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Organic Synthesis: March of the Machines

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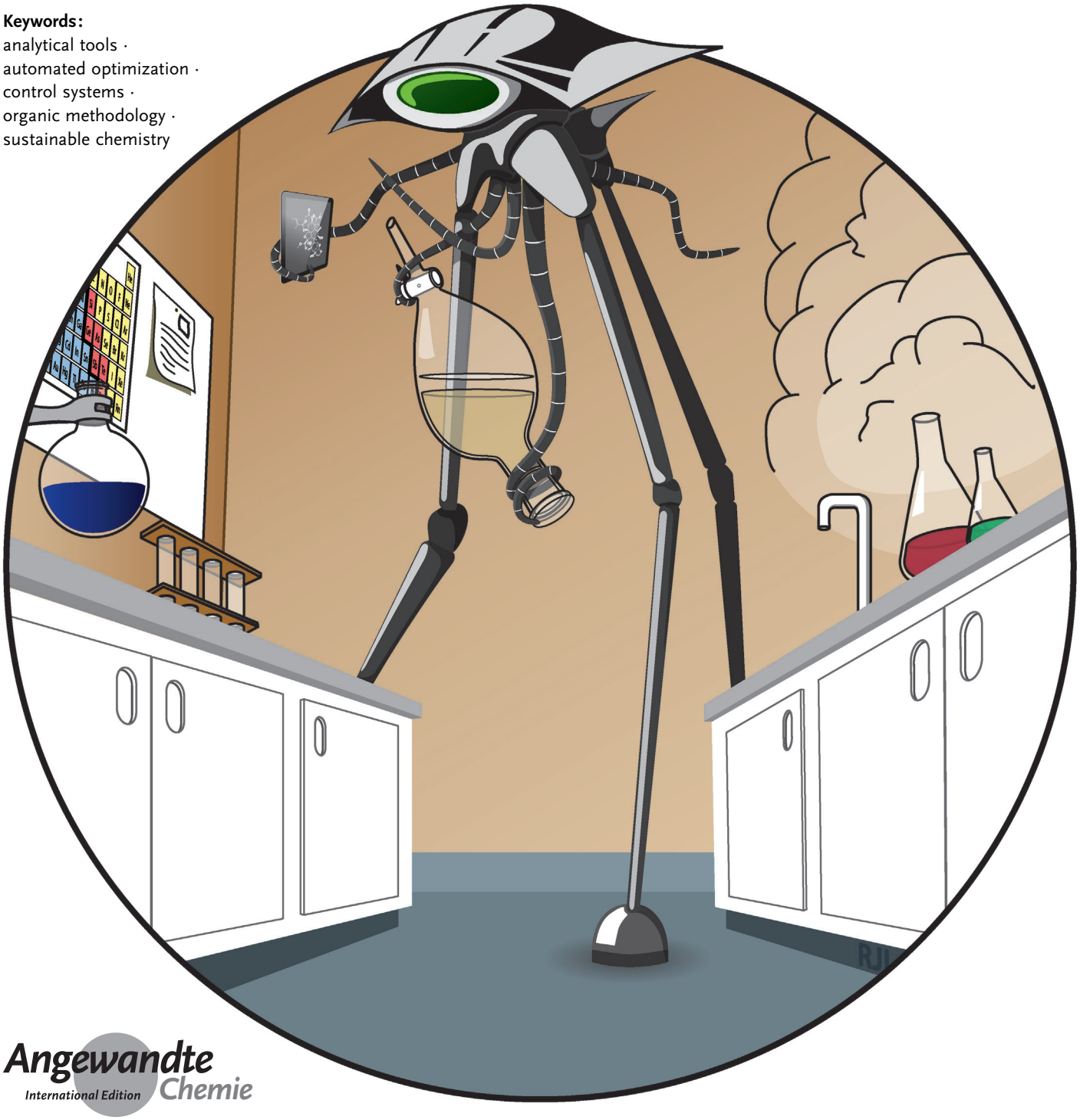

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Organic synthesis is changing; in a world where budgets are constrained and the environmental impacts of practice are scrutinized, it is increasingly recognized that the efficient use of human resource is just as important as material use. New technologies and machines have found use as methods for transforming the way we work, addressing these issues encountered in research laboratories by enabling chemists to adopt a more holistic systems approach in their work. Modern developments in this area promote a multi-disciplinary approach and work is more efficient as a result. This Review focuses on the concepts, procedures and methods that have far-reaching implications in the chemistry world. Technologies have been grouped as topics of opportunity and their recent applications in innovative research laboratories are described.

From the Contents

1. Introduction

We are pleased to contribute this article in celebration of the 150th anniversary of BASF under its new "*We create chemistry*" tagline.[1] This people-focused strategy embodies the power of modern chemistry in delivering Society's needs. It reflects the rich history of BASF and its belief that chemistry will continue to be an enabler of innovation and new ideas in response to future challenges. This will hopefully drive a creative agenda which will lead to new thinking, new strategies, and new tools for innovation and discovery—for the benefit of all. Indeed, one can argue that fantasy will fuel innovation.

It would seem timely, therefore, to have been invited to comment on the current state of the art of molecular assembly of our functional materials since today more than ever the dogmas of organic synthesis are being challenged. No longer do we slavishly accept the guidelines of reactivity and functional group compatibility instilled in our training; rather, we seek to explore new reactivities and technologies. These enhance our science and aid our planning of synthesis programs, opening up undreamt opportunities. We should not ignore, however, the truly phenomenal advances of the last 150 years, in terms of fundamental understanding, methods development, molecular complexity and function, and analytical capability. This can be readily measured by the economic success of modern materials and also by the levels of performance that they achieve in application. We now have to hand a truly impressive array of robust chemical processes capable of providing new bonds, controlling stereochemical features, and introducing diverse functionality by design. Yet we must not forget that all of this activity comes at a cost to our planet's resources. The future holds enormous challenges for sustainable manufacturing, healthcare provision, lifestyle management, smarter energy solutions and guaranteeing the security and quality of our food. The green agenda and the recognition that our precious metals footprint is as important as our carbon footprint have become significant new areas of responsibility.

Organic synthesis is at the heart of many molecular assembly processes, but we need to recognize that the flexible, rapidly changing and creative environment of a research laboratory is very different to the exacting demands of the process scale-up and manufacturing world; chemistry is a common theme that crosses these boundaries.

In this Review we shall highlight some of the issues encountered mainly in today's research laboratories, particularly from a reaction support point-of-view. We will then dare to suggest improvements, emanating from the fields of engineering and informatics, that can be made by employing a machine-assisted approach to transform the way we work. While we should be proud of our previous achievements, there are still of course many deficiencies in our current synthesis practices. Not least of these is the fact that it takes many years (and resources) to impart the required skills and knowledge into a synthesis chemist by training. Yet too often we waste these talents on menial tasks such as setting up or cleaning apparatus, routine reaction optimization, repetition of trivial experiments, and scaling-up of well established procedures. The list goes on.

For batch reactions, we still use large quantities of glassware in a wide range of sizes and that are often dispersed across our laboratories. In spite of our modern world, much of this apparatus has not changed significantly over the last century. We can still recognize the round-bottomed flasks, distillation columns, separating funnels and test tubes of the past, which continue to serve us well.

It is true that the general research laboratory infrastructure has improved enormously and we now have expensive (but often underutilized) facilities containing advanced equipment for heating (microwaves for example), separation and analysis. Effective ventilation, worker safety and comfort are also essential components of any modern

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laboratory. Nevertheless, it is still a very labor intensive environment. It can also be very territorial in character, which reflects the rigidity in our training. We tend to buy and store many more chemicals than we actually need for a specific purpose. Variation in experimental techniques can lead to lack of process robustness, especially during reaction scale-up. Repetitive and long reaction optimization sequences lead to levels of redundancy and general wastage—especially of the human resource. Therefore there is an anticipation that you must taste failure before you can experience success, and that discovery is rarely perfect first time round.

Whilst we may argue that our research laboratories should not always be constrained by their "green credentials", in an increasingly resource-conscious world, our consideration for the principles of "green chemistry" is an important component of our public image, and we must hold ourselves responsible for safeguarding the environment for future generations. It is safe to say that we still have much work to do in this area. For instance there is a tendency to choose solvents only based on their effect on the yield, and in the research environment solvents are rarely recovered and recycled. Similarly, in our desire for speed in a target-focused discovery process, little emphasis is placed on the cost of reagents (both financial and environmental) or on processes for their regeneration and reuse.

Although the uptake of electronic laboratory notebooks (ELNs) is now more common, the amount of data that is actually collected and then fully evaluated is still relatively small. Little use is made of the "cloud" or of new concepts such as neural networks to handle big data collection. Knowledge sharing is very fragmented and there is often an over-protective culture that inhibits scientific advancement. One particular area gaining traction is how the failed experiment can reveal important facts and yet these are not commonly shared.

Much of what we do in our laboratories today involves the application of standard procedures or recipes when in fact we would like more time to make discoveries and vastly improve our productivity. For these many reasons we believe the time is right to move towards a more machine-assisted approach to synthesis to greatly improve the way we work.

This Review brings together some of the concepts, procedures and methods that can aid this process and maybe even accelerate the change. These are listed as topics of opportunity, rather than being presented in any chronological order. We have also focused, where appropriate, on flow chemical methods of synthesis since we see wide-ranging advantages by applying these methods.

We have not focused on reactor technology as this area has been well documented on many occasions. Reviews for supercritical fluid,[2] photochemical,[3] electrochemical,[4] extreme temperature,[5] enzymatic[6] and slurry[7] reactors provide excellent overviews of how machines are helping to transform research in these areas.

2. Computation and Visualization

We begin with computational methods and visualization techniques. The term "machine-assisted" when used in an organic synthesis context is not limited to describing those devices which play a direct role in the creation of molecules at the bench. The community is now beginning to take advantage of increasingly powerful computing resources to

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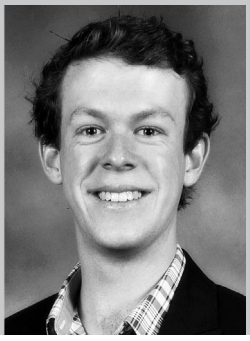
Richard Ingham completed his undergraduate degree in Natural Sciences at the University of Cambridge, working on natural product synthesis for his master's project. He then spent six months working on flow synthesis at Cyclofluidic Ltd, before returning to Cambridge in 2010 to work under Professor Steven Ley in the Innovative Technology Centre (ITC). His Ph.D. research focused on the integration of software and technologies for performing multi-step synthesis under flow conditions.



Daniel Fitzpatrick completed a BE in Chemical and Materials Engineering at the University of Auckland in 2012. In the same year he was awarded a Woolf Fisher Scholarship enabling him to begin Ph.D. studies at the University of Cambridge in October 2013 under the supervision of Professor Steven Ley. His research is focused on bridging chemistry with chemical engineering, with attention given to advanced control systems and separation techniques.

Rebecca Myers obtained her first degree in Chemistry at Imperial College (1994–97). She followed this with a Ph.D. in Organic Chemistry at the University of Cambridge under the supervision of Prof. Chris Abell (1997–2001). She joined the Ley group as a postdoctoral researcher in 2004 and was promoted to Senior Research Associate in 2010. She is also Associate Director of the Cambridge Ph.D. Training Program in Chemical Biology and Molecular Medicine.

help shape and modify chosen synthetic routes *before* experimentation takes place.

In research environments where budgets are increasingly constrained and the environmental impacts of chemical practice are being scrutinized more closely, the efficient use of people and materials is of utmost importance. The use of computational methods has been shown to mitigate these concerns by enabling researchers to obtain initial guiding results in silico prior to conducting any experiments. A recent review highlighted a number of applications of quantum chemical predictions that led to improved organic syntheses.[8] Examples described include the prediction of regioselectivity in novel chemical systems, the selection of substrates favoring the formation of various products, the design of new catalysts and even the prediction of reaction outcomes for new processes.

Most computation tools and algorithms are demonstrated on reactions under narrow constraints and involve a high degree of operational intricacy. For a chemist without a background in computational chemistry such complexity can be daunting, thereby limiting the uptake of what can be considerable time-saving tools. In a step towards the simplification of these processes, a tool that can predict reaction mechanisms and hence product outcomes from generalized inputs has been reported.[9] From user-supplied compound and reaction condition information, the system combines approximations of molecular orbital interactions and machine learning to rank a list of potential reaction mechanisms and products in order of most likely formation. It was demonstrated for both single- and multi-step reactions and was shown to produce reasonably accurate predictions (correct in nearly 90% of cases) across a variety of test reactions. It is easy to see how such a system could be transformative for retrosynthetic planning.

Significant time is spent during traditional drug screening and development programs on testing biological responses induced by a library of compounds. In traditional screening methods, compounds are tested against a variety of biological targets, and in the vast majority of cases no or very low responses are detected. A recent study adopted a different approach.[10] Following the optimization of reaction conditions, a library of 12 imidazopyridines was synthesized using a microfluidic platform combining reactor control and reagent addition with a software control system. Gaussian process regression models were then used to select 41 potential biological targets for these compounds from which five were selected for further testing based on potential pharmaceutical interest and assay availability. For the seven ligands that had favorable predicted computational results, assays were performed with results showing that 71% of the combinations had their predicted activities. These selected compounds all qualified as lead structure candidates for further drug development programs.

Computing resources do not necessarily have to be targeted at applications involving intensive theoretical calculations. Online tools such as the SciFinder and Reaxys databases are used throughout the research community, providing an easy and rapid method for chemists to search extremely large chemical datasets. Another recent review describes these tools, among others, and their uses in the practical organic chemistry context with particular attention given to synthesis planning, reaction prediction and reaction feasibility.[11]

Yet despite these successes theoretical computation is not in widespread use in organic chemistry laboratories during the planning stages of synthesis. This is due partly to the lack of trust in the techniques and the inability to interpret results for those without a background in computation. While some tools exist that simplify results (such as those described above), we believe that more comprehensive systems are required for chemists to truly appreciate their potential, especially when visualizing how molecules interact. Indeed augmented reality is emerging into our day-to-day activities, with devices such as Google Glass moving into our laboratories. We envisage that these tools will enhance the research environment, as they have already in education.[12] Three-dimensional simulation tools to propagate scientific information are already widely used in other research sectors such as biology;[13] the use of augmented reality in chemistry is bound to follow.

3. Downstream Processing

The most common reaction work-up procedures use standard equipment such as glass separating funnels and rotary evaporators. The tools developed for these tasks have not changed in any significant way for decades, despite being used on a daily basis by research chemists.

This stagnation in the area of downstream processing is now being seriously scrutinized as part of the recent growth of interest in machine-assisted chemistry and the development of machine-assisted workup tools. The use of these tools is particularly relevant for continuous multi-step reactions. These areas are thus strongly dependent on the development of innovative equipment.

3.1. In-line Evaporation and Solvent Switching

When designing reactor systems that pass products from one reactor directly to the next, one of the major considerations that must be taken into account is solvent compatibility between the steps. In ideal situations, the solvent and reagent concentration would not need to change, in which case no separate processing is required to produce a telescoped sequence. However this is generally not possible and reactions requiring a solvent switch have historically necessitated a time-consuming, manual intervention between stages.

A prototype in-line evaporation device has therefore been developed that overcomes this issue.[14] Constructed using a glass column and Swagelok fittings commonly found in flow chemistry laboratories (Figure 1), the device acts as a spray drier for an incoming liquid stream. During operation a fine dispersion of solution is nebulized by a gaseous stream (usually N_2) at an elevated temperature causing the partial evaporation of solvent and the concentration of remaining

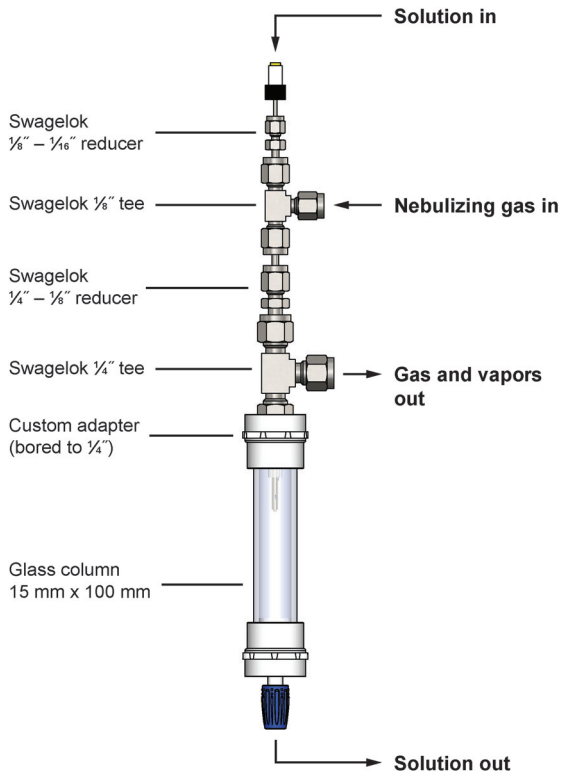


Figure 1. Spray drier constructed from common laboratory parts. The input solution stream was nebulized into a fine aerosol by a gas stream inside the glass column. Any solution that accumulates inside the column was removed by means of a peristaltic pump.

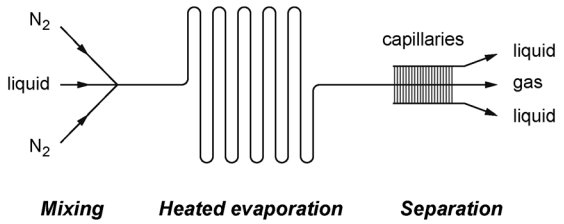


Figure 2. The three-stage microfluidic evaporation device used for solvent switching. An annular biphasic flow stream was heated inside a serpentine evaporation channel before capillaries effected gas–liquid separation.

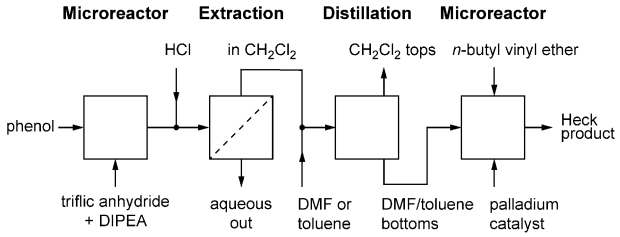


Figure 3. A telescoped, four-stage microreactor system for the preparation of a Heck product. This process incorporated two reaction stages, extraction and distillation.

solution. A notable advantage of this process is that the gaseous stream leaving the device can be passed through a condenser to recover evaporated solvent, ready for recycling.

By mixing an additional solvent with the incoming liquid stream, it was possible to manipulate the relative levels of solvent evaporation in the fluid spray in such a way as to preferentially evaporate the original solvent over that which was added. In other words, it was possible to switch solution solvents in a continuous manner by taking advantage of differences in their volatilities. This was demonstrated in the flow synthesis of Meclinertant (SR48692),[14] in which methanol replaced toluene between two reaction stages which had previously required solvents to be exchanged manually.

A similar evaporation process has also been demonstrated on a microfluidic scale.[15] Here a glass microchip was designed incorporating three distinct stages so as to effect selective solvent evaporation from a water/acetonitrile solution stream (Figure 2). In the initial stage two gaseous N_2 streams were injected into the liquid stream, producing an annular pattern within the flow channel. This biphasic stream then entered a heated channel inducing evaporation (second stage) before finally passing into the final stage in which the liquid was separated from the gas through side capillaries. In an example operation of this device, it was possible to reduce the acetonitrile component in the mixture from 50 wt% to 1 wt% in a matter of seconds with a liquid flow rate of 20–30 $\mu L\,min^{-1}$.

In another microfluidic process, distillation was utilized to achieve a solvent switch in a telescoped chip-based reaction system for the preparation of a Heck product.[16] This integrated process was comprised of four distinct stages each on a separate microchip (Figure 3): an aryl triflate synthesis step, carried out by reacting phenol with triflic anhydride in the presence of *N*,*N*-diisopropylethylamine (DIPEA); a membrane-based liquid–liquid extraction stage, taking the product mixture (in dichloromethane, DCM) from the first stage and mixing it with aqueous HCl to produce segmented flow in a microchannel before separating these two phases; a distillation process in which the DCM within the triflate-containing solution was exchanged for either dimethylformamide (DMF) or toluene; and finally a reaction segment where the resulting solution was reacted with *n*-butyl vinyl ether using a palladium catalyst.

The distillation process was conducted at 70 °C, specifically above the boiling point of DCM but below that of DMF and toluene. Under these conditions, the DCM was vaporized selectively while the triflate product remained in the liquid phase. A separation of gas and liquid at the end of the distillation chip was effected through the use of a polytetrafluoroethylene (PTFE) membrane, through which only the liquid stream passed. The overall process also incorporated proportional–integral–derivative (PID) controllers in order to regulate temperatures of the reaction stages and the distillation step. A similar membrane-based device has been used[17] to vent unwanted gases from a flow stream following a hydrogenation process carried out in a semipermeable, tube-in-tube gas reactor.

3.2. Extraction and Liquid–Liquid Separation

One of the more common work-up procedures carried out in laboratories is aqueous washing, extraction and subsequent liquid–liquid separation of product mixtures. This process also happens to be one of the most manually labor intensive processes. It is not surprising therefore that effort has gone into the development of machine-assisted platforms to automate such a routine task.

Using a combination of machine vision, pumps and self-developed open-source software control, a prototype process to effect continuous liquid–liquid extraction and separation has been reported.[18] In it, a lighter phase was vigorously mixed with a heavier phase before entering a chamber which housed a colored plastic float. At steady state, this float rested at the interface of the phases thus acting to demarcate relative fluid heights. A webcam continuously monitored the location of this float, sending position information back to a control system which adjusted pump flow rates of solutions leaving the column to ensure that phase levels remained within set limits and separation is achieved.

For example, the utility of this device was demonstrated during the flow preparation of hydrazones (Figure 4). A

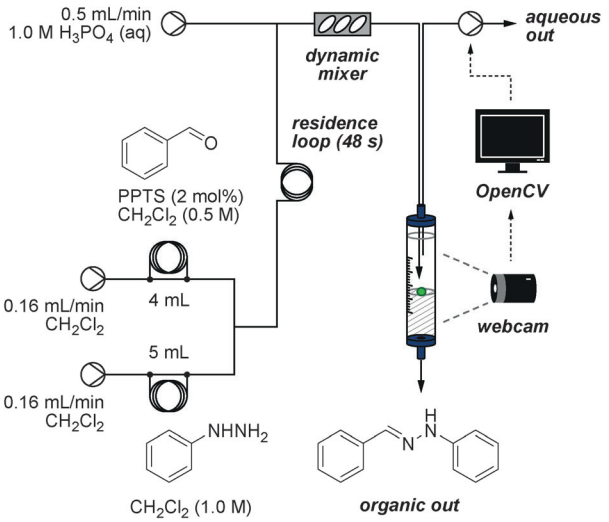


Figure 4. Automated liquid–liquid extractor which exploits the use of a webcam for phase boundary detection. An aqueous/organic biphasic mixture was agitated before being pumped into a glass column in which the position of a colored float marking the interphase boundary was used to adjust pump flow rates.

precursor solution containing benzaldehyde and pyridinium toluenesulfonate (PPTS) in DCM was reacted with a second solution of phenylhydrazine in DCM in a flow coil before being mixed with an aqueous solution containing phosphoric acid in a T-piece. An in-line mixer containing magnetic stirrer bars was placed after this junction to ensure that the two phases mixed completely. The resulting biphasic mixture was then pumped into a glass column containing the plastic float, the location of which was used to control the height of the interphase boundary. This process removed the need to perform manual extraction and its utility has been exploited in a number of additional studies.[19,20]

A different approach was taken in another study during the development of a static liquid–liquid separator.[21] In this device an aqueous/organic biphasic liquid stream was pumped tangentially to a hydrophobic membrane (Figure 5); the

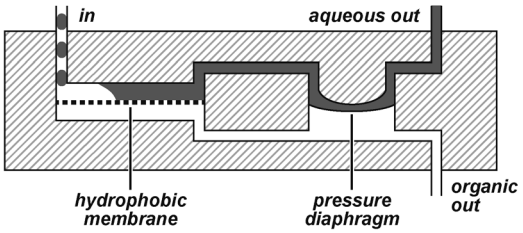


Figure 5. A hydrophobic membrane used for phase separation. The organic component of a biphasic stream passed through the membrane while the aqueous component did not.

organic phase passed through the membrane while the aqueous phase did not. An integrated pressure-control diaphragm maintained the required transmembrane conditions to promote a stable separation operation. The authors demonstrated the utility of this device in a counter current extraction process in addition to a solvent switching experiment. It has also been used in another study investigating the continuous synthesis of 3,3,3-trifluoromethylpropenes, in which it facilitated two aqueous/organic separations.[22]

Membranes have also been utilized to facilitate biphasic separation. Recently we used a simple commercially available membrane separator enabled liquid–liquid separation in a key step in the synthesis of Meclinertant (SR48692).[23] Much earlier in 2007 we were the first to report the use of the FLEXX membrane separator in the synthesis of allylic ethers using our bespoke parallel microcapillary flow disk reactor.[24] We later used this device on four separate occasions in the more sophisticated multi-step flow synthesis of the spirocyclic polyketides spirangien and spirodienal.[25]

3.3. Chromatography

The chromatographic separation of reaction mixtures is another labor intensive process that arises during day-to-day synthesis activities. Numerous automated tools have been developed to automate this time-consuming task and reduce the burden on researchers when isolating products.[26] Nevertheless, many fully telescoped synthesis processes are hampered by a requirement to carry out a manual chromatographic separation between steps.[25]

An in-line simulated moving bed chromatography (SMBC) system has been developed that was showcased in a study in which it was used to separate a reaction mixture immediately following a flow reactor.[27] SMBC processes utilize switching valves and multiple chromatography columns (usually four or more) to induce what is effectively a counter-current movement of the stationary and mobile phases. By doing so it is possible to separate multicomponent

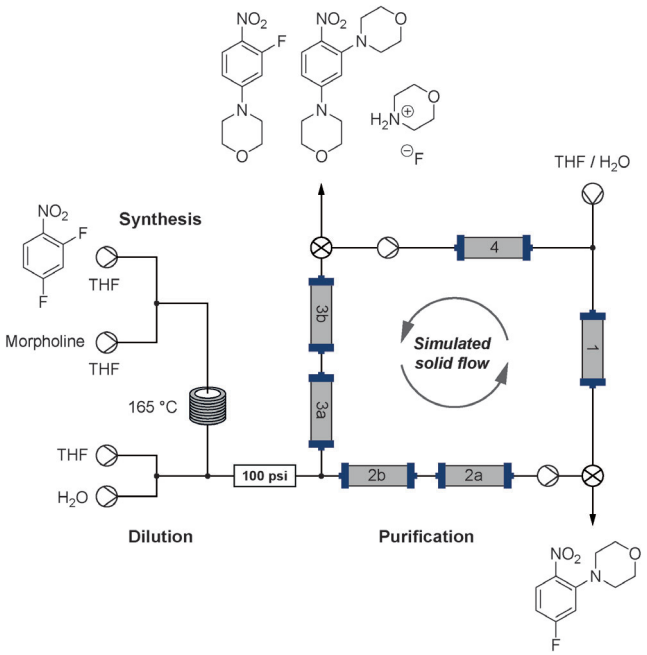


Figure 6. A six-column SMBC system coupled with a flow reactor to continuously purify the reactor's output stream. An in-line dilution system was used to prepare the product mixture prior to injection.

mixtures into two groups, one of which will consist of only the product of interest. Their system was demonstrated using the substitution reaction between 2,4-difluoronitrobenzene and morpholine which yields a mixture of four products (Figure 6). The crude product mixture, taken directly from the back-end of a Vapourtec R2/R4 flow reactor system, was diluted with THF and water before being injected into the SMBC unit. 89% of the *ortho*-2 product of interest was isolated with a purity of >99%. Since this purification was achieved in a continuous manner, the output could then be used directly in subsequent reaction processes.

SMBC systems clearly have great potential for in-line purification; however, currently available systems are limited to selecting either the most strongly or weakly retained component of a mixture. Therefore more development is required before SMBC can become a truly universal solution.

3.4. Crystallization

In a recent publication the application of a continuous crystallization process was described as applied to pharmaceutical production.[28] Two crystallization steps were combined with process analytical technology (PAT) tools to recover the product of interest which was then delivered to additional downstream processes. It was possible to operate the full process continuously for long periods, with the recovery of over 90% product (of >99% purity) demonstrated. This study was part of a larger investigation, which is described in more detail in Section 5.3.

3.5. In-Line Filtration

During reactions that involve precipitation, it is usually necessary to separate a solid from a liquid before any additional steps can be carried out. There are two desired outcomes that can arise when designing filtration processes: collection of solid (filter cake residue) or collection of liquid (filtrate).

In one of our recent studies, in which a fully automated telescoping of a six-stage chemical process was achieved (as described in more detail in Section 5.3), waste salts formed during an acid quench step needed to be removed before the product solution could be progressed to the next step.[20] This was achieved through the use of a rotating sintered glass disk onto which the slurry was pumped (Figure 7a). A PTFE scraper attachment was used to remove solids which accumulated on top of the disk, while solution was able to pass through. The rotation of this disk was controlled using a servo

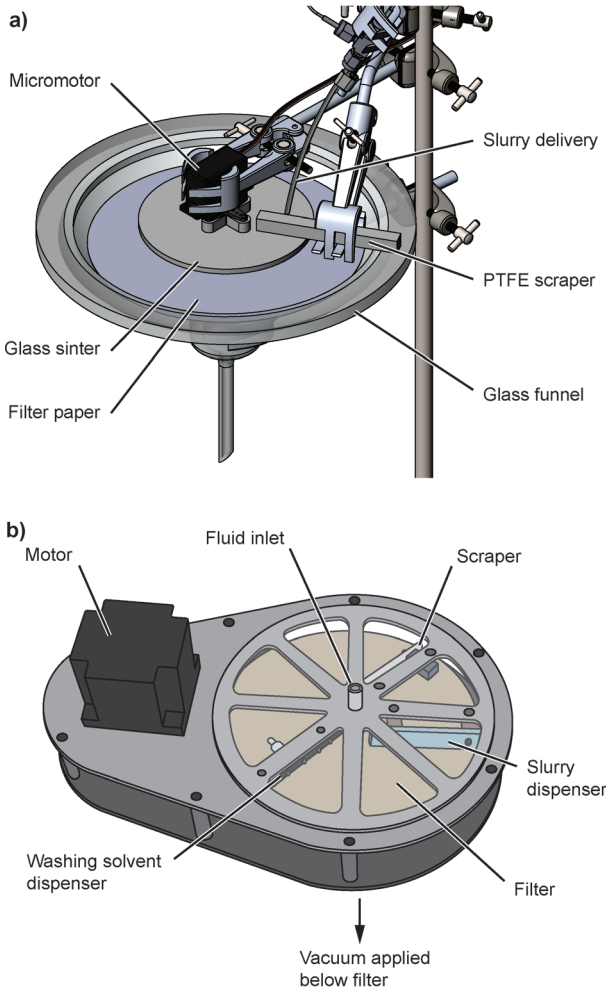


Figure 7. a) Rotating sintered glass filter system for liquid collection. Solids that accumulated on the top of the sinter were removed by a PTFE scraper arm onto replaceable filter paper. Liquids passed through and were pumped to downstream processes; b) vacuum-assisted filter used for the collection of solids. The collected filtrate was sent to waste while the filter cake was continuously removed and used in downstream processes.

motor connected to an open-source Arduino controller. This system enabled the complete removal of solids from the inlet stream, while ensuring that solution losses were eliminated.

Following the crystallization steps in the process described above, the slurry was processed using a vacuum supported filtration device.[29] In this case the aim of the system was to collect solids for downstream steps (Figure 7b). The overall process contained two such of these filtration units, following the two crystallization processes.

3.6. Free-Flow Electrophoresis

The integration of bespoke reaction equipment with downstream processing for more niche applications was demonstrated recently.[30] The authors devised a continuous microfluidic system (Figure 8) in which *ortho*-phthalaldehyde

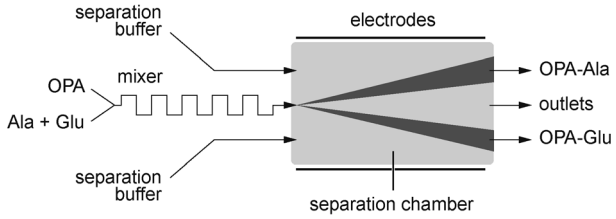


Figure 8. A microchip incorporating free-flow electrophoresis used to separate a product mixture containing OPA-Ala and OPA-Glu. Differences between product surface charges led to segregation when the stream was passed through an electric field.

(OPA) was reacted with a mixture of alanine (Ala) and glutamic acid (Glu) to form a binary product mixture consisting of OPA-Ala and OPA-Glu.

Free-flow electrophoresis is a separation technique that exploits differences in distribution of charge over the surface of product compounds, resulting in component segregation when passing the mixtures through an electric field. By placing electrodes on either side of a channeled pathway following the reactor, the team was able to separate this product mixture into its constituent components. The flow of streams was monitored using UV fluorescence and excellent separation was achieved.

4. Analytical Tools

There are many new advances in the area of analytical tools for sample characterization and thus a large number of publications in this area. As we talk in detail about computer-controlled automation later in this Review (refer to Sections 5.2 and 5.3), the discussion here is limited to those devices which were used in conjunction with some form of machine-assisted process and have provided a means by which to improve the way a particular synthesis procedure was conducted.

4.1. Infrared Spectroscopy

Our group particularly has been at the forefront of integrating IR analytical tools into chemical transformation processes. With Mettler-Toledo, we developed a flow cell for their ReactIR detector[31] that was eventually commercialized as a separate device named the FlowIR.

For multi-step flow syntheses operating under plug flow, the effects of dispersion make it difficult to predict exact concentration profiles of reagents and products in downstream processes, thus making the addition of further flow streams inaccurate. We approached this problem during the synthesis of an olefinic piperidine δ-opioid receptor agonist by employing the FTIR spectrometer as a switch to control a pump which delivered a downstream reagent.[32] The output stream from the second reaction step passed through the IR spectrometer, and when the desired product was detected the pump supplying the reagent for the third step was switched on. Through the use of this enabling technology in conjunction with solid-supported scavengers, it was possible to raise the previously reported batch synthesis yield from 6% to 35% under the new flow procedure.

However, the use of UV or IR detectors as simple on/off switches for downstream reagent pumps (Figure 9a) leads to

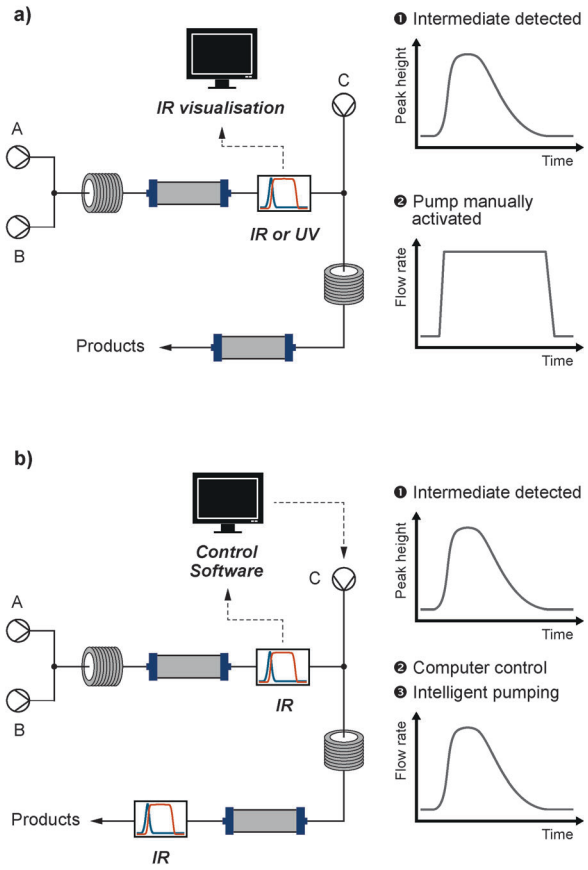


Figure 9. a) The use of a detector as a manual on–off switch leads to significant material waste and imprecise stoichiometric control. b) By adjusting the downstream pump flow rate based on detector signal using a computer control system, it was possible to precisely control stoichiometry and reduce excess material consumption.

considerable wastage of what may be expensive, toxic or hazardous materials. Therefore we adopted a more intelligent approach whereby the flow rate of a downstream reagent pump was adjusted in real-time based on concentration measurements (Figure 9b).[33] A computer control system developed in LabVIEW[34] used peak height data provided by the IR detector to set the flow rate of a third pump accordingly; this was adjusted to be proportional to the detector response, greatly reducing waste and ensuring that the stoichiometric ratio was fully controlled.

Another study also used feedback from a near-infrared detector (NIR) to manipulate pump flow rate settings during the course of a Grignard reaction carried out under flow conditions.[35] This reaction served as the first step towards the synthesis of the active pharmaceutical ingredient (API) zuclopenthixol; the formation of impurities during this reaction was found to be very sensitive to the dosing of the Grignard reagent. The reactor system consisted of two pumps feeding the starting materials 2-chlorothioxanthone and allylmagnesium chloride into a side-entry tubular reactor. The concentrations of the ketone substrate and excess Grignard reagent in the product stream from the reactor were monitored by the NIR unit, with information being sent into a control structure so as to manipulate the feed rate of Grignard-containing solution (Figure 10). Such a method for control was then simulated and positive results were obtained.

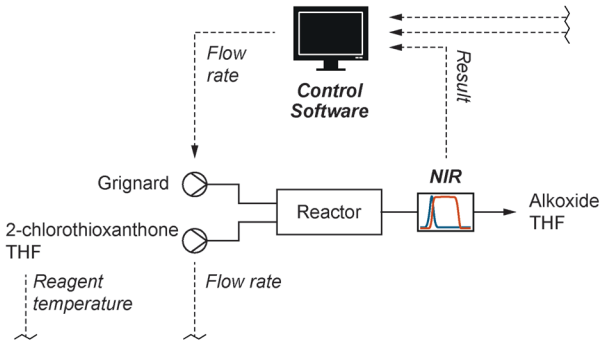


Figure 10. A near IR detector has been used to manipulate reagent addition in a continuous reaction system. The rate of a Grignard reagent addition was adjusted based on data received from the detector, ensuring that the ratio of reagents was precisely controlled and thus the reaction system operated at optimal conditions.

Much more recently, a microreactor and in-line IR detector have been used during the development of a platform for the measurement of batch chemical kinetics.[36] By assuming ideal conditions within the microfluidic chip reactor, it was proposed that it would be possible to gather kinetic data about batch reactions even when conducting experiments in flow. This concept was demonstrated by reacting ethanolamine with 2,5-hexanedione in a silicon microreactor with effluent passing through a ReactIR with a flow cell so as to gather IR spectra in real-time. The system was allowed to reach steady-state before the reactor residence time was adjusted by ramping reactant flow rate. In order to construct a kinetic model of the reaction taking place, this process was repeated for a number of step-wise changes of reactor temperatures. Conducting a similar process during traditional gathering of batch data would have taken nearly two days, rather than the 8 h in this case, and would have consumed almost three times the amount of starting materials.

4.2. Mass Spectrometry

Following from our early efforts in the area of using IR feedback for reaction control, we shifted our attention to the use of mini-mass spectrometry (MS) as a means by which to monitor flow reactions.[37] Previous efforts using MS to monitor flow reactions had done so on an in-line basis, in which all the material from the flow reaction was passed into the MS and subsequently destroyed. While acceptable for the analytical-scale generation of chemical libraries, this style of analysis would not be possible for preparative reactions. To remedy this, we developed a system that took representative samples from a flow stream only periodically, thus creating an on-line detection tool when used with a Microsaic miniature MS unit. Based on a six-way switching valve incorporating a sample loop and dilution pumps, we demonstrated this system during the cycloaddition of benzyne with furan. It was found that trends in peak height as gathered by the detector could be used to optimize flow conditions when correlated with residence time and temperature.

4.3. Nuclear Magnetic Resonance

Nuclear magnetic resonance (NMR) is a characterization tool that is used by every synthesis laboratory as a means by which to gather definitive compound structural information. Using NMR to monitor reactions gives an extremely detailed insight into what is occurring at a molecular level, and accordingly is extensively used to gather kinetic information from batch reactions while they are occurring.[38]

A flow-based microfluidic NMR probe for in situ monitoring of reaction kinetics has been reported.[39] The issues associated with microcoil winding distortion of the static magnetic field were overcome by creating a new NMR probe design using flat plates instead of coils. The output from the reactor passed through a constricted flow pathway between these plates. Samples were collected from a microreactor by means of a fused silica capillary. The team demonstrated the utility of their device by measuring the kinetic parameters for two flow reactions: the preparation of carbamate from toluene diisocyanate and ethanol; and the acetylation of benzyl alcohol with acetyl chloride. They also showcased its suitability for metabolomics studies by analyzing a sample of human cerebrospinal fluid.

In other work a different microfluidic NMR probe (with a resolution of 300 MHz) was used for the continuous monitoring of a microwave flow reaction.[40] A syringe pump was used to push the reaction mixture through a capillary placed in a microwave chamber. The reactor outlet was connected by a fused silica capillary to the NMR probe. The reported equipment layout provided representative data that

could be used for reaction scale up. It is worth noting that both this NMR probe and the one described above are able to work with typical, non-deuterated solvents, avoiding high solvent costs for these solvents.

4.4. Raman Spectroscopy

The use of Raman spectroscopy has recently been reported for the continuous monitoring of mesofluidic scale flow syntheses.[41] An off-the-shelf spectroscopic flow cell was placed into an assembly that enabled the position of the Raman light source to be adjusted to optimize the intensity of the gathered signal. Although the flow cell was unable to tolerate the high pressures present in the reactor, by placing it outside the pressurized zone, the group successfully monitored and optimized the synthesis of 3-acetylcoumarin, as well as Knoevenagel, Claisen–Schmidt and Biginelli reactions.

5. Advanced Computer Technology

5.1. Artificial Sight: Giving Machines Vision

When carrying out reactions, organic chemists intuitively interpret and react to large amounts of visual information. Researchers can monitor the progress of reactions by observing color changes or be alerted to potential hazards such as excessive gas release or solvent boiling. On the other hand automated computer control systems do not have the benefit of possessing natural sight and so they must rely on additional sensors or cameras connected to make visual observations.[42]

The use of web cameras will be familiar to anyone who communicates using consumer visual software. Their low-cost nature enables them to be readily adopted in a research environment;[43] indeed, there have been a number of published studies that have used such tools for organic synthesis as were outlined in a review.[44] A variety of different applications were described, ranging from the observing of laboratory environments and the gathering of information from closed environments such as high-pressure reaction chambers, to automated glass microchip recording, crystallization monitoring and liquid level detection (as described in Section 3.2).

In the studies described in the review, however, not all the full benefits provided by the camera-gathered information were exploited. Large amounts of information can be collected by analyzing reactions exposed to different wavelengths for example,[45] an approach adopted in a recent publication.[46] A two-dimensional, non-homogeneous reaction mixture was held in a petri dish which was placed on top of an LCD computer monitor (Figure 11). By alternating the color displayed on the LCD between three pre-defined wavelengths, the light passing through the reaction mixture could be observed by a camera that was positioned to capture light absorption images. In this way it was possible to obtain spatiotemporal information for three separate reactions.

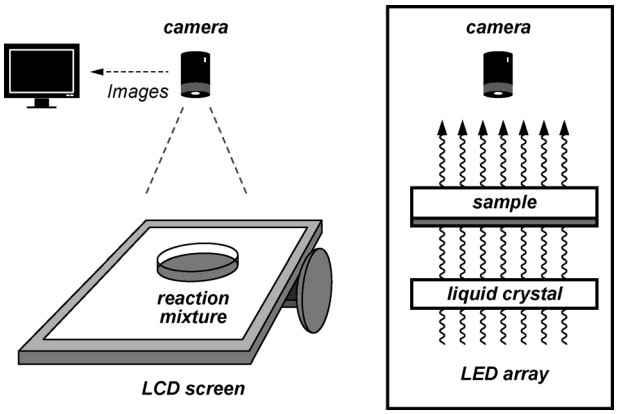


Figure 11. A computer LCD screen-based reaction monitoring system that enables the capturing of reaction front images. A camera is used to record the wavelengths absorbed by the reaction mixture placed in a petri dish.

Reaction fronts could be seen clearly and the special distribution of reaction products could be discerned.

Unlike humans, machine vision does not need to be limited to the wavelengths of the visual light spectrum. Thermal imaging effectively enables heat to be seen as a result of infrared radiation, giving additional insight into reactions that cannot be directly seen by chemists.[47] A study which presented a novel continuous-flow microwave applicator, used five infrared sensors to monitor the temperature distribution over a tubular reactor (Figure 12).[48] Sensor data were fed back to a software control system which adjusted the power and frequency settings of microwave hardware so as to keep the reactor within set temperature boundaries. In order to exemplify the utility of this new microwave reactor and control system, a broad selection of experiments were conducted including a Suzuki–Miyaura cross coupling reaction, Claisen rearrangement, and Diels–Alder reaction.

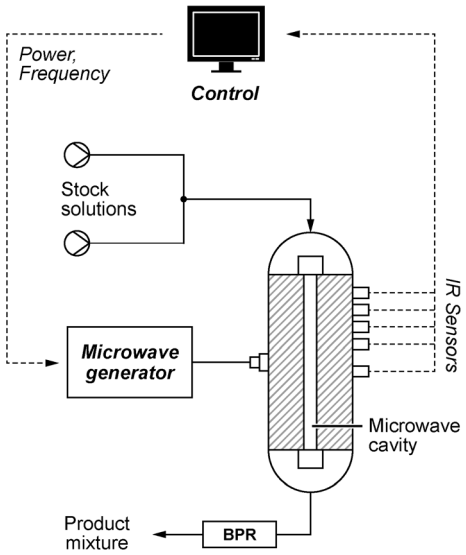


Figure 12. Infrared LEDs were used to monitor the temperature inside a prototype microwave reactor. A computer control system was used to adjust the power and frequency of the microwave generator heating the reaction chamber based on thermal readings from these LEDs.

In another study, the use of a thermographic camera to monitor the exothermic decomposition of methyl ethyl ketone peroxide by inorganic acids was reported.[49] Solutions of H_2SO_4, HCl and HNO_3 were used to initiate this process through the decomposition of the peroxide molecule, a process which was propagated by free radicals. Owing to the self-propagating nature of this reaction, the researchers were concerned about the possibility of thermal runaway. Images captured by the thermal camera enabled researchers to monitor the progress of the reaction from a hazard and safety perspective in real-time. Furthermore image information was analyzed following the reaction using computational methods, allowing the estimation of various kinetic parameters including activation energy and change in enthalpy. Using these results, it was possible for investigators to propose a mechanistic pathway for the decomposition reaction. Traditional methods for temperature monitoring, such as using a thermocouple, would not have had the capacity to give planar temperature distribution information required for this type of analysis.

5.2. Automated Reaction Optimization

When conducting new reactions, researchers often spend a long time performing reaction optimization procedures. This routine task consumes valuable resources in terms of both skilled labor and consumption of materials. It comes as no surprise then that there has been a significant focus on the development of tools and methods to automate what can be a tedious process.

Before discussing the machine-aspects related to this area, it is useful to mention one of the algorithms most commonly used to assist researchers with the planning of optimization experiments. Design of Experiments (DoE) is a statistical method that attempts to form a correlation between the parameters of a reaction and its outcome by varying the parameters individually and comparing the different results.[50] For example our group has used this technique for a number of studies, with some of our early work investigating optimization techniques for reactions involving polymer-supported reagents in 2000.[51] A detailed discussion of the many applications of DoE in process optimization has been published recently in a comprehensive review.[52]

Early efforts in this area focused on simply reducing the time taken for reaction optimization. For reactions whose parameters to be optimized are dependent on a large number of input parameters, this can be a complex task. By employing high-throughput screening techniques, researchers can utilize automated tools such as robotic workstations to carry out a predefined list of reactions on their behalf. A study in our laboratories combined a number of enabling technologies with automated software control for the optimization of a cyclocondensation reaction.[53] This reaction, a key part of the synthesis of an inhibitor for casein kinase I, was conducted using a Vapourtec R2 + /R4 flow chemistry platform with the parameters controlled by Vapourtec Flow Commander software (Figure 13). A series of 17 reactions were carried out automatically by this software to investigate the effect of

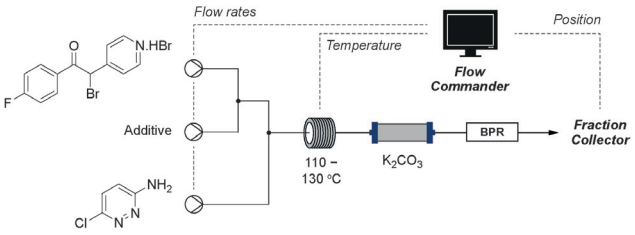


Figure 13. Automated system was used to trial 17 different reaction conditions during an optimization screening process.

residence times, temperatures and stoichiometric reagent ratios on final product yield.

The high-throughput screening approach does not necessarily have to be used for obtaining optimal yields, even though this is normally our focus. Other parameters can be optimized such as particle size, which may be of more interest when dealing with polymer formation or the creation of nanocrystals. Indeed this was exemplified by a study investigating the formation of cadmium selenide nanocrystals.[54] A robotic platform consisting of a liquid handler, heated needle, automated balance, vial-gripper and eight high-temperature reactors was placed inside a glove-box. Having preloaded a list of reaction conditions into a software control system, a series of experiments were carried out varying reaction time, temperature and reagent concentrations in order to find optimal conditions for the formation of nanoparticles of specific sizes. It was found that the system was capable of identifying ideal conditions rapidly and that results were reproducible between experimental trials. Conducting a large number of separate reactions manually would have consumed valuable researcher time, considering that these reactions had to be performed in a glove-box.

More recent developments in the area of automated reaction optimization have also considered the reduction of material consumption in addition to researcher time. The iterative approach of typical high-throughput screening protocols, while exhaustive, consumes large quantities of often expensive materials. With the introduction of on-line detection devices conversions can be determined in almost real-time and software control systems can gather important data about reaction performance and adjust conditions for subsequent reactions automatically.[55]

Gas and liquid chromatography are powerful detection methods in this context. In addition to providing quantitative information about the composition of the fluid stream being analyzed, when combined with mass spectrometry it is possible for control systems to obtain rudimentary structural information. A study utilized a gas–liquid chromatograph (GLC) in an automated optimization platform for a supercritical CO_2 reactor system (Figure 14).[56] The stream leaving the reactor was periodically injected into the GLC to obtain information about the degree of conversion resulting from a particular set of reaction parameters.

During the methylation of 1-pentanol, four parameters (reaction temperature, pressure, CO_2 flow rate and 1-pentanol:methylating agent molar ratio) were adjusted according to the output from a Super Modified Simplex

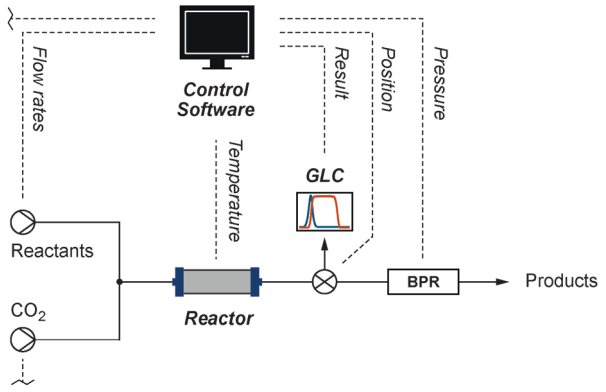
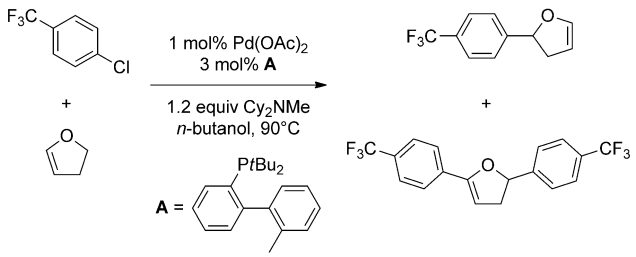


Figure 14. Adaptive process optimization for continuous methylation of alcohols in supercritical CO_2. The alcohol was mixed with CO_2 before passing through a reactor column packed with catalyst. The composition of the product stream was monitored by GLC. Measurements were used to automatically adjust pump and reactor parameters according to the output of an optimization algorithm.

algorithm. Using this system it was possible to optimize conditions to obtain >90% yield with only 10 experiments, with fully optimized conditions (>98% yield) found in 25 h and 74 h when using dimethyl carbonate and methanol as the methylating agents, respectively. Using the same apparatus, this group also reported the automated optimization of etherification reactions through the adjustment of three parameters.[57]

Another study used HPLC for the optimization of a Heck reaction on a microfluidic scale (Scheme 1).[58] In a manner similar to that shown in Figure 14, an HPLC system was placed immediately downstream from a microreactor and the



Scheme 1. HPLC was used for the optimization of this Heck reaction conducted using a microfluidic platform.

resulting information was fed back to a computer-based control system. In this case, two parameters were automatically adjusted by the control system (equivalents of alkene and reactor residence time) and optimized conditions were found after 19 trials (approximately 6 h 20 min). In order to test the scalability of this system, the optimized conditions were applied on a mesofluidic platform (representing a 50-fold increase in scale) with a good agreement found between the yield produced by the microfluidic and the mesofluidic systems.

However, the use of chromatography comes at the cost of speed as it takes more time for quantitative information to be fed back to the optimization control system. Invariably this causes self-optimizing systems to run for extended periods. In-line detection tools, on the other hand, such as the Mettler-Toledo FlowIR,[31] counter this problem by providing real-time feedback of the composition of the output stream (described in Section 4.1).

In a follow-up study to the methylation of 1-pentanol described above, an in-line FTIR spectrometer was utilized in conjunction with GLC for yield measurements.[59] One of the limits of FTIR spectroscopy is that direct measurement of yields is not possible; accordingly, GLC was used to obtain yield information for the initial experiments which was then correlated with the FTIR response. From this, the authors were able to obtain a calibration curve to calculate yield from FTIR data and GLC was not required for subsequent experiments. Using the same optimization algorithm as before, fully optimized conditions were found in approximately 150 min (3.2 min on average per data point, contrasting with 35 min in the previous study using just the GLC). The time savings were identified to be as a result of the increased sampling rate of the FTIR unit and the ability to determine precisely when the reaction had reached steady-state.

An in-line FTIR cell has also been used to optimize a Paal–Knorr reaction.[60] In this case, LabVIEW controlling software with embedded Matlab optimization routine scripts was used to adjust residence time and temperature of a microfluidic reactor. A multitrajectory optimization strategy was adopted, providing greater efficiency over other algorithms.

It ought to be noted that the self-optimization methods described above rely solely on statistical algorithms, for which numerous experiments must be carried out on a trial-and-error basis, basing subsequent experimentation on past results. While this approach provides extensive benefits when compared to the brute-force nature of high-throughput screening methods, taking a more considered and intelligent approach should lead to further reductions in material consumption.

Some developments have been made in the area of model-based optimization feedback, in which kinetic parameters determined through a small number of initial trial experiments are used for subsequent optimization calculations.

In another study, a system was devised that divided the model-based optimization of a Diels–Alder reaction in flow by our group[61] into three parts: kinetic model selection, parameter estimation, and upscaling.[62] The initial experimental conditions were selected automatically, varying the residence time and inlet concentration, and these reactions were analyzed by on-line HPLC apparatus. The platform selected one of four rate equations that best matched the data and subsequently carried out experiments varying reactor temperature and residence time to estimate the equation parameters. Finally, results from the previous two stages were combined with residence time distribution and heat transfer calculations to model the expected conversion in a flow reactor with a 500-fold increase in volume.

5.3. Equipment Control

Following discussions of automated reaction optimization, it is worthwhile to highlight some of the other work in the area of equipment control especially in relation to the telescoping of chemical reactions. Without automated control of reactors, pumps, valves and other necessary equipment, continuous multistage reactions would quickly become too complex to be managed by a single researcher. Computer control can process numerous streams of sensor information while adjusting reaction parameters, valve positions, and pump flow rates simultaneously. Furthermore, should something run foul in upstream operations, computer control systems are able to rapidly modify downstream conditions to minimize any negative impacts while attempting to rectify any issues.

We have recently published a study which incorporated a number of the technologies described previously into a fully automated, self-controlling, telescoped seven-step synthesis process incorporating Grignard, Ritter and cyclization reactions (Figure 15).[20] The extraction, solvent-switching, filtration and quenching procedures were carried out in-line. The control system monitored all parameters and controlled all aspects of the process, including reaction and detection steps. The use of this control scheme enabled a single researcher to monitor the status of the system remotely, with self-rectifying functions designed into the control algorithms to handle minor deviations from normal behavior without human intervention.

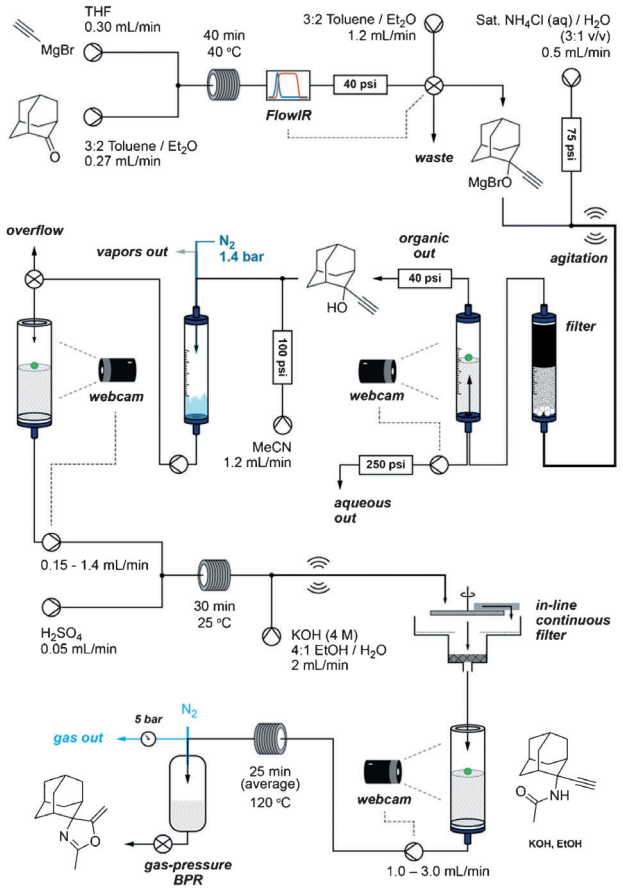


Figure 15. The individual processes in a fully telescoped, self-controlled seven-step synthesis. This entire process was controlled by one control system and was managed by a single researcher.

Our group has also pioneered the application of such chemical engineering-derived control strategies in a chemistry environment, such as our synthesis of grossamide in 2006.[63] The liquid handlers, pumps, detectors, and reactors associated with this synthesis were all controlled by software so as to automate the process. We have also used similar strategies for the synthesis of secondary sulfonamides[64] and an automated hydrogenation process.[65]

In more recent times, a continuous platform for the final few stages of aliskiren hemifumarate production, an active pharmaceutical ingredient used for the treatment of high blood pressure, has been described.[29,66] Consisting of a number of unit operations this telescoped process, combining two chemical synthesis steps (amide bond formation and *tert*-butoxycarbonyl deprotection) followed by separation, drying, crystallization, and tablet formulation, produces 45 $g\,h^{-1}$ of the target compound. In order to regulate this process, a large number of controllers were utilized with functions ranging from temperature and pressure control to monitoring material stream compositions. The control system in this case used this information to adjust the equipment parameters to ensure that they fell within the desired limits. Such a control scheme is common in manufacturing applications such as those encountered in industrial-scale pharmaceutical or oil production.

While one might argue that the area of equipment control from a process chemistry or chemical engineering perspective is saturated with relevant publications, there are considerably fewer discussing applications on a research laboratory scale. In the research environment equipment layouts and configurations are changed frequently, leading to problems when attempting to use previously defined and rigid control systems for new experiments. *Platforms used at a research level must be flexible and completely modular so as to facilitate multiple reactions that may be carried out within the space of a few hours.*

Recently we published an open-source software system that utilized the low-cost Raspberry Pi computer for the control of flow chemistry equipment and reactions.[42a] This system was nicely demonstrated for the machine-assisted synthesis of (*R*,*S*)-piperazine-2-carboxamide consisting of two transformation stages: the hydrolysis of pyrazine-2-carbonitrile; and reduction of pyrazine-2-carboxamide to form the final fully reduced product (Figure 16).

The initial reaction was carried out by passing a liquid stream through a column packed with hydrous zirconia housed on a Vapourtec R2+/R4 flow chemistry unit. A set quantity of product mixture from this step was stored in a reservoir whose level was controlled using a webcam and plastic float, before being pumped into the latter stage which was conducted using a ThalesNano H-Cube reactor. The software system monitored and controlled pump flow rates, temperatures and pressures while simultaneously monitoring the reaction product stream using an in-line FTIR detector. Optimized conditions for this stage had been previously found by employing an automated screening approach. All

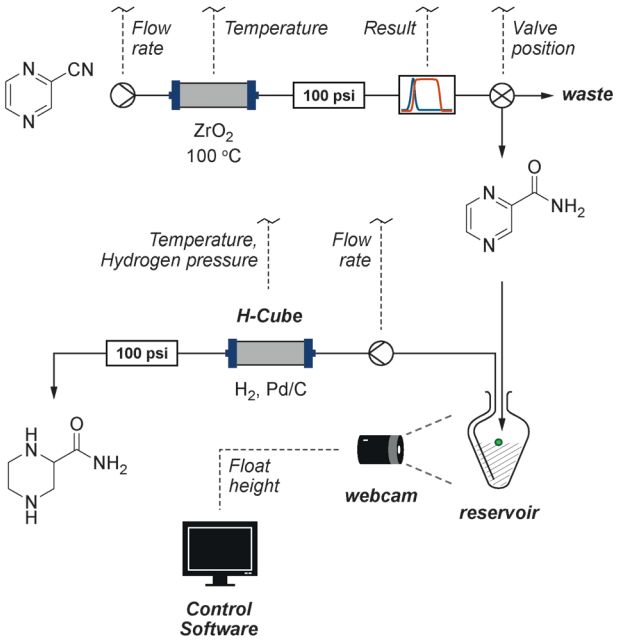


Figure 16. All experiment variables were monitored and adjusted by an open-source control system, enabling the automation of a hydrolysis step followed by a reduction step.

reaction parameters were gathered and controlled by the control system, enabling a single researcher to operate the entire process. Furthermore, automated procedures could be defined for the control system to implement should any deviation from normal behavior be detected, a feature notable from a safety perspective.

This open-source control system was also used in a separate study to monitor a Curtius rearrangement under flow conditions (Figure 17).[42b] Two balances measured the mass of feedstock present, which was used to ensure that the pump flow rates were accurate and stoichiometric ratios were consistent for extended periods. This data, along with the reactor temperature and pressure, could be viewed and

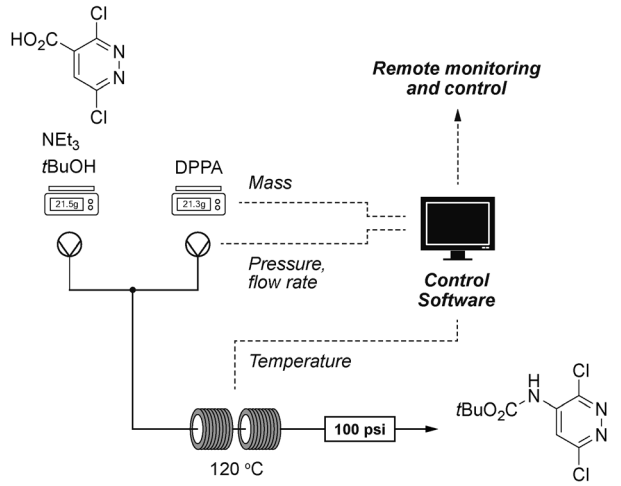


Figure 17. A control system was used to monitor balance readings and reactor temperature during a Curtius rearrangement.

adjusted *over the internet*, enabling researcher interaction from any location in the world.

6. Innovation

Before offering our summary of this Review, it is important to appreciate just how exciting the future of chemistry really looks by highlighting some of the more unusual and innovative applications of machinery in laboratories. Involving modern developments in technology including computing, hardware and robotics, this may lead to the exploration and discovery of new chemistries[67] as "accelerated serendipity" has shown,[68] or may enable researchers to rapidly test reactor configurations to maximize reaction outcomes.[69]

The work by Cronin and co-workers in the area of three-dimensional (3D) printing[70] is a good example, since with this method new reaction vessels can be fabricated from inert plastics in a matter of hours. The group have incorporated multi-step synthesis processes in a single printed device,[71] created custom flow chemistry components,[72] and shown the applications of 3D printing for routine tasks such as optimization and reaction scale-up.[73]

In our gadget-filled lives, the Internet of Things (IoT) is finding applications in areas such as home automation and shopping.[74] In an IoT ecosystem, electronic sensors constantly share information with those devices near to it, leading to a large web of connections that control systems can monitor. Such a system is bound to find use in chemistry, enabling simultaneous measurement of parameters such as temperature, pressure, pH and composition across a whole laboratory. One report outlined some initial efforts in the area of optical sensor development and its potential use in IoT applications.[75]

The multi-disciplinary approach of using modern technology with chemistry was extended even further to include biology and materials science in a recent review.[76] In it the authors described research capable of bridging living organisms with machines to create machine-assisted life, not entirely dissimilar to cyborgs in popular science fiction films of the late 20th century. Yet while this seems remarkable and unlikely, modern scientific developments are certainly moving in this direction. With opportunities to extend human life, it comes as no surprise that large companies such as Google are investing heavily in the life sciences.

7. Summary and Outlook

With the limited space available to us we have tried to convey an excitement for a machine-assisted approach to organic synthesis to transform where we are today to a new level of responsibility and capability. By taking a more holistic approach and by harnessing all the tools present in modern society, we can envisage a world that greatly extends our current processes by creating more time for discovery.

The ability to generate, capture and evaluate information leads to unprecedented opportunities for the synthesis of our

molecules. Integrated screening for function, calorimetry and for physical properties opens up new chemical space and provides a cultural change in attitudes. Multi-tasking, extended working regimes via improved monitoring and reaction control algorithms encourages multi-disciplinary behavior.

Science effects change and change effects science, and while people are always more important than machines, increasingly we think that it is foolish to do something machines can do better than ourselves.

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