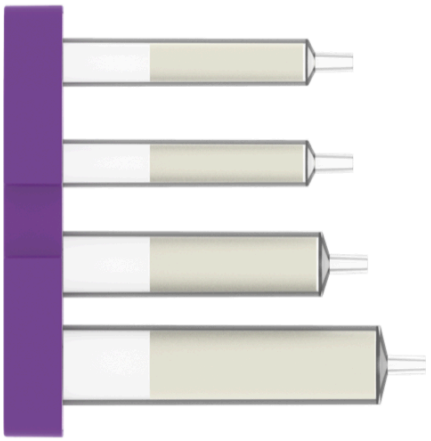
Application Note – Deoxyfluorination

Introduction

Deoxyfluorination involves the reaction between an alcohol and a fluorinating agent. It allows to generate the corresponding fluorinated product. Fluorination is among the most interesting reaction in medicinal chemistry and mostly used for late stage functionalization.
Using the approach in this application note, the Synple Chem synthesizer offers an easy 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 reductive amination on a scale of up to 0.2 mmol.



SulfoxFluor

DBU on Carrier

SCX

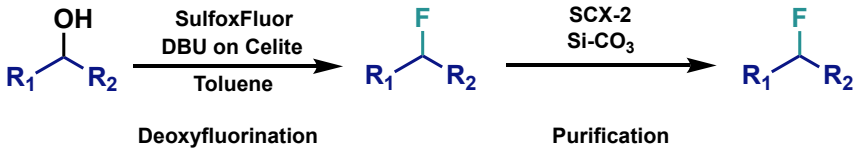
Silica supported carbonate

This method can be used for the following transformations:

- Deoxyfluorination with primary alcohols
- Deoxyfluorination with secondary alcohols

Reaction Scheme

This section describes the general course of the deoxyfluorination:



In a standard deoxyfluorination reaction, the fluorinated product is formed (in a presence of a base). Then, the salt generated during the transformation is partially filtered off. The reaction crude is purified by silica flash chromatography.

Publication:
Based on J. Guo., C. Kuang, J. Rong, L. Li, C. Ni, J. Hu: Rapid Deoxyfluorination of Alcohols with N-Toysl-4-chlorobenzenesulfonimidoyl Fluoride (SulfoxFluor) at Room Temperature, *Chem. Eur. J.* **2019**, 7259–7264, Link.

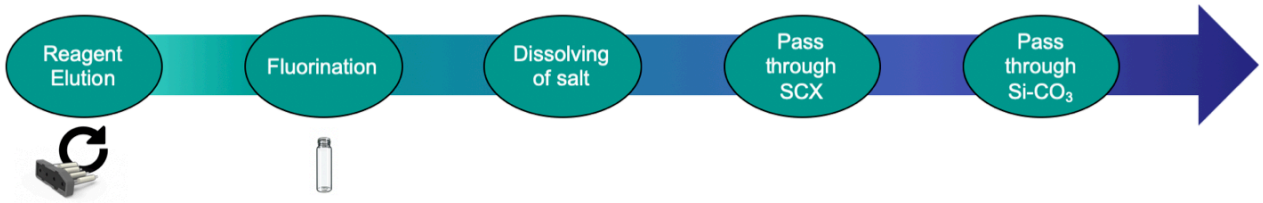
Reaction Procedure

1) Deoxyfluorination

The compartment 1 is heated up to 40°C. SulfoxFluor (compartment 1) are eluted with 1.5 mL of anhydrous toluene at 1 mL/min. The solution is stirred for 3 minutes at room temperature. DBU is then eluted from Celite (compartment 2) with 1 mL of anhydrous toluene at 1 mL/min. The reaction mixture is stirred for 2 hours at room temperature

2) Purification

Acetonitrile (7 mL) is added to the vial in order to dissolve the formed salt. The solution is passed 2 times through compartment 3 (SCX-2) at 1 mL/min. The compartment 3 is rinsed 4 times with 1 mL of acetonitrile. The solution is passed once through compartment 4 (silica supported carbonate) at 1 mL/min. The compartment 4 is rinsed 4 times with 1 mL of acetonitrile. The solution in the vial contains the fluorinated product.

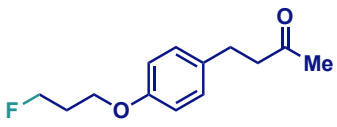


Substrate Scope

Tolerated functional groups

A range of different functional groups are tolerated (ester, ketone, amide, aldehyde).
At present the reaction has not been fully optimised for N-Boc protected product or molecules bearing a basic or nucleophilic site.

Example substrate scope



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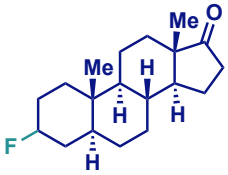

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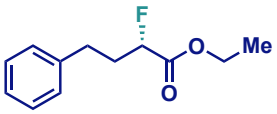

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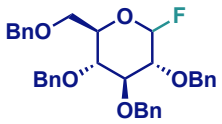

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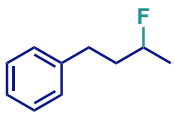

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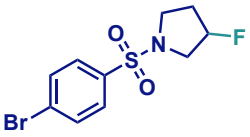

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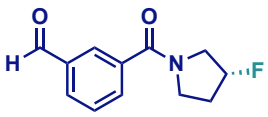

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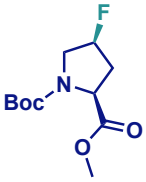

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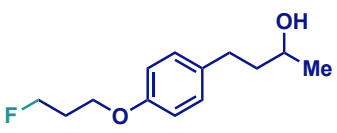

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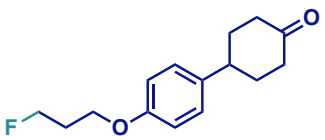

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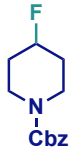

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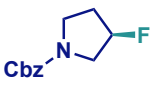

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Known Chemistry-Limitations

Basic or nucleophilic functional groups
If the alcohol contains a basic or nucleophilic group, the reaction may not occur due to the competition of the basic or nucleophilic site with the alcohol.

Boc deprotection
N-Boc product are very useful for the deoxyfluorination due to the deactivation of the nucleophilicity of the amines. When Boc containing starting materials are employed, a degree of Boc deprotection can be observed. This can be avoided by disabling the SCX purification step. A new method of buffering the SCX is in development, which avoids Boc deprotection.

Reaction Parameter Editing

Editing parameters:

Parameter 1	Reaction time for reduction (seconds)

Enabling and Disabling parts:

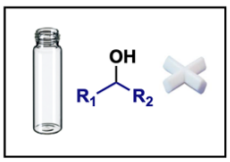
Part 1: Purification step
The purification step of the sequence can be disabled.

Sample Preparation

Setup

Components for sample preparation:

- Vial
- Alcohol (up to 0.2 mmol)
- Crossed stirbar
- No solvent



Machine Solvents for use with Deoxyfluorination cartridges

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

	S1: Dichloromethane Anhydrous, 150ppm amylene tolerated
	S2: Toluene Anhydrous with molecular sieves 4Å
	S3: MeOH HPLC grade
	S4: –
	S5: Acetonitrile HPLC grade