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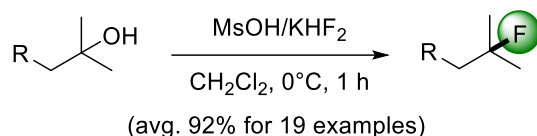
Synthesis of Tertiary Fluorides Through an Acid-Mediated Deoxyfluorination of Tertiary Alcohols.

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Supporting Information Placeholder



- Mild conditions
- Readily available reagents
- No additional purification generally required

ABSTRACT: The combination of methanesulfonic acid and potassium bifluoride is reported for the deoxyfluorination of tertiary alcohols. Under those metal-free conditions that use readily available, cheap, and easy-to-handle reagents, a range of tertiary alcohols could be converted to the corresponding fluorides in excellent yields (average yields of 92% for 19 examples) without the formation of any side product. The application of these conditions for the fluorination of ether and ester is also demonstrated.

The importance of fluorine in many fields of chemistry, such as in pharmaceutical, agrochemical and material science has long been recognized.¹ From 2015 to 2020 between 23 and 53% of new small-molecule drugs approved by the FDA contained at least one atom of fluorine.² Yet, most of the functional group present were either aryl fluoride or trifluoromethylated arenes.^{2a} The presence, or the absence, of a fluorinated functional group can be, in part, correlated to the ease of its synthetic incorporation.³ Tertiary alkyl fluoride has recently emerged as a potentially useful motif in medicinal chemistry (e.g., odanacatib).

A number of methods for its synthesis has been reported starting from various precursors such as alkanes,⁴ carboxylic acids and derivatives,⁵ tertiary halides,⁶ alkenes⁷ as well as others (Scheme 1a).⁸ The direct conversion of an alcohol to a fluoride, namely the deoxyfluorination reaction, is another useful way for the incorporation of a single fluorine atom onto an organic molecule.⁹ Most of the reagents commonly used for the deoxyfluorination exploit the sulfur-fluorine bond.¹⁰ Sulfur tetrafluoride was first reported by DuPont in 1958 for the conversion of carbonyl functions to the difluoromethylene moiety.¹¹ Since then, it has been used for the fluorination of alcohols, ketones, and carboxylic acids.¹² Over the years, new reagents have been developed to make this transformation easier. Notably, DAST, Deoxo-Fluor[®], XtalFluor[®] reagents, Pyfluor and AlkylFluor, as well as many others, have all been used for the fluorination of oxygenated functions, such as alcohols, phenols, aldehydes, ketones, and carboxylic acids.^{13,14} Although these reagents are

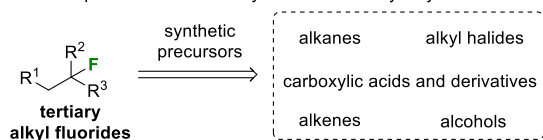
widely used, they still present issues in terms of thermal stability, reactivity, accessibility, and storage.¹⁵ While there have been many reports for primary and secondary alcohols; the deoxyfluorination of tertiary alcohols remains challenging as the activated intermediate tends to eliminate and generates the corresponding alkene (Scheme 1b).^{13,16} Therefore, the development of an efficient method for the conversion of tertiary alkyl alcohols, which are easily accessible, to the corresponding fluoride would be of great interest. To overcome this complication, alternative approaches have been proposed. The derivatization of alcohols to oxalates, followed by radical decarboxylation and fluorination has been reported by a few groups (Scheme 1c).¹⁷ Later on, the group of Xiao reported the direct conversion of tertiary alcohol to fluoride by an *in situ* generation of the corresponding bromide or iodide, followed by radical fluorination using Selectfluor (Scheme 1d).¹⁸

Along those lines, we recently reported the synthesis of tertiary alkyl fluoride by hydrofluorination of alkenes.^{7a} This reaction was performed using a combination of a strong acid (i.e., methanesulfonic acid), and a nucleophilic source of fluorine (i.e., triethylamine trihydrofluoride).^{19,20} We envisioned that we could apply similar conditions to tertiary alcohols, which in the presence of a strong acid could lose a molecule of water to generate the analogous carbocation. A nucleophilic source of fluoride could then yield the desired tertiary alkyl fluoride compound. Herein, we report the use of a combination of methanesulfonic acid and potassium bifluoride for the deoxyfluorination of tertiary alcohols (Scheme 1e). This method employs

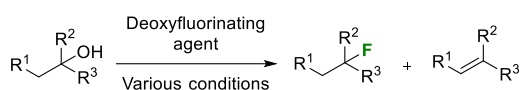
inexpensive and easy-to-handle reagents for the simple transformation of alcohol to fluoride without the need for prior alcohol derivatization. With these optimized conditions, the elimination product was never observed for all tertiary alcohols that were tested.

Scheme 1. Tertiary alkyl fluorides

(a) Common precursors with the synthesis of tertiary alkyl fluorides

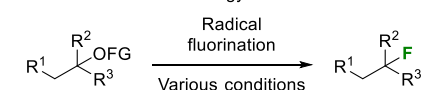


(b) Side-product of tertiary alcohol deoxyfluorination



■ Hard to separate product from alkene side-product

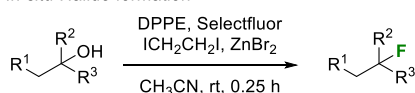
(c) Alcohol derivatization strategy



FG = C(O)COOX

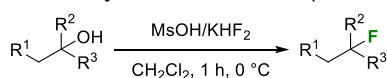
■ Prefunctionalization required

(d) *In situ* Halide formation



■ Excess of expensive reagents

(e) Direct deoxyfluorination of alcohol (This work)



- Mild conditions
- No elimination
- Readily available inexpensive reagents

Considering the similarities between the mechanism of the hydrofluorination of alkenes and our proposed deoxyfluorination, we started investigating the reaction on **1a** using similar reaction conditions and the results are shown in Table 1.^{7a} Hence, with a combination of methanesulfonic acid (5 equiv) and triethylamine trihydrofluoride (5 equiv), the corresponding fluoride (**2a**) was obtained in a promising 64% NMR yield (Table 1, entry 1). Inorganic sources of fluoride afforded the desired product in similar yields, with KHF₂ showing the best results (Table 1, entries 2-3). Using concentrated sulfuric acid significantly diminished the yield of the reaction (Table 1, entry 4). Based on these results, we selected a combination of methanesulfonic acid and KHF₂ for the rest of the optimization. By screening the temperature (Table 1, entries 5-6) and the time (Table 1, entries 7-8) of the reaction, we found that running the reaction at 0 °C for one hour afforded the desired fluorinated compound in 96% yield (Table 1, entry 9). While the elimination product was formed at room temperature, only the fluorinated product was obtained at 0 °C. Efforts to diminish the number of equivalents of acid and fluoride decreased the yields significantly (Table 1, entries 10-11) with an increased variability of the outcome (a typical result is shown in the Table 1). The time of the reaction could be lowered to 5 minutes without sig-

nificant loss of yield (Table 1, entry 12). To ensure a full conversion for all substrates, we still ran the reaction for one hour for the rest of the study.

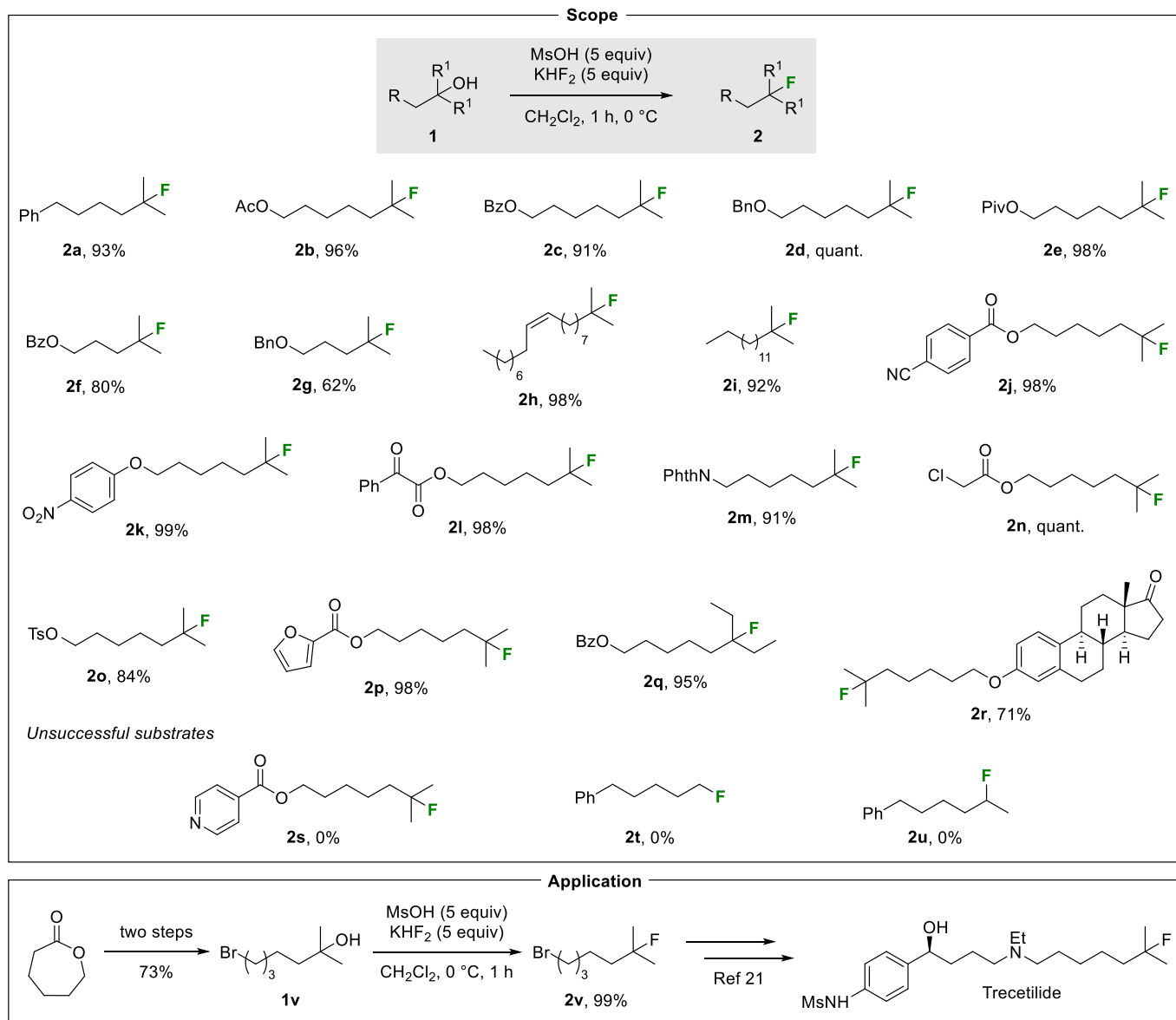
Table 1. Optimization for the deoxyfluorination of 1a^a

| Entry | Fluoride | Acid | Temp. (°C) | Time (h) | Yield (%) ^b |
|-----------------|-----------------------|---|------------|----------|------------------------|
| 1 | Et ₃ N·3HF | MsOH | 20 | 22 | 64 |
| 2 | KF | MsOH | 20 | 22 | 57 |
| 3 | KHF ₂ | MsOH | 20 | 22 | 70 |
| 4 | KHF ₂ | H ₂ SO ₄ ^c | 20 | 22 | 24 |
| 5 | KHF ₂ | MsOH | 40 | 22 | 40 |
| 6 | KHF ₂ | MsOH | 0 | 22 | 81 |
| 7 | KHF ₂ | MsOH | 20 | 8 | 80 |
| 8 | KHF ₂ | MsOH | 20 | 1 | 86 |
| 9 | KHF ₂ | MsOH | 0 | 1 | 96 (93) ^d |
| 10 ^e | KHF ₂ | MsOH | 0 | 1 | 33/29/67 |
| 11 ^f | KHF ₂ | MsOH | 0 | 1 | 6 |
| 12 | KHF ₂ | MsOH | 0 | 5 min | 90 |

^aSee the Supporting Information for the detailed experimental procedures. ^bEstimated by ¹⁹F NMR analysis of the crude mixture after workup using 2-fluoro-4-nitrotoluene as the internal standard. ^cConcentrated sulfuric acid (95–97%). ^dIsolated yield. ^e3 equivalents of KHF₂ and MsOH were used. ^f1 equivalent of KHF₂ and MsOH was used.

With these optimized conditions in hand, we went on to investigate the scope of the reaction for various tertiary alcohols with the results presented in Scheme 2. A variety of commonly used alcohol protecting groups were tested and were found to be compatible with the reaction conditions (**2b-g**). Tertiary alcohol derived from fatty acids were obtained in excellent yields (**2h-i**), with the internal disubstituted alkene of the oleic acid derivative remaining untouched, without isomerization. Alcohol bearing other functional groups such as nitrile, nitro, glyoxyl and phthalimide could also be converted to the corresponding fluoride in excellent yields (**2j-m**). No substitution was observed on the α -chloroester (**2n**) as well as on the tosylate (**2o**). The presence of a furan group (**2p**), as well as variety in the side chain (**2q**) were also tolerated in the reaction. A natural product derivative could also be used, with the substrate **2r** being obtained in a good 71% yield. However, the presence of a pyridine on the substrate seemed to shut down the reaction (**2s**). Primary and secondary alcohols were also tested (**2t-u**), but no conversion was observed in both cases, pointing that the formation of a tertiary carbocation might be the limiting step.

Scheme 2. Scope of the deoxyfluorination of tertiary alcohols^{a,b}



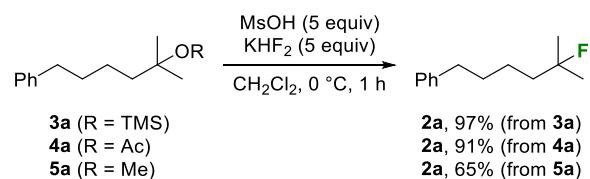
^aSee the Supporting Information for the detailed experimental procedures. ^bIsolated yield.

This reaction could be applied for the synthesis of 1-bromo-6-fluoro-6-methylheptane (**2v**), a key synthetic intermediate of trecetilide, a compound being developed for the treatment of atrial arrhythmia. A first synthesis was reported by Hester and coworkers in 2001 using a convergent synthesis for the introduction of the fluorinated chain.²¹ In their synthesis, the secondary amine is alkylated with 1-bromo-6-fluoro-6-methylheptane (**2v**), synthesized in 5 steps from 5-chloropentanol, to obtain trecetilide. We therefore considered using our conditions for the synthesis of this intermediate. Starting from fairly inexpensive caprolactone, we could obtain the 7-bromo-2-methylheptan-2-ol (**1v**) in 73% yield over two steps.¹⁸ We were pleased to see that in our conditions, not only is the bromide not substituted nor eliminated, but the desired product **2v** is obtained in an excellent 99% yield without the need for chromatography purification (Scheme 3).

Based on the assumed mechanism of the reaction, we envisioned that other C–O bonds could also be fluorinated under these conditions. To test this hypothesis, we synthesized the

corresponding trimethylsilyl ether (**3a**), acetate (**4a**) and methyl ether (**5a**). Upon treatment with the standard fluorination conditions, the corresponding fluoride **2a** were obtained in excellent yields of 97% and 91% starting from the silyl ether (**3a**) and the acetate (**4a**) respectively, and a good yield of 65% from the methoxy (**5a**) (Scheme 6). This could be useful for late-stage fluorination of protected alcohols.

Scheme 6. Deoxyfluorination of tertiary alcohols derivatives



In summary, we have described a simple and effective method for the deoxyfluorination of tertiary alcohol using a combina-

tion of methanesulfonic acid and potassium bifluoride. The reaction has been applied to a wide range of tertiary alcohols with excellent yields, and the corresponding elimination product has never been observed in these conditions. Being selective for tertiary alcohol, this method is complementary to the well established deoxyfluorination of primary and secondary alcohols.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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