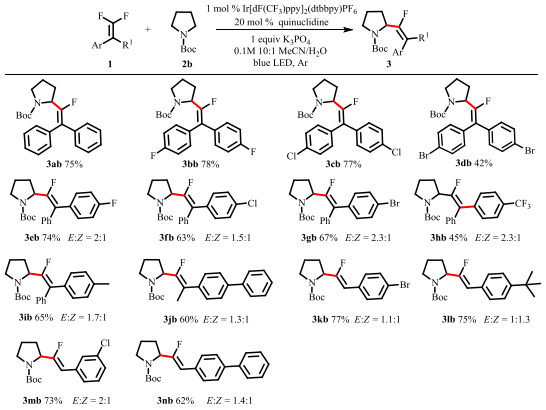
entry	variation from conditions shown above	yield[b] (%)
1	none	79 (75)
2	$Ir(ppy)_3$ as photocatalyst	NR
3	$Ru(bpy)_3Cl_2{\cdot}6H_2O$ as photocatalyst	NR
4	Acid Red 87 as photocatalyst	NR
5	MeCN instead of 10:1 MeCN/H_2O	43
6	aceclidine instead of quinuclidine[c]	40
7	3-quinuclidinol instead of quinuclidine	NR
8	K_2CO_3 instead of K_3PO_4	60
9	no photocatalyst	NR
10	no HAT catalyst	NR
11	no light	NR
12	no base	14
13	under air	20

[a]Reaction conditions, unless otherwise noted: **1a** (0.2 mmol), **2b** (0.3 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol), quinuclidine (0.04 mmol), and K_3PO_4 (0.2 mmol) in 10:1 MeCN/H_2O (2 mL, volumetric ratio) were stirred in an 8 mL bottle while being irradiated by a blue LED lamp (40 W) at rt under Ar for 24 h. [b]Yields were determined by ^{19}F NMR with fluorobenzene as an internal standard. The yield in parentheses is an isolated yield. NR = no reaction. [c]The solvent was MeCN.

$(dtbbpy)PF_6$, $Ir(ppy)_3$, Acid Red 87, and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (entries 1–4). To our delight, irradiation of the substrates, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol %), quinuclidine (HAT catalyst), and K_3PO_4 in 10:1 MeCN/H_2O under argon resulted in the formation of desired product **3ab** (79%, entry 1). When $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was replaced with another photocatalyst, none of the desired product was detected. The yield decreased substantially when pure MeCN was the solvent (entry 5). We reason that water increased the solubility of base in the reaction system (which is barely dissolved in MeCN) and thus raised the reaction efficiency (for details, see Table S7). The use of aceclidine or 3-quinuclidinol as the HAT catalyst resulted in inferior results (entries 6 and 7). A moderate decrease in yield was observed when K_3PO_4 was changed to K_2CO_3 (entry 8). Control experiments showed that in the absence of the photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, the HAT catalyst quinuclidine, or light, the desired product was not detected (entries 9–11), indicating that all three were essential. What is more, when the reaction was carried out without the base or under air, the yield of the product was low (entries 12 and 13), which indicates that the base was necessary to neutralize hydrogen ions produced during the reaction and that oxygen interfered with the reaction.

Having optimized the conditions, we then examined the generality of the monofluoroalkenylation reaction. To our delight, a variety of *gem*-difluoroalkenes **1** could be converted to the desired products (**3ab**–**3nb**) in 42–78% yields (Scheme 2). Both electron-withdrawing and electron-donating substituents on the aromatic rings of **1** were compatible with satisfactory yields of products **3ab**–**3ib**. In addition, good yields could still be obtained when one of the aromatic groups on the *gem*-difluoroalkene was exchanged for a methyl group or

Scheme 2. Substrate Scope with Respect to the *gem*-Difluoroalkene[a]

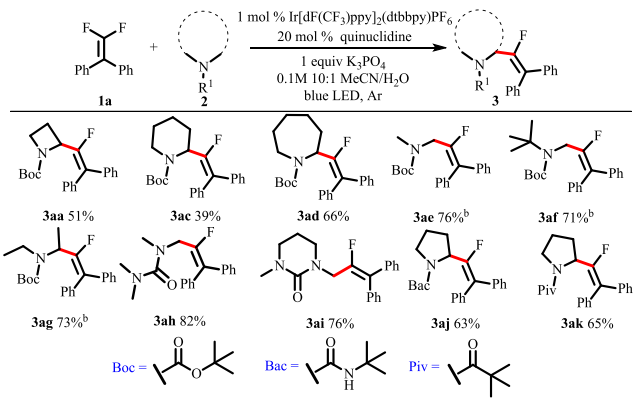


[a]Reaction conditions, unless otherwise noted: **1** (0.2 mmol), **2b** (0.3 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol), quinuclidine (0.04 mmol), and K_3PO_4 (0.2 mmol) in 10:1 MeCN/H_2O (2 mL, volumetric ratio) were stirred in an 8 mL bottle while being irradiated by a blue LED lamp (40 W) at rt under Ar for 24 h. Isolated yields are given.

a hydrogen atom (**3jb**–**3nb**). It is notable that the *E*/*Z* selectivity was low when unsymmetrical *gem*-difluoroalkenes were used as substrates (**3eb**–**3nb**, up to *E*/*Z* = 2.3:1). This result is evidence that the reaction occurred via a radical–radical coupling. The recombination of fluoroalkenyl radicals was fast and therefore difficult to control, so the diastereoisomeric ratio was low.

We next examined the generality of the reaction with respect to amines **2** by using diphenyl *gem*-difluoroethylene (**1a**) as the monofluoroalkenylation agent (Scheme 3). Boc-protected

Scheme 3. Substrate Scope with Respect to the Amine[a]



[a]Reaction conditions, unless otherwise noted: **1a** (0.2 mmol), **2** (0.3 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol), quinuclidine (0.04 mmol), and K_3PO_4 (0.2 mmol) in 10:1 MeCN/H_2O (2 mL, volumetric ratio) were stirred in an 8 mL bottle while being irradiated by a blue LED lamp (40 W) at rt under Ar for 24 h. Isolated yields are given. [b]30 equiv of **2e**–**g** was used for this reaction.

cyclic amines azetidine, piperidine, and azepane afforded desired products **3aa**, **3ac**, and **3ad**, respectively, in moderate yield (39–66%). Reactions of BOC-protected acyclic amines were somewhat sluggish, but when the amount of the amine was increased to 30 equiv, the target products (**3ae**–**3ag**) were obtained in satisfactory yields (71–76%). Changing the Boc

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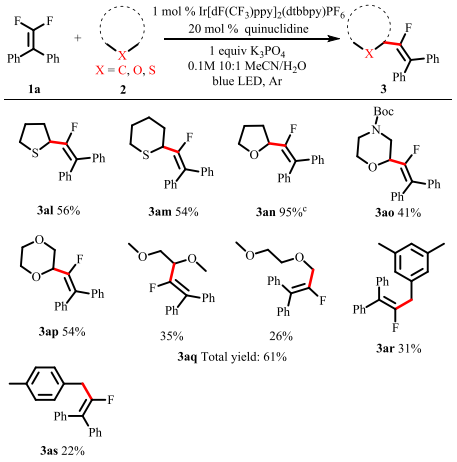
group (**2e**) to an amide group (**2h**) resulted in an excellent yield of the corresponding product (**3ah**, 82% yield), even when only 1.5 equiv of **2h** was used, suggesting that an amide protecting group was more suitable for acyclic amines. Notably, when the amine contained two different types of α-carbons, only a single product was obtained (**3ai**, 76% yield). We speculated that the primary carbon radical was more active than the secondary carbon radical attributed to the effect of the steric component, which turned out to be an excellent regional selectivity in **3ai**. Furthermore, carbamate, urea, and amide substrates were suitable, affording the corresponding products (**3ah**–**3ak**) in good yields (63–82%).

Next we evaluated ethers and thioethers as substrates (Scheme 4). We found that both cyclic and acyclic ethers and

Scheme 4. Reactions of Ethers, Thioethers, And Alkanes[a]



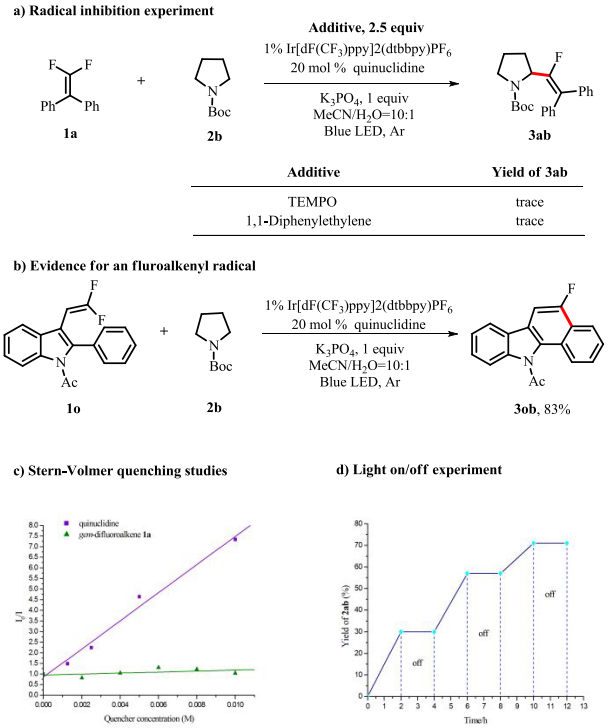
[a]Reaction conditions, unless otherwise noted: **1a** (0.2 mmol), **2** (0.3 mmol), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (0.002 mmol), quinuclidine (0.04 mmol), and K_3PO_4 (0.2 mmol) in 10:1 MeCN/H_2O (2 mL, volumetric ratio) were stirred in an 8 mL bottle while being irradiated by a blue LED lamp (40 W) at rt under Ar for 24 h. Isolated yields are given. [b]THF was used as the solvent.

thioethers were acceptable substrates, affording desired products **3al**–**3as** in moderate to excellent yields (41–95%). Notably, the reaction of **2n** in THF rather than MeCN/H_2O gave **3an** in 95%. To our surprise, the reaction was chemoselective: only one product (**3ao**, 41% yield) was obtained from substrate **2o**, which contains multiple possible reaction sites. We also tested two alkane substrates, xylene and trimethylbenzene, and were pleased to find that anticipated products **3ar** and **3as** could be obtained, albeit in low yields (22% and 31%, respectively).

Next, we performed a series of mechanistic experiments. When a radical inhibitor (TEMPO or 1,1-diphenylethylene) was present, reaction of **1a** and **2b** under the standard conditions gave only a trace of desired product **3ab** (Scheme 5a); this result indicates that the reaction proceeds via a radical mechanism. Then we designed and synthesized substrate **1o** and allowed it to react with amine **2b** (Scheme 5b); the formation of cyclization product **3ob** (83%) confirmed that a fluoroalkenyl radical was generated in the reaction system.

We also conducted a series of Stern–Volmer quenching studies with Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ and *gem*-difluoroalkene **1a** or quinuclidine as a soluble additive (Scheme 5c). The results clearly demonstrate that quinuclidine, but not the *gem*-difluoroalkene, could quench the excited photocatalyst to

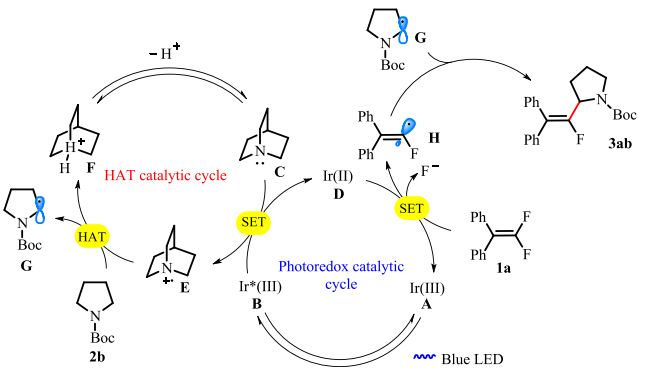
Scheme 5. Mechanistic Experiments



a large extent. Therefore, we concluded that the initial step of the reaction was reduction of the photocatalyst. Finally, we performed a light on/off experiment involving **1a** and **2b**, which showed that **3ab** formed only under irradiation by the blue LED lamp (Scheme 5d); that is, the transformation required continuous irradiation.

On the basis of these mechanistic experiments and literature results, we propose the mechanism outlined in Scheme 6 for

Scheme 6. Proposed Mechanism



the reaction of diphenyl *gem*-difluoroethylene (**1a**) and *N*-Boc-pyrrolidine (**2b**). Under irradiation with blue light, the photocatalyst is excited from ground-state Ir(III) species **A** to excited-state Ir*(III) species **B**. SET between **B** ($E_{1/2}$ [*Ir(III)/Ir(II)] = +1.21 V vs SCE)[14] and quinuclidine (E_p = +1.1 V vs SCE)[15] forms radical cation **E** and reduced Ir(II) complex **D**. At this stage, desired α-aminoalkyl radical **G** can be formed via HAT between **2b** and radical cation **E**. Fluoroalkenyl radical **H** can be generated through SET reduction of **1a** ($E_{1/2}^{red}$ = −1.04 V vs SCE)[7] by Ir(II) complex **D** ($E_{1/2}$ [*Ir(III)/Ir(II)] = −1.37 V vs SCE)[14] and cleavage of

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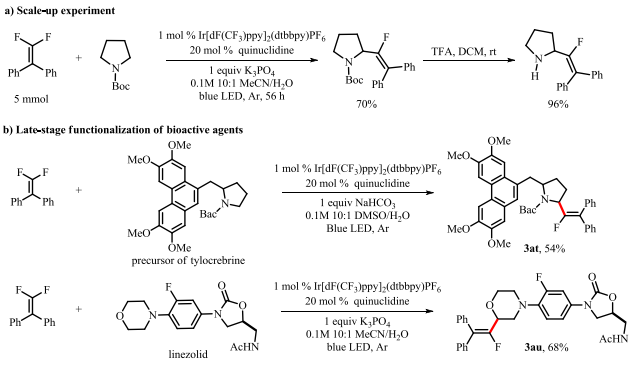
the C−F bond. Finally, target product **3ab** is generated by selective cross-coupling of radicals **G** and **H**.

To demonstrate the synthetic utility of the target products, we carried out a gram-scale reaction of **1a** and **2b** under the standard conditions and then removed the protecting group to obtain a monofluoroalkenylation product of a secondary amine (67% yield for two steps, Scheme 7a). In addition, because

Scheme 7. Demonstration of Synthetic Utility



most known medicinal agents contain one or more heteroatoms (N, O, and/or S) and because the incorporation of a monofluoroalkenyl group may improve the bioactivity, fat solubility, and other properties of such agents, we used our protocol to accomplish the late-stage functionalization of two bioactive agents: precursor of tylocrebrine and linezolid (Scheme 7b). We were pleased to find that the desired products could be obtained with excellent regioselectivity, especially in the case of linezolid. That is, this reaction has the potential to serve as a powerful method for late-stage monofluoroalkenylation of medicinal agents containing several heteroatoms.

In summary, we have developed a protocol for a novel monofluoroalkenylation reaction of inert α-C(sp^3)−H bonds of a variety of heteroalkanes, including ethers and thioethers. The resulting products, which have easily removable protecting groups, show remarkable potential for further functionalization. Mechanistic studies demonstrated that the reaction involves cross-coupling between an α-aminoalkyl radical and a monofluoroalkenyl radical. The mild conditions, high selectivity, and broad substrate scope make this reaction an advance in monofluoroalkenylation strategies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01491.

General information, preparation of photocatalyst and *N*-Boc amines, investigation of the key reaction parameters, investigation of the mechamism, experimental procedures and product characterization, references, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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