



Synthesis of Tertiary Fluorides through an Acid-Mediated Deoxyfluorination of Tertiary Alcohols

Xavier Bertrand, Mathieu Pucheault, Laurent Chabaud, Jean-François Paquin

► To cite this version:

Xavier Bertrand, Mathieu Pucheault, Laurent Chabaud, Jean-François Paquin. Synthesis of Tertiary Fluorides through an Acid-Mediated Deoxyfluorination of Tertiary Alcohols. *Journal of Organic Chemistry*, 2023, 10.1021/acs.joc.3c01558 . hal-04247594

HAL Id: hal-04247594

<https://hal.science/hal-04247594v1>

Submitted on 18 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

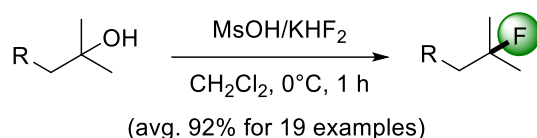
Synthesis of Tertiary Fluorides Through an Acid-Mediated Deoxyfluorination of Tertiary Alcohols.

Xavier Bertrand,^{a,b} Mathieu Pucheault,^b Laurent Chabaud^{b,*} and Jean-François Paquin^{a,*}

^a CCVC, PROTEO, Département de chimie, Université Laval, 1045 Avenue de la médecine, Québec, Québec, G1V 0A6, Canada

^b Univ. Bordeaux, CNRS, Bordeaux INP, ISM, UMR 5255, F-33400 Talence, France

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

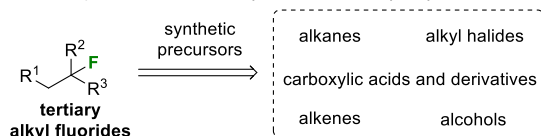
widely used, they still present issues in terms of thermal stability, reactivity, accessibility, and storage.¹⁵ While there have been many reports for primary and secondary alcohols; the deoxyfluorination of tertiary alcohols remains challenging as the activated intermediate tends to eliminate and generates 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

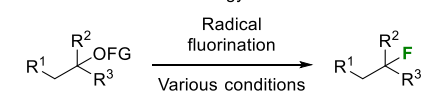


(b) Side-product of tertiary alcohol deoxyfluorination



■ Hard to separate product from alkene side-product

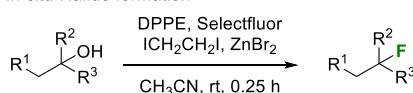
(c) Alcohol derivatization strategy



FG = C(O)COOX

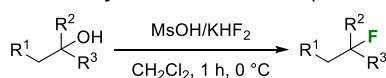
■ Prefunctionalization required

(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.

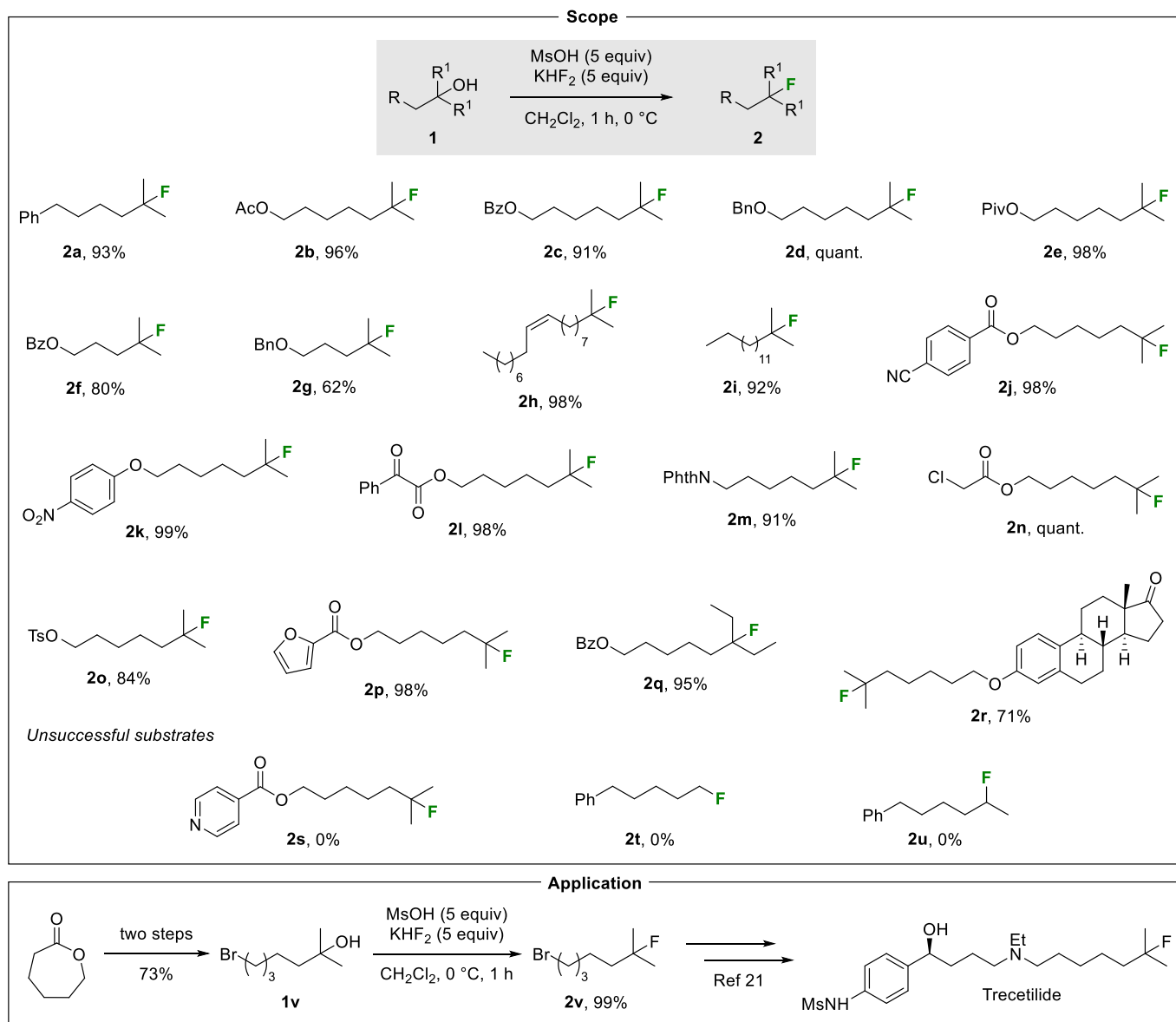
Table 1. Optimization for the deoxyfluorination of **1a^a**

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}



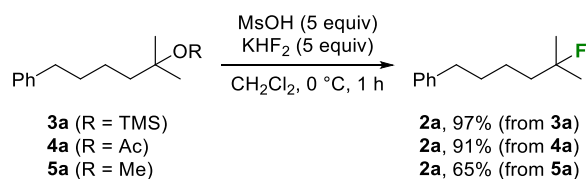
^aSee the Supporting Information for the detailed experimental procedures. ^bIsolated yield.

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)

AUTHOR INFORMATION

Corresponding Author

*E-mail: laurent.chabaud@u-bordeaux.fr and jean-francois.paquin@chm.ulaval.ca

ORCID

Jean-Francois Paquin: 0000-0003-2412-3083

Laurent Chabaud: 0000-0002-2590-8707

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds de recherche du Québec–Nature et technologies (FRQNT), Campus France, the Université Laval, the University of Bordeaux and CNRS. This work has benefited from the facilities and expertise of the Biophysical and Structural Chemistry platform (BPCS) at IECB, CNRS UMS3033, Inserm US001, Bordeaux University.

REFERENCES

- (1) a) O'hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **2008**, *37*, 308–319. b) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369.
- (2) a) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633–10640. b) Yu, Y.; Liu, A.; Dhawan, G.; Mei, H.; Zhang, W.; Izawa, K.; Soloshonok, V. A.; Han, J. Fluorine-containing pharmaceuticals approved by the FDA in 2020: Synthesis and biological activity. *Chinese Chem. Lett.* **2021**, *32*, 3342–3354.
- (3) Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443–4458.
- (4) a) Zhang, Y.; Fitzpatrick, N. A.; Das, M.; Bedre, I. P.; Yayla, H. G.; Lall, M. S.; Musacchio, P. Z. A photoredox-catalyzed approach for formal hydride abstraction to enable C_{sp}³–H functionalization with nucleophilic partners (F, C, O, N, and Br/Cl) *Chem Catal.* **2022**, *2*, 292–308. b) Halperin, S. D.; Kwon, D.; Holmes, M.; Regalado, E. L.; Campeau, L. C.; DiRocco, D. A.; Britton, R. Development of a Direct Photocatalytic C–H Fluorination for the Preparative Synthesis of Odanacatib. *Org. Lett.* **2015**, *17*, 5200–5203. c) Harry, S. A.; Xiang, M. R.; Holt, E.; Zhu, A.; Ghorbani, F.; Patel, D.; Lectka, T. Hydroxy-directed fluorination of remote unactivated C(sp³)–H bonds: a new age of diastereoselective radical fluorination. *Chem. Sci.* **2022**, *13*, 7007–7013. d) Guan, H.; Sun, S.; Mao, Y.; Chen, L.; Lu, R.; Huang, J.; Liu, L. Iron(II)-Catalyzed Site-Selective Functionalization of Unactivated C(sp³)–H Bonds Guided by Alkoxy Radicals. *Angew. Chem. Int. Ed.* **2018**, *57*, 11413–11417. e) Zhang, X.; Guo, S.; Tang, P. Transition-metal free oxidative aliphatic C–H fluorination. *Org. Chem. Front.* **2015**, *2*, 806–810. f) Liu, W.; Huang, X.; Placzek, M. S.; Krska, S. W.; McQuade, P.; Hooker, J. M.; Groves, J. T. Site-selective ¹⁸F fluorination of unactivated C–H bonds mediated by a manganese porphyrin. *Chem. Sci.* **2018**, *9*, 1168–1172.
- (5) a) Yin, F.; Wang, Z.; Li, Z.; Li, C. Silver-Catalyzed Decarboxylative Fluorination of Aliphatic Carboxylic Acids in Aqueous Solution. *J. Am. Chem. Soc.* **2012**, *134*, 10401–10404. b) Ventre, S.; Petronijevic, F. R.; Macmillan, D. W. C. Decarboxylative Fluorination of Aliphatic Carboxylic Acids via Photoredox Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 5654–5657. c) Webb, E. W.; Park, J. B.; Cole, E. L.; Donnelly, D. J.; Bonacorsi, S. J.; Ewing, W. R.; Doyle, A. G. Nucleophilic (Radio)Fluorination of Redox-Active Esters via Radical-Polar Crossover Enabled by Photoredox Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 9493–9500. d) Zhang, Y.; Qian, J.; Wang, M.; Huang, Y.; Hu, P. Visible-Light-Induced Decarboxylative Fluorination of Aliphatic Carboxylic Acids Catalyzed by Iron. *Org. Lett.* **2022**, *24*, 5972–5976.
- (6) a) Lovett, G. H.; Chen, S.; Xue, X. S.; Houk, K. N.; MacMillan, D. W. C. Open-Shell Fluorination of Alkyl Bromides: Unexpected Selectivity in a Silyl Radical-Mediated Chain Process. *J. Am. Chem. Soc.* **2019**, *141*, 20031–20036. b) Chen, H.; Liu, Z.; Lv, Y.; Tan, X.; Shen, H.; Yu, H. Z.; Li, C. Selective Radical Fluorination of Tertiary Alkyl Halides at Room Temperature. *Angew. Chem. Int. Ed.* **2017**, *56*, 15411–15415.
- (7) a) Bertrand, X.; Paquin, J. F. Direct Hydrofluorination of Methylallyl Alkenes Using a Methanesulfonic Acid/Triethylamine Trihydrofluoride Combination. *Org. Lett.* **2019**, *21*, 9759–9762. b) Bertrand, X.; Chabaud, L.; Paquin, J. Hydrofluorination of Alkenes: A review. *Chem. – An Asian J.* **2021**, *16*, 563–574.
- (8) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; S Coelho, J. A.; Dean Toste, F. Modern Approaches for Asymmetric Construction of Carbon–Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev.* **2018**, *118*, 3887–3964.
- (9) Champagne, P. A.; Desroches, J.; Hamel, J. D.; Vandamme, M.; Paquin, J.-F. Monofluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073–9174.
- (10) Ni, C.; Hu, M.; Hu, J. Good Partnership between Sulfur and Fluorine: Sulfur-Based Fluorination and Fluoroalkylation Reagents for Organic Synthesis. *Chem. Rev.* **2015**, *115*, 765–825.
- (11) Smith, W. C.; Tullock, C. W.; Muetterties, E. L.; Hasek, W. R.; Fawcett, F. S.; Engelhardt, V. A.; Coffman, D. D. *J. Am. Chem. Soc.* **1959**, *81*, 3165–3166.
- (12) Hasek, W. R.; Smith, W. C.; Engelhardt, V. A. Fluorination reactions of sulfur tetrafluoride. *J. Am. Chem. Soc.* **1960**, *82*, 543–551.
- (13) a) Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. Late-Stage Deoxyfluorination of Alcohols with PhenoFluor. *J. Am. Chem. Soc.* **2013**, *135*, 2470–2473. b) Goldberg, N. W.; Shen, X.; Li, J.; Ritter, T. AlkylFluor: Deoxyfluorination of Alcohols. *Org. Lett.* **2016**, *18*, 6102–6104. c) Li, L.; Ni, C.; Wang, F.; Hu, J. Deoxyfluorination of alcohols with 3,3-difluoro-1,2-diarylcyclopropene. *Nat. Commun.* **2016**, *7*, 1–11. d) Guo, J.; Kuang, C.; Rong, J.; Li, L.; Ni, C.; Hu, J. Rapid Deoxyfluorination of Alcohols with N-Tosyl-4-chlorobenzenesulfonimidoyl Fluoride (SulfoxFluor) at Room Temperature. *Chem. Eur. J.* **2019**, *25*, 7259–7264. e) Xu, J.; Peng, C.; Yao, B.; Xu, H. J.; Xie, Q. Direct Deoxyfluorination of Alcohols with KF as the Fluorine Source. *J. Org. Chem.* **2022**, *87* (9), 6471–6478.
- (14) a) Middleton, W. J. New Fluorinating reagents. Dialkylamino-sulfur Fluorides. *J. Org. Chem.* **1975**, *40*, 574–578. b) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. Bis(2-methoxyethyl)aminosulfur Trifluoride: A New Broad-Spectrum Deoxyfluorinating Agent with Enhanced Thermal Stability. *J. Org. Chem.* **1999**, *64*, 7048–7054. c) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; Laflamme, F.; Mirmehrabi, M.; Tadayan, S.; Tovell, D.; Couturier, M. Aminodifluorosulfonium Salts: Selective Fluorination Reagents with Enhanced Thermal Stability and Ease of Handling. *J. Org. Chem.* **2010**, *75*, 3401–3411.
- (15) a) Messina, P. A.; Mange, K. C.; Middleton, W. J. Aminosulfur Trifluorides: Relative Thermal Stability. *J. Fluorine Chem.* **1989**, *42*, 137–143. b) Deoxo-Fluor® has a limited commercial availability especially from the major distributors.
- (16) For reviews on deoxyfluorination of alcohols see: a) Hu, W. L.; Hu, X. G.; Hunter, L. Recent Developments in the Deoxyfluorination

of Alcohols and Phenols: New Reagents, Mechanistic Insights, and Applications. *Synthesis*, **2017**, 49, 4917–4930. b) Aggarwal, T.; Sushmita; Verma, A. K. Achievements in fluorination using variable reagents through a deoxyfluorination reaction. *Org. Chem. Front.* **2021**, 8, 6452–6468.

(17) a) Su, J. Y.; Grü, D. C.; Takeuchi, K.; Reisman, S. E. Radical Deoxychlorination of Cesium Oxalates for the Synthesis of Alkyl Chlorides. *Org. Lett.* **2018**, 20, 4912–4916. b) Brioché, J. One-pot synthesis of tertiary alkyl fluorides from methyl oxalates by radical deoxyfluorination under photoredox catalysis. *Tetrahedron Lett.* **2018**, 59, 4387–4391. c) Gonzalez-Esguevillas, M.; Mir, J.; Jeffrey, J. L.; Macmillan, D. W. C. Photoredox-catalyzed deoxyfluorination of activated alcohols with Selectfluor. *Tetrahedron* **2019**, 75, 4222–4227. d) Aguilar Troyano, F. J.; Ballaschk, F.; Jaschinski, M.; Özkaya, Y.; Gómez-Suárez, A. Light-Mediated Formal Radical Deoxyfluorination of Tertiary Alcohols through Selective Single-Electron Oxidation with TEDA²⁺. *Chem. A Eur. J.* **2019**, 25, 14054–14058. e) Vincent, É.; Brioché, J. Synthesis of Alkyl Fluorides by Silver-Catalyzed Radical Decarboxylative Fluorination of Cesium Oxalates. *Eur. J. Org. Chem.* **2021**, 2021, 2421–2430.

(18) Zhang, W.; Gu, Y.-C.; Lin, J.-H.; Xiao, J.-C. Dehydroxylative Fluorination of Tertiary Alcohols. *Org. Lett.* **2020**, 22, 6642–6646.

(19) Franz, B. Ueber Trishydrofluoride Tertiärer Amine Und Ihren Einsatz Als Fluorierungsmittel. *J. Fluorine Chem.* **1980**, 15, 423–434.

(20) For reviews on the properties and reactivity of Et₃N·3HF, see: (a) McClinton, M. A. Triethylamine Tris(hydrogen fluoride): Applications in Synthesis. *Aldrichimica Acta* **1995**, 28, 31–35. (b) Haufe, G. Triethylamine Trishydrofluoride in Synthesis. *J. Prakt. Chem./Chem.-Ztg.* **1996**, 338, 99–113.

(21) a) Hester, J. B.; Gibson, J. K.; Buchanan, L. V.; Cimini, M. G.; Clark, M. A.; Emmert, D. E.; Glavanovich, M. A.; Imbordino, R. J.; LeMay, R. J.; McMillan, M. W.; Perricone, S. C.; Squires, D. M.; Walters, R. R. Progress toward the Development of a Safe and Effective Agent for Treating Reentrant Cardiac Arrhythmias: Synthesis and Evaluation of Ibutilide Analogues with Enhanced Metabolic Stability and Diminished Proarrhythmic Potential. *J. Med. Chem.* **2001**, 44, 1099–1115. b) Mackey, Sonja Suzanne; Matison, Michael E.; Wu, Haifeng; Herrinton, Paul M.; Goble, Michael Paul; McMillan, Moses W.; Kalthod, Vikram Gurudath Compounds and Methods for Preparing Methanesulfonamides WO02098845A1 PCT Int. Appl. (2002), 23 pp. c) Mackey, S. S.; Wu, H.; Matison, M. E.; Goble, M. Chemistry development of a convergent route to trecetilide hemi-fumarate *Org. Process Res. Dev.* **2005**, 9, 174–178.
