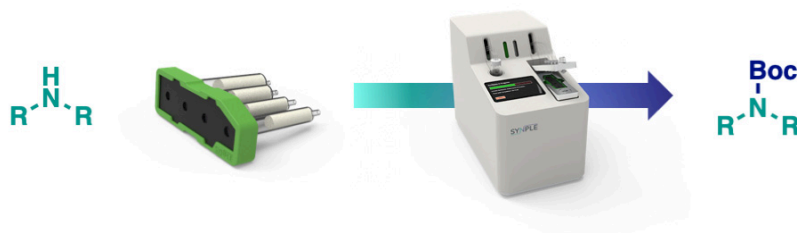


Application Note – N-Boc protection

Introduction

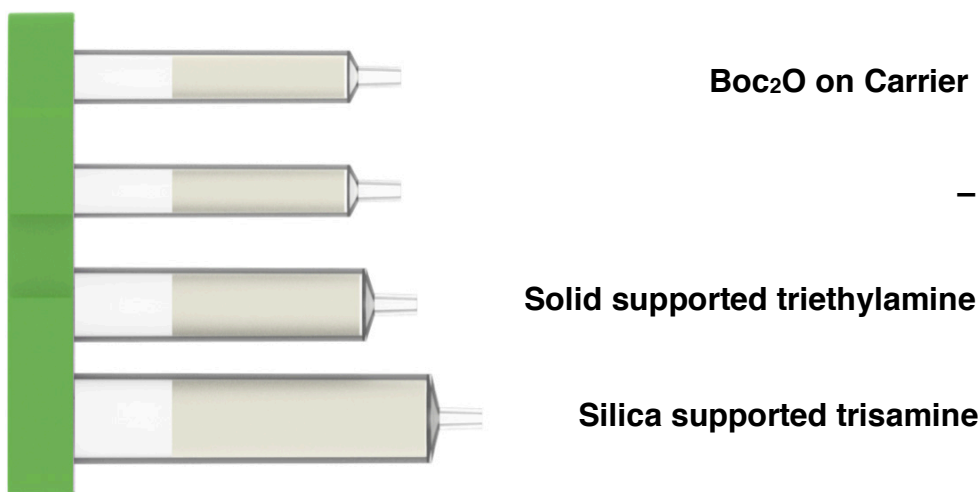
N-Boc protection involves the reaction between an amine and boc anhydride. It allows to generate N-*tert*-butylcarbamates, which are stable toward a variety of routinely used conditions. N-Boc protection is one of the most widely used reaction in medicinal chemistry.

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



Cartridge Contents

The cartridge contains a set of reagents to carry out a Boc protection reaction on a scale up to 0.5 mmol for B001 and 1.2 mmol for B002. Both free amines and amine salts are supported.

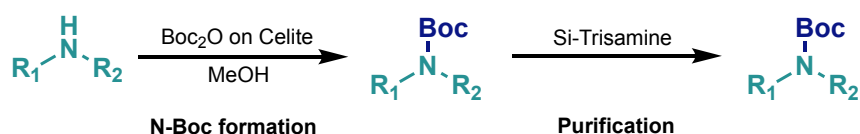


This method can be used for the following transformations:

- Boc protection with primary amines
- Boc protection with secondary amines
- Boc protection with primary amine salts
- Boc protection with secondary amine salts
-

Reaction Scheme

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



In a standard N-Boc protection, the N-Boc product is formed (sometimes in a presence of a base) and then worked-up in order to remove the excess of Boc_2O .

Reaction Procedure

1) Freebasing (optional)

If the sequence for amine salts was selected the substrate is dissolved and passed over solid supported triethylamine at 1 mL/min to free-base the amine for 3 hours. This step is skipped if the sequence for free amines was selected

2) N-Boc formation

Boc_2O is eluted from the carrier (compartment 1) to the vial using MeOH (2.4 mL) at 1 mL/min at room temperature. The reaction is stirred for 3 hours.

3) Purification

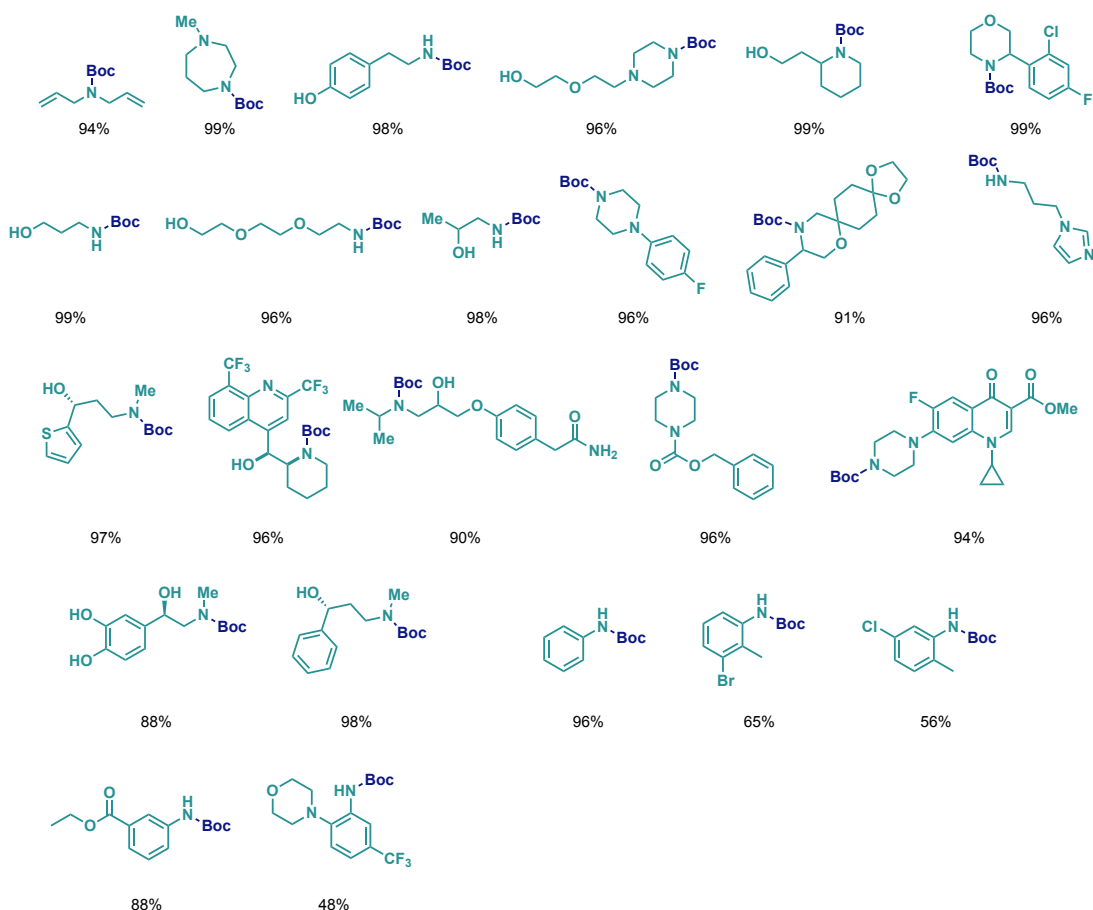
In order to remove the excess of Boc_2O , 4 mL of MeOH is added to the vial. The reaction mixture is then passed through compartment 4 (polymer supported trisamine) at 2 mL/min for 2 hours. The compartment is washed with MeOH (2.4 mL) five times. The solution in the vial contains the N-Boc product.

Substrate Scope

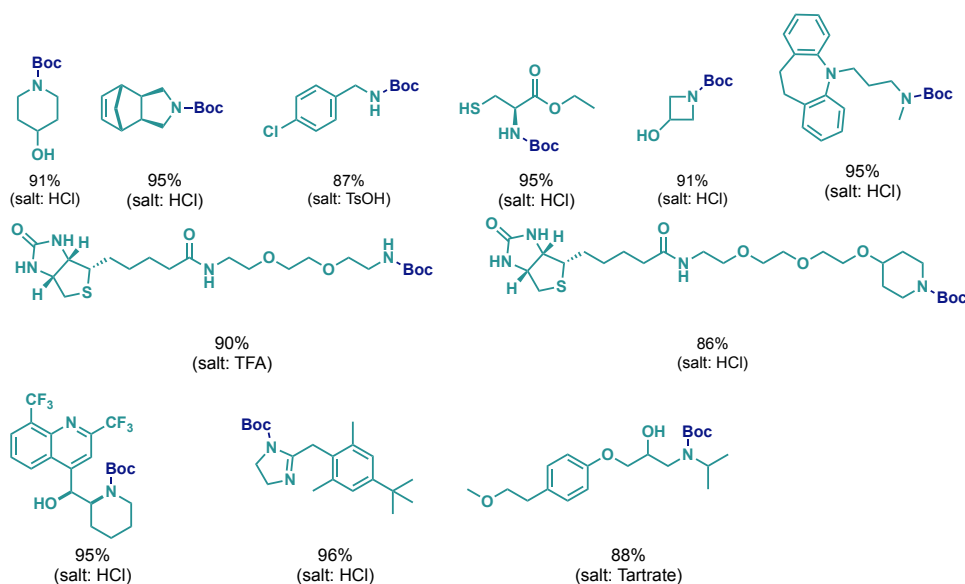
Tolerated functional groups

A wide range of different functional groups are tolerated. The substrates should be soluble in MeOH.

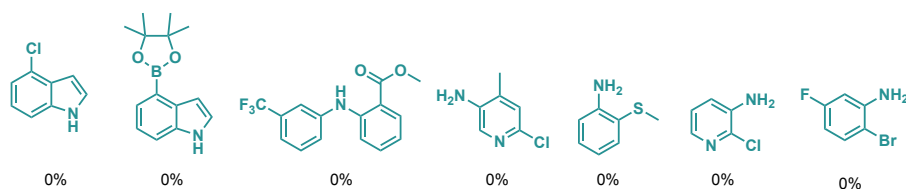
Example substrate scope – free amines



Example substrate scope – amine salts



Not supported substrates example



Known Chemistry-Limitations

Insoluble starting materials

Zwitterions like amino acids or compounds containing an amine and a carboxylic acid are poorly soluble in methanol. Because of the zwitterion the reaction runs very slowly.

Selectivity problems

This method is not selective with molecules containing at least two amines (primary and/or secondary). This method can lead to several N-Boc products.

Poorly nucleophilic substrates

This method performs very slowly or generates no product with poorly nucleophilic amines like indoles, amino pyridines or substituted anilines.

Electron Poor Anilines

Anilines are often less nucleophilic and reaction poorly with Boc_2O . This can be especially observed for anilines decorated with electron-withdrawing groups (see above; not supported examples)

Reaction Parameter Editing

Editing parameters:

Parameter 1	Reaction time of Boc protection step
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Enabling and Disabling parts:

No parts to disable.

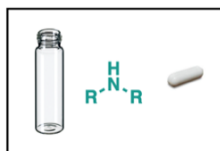
Sample Preparation



Setup






Components for sample preparation:

- Vial
- Amine (up to 0.5 or 1.2 mmol)
- Stir bar
- No solvent



Machine Solvents for the use with Boc protection cartridges

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

	S1: Dichloromethane, anhydrous
	S2: –
	S3: MeOH
	S4: –
	S5: –