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Pyridinium-Masked Enol as a Precursor for Constructing Alpha-Fluoromethyl Ketones

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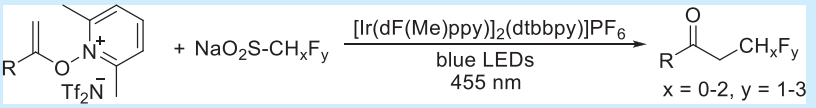

ABSTRACT: We present herein a pyridinium-masked enol as a versatile platform to produce ketones bearing tri-, di-, and monofluoromethyl in the presence of $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ under blue light (455 nm) irradiation. By simply changing the F-source, α-trifluoromethyl ketones, α-difluoromethyl ketones, and α-monofluoromethyl ketones could be easily prepared in moderate to excellent yields in one step, making it a practical tool for the synthesis of fluorine-containing ketones. In addition, the pyridinium-masked enol could also be extended to the synthesis of sulfonyl ketones. The findings of the present protocol contribute to the arsenal of fluorine chemistry and might have potential applications in the pharmaceutical and agrochemical industries.

Alpha-fluoromethyl ketones are a class of organic compounds that have gained extensive application across various fields, including medicinal chemistry,[1] agrochemistry,[2] and material science.[3] The incorporation of fluorine atoms in ketones imparts distinctive physicochemical properties to these compounds, which are often highly sought after for their intended applications.[4] In recent decades, several methods have been developed to synthesize α-fluoromethyl ketones, with significant emphasis placed on the development of effective fluorination reagents, for instance Selectfluor, Umemoto's reagent, and Togni's reagent et al.,[5] and also easily accessible starting materials, such as alkynes,[6] alkenes,[7] ketones,[8] and masked enols (the widely used masks include Li,[9] $ZnEt_2Li$,[10] SiR_3,[11] TBS,[12] GeR_3,[13] COMe,[14] $Ti(OiPr)_4Li$,[15] SO_2CF_3[13,16]) (Scheme 1(1)). Despite these advancements, the development of a versatile platform for constructing α-fluoromethyl ketones remains an ongoing challenge. This can be attributed to the varying electron-withdrawing nature of CF_3, CF_2H, and CFH_2 groups, leading to the more practical synthesis of α-fluoromethyl ketones being sometimes difficult to realize under mild reaction conditions. Therefore, the establishment of a versatile method for constructing α-fluoromethyl ketones would be highly desirable for organic chemists.

Pyridinium-masked enols are newly developed reagents that can be easily prepared through the cross-coupling reactions of alkynes and pyridine *N*-oxide in the presence of gold or silver complexes.[17] These reagents exhibit reactivity toward nucleophilic reagents, leading to the formation of α-alkoxyketones and α-thioketones,[18] α-amino ketones,[19] α-trifluoromethylthiolated ketones and α-thiocyanated ketones,[20] α-aryl/α-heteroaryl ketones,[21] et al. These studies conducted thus far demonstrate the effectiveness of pyridinium as a leaving group in a variety of nucleophilic substitution reactions, enabling convenient access to various functionalized ketones.[18−20] As photomediated catalytic reactions have gained popularity, pyridinium side has been found to act as an electron acceptor to provide an α-carbonyl radical.[22] For example, Hong and co-workers reported that the excited $[Ir(dF(CF_3)ppy)]_2(dtbbpy)]PF_6$ can boost the direct N−O bond cleavage of *N*-alkenoxypyridinium salt to generate an active α-carbonyl radical, thus realizing the carbopyridylation of alkenes.[23] In 2020, Chen and co-workers found that the pyridinium could also accept one electron from the I^- to release 2,6-lutidine and an α-carbonyl radical which can be trapped by an *in situ* formed iodine radical to prepare α-iodo ketones as shown in Scheme 1(2).[24] Inspired by these contributions, we were curious about the behaviors of pyridinium-masked enols in the synthesis of α-fluoromethyl ketones. In this study, the pyridinium-masked enol was used as a versatile platform to provide α-fluoromethyl ketones in the presence of an iridium catalyst with blue light (455 nm) irradiation. Mechanistic studies were also performed based on the deuterium labeling and control experiments.

Preliminary experiments focused on the screening of catalysts (Table 1). We first treated the mixture of **1a** and commonly used sodium trifluoromethanesulfinate (CF_3SO_2Na, **a**) in MeCN under reflux conditions because some reported reactions of pyridinium masked enols required no use of catalysts (entry 1).[18] However, no reaction occurred, albeit

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Scheme 1. Synthesis of α-Fluoromethyl Ketones from Different Starting Materials

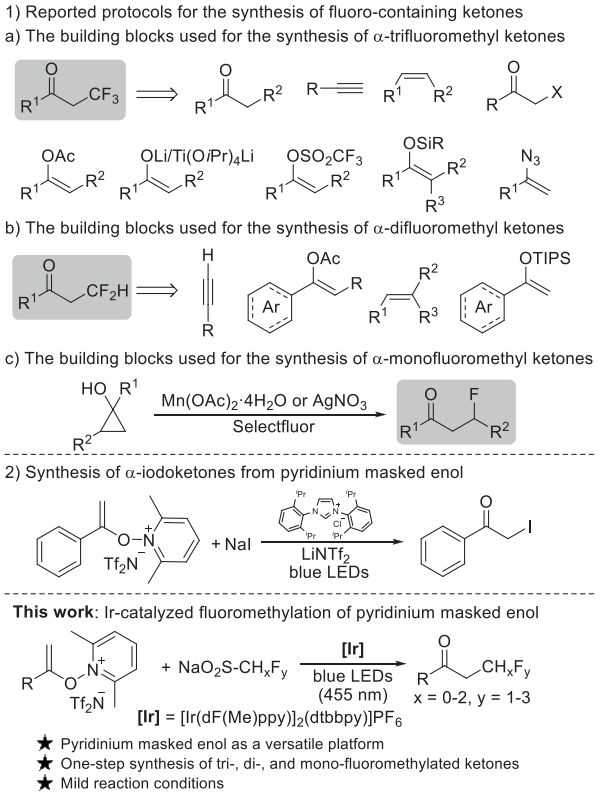
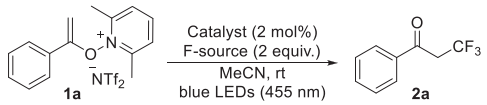
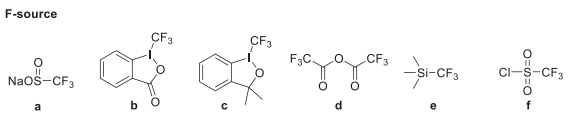


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	F source	yield (%)[b]
1	no	**a**	0[c]
2	$Ru(bpy)_3Cl_2$	**a**	78
3	$Ru(Phen)_3(PF_6)_2$	**a**	75
4	*fac*-$Ir(ppy)_3$	**a**	45
5	**$[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$**	**a**	**85**
6	$[Ir(dF(CF_3)ppy)]_2(dtbbpy)]PF_6$	**a**	83
7	$[Ir(dFppy)_2(dtbbpy)]PF_6$	**a**	81
8	$[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$	**b**	0
9	$[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$	**c**	0
10	$[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$	**d**	27
11	$[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$	**e**	0
12	$[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$	**f**	73

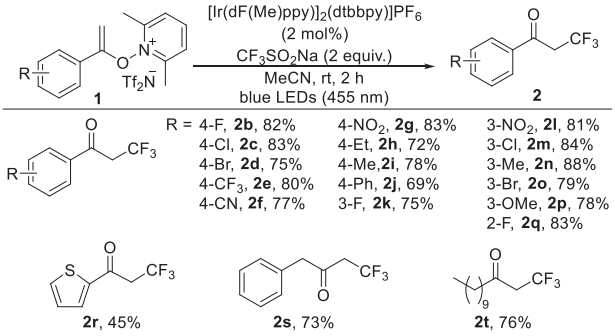
[a]Reaction conditions: **1a** (101.3 mg, 0.2 mmol), metal catalyst (0.004 mmol), F source (0.4 mmol), blue light (wavelength: 455 nm), reaction time (2 h), rt = 25 °C. [b]Isolated yield. [c]Reaction time (24 h).



with a prolonged reaction time (24 h). The lack of reactivity could possibly be attributed to the absence of a nucleophilic unit or a single-electron donor in the absence of catalyst. Based on this assumption, an external blue light source (455 nm) was exerted to promote the generation of free radicals. Interestingly, the use of $Ru(bpy)_3Cl_2$ and $Ru(Phen)_3(PF_6)_2$ gave corresponding **2a** in satisfactory yields, accompanied by a small amount of inseparable mixture and recovered starting material (entry 2 and 3). To further improve the yield of **2a**, a series of iridium complexes were examined, revealing that $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ is able to produce **2a** in 85% yield (entry 5 versus entries 2−4 and 6−7). Further screening of the F-source indicated that the CF_3SO_2Na gave the best results in terms of the yield of **2a** (entry 5 vs entry 8−12).

With the best reaction conditions in hand (0.2 mmol of **1**, 2 mol % of $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$, blue light (455 nm), MeCN), we investigated the applicability of the present protocol in the synthesis of α-trifluoromethyl ketones (Scheme 2). The catalytic results showed that a series of α-CF_3 aromatic

Scheme 2. Scope for the Synthesis of α-Trifluoromethyl Ketones[a,b]



[a]Reaction conditions: **1** (0.2 mmol), $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ (4.2 mg, 0.004 mmol), CF_3SO_2Na (62.4 mg, 0.4 mmol), blue light (wavelength: 455 nm), MeCN (2 mL), reaction time (2 h). [b]Isolated yield.

ketones could be easily prepared in good to very good yields under mild reaction conditions, no matter the position and electronic nature of the substituents (**2b−2q**). However, the thienyl group substrate (**1r**) led to the diminished yield (**2r**, 45%). Interestingly, the benzyl functionalized pyridinium salt could also be well tolerated in terms of the yield of **2s** (73%). This result encourages us further to investigate the behaviors of all aliphatic chains as reflected by the result of **2t** (76%).

During the synthesis of α-difluoromethyl ketones, it was found that all corresponding products could be obtained by simply changing the F-source from CF_3SO_2Na to CHF_2SO_2Na without modifying the reaction conditions (Scheme 3). However, in some cases, the isolated yields of α-difluoromethyl ketones are moderate (**3g**: 49%, and **3q**: 67%). This was induced by the low stability of products during the column chromatography process. Gratifying, the yield of thienyl group **3r** could be improved to 72% with respect to that of **2r** (Scheme 2). As expected, the benzyl- and alkylpyridinium salts are also good substrate candidates in terms of the yields of **3s−3t** (75% and 61%).

After successful preparation of α-trifluoromethyl ketones and α-difluoromethyl ketones, we then turned our interest to the synthesis of α-monofluoromethyl ketones from pyridinium masked enols, as shown in Scheme 4. In some cases, the corresponding α-monofluoromethyl ketones (**5f−5h**, **5l**, and **5o−5p**) can be prepared. However, the yields are not satisfactory (<41%). The major product was isolated as α-monofluoromethylsulfonyl phenylethanones (**4a−4r**). The reason might be attributed to the weak electron-withdrawing property of the CH_2F- unit, possibly leading to the release of

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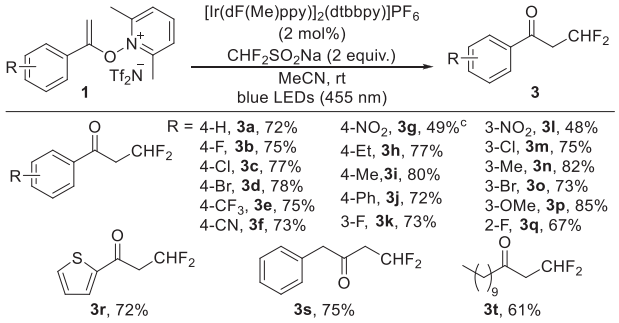
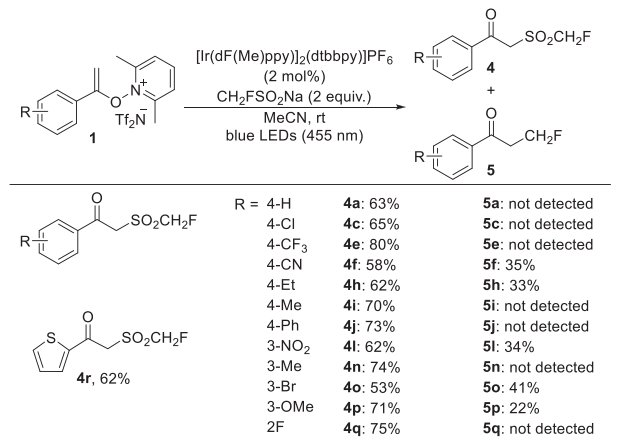
Scheme 3. Scope for the Synthesis of α-Difluoromethyl Ketones[a,b]



[a]Reaction conditions: **1** (0.2 mmol), $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ (4.2 mg, 0.004 mmol), CHF_2SO_2Na (55.2 mg, 0.4 mmol), blue light (wavelength: 455 nm), MeCN (2 mL), reaction time (2 h). [b]Isolated yield. [c]**3g** decomposed during column chromatography and a mixture was obtained.

Scheme 4. Scope for the Synthesis of α-Monofluoromethyl Ketones and α-Monofluoromethylsulfonyl Ketones[a,b]

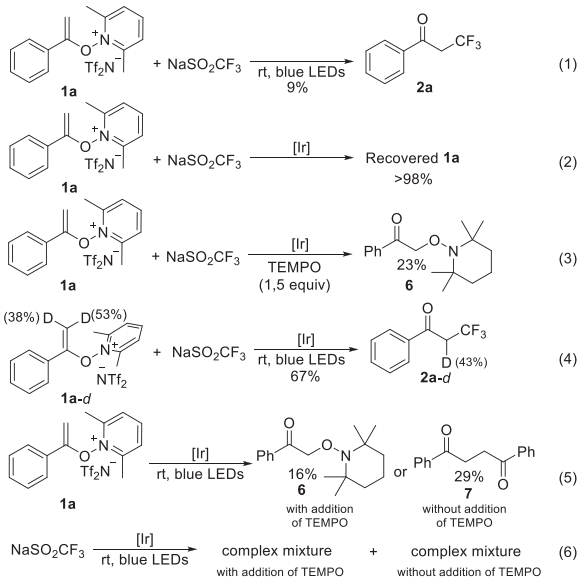


[a]Reaction conditions: **1** (0.2 mmol), $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ (4.2 mg, 0.004 mmol), CH_2FSO_2Na (48.3 mg, 0.4 mmol), blue light (wavelength: 455 nm), MeCN (2 mL), reaction time (2 h). [b]Isolated yield.

SO_2 from the $CH_2FSO_2\cdot$ radical being difficult (for more details, please see the mechanistic discussion part).

To obtain mechanistic insight into the present fluoromethyl reactions, a series of control experiments and deuterium labeling experiments were performed using **1a** and CF_3SO_2Na (**a**) (Scheme 5). The absence of $[Ir(dF(Me)ppy)]_2(dtbbpy)]$-$PF_6$ led to corresponding **2a** in 9% yield (eq 1 in Scheme 5). Removal of blue light failed to convert **1a** into **2a** or other products, suggesting that blue light is mandatory for this catalytic reaction (eq 2 in Scheme 5). However, addition of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) is detrimental for the trifluoromethylation of **1a** since **2a** was totally not observed and **6** was isolated in 23% yield, revealing that the free radical might be involved in this catalytic reaction (eq 3 in Scheme 5). The use of deuterated **1a** (**1a**-*d*) lead to the **2a**-*d* in 67% yield with 43% deuteration (eq 4 in Scheme 5). The loss of deuterium should be attributed to the tautomerization between the α-carbonyl radical and enol radical. According to previous reports,[7a,11c,23,25] both pyridinium salt and CF_3SO_2Na are able to generate respective radical in the presence of iridium complexes under light irradiation. Therefore, we next focused

Scheme 5. Deuterium-Labeling and Control Experiments[a,b]

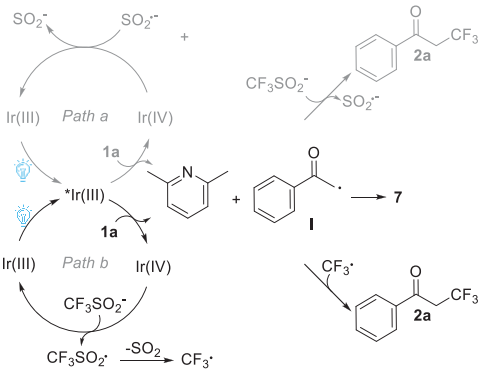


[a]Reaction conditions: **1** (0.2 mmol), [Ir] = $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ (4.2 mg, 0.004 mmol), CF_3SO_2Na (62.4 mg, 0.4 mmol), blue light (wavelength: 455 nm), MeCN (2 mL), reaction time (2 h). [b]Isolated yield.

on the confirmation of preferentially generated free radicals under blue light irradiation. Treatment of the mixture of **1a** with 1.5 equiv of TEMPO under the optimized reaction conditions afforded **6** in 16% yield. Removal of TEMPO yielded diketone **7** in 29% yield instead of **6** (eq 5 in Scheme 5). These results suggested that α-carbonyl radical formed in the case of $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ as catalyst under blue light irradiation, suggesting that the electron-acceptor might be the pyridinium side. However, the marriage of TEMPO to CF_3SO_2Na gave a complex mixture. Both CF_3-TEMPO and CF_3-TEMPO were not observed based on HRMS and ^{19}F NMR analysis.

Based on the above results, a plausible mechanism was proposed using the formation of **2a** as a model (Scheme 6).

Scheme 6. Proposed Catalytic Mechanism



First, the photoexcited iridium *Ir(III) species reacted with **1a** to afford lutidine and α-carbonyl radical **I**. This was also supported by the redox potential based on DFT calculation, where E^*_{ox} of excited $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ is 2.60 V, which is higher than the E_{ox} of **1a** (−0.25 V). Next, there are two possibilities. Path a favors that the α-carbonyl radical **I**

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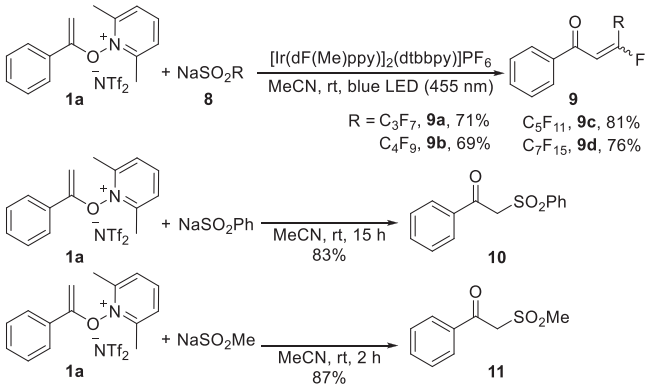
reacts with $CF_3SO_2^-$ to yield **2a** and $SO_2\cdot^-$ which is able to reduce the active iridium species from Ir(IV) to Ir(III). For Path b, the active *Ir(IV) serves as the oxidant to recruit an electron from CF_3SO_2Na (E_{ox} = −0.25 V), furnishing $CF_3SO_2\cdot$ radical, which can further release SO_2 to form $CF_3\cdot$. Subsequently, the combination of $CF_3\cdot$ with **I** gave rise to **2a**. Notably, the proposed mechanism also favors the formation of α-difluoromethyl ketones and α-monofluoromethyl ketones based on the redox potentials of CHF_2SO_2Na (0.09 V) and CH_2FSO_2Na (0.31 V). Although we have no experimental evidence, we favor path b at the present stage based on the calculation results.

To achieve a more practical application of pyridinium masked enols, the other kinds of long-chain F-sources, sodium benzenesulfinate and sodium methylsulfinate, were tested (Scheme 7). In the case of long-chain F-source, a series of

Scheme 7. Extended Application of Pyridinium Masked Enol as Precursor



fluorinated α,β-unsaturated ketones (**9a**−**9d**) were obtained in good yields (69% to 81%). Notably, the formation of **9a**−**9d** could be attributed to the dehydrofluorination process from their corresponding α-difluoromethyl ketones. However, in the case of sodium benzenesulfinate and sodium methylsulfinate, both reactions proceeded smoothly in the absence of $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ and blue light, and 1-phenyl-2-(phenylsulfonyl)ethan-1-one (**10**) and 1-phenyl-2-(methylsulfonyl)ethan-1-one (**11**) can be easily prepared in 83% and 87% yields, respectively. These results indicated that the formation of **10** and **11** could be attributed to the attack of sodium sulfonate on the terminal carbon of **1a** rather than the radical mechanism we previously proposed, possibly due to the stronger nucleophilicity of sodium benzenesulfinate and sodium methylsulfinate.

In conclusion, the pyridinium-masked enols were used to provide tri-, di-, and monofluoromethyl ketones in the presence of $[Ir(dF(Me)ppy)]_2(dtbbpy)]PF_6$ with irradiation of blue light (455 nm). As a versatile platform, the synthesis of fluoromethyl ketones can be achieved by variation of the F source (CF_3SO_2Na, CHF_2SO_2Na and CH_2FSO_2Na). Mechanistic investigation based on control experiments indicated that the excited iridium species first react with pyridinium-masked enols to provide α-carbonyl radical, which further reacts with the F-source to provide α-fluoromethyl ketones. In addition, the pyridinium-masked enols can be extended to the synthesis of α-sulfonyl ketones. The findings of this research contribute to the growing body of knowledge in the field of fluorine chemistry and have potential applications in the pharmaceutical and agrochemical industries.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02419.

Methods and experimental procedures; optimization of reaction conditions; deuterium labeling experiment; characterization data; NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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