Application Note – N-Heterocycle Formation

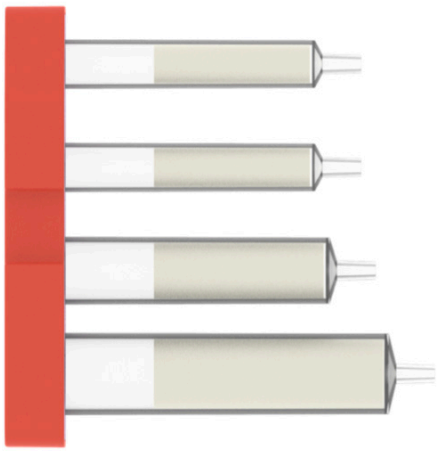
Introduction

N-Heterocycles are a desirable moiety for the development of new drugs but their synthesis is not necessarily easy. One powerful method utilizes the SnAP (stannyl amine protocol) reagents developed in the laboratory of Prof. Jeffrey Bode. This chemistry is recognized as one of the most versatile approaches to substituted morpholines, piperazines, oxazepanes, spirocyclic N-heterocycles and many other attractive scaffolds, and is already widely used by drug discovery groups in the pharmaceutical and biotech industries. There are many advantages of SnAP chemistry, including the structurally diverse SnAP reagents that can be prepared, an exceptionally broad substrate scope, and the fact that a standard set of reaction conditions is used regardless of the substrate. Therefore, SnAP chemistry offers the potential to form a large number of different 'flavors' of N-unprotected saturated N-heterocycle products. However, the SnAP chemistry – like almost every other organic reaction – requires several labor intensive steps, including the weighing of the reagents, prior complexation of copper and ligand, preparation of an imine intermediate, a multi-step aqueous workup, and finally column chromatography. Also, it uses toxic tin reagents which makes the handling of the reaction difficult und undesirable.

With the approach described in this application note the Synple Chem synthesizer offers an easy and fast approach for the synthesis of substituted, saturated N-heterocycles from aldehydes and stannyl amine protocol (SnAP) reagents, without the need for optimization, and which minimizes the user's contact with tin reagents.

Cartridge Contents

The cartridge contains a set of reagents that enable SnAP reactions up to a maximum 0.5 mmol scale. For all available N-heterocycle formation cartridges the contents are identical, with the exception of the SnAP reagent, which varies depending on the type of N-heterocycle to be formed.



SnAP Reagent
(immobilized), 4 Å MS

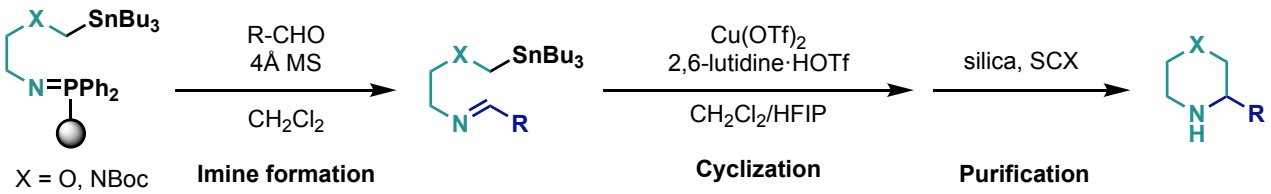
Cu-Catalyst
($Cu(OTf)_2$ and 2,6-lutidinium triflate)

SCX

Silica

Reaction Scheme

This section describes the general course of the SnAP reaction:



The SnAP chemistry for the synthesis of saturated N-heterocycles, consists of four steps:

1) **Imine formation**: In the automated sequence the starting aldehyde reacts with the SnAP reagent (immobilized on a triphenylphosphine resin) in CH_2Cl_2. The triphenylphosphine oxide byproduct remains on the solid support.

2) **Cyclization:** The copper-mediated cyclization utilizes a preformed $Cu(OTf)_2$/2,6-lutidine complex in HFIP (hexafluoroisopropanol).

3) **Work up:** The standard basic aqueous workup to remove copper salts is replaced in the automated sequence by filtering the reaction solution through a plug of silica.

4) **Purification:** In the automated sequence the filtrate is subjected to a catch and release purification process using SCX.

Selected Literature References:

Vo, C.-V. T.; Mikutis, G.; Bode, J. W. SnAP Reagents for the Transformation of Aldehydes into Substituted Thiomorpholines—An Alternative to Cross-Coupling with Saturated Heterocycles. *Angew. Chem. Int. Ed.* **2013**, *52*, 1705–1708.

Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. SnAP Reagents for the One-Step Synthesis of Medium-Ring Saturated N-Heterocycles from Aldehydes. *Nat. Chem.* **2014**, *6*, 310–314.

Luescher, M. U.; Geoghegan, K.; Nichols, P. L.; Bode, J. W. SnAP Reagents for a Cross-Coupling Approach to the One-Step Synthesis of Saturated N-Heterocycles. *Aldrichim. Acta* **2015**, *48*, 43–48.

Reaction Procedure

1) Imine formation:

In the first step the neat aldehyde is dissolved in anhydrous CH_2Cl_2 (4.5 mL). The solution is then circulated through cartridge compartment 1 (SnAP reagent) at 1 mL/min. Compartment 1 is heated at 50 °C and the reaction vial is heated at 35 °C. After the imine formation is complete, compartment 1 is rinsed into the vial with anhydrous CH_2Cl_2 (3.5 mL).

N-Heterocycle reagent cartridge	Time for imine formation step - full sequence (h)
Morpholine	6
Oxazepane	6
Benzoxazepane	9
2-Methylmorpholine	6
Piperazine	6
Diazepane	6

N-Heterocycle reagent cartridge	Time for imine formation step - full sequence (h)
3-Methylmorpholine	16
Morpholine-2-spiro-(2-Pyr)	9
Morpholine-2-spiro-(2-Pip)	9
9-OMe-Benzoxazepane	9
7-Br-9-OMe-Benzoxazepane	9

2) Cyclization:

Anhydrous HFIP (2.0 mL) is added via compartment 2 (Cu-Catalyst) into the reaction vial. The solution of imine in anhydrous CH_2Cl_2 and HFIP is circulated through compartment 2 at 2 mL/min. Compartment 2 is heated at 40 °C and the reaction vial is heated at 37 °C. After the reaction time, compartment 2 is rinsed with anhydrous CH_2Cl_2 (2 mL).

N-Heterocycle reagent cartridge	Time for cyclization step - full sequence (h)
Morpholine	3
Oxazepane	3
Benzoxazepane	3
2-Methylmorpholine	3
Piperazine	3
Diazepane	3

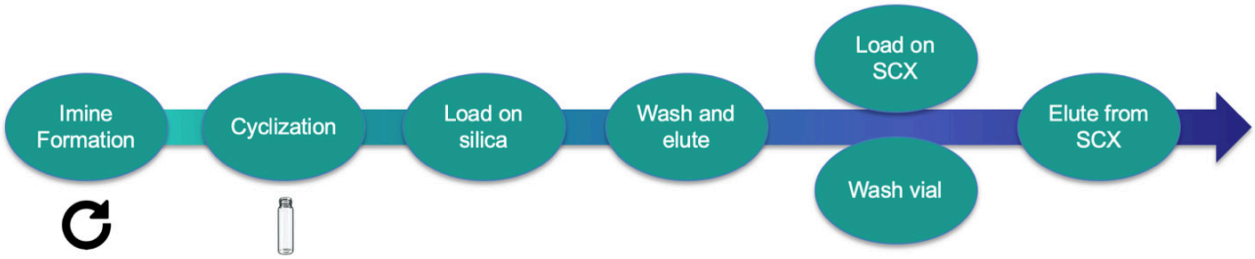
N-Heterocycle reagent cartridge	Time for cyclization step - full sequence (h)
3-Methylmorpholine	3
Morpholine-2-spiro-(3-Pyr)	4
Morpholine-2-spiro-(4-Pip)	4
9-OMe-Benzoxazepane	3
7-Br-9-OMe-Benzoxazepane	3

3) Purification:

The reaction mixture is loaded into compartment 4 (Silica). The filtrate is then loaded into compartment 3 (SCX) and the filtrate is discarded to waste.
Compartment 4 is washed with MeOH (12 mL) and the filtrate is loaded again into compartment 3. The filtrate from compartment 4 is discarded to waste. This step is repeated once more.
Compartment 3 is washed with MeOH (12 mL) and the filtrate is discarded to waste. This step is repeated once more.

4) Product release:

Compartment 3 is washed into the vial with 2.5 M DIPA/THF (20 mL). The filtrate contains the N-heterocycle product.



Substrate Scope

Tolerated functional groups

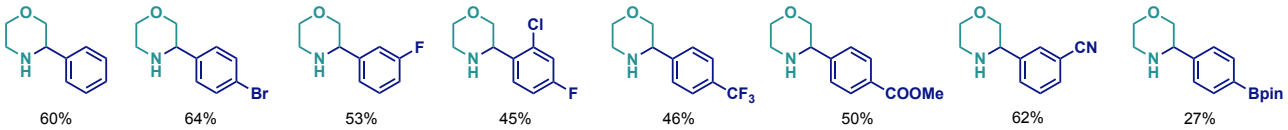
The reaction tolerates a large array of different functional groups, from aromatic aldehydes to aliphatic aldehydes. Generally, the functional groups should be able to tolerate radical conditions.

Trends for aldehyde substrates

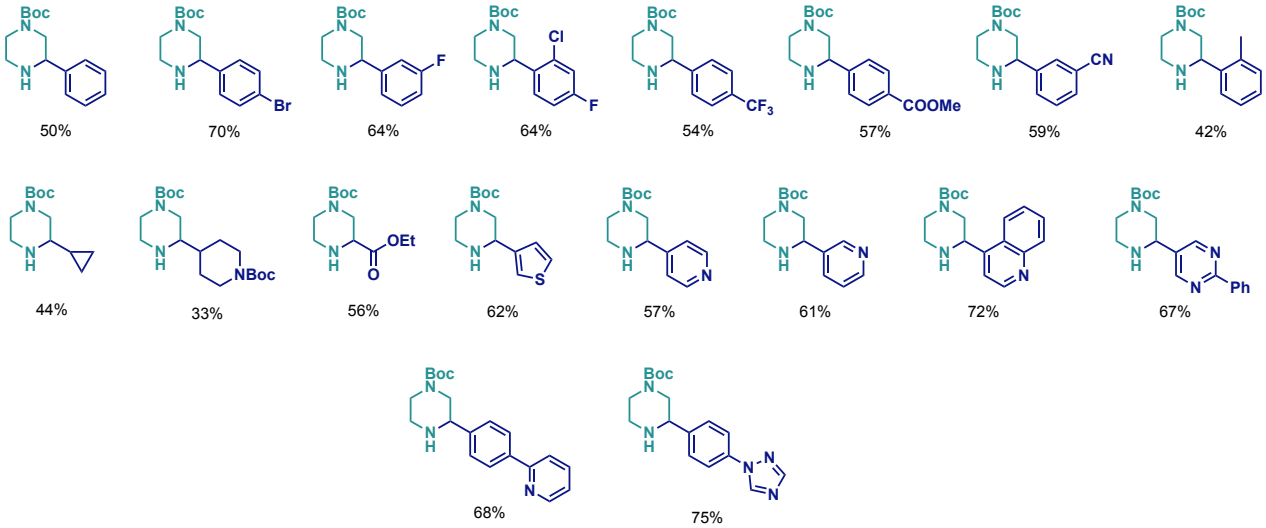
Generally, higher yields can be obtained for aromatic, electron poor aldehydes.
Yields for electron rich aldehydes tend to be slightly lower because of the slower imine formation.
When using aliphatic aldehydes lower yields are observed. This results from the possible enamine tautomerization after the imine formation.
Sterically hindered combinations of SnAP reagents (e.g. spirocyclic SnAP reagents) and aldehydes can also result in decreased yields.

Example substrate scope

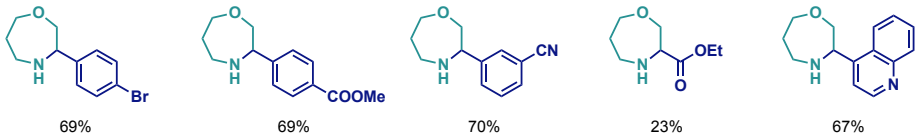
Morpholines:



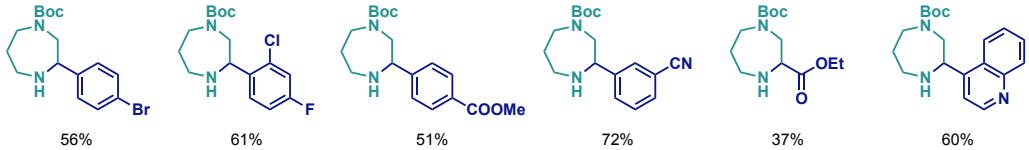
Boc-Piperazines:



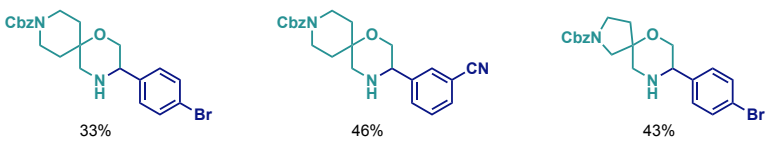
Oxazepanes



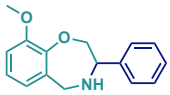
Diazepanes



Spirocyclic products



Benzoxazepanes



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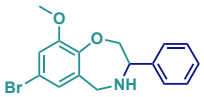

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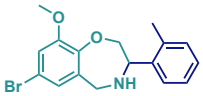

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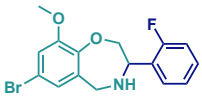

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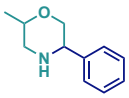
Methylmorpholines



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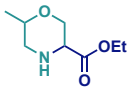

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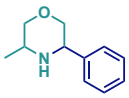

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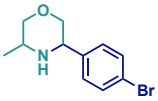

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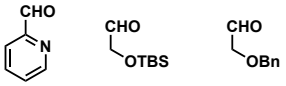
Known Chemistry-Limitations

Non-tolerated functional groups:
Carboxylic acids are not tolerated because of the interference in the imine formation step and quenching of the cyclization step.

Ketones:
Ketones are currently not supported due to their very slow reaction in the ketimine formation step. However, it is possible to pre-form the ketimine in batch and use a cartridge containing only the catalyst and purification materials and run only the available cyclization and purification sequence. Just ask us!

Beta heteroatom containing aldehydes:
Aldehydes containing a heteroatom in beta position to the aldehyde do not result in product formation. The intermediate formed acts as a bidentate ligand that complexes the Cu-catalyst. This stops the cyclization reaction and/or leads to fast decomposition of the imine.



Insoluble aldehydes
The aldehyde must be soluble in CH_2Cl_2 in order to be pumped through the immobilized SnAP reagent. Insoluble aldehydes will not react in the imine formation step or, in the worst case, lead to clogging of the lines. It is possible to use Acetonitrile as co-solvent to increase solubility. However, slightly lower yields will be obtained in comparison. See section “Reaction Parameter Editing” to disable the automatic solvation of the substrate with CH_2Cl_2.

Acetal formation
For rare cases of N-containing aldehydes, acetal formation of any residual aldehyde can be observed during the SCX purification, which may then also be present in the product. This requires further purification but the yield of the desired products remains good.

Boc deprotection
In rare cases up to 20% Boc deprotection can be observed. This can be avoided by disabling the SCX purification step. For an alternative of the Boc containing SnAP reagents ask us for the Cbz protected version!

Reaction Parameter Editing

Editing parameters:

Parameter 1	Imine formation temperature of cartridge (°C)
Parameter 2	Imine formation temperature of reaction vial (°C)
Parameter 3	Imine formation reaction time (seconds)
Parameter 4	Cyclization temperature of cartridge (°C)
Parameter 5	Cyclization temperature of vial (°C)
Parameter 6	Cyclization reaction time (seconds)

Enabling and Disabling parts:

Part 1:
Substrate solvation step

This can be disabled if the user prefers to dissolve the aldehyde substrate him-/herself instead of loading it crude into vial. For dissolving use 4.5 mL of dry CH_2Cl_2. Other amounts or type of solvents can lead to lower conversion. It is possible to use Acetonitrile instead as solvent but slightly lower yields will be obtained.

Part 2:
Purification step

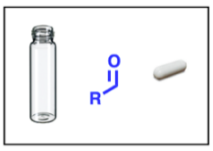
The purification step of the reaction sequence can be disabled. In case of very acid sensitive functional groups the purification might not be suitable. The machine will then provide the reaction product in solution in the reaction vial after the cyclization step.
For a manual workup we recommend an aqueous work-up with commercial 25% aqueous ammonium hydroxide solution and CH_2Cl_2 to remove the copper, followed by flash column chromatography.

Sample Preparation

Setup

Components for sample preparation:

- Vial
- Aldehyde
- Stirbar
- No solvent



Machine Solvents for the use with SnAP cartridges

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

	S1: CH_2Cl_2 Anhydrous, 150 ppm amylene tolerated
	S2: Hexafluoroisopropanol Anhydrous, distilled, Available from Synple Chem
	S3: MeOH HPLC grade
	S4: Diispropylamine (175 mL) in THF (325 mL)
	S5: –