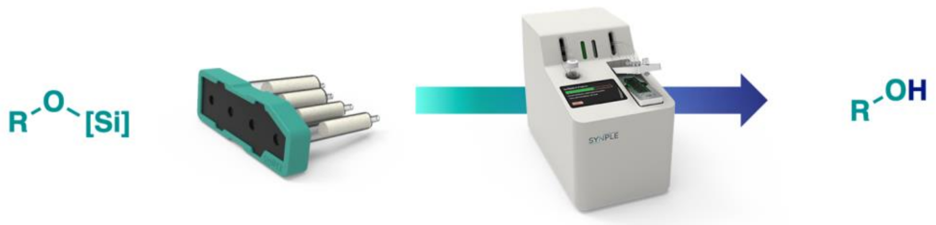
Application Note – Silyl deprotection

Introduction

Alcohols are highly important intermediates in synthetic chemistry because they can easily be derivatized via oxidation, substitution or esterification to generate new functionalities. Owing to the protic hydrogen, free alcohols (OH) must sometimes be masked with protecting groups during multistep synthesis. Among many protecting groups, silyl ethers are one of the most frequently used attributed to the tunable stability of silyl ethers through different substituents on the silicon atom. For converting silyl ethers back to free alcohols, this deprotection reaction is usually carried out with a fluoride source such as tetrabutylammonium fluoride (TBAF) and hydrogen fluoride and its derivatives, which may raise safety concerns over etching of glassware (made from borosilicate) and/or exposure to operating personnel. Alternatively, silyl deprotection can be achieved under acidic conditions with either Lewis or Brønsted acids in aqueous or other protic media. Commonly used Brønsted acids are hydrogen chloride (HCl) and trifluoroacetic acid (TFA). These acidic conditions, albeit effective, present a major drawback as both HCl and TFA are used in large excess amounts and removing these volatile, but highly corrosive acids poses a clear threat to laboratory safety and durability of instruments.

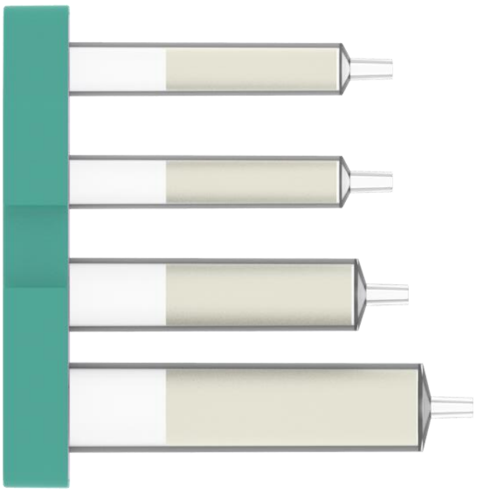
Using a suitable solid or solid-supported strong acid for the silyl deprotection has emerged as an ideal solution in both batch and flow setup for the development of safer and more user-friendly protocols. *p*-Toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) has been identified as an efficient and easy-to-handle alternative to replace the volatile and corrosive acids mentioned above.



Using the approach described in this application note, the Synple Chem synthesizer offers an easy and fast automated method for the acid-promoted silyl deprotection of primary and secondary alcohols.

Cartridge Contents

The cartridge contains a set of reagents to carry out a silyl deprotection reaction on a scale up to 0.5 mmol.



***p*-TsOH·H_2O**

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silica-supported triethylamine

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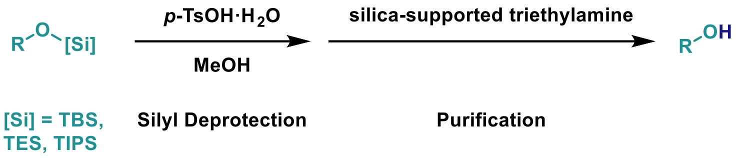
This method can be used for the following transformations:

- O-TBS (*tert*-butyldimethylsilyl) deprotection to the free alcohol.
- O-TES (triethylsilyl) deprotection to the free alcohol.
- O-TIPS (triisopropylsilyl) deprotection to the free alcohol.

Reaction Scheme

This section describes the general course of the silyl deprotection:



Reaction Procedure

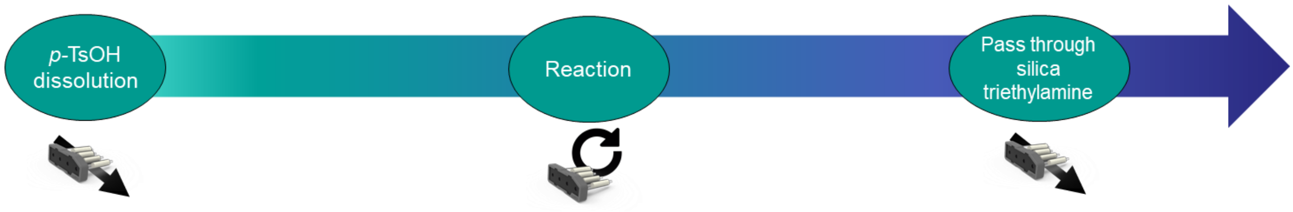
1) Silyl deprotection

In the first step, a pre-mixed solution of silyl-protected alcohol in MeOH (2.0 mL) or an alternative alcohol is circulated through compartment 1 to dissolve containing *p*-TsOH·H_2O at 2 mL/min for 10 minutes. The reaction mixture is further stirred for 2.5 hours at room temperature.

2) Purification

Anhydrous CH_2Cl_2 is added to the vial to dilute the mixture. The crude mixture is passed through compartment 3 (silica-supported triethylamine) at 1 mL/min for 2 times. Excess amount of *p*-TsOH·H_2O is scavenged in this step. Compartment 3 is further rinsed with MeOH, which goes into the vial.

After purification, the solution in the vial contains the free alcohol product.

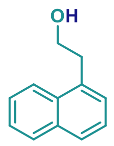


Substrate Scope

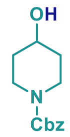
Tolerated functional groups

A wide range of functional groups are tolerated including amides, azides, alkyl halides, ethers, nitriles, sulfonamides, etc.

Example substrate scope (from 0.5 mmol silyl-protected alcohol)



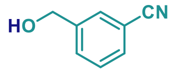
91% (TES)
98% (TBS)
97% (TIPS)
87% (TBDPS)



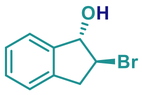
97% (TES)
98% (TBS)

96% (TES)
99% (TBS)

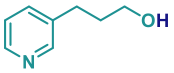
99% (TBS)



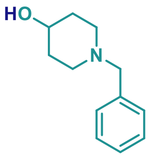
99% (TBS)



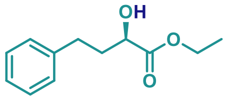
91% (TBS)



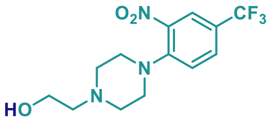
94% (TBS)



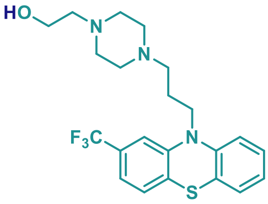
95% (TBS)
96% (TBS, 0.14 mmol)



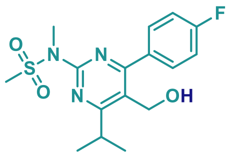
96% (TBS)
(in EtOH, 12 h)[a]



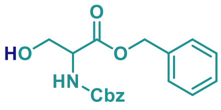
98% (TBS)



91% (TBS)



93% (TBS)
(in MeOH/CH_2Cl_2 = 1/1)



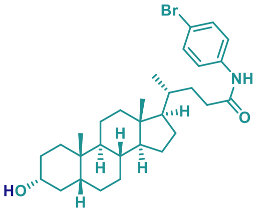
96% (TBS)
(in *i*-PrOH or EtOH, 12 h)[a]

a) see Identified Chemistry Limitation.

Identified Chemistry Limitation

Solubility

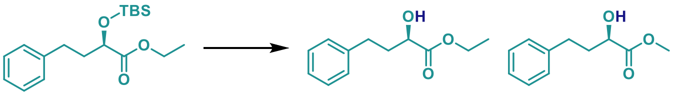
The starting silyl-protected alcohols shall be soluble in MeOH or an alternative alcohol (EtOH or *i*-PrOH). In rare cases of insoluble silyl-protected alcohols, CH_2Cl_2 can be used as a co-solvent. In the case below, the generated alcohol product is insoluble in MeOH or CH_2Cl_2/MeOH (1:1).



Full conversion
Insoluble in MeOH
or CH_2Cl_2/MeOH (1:1)

Transesterification

Ester groups sometimes undergo transesterification with MeOH in the presence of *p*-TsOH·H_2O. To avoid this undesired side reaction, MeOH can be replaced by EtOH or *i*-PrOH.



96%
(in EtOH, 12 h)

79%
(Me/Et ester = 92/8)
(in MeOH, 2.5 h)

Non-tolerated functional groups

Ketones and aldehydes react with MeOH (or an alternative alcohol) to form methyl acetals in the presence of *p*-TsOH·H_2O. Therefore, they are not compatible with the current setup of silyl deprotection reaction. Other acid sensitive functional groups including Boc and THP are incompatible either.

Reaction Parameter Editing

Editing parameters:

Parameter 1	Reaction time of silyl deprotection (seconds) e.g. 12 hours = 43200 seconds

Enabling and Disabling parts:

Part 1:
Purification step

The purification step of the sequence can be disabled.

Reaction Planning

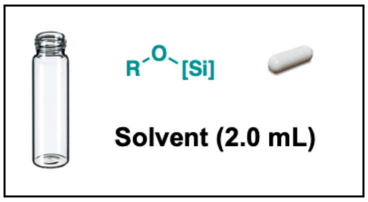
Solubility of reactants
The starting silyl-protected alcohols shall be soluble in the reaction solvents (MeOH, or an alternative alcohol such as EtOH or *i*-PrOH). If the silyl-protected alcohol is insoluble in MeOH (or an alternative alcohol), a solution of CH_2Cl_2/alcohol (v/v = 1/1) can be used.

Tolerance of air and/or moisture
Silyl deprotection reaction using Synple Chem synthesizer is insensitive toward air or moisture.

Sample Preparation

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

Setup
Components for sample preparation:
- Vial
- Silyl-protected alcohol (0.5 mmol)
- Stir bar
- solvent (2.0 mL)
  (see below for potential changes)



Guide of selecting solvents:
1) MeOH is the most ideal solvent for this reaction.
2) MeOH can be replaced by EtOH or *i*-PrOH when the starting silyl-protected alcohol contains acid sensitive functional groups, but the reaction time shall be prolonged to 12 h (43200 s, see Reaction Parameter Editing).
3) If the starting silyl-protected alcohol is not soluble in MeOH (or EtOH and *i*-PrOH), a mixture of CH_2Cl_2 (1.0 mL) and MeOH (or EtOH and *i*-PrOH, 1.0 mL) can be used.

Machine Solvents for the use with silyl deprotection cartridges

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

🟩	S1: CH_2Cl_2, 99.8%, anhydrous, 50 ppm amylene stabilized
🟦	S2: –
🟥	S3: MeOH, >99.9%
🟨	S4: –
🟧	S5: –

Machine Cleaning after Silyl Deprotection Reaction

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

Solvent Consumption and Run Time

SEQUENCE RUNTIME	
Reaction Sequence	**Time**
Silyl deprotection	3 h 8 min

SOLVENT COMSUMPTION FOR BOC DEPROTECTION	
For Reaction Setup	**Amount**
Methanol (MeOH)	2 mL
Machine Solvents:	
Dichloromethane (CH_2Cl_2)	23 mL
Methanol (MeOH)	6 mL