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Light-mediated Formal Radical Deoxyfluorination of Tertiary Alcohols via Selective Single Electron Oxidation with TEDA^{2+•}

Francisco José Aguilar Troyano, Frederic Ballaschk[§], Marcel Jaschinski[§], Yasemin Özkaya[§] and Adrián Gómez-Suárez*

Abstract: Herein we describe the synthesis of tertiary alkyl fluorides via a formal radical deoxyfluorination process. This light-mediated, catalyst-free methodology is fast and broadly applicable allowing for the preparation of C–F bonds from (hetero)benzylic, propargylic, and unactivated tertiary alcohol derivatives. Preliminary mechanistic studies support that the key step of the reaction is the single electron oxidation of caesium oxalates – which are readily available from the corresponding tertiary alcohols – with *in situ* generated TEDA²⁺⁺, a radical cation derived from Selectfluor®.

Nucleophilic deoxyfluorination reactions constitute one of the main strategies for the construction of aliphatic C-F bonds.^[1] Historically, DAST (diethylaminosulfur trifluoride) has been the primary deoxyfluorination reagent;^[2] nevertheless, due to its intrinsic reactivity it suffers from limited functional group tolerance. This has prompted the development of milder and more effective deoxyfluorination reagents, such as PyFluor by Doyle,^[3] or PhenoFluor^[4] and AlkylFluor by Ritter.^[5] However, given that these reagents react via $S_N 2$ pathways they are ineffective with sterically congested tertiary and neopentyl alcohols. A radical approach might be able to overcome these limitations and complement the existing nucleophilic strategies. Indeed, during the preparation of this manuscript formal radical deoxychlorination and deoxyfluorination processes, using caesium oxalates and an iridium-based photocatalyst, were reported by Reisman, Brioche and MacMillan.^[6]

Selectfluor® is an air stable, commercially available and inexpensive reagent, which can behave as a two electron oxidant or as an electrophilic fluorine source in fluorination reactions.^[7] Moreover, it can also participate in radical processes, either through single electron oxidations of metal catalysts, or as a fluorine transfer reagent to alkyl radicals.^[8] In these radical reactions, TEDA^{2+•} (*N*-(chloromethyl)triethylenediamine) is generated after the electron or fluorine transfer step. This is a highly reactive species that displays reactivity that is not commonly associated with Selectfluor®, *e.g.* it can act as a selective hydrogen atom transfer (HAT) catalyst to activate sp³C– H bonds^[9] or as an aminating reagent to build C–N bonds (Figure 1A).^[10] However, there is another reactivity pathway offered by TEDA^{2+•} that remains greatly underexplored, *i.e.* its use as a

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 [[§]] These authors contributed equally to this work. single electron oxidant.^[11] The main challenge to exploit the latter reactivity is that, given the opportunity, TEDA^{2+•} would readily react through either of the aforementioned pathways or via unproductive single electron oxidations to generate TEDA⁺. If TEDA^{2+•} can be harnessed as a single electron oxidant to selectively oxidise given organic molecules, it might be possible to open the door for new and interesting reactivity to be explored. Light-mediated methodologies have become popular strategies to initiate radical reactions, as they allow for a mild and controlled generation of open-shell species.^[12] Therefore, we wondered if it could be possible to access TEDA^{2+•} using visible light, and then have it selectively react with a suitable radical precursor, *e.g.* oxalate salts, which can be readily accessed from the corresponding alcohols,^[13] to achieve the formal deoxyfluorination of tertiary alcohols under very mild conditions (Figure 1B).



Figure 1. Reactivity of Selectfluor®, TEDA^{2+•}, and proposed transformation

Caesium oxalate **1** presents three possible reactive sites towards $TEDA^{2+\bullet}$: a) an oxalate anion, b) an activated benzylic C–H bond, and c) an aryl moiety. $TEDA^{2+\bullet}$ has been shown to engage in HAT reactions with benzylic C–H bonds, ^[9a, 9b, 9e-h] as well as to undergo radical addition to aryl groups to form C–N bonds. Therefore, **1**

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was chosen as substrate for the optimisation studies. Initially, **1** and Selectfluor®, were irradiated with a 32 W blue LED (λ_{max} = 440 nm) in a 1:1 mixture of 1,4-dioxane/H₂O, inside an EvoluChemTM PhotoRedOx Box for 16 h. Analysis of the reaction mixture by ¹⁹F NMR, using trifluorotoluene as internal standard, revealed that the desired tertiary fluoride (**2**) was formed in 70% yield. No products derived from either benzylic C–H abstraction or radical addition of TEDA²⁺⁺ to the phenyl group were observed. Next, we proceeded to optimize the reaction conditions (Table 1).^[14] First, the irradiation time was reduced to 2.5 h without affecting the outcome of the reaction. Control experiments in the absence of light, at 30 °C and 50 °C, failed to deliver the desired product, showing that irradiation is crucial for the reaction to proceed, while a solvent screen revealed that with a 1:1 mixture of acetone/H₂O, **2** could be obtained in 79% yield in only 1 h.

Table 1. Selected results from the optimization of the reaction conditions.^[a]

	Ph OCOCO-Cs	nv (λ _{max} = 440 nm) Selectfluor [®] (2.5 equiv.)		
	1	Solvent (0.1 M)	2	
Entry	Solvent	Change from conditions	Time (h)	Yield (%) ^[b]
1	1,4-dioxane:H ₂ O	none	2.5	72
2	1,4-dioxane:H ₂ O	No hv	2.5	0
3	1,4-dioxane:H ₂ O	No hv, 50 °C	2.5	4
4	Acetone:H ₂ O	none	1	79

[a] Reaction conditions: **1** (0.10 mmol), Selectfluor® (0.25 mmol), solvent (ratio 1:1, 0.1 M), irradiated with Blue LEDs (32 W, λ_{max} = 440 nm), under N₂ atmosphere. [b] ¹⁹F NMR yields using trifluorotoluene as internal standard.

The scope of the methodology was then explored using the optimised conditions (Scheme 1). Tertiary fluoride 2 was isolated in 74% yield. Substrates bearing primary chlorides, which might be susceptible to nucleophilic substitutions using traditional deoxyfluorination technologies, afforded the desired product 4 in high yield (81%). Tertiary fluoride 5, derived from 1-adamantol and bearing a benzylic amide was obtained in 57% yield. Exocyclic fluorinated piperidine derivatives, with N-Ts (6) or N-Boc (7) protecting groups, were obtained in 91% and 41% respectively, while endocyclic fluorinated derivatives 8 and 9, were isolated in moderate yields. Smaller 4- or 5-membered ring systems, such as 10 and 11, as well as internal alkynes (12) were also tolerated affording the desired products in moderate to good yields. Furthermore, mestanolone derived product 11,[15] showcases the improved functional group tolerance of our protocol, since if DAST were used in this reaction, the carbonyl group would be converted to the corresponding gem-difluoride species. Substrates derived from β -amino alcohols can also be readily fluorinated using our methodology (13-14). Substrate 14, derived from enantiomerically pure L-phenylalanine, was obtained with complete stereoretention.^[16] When a gram-scale reaction was performed with this substrate, 14 was isolated in 75% yield after 3 h of irradiation. Basic heterocycles, such as pyrimidines (15) pyridines (16) or pyrazines (17a) are also tolerated (55%, 64% and 25% yield, respectively). Interestingly,

the reaction with the pyrazine derivative afforded the fused bicyclic molecule **17b** as the main product in 56% yield. Formation of **17b** can be readily explained by generation of the corresponding tertiary radical followed by radical cyclization and subsequent rearomatisation by oxidation with Selectfluor®. The reaction with an electron rich *p*-methoxy substituted oxalate failed to provide the desired product (**3**). This presumably suggests a



Scheme 1. Scope of the reaction. Reaction conditions: Caesium oxalate (0.5 mmol), Selectfluor® (1.25 mmol), acetone (2.5 mL), H₂O (2.5 mL), irradiation with 32 W Blue LEDs (λ_{max} = 440 nm) under N₂ atmosphere for 2 h. Isolated yields. [a] Average of 2 runs. [b] Using 1 equiv. of anisole as additive. [c] NMR yield. [d] 2.4 mmol of caesium oxalate, 3 h irradiation.

COMMUNICATION

competition during an electron transfer event, where TEDA^{2+•} oxidises the electron rich aromatic ring rather than the oxalate anion. To test this hypothesis, the standard reaction using **1** was run in the presence of 1 equiv. of anisole and, as expected, **2** was obtained in a diminished 24% yield.

Cyclic (hetero)benzylic fluorides are key building blocks in agrochemicals and pharmaceuticals,^[17] as the incorporation of fluorine atoms can increase the metabolic stability of benzylic centres.^[18] Benzylic tetrahydropyran derivative **18** was obtained in 66% yield, while piperidine derivatives **19-21**, bearing phenyl and *p*-chloro substituents, were isolated in good yields (52-74%). Heterobenzylic piperidine **22**, bearing a 3-pyridinyl substituent was also successfully obtained (52%). However, compound **23** bearing a 2-pyridinyl substituent, could only be obtained in 15% yield. Sterically congested tertiary benzylic fluorides, such as **24**, can also be obtained.

Tertiary propargylic fluorides are notoriously challenging to prepare using nucleophilic deoxyfluorination strategies, due to competing elimination processes and 1,2-alkyl shifts.^[19] In 2015, Cordier reported an elegant approach towards the formal deoxyfluorination of secondary/tertiary terminal propargylic fluorides using a Cu catalyst and Et₃N•3HF as fluoride source.^[20] However, this methodology was completely ineffective for the synthesis of internal propargylic fluorides **25** and **26** could also be accessed with our methodology.

The selectivity of the reaction towards tertiary alcohols was also investigated (Scheme 2). Initially, the reaction was conducted in the presence of secondary oxalates, both benzylic and aliphatic, as well as a primary oxalate. In all cases, tertiary fluoride **2** was the main product of the reaction and only 10% of the secondary fluorinated products could be observed. In contrast, when the reaction was carried out in the presence of a primary oxalate, **2** was the only fluorinated product. When the reactions were carried in the absence of **1**, similar yields were observed for the





secondary oxalates, while no fluorinated products were observed with the primary species. Increasing the reaction temperatures did not increase the yields to synthetically useful values.

Preliminary mechanistic studies were conducted to shed some light on the reaction pathway. First, the radical nature of the process was examined.^[14] When the reaction was performed in the presence of TEMPO as radical scavenger (1 or 3 equiv.), no fluorinated products were observed. These results, in combination with the formation of **17b** as by-product when the reaction was performed with the pyrazine derived oxalate, strongly suggest that the process is radical in nature. This was further confirmed by measuring the quantum yield of the reaction ($\Phi = 2185.4$), which showed that a very efficient radical chain mechanism is in operation.^[14] Two possible pathways can be envisioned for the initiation step (Scheme 3):

- A. Generation of TEDA^{2+•} via an electron donor-acceptor (EDA) complex: electrostatic interactions might favour the formation of an EDA-complex^[21] between Selectfluor® and the corresponding oxalate derivative.^[22] Subsequent excitation of this species, followed by SET, would result in the formation of an acyloxy radical which, upon double decarboxylation, would afford the desired tertiary radical species. The latter would engage in a fluorine transfer process with a second molecule of Selectfluor® to deliver the desired tertiary fluoride and TEDA^{2+•}, which would act as a chain carrier, by oxidising a new oxalate molecule, thus further promoting the reaction.
- **B.** Generation of TEDA^{2+•} via direct irradiation of Selectfluor®: Lei^[23] and Jin^[24] have independently shown that it is possible to access TEDA^{2+•} by direct irradiation of Selectfluor® with blue LEDs and exploit it as a HAT catalyst. In this scenario, it is proposed that irradiation of Selectfluor® results in the homolytic cleavage of the N–F bond, generating TEDA^{2+•} which can engage in a selective single electron oxidation of the oxalate species. Subsequent decarboxylation and fluorine transfer events, would regenerate TEDA^{2+•} and afford the desired tertiary fluorides via a radical chain mechanism.



Scheme 3. Envisioned reaction mechanisms.

The UV/Vis spectra of Selectfluor®, **1**, and the reaction mixture were measured.^[14] While no absorption bands were observed above λ = 325 nm in the spectra of both Selectfluor® and **1**, an absorption band can be observed starting at *ca*. λ = 410 nm in the

COMMUNICATION

spectrum of the reaction mixture. Furthermore, when UV/Vis spectra were recorded with increasing concentrations of Selectfluor® vs 1 (from 0.5 to 2.5 equiv.) an increase in absorption was observed, suggesting the formation of an EDA-complex.^[14] ^[25] There is a better overlap between the absorption spectrum of the reaction mixture and the emission spectrum of blue LEDs with λ_{max} = 405 nm than with the blue LEDs with λ_{max} = 440 nm.^[14] Therefore, to further test the influence of light on the transformation, we followed the standard reaction under different wavelengths of irradiation (λ_{max} = 365, 405 and 440 nm).^[14] These studies revealed that regardless of the λ_{max} of irradiation, all reactions reached completion after 30 min. However, at shorter reaction times the highest yields were observed when blue LEDs with λ_{max} = 405 nm were employed. At this wavelength of irradiation the reaction likely proceeds via pathway A (Scheme 3). Light ON/OFF experiments confirmed that the reaction only proceeds when irradiated, thus further confirming the crucial role of the light in the reaction.^[14]

In conclusion, a light-mediated, catalyst-free, mild and general strategy to tackle the challenging deoxyfluorination of tertiary alcohols has been developed. Preliminary mechanistic investigations support the proposed radical chain mechanism, where the key species TEDA^{2+•} is likely generated via irradiation of an EDA-complex between Selectfluor® and the corresponding oxalate.

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Page No. – Page No.

Light-mediated Formal Radical Deoxyfluorination of Tertiary Alcohols via Selective Single Electron Oxidation with TEDA²⁺⁺