Group	**:**	Bio-Organic Chemistry
Project	**:**	**Deoxyfluorination of Phenols using Bench-Stable Sulfonimidoyl Fluoride Reagents**
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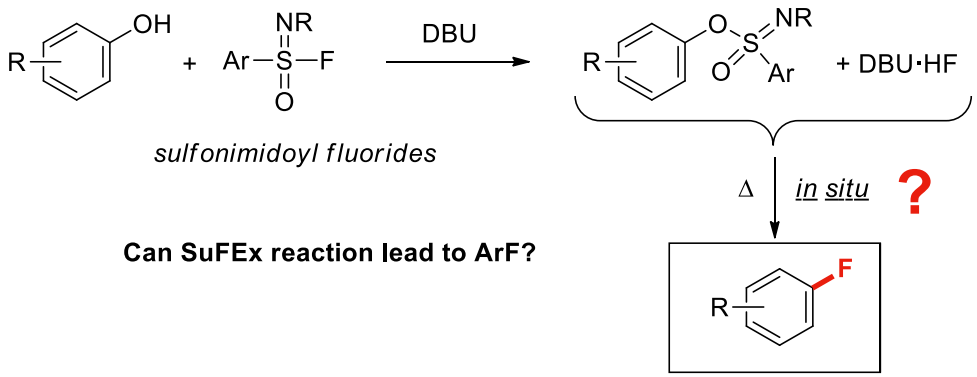
Keywords. Organic Synthesis, Methodology Development, Organofluorine Chemistry.

Introduction. Aryl and heteroaryl fluorides are widely present in pharmaceutical and agrochemical compounds.[1] It is synthetically attractive to make Ar-F bond from the readily available phenols Ar-OH by deoxyfluorination reactions. This type of transformations was introduced by Ritter et al. in 2011 utilizing PhenoFluor™ / CsF system.[2] Recently Sanford introduced alternaive reaction conditions with two-step SO_2F_2 / NMe_4F protocol.[3] Conditions developed by Ritter and Sandford groups require a rigorously dry reaction media, because reagents are extremely moisture-sensitive. The goal of this project is to develop an operationally simple protocol for deoxyfluorination of phenols that will utilize the recently emerged chemistry of bench-stable sulfonimidoyl fluoride reagents.

Goal. The suggested deoxyfluorination of phenols includes two steps. The first step is the sulfur-fluoride exchange (SuFEx) reaction between phenols and sulfonimidoyl fluoride reagents, and it was recently studied at ORC.[4] Current work will focus on the development of the second step of this transformation, which is an aromatic nucleophilic substitution with fluoride. Different solvents, temperatures, fluoride sources and substituents on the phenol substrate and sulfonimidoyl reagent will be tested in order to enable this transformation. Previously it was demonstrated that sulfonimidoyl fluoride reagents can deoxyfluorinate aliphatic alcohols[5] in one operational step, where the *in situ* generated DBU·HF acts as a fluoride source. The possibility of similar *one-pot* protocols for deoxyfluorination of phenols will be evaluated.



Topics to be studied. The project focuses on organic chemistry. The work will involve the synthesis of sulfonimidoyl fluoride reagents; rational-based step by step development of the novel synthetic methodology; reaction monitoring; analysis of reactions outcome.

Techniques to be used. General organic synthesis techniques, Schlenk-line techniques, TLC, column chromatography, NMR (including ^{19}F NMR), GC-MS.

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[1] Zhou, Y. et al. *Chem. Rev.* **2016**, *116*, 422-518.
[2] a) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482-11484; b) Fujimoto, T.; Ritter, T. *Org. Lett.* **2015**, *17*, 544-547.
[3] Schimler, S. D.; Sanford, M. S. et al. *J. Am. Chem. Soc.* **2017**, *139*, 1452-1455; b) Schimler, S. D.; Sanford, M. S. et al. *J. Org. Chem.* **2018**, *83*, 11178-11190.
[4] Liang, D.-D.; Streefkerk, D. E.; Jordaan, D.; Wagemakers, J.; Baggerman, J.; Zuilhof, H. *Angew. Chem. Int. Ed.* **2020**, *59*, 7494-7500.
[5] Guo, J.; Kuang, C.; Rong, J.; Li, L.; Ni, C.; Hu, J. *Chem. Eur. J.* **2019**, *25*, 7259-7264.