Application Note – N-Boc deprotection

Introduction

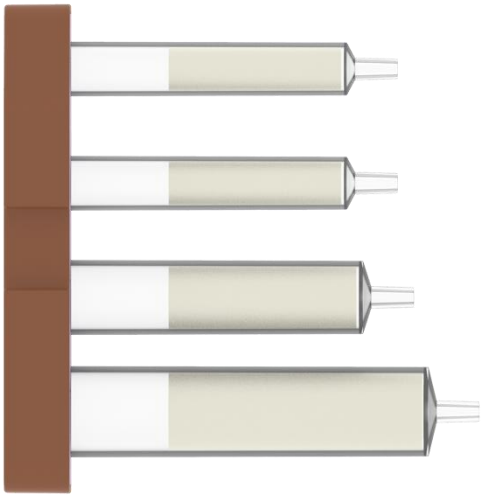
The Boc (*tert*-butyloxycarbonyl) group is broadly used in organic and medicinal chemistry to protect free amines. This protecting group is often used to induce favorable solubility characteristics, block reactive sites in close proximity, and sometimes acts as a directing group for specific site functionalization. The Boc group is also commonly used for the derivatization of amines, as the Boc-protected amines have lowered polarity enabling facile purification. While being stable against basic conditions and inert toward many nucleophilic reagents, the Boc group is easily removed with the treatment of strong acids. Commonly used acids for the deprotection of N-Boc protected amines are hydrogen chloride (HCl) and trifluoroacetic acid (TFA). These standard conditions, albeit effective, present a major drawback—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 N-Boc 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. More importantly, the composition of the amine *p*-TsOH salts (ratio between amine and acid) can be quantified more easily by ^{1}H NMR comparing to the amine HCl or TFA salt.

Using the approach in this application note, the Synple Chem synthesizer offers an easy and fast automated method for the N-Boc deprotection of primary and secondary N-Boc protected amines.

Cartridge Contents

The cartridge contains a set of reagents to carry out the N-Boc deprotection on a scale up to 0.5 mmol.



_p_-TsOH·H_2O

–

silica-supported triethylamine

–

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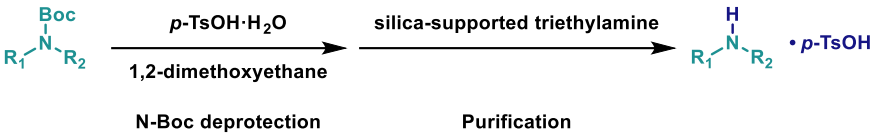
Cartridge product numbers : B011, B111

This method can be used for the following transformations:

- N-Boc deprotection of primary amines
- N-Boc deprotection of secondary amines

Reaction Scheme

This section describes the general course of the N-Boc deprotection:



Reaction Procedure

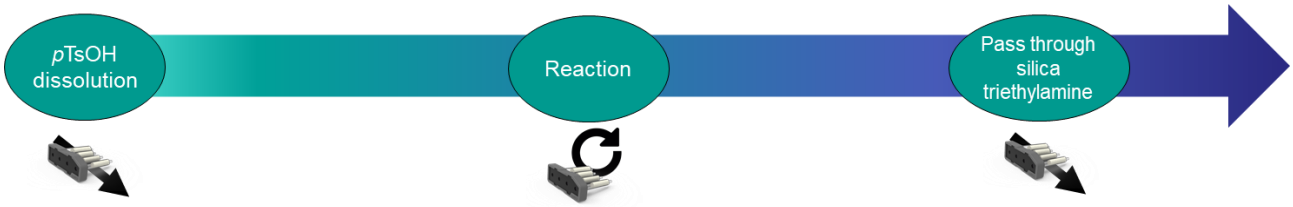
1) N-Boc deprotection

In the first step, after compartment 1 (*p*-TsOH·H_2O) is heated to 40 °C, 1,2-dimethoxyethane (1.0 mL) is loaded by the synthesizer and dosed through compartment 1 at 1 mL/min to dissolve *p*-TsOH·H_2O, which goes into the vial containing an N-Boc protected amine. The reaction mixture is stirred for 2 hours at 40 °C.

2) Purification

MeOH is added to the vial to dissolve formed salts. The reaction mixture is passed through compartment 3 (silica-supported triethylamine) at 2 mL/min for 5 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 amine *p*-TsOH salt.

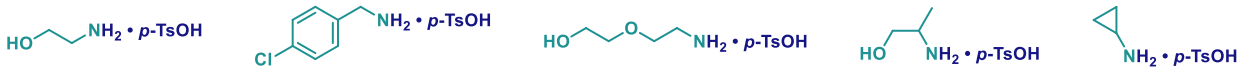


Substrate Scope

Tolerated functional groups

A wide range of functional groups is tolerated including unprotected alcohols, amides, carbamates, aryl halides, cyclopropanes, olefins, and various heterocycles (quinoline, pyrimidine, morpholine, piperazine, azepine, biotin-core, etc.).

Example substrate scope (from 0.5 mmol N-Boc protected amine)



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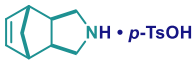
92%
95% (0.17 mmol)

92%

93%

90%



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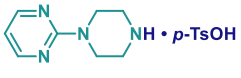
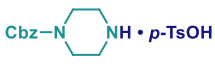


85%



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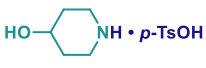

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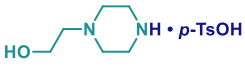

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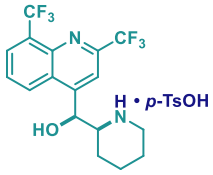

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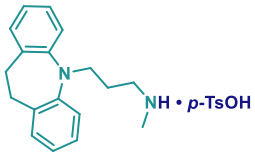

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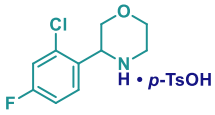

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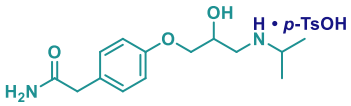

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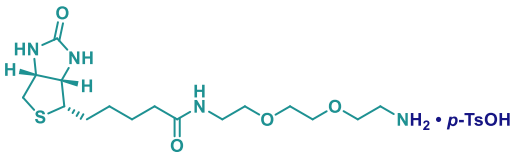

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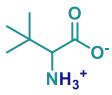
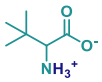


95%[a]

a) see Identified Chemistry Limitation

Identified Chemistry Limitation

Amino acids as reactants
Carboxylic acids are tolerated, but it might generate the corresponding zwitterion instead of the amine *p*-TsOH salt.



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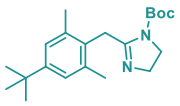
Basic sites
The starting N-Boc amines bearing multiple basic sites (≥2) might result in low to no conversion due to the overall lowered acidity (acid-base interaction).



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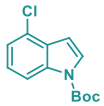

0%
(no conversion)

Non-tolerated functional groups
Carbonyl compounds, such as aldehydes and ketones, would react with MeOH in the presence of acid during the washing step and form the corresponding methyl acetal.

Reaction Parameter Editing

Editing parameters:

Parameter 1	Reaction time of N-Boc Deprotection e.g. 12 hours = 43200 seconds

Enabling and Disabling parts:

No parts to disable.

Reaction Planning

Solubility of reactants
The starting N-Boc amine is added neat into the vial, therefore pre-dissolving is not required.

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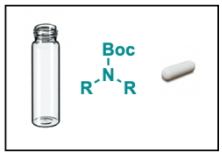
Tolerance of air and/or moisture
N-Boc deprotection reaction using Synple Chem synthesizer is insensitive toward air or moisture.

Sample Preparation

Precaution
To ensure a successful reaction in the Synple Chem synthesizer, automated CH_2Cl_2 wash shall be run before setting up an N-Boc deprotection.

Setup
Components for sample preparation:

- Vial
- N-Boc protected amine (0.5 mmol)
- Stir bar
- Neat (no solvent)



Machine Solvents for the use with Boc 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: 1,2-dimethoxyethane, >99%
	S3: MeOH, >99.9%
	S4: –
	S5: –

Machine Cleaning after N-Boc Deprotection Reaction

1) Run automated MeOH wash after the N-Boc deprotection reaction.
2) Run automated CH_2Cl_2 wash before the N-Boc deprotection reaction.

Solvent Consumption and Run Time

SEQUENCE RUNTIME	
Reaction Sequence	**Time**
Boc deprotection	4 h 39 min

SOLVENT COMSUMPTION FOR BOC DEPROTECTION	
For Reaction Setup	**Amount**
no solvent	-
Machine Solvents	
Dichloromethane (CH_2Cl_2)	10 mL
Methanol (MeOH)	47 mL
Dimethoxyethane (DME)	7 mL

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