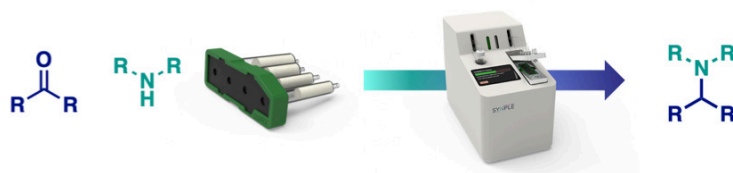


Application Note – Reductive Amination

Introduction

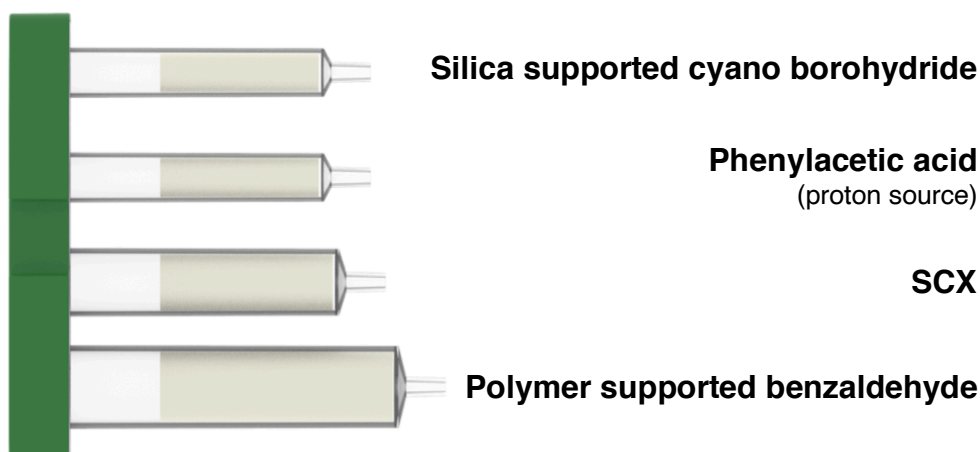
Reductive aminations (reductive alkylations) involve the formation of a new carbon-nitrogen bond via the reaction of a carbonyl group and an amine. The resulting amine products are important features in many pharmaceutical drugs and as such, reductive amination is one of the most widely utilised reactions in medicinal chemistry.



Using the approach described in this application note, the Synple Chem synthesizer offers an easy and fast automated method for the coupling of amines and carbonyl compounds using a reductive amination process.

Cartridge Contents

The cartridge contains a set of reagents to carry out the reductive amination on a scale of up to 0.5 mmol.

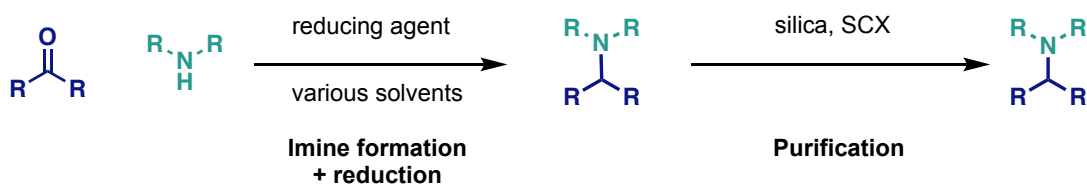


The method can be used for the following transformations:

- Reductive Amination between an aldehyde and a primary amine
- Reductive Amination between an aldehyde and a secondary amine
- Reductive Amination between a ketone and a primary amine
- Reductive Amination between a ketone and a secondary amine
- N-Methylation by reductive amination between and aldehyde/ketone and formaldehyde

Reaction Scheme

This section describes the general course of the reductive amination:



In a standard reductive amination, the imine is formed and then subsequently reduced. Imine formation can occur prior to addition of the reducing agent, or it can also form in the presence of the reducing agent, depending on the nature of the reducing agent.

Commonly employed reducing agents for reductive aminations include NaBH_4 , NaBH_3CN or $\text{Na}(\text{CH}_3\text{COO})_3\text{BH}$.

Reaction Procedure

1) Imine formation / Reduction

In the first step the solution is circulated through cartridge compartment 1 (silica supported cyanoborohydride) at 2 mL/min at room temperature. After the reduction is complete, compartment 1 is rinsed into the vial using CH_2Cl_2 (5 mL).

Reductive Amination Type	Time for reduction step (h)
Aldehyde + primary amine	2.5
Aldehyde + secondary amine	3.0
Ketone + primary amine	2.5
Ketone + secondary amine	4.0

Note: For the reaction of ketones with secondary amines the reaction mixture is passed through compartment 2 (phenylacetic acid) before the start of the reduction. The compartment is then rinsed into the vial with CH_2Cl_2 (2mL).

2) Excess Amine Scavenger (only for aldehydes + primary amines)

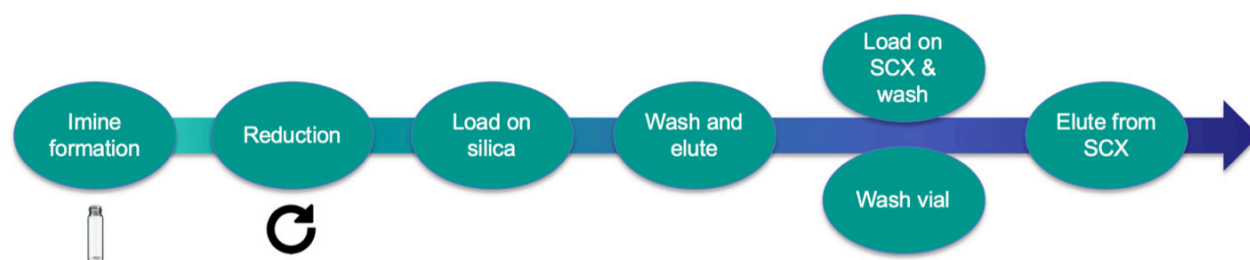
The reaction mixture is passed through compartment 4 (polymer supported benzaldehyde) at 1 mL/min. The compartment is then washed with CH_2Cl_2 .

3) SCX purification

The reaction mixture is loaded into compartment 3 (SCX) at 2 mL/min. The compartment is then washed with CH_2Cl_2 and MeOH.

4) Product release:

Compartment 3 is washed into the vial with 2.5 M DIPA/MeOH (15mL). The filtrate contains the reductive amination product.



Substrate Scope

Tolerated functional groups

A wide range of different functional groups are tolerated.

At present the reaction has not been fully optimised for aliphatic aldehydes, weakly nucleophilic or very hindered amines. The reaction does work but the purity is less than ideal so efforts are on-going to optimise these.

N-Methylation

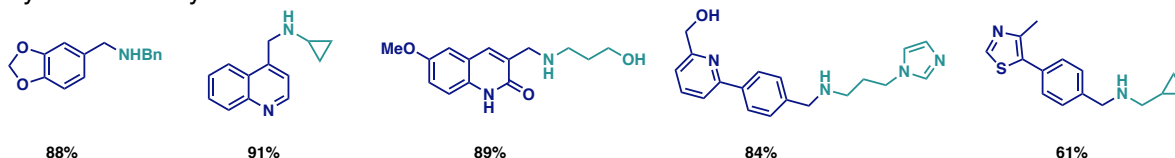
N-Methylation of an amine can be achieved using 2 equivalents of aqueous formaldehyde solution (30% in water) as the carbonyl reaction partner.

Trends for aldehyde substrates

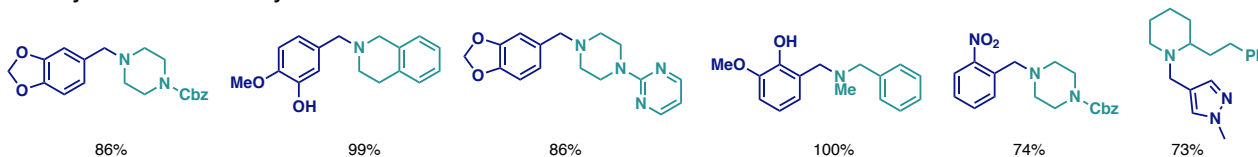
Electron rich aldehydes tend to give higher yields than electron poor aldehydes.

Example substrate scope

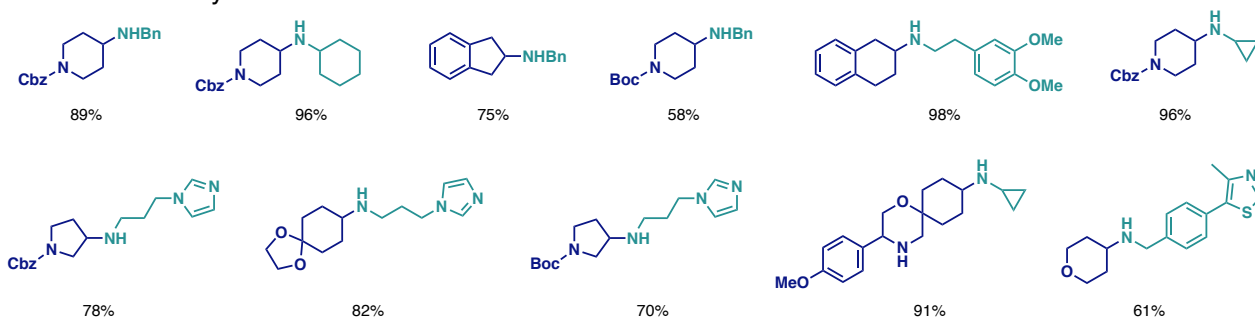
Aldehydes + Primary Amines:



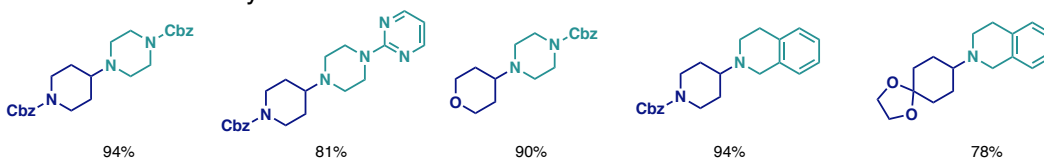
Aldehydes + Secondary Amines



Ketones + Primary Amines



Ketones + Secondary Amines



Known Chemistry-Limitations

Insoluble starting materials

The aldehyde, ketones and amines must be soluble in the reaction solvent when the sample is prepared initially. Insoluble materials will lead to low or even zero conversion, and in the worst case, lead to blockage of the system.

Basic functional groups

If the aldehyde/ketone contains a basic group a further purification step may be needed, because any excess starting material and side products could contaminate the product.

Boc deprotection

For some cases 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.

Trans-esterification / Trans-acetalization

For ester or acetal containing substrates some amount of trans-esterification or trans-acetalisation of the product to the corresponding methyl-ester or methyl-acetal can be observed during the SCX purification step. By disabling this purification step, these byproducts can be avoided.

CN addition

Occasionally the product can contain up to 20% of a CN addition byproduct due to the use of cyano borohydride as reducing agent.

Amine salts

Amine salts do not work directly with this particular method. They currently need to be free-based and subjected to a short work-up before setting up the reaction. A new reductive amination method for amine salts is in development.

As an alternative 1.0 equiv. of NEt₃ can be added to the reaction mixture before starting the sequence. However, this can sometimes lead to a reduction of yield between 5 to 15%.

Aryl Amines

In most cases, with electron poor aryl amines no products are formed.

Reaction Parameter Editing

Editing parameters:

Aldehydes and primary amines / Aldehydes and secondary amines / Ketones and primary amines

Parameter 1	Reaction time for reduction (seconds)
Parameter 2	Amount of solvent for elution from "catch & release" resin: In case of very polar substrates more solvent could be required to wash of the last bit of product from the catch & release resin. Therefore, the value can be increase. To calculate the input value multiply the volume in mL by 600. For example the value 9000 is equivalent to 15 mL (Maximum value 12000)

Ketones and secondary amines

Parameter 1	Reduction step temperature for cartridge
Parameter 2	Reduction step temperature for reaction vial
Parameter 3	Reaction time for reduction (seconds)
Parameter 4	Amount of solvent for elution from "catch & release" resin: In case of very polar substrates more solvent could be required to wash of the last bit of product from the catch & release resin. Therefore, the value can be increase. To calculate the input value multiply the volume in mL by 600. For example the value 9000 is equivalent to 15 mL (Maximum value 12000)

Enabling and Disabling parts:

Aldehydes and primary amines

Part 1: Excess amine scavenging

The reaction solution is passed through polymer supported benzaldehyde to scavenge any left-over or excess amine from the solution. If this is unwanted to recover the left-over amine or because the product contains another amine the step can be disabled.

Part 2: Purification step

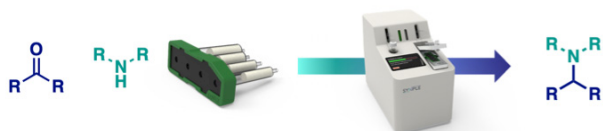
The purification step of the sequence can be disabled. In case of very acid sensitive functional groups the purification might not be suitable. The machine will then provide the reaction product in solution in the reaction vial after the reduction step.

Ketones and secondary amines / Ketones and primary amines / Aldehydes and secondary amines

Part 1: Purification step

The purification step of the sequence can be disabled. In case of very acid sensitive functional groups the purification might not be suitable. The machine will then provide the reaction product in solution in the reaction vial after the reduction step.

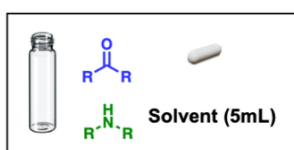
Sample Preparation



Setup

Components for sample preparation:

- Vial
- Aldehyde / Ketone
- Amine
- Stirbar
- 5 mL solvent (see below)



Guide for solvents and ratios for sample preparation:

Aldehyde + primary Amine

CH_2Cl_2 : HFIP = 4:1 (5 mL)

CH_2Cl_2 can be partially replaced with MeOH for improving solubility

For best results choose a ratio of Aldehyde:Amine = 1:2

Aldehyde + secondary Amine

CH_2Cl_2 : HFIP = 4:1 (5 mL)

CH_2Cl_2 can be partially replaced with MeOH for improving solubility

For best results choose a ratio of Aldehyde:Amine = 2:1

Ketone + primary Amine

CH_2Cl_2 : HFIP = 4:1 (5 mL)

CH_2Cl_2 can be partially replaced with MeOH for improving solubility

For best results choose a ratio of Ketone:Amine = 1:1 to 2:1

Ketone + secondary Amine

Toluene (5 mL)

Toluene can be partially replaced with MeOH for improving solubility

For best results choose a ratio of Ketone:Amine = 1:1 to 2:1

Machine Solvents for use with Reductive Amination cartridges

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

	S1: Dichloromethane Anhydrous, 150ppm amylene tolerated
	S2: –
	S3: MeOH HPLC grade
	S4: Diisopropylamine (175 mL) in MeOH (325 mL)
	S5: –