eFluorination of Activated Alcohols using Collidinium Tetrafluoroborate

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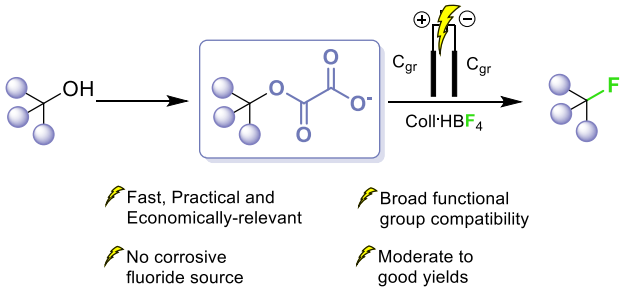
Supporting Information Placeholder



ABSTRACT: Tertiary C-F bonds are important structural designs; however, they suffer from challenging synthesis. Current methodologies use corrosive amine-HF salts or expensive and hazardous catalysts and reagents. Our group recently introduced collidinium tetrafluoroborate as an efficient fluorinating agent for anodic decarboxyfluorination reactions. Nevertheless, tertiary carboxylic acids are less readily available and more challenging to prepare than their alcohol analogues. Herein we report a practical, mild, and cheap electrochemical method to achieve deoxyfluorination of hindered carbon centres.

Fluorine has long been an atom of interest for the organic chemistry community, especially for the agrochemical industry where 424 fluoro-agrochemicals[1] (herbicides, fungicides, insecticides combined) can be listed, and the pharmaceutical industry where approximately 20% of all small molecules contain fluorine,[2] such as sofosbuvir (figure 1). Medicinal chemists take advantage of fluorine's small size to use it as a valuable bioisostere for the hydrogen atom[3,4] (1.47Å and 1.20Å, respectively), exchanging a C-H bond for a C-F bond. Due to fluorine's strong electronegativity, C-F bonds display a strong polarity, and this change has a significant impact on the physicochemical properties of a molecule and pharmacokinetics of a drug candidate (improved metabolic stability e.g. (*R*)-fluorothalidomide (figure 1), enhanced membrane permeation). Furthermore, charge-dipole interaction (*gauche* effect) provides conformational stability.[5] Substituting a hydrogen atom for a fluorine atom also finds applications in medical imagery where ^{18}F is utilised as a radiolabelled tracer for Positron Emission Tomography (PET) experiments.[6] On these grounds, it is safe to say that fluorine incorporation into drug candidates has become crucial as a key strategy to advance to the clinical stage. Over the past decade, numerous fluorination methods have been developed and extensively reviewed.[7,8] Due to the wide availability and ease of preparing alcohols, the deoxyfluorination approach is widely utilised for converting hydroxyl groups into their analogous fluorides. It involves displacing an activated alcohol by a fluoride ion, which is especially challenging on hindered centres. Fluorination techniques are usually carried out with Selectfluor, HF salts such as Et_3N•3HF and Olah's reagent (pyridine•9HF) or S-F bond type reagents (DAST, SF_4, Deoxo-Fluor, Pyfluor).[9] However, the handling of those reagents can require additional considerations. Selectfluor displays poor solubility in organic solvents;[10] HF salts often require high temperatures to be effective[2], and the higher the amount of HF, the higher the risk for the user.[11] In the same vein, the toxicity and thermal instability of S-F reagents are well known in addition to their complex handling, narrow functional group tolerance and price.[12,13] Alternatively, Ishikawa's reagent can be used and has proved successful on both primary and secondary alcohols. Yet, the fluorination of tertiary centres remains challenging as it often competes with elimination and rearrangement reactions.[14] Another approach has been found in using inorganic fluoride salts. Successful fluorination using XeF_2 as a powerful oxidant and fluoride source has been described.[15] Nevertheless,

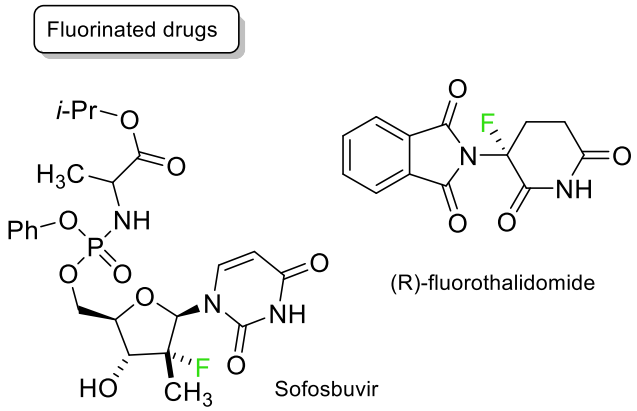
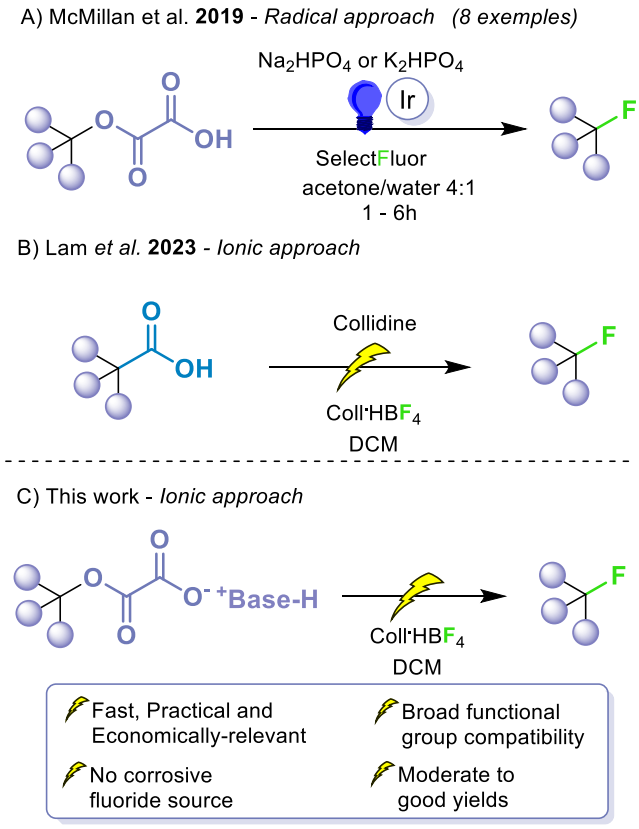


Figure 1. Examples of fluorinated drugs and fluorinated agents

XeF_2 is quite costly, hygroscopic and should be handled with great care as it sublimates at room temperature, leaving behind a pungent odour.[15] Cheaper options can be found in alkali-metal fluoride salts, representing a drastically safer option than the HF salts.[11] They are inexpensive and abundant, yet they also suffer from challenges. Indeed, their main issue remains their poor solubility in organic solvents, which necessitates the addition of wasteful and expensive phase transfer catalysts or crown ethers. In addition, the low nucleophilicity of fluoride ions renders the transformation quite challenging and usually requires the use of additives or harsh reaction conditions.[2,11] The Watson group recently described a clean deoxygenative fluorination using CuF_2 as an alternative to alkali-metal fluoride salts.[16] This protocol suffers from the need to use anhydrous CuF_2, as the dihydrate can significantly drop the yield of the reaction, and high temperature. Moreover, this protocol shows its limits when dealing with tertiary alcohols. McMillan and co-workers have disclosed an elegant radical photoredox approach for the deoxyfluorination of activated alcohols (scheme 1), which involves Selectfluor as a fluorine atom source and hemioxalates as activating group.[10] The scope focuses mainly on the deoxyfluorination of secondary alcohols, and only eight examples have been reported for the deoxyfluorination of tertiary alcohols. In addition, the transformation requires additives, such as costly iridium catalysts. Electrochemical fluorination is also well described in the literature. Nagorny and Kim have recently reported an outstanding electrochemical deoxyfluorination using sulfur (VI) hexafluoride, affording glycosyl fluorides with excellent yield.[17] Nonetheless, the Kyoto protocol classified this SF_6 as a major greenhouse gas, which severely restrict its use.[18] The tetrafluoroborate anion (BF_4^-) is also known as a mild fluorinating agent[19] since the last century with the conversion of aryls amines into aryl fluorides via the diazonium ion introduced by Balz and Schiemann.[20] As part of the ongoing collaboration between the Lam group and GSK identifying simple, efficient and safe electrochemical reactions of utility in industry, our group recently showcased the use of collidinium tetrafluoroborate salt (Coll•HBF_4) as an efficient, cheap and safer fluorinating agent in an anodic decarboxyfluorination reaction.[21] Tertiary centres were successfully fluorinated, but the synthesis of tertiary carboxylic acids remained the main drawback of this protocol and a need remains for a more accessible protocol. Herein we describe the electrochemical deoxyfluorination of activated tertiary alcohols using Coll•HBF_4 as a fluoride source and a supporting electrolyte. Tetrabutylammonium tetrafluoroborate (NBu_4BF_4) is widely used in the electrosynthetic field as a supporting electrolyte, but its action as fluorinating agent



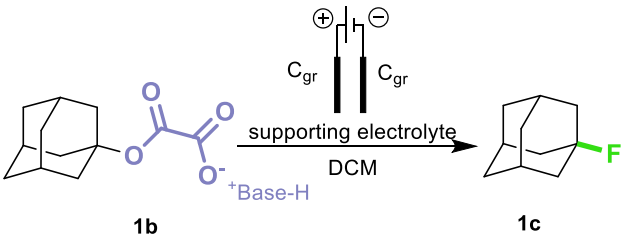
Scheme 1. Summary of fluorination on hindered centres

is also well-known. Miyata, Ueda and co-workers have disclosed a clean fluorination protocol using silver tetrafluoroborate ($AgBF_4$) and NBu_4BF_4 as fluorinating agents.[22] Considering the cost of $AgBF_4$ and our will to render our method as cheap and accessible as possible, we started our investigation using only NBu_4BF_4 as both a supporting electrolyte and fluorinating agent. Our approach first consisted of converting tertiary alcohols into their hemioxalic acid analogues and then anodically oxidising them into their corresponding carbocations, in a weakly nucleophilic solvent such as dichloromethane, in the presence of NBu_4BF_4 and a base. Nevertheless, tertiary hemioxalic acids are unstable over time, making the reactions hardly reproducible.[23] Protocols to render them more stable include using them as caesium salts,[10,24,25] which are costly and lengthy to prepare. To circumvent this issue, our lab previously developed the preparation and use of ammonium hemioxalates as stable hemioxalic acids analogues. Unfortunately, they exhibit very poor solubility in non-polar solvents. Instead, we opted for preparing collidinium analogues, which exhibit higher solubility in dichloromethane. Using a collidinium salt is convenient as the collidinium is being reduced at the cathode into hydrogen and collidine, hampering any undesired cathodic side-reaction. To perform the transformation, carbon graphite (C_{gr}) was chosen as both anode and cathode (table 1). As an anode, carbon electrodes are known to strongly adsorb organic molecules and favour the overoxidation of carbon radicals into their carbocations.[26] We optimised the fluorination protocol using the adamantane-1-hemioxalate salt (**1b**) as a model-substrate.

An ElectraSyn vial was charged with 3 mL of a 0.07M solution of **1b** and 1 equivalent of NBu_4BF_4 and underwent electrolysis at an applied current of 30 mA (J = 2.80 $mA.cm^{-2}$) alternating the polarity of the electrodes every 2 minutes (Table S1, entry 1). In these conditions, 1-fluoroadamantane (**1c**) could be

observed by GC-MS in small amounts, indicating the need for further optimisation. Electrolysis of **1b** alongside 1 equivalent of NBu_4BF_4 at a lower current of 10 mA (J = 2.40 $mA.cm^{-2}$) showed promising fluorination results (Table 1, entry 1). Attempting to change the fluorine source (PF_6^- instead of BF_4^-) resulted in a lower yield in the desired fluorination product (Table 1, entry 2). Yet, adamantan-1-ol (**1a**) was found to be the only side-product of this reaction, presumably due to residual moisture presents in the solution due to the inherent high hygroscopicity of tetrabutylammonium salts.[27] Attempts to decrease the amount of **1a** by increasing the concentration of BF_4^- ion in the solution and adding molecular sieves were successful (Table 1, entry 3). Replacing the supporting electrolyte with Coll•HBF_4 further improved the yield as this salt is less hygroscopic than NBu_4BF_4 and provides additional protons to be reduced, further reducing the risks of having any undesired cathodic reactions. A final increase to 5 equivalents of Coll•HBF_4 in a 0.04 M solution of **1b** alongside the presence of molecular sieves and electrolysing until a charge of 5 $F.mol^{-1}$ has been passed led to excellent fluorination yields (Table 1, entry 5). While scaling-up reaction to 1 mmol reduced the yield, it still led to 55% of 1-fluoro adamantane accompanied by 1-adamantanol as the major side-product (by GC-MS). Most of the time, collidinium hemioxalate salts could easily be prepared by adding collidine to a solution of the desired hemioxalic acid in diethyl ether. Washing and filtration of the resulting precipitate would provide a white solid with a composition, determined by NMR, corresponding to the collidinium hemioxalate crystalised with a molecule of hemioxalic acid. Nevertheless, the reaction proved challenging on some occasions and led to an unpurifiable deliquescent solid or thick oil with an ill-defined ratio of collidinium hemioxalate/hemioxalic acid. Therefore, a more reliable alternative had to be sought. Even though ammonium hemioxalates are bench stable and crystalline, they are insoluble in dichloromethane alone. The addition of Coll•HBF_4 dramatically enhanced their solubility. Interestingly, such an effect was not observed when NBu_4BF_4 was used. Much to our delight, the electrolysis of the adamantyl ammonium hemioxalate salt under the previously optimised conditions led to a high yield of the desired fluoroadamantane (Table 1, entry 6). With the best conditions in hand, the scope and limitation of the methodology were explored by electrolysing a series of tertiary alcohols derivatised as their hemioxalate ammonium salt (Scheme 2). Tertiary cyclic compounds (**2c** – **6c**) were tested and showed moderate to good yields (46% - 70%). The methodology is mild enough to be compatible with a wide range of functional groups, such as benzyl groups (**2c – 4c**) or benzylic ethers and halides (**12c –16c**). Direct fluorination of a cyclobutane ring (**5c**) was also successful. Remarkably, while silyl ethers are usually incompatible with most classical fluorination methodologies, due to the presence of fluorides, they remained untouched in our novel electrochemical fluorination method (**6c and 21c**). Heterocycles and *N*-protected heterocycles **7c** – **9c** gave satisfactory yields and showed no trace of Shono-type oxidation.

Table 1. Summary of optimization

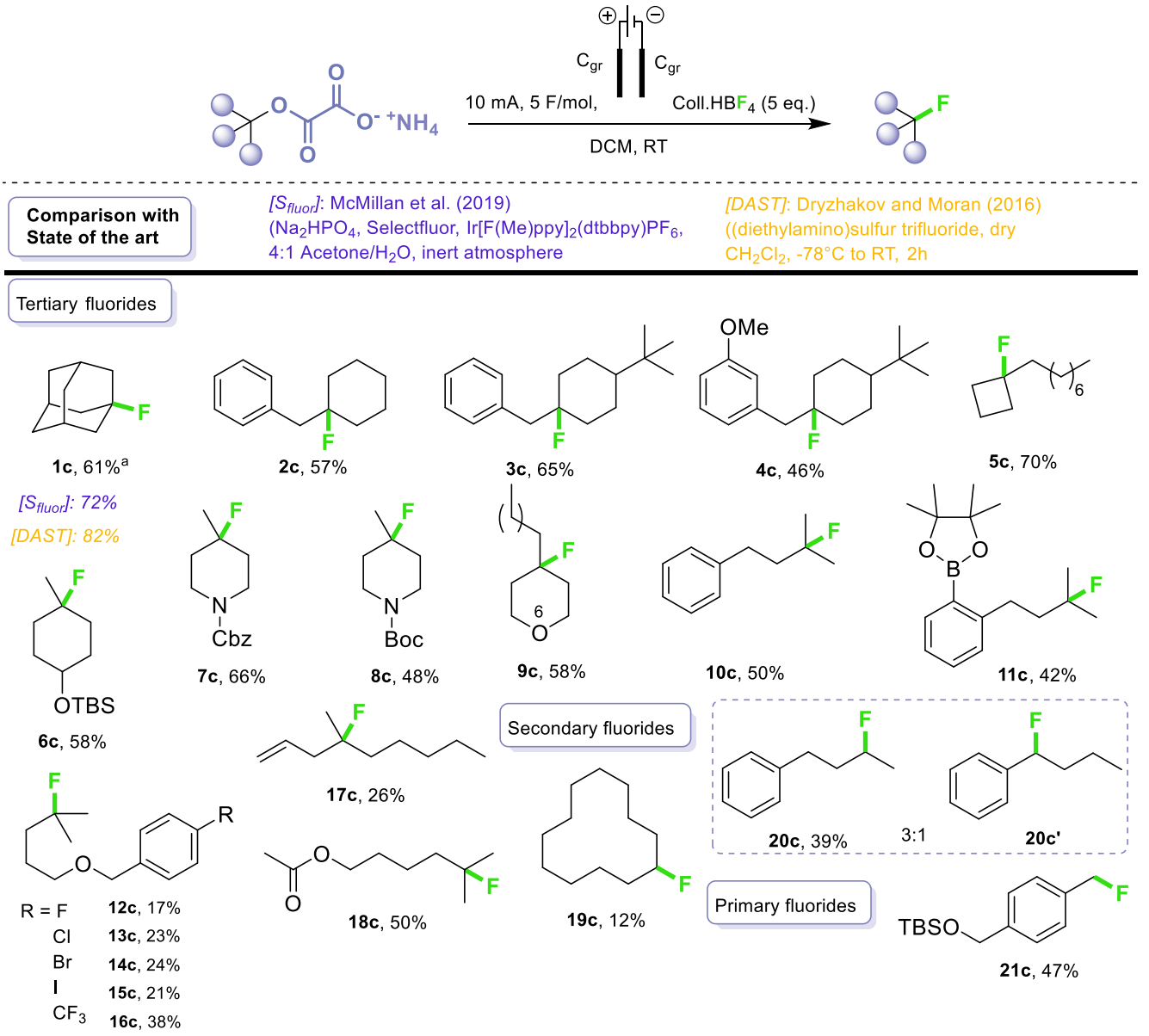


1b **1c**

Entry	Sup.electrolyte	Equiv.	+Base-H	F/mol	Yield[a]
1	NBu_4BF_4	1	Coll-H^+	4	63%
2	NBu_4PF_6	1	Coll-H^+	4	37%
3	NBu_4BF_4	3	Coll-H^+	4	85%
4	Coll•HBF_4	3	Coll-H^+	4	90%
5[b]	Coll•HBF_4	5	Coll-H^+	5	96% (61%)[c]
6[b]	Coll•HBF_4	5	NH_4^+	5	92% (53%)[c]

[a] GC-MS measured yields. [b] Experiments were done on a scale of 0.4 mmol. [c] Isolated yields.

Linear aliphatic tertiary alkyl fluorides could also be generated under these conditions. Substrate **11c** bearing an aryl boronic acid pinacol ester was well tolerated under the fluorination conditions. An external alkene was also tolerated and provided **17c,** although, in more humble yields due to the high occurrence of elimination, conjugation being a driving force for the elimination reaction. Finally, ester **18c** readily afforded the corresponding fluorinated compound. Encouraged by our results on tertiary centres, we decided to test our methodology on secondary and primary alcohols. As expected, electrolysis on secondary centres proved more difficult, considering the decrease in stability of the electrogenerated carbocation. Yet **19c** and **20c** still produced the desired fluorinated compounds in 12% yield and 39% yield, respectively. The major product for both fluorinations remain the elimination product. Moreover, **20c** has been obtained alongside **20c'**, in a 3:1 ratio, respectively, via a possible 1,3-hydride migration (scheme S1). This rearrangement is in line with the anodic generation of a carbocation. Aliphatic primary hemioxalates showed no trace of fluorination due to the difficulty of generating primary carbocations anodically. However, primary benzylic derivatives could be fluorinated effectively, producing the desired product (**21c**)**.** Unfortunately, benzylic hemioxalates bearing easily oxidisable heterocycles such as benzothiophene-3-methanol's hemioxalate, furan-2-methanol's hemioxalate and thiophene-2-methanol's hemioxalate failed at providing the corresponding fluorinated compound



Scheme 2. Substrate scope. [a] yield obtained using the corresponding collidinium salt

A plausible mechanism for the deoxyfluorination of activated alcohols with Coll•HBF_4 is depicted in scheme S2. To begin, the hemioxalate undergoes a first anodic oxidation, affording the hemioxalate radical. Then, a first decarboxylation occurs, forming the acyloxy carbonyl radical, which rapidly undergoes another decarboxylation. Then, overoxidation of the alkyl radical lead to the corresponding carbocation. Finally, a fluoride transfer occurs between BF_4^- and the carbocation to obtain the desired alkyl fluoride. Cyclic Voltammetry experiments have been conducted on **1b** in the presence of NBu_4PF_6 as a supporting electrolyte (See SI). A single chemically and electrochemically irreversible oxidation can be observed at 1.50V vs $Fc^{+/0}$.

No reduction event was observed on reverse scans. This anodic event could be attributed to the oxidation of the carboxylate into its corresponding oxalyl radical, which rapidly decomposes (EC-type mechanism).

To conclude, we reported a new, safer, greener practical electrochemical method to access hindered alkyl fluorides under mild oxidative conditions from activated tertiary alcohols. Our protocol uses collidinium tetrafluoroborate as a fluoride donor and a supporting electrolyte. This method can be of use to the synthetic community as another addition to the deoxyfluorination toolkit.

ASSOCIATED CONTENT

Data Availability

All underlying data available in the article itself and its Supporting Information

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, spectral data, and characterisation of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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