Organic & Biomolecular Chemistry

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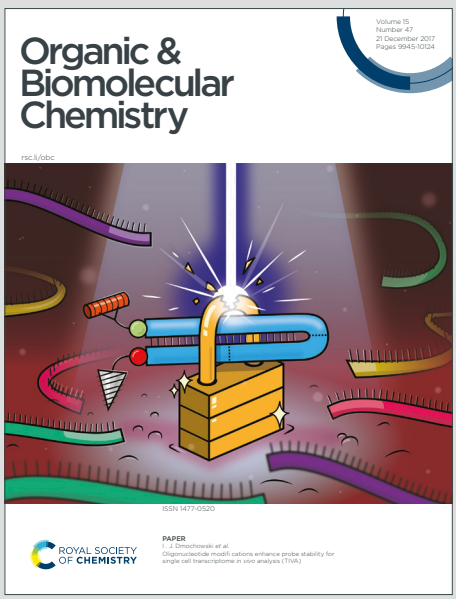

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DOI: 10.1039/D0OB00267D

COMMUNICATION

Synthesis of monofluorooxazoles with quaternary C-F centers through photoredox-catalyzed radical addition of methylene-2-oxazolines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A novel photoredox-catalyzed radical addition of methylene-2-oxazolines has been developed under visible light irradiation to synthesize monofluorooxazoles with a quaternary carbon center using 2-bromo-2-fluoro-3-oxo-3-phenylpropionates as radical source. This method with simple protocol, scalability and high yield offers a facile path to get diverse monofluorinated oxazoles with quaternary C-F centers, which are a class of highly valuable motifs and synthons.

The most prescribed, best performing, and bestselling drugs are usually those fluorine-containing pharmaceutical agents.[1] Indeed, the selective incorporation of fluorine into organic compounds generally leads to an improved membrane permeability and higher stability toward oxidative degradation,[2,3] thus arousing a great interest in the synthesis of fluorine-containing compounds.[4] In particular, compounds with a quaternary C-F center are of high pharmaceutical potential.[1a,b,5] Therefore, the synthesis of monofluoro compounds containing quaternary carbon centers has attracted the attention of many synthetic chemists.[6] However, there are still very limited approaches to allow the catalytic synthesis of C-F quaternary carbons. Thus, it would be highly desirable to develop a novel alternative method for preparing compounds with C-F quaternary carbon centers. Notably, oxazole is an important heterocycle present in a variety of natural products and biologically active compounds,[7] as exemplified by anti-diabetic agent AD-5061,[8a] anti-mycobacterial texaline[8b] as well as anti-inflammatory[8c] and bronchodilator 4-aminooxazoles[8d] (Figure 1). Consequently, the combination of a C-F quaternary carbon center and an oxazole unit through photoredox catalyzed monofluoroalkylation of methylene-2-oxazolines could enrich the diversity of oxazoles, which in turn could provide novel bioactivities for drug discovery campaign.

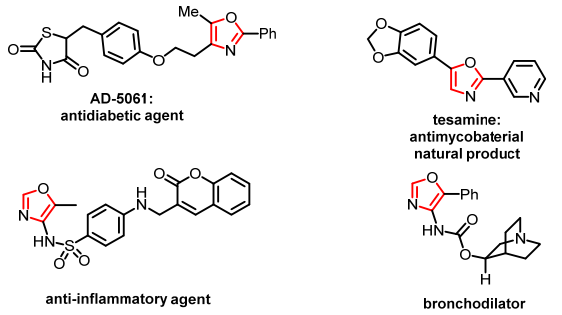
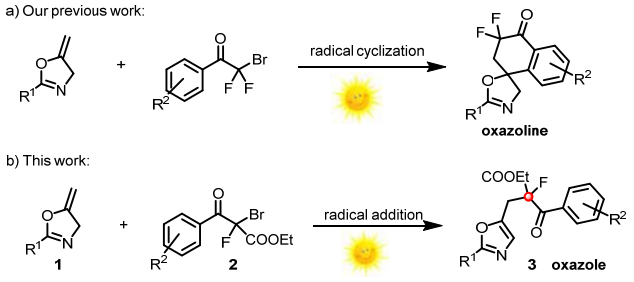


Fig.1 Representative biologically active molecules containing oxazole motif.

Carbon-carbon bond formation plays a pivotal role in synthetic organic and medicinal chemistry, and accordingly, many protocols to construct new carbon-carbon bonds have been developed. One of the unique protocols for catalytic C-C bond construction is photoredox catalyzed radical addition with π acceptors, such as alkenes, arenes, alkynes, isocyanides, and imines.[9] The protocol is mild and versatile, and typically produces carbon radical quickly at room temperature. Although various carbon radicals have been adopted to this conversion, the 2-fluoro-3-oxo-3-phenylpropanoate-type radical has rarely been reported to undergo such transformation. In our previous work, we developed an electron catalyzed radical cyclization of methylene-2-oxazolines protocol



Scheme 1 Cascade C(sp^3)-CF and aromatization of methylene-2-oxazolines.

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Electronic Supplementary Information (ESI) available: Experimental details and spectroscopic characterization information. See DOI:10.1039/x0xx00000x

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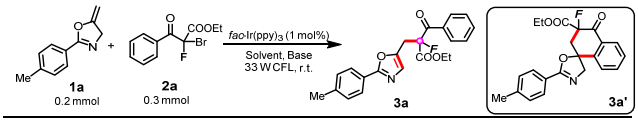
DOI: 10.1039/D0OB00267D

(Scheme 1a).[10a] In line with our interest in the development of methods for the synthesis of fluoroorganic compounds,[10] herein, we report an unprecedented approach towards the synthesis of fluorinated oxazole with a quaternary C-F center using ethyl 2-bromo-2-fluoro-3-oxo-3-phenylpropanoate as radical CFR^1R^2 source via a photoredox catalyzed tandem radical addition and aromatization of methylene-2-oxazolines (Scheme 1b). This strategy provides a facile approach to highly-valued oxazole derivatives.

At the outset, the reaction of methylene-2-oxazoline **1a** with ethyl 2-bromo-2-fluoro -3-oxo-3-phenylpropanoate **2a** was chosen as a model system to optimize the reaction conditions (Table 1). A mixture of **1a** and **2a** in dichloromethane was exposed to 1 mol% *fac*-$Ir(ppy)_3$ in the presence of Na_2CO_3 at room temperature under visible light irradiation. The desired product **3a** was then isolated in 78% yield along with the cyclization product **3a'** (Table 1, entry 1). Because of this promising result, screening of various solvents indicated that other solvents (such as $(CH_2)Cl_2$, DMF, DMA, THF, and MeCN) also worked well, but the yields are lower (Table 1, entries 2-6). The screening of bases showed that K_3PO_4 was the best with 80% yield (Table 1, entry 9). Other bases such as K_3CO_3, Cs_2CO_3, KOAc and $NaBF_4$ were less effective (entries 7-8 and 10-11). Control experiments indicated that visible light irradiation, photocatalyst and base were critical for this transformation (Table 1, entries 12-14). The reaction could not proceed smoothly when other photocatalysts were tested (Table 1, entries 15-17).

Table 1 Optimization of reaction conditions[a]

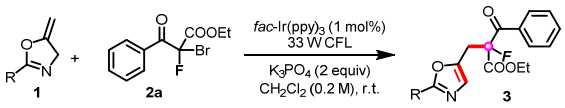


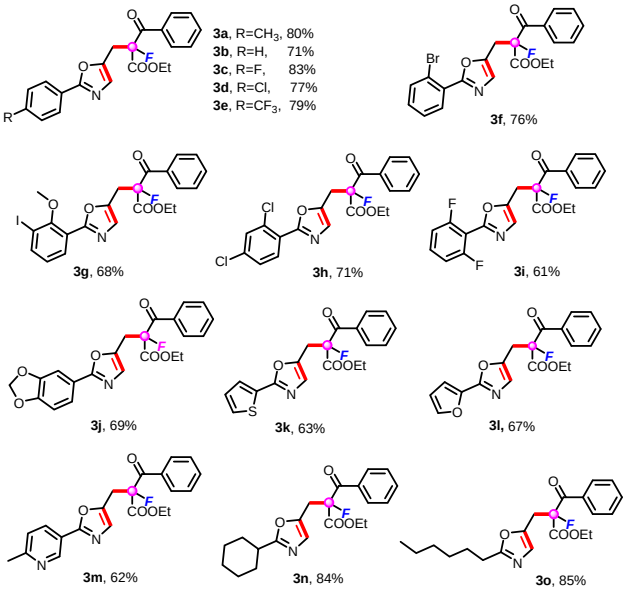
Entry	Photocatalyst	Solvent	Base	Yield(**3a**)[b]	Yield(**3a'**)[b]
1	*fac*-Ir(ppy)$_3$	CH_2Cl_2	Na_2CO_3	78%	16%
2	*fac*-Ir(ppy)$_3$	$(CH_2)_2Cl_2$	Na_2CO_3	71%	13%
3	*fac*-Ir(ppy)$_3$	DMF	Na_2CO_3	46%	trace
4	*fac*-Ir(ppy)$_3$	DMA	Na_2CO_3	42%	trace
5	*fac*-Ir(ppy)$_3$	THF	Na_2CO_3	75%	<10%
6	*fac*-Ir(ppy)$_3$	MeCN	Na_2CO_3	73%	<10%
7	*fac*-Ir(ppy)$_3$	CH_2Cl_2	K_2CO_3	69%	20%
8	*fac*-Ir(ppy)$_3$	CH_2Cl_2	Cs_2CO_3	47%	17%
9	***fac*-Ir(ppy)$_3$**	**CH_2Cl_2**	**K_3PO_4**	**80%**	**<10%**
10	*fac*-Ir(ppy)$_3$	CH_2Cl_2	KOAc	74%	<10%
11	*fac*-Ir(ppy)$_3$	CH_2Cl_2	$NaBF_4$	48%	trace
12[c]	*fac*-Ir(ppy)$_3$	CH_2Cl_2	K_3PO_4	trace	\
13	\	CH_2Cl_2	K_3PO_4	trace	\
14	*fac*-Ir(ppy)$_3$	CH_2Cl_2	\	<20%	\
15	$[Ru(bpy)_3]PF_6$	CH_2Cl_2	K_3PO_4	trace	\
16	$[IrdF(CF_3)(ppy)_2(dtbbpy)]PF_6$	CH_2Cl_2	K_3PO_4	<10%	\
17	Eosin Y	CH_2Cl_2	K_3PO_4	trace	\

[a]Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), **2a** (0.3 mmol), base (0.4 mmol) and photocatalyst (1.0 mol%) in solvent (1.0 mL) under 33W fluorescent light bulb at room temperature with Ar atmosphere for 12 h. [b]Isolated yield based on **1a**. [c]In the dark.

With the optimized reaction conditions for the synthesis of fluorinated oxazole containing a quaternary C-F center in hand (Table 1, entry 9), we examined the substrate scope of methylene-2-oxazolines **1** and 2-bromo-2-fluoro -3-oxo-3-phenylpropanoate **2a**. As shown in Scheme 2, the presence of a substituent on the aryl ring of methylene-2-oxazolines **1** had no significant effect for reaction yield. The reaction of methylene-2-oxazolines **1** with an electron-donating group, electron-withdrawing group or just hydrogen atom at the para position furnished the corresponding products **3a-e** with 71-83% yields. Gratifyingly, methylene-2-oxazolines possessing various halogens (such as fluorine, chlorine, bromine, iodine) with various substitution patterns were well-compatible, and the desired products **3f-3i** could be obtained in moderate to good yields. It was worth noting that methylene-2-oxazolines derived from polycyclic arenes **3j** were also well-tolerated. It was noteworthy that heteroaryl derived methylene-2-oxazolines were also good substrates for this transformation (**3k**-**3m**). Alicyclic substituted methylene-2-oxazolines could also serve as efficient reaction partners and furnished the corresponding monofluoroalkylated oxazoles **3n** and **3o** in good yields.

Table 2 Scope with respect to methylene-2-oxazolines[a,b]





[a]Unless otherwise noted, all reactions were performed with **1** (0.2 mmol), **2a** (0.3 mmol), *fac*-$Ir(ppy)_3$ (1 mol%) and K_3PO_4 (0.4 mmol) in CH_2Cl_2 (1 mL) under 33W fluorescent light bulb at room temperature with Ar atmosphere for 12-24 h. [b]Yields are reported for the isolated products based on **1**.

Next, the substrate scope of keto esters **2** was explored to examine their applicability in our system (Scheme 3). Keto esters with various halogens, such as fluorine, chlorine, bromine, iodine, which were useful modules for further functionalization, were well-compatible, and the desired

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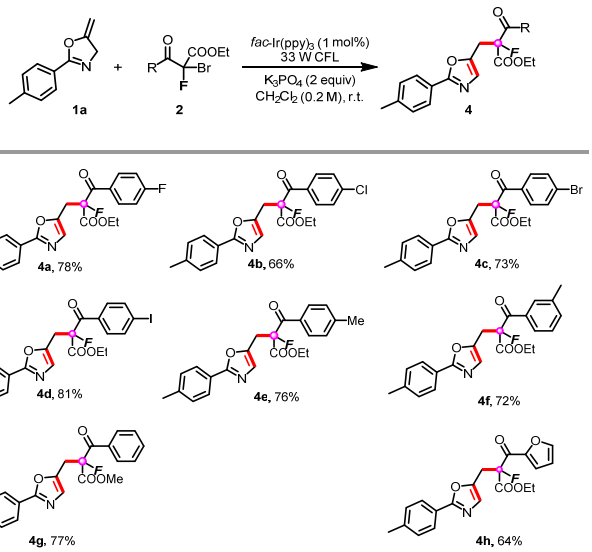
products **4a-4d** could be obtained in 66% to 81% yields. Electron-donating methyl at the para or meta position proceeded well with **1a** to deliver the expected products **4e** and **4f** in 72% and 76% yield, respectively. The reaction also occurred smoothly with methyl ketoate to obtain product **4g** in 77% yield. Especially, keto ester with heteroaromatic ring was also effective in undergoing the radical reaction to deliver **4h**.

Importantly, this transformation was scalable. The reaction of **1a** (0.52 g) with **2a** (1.3 g) was conducted under the standard conditions, providing **3a** (0.99 g) in the isolated yields of 87%, demonstrating that this process is practical and reliable (Scheme 2, eqn.(1)).

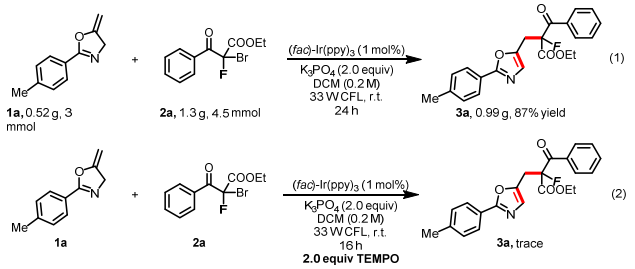
Table 3 Scope with respect to monofluorobromoacyl arenes [a,b]



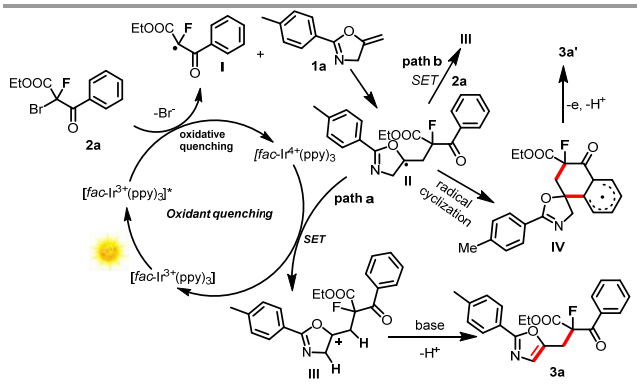
[a]Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), **2** (0.3 mmol), *fac*-Ir(ppy)$_3$ (1.0 mol%) and K_3PO_4 (0.4 mmol) in CH_2Cl_2 (1.0 mL), under 33W fluorescent light bulb at room temperature with Ar atmosphere for 12-24 h. [b]Yields are reported for the isolated products based on **1a**.

To shed light on the reaction mechanism, we conducted a radical trapping experiment with the presence of the radical scavenger 2,2,6,6-tetramethylpiperdine 1-oxyl (TEMPO). When this radical inhibitor TEMPO was introduced into a solution of methylene-2-oxazoline **1a**, keto ester **2a**, K_3PO_4, and the photocatalyst *fac*-Ir(ppy)$_3$ in CH_2Cl_2, the reaction was completely inhibited, which indicates that a radical process is operating (Scheme 2, eqn.(2)).

Based on our findings and previous studies,[9a,10a,11] a mechanism for the monofluoroalkylation of methylene-2-oxazolines was proposed (Scheme 3). Initially, irradiation of the heteroleptic *fac*-[Ir^{3+}(ppy)$_3$] with visible light results in a metal to ligand charge-transfer (MLCT) process, which furnishes an excited state *fac*-[Ir^{3+}(ppy)$_3$]*, which can undergo oxidative quenching in the presence of α-bromo-α-monofluoro keto ester as an appropriate electron acceptor via a single electron transfer (SET) process with the formation of the strongly oxidizing *fac*-[Ir^{4+}(ppy)$_3$] and radical **I**. Subsequently, the electrophilic radical **I** will attack the carbon–carbon double bond of the methylene-2-oxazoline **1a** to give the oxy-alkyl radical **II**. At this stage, intermediate **II** is oxidized to the β-monofluoroalkylated carbocation intermediate **III** by *fac*-[Ir^{4+}(ppy)$_3$] (+0.77V vs. SCE in CH_3CN). Ultimately, monofluoroalkylated oxazole **3a** is formed by deprotonation in the presence of base. Alternatively, intermediate **II** would also proceed through a radical cyclization pathway, with concomitant production of the cyclohexadienyl radical **IV**. Further SET-oxidation and deprotonation will give product **3a'**. In addition, radical chain mechanism could not be ruled out. The intermediate II could transfer one electron (SET) to the bromo derivative forming the radical I and the intermediate III.



Scheme 2 (1) Gram-scale reaction and (2) radical trapping experiment.



Scheme 3 Proposed mechanism.

In conclusion, an efficient methodology of the photoredox-catalyzed monofluoroalkylation of methylene-2-oxazolines via tandem radical addition and aromatization has been developed. This method provides a facile path to diverse substituted monofluorinated oxazoles with quaternary C-F centers, which are a class of highly valued structural motifs and novel synthons. The synthesis proceeds rapidly under visible light irradiation and demonstrated a broad substrate scope with high functional group compatibility. Further applications of α-monofluoro keto ester radicals in organic synthesis are underway in our laboratory.

Acknowledgements

We gratefully acknowledge the Science and Technology Research Program of Chongqing Municipal Education Commission (KJQN201901345, KJQN201901346), Chongqing Natural Science Foundation Postdoctoral Science Foundation Project (cstc2019jcyj-bshX0053), and the Scientific Research Foundation of the Chongqing University of Arts and Sciences (R2019FXY11).

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Conflicts of interest

There are no conflicts to declare.

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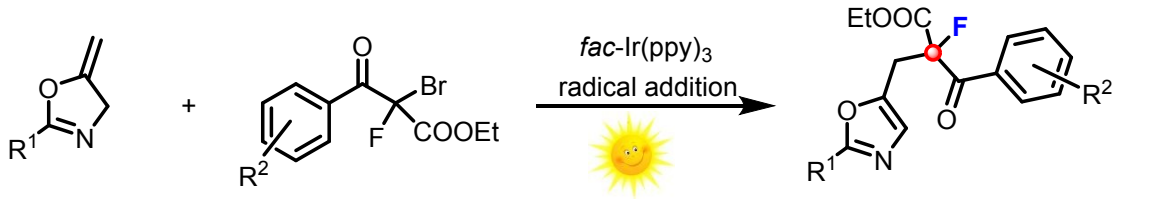
DOI: 10.1039/D0OB00267D

Synthesis of monofluorooxazoles with quaternary C-F centers through photoredox-catalyzed radical addition of methylene-2-oxazolines

Gui-Ting Song,†[a,b] Chuan-Hua Qu,†[a] Jin-Hong Chen,[a] Zhi-Gang Xu,[a] Cheng-He Zhou,[b,*] and Zhong-Zhu Chen[a,*]

A photoredox-catalyzed radical addition of methylene-2-oxazolines has been developed under visible light irradiation to synthesize monofluorooxazoles with quaternary C-F centers using 2-bromo-2-fluoro-3-oxo-3-phenylpropionates as radical source.



cascade pathway
mild condition
a quaternary C-F center construction
excellent reaction selectivity