Application Note – Deoxyfluorination

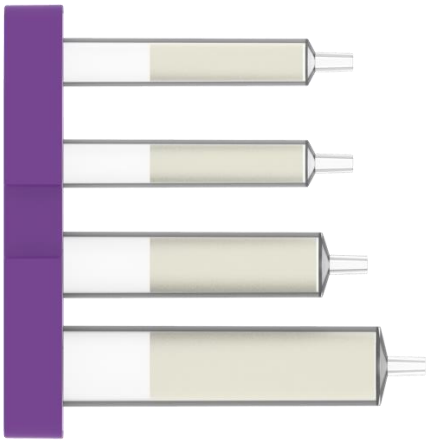
Introduction

Since half a century, over 150 fluorinated drugs have come to market and now make up ~20% of all pharmaceuticals, with even higher figures for agrochemicals (up to 30%). The selective introduction of a fluorine atom is a well-established strategy in the design of new drugs because it confers unique chemical, physical and biological properties on organic molecules, and has become a standard routine to discover new candidates of pharmaceuticals. Over the last decade, several groups have developed a very promising method of deoxyfluorination. The deoxyfluorination of alcohols allows the formation of aliphatic carbon-fluorine bonds and is well recognized as a straightforward and efficient approach to modify numerous alcohol-containing precursors, both commercially available and self-prepared. Common reagents for deoxyfluorination of alcohols include DAST, PhenoFluor, AlkylFluor and PyFluor, but all of them are limited by thermally instability, high cost, and/or narrow scope of functional group tolerance. In 2019, SulfoxFluor with nice balance between high reactivity and good stability, distinguished itself as a more attractive alternative. The use of SulfoxFluor allows to perform a selective deoxyfluorination at room temperature without requiring strictly inert conditions.

Using the approach in this application note, the Synple Chem synthesizer offers an easy, safe and fast automated method for the deoxyfluorination of primary and secondary alcohols.

Cartridge Contents

The cartridge contains a set of reagents to carry out the deoxyfluorination reaction on a scale of up to 0.2 mmol.



SulfoxFluor

DBU on carrier

SCX

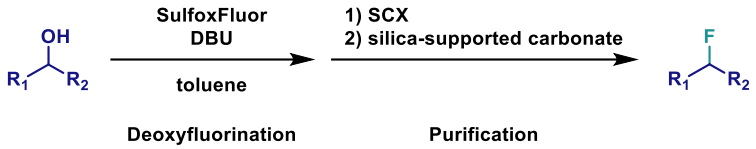
silica-supported carbonate

This method can be used for the following transformations:

- Deoxyfluorination of primary alcohols
- Deoxyfluorination of secondary alcohols

Reaction Scheme

This section describes the general course of the deoxyfluorination:



References and Publications

(1) 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. Link.

(2) Goldberg, N. W.; Shen, X.; Li, J.; Ritter, T. AlkylFluor: Deoxyfluorination of Alcohols. *Org. Lett.* **2016**, *18*, 6102-6104. Link.

(3) Sladojevich, F; Arlow, S. I.; Tang, P.; Ritter, T. Late-Stage Deoxyfluorination of Alcohols with PhenoFluor. *J. Am. Chem. Soc.* **2013**, *135*, 2470-2473. Link.

(4) Nielsen, M. K.; Ugaz, C. R.; Li, W; Doyle, A. G. PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination Reagent. *J. Am. Chem. Soc.* **2015**, *137*, 9571-9574. Link.

Reaction Procedure

1) Deoxyfluorination

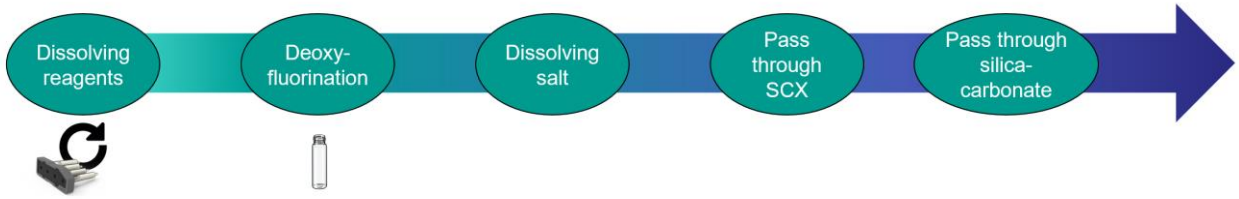
In the first step, compartment 1 (SulfoxFluor) is heated to 40 °C. Anhydrous toluene (1.5 mL) is loaded by the synthesizer and dosed through compartment 1 into the vial containing the alcohol. The mixture is stirred for 3 min at room temperature. Anhydrous toluene (1.0 mL) is loading by the synthesizer and dosed through compartment 2 (DBU on carrier) into the vial. The reaction mixture is stirred for 2 hours at room temperature.

2) Purification

MeCN is added to the vial to dissolve the formed salt. The solution is passed twice through compartment 3 (SCX) at 1 mL/min. DBU and its byproduct are scavenged in this step. Compartment 3 is further rinsed with MeCN, which goes into the vial.

The solution in the vial is further loaded into compartment 4 (silica-supported carbonate) at 1 mL/min. Byproduct of SulfoxFluor is scavenged in this step. Compartment 4 is further rinsed with MeCN, which goes into the vial.

After purification, the solution in the vial contains the deoxyfluorinated product.

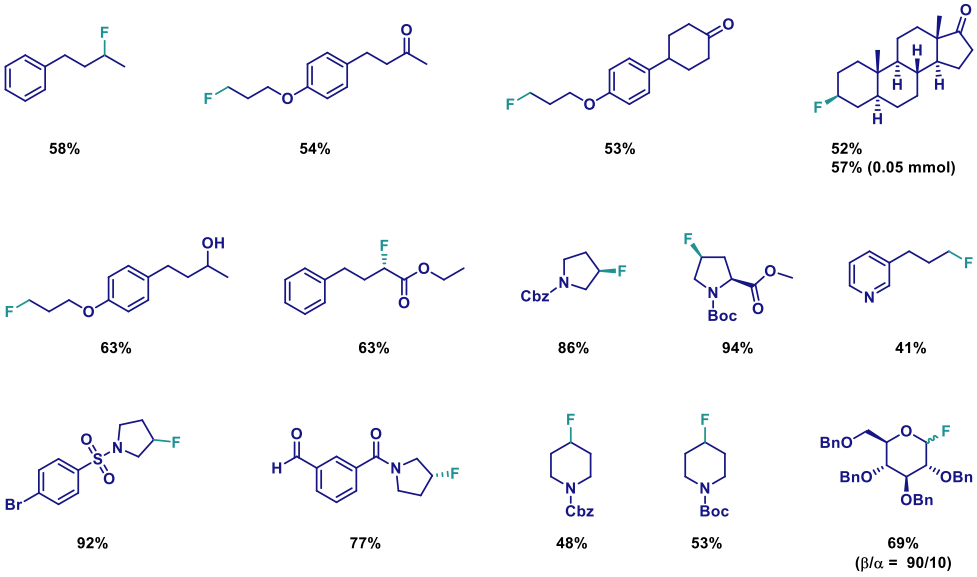


Substrate Scope

Tolerated functional groups

A range of different functional groups are tolerated including aldehydes, amides, carbamates, esters, ethers, ketones, sulfonamides, etc.

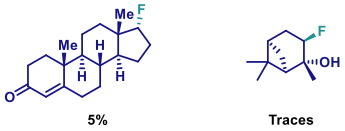
Example substrate scope (from 0.2 mmol alcohol)



Identified Chemistry Limitation

Basic and/or nucleophilic functional groups
If basic and/or nucleophilic functional groups (imidazole, trialkyl amines, thiols) present in the starting alcohols, they react with SulfoxFluor and lead to the formation of side products. Therefore, the deoxyfluorinated product would be obtained in low yield with low purity.

Steric hindrance
Sterically hindered alcohols may give low to no conversion. Longer reaction time does not improve the conversion, and often more alkene product via β-elimination is observed (see Possible impurities below).



Possible impurities
If the reaction does not reach full conversion, the starting alcohol remains in the crude mixture. It is also possible to observe the formation of alkene side products via β-elimination during the reaction.

Reaction Parameter Editing

Editing parameters:

Parameter 1	Reaction time for deoxyfluorination (seconds)

Enabling and Disabling parts:

Part 1: Purification step
The purification step of the sequence can be disabled.

Reaction Planning

Solubility of reactants
The starting alcohol shall be soluble in the reaction solvent (toluene).

Tolerance of air and/or moisture

Deoxyfluorination reaction using Synple Chem synthesizer is sensitive toward moisture but insensitive toward air. The use of anhydrous toluene is necessary for a better conversion and yield.

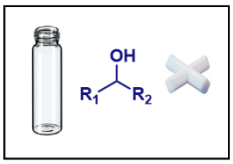
Sample Preparation

Precaution
To ensure a successful reaction in the Synple Chem synthesizer, automated CH_2Cl_2 wash shall be run before setting up a deoxyfluorination reaction.

Setup

Components for sample preparation:

- Vial
- Alcohol (0.2 mmol)
- Crossed stir bar
- No solvent



Machine Solvents for use with Deoxyfluorination cartridges

Please connect the following solvents to the color-coded solvent lines:

	S1: CH_2Cl_2, 99.8%, anhydrous, 50 ppm amylene stabilized
	S2: toluene, 99.85%, anhydrous over 4 Å molecular sieves
	S3: MeOH, >99.9%
	S4: –
	S5: MeCN, 99.9%

Notes:

- For a better agitation, a crossed stirring bar shall be used (as drawn in the figure above).
- Anhydrous toluene is required for this reaction. It is commercially available or can be dried using freshly activated 4 Å molecular sieves (beads).
- Store the cartridge at 4 °C.

Machine Cleaning after Deoxyfluorination Reaction

1) Run automated MeOH wash after the deoxyfluorination reaction.
2) Run automated CH_2Cl_2 wash before starting a new deoxyfluorination reaction.

Solvent Consumption and Run Time

SEQUENCE RUNTIME	
Reaction Sequence	**Time**
Fluorination	3 h 24 min

SOLVENT COMSUMPTION FOR BOC DEPROTECTION	
For Reaction Setup	**Amount**
no solvent	-
Machine Solvents	
Methanol (MeOH)	20 mL
Acetonitrile (ACN)	17 mL