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Photocatalytic α -Difluoroalkoxyketones Synthesis via Radical Intermolecular Alkoxylation of Difluoroenol Silyl Ethers

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Abstract: We present a metal-free photocatalytic approach for the synthesis of difluoroalkoxylatedketones. This strategy involves the generation of alkoxy radicals from pyridinium salts upon the activity of a catalytic electron-donor-acceptor (EDA) complex. This mild process tolerates several functional groups and can be scaled up to gram scale. Diverse products manipulations accounts for the versatility of the obtained fluorinated products, highlighting the synthetic usefulness of this method.

Keywords: α -Difluoroalkoxyketones; Pyridinium salts; Photoredox catalysis; Difluoroenol silyl ethers; EDA complex

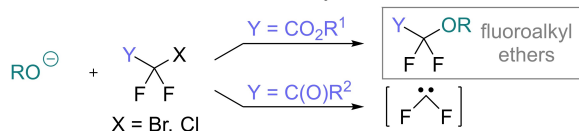
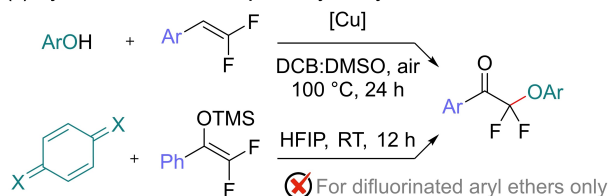
Introduction

Due to the unique effect of the fluorine atom on physical and biological properties of chemicals, organofluorine chemistry holds a central role in various areas, with many applications in materials, agrochemical, and medicinal sciences.^[1] Notably, α -fluoroalkyl ethers, in particular trifluoromethyl and difluoromethyl ethers (Y=F and Y=H, respectively, Scheme 1a), have recently attracted increased attention.^[2] The development of efficient protocols to prepare those molecules is most probably the reason why they can now be found in numerous biorelevant compounds.^[2] By contrast, the access to more functionalized difluoromethoxy units has been much less studied, despite their potential high interest. Available methods mainly focus on the electrophilic difluoromethylation of alcoholates (mostly phenolates) with ethyl bromodifluoroacetate (Y=CO₂Et, Scheme 1a).^[3] A similar approach towards difluoroalkoxymethylketones (Y=C-

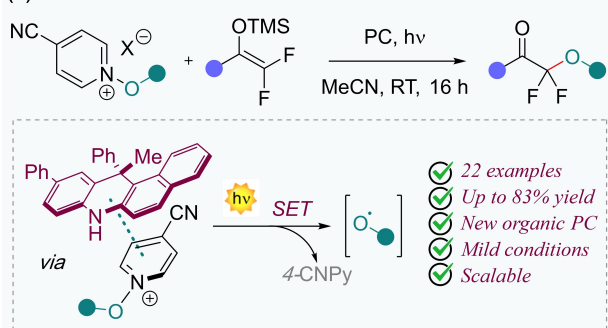
(O)R²) is however more challenging, as the O-centered nucleophile can add onto the carbonyl group and release difluorocarbene.^[4] An alternative route to these compounds was proposed in 2023 by Len, Hu *et al.* using *gem*-difluorinated electron-rich styrenes as fluorinated building blocks.^[5] However, the reaction required a large excess of alcohol (40–120 equiv.) to reach high efficiency, which can hamper its application in the case of more complex alcohols (Scheme 1b).^[5] Very recently, complementary approaches involving O-centered radicals were independently developed by Zhu, Yang *et al.*^[6] and by Cheong, Altman *et al.*^[7] Although performant, these strategies were limited to phenoxy groups (R=Ar, Scheme 1c).

Consequently, the development of an efficient and more general synthesis of α -difluoroalkoxymethylketones is highly needed. Herein, we document our efforts to fill this synthetic gap. Based on our recent expertise in pyridinium chemistry,^[8] the key strategy of this work involves the mild photocatalytic generation

(a) Access to functionalized fluoroalkyl ethers

(b) Len, Hu *et al.* 2023(c) Synthesis of α -difluorophenoxymethyl ketones

(d) This work



Scheme 1. Access to functionalized fluoroalkyl ethers.

of alkoxy radicals and their trapping with *gem*-difluoroenoxy silanes. Importantly, a new and readily accessible organophotocatalyst was prepared and used to develop a metal-free photocatalytic protocol (Scheme 1d).

Results and Discussion

We initially embarked on a study of the reaction between 4-cyano-*N*-methoxypyridinium tetrafluoroborate **1a** and ((2,2-difluoro-1-phenylvinyl)oxy)trimethyl silane **2a** as the model substrate. Pleasingly, when using the same conditions than in our previous work to generate the corresponding MeO \cdot radical (1 mol% of Ru(bpy)₃(PF₆)₂ **3a** irradiated at 456 nm by a Kessil lamp (10 W) in acetonitrile,^[8c] the expected difluoromethoxymethylketone **4a** was obtained in 47% NMR yield (Table 1, entry 1). Moved by our efforts to avoid the use of metal catalysts, a set of organophotocatalysts were tested. If eosin Y **3b** provided only 11% of the product **4a** (entry 2), the two recently developed by one of us (see SI for details) acridine-derived photosensitizers, **3c** and **3d**, outperformed the

Table 1. Optimization of the α -methoxylation of silyl dienol ether **2a** with pyridinium **1a**.

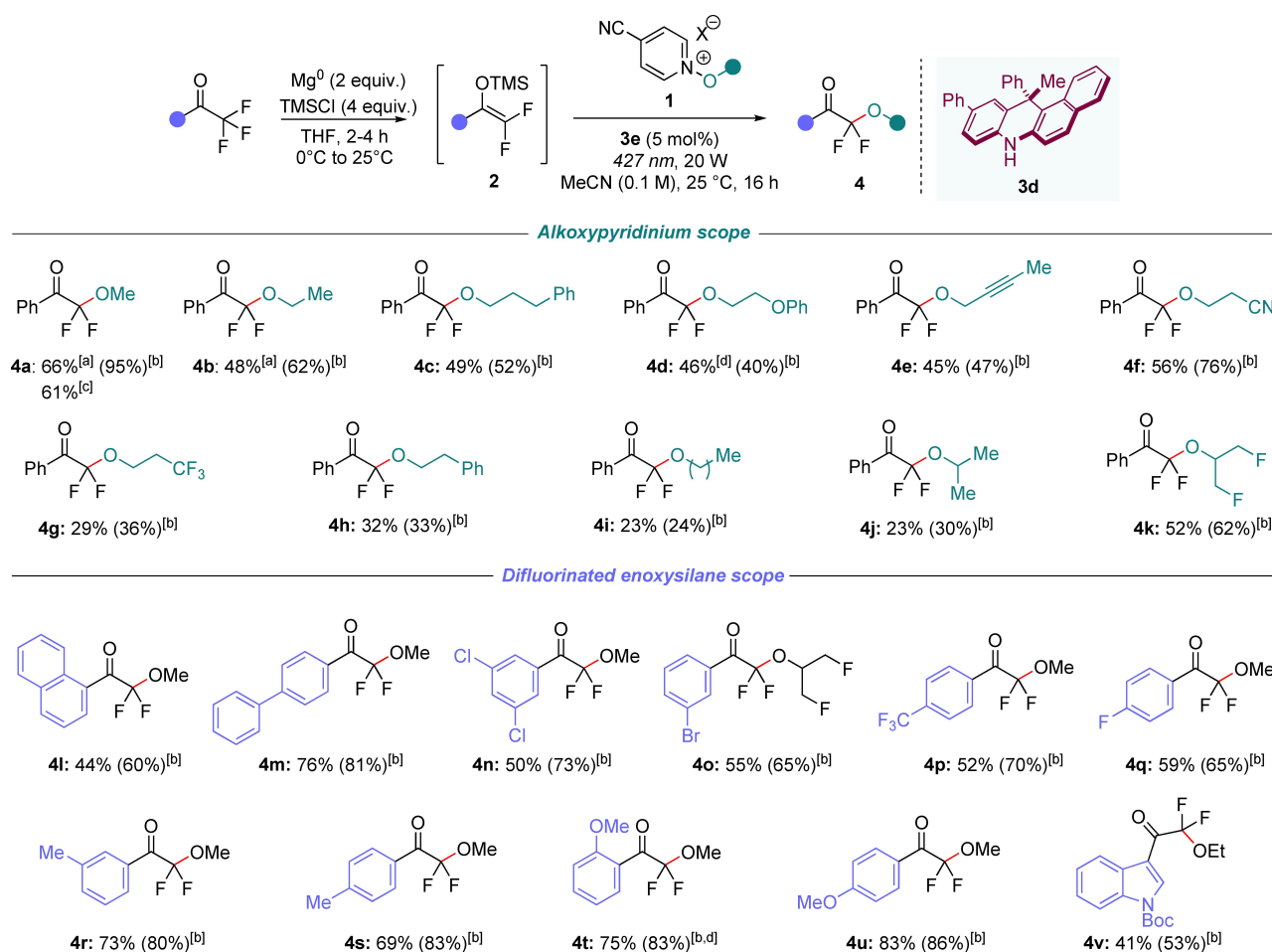
Entry	PC	x	light source (nm)	Yield (%) ^[a,b]
1	Ru(bpy) ₃ (PF ₆) ₂ 3a	1	456 (10 W)	47
2	Eosin Y 3b	1	456 (10 W)	11
3	3c	5	427 (10 W)	60
4	3d	5	427 (10 W)	76
5	3d	2.5	427 (10 W)	73
6	3d	5	427 (20 W)	95
7	3d	5	–	–
8	–	–	427 (20 W)	–

^[a] General conditions: **1a** (0.1 mmol), **2a** (1.5 equiv.), **3** (x mol%), dry MeCN (0.1 M), irradiated with Kessil lamp, at RT for 16 h under Argon.

^[b] Yields determined by ¹⁹F NMR using (chlorodifluoromethyl)benzene as an internal standard. Potential measured with ESC as reference electrode (See ESI for more details). PC: photocatalyst.

Ru-complex **3a**. Irradiation at a wavelength of 427 nm and with a catalytic loading of 5 mol% led indeed to NMR yields of 60% and 76%, respectively (entries 3–4). These results, given by the remarkable properties of these acridinium derivatives, prompted us to continue with these new photocatalysts.^[9] Varying the catalytic loading of **3d** from 5 to 2.5 mol% showed a slight decrease in yield (from 76% to 73% yield, entry 5). Finally, varying the power of the lamp resulted in a significant gain in efficiency, reaching 95% NMR yield with 20 W (entry 6). To prove the key role of the PC, control experiments were carried out in the dark and without organophotocatalyst **3d**, which showed no formation of the expected product **4a** (entries 7–8).

With these optimal reaction conditions in hand, the scope of this methodology was then evaluated (Scheme 2). Firstly, various pyridinium salts **1a–1g**, bearing a wide variety of functional groups (ether, alkyne, cyano, trifluoromethyl) afforded the corresponding α -difluorinated alkoxy methylketones **4a–4g** in up to 66% isolated yield. It is worth noting that ketones **4a** and **4b** were found to be volatile products, which resulted in lower isolated yields (66%–20%)



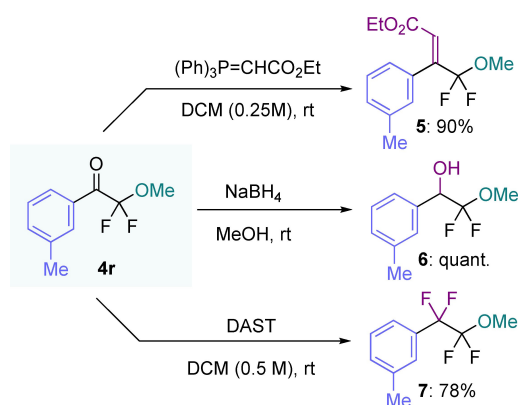
Scheme 2. Scope of the reaction. General conditions: **1** (0.1 mmol, 1 equiv.), **2** (1.2–1.5 equiv.), **3d** (5 mol%), dry MeCN (0.1 M) irradiated with a Kessil lamp (427 nm, 20 W) at 25 °C for 16 h under argon. Unless otherwise noted, given yields refer to chromatography pure products. ^[a] Volatile products. ^[b] Yields into brackets refer to ¹⁹F NMR yields using (chlorodifluoromethyl)benzene as an internal standard. ^[c] Reaction performed on a gram-scale. See ESI for more details. ^[d] Isolated with traces of non-alkoxylated –CF₂H. See ESI for more details. Each difluoroenoxy silanes were engaged directly in PC reaction without purification step. See ESI for more details.

compared to the corresponding higher NMR yields (95%–62%, respectively). A gram-scale experiment was also carried out for compound **4a**, yielding 1.04 g with no loss of efficiency (61% isolated yield). We also evaluated the reactivity of more challenging N-alkoxy pyridiniums **1h** and **1i**. These reagents are indeed sources of alkoxy radicals which can react in an intramolecular fashion *via* either a β -scission pathway (leading to a benzylic radical for **1h**) or a fast 1,5-HAT process (Hydrogen atom transfer, for **1i**). Importantly, these favoured side reactions are competing with the intermolecular C–O bond formation, and they led to no desired reactivity in previous alkoxylation studies.^[8a] We were therefore pleased to see that the corresponding difluoroalkoxymethylketones **4h–i** could still be prepared in 23–32% yield, which highlighted the relative high efficiency of this intermolecular alkoxylation of difluoroenoxy silanes. Two secondary pyridi-

nium salts exhibited also interesting reactivities and allowed the isolation of ketones **4j** and **4k** in acceptable yields. In a second time, the variation of the difluorinated silyl enol ether **2** was explored. As depicted in Scheme 2, various substrates **2b–k** could be smoothly alkoxyated under our mild organophotocatalyzed conditions, regardless of their substitution pattern in *ortho*, *meta* or *para* position. In addition, a large range of substituents (naphthyl, phenyl, methyl, halogens, CF₃, methoxy) were well-tolerated, electron-donating substituents in **4r–u** being slightly more efficient (up to 83% isolated yield) than other electron-withdrawing moieties (**4n–q**, 50%–59% isolated yield). Finally, it is worth noting that heteroaryl substrate **2l** was also compatible with our process, furnishing the corresponding indolyl adduct **4v** in good yield.

To illustrate the synthetic utility of this new protocol, a series of post-functionalization reactions were performed on difluoromethoxymethylketone **4r** which was readily obtained on a large scale (Scheme 3). First, a Horner-Wadsworth-Emmons reaction was successfully carried out, leading to the corresponding difluorinated α,β -unsaturated ester **5** in excellent yield and as a single stereoisomer. Then, reduction and difluorination of the carbonyl moiety of **4r** proceeded smoothly to give the corresponding products **6** and **7** in high isolated yields.

To elucidate the reaction manifold, we performed diverse optical and photophysical studies. First UV/Vis experiments showed a clear red-shift when **1a** was mixed with **3d**. That suggests the formation of a catalytic electron donor-acceptor (EDA) complex (see ESI for more details). To confirm this hypothesis, we conducted a control carrying out a reaction at 456 nm - a wavelength where only the EDA complex absorbs

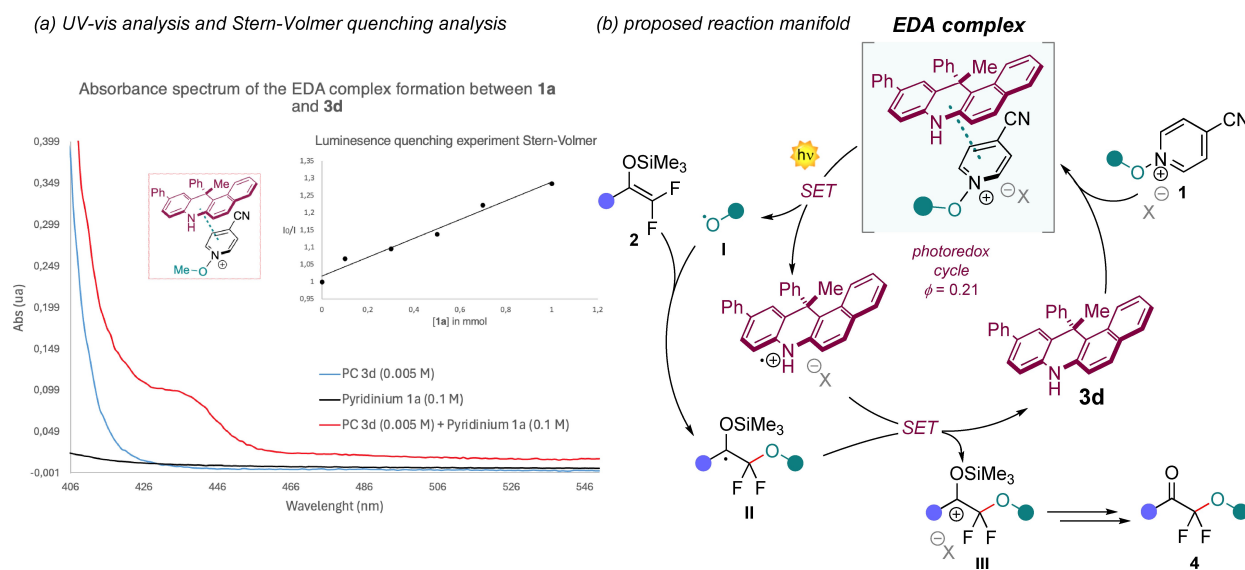


Scheme 3. Post-functionalizations of **4r**.

photons. Under these conditions, the product **4a** was obtained in 68% NMR yield, thus confirming the key activity of such complex in the reaction manifold. To gain insights into the initial reductive step of the reaction, we carried out Stern-Volmer quenching studies. As expected, only the pyridinium salt **1a** efficiently quenches the excited state of **3d** ($k_{ST}=4.2 \times 10^7 \text{ M}^{-1} \cdot \text{s}^{-1}$, compared to $k_{ST}=4.7 \times 10^6 \text{ M}^{-1} \cdot \text{s}^{-1}$ for substrate **2a**, see ESI for more details). This is in line with a single electron transfer (SET) between **1a** ($E_{1a}=-0.47 \text{ V vs SCE}$)^[8a] and the excited PC **3d*** ($E_{3d^*}=-2.28 \text{ V vs SCE}$, see ESI for more details). In addition, the quantum yield of the reaction was also measured with a maximum value of $\Phi=0.21$, indicating that a radical chain process is rather unlikely. Consequently, we propose that after the in-situ formation of a catalytic EDA complex the pyridinium salt **1a** undergoes a SET reduction (Scheme 4b), leading to the corresponding alkoxy radical **I**. The latter is directly engaged in a radical addition with the difluoroenoxy silane **2**. SET oxidation of the resulting C-centered radical intermediate **II** regenerates the ground state of **3d** and releases the carbocation **III**. Finally, desilylation of **III** gives access to the desired alkoxyated adduct **4**.

Conclusion

In summary, we have developed an intermolecular $\text{CF}_2\text{-O}$ bond forming process that makes use of readily accessible fluorinated silyl enol ether and pyridinium salts. The reaction proceeds thanks to the activity of a catalytic EDA complex between the electron-rich PC and the electron-deficient pyridinium, leading access to *gem*-difluorinated alkoxy methylketones (22 examples).



Scheme 4. (a) UV-vis and Stern-Volmer quenching analysis of **3d** and **1a**. (b) Proposed mechanism.

Such versatile fluorinated building blocks are obtained smoothly in moderate to high isolated yields (23%–83%). We foresee the extension of this mild methodology for accessing alternative fluorinated targets.

Experimental Section

In a vial of 4 mL, equipped with a magnetic stirring bar, was added the PC **3d** (2 mg, 0.005 mmol, 5 mol%), pyridinium salt **1** (0.1 mmol, 1 equiv.), silyl enol ether **2** (0.12–0.15 mmol, 1.2–1.5 equiv.), then the dry MeCN (1 mL, C=0.1 M). The vial was closed with septum, then the mixture was degassed with argon for 30–40 seconds. The vial was irradiated with Kessil Lamp at 427 nm, 20 W (50% power) for 16 h at rt (22–25 °C). After reaction, the solvent was removed under reduced pressure, and the residue was purified directly by silica gel column chromatography (Hexane/Ethyl acetate) as eluent to give the desired product **4**.

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