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Predictable site-selective radical fluorination of tertiary ethers

Junyang Ma, Wentao Xu & Jin Xie*

State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Chemistry and Biomedicine Innovation Center, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China

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In this communication, we disclose the first example of metal-free and site-selective radical fluorination of readily available tertiary alkyl ethers, enabled by synergistic photocatalysis and organocatalysis. This catalytic combination allows for exclusive fluorination of tertiary C–O bonds under mild conditions even in the presence of competing reaction sites. The excellent functional group tolerance affords valuable access to sterically hindered alkyl fluorides through late-stage modification of complex molecules. The successful use of tertiary alkyl ethers in radical fluorination enhances the structural diversity of aliphatic fluorides that can be derived from naturally abundant alcohols.

cooperative catalysis, C–O bond activation, radical fluorination, polarity-matching effect, umpolung

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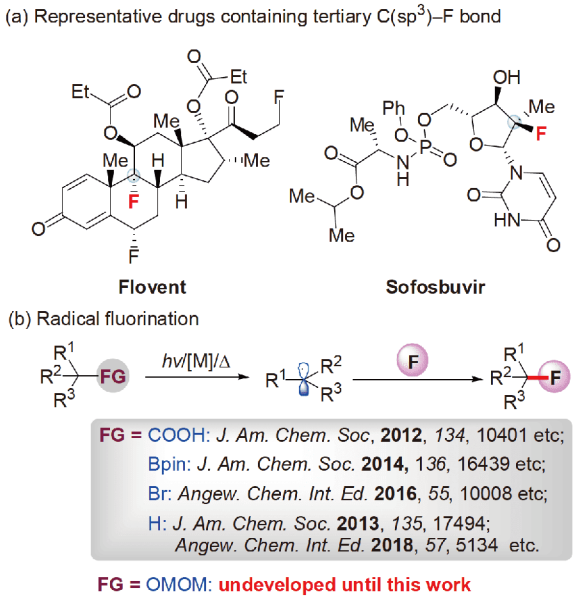
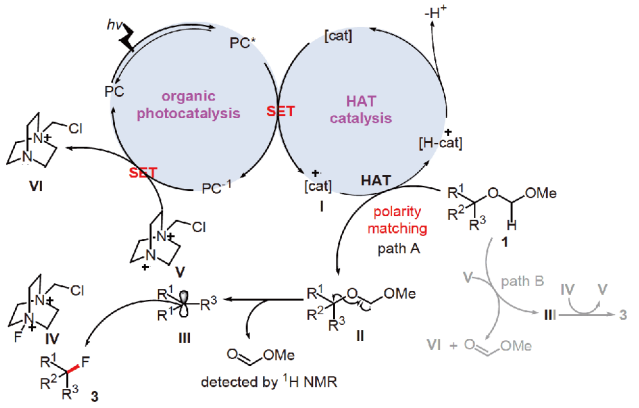
Fluorine, a small atom plays an important role in all fields of science. For example, the fluorine atom has been recognized as a bioisostere of the hydroxyl group [1]. In general, organofluorine compounds are increasingly common in pharmaceuticals and agrochemicals (Scheme 1(a)) owing to their unique physical and biological properties such as lipophilicity, permeability and metabolic stability [2]. The development of new strategies to construct C–F bonds has gained considerable momentum in recent years [3].

Radical fluorination of alkyl radical precursors (Scheme 1(b)) can afford a powerful route to tertiary aliphatic fluorine compounds [4], which are a class of important substructures in drugs (Scheme 1(a)). In the past decades, several readily available aliphatic starting materials, such as alkyl carboxylic acids [5], alkyl boronates [6], alkyl halides [7] and alkanes [8] have been successfully used in radical fluorination (Scheme 1(b)). Despite these advances, most of the cases are mediated by transition metals and the precise selectivity and the feasibility of late-stage modification in radical fluorination remains challenging. A few methods of radical fluorination originating from alcohols have been reported during our preparation, but these methods indeed undergo widely reported decarboxylation process [9]. Aliphatic ethers are readily available starting materials in organic synthesis [10] but the direct radical fluorination of tertiary C–O bonds is unprecedented. The success of this process will inarguably enhance the structural diversity of aliphatic organic fluorides provided by the naturally abundant precursor. In addition, photoredox catalysis is an emerging strategy in organic synthesis [11]. Herein, we report the first site-selective radical fluorination of tertiary ethers under metal-free conditions. Commercially available Selectfluor was used as the fluorination reagent and the reaction proceeds by means of synergistic photocatalysis and organocatalysis. This new protocol can be applied to late-stage monofluorination of complex pharmaceutical analogues with excellent regioselectivity and functional group compatibility and, for substrates bearing competing reaction sites, controllable radical fluorination can be achieved predictably.

*Corresponding author (email: xie@nju.edu.cn)



Scheme 1 The prevalence of tertiary alkyl fluorides in bioactive compounds and general radical fluorination strategies (color online).



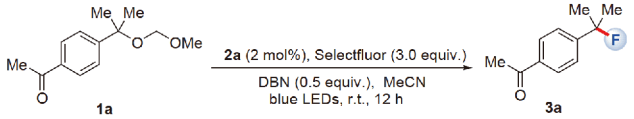
Scheme 2 Mechanistic hypothesis (radical chain pathway was added: path B) (color online).

To achieve a reaction site with precision, a hydrogen atom transfer (HAT) catalyst can be used because it usually plays a crucial role in generating the corresponding alkyl radical. An excessively strong HAT ability will decrease the regioselectivity while too weak ability will result in failure [12]. Based on our recent investigations, the HAT process can be tuned by the use of suitable kinds of HAT catalysts, typically thoils or tertiary amines [12,13]. A plausible mechanistic pathway for a possible catalytic cycle is proposed in Scheme 2. Under the irradiation of visible-light, the photo-excited photocatalyst with a high oxidation potential [e.g., Arc-Mes-Me$^+$* [$^{1/2}E$(Arc-Mes-Me$^+$*/Arc-Mes-Me)]=2.06 V vs. SCE] can undergo a single electron oxidation of the hydrogen-atom transfer catalyst to give the radical cation (**I**). This can go through a rapid polarity-matched HAT process with the hydridic C–H of the tertiary ether (**1**) to form the alkoxyl radical (**II**). Subsequently, C–O homolysis of alkoxyl radical (**II**) generates the tertiary alkyl radical (**III**), with the release of methyl formate (identified by ^{1}H NMR, see Supporting Information online for details). The resulting nucleophilic tertiary alkyl radical immediately attracts a fluorine atom from Selectfluor to produce the corresponding tertiary fluorides (**3**) [14]. Finally, the generated radical cation (**V**) accepts an electron, completing the photoredox cycle. On the other hand, since **V** has the similar radical cation structure with **I**, it may trigger analogous HAT process [15], which leads to a radical chain pathway to generate target product **3** (path B).

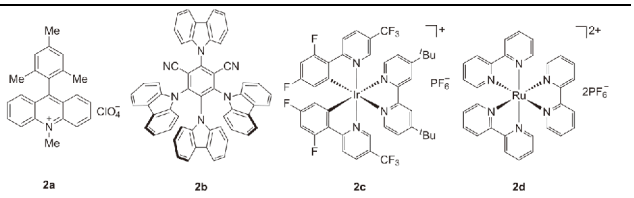
Selectfluor (212.5 mg, 0.6 mmol) and 9-mesityl-10-methylacridin-10-ium perchlorate (**2a**) (1.7 mg, 0.004 mmol) were placed in a 4 mL transparent vial equipped with a stirring bar. Then the vial was carried into glovebox which was equipped with nitrogen. Then MeCN (3.0 mL), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (12.4 mg, 0.1 mmol) and 1-(4-(2-(methoxymethoxy)propan-2-yl)phenyl) ethan-1-one (**1a**) (44.5 mg, 0.2 mmol) were added in sequence under N_2 atmosphere. The reaction mixture was stirred under the irradiation of 45 W blue light-emitting diodes (LEDs, distance app. 10.0 cm from the bulb) at room temperature for 12 h. When the reaction finished, the mixture was quenched with water and extracted with ethyl acetate (3×10 mL). The organic layers were combined and concentrated in vacuo. The product was purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 20:1) and 27.0 mg product 1-(4-(2-fluoropropan-2-yl)phenyl) ethan-1-one (**3a**) was obtained in 75% yield.

A model reaction to investigate the reaction conditions, **1a** with Selectfluor was selected. Although direct nucleophilic deoxyfluorination of alcohols with diethylaminosulfur trifluoride (DAST) [16], PhenoFluor [17], PyFluor [18], or SulfoxFluor [19] is workable, these methods usually have the disadvantage of limited functional group tolerance. The success of the radical fluorination of **1a** can further strengthen its synthetic value. To initiate the C–O bond cleavage, a suitable hydrogen-atom transfer co-catalyst is necessary. However, the initial use of thiols as HAT catalysts only gave moderate yields (see Supporting Information online for details). We speculated that the HAT ability of thiols was insufficient because of the moderate bond dissociation energy (BDE). In the light of recent literatures [12,20], we focused on tertiary amines, another class of frequently-used HAT catalysts and found that DBN was a suitable HAT catalyst. As shown in Table 1, under the optimized reaction conditions (entry 1), the target product (**3a**) was obtained from **1a** in 81% gas chromatography (GC) yield. The use of other photocatalysts (**2b**–**2d**) in place of **2a** resulted in lower yields (entries 2–4). The screening of HAT catalysts showed that DBN could give a better result (entries 5–7) and the amount of DBN could significantly influence the reaction

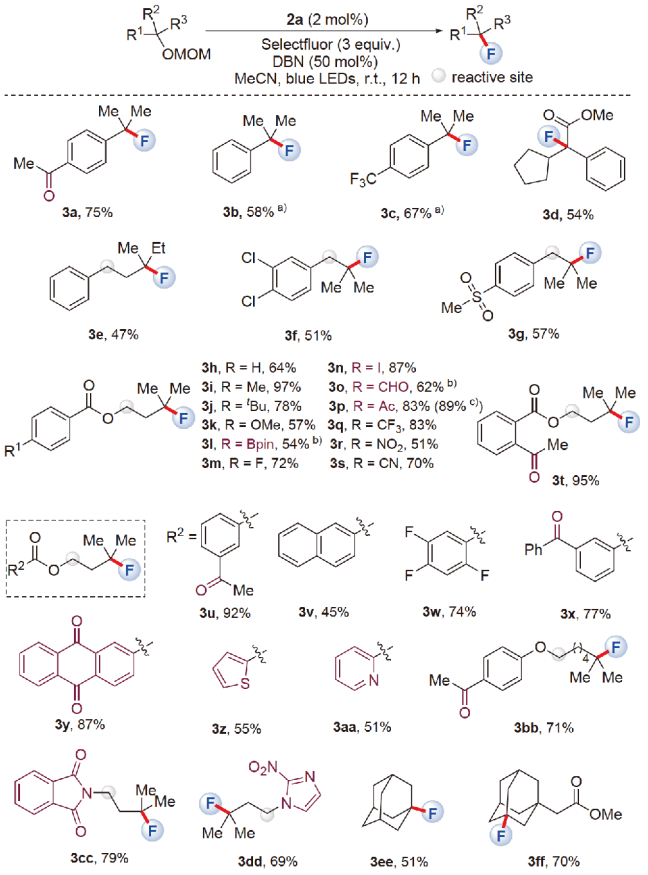
Table 1 Optimization of the reaction conditions [a]



Entry	Variation of standard conditions	Yield [b] (%)
1	None	81 (75)
2	**2b** instead of **2a**	22
3	**2c** instead of **2a**	7
4	**2d** instead of **2a**	19
5	DBU [c] instead of DBN	56
6	Quinuclidine instead of DBN	56
7	*N*-phenylmethanesulfonamide instead of DBN	18
8	1 equiv. DBN	23
9	0.1 equiv. DBN	46
10	No DBN	24
11	No photocatalyst	10
12	Dark	0



a) Standard conditions: **1a** (0.2 mmol), **2a** (2 mol%), DBN (50 mol%), Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate), 3 equiv.), MeCN (3 mL), blue LEDs, room temperature, 12 h. b) Measured by GC using acetophenone as internal standard. The isolated yield was given in the parentheses. c) DBU=1,8-diazabicyclo [5.4.0] undec-7-ene.



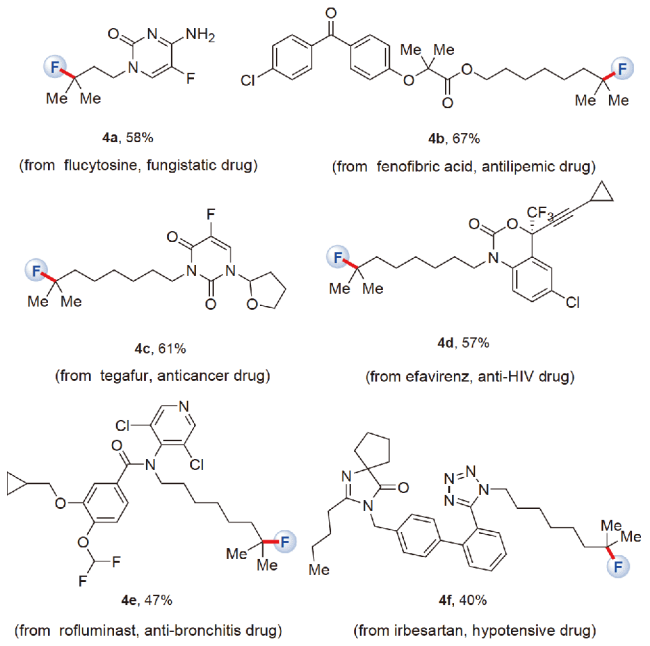
a) The yield was determined by ^{19}F NMR; b) 24 h; c) 1 mmol scale.

Scheme 3 Scope of the ethers in 0.2 mmol scale (yields of isolated products are given) (color online).

yield (entries 8–10). We envisioned that DBN had two possible roles, as an HAT catalyst and as an organic base which facilitates the deprotonation of $[H\text{-cat}]^+$ species. In the absence of DBN, a 24% yield of the desired product was delivered (entry 10). The reason for this is the generated tertiary ammonium radical cation from Selectfluor reagents as an alternative HAT catalyst during the reaction. In addition, we have tested other products, such as **3p** and **3ee**. In the absence of DBN, only a small amount of the desired product could be formed (see Supporting Information online for details). A 10% yield of product was also obtained for the model reaction in the absence of a photocatalyst (entry 11). We speculate that nitrogen-fluorine halogen bonding [21] might exist between DBN and Selectfluor and that the non-covalent compounds could be somewhat excited by visible light (see Supporting Information online for details). Therefore, to a certain extent the further increase of DBN to 1 equiv., leading to a decreased yield (entry 8) can be rationalized due to the consumption of Selectfluor via nitrogen-fluorine halogen bonding.

With the optimized reaction conditions in hand, we investigated the reaction scope of tertiary ethers (Scheme 3). In general, the protocol can achieve exclusive radical fluorination of a wide series of tertiary alkyl ethers with excellent functional group tolerance. Benzylic tertiary ethers can be converted to the corresponding tertiary fluorides in moderate to good yields (**3a**–**3d**). Alkyl ethers containing weak C(sp^3)–H bonds (e.g., benzylic C–H bonds or the α-C–H of a heteroatom) are also competent substrate partners and give predictable site-selectivity products (**3e**–**3dd**). Various electron-withdrawing and -donating substituents on phenyl rings are well tolerated, furnishing the desired tertiary aliphatic fluorides (**3h**–**3s**) in satisfactory yields of up to 97%. This new protocol exhibits excellent functional group compatibility, involving ketones (**3p**, **3t**, **3u**), aldehydes (**3o**), boronates (**3l**), phthalimides (**3cc**), iodo (**3n**) as well as nitro (**3r**) and heteroaryl groups (**3z**, **3aa**, **3dd**), further increasing its synthetic value. Importantly, the success of radical fluorination of the pinyl borate-substituted ether (**3l**) is complementary to deboronofluorination and can facilitate downstream transformations.

To demonstrate the synthetic robustness of this radical fluorination of ethers, we applied it to late-stage fluorination (Scheme 4). We found that it was very efficient and site-selective, accomplishing radical fluorination of tertiary C–O

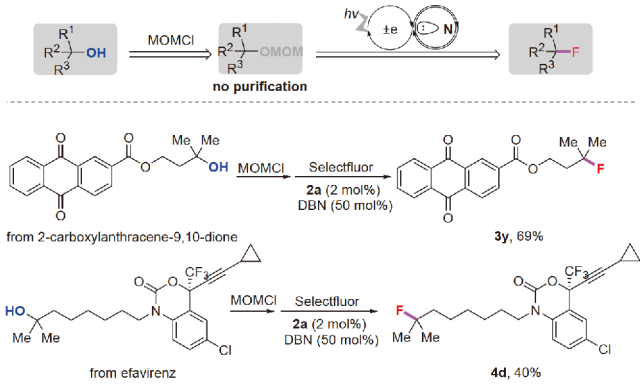


Scheme 4 Late-stage modification of complex molecules. See Supporting Information online for details of conditions (color online).

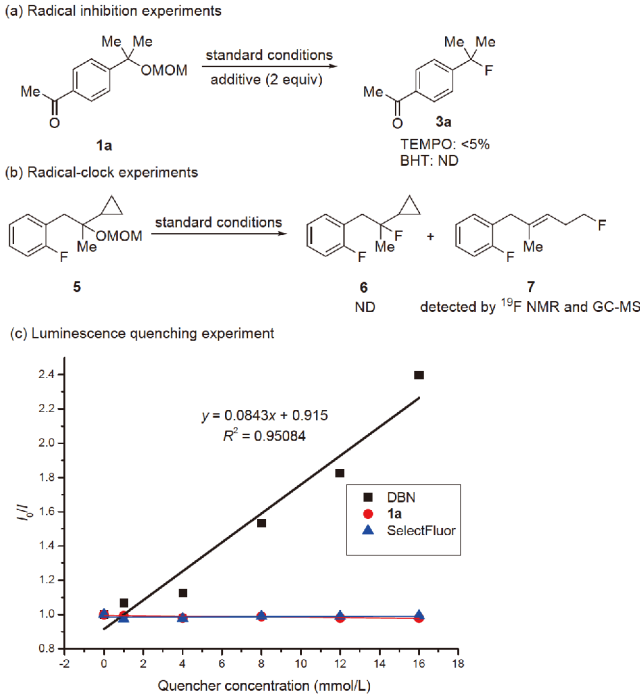
bonds in complex molecules. A series of derivatives of biologically important compounds, containing alkynes, tetrazoles, pyrimidines or strained rings successfully deliver the desired sterically hindered alkyl fluorides (**4a**–**4f**). This illustrates the generality of the synthetic methodology.

To further demonstrate the practicality of our protocol, the radical fluorination of ethers was applied to fluorination of the corresponding alcohols via a consecutive synthetic pathway (Scheme 5). After the treatment of tertiary alcohols (**5** and **6**) with chloromethyl methyl ether (MOMCl), the resulting MOM-type ethers could be directly used for the radical fluorination in moderate yields without further purification. In comparison, the target fluorination products could not be obtained when treating the tertiary alcohols with DAST (see Supporting Information online for details). This synthetic route generates tertiary alkyl fluorides from tertiary alcohols, with better functional group compatibility than the classical methodology using DAST.

A series of control experiments were performed to gain insight into the mechanism of this reaction. It was found that addition of radical trapping reagents (TEMPO (2,2,6,6-tetramethylpiperidinyloxy) and BHT (2,6-di-tert-butyl-4-methylphenol)) to the reaction of **1a** sharply decreased the yield of **3a**, indicating that a free radical process might be involved (Scheme 6(a)). The radical clock experiment further confirmed this possibility (Scheme 6(b)). In addition, a luminescence quenching experimental result demonstrated that the photocatalyst was quenched by DBN (Scheme 6(c)), supporting the proposed HAT catalytic pathway in Scheme 2. The quantum yield of the reaction was measured to be 0.7, which indicated that a short radical chain pathway was



Scheme 5 Consecutive procedures for C–O bond radical fluorination of complex tertiary alcohols (color online).



Scheme 6 The mechanistic investigation. (a) Radical inhibition experiments; (b) radical-clock experiments; (c) luminescence quenching experiments (color online).

possible. The use of radical initiator 2,2′-azobis(2-methylpro-pionitrile) (AIBN) could trigger the reaction in 16% yield (see Supporting Information online for details), suggesting the possibility of radical chain pathway.

In conclusion, we have developed a predictable site-selective radical fluorination of tertiary ethers under metal-free conditions by means of synergistic photoredox catalysis and organocatalysis. This unprecedented protocol allows for excellent functional group compatibility and site-selectivity. Its synthetic robustness is illustrated by late-stage fluorination of complex drug analogs and radical fluorination of tertiary alcohols by consecutive one-pot operation. This radical fluorination provides a new access to tertiary alkyl fluorides from readily available ethers as a new radical

precursor, and is complementary to the classical nucleophilic fluorination of alcohols with DAST.

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Conflict of interest The authors declare that they have no conflict of interest.

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