Article

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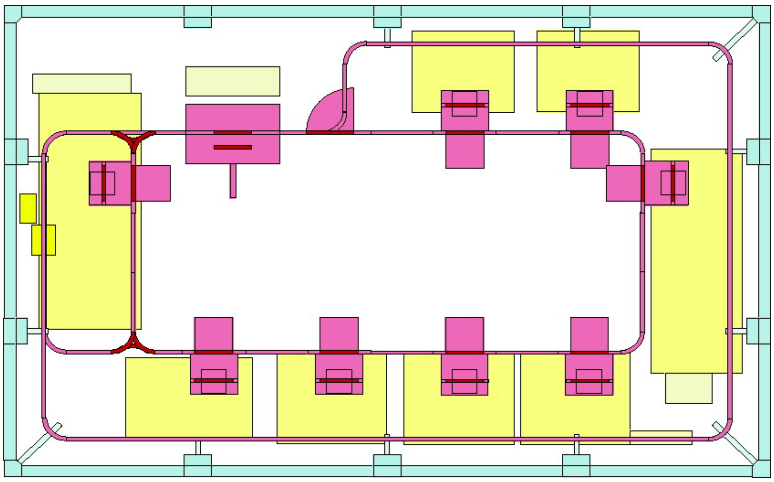

Articles

SynCar: An Approach to Automated Synthesis

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The automation of all aspects of manual solution-phase synthesis into one integrated, efficient, and reliable system could be regarded as something of an unmet challenge in organic chemistry. The requirements for modern solution-phase libraries in mainstream drug discovery is typically 50−250 high-purity compounds on a 10−100-mg scale, whether for target class libraries or lead optimization, and short cycle time in combination with high capacity is critical. To achieve these goals, in a codevelopment between Aventis and Accelab GmbH, Kusterdingen, Germany, we designed a completely novel system of independent workstations connected by a shuttle transfer system produced by Montech, Derendingen, Switzerland. Seven modular workstations process four reactions on each shuttle in parallel, with the ability to perform synthesis (temperature control and liquid reagent handling), filtration, liquid−liquid extraction, evaporation, weighing, solid-phase extraction, and HPLC/MS analysis. The modular design enables the continuous loading of shuttles at any time, and each shuttle can have its own workflow. The design also allows easy expansion for future needs. The result is a combination of high flexibility and high throughput.

Introduction

The value of automated laboratory equipment to enhance output of research synthesis in drug discovery is usually no longer questioned. However, the "right" implementation of automation equipment that is best for libraries to support medicinal chemistry is an ongoing discussion.[1−3] The first automated systems were developed for solid-phase synthesis, initially in the field of peptide chemistry. These techniques were further developed during the gold rush of combinatorial chemistry in the mid- to late 1990s.[4] Driven by the hope of finding the elusive needle in the haystack, that is, active drug substances, huge numbers of compounds of questionable purity, physical properties, and diversity were produced and tested. The often poor hit rate of these early libraries led to a reevaluation of the techniques.[5] Today, libraries tend to be smaller and are designed more carefully using interdisciplinary knowledge from chemists, biologists, and molecular modelers, often focusing on biological target classes and using diversity tools and property calculations. Target-specific libraries are becoming an exciting and potentially powerful tool for lead finding.[6,7] Furthermore, the production of libraries is becoming indispensable for medicinal chemistry projects during the hit and lead optimization phases.[8] More and more, these small libraries are preferentially synthesized in solution phase. For smaller libraries, solution-phase chemistry has an advantage over solid-phase chemistry because it allows a direct use of established chemistry with limited work for process adaptation, more flexible variations (e.g. no linker technology), and the production of higher amounts of material. The disadvantages of solution-phase synthesis come when more complex reaction procedures are required and the difficulties associated with the necessary final purification step. To solve these problems, at the end of the 1990s, several leading pharmaceutical companies set up customized robotic systems, which attempted to integrate solution-phase chemistry reactions, complex workup procedures, analysis, and purification in one single unit. A few ready-to-use and off-the-shelf systems, which go some way to fulfilling the demands of complex chemistry workflows, were offered in the following years; however, the company Chemspeed Ltd., Augst, Switzerland, is at the time of this writing the only remaining vendor for such a system.[9] Today, the main trend in the automation of synthetic solution-phase chemistry in research labs is to invest in small, nonintegrated, and manually loaded benchtop workstations that have a low level of automation, or simple reaction blocks.[3]

We have organized our automated solution-phase synthesis and purification in a specialized unit in Frankfurt, Germany. This unit has three major tasks: first, the development and the synthesis of target class libraries; second, the automated synthesis of libraries to support hit and lead optimization; and third, a purification service by preparative chromatography for the entire medicinal chemistry department. The unit consists of a library development group, the automated synthesis laboratories, and three different chromatography labs that purify samples in the range of from 5 mg to 100 g

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in a high-throughput mode. The library development group bridges the gap between medicinal chemistry and automation by developing and optimizing the chemistry for libraries running on our automated synthesis platforms and also provides the necessary building blocks and scaffolds. We see an advantage in this setup because the staff from each group are highly specialized in their particular roles.

The first automated solution-phase synthesis system in Frankfurt, known as SynRob, consisted of integrated synthesis, workup, analysis, and purification units.[10] It was set up in 1997 and is still in use. The key element is a "humanlike" robot arm, which is movable on six independent rotatable joints on a linear track. The robot performs all manipulations of glassware at the workstations, and the system performs synthesis (temperature control and liquid reagent handling), filtration, liquid−liquid extraction, evaporation, weighing, solid-phase extraction, and HPLC/MS analysis. This system can process batches of 30−50 reactions with identical reaction conditions and identical workup procedures. The average throughput is somewhat limited: ∼3−4 batches (100−200 compounds) per week. The workflow is carried out sequentially, and only one batch can be run at a time (hence, rarely more than one batch per day). But there were other disadvantages as well. Because of the "teamwork" between the workstations and the robot and the complex nonsubdivided software, later hardware and software changes and extensions were difficult to realize. The online preparative HPLC purification was therefore dismantled, and today, the reaction products are transferred to the purification lab for separate HPLC/MS purification.

On the basis of the experiences with the inflexible SynRob system and the need for a significantly higher throughput, we set about designing a new system with a unique concept to meet our specific needs.

Design and Implementation

The following specifications were required for the new system:

- The system should be able to carry out a wide variety of solution-phase syntheses using any workup procedure and have onboard analysis by HPLC/MS.
- The sizes of the glassware and reaction vessels had to be sufficient to yield 20−200 mg/reaction.
- The system should be able to deliver a throughput of a minimum of 100 reactions and workup procedures in a 24-h period and, furthermore, should be able to operate unsupervised for overnight and weekend running.
- One chemical engineer and three technicians should staff the lab in a single shift mode.
- The flexibility of the system should allow the running of samples with different kinds of work procedures at the same time and the addition of new samples with individual workflows at any time while the system is running.
- The hard- and software design should be easily expandable for future needs.
- Whenever possible, the system should consist of robust and proven industrial components.

The experiences from our first system showed that the throughput is very limited if one robotic system is performing all transfer steps *and* the manipulations at the workstations. Although robots on linear tracks and portal robots can reach a high transfer speed, the speed has to be reduced when open tubes with liquids are in transit. The initial idea for the new system was based on the use of a conveyer belt for the transfer tasks, which feeds adjacent, independent, and modular workstations to process the samples. After an evaluation of the commercially available conveyer belt transfer systems, we chose the shuttle transfer system from Montech AG, Derendingen, Switzerland. In contrast to a conveyer belt, this system consists of a track with electrically powered shuttles. The shuttles carrying the samples are moved under software guidance from one working position to another. While the samples are being processed in the workstations, the transfer system is not blocked for subsequent shuttles. Shuttles can be continuously loaded into the system. The Montech shuttle transfer system combined with independent workstations met the most important requirements of our concept, namely, a *flexible, continuous, modular, and expandable* synthesis system.

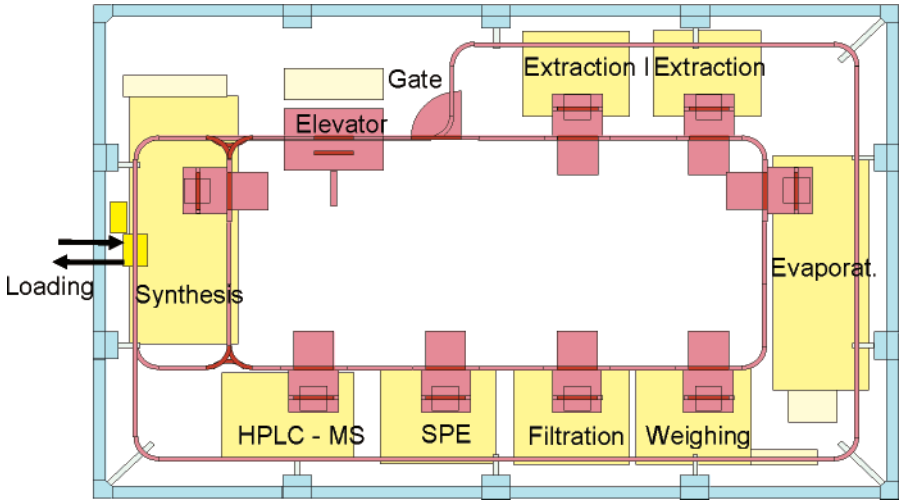
The glassware and reaction tubes were adopted basically unchanged from the old system because of their size and automation-friendly behavior and their common use throughout our chemistry department. These reaction tubes (25 × 140 mm, 25 mL) are sealed with septa and crew caps. Workup procedures are performed in open tubes (40 × 140 mm, 80 mL). Filters are customized and can take a volume of 80 mL. For solid-phase extractions and drying of organic layers after a liquid−liquid extraction, we use commercially available prefilled cartridges.

In general, automated workflows can be divided into two types: sample- and batch-orientated processes. In sample-orientated processes, every single sample can have an individual workflow, whereas in batch-orientated processes, the workflow is the same for a certain number or all of the samples. Usually, batch-orientated processes have a significantly higher throughput if the processing of the samples in the batch takes place in parallel. We decided to place up to four different samples on every shuttle and handle them in parallel at each workstation, since the workstations carry out the rate-limiting procedures. A larger number of reactions can be performed in parallel by linking shuttles in batches of four, and all of these shuttles will have the same workflow. The compromise of this semibatch operation combines individual sample handling and parallel batch-orientated work processes at the same time.

We decided to carry all necessary consumables, such as reaction and workup tubes, filters, and cartridges, for every reaction on the shuttle. Up to eight pieces of consumable hardware can be taken for every sample. This simplifies the engineering, because no glassware, filters, or cartridges have to be kept in stock at the workstations.

The first implementation phase consisted of workstations to handle the synthesis, capping and decapping of reaction tubes, tube weighing, liquid−liquid extraction, filtration, solid-phase extraction, solvent evaporation, and HPLC/MS

Scheme 1. Layout of SynCar, Transfer System (red), Workstations (yellow), Cabin (blue)



analysis. From the beginning, additional space for more workstation modules was planned.

Several specialist companies were addressed to come up with a design study and a hard- and software solution based on our requirements. The concepts were rated in terms of ability, realization, and cost. We finally chose Accelab Laborautomations GmbH, Kusterdingen, Germany,[11] as the main contractor. Their design is shown in Scheme 1.

The detailed design study, including process definitions, engineering layouts, and software architecture, took 6 months. While Accelab began the construction of SynCar in Kusterdingen, including the complete Montech transfer system, we began to build the infrastructure in Frankfurt. The size of the installation and the space needed for preparation work made an extensive reconstruction of lab space necessary, including a huge ventilated carbinet. After the factory acceptance of the Montech transfer system and the synthesis, extraction, capping, and weighing module, the implementation of the system in Frankfurt followed step-by-step. The first test was run ~9 months after placing the order. During the following 12 months, the remaining modules (filtration and solid-phase extraction) were installed, and the software for module control and the master software for the entire system were implemented. It took another 6 months to optimize and debug the software after the first compounds were synthesized on SynCar.

Infrastructure and Transfer System. The SynCar system is housed in a cabinet build by WRT-Laborbau, Stadtlohn (9 × 6 × 3 m), which is equipped with an air conditioned ventilation and exhaust system independent from the surrounding lab area. Furthermore, SynCar is protected with fire detection and extinguishing equipment, which floods the cabin with inert gas in case of an alarm. While the system is in operation, all doors of the cabin are locked. Before an operator may enter the cabinet, the system has to be deactivated. The cabinet is an integral part of the design: parts of the shuttle transfer system are directly mounted on its pillars (Scheme 1).

The key element of SynCar is the Montech shuttle transfer system (Figure 1). This looks rather like a large model railway system, but the system is an industrial component that is found in use in all areas of material flow logistics and production. A contact rail is attached to the track to power the shuttles that are equipped with their own drive; each shuttle can carry a load up to 13 kg and has a radio frequency tag for clear identification. These shuttles transport reaction vessels and all extra glassware needed for the synthesis and workup procedures. The glassware is put into racks, which are loaded onto the shuttles. The so-called shuttle destination control software from FASTEC GmbH, Paderborn, Germany, controls the shuttles individually. This control level makes it possible to request free shuttles and to send them to a particular station. Every shuttle receives its individual processing procedure. For the processing, the shuttles are moved from the track by means of linear bypasses into the stations. After a shuttle is brought into a station, the track is opened again for further shuttles (so the model railway analogy extends even further). All workstations are located around a circular track. Shuttles not part of a process are directed from the working level into a waiting circle. This waiting circle is located on a second circular track in an upper level just beneath the ceiling, and a shuttle elevator connects the two levels. Loading and unloading of the shuttles with racks takes place on a second circle on the lower level. Additional linear bypasses can replace certain parts of the track, and another five stations can be easily added.

Synthesis Module. This module consists of a portal robot as well as eight heating blocks and two cooling blocks, which cover a temperature range from −60 to +200 ° C, sufficient for coverage of most laboratory chemical reactions. The reaction blocks from H+P laboratory technology agitate the reaction mixtures by magnetic stirring. The portal robot is equipped with grippers to move the reaction tubes from the shuttles to the reaction blocks and back. Reagents can be added to the reaction with a pipet needle, which is also part of the portal robot. Up to 96 reagents can be stocked up in 10-mL vials, and three bottles are provided for larger volumes (150 mL). The reagents are managed by an in-house software module, which connects the company reaction databases with the synthesis module software via a CSV table format file. This software module permits multiple accesses

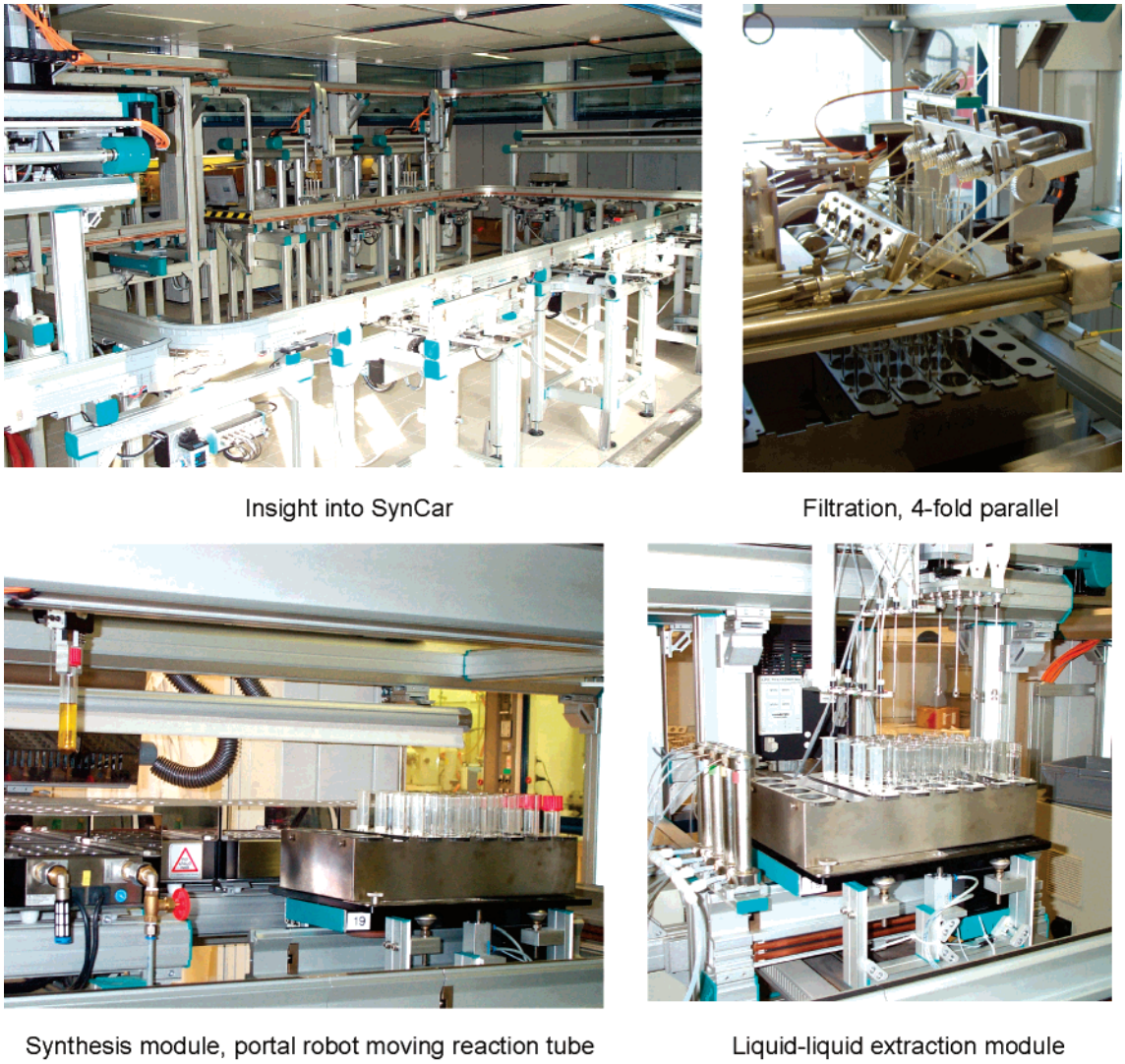


Figure 1. Insight into the SynCar automated synthesis system.

of several reactions to one reagent and also manages the reagent volumes.

Capping and Weighing Module. Different working steps, such as capping and uncapping, removing stirrer bars from the reaction vials, and tare and gross weighing of filters and glass vials, are realized on this module. To remove the lid, the portal robot puts the glass into a mount. The lid is held in place by a pneumatic gripper, and the mount turns the glass. The stirrer bars are removed by a magnetic manifold handled by the portal robot. The Mettler Toledo balance is equipped with a mount that fits all the required types of tubes and filters. The weighing results are transferred from the module control software to the reaction database.

Liquid−Liquid Extraction Module. The module processes four samples in a parallel mode (Figure 1). It is equipped with a stirrer, pipet needles to dispense and aspirate liquids, and a washing station for these tools. All glass tubes stay in their positions on the shuttle while the samples are processed. The tools are mounted on a horizontal axis and can be moved to any position of the rack then moved vertically to the working position. The software allows dispensing and aspirating of solvents and solutions to every tube. The software keeps track of the type and volume of solvent added (aqueous or organic) or removed from a tube and, thus, calculates the volumes required for aspiration and assigns the upper and lower layer; therefore, no phase detection is needed for a phase separation. High-speed stirrers mix the phases. The software is flexible, so virtually any extraction sequence can be set up. All extraction phases can be stored separately for later analysis and recovery. Usually ∼10 min is needed for phase separation. During this time, the shuttle exits the station so that it is free for other shuttles to enter. Because liquid−liquid extraction is the most frequently used and most time-consuming workup method, we implemented this module twice. Waste and wash solutions are collected in a central waste collection system and removed automatically.

Evaporation Module. The module consists of a portal robot, which moves the glass tubes between the shuttle and the evaporators. We implemented two evaporators from Hettich AG, Bäch, Switzerland, which control the heat supply and the vacuum and use orbital shaking to prevent splashing. These evaporators are ideal for use in automated systems because they have a electrically powered lid and a defined stop position for the shaker; therefore, a portal robot can easily carry out loading and unloading. The racks inside each

evaporator are designed to take 20 tubes of the two diameter values that are used in the system. Different volumes and solvents with similar boiling points can be evaporated in parallel. During the evaporation process, the shuttles are sent via the elevator to the upper waiting circle. After a certain time, which is individually adjustable for every sample, the shuttle returns to the module and is loaded with the dried tubes.

Filtration Module. In most reactions, a filtration process is needed to remove solids such as catalysts or salts. In a few cases, precipitated product is filtered off. The module was designed to process four samples in parallel (Figure 1). A portal robot simultaneously places four filters in a mount and four sample tubes in a turning device. The filter mount and turning device are located on a linear moveable bridge. This bridge is moved to a position to enable four destination tubes, which stay in the shuttle rack, to take up the filtrate from the filter. By rotating the turning device, the contents of the tubes are poured into the filter. A spray needle rinses the tubes and the filters, and the filtrate is pressed through the filter by compressed air.

Drying: Solid-Phase Extraction Module. The drying of organic solutions and solid-phase extractions (SPE) have the same hardware requirements, but they need different workflows. In both cases, organic solutions are pumped through prefilled cartridges. To dry organic solutions, ready-to-use cartridges filled with diatomaceous earth are used, and only one tube of dry solution needs to be collected. For SPE, the material in the cartridges usually needs to be preconditioned, so the liquid extracts must be collected in several fractions. The drying/SPE module is again designed for a four-fold parallel process, and the overall design is similar to that of the filtration module. A portal robot places four cartridges simultaneously in a mount, which is located on a linear moveable bridge. This bridge is moved to enable four destination tubes, which stay in the shuttle rack, to take up the eluent from the cartridges. A needle comb, which is handled by the portal robot, as well, aspirates four solutions in parallel. The solutions are sucked up into a loop and then dispensed via a valve switch over the cartridges into tubes in the shuttle rack. The glass and the cartridges are rinsed with solvent and then emptied by compressed air. For SPE, the cartridges can be preconditioned and eluted by up to six different liquids, and the eluents can be collected in several fractions.

Analysis Module. The reaction mixtures and all kinds of collected liquids from the workup procedures can be analyzed by an analytical Agilent HPLC/MS at any step in the workflow. The shuttles are moved via a linear bypass from the transfer system to a Gilson 215 pipet robot, which takes aliquots, dilutes them, and serves as an injector for the HPLC/MS. Three deepwell microtiter plates provide a sufficient capacity to store the aliquots. Communication between the master software and the LC/MS system, management of the microtiter plates, and data reporting are based on customized software from Agilent.

Software. The software design slavishly follows the analogous setup of the modular hardware. The shuttle transfer system and each module has its own computer with independent software control. The master software is located on an additional computer, which controls all the workflows and the shuttle scheduling. Every workstation module has an interface for the export and import of necessary parameters, which are required to process the samples on the workstations. All computers use Microsoft Windows 2000 as an operating system and are connected by a LAN network. Every computer in the system can be manually remote controlled by the PC-Anywhere software from the master PC. This type of software and communication setup is important to keep the system flexible to allow future expansions. In such a case, a new module is registered in the "Planner" software, and a list of handing-over parameters is defined. It is simple to add workstation modules from different vendors without the need for major changes in the master software. Accelab wrote the softwar,e and the user specific high-level workflow commands were implemented in close cooperation with the system operators.

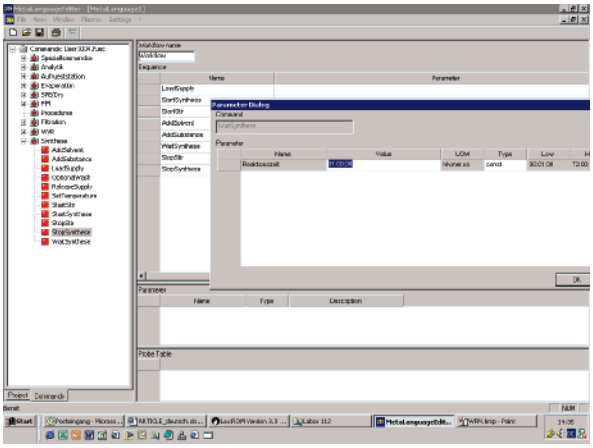


Figure 2. Screen shot of the "Workflow Manager".

Software Architecture. Software architecture on the workstation modules is designed hierarchically from different software modules with independent functionality. The low-level software drivers for hardware components provide the basic communication between the individual functionality of a device, such as opening or closing a balance door, and the control software. On these levels, hardware devices can be addressed manually for maintenance and test reasons. These basic hardware commands are combined with methods, which are used as logical process commands accessible in the normal operation mode. For example, the command "Weigh_Tare": the methods consist of opening the balance door, calibrating the balance, transfer of the tube to the balance, determination of the weight, transmission of the weight to the data table and so on. These logical process commands are the lowest software level visible to the SynCar operator.

The operator creates a workflow for a shuttle by stringing together a list of process commands, using the software tool known as "Workflow Manager". Workflow Manager allows the operator to choose from a list of available process commands, to combine these by drag and drop mouse operations, and to fill the commands with relevant parameters (Figure 2). The Workflow manager provides default parameters and carries out a plausibility check.

The workflows of all registered shuttles are managed and controlled by the scheduling tool "Planner". The Planner module distributes newly started workflows in accordance with the process commands to the workstations. Process times at the different stations are taken into account for every shuttle, and the workflow processes from different shuttles are interleaved. Each time new shuttles are loaded on SynCar and the workflow is registered to the Planner, the whole schedule is recalculated; this affects all previous workflows in the system.

Sample-specific data, which is necessary for the control of the synthesis module, is assigned to the workflow from a table file. The sample table file contains parameters such as reaction educts, pipetting volumes, temperatures, molecular weights, etc. Reagents and synthesis educts are managed by the reagent management database. This tool assigns the reagents to a rack position and keeps track of the volumes of the stock solutions.

SynCar in Use

The automated synthesis system SynCar is most efficiently used to run the final one to a maximum of three sequential reaction steps in the synthesis of a library. Most commonly, the building blocks provided from the library development group are reacted with 10−200 reagents. SynCar is now in routine production mode and achieves a maximum turnover of 120 reactions and workup steps per 24 h, 7 days a week. A staff of three FTEs is needed to provide the system with reagents and solvents for continuous operation, including necessary maintenance work. Loading and unloading is done during regular work hours, and the system runs unattended during nights and into the weekends.

Theoretically, the majority of possible reactions can be translated to SynCar. Of course, in practice, there are robust and general library reactions that are used again and again. These include amide couplings, sulfonyl amide formation, urea formations, reductive aminations, alkylations, Mitsunobu reactions, epoxide openings, nucleophilic aromatic substitutions, multicomponent reactions (Petasis reaction), Suzuki couplings, Buchwald−Hartwig reactions, and other transition metal couplings. In its current format, the system has limitations with chemistry in which gases or solids have to be added during the reaction (e.g., hydrogenations) and all reactions under pressure. An inert atmosphere must be provided manually by displacing the air with argon and subsequent sealing when preparing the reaction vessels. The reaction blocks of the synthesis module are not equipped with a reflux device. We observed that reflux is generally not needed in sealed vessels on a small scale and an accurate external temperature control.

A typical library synthesis on SynCar is described in the following example of a simple amide coupling. In collaboration with the molecular modeling group, the library development group designs the chemical library. The library development group provides the SynCar operators with 10 acid building blocks and a list of 24 amines to react and an ISIS−Base reaction database with the reagents and products. Building blocks are usually prepared in-house, sometimes exclusively synthesized by outside vendors. The amines are requested from the in-house reagent management or are ordered. DMF stock solutions (usually 0.1 M) of the 10 acids, the 24 amines, and the coupling reagents are prepared and placed in the synthesis module.

The database with the 240 reactions is transferred into the SynCar software, and the reaction method is entered with the "Method Manager":

Go to synthesis workstation; reaction block at 20 °C; Stirrer on; add 1 mL acid building block; add 1 mL of coupling reagent; wait 10 min.; add 1 mL amine solution; wait 180 min.; go to decapping station; remove cap; remove stirrer bar; go to filtration station, filter into first workup tube and rinse tube with 5 mL DMF, go to evaporation station; remove DMF from first workup tube; go to liquid−liquid extraction station; add 15 mL 0.5 M citric acid to the first workup tube; extract three times with 10 mL of ethyl acetate, and combine the upper organic layer in a second workup tube; go to weighing station; determine tare weight of third workup tube; go to drying station; transfer organic layer from second workup tube over a drying cartridge into the third workup tube; go to analysis station; take aliquot from first workup tube (aqueous layer) and analyze by HPLC/MS; take aliquot from third workup tube (organic layer) and analyze by HPLC/MS; go to evaporation station; remove ethyl acetate from third workup tube; go to weighing station; determine gross weight of third workup tube; go to waiting circle and wait for unloading.

The shuttles are loaded with the shuttle racks, which are equipped for each reaction with empty, capped 24-mm reaction tubes, three 40-mm workup tubes, the filter, and the drying cartridge. Four reactions are assigned to one shuttle from the reaction database when it is loaded into the system, and the shuttle is started. After the shuttles have finished the method described above, the operator orders them from the waiting circle to the unloading station. The shuttle racks with the used glassware and the product are removed. The operator checks the LC/MS analysis from the aqueous and organic layers. The tubes containing product are labeled with barcodes and collected in a rack. Together with the LC/MS analysis, the products are registered in our in-house chromatography database and handed over to the final purification team. The final purification team purifies every sample on preparative HPLC/MS systems and delivers products that fulfill the company purity criteria as solid compounds in 4-mL bar-coded vials to the compound collection. In addition, the analytical department characterizes every compound delivered by the final purification team by both LC/MS and ^{1}H NMR.

The synthesis and workup of the described 240-member library would typically take ∼48 h for processing on SynCar. It takes another 7−10 days to get the samples through purification, including freeze-drying, analysis, bottling, registration, and submitting. A success rate of 80−95% for this chemistry, in terms of final compound submission, would be expected. Primarily, the success of the library synthesis depends on the efficiency of the chemical reaction and the reactivity and diversity of the building blocks. For new chemistry, test reactions with a small but representative set of building blocks prior to the start of SynCar are essential

for a successful outcome. The workup procedures are extremely reliable, and only an insignificant number of samples is lost because of unexpected behavior, such as precipitation, etc. The workup modules are designed for maximum robustness; e.g., reaction mixtures are poured into the filters rather than transfered by needle-based liquid handling.

The error rate of the hardware and software has decreased throughout the time SynCar has been in use. Today, mechanical failures are mostly caused by natural wear and tear (e.g., worn-out rubber coatings on grippers), which can be minimized by regularly maintenance. If a workstation malfunctions, all shuttles continue their specified procedure until this point. The workflow can then be continued after manual intervention. Software errors have become very rare too, but with complex software, the possibility can never be ruled out.

Conclusion

To our knowledge, the use of an industrial transfer system with adjacent modular workstations in an automated research synthesis system has not been attempted before. The system was a huge design and engineering challenge, which took some time to come to fruition. The project would not have been possible without a group of dedicated experts and farsighted support from management. It has been fully operational for some time and has truly fulfilled the expectations we had of it. We are planning to extend the functionality of SynCar by implementing a microwave synthesis station as an additional module. The ease with which this can be done is testimony to the flexibility of the design. The advantages of the original concept can be confirmed: high flexibility, semiparallel processes to allow continuous working, and expandable hardware and software all help to ensuring reliable high-throughput synthesis, workup, and evaporation. The combination of high throughput and flexibility allows many applications, from larger lead generation libraries to smaller optimization libraries with sufficient material for early in vitro studies and the ability to perform an almost infinite array of possible reactions.

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