A Fully Automated Capsule-Based Machine for Organic Chemical Synthesis

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Introduction

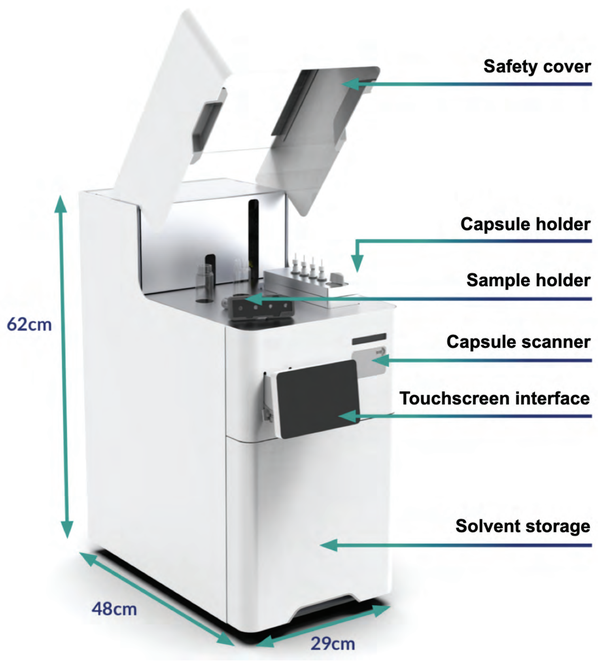
The automation of organic reactions – particularly for applications in drug discovery – is currently a major goal due to its ability to save time, improve safety, and interface with ongoing efforts to employ artificial intelligence and reaction optimization. A number of custom-built and commercial instruments for reaction automation and optimization are available or under active development, but these are largely geared towards scale-up and facilitating screening of reaction conditions. The desire for automation in medicinal chemistry laboratories is easily observed with the widespread adoption of automated purification instruments, which use pre-packed silica-gel cartridges for the purification of organic compounds with little user involvement. We sought to bring the same level of convenience, reliability, and automation to the setup, execution, work-up, and purification of organic reactions, using a compact, user-friendly setup.

Concept

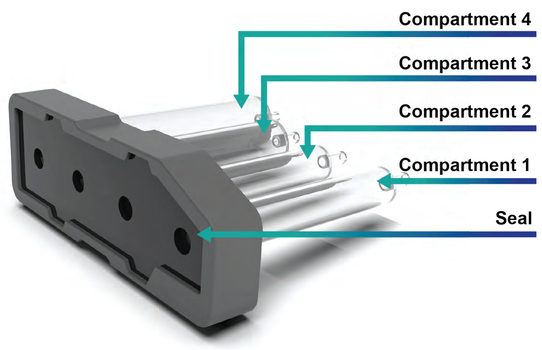
We have developed an integrated, capsule-based, fully automated synthesizer for the transformation of aldehydes to a variety of substituted saturated N-heterocycles. Unlike other approaches to reaction automation, the automated synthesizer can utilize new substrates without any change to the instrument configuration, requires no weighing or handling of any chemicals other than the starting aldehyde. Most importantly, it a delivers pure (> 90%) products without user intervention. Currently, capsules are available to carry out SnAP chemistry, reductive aminations and PROTAC formations. We plan to extend this easy-to-use, capsule-based approach to allow many other reaction types on the fully automated system.

- Preparing valuable organic compounds
- Quick and easy reaction setup
- Start process with one button
- No method programming necessary
- Easy to use without special training
- RFID reader for capsule

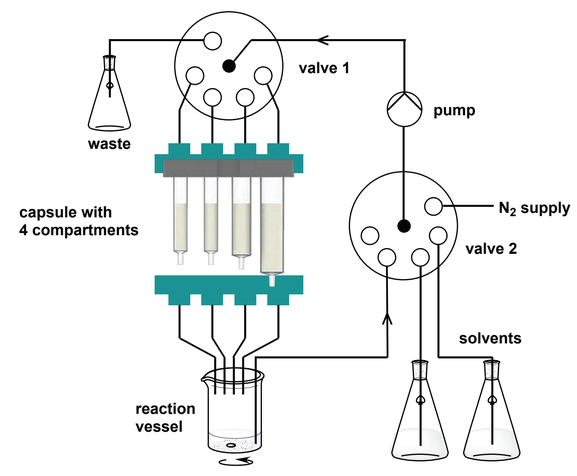
Overview of automated synthesizer



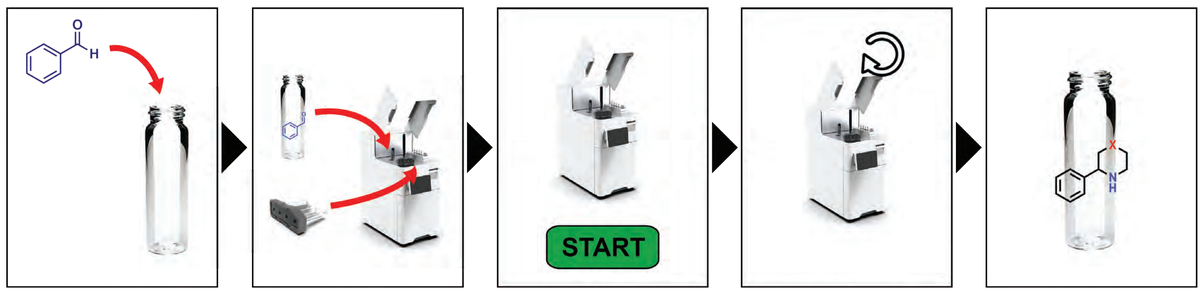
Reagent capsule with 4 compartments



Fludics setup of the synthesizer



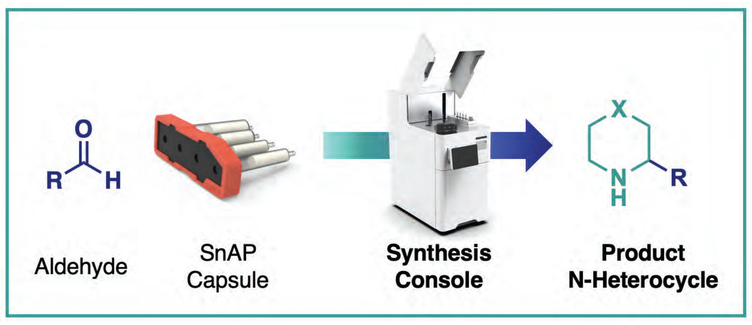
Steps to setup a reaction with the synthesizer. A maximum of 5 minutes are necessary to setup a reaction. This will run autonomously and the user can pick up the purified product after the sequence.

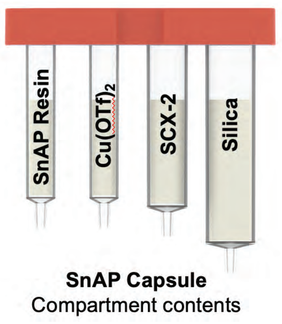


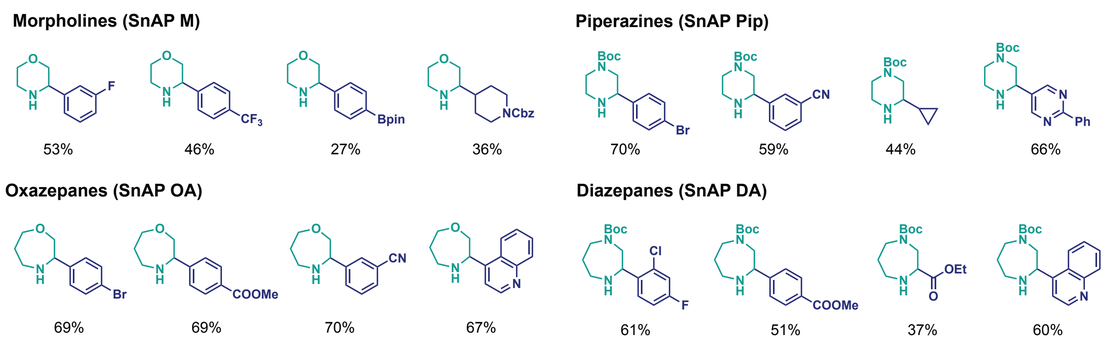
1. Add aldehyde to vial
2. Insert vial and capsule into console
3. Script is loaded by RFID tag and START is pressed
4. Automated reaction is performed
5. Collect purified product

Automated Reactions

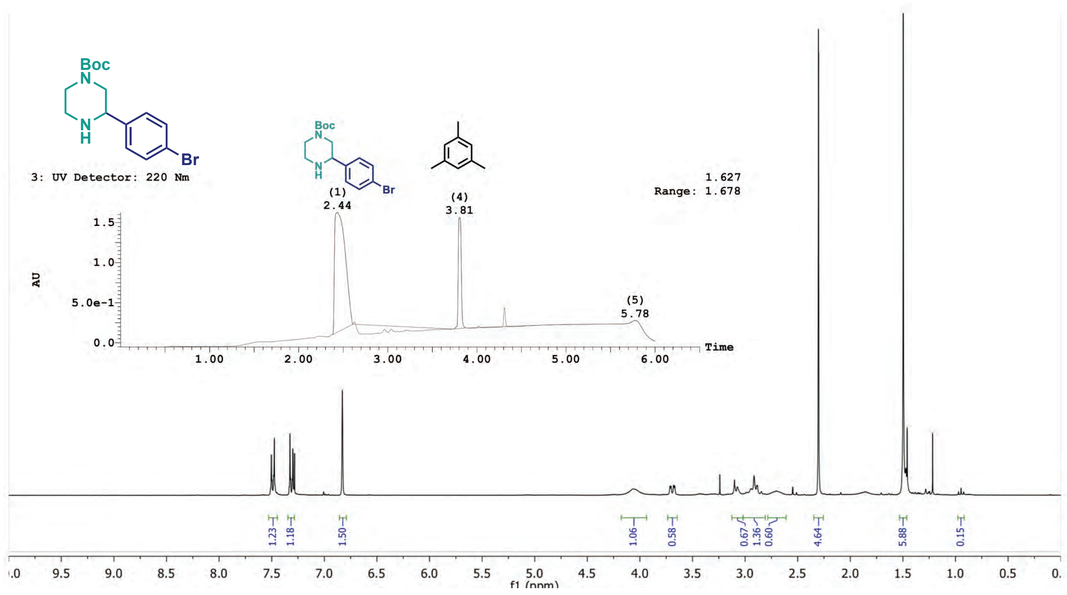
SnAP - N-Heterocycle Formation



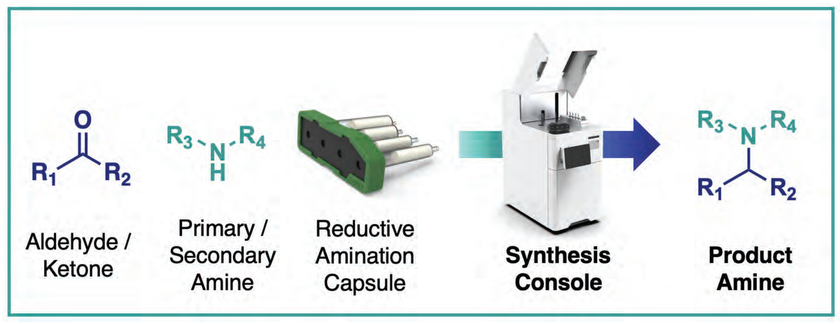


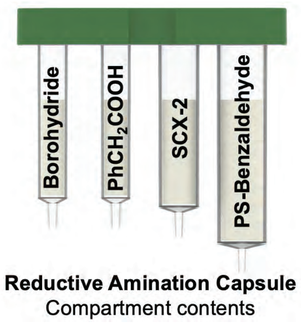


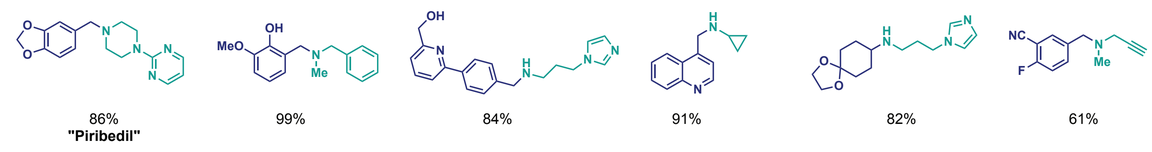
Analytical data of product obtained from the synthesizer directly after the reaction without any further purification. Mesitylene was added as internal standard.



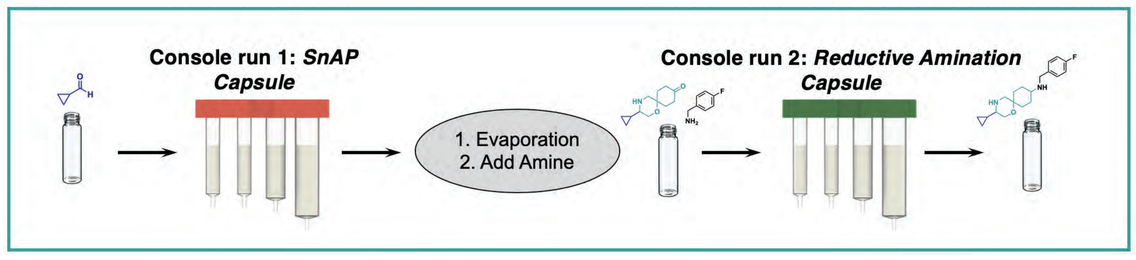
Reductive Amination

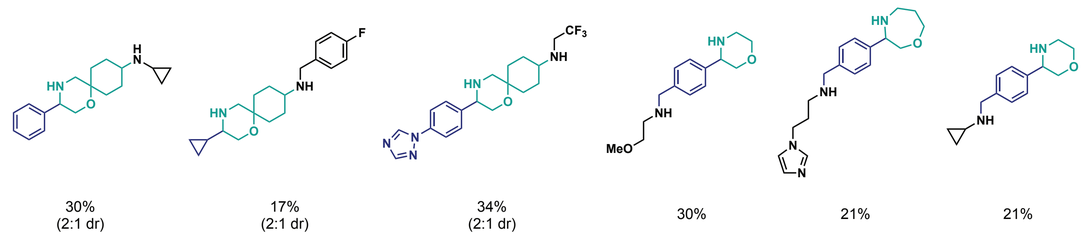






Automated Multistep Preparation of Drug-like Molecules





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References

Jiang, T.; Bordi, S.; McMillan, A.; Chen, K.-Y.; Saito, F.; Nichols, P.; Wanner, B; Bode, J. PrePrint on ChemRxiv: 10.26434/chemrxiv.7882799 **2019**