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Formal Radical Deoxyfluorination of Oxalate-Activated Alcohols Triggered by the Selectfluor-DMAP Charge-Transfer Complex

Haralds Baunis[a, b] and Bartholomäus Pieber*[a, b]

We present a photon- and metal-free approach for the radical fluorination of aliphatic oxalate-activated alcohols. The method relies on the spontaneous generation of the *N*-(chloromethyl)triethylenediamine radical dication, a potent single electron oxidant, from Selectfluor and 4-(dimethylamino)pyridine. The protocol is easily scalable and provides the desired fluorinated products within only a few minutes reaction time.

Introduction

Approximately 20% of marketed drugs[1] and 15% of pesticides[2] contain fluorine atoms. This results from the increased metabolic stability and lipophilicity of small molecules upon fluorination. Further, incorporating fluorine in biomolecules facilitates structural analysis of proteins and nucleic acids via ^{19}F-NMR spectroscopy.[3] Moreover, radiolabeling with ^{18}F is key to studying biochemical pathways and physiological processes using positron emission tomography (PET).[4] As such, the selective fluorination of organic compounds is intensively studied and spans from nucleophilic and electrophilic fluorination strategies to the generation of C-centered radicals and their reaction with a suitable fluorine source.[5,6]

Deoxyfluorination of alcohols using nucleophilic, sulfur-based fluorinating agents is commonly used to prepare aliphatic fluorides (Scheme 1a).[5,6] However, this approach fails to convert tertiary alcohols due to steric limitations inherent to the underlying S_N2 mechanism. Radical fluorination of oxalate-activated alcohols overcomes this limitation and provides a complementary approach (Scheme 1b). A seminal study by the group of Reisman applied photoredox catalysis to generate C-centered radicals from tertiary and secondary oxalates to obtain the respective fluorination product in presence of the electrophilic N–F reagent Selectfluor (*N*-chloromethyl-*N*′-fluorotriethylenediammonium bis(tetrafluoroborate)).[7] Similarly, the groups of Brioche[8] and MacMillan[9] published almost identical protocols. Soon after, Gómez-Suárez and coworkers showed that these photochemical reactions also proceed in absence of a photocatalyst, albeit with a more limited scope.[10] Reactivity was rationalized with the formation of an electron donor-acceptor complex between Selectfluor and the oxalate. More recently, Brioche and colleagues reported a light-free strategy using silver catalysis, but long reaction times (24 h) were required.[11]

In an alternative approach, Xiao, Lin and coworkers activated tertiary alcohols using a combination of 1,2-diiodoethane, 1,2-bis(diphenylphosphino)ethane and $ZnBr_2$ to access a similar radical mechanism in the absence of light.[12] Even though the latter methods provide an attractive alternative to photochemical approaches that address limitations regarding scalability, the long reaction times and complex reagent cocktail, respectively, are drawbacks.

Our group recently discovered that the combination of Selectfluor and 4-(dimethylamino)pyridine (DMAP) forms a charge-transfer (CT) complex that spontaneously generates the *N*-(chloromethyl)triethylenediamine radical dication ($TEDA_2^{+\bullet}$), a potent single electron oxidant (SET) and hydrogen atom transfer (HAT) reagent (Scheme 1c).[13] This accessed a solvent-dependent, divergent approach to convert phenylacetic acids selectively to the corresponding benzyl fluorides or α-fluoro-α-arylcarboxylic acids without the need of light as external stimulus within a few minutes. Here, we show that this approach can be also used to realize a rapid and easily scalable radical fluorination of oxalate-activated alcohols.

Results and Discussion

We started our investigations by studying whether the Selectfluor-DMAP CT complex triggers the decarboxylative fluorination of alkyl cesium oxalates. To our delight, the conditions that were previously optimized for the decarboxylative fluorination

[a] H. Baunis, Prof. Dr. B. Pieber
Department of Biomolecular Systems
Max-Planck-Institute of Colloids and Interfaces
Am Mühlenberg 1, 14476 Potsdam (Germany)

[b] H. Baunis, Prof. Dr. B. Pieber
Institute of Science and Technology Austria (ISTA)
Am Campus 1, 3400 Klosterneuburg (Austria)
E-mail: bartholomaeus.pieber@ist.ac.at
Homepage: http://www.pieberlab.com/

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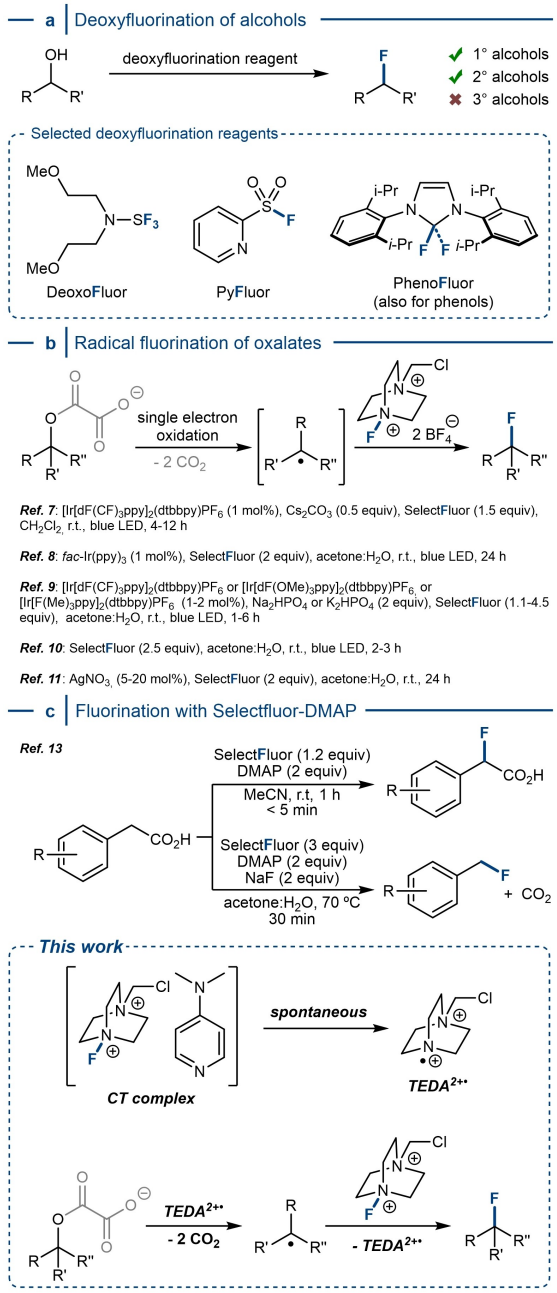
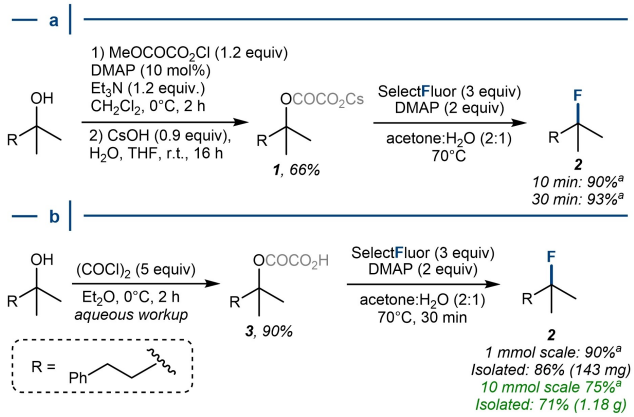


Scheme 1. Deoxyfluorination of aliphatic alcohols (**a**, **b**) and radical fluorinations using the Selectfluor-DMAP CT complex (**c**).

of phenylacetic acid derivatives[13] also converted **1** selectively to fluorination product **2**. Optimization of reaction parameters (see Table S1-S4 in the supporting information) resulted in conditions that provide **2** in almost quantitative yields (Scheme 2a). The decarboxylative fluorination of oxalates works best in acetone:water (2:1) at 70 °C using Selectfluor (3.0 equiv.) and DMAP (2.0 equiv) in excess. Reaction time of 30 min was used for practical reasons during most experiments, but similar results were obtained within 10 min. Longer reaction times led to diminished yields (Table S4) and formation of significant amounts of the corresponding alcohol (Figure S1), presumably



Scheme 2. Optimized conditions for the radical fluorination of an oxalate-activated tertiary alcohol using the Selectfluor-DMAP CT complex. [a] Yield determined by ^{1}H NMR using dimethylmaleate as internal standard.

due to a unimolecular nucleophilic substitution of the fluorine atom upon activation through hydrogen bonding.[14]

Switching from cesium salt **1**, which requires a preparation via two steps from the corresponding alcohol, to alkyl hydrogen oxalate **3** that is accessible in a single step with high yield gave identical results which streamlines the overall fluorination procedure (Scheme 2b). The straightforward scalability of this photon- and metal-free radical fluorination was demonstrated in the gram scale synthesis of **2** from **3**.

Monitoring the fluorination of **3** using in situ FTIR spectroscopy (ReactIR) showed that the reaction proceeds instantaneously when Selectfluor is added to a preheated mixture of the substrate and DMAP (Figure 1). This observation is similar to the reaction profile of the direct benzylic C–H fluorination of phenylacetic acids using the same approach[13] and underlines

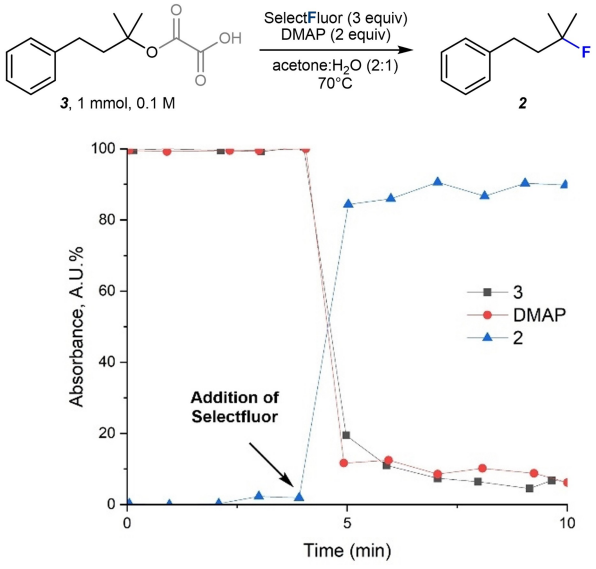


Figure 1. Reaction monitoring using in situ FTIR spectroscopy (ReactIR, normalized data).

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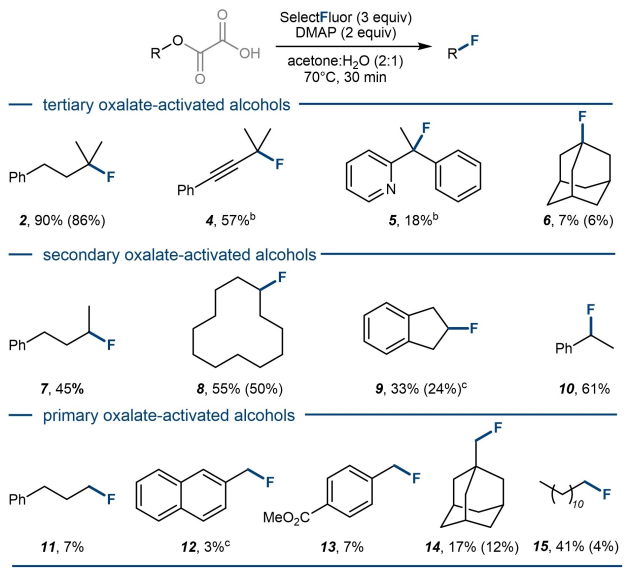
the high reactivity of the Selectfluor-DMAP charge-transfer complex.

Next, the optimized conditions were applied to a selection of oxalate-activated alcohols (Table 1). This investigation provided similar results as previous radical fluorination protocols of oxalates using Selectfluor,[7–11] such as a low functional group tolerance and modest yields for primary alcohols.

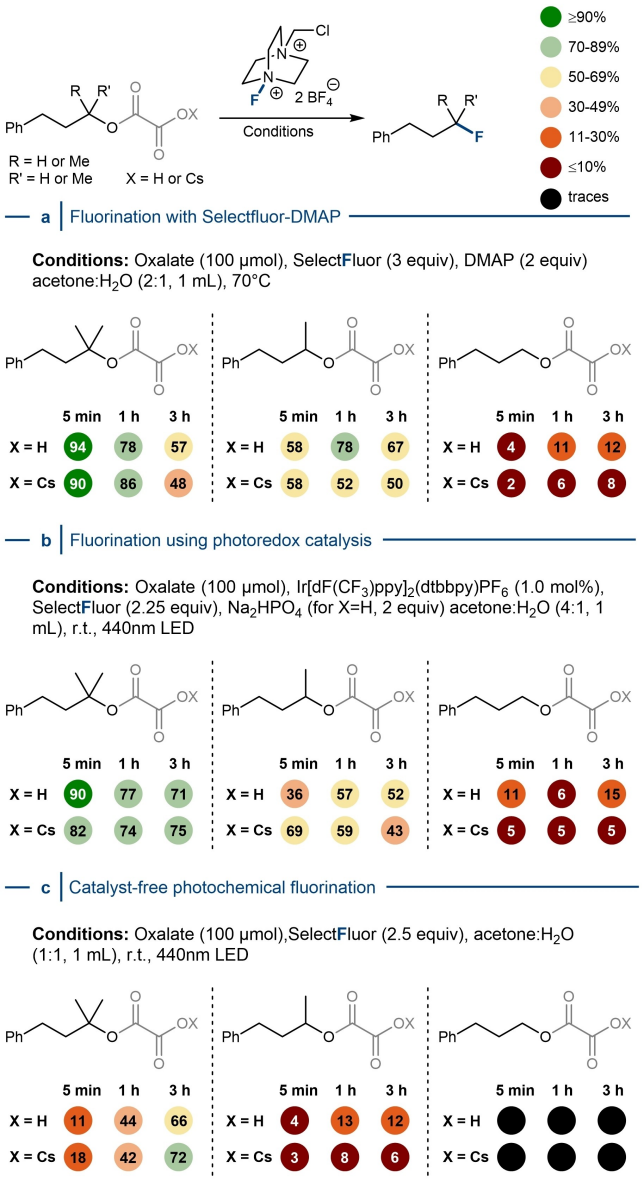
In case of tertiary oxalate-activated alcohols, excellent yield was obtained using model substrate **3**, but an unsaturated analogue only resulted in 57% of the desired compound (**4**). A tertiary oxalate containing a pyridine motif as well as oxalate-activated 1-adamantanol resulted both in low yields (**5** and **6**). Secondary oxalate-activated alcohols that do not contain functional groups gave 33 to 61% under the exact same conditions (**7**–**10**). Primary oxalates generally afforded the corresponding fluorinated compounds **11**–**14** in poor yields (3–17%). Compound **15** is an exception and was obtained with a comparably high NMR yield of 41%.

These inconsistencies, in combination with the observation that long reaction times resulted in low yields in case of the model substrate, prompted further investigations. We therefore sought to study the influence of reaction time for both the alkyl hydrogen oxalate and the corresponding cesium salt of a tertiary, a secondary and a primary alcohol precursor (Scheme 3a; the entire data sets can be found in Table S5 in the supporting information). We also carried out the same set of experiments using photoredox catalysis with Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$[9] using 440 nm LEDs (Scheme 3b).[15] In general, the photoredox protocols compared well to the DMAP-Selectfluor approach. In case of the tertiary oxalate, high yields were observed after 5 min and the amount of the desired product decreased with prolonged reaction times using both, the alkyl hydrogen oxalate and the corresponding cesium salt.

Table 1. Scope and limitations.[a]



[a]Reaction conditions: Oxalate (1.0 mmol, 1.0 equiv.), Selectfluor (1068 mg, 3.0 mmol, 3.0 equiv.), DMAP (244 mg; 2.0 mmol; 2.0 equiv) stirred in acetone:H$_2$O (2:1) at 70 °C for 30 min. Yields were determined by ^{1}H or ^{19}F NMR using dimethylmaleate or fluorbenzene as internal standard, repsectively. Isolated yields are in parentheses. [b]alkyl cesium oxalate was used instead of the alkyl hydrogen oxalate. [c]Reactions were carried out on a 2 mmol scale.



Scheme 3. Influence of reaction time for both the alkyl hydrogen oxalate and the corresponding cesium salt of a tertiary, a secondary and a primary alcohol precursor under different radical fluorination conditions.

This effect was more pronounced using the Selectfluor-DMAP conditions. In case of secondary alkyl hydrogen oxalates, we observed that product formation reaches a maximum after around 1 h followed by product decomposition in case of both protocols. The cesium salt, on the contrary, gave the highest yield after a few minutes. Both approaches failed to generate significant amounts of the desired product when the primary oxalate was used. The previously reported, catalyst-free photochemical conditions[10] gave significantly different results (Scheme 3c). Here, both tertiary oxalate-activated alcohols gave steadily increasing yields with prolonged reaction time. Secondary oxalates gave modest yields and both primary substrates only resulted in trace amounts of the desired product. Overall, our results indicate that, in case of the DMAP-Selectfluor CT

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complex and photoredox catalysis, secondary and tertiary oxalate-activated alcohols require individual careful optimization of reaction times (among other parameters) to minimize unwanted follow-up reactions and obtain satisfactory yields.

Conclusions

In summary, we developed a metal- and light-free fluorination of oxalate-activated alcohols using the DMAP-Selectfluor CT complex. This protocol allows for the facile and easily scalable conversion of secondary and tertiary alcohols to the corresponding fluorides. A detailed investigation of reaction time suggests that each substrate has a "sweet-spot" for high yields, after which product decomposition leads to low yields and complex reaction mixtures.

Experimental Section

General experimental procedure: An oven-dried microwave vial equipped with a magnetic stirred was flushed with argon and charged with the starting material (1.0 mmol, 1.0 equiv.), Selectfluor (1068 mg, 3.0 mmol, 3.0 equiv.), and DMAP (244 mg, 2.0 mmol, 2.0 equiv.). Degassed solvent (acetone:H_2O (2 : 1), 0.1 M) was added, the vial was sealed and the mixture was stirred at 70 °C for 30 min. Afterwards, the mixture was cooled by immersing the vessel in an ice bath.

NMR yield determination: Dimethyl maleate or fluorobenzene (1.0 equiv.) was added to the reaction mixture. An aliquot (1.0 mL) was diluted with HCl (1 M, 1.0 mL) and extracted with $CDCl_3$ (1.0 mL). The organic phase was removed and analyzed by ^1H or ^{19}F NMR.

Product isolation: The reaction mixture was diluted with CH_2Cl_2 (20 mL) and aqueous HCl (1 M, 20 mL) was added to extract basic compounds. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Subsequently, the product was purified with by flash chromatography.

Supporting Information

The authors have cited additional references within the Supporting Information.[16–27]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Oxalate · Fluorination · Selectfluor · DMAP · Charge-Transfer Complexes

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