

Photochemistry

Light-Mediated Formal Radical Deoxyfluorination of Tertiary Alcohols through Selective Single-Electron Oxidation with TEDA²⁺

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Abstract: The synthesis of tertiary alkyl fluorides through a formal radical deoxyfluorination process is described herein. This light-mediated, catalyst-free methodology is fast and broadly applicable allowing for the preparation of C–F bonds from (hetero)benzylic, propargylic, and non-activated tertiary alcohol derivatives. Preliminary mechanistic studies support that the key step of the reaction is the single-electron oxidation of cesium oxalates—which are readily available from the corresponding tertiary alcohols—with in situ generated TEDA²⁺ (TEDA: *N*-(chloromethyl)triethylenediamine), 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 through *S_N2* 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 cesium oxalates and an iridium-based photocatalyst, were reported by Reisman, Briche, 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, TEDA²⁺ (TEDA: *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[®], for example, it can act as a selective hydrogen-atom transfer (HAT) catalyst to activate *sp*³ C–H bonds^[9] or as an aminating reagent to build C–N bonds (Figure 1 A).^[10] However, there is another reactivity pathway offered by TEDA²⁺ that remains greatly underexplored, that is, its use as a single-electron oxidant.^[11] The main challenge to exploit the latter reactivity is that, given the opportunity,

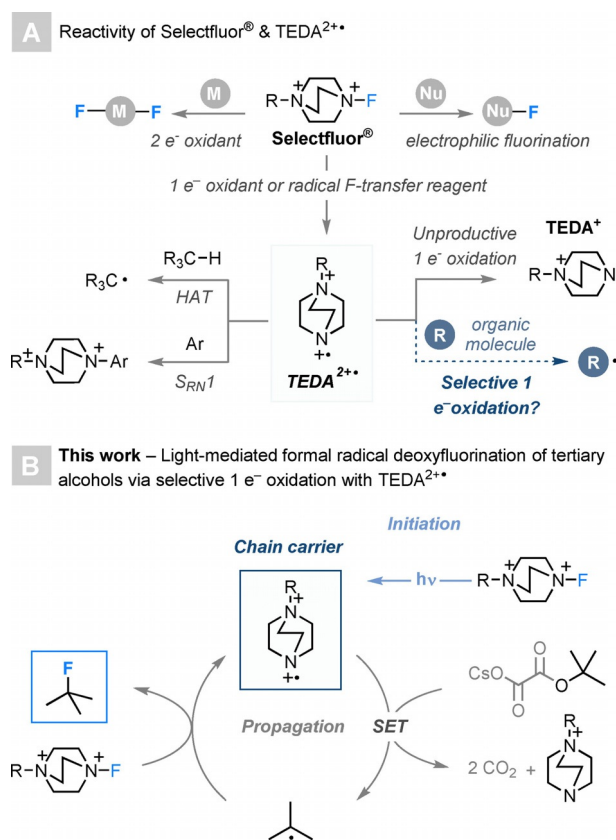


Figure 1. Reactivity of Selectfluor[®], TEDA²⁺ and proposed transformation.

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TEDA²⁺ would readily react through either of the aforementioned pathways or through unproductive single-electron oxidations to generate TEDA⁺. If TEDA²⁺ can be harnessed as a single-electron oxidant to selectively oxidize 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, because they allow for a mild and controlled generation of open-shell species.^[12] Therefore, we wondered if it could be possible to access TEDA²⁺ using visible light, and then have it selectively react with a suitable radical precursor, for example, 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 1 B).

Cesium oxalate **1** presents three possible reactive sites towards TEDA²⁺: a) an oxalate anion, b) an activated benzylic C–H bond, and c) an aryl moiety. TEDA²⁺ has been shown to engage in HAT reactions with benzylic C–H bonds,^[9a,b,d-g] as well as to undergo radical addition to aryl groups to form C–N bonds. Therefore, **1** was chosen as substrate for the optimization studies. Initially, **1** and Selectfluor[®] were irradiated with a 32 W blue LED ($\lambda_{\text{max}} = 440$ nm) in a 1:1 mixture of 1,4-dioxane/H₂O, inside an EvoluChem[™] 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

ed in 74% yield. Product **4**, bearing a primary chloride, was isolated 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**; Ts: *p*-toluenesulfonyl) or N-Boc (**7**; BOC: *tert*-butoxycarbonyl) protecting groups, were obtained in 91 and 41% yield, respectively, whereas 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, because if DAST would be used in this reaction, the carbonyl group would be converted to the corresponding *gem*-difluoride species. Substrates derived from β -amino alcohols also were 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**) were 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. The formation of **17b** can be readily explained by generation of the corresponding tertiary radical followed by radical cyclization and subsequent re-aromatization 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 competition during an electron transfer event, where TEDA²⁺ oxidizes 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] because the incorporation of fluorine atoms can increase the metabolic stability of benzylic centers.^[18] Benzylic tetrahydropyran derivative **18** was obtained in 66% yield, whereas 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 was only obtained in 15% yield. Sterically congested tertiary benzylic fluoride **24** was obtained in 48% yield.

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 fluoride derivatives. Gratifyingly, tertiary internal propargylic fluorides **25** and **26** were also accessed with our methodology.

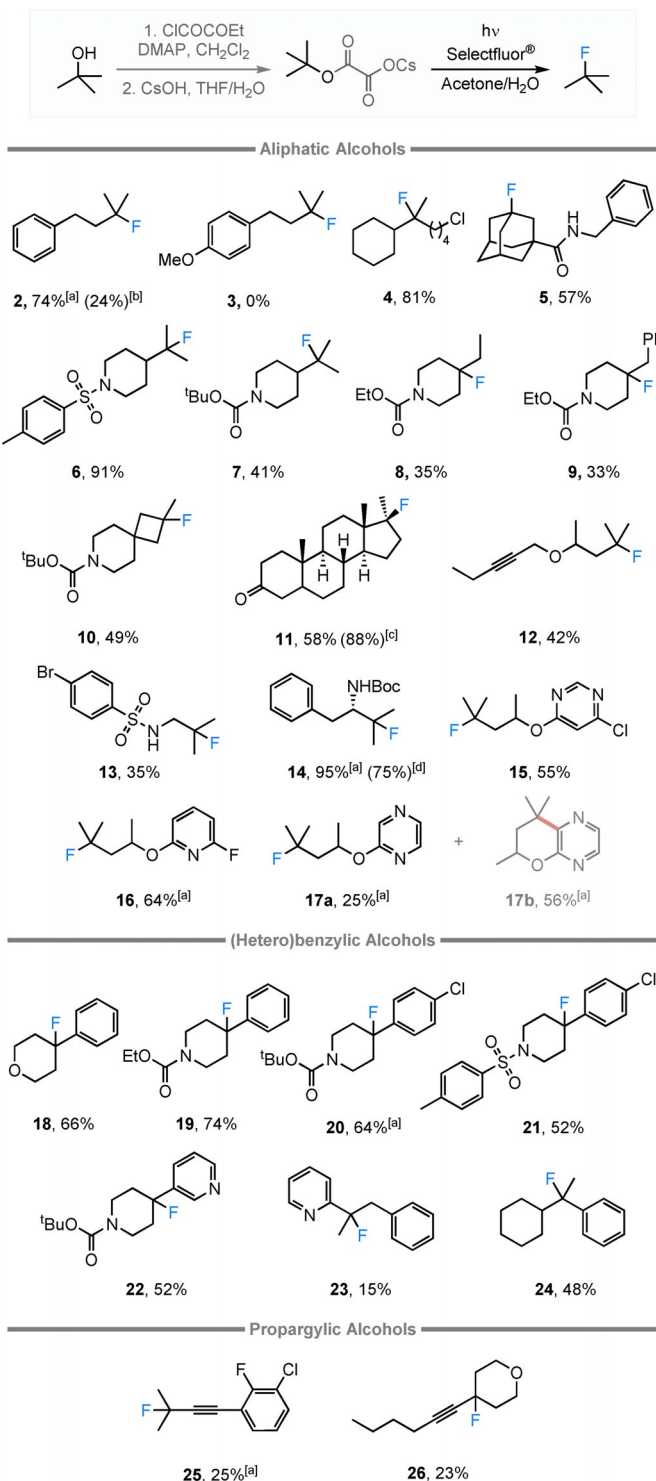
Table 1. Selected results from the optimization of the reaction conditions.^[a]

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 <i>hν</i>	2.5	0
3	1,4-dioxane:H ₂ O	no <i>hν</i> , 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, $\lambda_{\text{max}} = 440$ nm), under N₂ atmosphere. [b] ¹⁹F NMR yields using trifluorotoluene as internal standard.

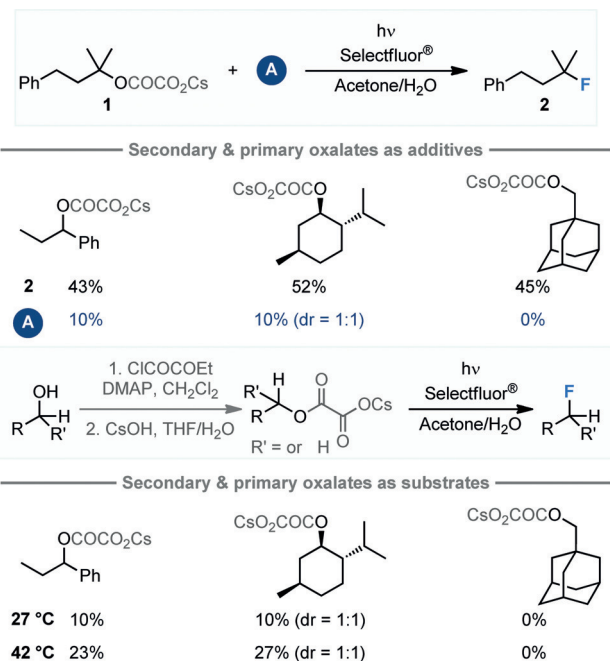
was reduced to 2.5 h without affecting the outcome of the reaction. Control experiments in the absence of light, at 30 °C and 50 °C, failed to deliver the desired product, showing that irradiation is crucial for the reaction to proceed, whereas a solvent screen revealed that with a 1:1 mixture of acetone/H₂O, **2** was obtained in 79% yield in only 1 h.

The scope of the methodology was then explored using the optimized conditions (Scheme 1). Tertiary fluoride **2** was isolat-



Scheme 1. Scope of the reaction. Reaction conditions: Cesium oxalate (0.5 mmol), Selectfluor[®] (1.25 mmol), acetone (2.5 mL), H₂O (2.5 mL), irradiation with 32 W blue LEDs ($\lambda_{\text{max}} = 440$ nm) under N₂ atmosphere for 2 h. Yields of isolated material. [a] Average of 2 runs. [b] Using 1 equiv of anisole as additive. [c] NMR yield. [d] 2.4 mmol of cesium oxalate, 3 h irradiation.

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

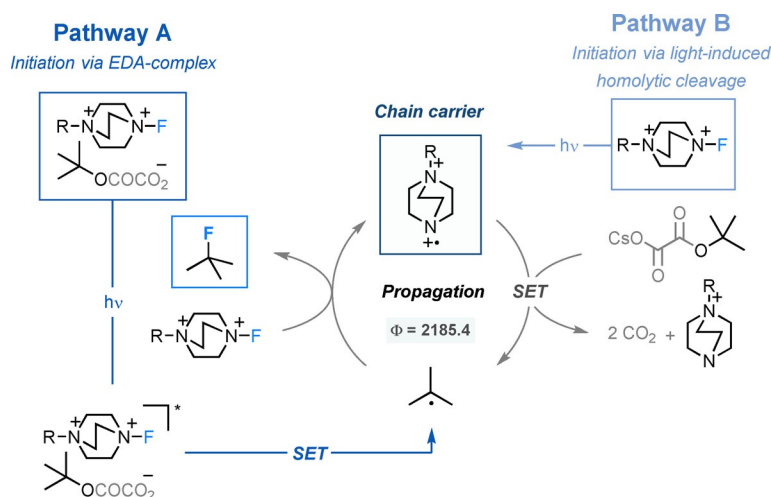


Scheme 2. Selectivity of the reaction. ¹⁹F NMR yields using trifluorotoluene as internal standard.

fluoride **2** was the main product of the reaction and only 10% of the secondary fluorinated products were 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, whereas 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 byproduct 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):

Path A: Generation of TEDA²⁺ through an electron donor–acceptor (EDA) complex: electrostatic interactions might favor 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 TEDA²⁺, which would act as a chain carrier, by oxidizing a new oxalate molecule, thus further promoting the reaction.



Scheme 3. Envisioned reaction mechanisms.

Path B: Generation of TEDA²⁺ through direct irradiation of Selectfluor®. Lej^[23] and Jin^[24] have independently shown that it is possible to access TEDA²⁺ 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 TEDA²⁺ which can engage in a selective single-electron oxidation of the oxalate species. Subsequent decarboxylation and fluorine-transfer events would regenerate TEDA²⁺ and afford the desired tertiary fluorides through a radical-chain mechanism.

The UV/Vis spectra of Selectfluor®, **1**, and the reaction mixture were measured.^[14] Although no absorption bands were observed above $\lambda = 325$ nm in the spectra of both Selectfluor® and **1**, an absorption band was observed starting at approximately $\lambda = 410$ nm in the spectrum of the reaction mixture. Furthermore, when UV/Vis spectra were recorded with increasing concentrations of Selectfluor® versus **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 $\lambda_{\text{max}} = 405$ nm than with the blue LEDs with $\lambda_{\text{max}} = 440$ nm.^[14] Therefore, to further test the influence of light on the transformation, we followed the standard reaction under different wavelengths of irradiation ($\lambda_{\text{max}} = 365, 405, \text{ and } 440$ 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 $\lambda_{\text{max}} = 405$ nm were employed. At this wavelength of irradiation, the reaction likely proceeds through 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, in which the key species TEDA²⁺ is likely generated through irra-

diation of an EDA-complex between Selectfluor® and the corresponding oxalate.

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Conflict of interest

The authors declare no conflict of interest.

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