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A GRAND SYNTHESIS

Automation is changing how scientists synthesize chemicals

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Introduction

Synthetic chemistry—the art of making complex chemical compounds from simpler ones—is a cornerstone of the chemical industry. Synthetic processes are critical to the development and manufacture of products ranging from plastics to pharmaceuticals.[1] Yet synthesis can be a bottleneck, as traditional methods must typically rely heavily on manual labor. As lab technology advances, researchers are looking to streamline chemical synthesis through automation.

The US market for organic chemicals was estimated at

$127B

Organic synthesis, or the creation of molecules primarily composed of carbon, may be particularly well suited to an automation revolution. In spite of a robust industry—the US market for organic chemicals was estimated at $127 billion in 2021—most organic synthesis has barely changed in the past century.[2–4] Reactions can require laborious setups with particular equipment and reagents, some of which are hazardous. In addition, chemists must typically spend time optimizing reactions to their lab environment.

“In synthetic chemistry, there are a lot of potential conditions we could try for a given reaction,” says Reinaldo Jones, principal scientist in process and scale-up chemistry at EMD Serono. “You may have to start by going to the literature to search for conditions, or find multiple conditions to try first and then optimize from there—those things can take a lot of time.” These challenges, as well as higher research costs and a fast-paced market, have highlighted the need for new solutions to organic synthesis.[4]

“We always look for new chemistry technologies to make lab life easier,” says Jones, who specifically wants to simplify the design-make-test cycle of product development. In this cycle, researchers design a chemical product using in silico tools, past data, or alternate strategies; the product is then synthesized in the lab and undergoes a series of tests to see if it has the desired properties. “The ‘make’ piece is where automated synthesis comes into play and can be beneficial,” Jones says.

The goals of automating organic chemical synthesis can include improving productivity,

Figure 1. With ready-to-use automated synthesis platforms, chemists can conduct organic synthesis reactions within a contained system. Synple relies on reaction-specific disposable reagent cartridges to produce desired synthesis products.[4]

safeguarding laboratory personnel, or reducing costs. Automation can be implemented in every phase of the synthesis process, from the synthetic reaction itself to the purification and analysis of the target product. Each step can present complications.[4] Automation may also improve a synthesis process's reproducibility by eliminating some sources of variation.[4]

Automation approaches can also have drawbacks, depending on the details of a given system. For example, many of the instruments and technologies aimed at automating organic synthesis require significant training, programming, and time for optimization, making them less than ideal for most discovery chemists.[4] Meanwhile, automated systems that don't require extensive training or optimization protocols can provide a broadly applicable solution to overcoming the obstacles associated with organic synthesis.

One approach to the democratization of organic synthesis automation is capsule chemistry. With this technology, chemists can use a range of prefilled chemical capsules and an automated instrument to carry out their synthesis, much like at-home coffee systems such as Nespresso. The capsules contain all the reagents needed to execute a specific type of synthesis reaction, as well as the materials needed to isolate the product.[4] For example, the Synple Chem automatic chemical synthesis platform provides cartridges that allow chemists to carry out eight classes of organic synthesis reactions (figure 1).

With Synple, chemists add the starting material and appropriate reagent cartridge to the synthesis instrument and press a button to start the process. They can then apply their attention to other tasks as the instrument generates, isolates, and purifies the desired synthesis product.

By addressing the need for readily accessible and easy-to-use technology, automated synthesis platforms provide a new toolbox for chemical developers. This e-book will explore how technologies such as Synple help organizations enhance productivity and accelerate the R&D process.

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CHAPTER 1

Seeking simpler synthesis

Preparing and executing an organic synthesis reaction involves multiple steps and an investment of time. Finding, measuring, and weighing out the reactants is the first step, followed by setting up the synthesis apparatus and other laboratory equipment. Finally, chemists set up the reaction itself and start to monitor its progress. After all that work, they might step out of the lab for a coffee—where all they have to do is load up the capsule and press a button on a machine.

That could leave them wondering: Could organic synthesis be as simple as making a cup of coffee? Automation has helped move chemistry toward this goal, relieving chemists of some of the burdens associated with organic synthesis.

"There seems to always be another project, and having automated reaction instruments would allow an individual more time to handle multiple projects," says Paul Frail, advanced senior engineer at Suez, a water technologies firm. That extra time would provide other benefits, he adds: "Perhaps most importantly, it would give chemists the ability to connect and collaborate with other researchers externally or internally."

Continuous-flow automated synthesis systems, which aid synthesis by controlling when reactants are added to a continuous stream, are commercially available and can be used to make various molecular products under a wide variety of reaction conditions. However, these instruments and systems typically require significant time and skill to optimize and operate, making them less accessible to chemists.[1]

Capsule chemistry can provide an alternative. In this case, the necessary reaction components are contained in a chemical cartridge, much like coffee pods used with at-home machines. For example, Synple uses cartridge-based automatic organic synthesis technology that allows chemists to carry out a series of preprogrammed reaction types (figure 1).[2] Instead of weighing out reagents and setting up glassware, a chemist can simply add the chemical cartridge to the Synple

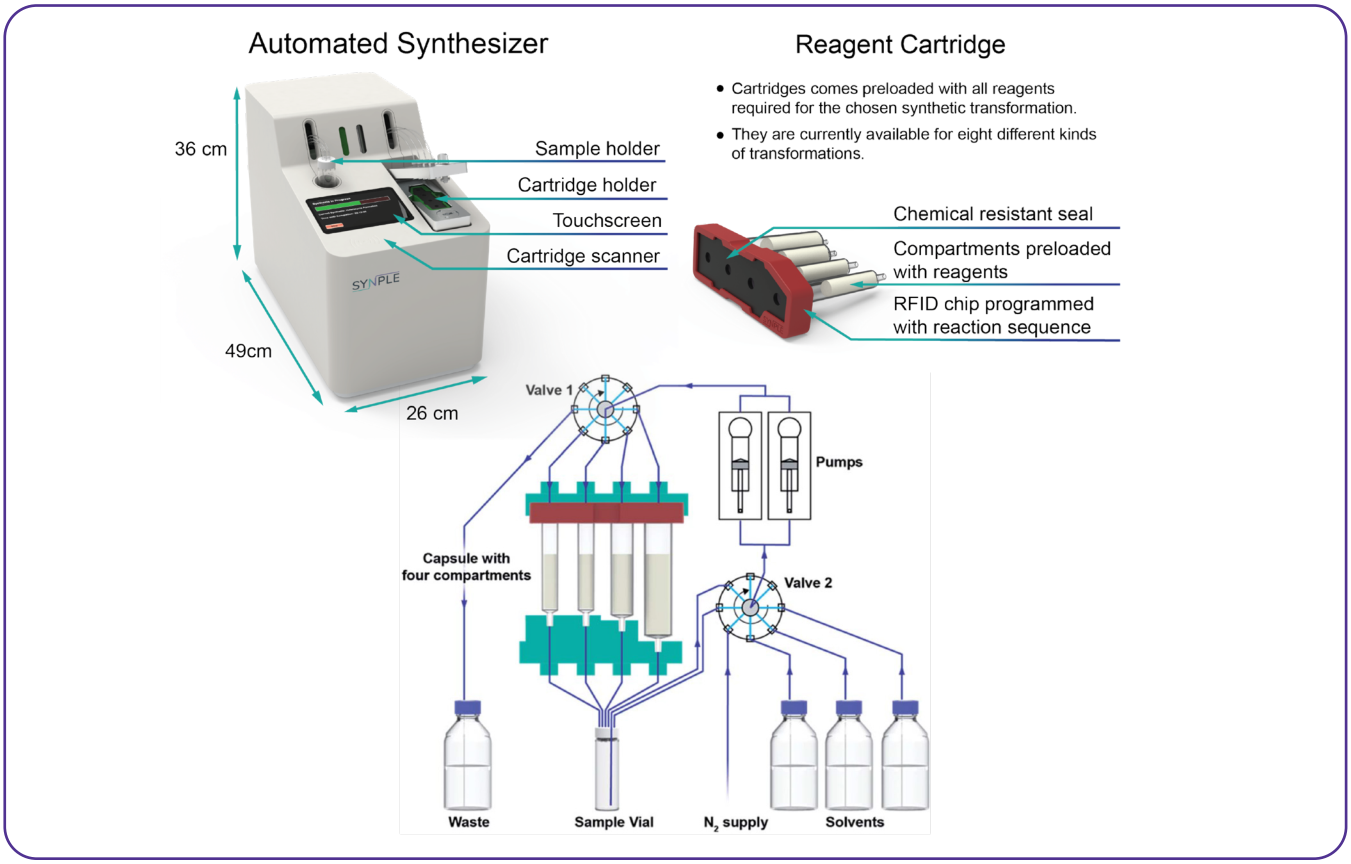

Figure 1: The Synple automated synthesizer setup and reagent cartridge features are shown in the top panel; the fluidics of the automated console is detailed on the bottom. With different valve settings, solvents can be pumped from the solvent reservoirs or sample vial into the individual compartments of the reagent cartridge or into the waste reservoir. The system is also connected to a nitrogen line to preserve an inert environment. The cartridge contains four compartments prefilled with the necessary reagents and materials to isolate the final product. The top of the cartridge is covered with a chemical-resistant seal. After the cartridge is inserted, fluidic lines connect automatically. The entire system is contained during the reaction process.[1,2]

instrument and starting material substrates, press a button, and walk away.

Making time for innovation

Organic synthesis reactions are part of the chemist's toolbox and can help in developing new pharmaceuticals, dyes, and polymers, among many other chemical products. Though tried and true, these processes demand a lot from researchers.

"Organic synthesis relies a lot on traditional manual techniques," Synple Chem cofounder Paula Nichols, says. "There are many routine, mundane, laborious tasks that chemists have to get through to get to the final product."

These tasks add up to a significant time burden for chemists. For instance, heterocycle formation can take up to 38 hours to set up and run to completion and can represent a significant bottleneck during product development processes (table 1).[3] Automated capsule chemistry platforms can cut that time in half. For example, chemists can purchase off-the-shelf heterocycle formation reaction cartridges, much like purchasing specific coffee pods. They can then plug these cartridges into an automated instrument, such as Synple, along with their own starting material and press go. Instead of spending hours, chemists can spend minutes setting up and completing their reactions (table 1).

Chemists are then free to do value-added work, Nichols says, "such as providing intellectual and strategic input during product development, or they can focus on chemistry that's not so easily automated."

According to Nichols, the functional output is increased productivity. Chemists no longer

“One of the biggest challenges with synthetic chemistry is that it can be really unpredictable”
PAULA NICHOL, SYNPLE CHEM COFOUNDER

	Traditional Synthesis		Synple Chem	
	Hands-on Time	*Reaction Time*	*Hands-on Time*	*Reaction Time*
Heterocylce Formation	4-6 hours	32 hours	5 min	11 hours
Reductive Amination	1-2 hours	2-24 hours	5 min	2-5 hours
PROTAC Formation	3 hours	2-24 hours	5 min	5-12 hours

Table 1. The Synple automated chemistry platform saves chemists considerable time. Chemical cartridges containing all the necessary reagents for the reactions (listed on the left-hand side of the table) can be purchased and plugged into the Synple instrument to generate the synthesis product.[5]

need to spend time setting up and standing in front of chemical reactions to see if they are proceeding as planned. Instead, they can focus on other work to ensure that product discovery and development is moving forward.

Consistency counts

Another potential advantage of automated synthesis platforms is their ability to reduce variability in processes. Humans themselves introduce variability, but factors such as reagent sources or the specifics of apparatus setup can also influence reaction outcomes.[1,4]

“One of the biggest challenges with synthetic chemistry is that it can be really unpredictable,” Nichols says. “The slightest change to one of the building blocks or the reaction conditions can have a big impact on whether the reaction is successful or not.”

To effectively manage so many variables, researchers may need to expend a lot of energy on working out the ideal conditions for a given reaction. Nichols also notes that even though a particular reaction is working in one environment, individual labs may do things slightly differently, which can lead to different outcomes that can hinder reproducibility.

Commercially available automated organic synthesis platforms like Synple help overcome some of the challenges associated with variability and reproducibility. Each synthesis method is preinstalled in the instrument, guaranteeing that it will run exactly the same way every time.[5] The chemical cartridges are produced with quality control checks to ensure that they function reliably. These features help reduce variability due to differences in chemical reagent sources or the experience and skills of the chemists using the instrument (figure 2).[4]

Just as with at-home coffee machines, chemists using automated synthesis platform can expect consistent results, regardless of location or the weather. This isn’t normally the case when doing synthesis reactions manually. Yields for processes such as N-heterocycle formation can vary by up to 55% between chemists at the same facility conducting the process manually; yield variability is 5% with an automated platform for the same reaction, (figure 2).[4] Reaction yields are also much higher when researchers at different facilities use an automated synthesis platform than when conducting the synthesis manually (figure 2).[4]

This reproducibility can help chemists consistently conduct and complete chemical reactions across and between organizations and may also improve yield, all of which equates to cost savings.[4]

With time savings and consistency in mind, automated synthesis can help chemists jump-start or accelerate their processes. These platforms are intended for both chemists who know a specific organic synthesis process will work with their product and those in the initial stages of product discovery who may want to broadly explore various chemical reactions.

“If it’s your first time attempting a reaction with a given starting material, you can quickly

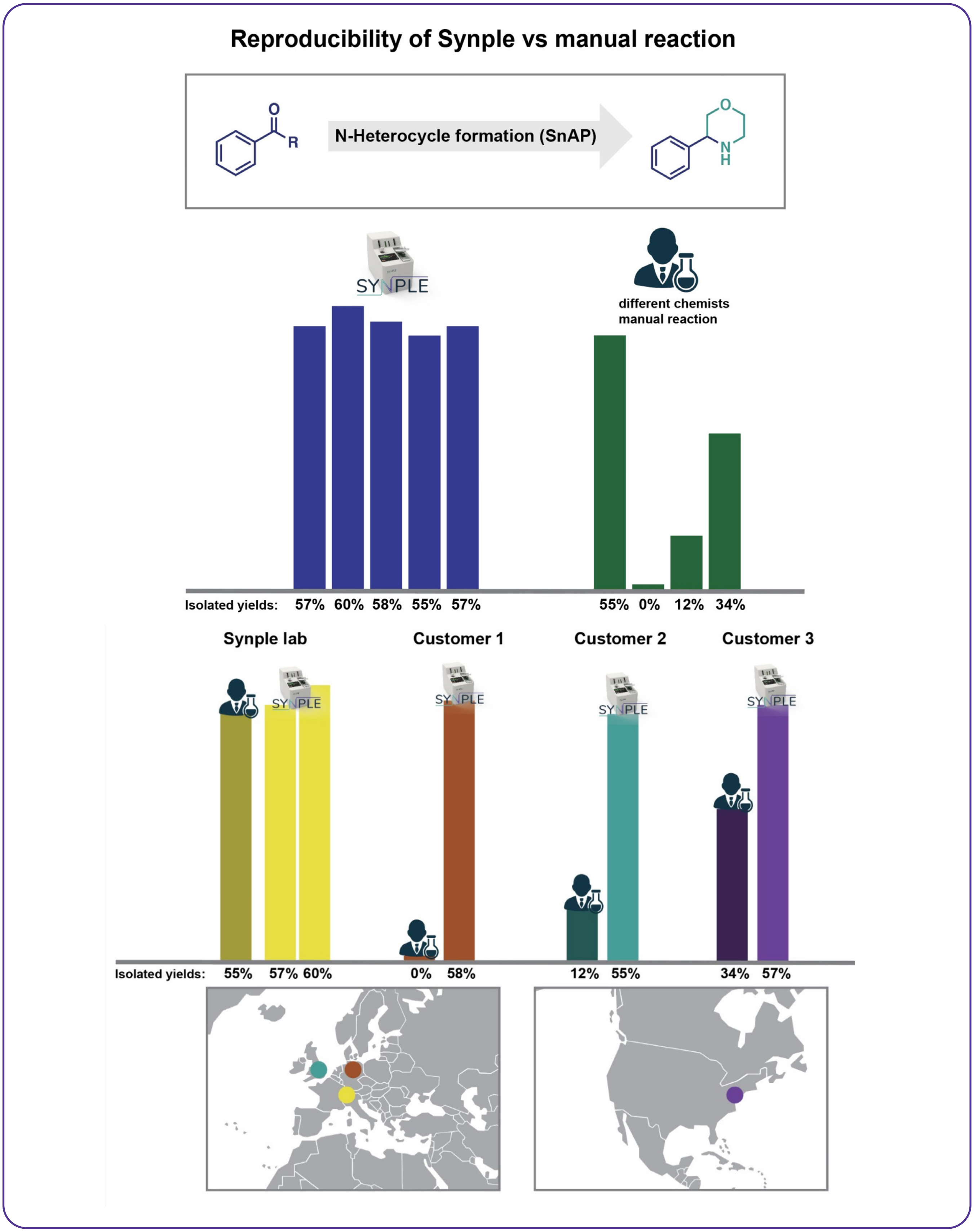

Figure 2: For N-heterocycle formation using SnAP chemistry, synthesis yields when employing Synple (blue bars, top) were compared with those employing manual reactions conducted by different chemists (green bars, top). The former were consistently higher. In addition, Synple results were also consistent regardless of location. This is illustrated in the bottom bars, which indicate operators in four locations that compared manual versus automated synthesis of the same SnAP reaction.[4]

assess its success," says Reinaldo Jones, principal scientist in process and scale-up chemistry at EMD Serono.

This helps push productivity and innovation by allowing chemists to test chemical products more quickly than they could with manual synthesis.

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CHAPTER 2

Automated synthesis in action

The chemical industry relies on many organic synthesis reactions. But according to an analysis of literature published between 1984 and 2014, several key reactions dominate the chemical landscape because of their robustness and wide-ranging applicability. They include heterocycle synthesis, alkylation of amines, amine deprotection and protection, and amide synthesis.[1]

Despite the prevalence of these reactions, the hands-on approach to executing them has remained largely unchanged over the past several decades.[1] Automated capsule-based systems are giving chemists new ways to carry out common reactions with a simple plug-and-play interface. For example, the Synple Chem system includes reagent cartridges with common reagents to achieve a hands-off approach to organic synthesis (figure 1). One type of reagent cartridge is optimized for a broad scope that allows for maximum variability of the building blocks of the starting material.

Chemical reaction cartridges provide chemists with a toolbox of reactions to choose from to meet their needs, including

- Reductive amination
- N-heterocycle formation (SnAP)
- Mitsunobu
- tert-butoxycarbonyl (Boc) protection
- Boc deprotection
- Protein degrader formation
- Fluorination
- Biotin tags

Automation in the lab

Yanping Wang, associate principal scientist in medicinal chemistry at EMD Serono, uses multiple organic synthesis processes during product discovery and development.

“We use all kinds of chemistry to make small molecules,” Wang says.

Reductive amination is one synthesis process Wang and his team employ frequently. Amines— compounds that contain a basic nitrogen atom—are widely used in chemistry, medicine, materials, and energy.[2] In the pharmaceutical industry, many top-selling drugs contain nitrogen or amino groups that are vital to the medications’ function.[2] They also serve as important building blocks during the synthesis and development of dyes, agrochemicals, and specialty materials.[3]

Reductive amination involves the conversion of a carbonyl group to an amine and represents an important method of amine production for the chemical industry.[2] A traditional, manual reductive amination reaction can take hours to complete and can require multiple types of equipment; researchers must use various flasks and glass vials and run the reactions in heating mantles or microwave reactors, according to Wang.

Automating this process—for example, by using the reductive amination reaction cartridges developed for the Synple system—can help simplify and accelerate it (figure 2).

“Reductive aminations are one of the main reactions we use Synple for,” says Reinaldo Jones, principal scientist in process and scale-up chemistry at EMD Serono.

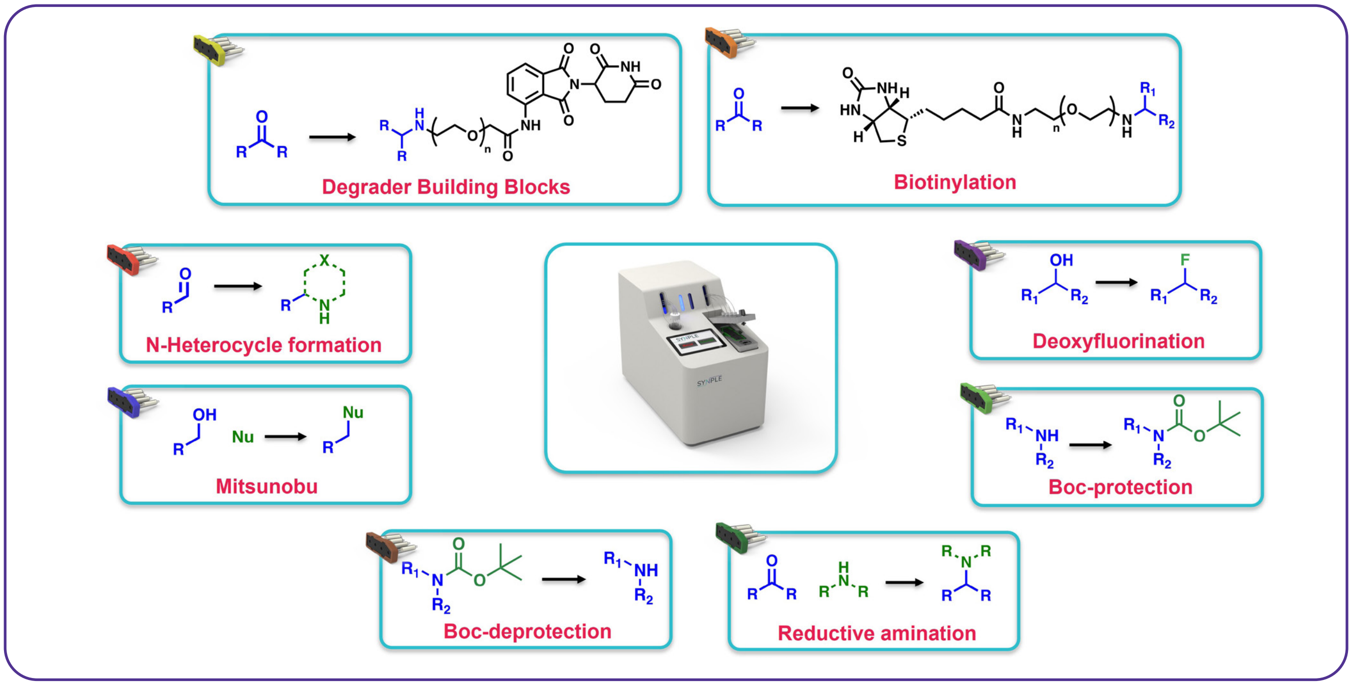

Figure 1: Synple's off-the-shelf reaction cartridges are available for a range of organic synthesis reactions. Each cartridge is complete with the materials needed for the chemical transformation and purification of the desired product. Source: Synple Chem

The reductive amination cartridge contains the reagents necessary to conduct a reductive amination reaction on a scale of up to 0.5 mmol. Instead of weighing out reagents and setting up flasks and heating mantles, chemists just need to pop the reaction cartridge into the Synple instrument with the aldehyde or ketone and amine.

"The Synple system knows exactly what to do after it scans the reaction cartridge," Jones says. "All you need to do is have your starting material in the vial, scan your cartridge, and press 'go.'"

Wang agrees that setting up reactions with Synple is straightforward, regardless of the reaction type. "It is relatively easy to acquire the knowledge to operate the instrument," Wang says. Users avoid the detailed or intensive training often needed for operation of the continuous-flow automated synthesis instruments described in chapter [1].

Going beyond the capsule

Automated capsule chemistry can provide chemists with easy-to-use methods for common organic synthesis reactions. But they may sometimes want to make additional modifications to the chemical product to enhance or eliminate key properties.

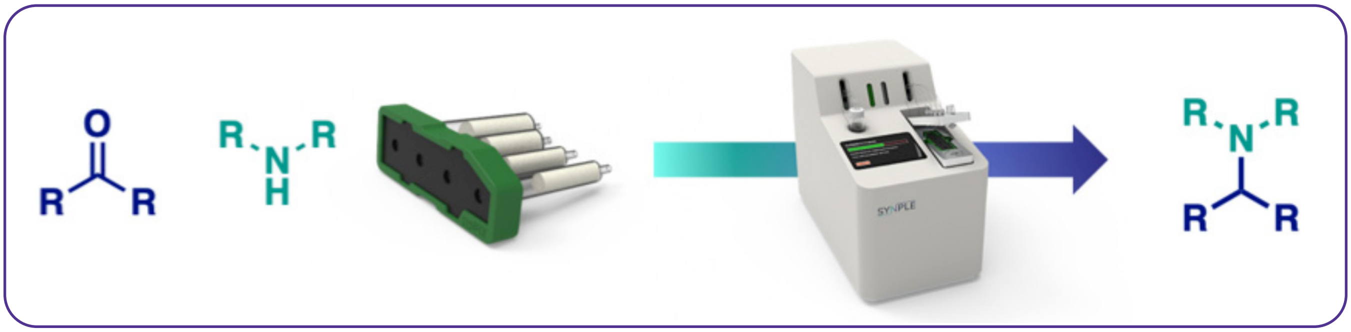

Figure 2: The Synple reductive amination cartridge comes with a reducing agent, proton source, silica, and scavenger, all of which enable the success of the reaction process and subsequent purification. The researcher provides the starting aldehyde or ketone, with an amine being the expected end product.[4]

“The Synple system knows exactly what to do after it scans the reaction cartridge.”

REINALDO JONES, PRINCIPAL SCIENTIST IN PROCESS AND SCALE-UP CHEMISTRY AT EMD SERONO

Reductive amination is fertile ground for chemical modifications, which can be made by tweaking the reaction components and conditions. With the Synple system, each reaction capsule comes with a detailed application note describing the possibilities. The note for automated reductive amination lists the wide range of functional groups that are tolerated during the reaction. Alcohols, phenols, esters, and other groups can be incorporated into the reaction chemistry by changing the starting material and buffering systems to yield amines with a variety of physiochemical properties to meet the end user’s needs.[4]

Take the N-methylation of amines. In this reaction, a methyl group is attached to a nitrogen, creating molecules with applications as polymers, dyes, pharmaceuticals, surfactants, and agrochemicals.[4] To synthesize an N-methylated amine with the Synple reductive amination cartridge, users can simply add formaldehyde to the buffer system.[4]

Steps after synthesis

When the automated synthesis is complete, chemists have a solution containing their product.

“All you need to do is then either carry forward that solution into the next chemical reaction,” Jones says, “or you can concentrate it down to dryness for a solvent switch for your next step or next reaction.”

The machine also runs a self-cleaning operation after each reaction and puts the waste material in a bottle, thereby reducing human contact with it. Jones says such safety enhancements are one of the biggest advantages of automated synthesis.

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CHAPTER 3

Time, money, and risk: The automation equation

90%

A cartridge-based synthesis system can reduce the time required to carry out an organic synthetic chemistry reaction by up to 90% compared with traditional, manual methods

Automated systems have long been used in industrial settings to improve and accelerate processes. The systems can alleviate the burden of mundane or repetitive laboratory tasks, freeing up researchers to focus on innovating and on more interesting projects.[1]

There are a variety of automation systems for synthetic chemistry, each with benefits and drawbacks. Some complex approaches require heavy initial investment and training but may offer a high degree of customization, while less complicated systems have a lower entry point and the potential to democratize automation. Though the cost may give some scientists pause, savings could be significant, depending on a particular laboratory's synthesis needs.

Synthesizing savings

Organic synthesis reactions can be expensive, requiring investments in equipment, reagents, and personnel. Labor represents one of the biggest expenditures when calculating how much a particular reaction costs to run or how much a product costs to make.[2] This is especially true for difficult or tricky reactions, where additional training or highly skilled operators are needed.

The more hands-on time a researcher needs to spend completing a reaction, the more costly it is.[2] Reducing how long it takes a researcher to set up, monitor, and analyze synthesis reactions can translate into savings. Consistency also reduces costs associated with rerunning reactions.

Consider a reductive amination reaction. The cost of the reagents needed to generate up to 0.5 mmol of product is typically between $1 and $10. Add the cost of labor—$110–$215—for setup and execution.[3] That's an estimated total of $111–$226 per reaction. By reducing labor, automated platforms like Synple can lower the outlay for running reactions like reductive amination. The price tag for cartridges and other reagents needed for Synple is $60–$90, and hands-on labor would be about $9—for a total of $69–$100 per reaction.[3]

A cartridge-based synthesis system can reduce the time required to carry out an organic synthetic chemistry reaction by up to 90% compared with traditional, manual methods.[4] This translates to an average cost reduction of 70% per reaction.[4]

Specialized instrumentation often comes with a hefty tab, so savings might seem a far-fetched idea. Some companies have introduced price calculators to help organizations better estimate savings from automating their synthesis process. For example, the Synple Savings

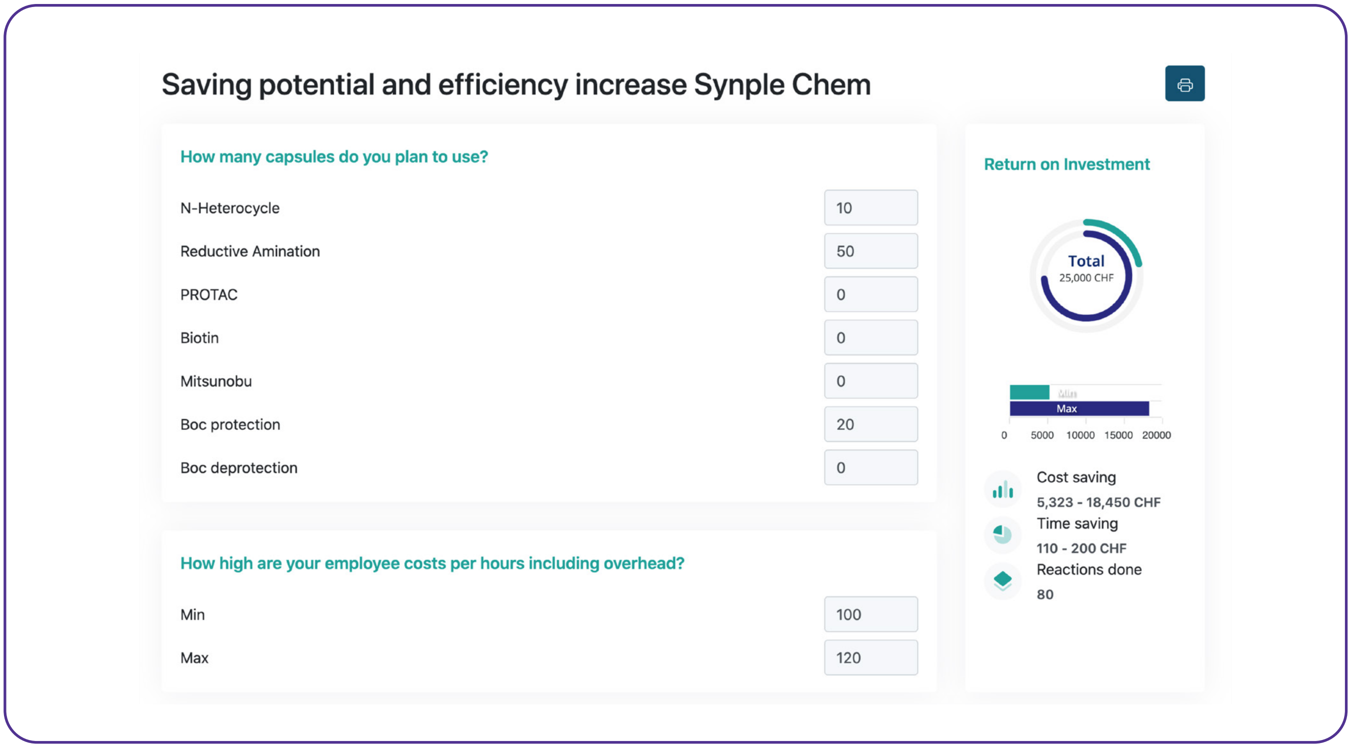

Figure 1: Organizations can use the Synple Savings Simulator to help determine whether adopting Synple would translate into cost savings and efficiency improvements. They specify the number and type of reactions they would be conducting and input labor costs, represented by hourly salary. The software then displays an analysis of return on investment.[4]

Simulator lets users add labor costs and the number of reactions their chemists typically do (figure 1). They can then get a clear picture of whether adopting an automated process will save the laboratory money.

Space constraints

Automated synthesis systems can also help chemical laboratories save on space. Traditional manual organic synthesis processes require specialized glassware, equipment, and setups that vary according to the specific reaction. When conducting multiple reactions, chemists may have to set up separate apparatuses for each.[1]

Automated synthesis platforms employing capsule chemistry typically have a small footprint in the lab, which can be beneficial for chemists dealing with space constraints.[1] For instance, the Synple system can rest on a benchtop or in a fume hood and requires only a power source and a flow of nitrogen.

This trimmer footprint can clear the way for other instruments or workspaces and streamline the overall needs for organic synthesis.

Risk management

Certain reactions involve toxic or hazardous materials that put researchers at risk. Automated synthesis can help reduce risk and ensure workplace safety by allowing researchers to use instruments with self-contained systems.

For example, the compact size of the Synple system means it can fit in a variety of laboratory setups, including fume hoods and benchtops.[4] In addition, the synthesis reaction reagents, purification materials, and solvents are self-contained within the reaction cartridges, the instrument itself, or the solvent bottles, which reduces researchers' exposure to potentially hazardous chemicals.

"There are many types of chemistry that may be hazardous, and the Synple instrument removes the need for researchers to handle these hazardous, very dangerous reagents," says

“By having a simple machine that can automate synthesis, chemists can more easily run the experiments they need to while also completing the other tasks and meetings they have during the day”

BENEDIKT WANNER, SYNPLE CHEM COFOUNDER

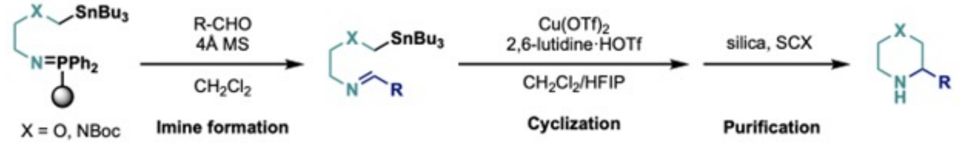

Figure 2: The Synple reaction chemistry for the formation of N-heterocycles consists of four steps, all of which are carried out based on the N-heterocycle reaction cartridge with minimum exposure and hands-on time for researchers.[3]

Reinaldo Jones, principal scientist of process and scale-up chemistry at EMD Serono.

N-heterocycles, which are cyclic molecules composed of at least two atom types and include nitrogen, are some of the most significant structural components in pharmaceutical compounds. An estimated 59% of FDA-approved small-molecule drugs contain an N-heterocycle.[6,7] A common method adopted by the pharmaceutical and biotechnology industries to synthesize N-heterocycles uses SnAP. But that chemistry requires toxic tin reagents, which can be risky to handle.[6]

Automated synthesis platforms can help protect chemists conducting potentially hazardous reactions such as SnAP chemistry. Synple SnAP cartridges contain different reagents, depending on the desired N-heterocycle. In four steps, the Synple instrument can carry out the SnAP reaction, yielding purified N-heterocycle products with minimal operator handling (figure 2).

After each reaction run, the Synple instrument also runs an automated self-cleaning method.[3] All waste is flowed through the instrument to be disposed of in a reservoir, reducing the user’s exposure to potentially dangerous or toxic substances. Labs that are working with such chemicals or reactions may benefit from automated synthesis systems to help ensure chemists’ safety.

Moving forward with automated synthesis

Although automation has made an impact in other areas of research and development, organic synthetic chemiists have not yet felt the widespread benefits.[1,2] Platforms such as Synple aim to change that.

“By having a simple machine that can automate synthesis, chemists can more easily run the experiments they need to while also completing the other tasks and meetings they have during the day,” Synple Chem cofounder Benedikt Wanner says.

As cartridge-based automated systems become more widely available, chemists across the discovery space can use them to bridge the gap between traditional synthesis and more complex, expensive automated synthesis systems, providing a more accessible system.[4]

The range of reactions covered by cartridge-based systems is still limited. Synple now has eight commercially available reagent applications, and Jones says he is excited about future reagent cartridges that will expand the technology’s breadth. Specifically, cartridges for Buchwald and Suzuki reactions are being optimized.

“As more cartridges are introduced, I see much more utilization of this instrument in my labs,” Jones says.

With an automated organic synthesis platform, chemists can pull from the ready-to-use toolbox of reactions to complete synthesis with ease and concentrate on more challenging and interesting aspects of chemistry.

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