Accelerating Discovery with Automation

Discovery chemistry challenges

Despite the fact that synthetic chemistry plays an integral role in the discovery of new medicines, materials and crop protections agents, most of the synthetic processes utilised by chemists today have barely changed in the last century. Many reactions are still done manually in round-bottom flasks, using traditional techniques. As such, current processes remain expensive, laborious, time- and resource-consuming, environmentally unfriendly, and prone to safety-liabilities.

With the increasing burden of productivity pressures and spiralling costs that research and development organisations have been facing in recent decades, there is a very urgent strategic need to seek and implement efficient and effective solutions. In an effort to rein in R&D spending and increase productivity without an increase in fixed costs, during the last 10-15 years, an increasing amount of synthesis work has been outsourced to overseas providers of synthetic services. However, outsourcing inevitably introduces delays and risks in the discovery process, where speed and flexibility are of upmost importance. In addition, without the flexibility to explore and react to emerging biological data in-house, the opportunity to exploit serendipitous discoveries can be lost.[1] Therefore, although outsourcing remains a valuable tool and provides resourcing flexibility, it is essential that methods for enhancing in-house productivity are fully explored. For chemical synthesis, which involves a reasonable proportion of mundane, repetitive tasks, automation would appear to be an obvious solution.[2]

Progress in automating chemistry

Automation in synthesis can be implemented at all stages of the synthesis process, including making the new molecules, purification and analysis. The potential that automation holds is attractive for many reasons. Such technologies tend to be both time and resource efficient, minimising the amount of manual labour and raw materials required. This can result in significantly enhanced productivity when the available tools are used appropriately. In addition, such technologies often offer both environmental and safety benefits, since human interaction is reduced and chemical processes can be more reliably controlled. However, while much progress has been made, it is clear that in this ever evolving field, most of the existing automated synthesis technologies still have limitations.

Even though much of organic synthesis is, even today, still carried out manually, there has been a significant amount of effort invested in recent years, from both academic and industrial groups. The developments have sought to implement automated solutions for each and every step in the synthesis process, from planning a reaction, to forming the product, and finally confirming the identity of the new product. Each of these processes can constitute a bottle-neck in chemical synthesis. Therefore, automation of any of these steps can help expedite the preparation of compounds in a more effective and time-efficient manner.

Many of the new automated synthesis tool utilise the advantages of continuous flow chemistry, which overcomes the need for a human to manually move materials from one step to the next. Several companies offer versatile, commercially available flow chemistry-based systems, which are flexible enough to conduct a range of chemistries and offer the opportunity to scale up chemical synthesis. [3,4,5] However, these systems need programming and time for optimisation, which although desirable for some, is not ideal for most discovery chemists whose primary goal is to make compounds for biological testing as quickly and easily as possible.

Automation needs in discovery chemistry

While the commercially available continuous flow automated synthesis systems do provide the flexibility to make a huge range of molecules under a broad scope of reactions conditions, these systems typically require significant skill to programme and operate, as well as time for optimisation. Such functionality can be highly beneficial for some applications, e.g. process development, but within discovery chemistry there is little time for reaction optimisation and finely tuning parameters since the project progresses only by the making and screening of new compounds. Therefore, for chemists in the discovery phase, very simple, easy to use technologies are far more appealing. As with any automation technology, they will only be appealing and desirable if they are perceived to bring significant advantages to a particular task, relative to the effort required to actually use the systems.

Figure 1: Transformation of a starting material into the desired product using the Synple synthesiser and single-use, prefilled reagent cartridges, which are available for a range of chemical reactions.

Considering the technologies that have been widely adopted by medicinal chemists, including automated purification systems, microwave reactors, and manual parallel synthesis equipment, it is clear that they are all very easy to use, require little training for their use, and do not require a period of optimisation for each new reaction. Synple Chem, an ETH Zurich start-up company, has sought to address the need for automated synthesis technologies and has developed a safe, easy to use, cartridge-based, automated synthesis technology, which has pre-programmed and highly optimised reaction protocols requiring no programming or optimisation (Fig. 1).[6] This system, which provides "*off the shelf*" reaction solutions, has been designed primarily to address the need for such simple, readily accessible technologies within discovery chemistry, and can be used to enhance productivity and contribute to the acceleration of the discovery process.

Automated, cartridge-based synthesis

The aim of our safe, easy to use, time-saving technology for chemical synthesis is to enable chemistry-based research and development organizations to simplify chemical synthesis

and accelerate the discovery process by speeding up the feedback loop between preparing and testing molecules. Our technology consists of an automated flow-batch hybrid synthesiser system, which utilises a range of pre-packed reagent cartridges for different reaction classes, along with pre-programmed, highly optimised but editable reaction protocols, which can be loaded by simply scanning the cartridge on the synthesiser (Fig. 2). The combination of these three key elements, provides users with a convenient, easy to use, time-saving technology that makes the synthesis of molecules far simpler, faster and more efficient.

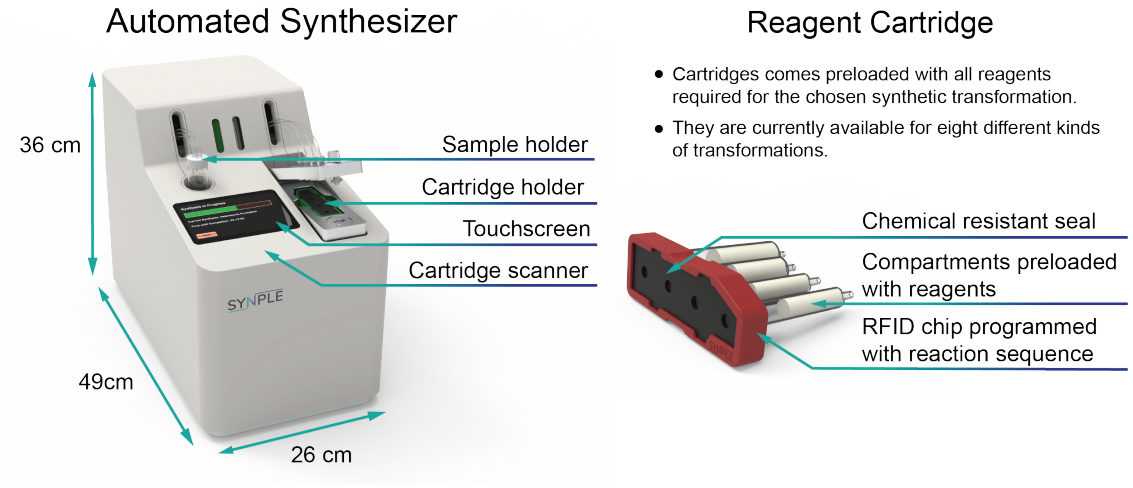


Figure 2: Features of the Synple automated cartridge-based synthesizer and the reagents cartridges.

The small (26 cm x 49 cm), bench-top instrument works in an analogous manner to well-known household capsule coffee systems and combines the same three key elements that guarantee simplicity and convenience – the automated synthesiser (coffee machine), reagents cartridges with high quality QC checked materials (coffee capsules) and the pre-optimised reaction protocols (automated sequence for the ideal coffee preparation process). However, unlike the coffee systems, which use only one starting material (water), many unique, bespoke molecules can be prepared at the touch of a button using the Synple system. The user simply loads their starting material into the sample holder and selects an appropriate cartridge for their transformation from the range of available reagent cartridges (Fig. 3).

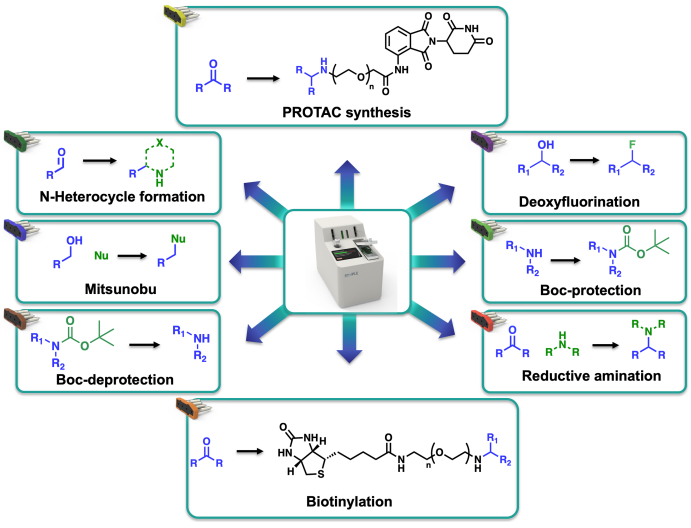


Figure 3: Range of available reaction classes and cartridges for the Synple system.

All the cartridges are prefilled with the required QC checked reagents for the transformation and purification. They also contain an RFID chip, which upon scanning, automatically loads the required reaction protocol on the machine, thereby simplifying reaction set up and minimizing operational error. The majority of the cartridges can be used for any amount of starting material, up to a maximum of 0.5 mmol (except for chemical biology applications, which are 0.1 mmol), which is a scale compatible with the needs of discovery chemistry.

Benefits of Synple

The use of the technology has several key advantages, including time-saving, cost-saving, convenience, reproducibility and safety. The technology is also readily accessible via our flexible purchasing models. There is option to get a machine on a Pay Per Use basis, hence no capex investment is required. Alternatively, customers can buy the machine and then benefit from reduced price cartridges (50% less). In addition, we also have a collaborative model in which we work together with customers to develop new applications and cartridges, and there is even the possibility to earn royalties on the sales of these cartridges.

Time-saving: This is a clear advantage of our technology and the benefits of the Synple system are two-fold. Firstly, most chemical reactions on new substrates typically require some optimization of the reaction parameters. Since the Synple technology comes with pre-installed, highly optimised reaction protocols and a fully defined scope (available in the application notes), the need to do this reaction optimization is obviated. Secondly, the "hands on" time for each reaction using the Synple system is only 5 minutes, even for labour intensive reactions that would typically require hours of hands on time when carried out manually. This frees up the user to focus on other tasks that cannot be so easily automated and enables them to spend their time doing more intellectual, demanding work.

Cost savings: The obvious time-savings translate to significant cost savings. Since the use of this cartridge-based synthesis technology can reduce the time required to carry out a reaction by up to 90%, the average reduction in the cost per reaction, vs doing a manual reaction, is 70%. It is now possible to calculate your own costs using the Synple Savings Simulator. Just add in amounts for your own labour costs and the number of reactions your chemists typically do, and see how much you could be saving with Synple (Fig. 4).

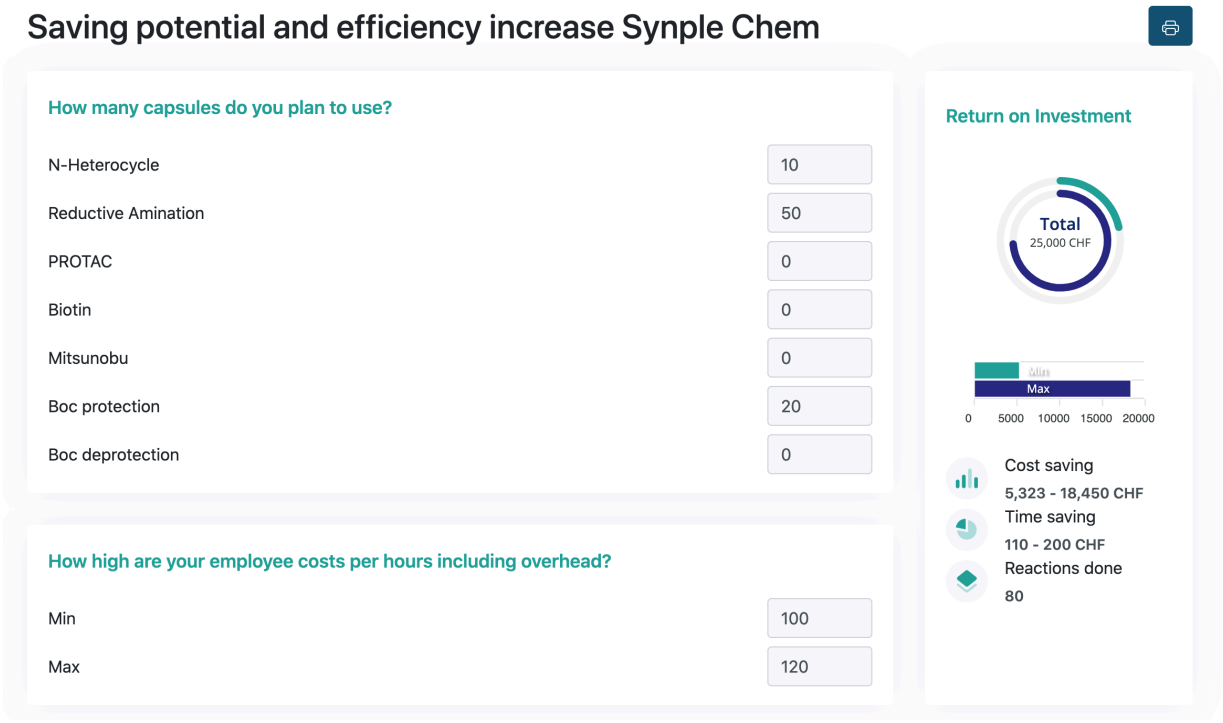
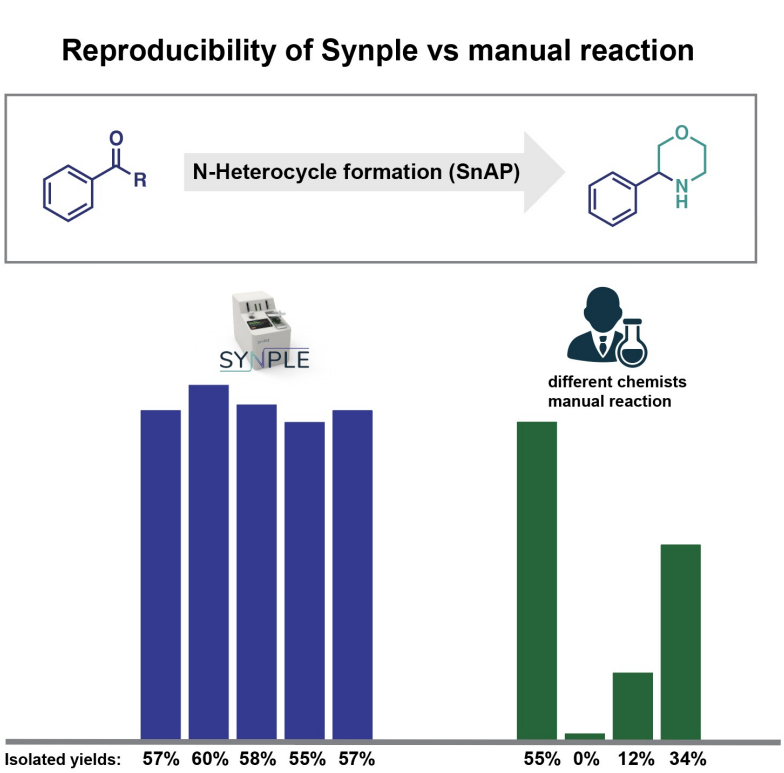


Figure 4: Synple Saving Simulator

Convenience: Ease of use is another major benefit of the technology. As a plug and play system, it can be simply attached to a power source and connected to a flow of nitrogen, and it is ready for use. No specialist training is required, with it typically taking less than 15 minutes to fully train a user. The pre-optimised methods and defined reaction scope avoid the need to carry out multiple optimization reactions in order to identify the best conditions. Automatic protocol loading by simply scanning the cartridge obviates the need for programming and minimizes the potential for user error, meaning that synthesis can be carried out in a more robust, reproducible manner. The cartridges themselves are very convenient to use and having all the materials for the reaction, work up and purification means that only the cartridge needs to be located rather than multiple reagents and chemicals. Ultimately, this technology offers all discovery chemists access to real synthesis automation without any of the barriers that have previously restricted its utility.

Reproducibility: The ability to replicate literature reports, the work of another colleague or even a chemist's own work is a problem that is frequently reported. Given that there are so many variables in synthetic chemistry, it can be hard to fully capture exactly what was done to the tiniest level of detail, which results in variability of the outcome.



Consistent reproducible results can be obtained with runs on different Synple 2 devices setup at different locations
This is often not the case for running chemical reactions manually by different chemists

Figure 5: Reliability and reproducibility of Synple technology vs chemists.

Since the pre-installed methods run in exactly the same way every single time, the reproducibility is far higher than it is when chemists are carrying out reactions manually (Fig. 5). In addition, variability can also be introduced due to differences in the chemical reagent sources, and difference in the skills and experience of various chemists. With the Synple cartridges, all materials are QC checked and each batch of cartridges is function tested prior to release. Therefore. If a reaction works once in the Synple system, it will work just as well the next time, irrespective of who the operator is, what their level of experience is and what the operating conditions are like in their labs (Fig. 6).

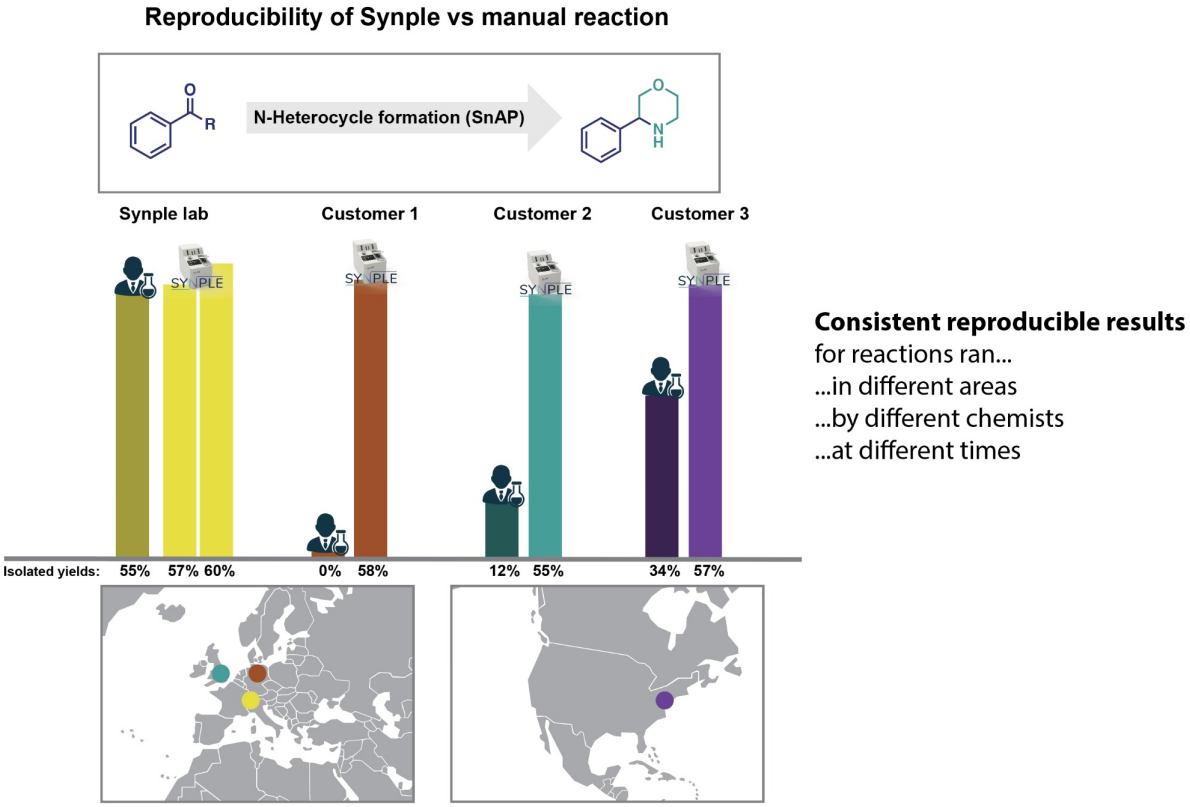


Figure 6: Consistently reproducible results using the Synple machine irrespective of the time, person or place.

Safety: All the reagents, purification materials and solvents are contained either within the cartridge, machine or solvent bottles. The machine also runs an automated self-cleaning method, disposing of all the washings in the waste bottle. As such, through the use of this technology, the user's exposure to potentially toxic or harmful substances is significantly reduced.

Future of Synple

Alongside the eight existing commercially available reaction application, we also have a long pipeline of new applications in development, including azide formation, amide couplings, and cross-couplings. In addition, we will continue to expand the scope and cartridge ranges within our existing applications. More protecting group chemistries are in development, as are an expanded range of chemical biology cartridges, e.g. PROTACs with alternative linkers. The goal is to develop as many applications as possible for the existing hardware. Following this, the aim is to introduce new, low cost, add on modules for expanding the capabilities, e.g. a photochemistry module and a large-scale module.

Ultimately, Synple aims to bridge the gap between manual synthesis and highly complex, expensive automated synthesis system. By doing so, and really addressing the needs of the discovery chemistry community, we hope to make automated synthesis accessible to a much broader range of users. Only by enabling automation for the vast majority of chemists, can we hope to shorten discover cycle times and thus start to see acceleration of the discovery process.

References:

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(2) a) T. Tsukamoto, *ACD Med. Chem. Let.,* **2013**, *4*, 369–370. b) V. A. Steadman, *ACS Med. Chem. Let.*, **2018**, *9*, 581–583.
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