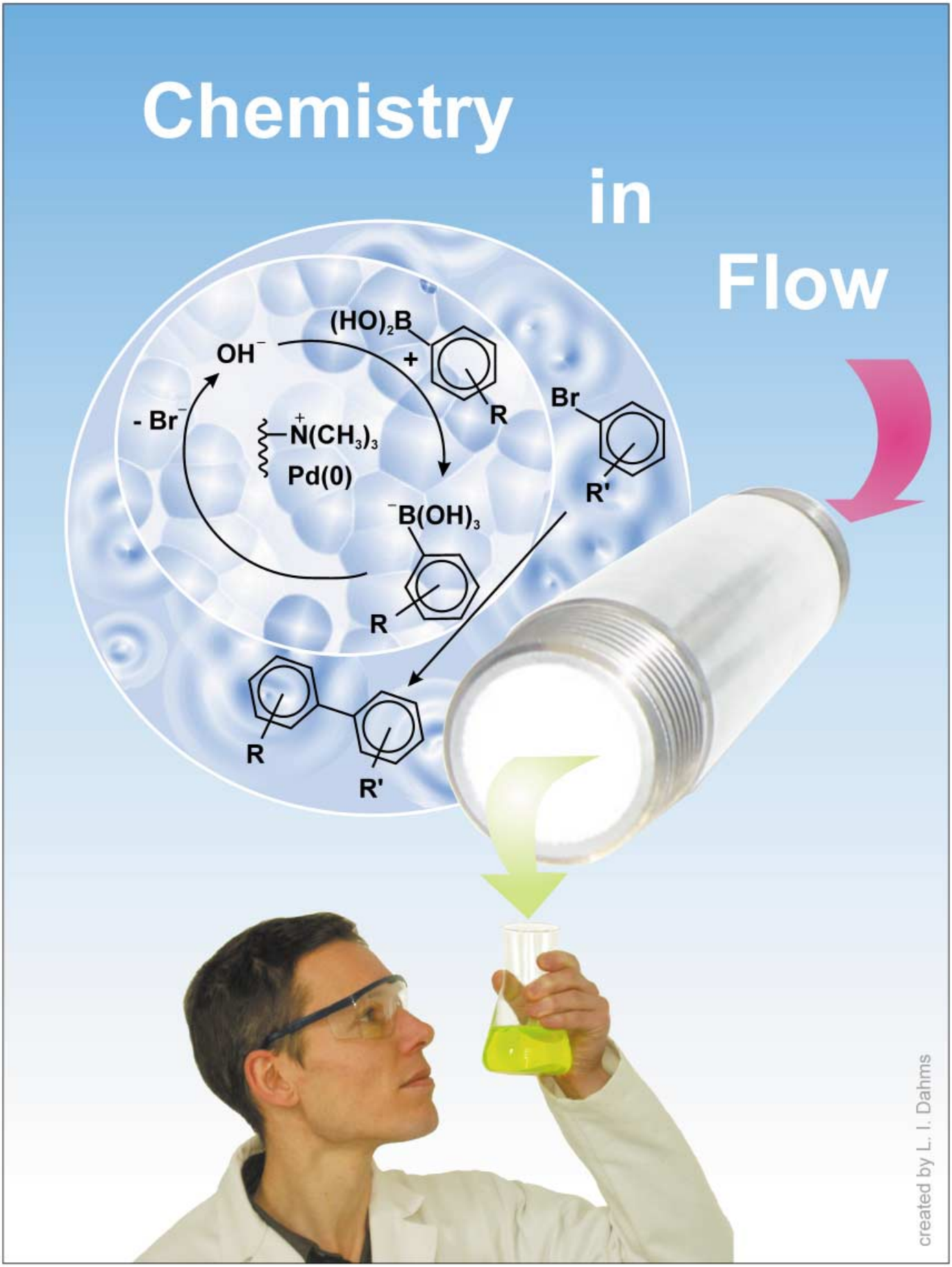

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Continuous Flow Techniques in Organic Synthesis

Gerhard Jas*[a] and Andreas Kirschning*[b]

Dedicated to Professor Ernst Schaumann on the occasion of his 60th birthday

Abstract: As part of the dramatic changes associated with the need for preparing compound libraries in pharmaceutical and agrochemical research laboratories, the search for new technologies that allow automation of synthetic processes has become one of the main topics. Despite this strong trend for automation high-throughput chemistry is still carried out in batches, whereas flow-through processes are rather restricted to production processes. This is far from understandable because the main advantages of that approach are facile automation, reproducibility, safety, and process reliability, because constant reaction parameters can be assured. Indeed, methods and technologies are missing that allow rapid transfer from the research level to process development without time-consuming adaptation and optimization of methods from the laboratory scale to production plant scale. Continuous-flow processes are considered as a universal lever to overcome these restrictions and, only recently, joint efforts between synthetic and polymer chemists and chemical engineers have resulted in the first continuous-flow devices and microreactors; these allow rapid preparation of compounds with minimum workup. Many of these approaches use immobilized reagents and catalysts, which are embedded in a structured flow-through reactor. It is generally accepted, that for achieving best reaction and kinetic parameters for convective-flow processes monolithic materials are ideally suited as solid phases or polymer supports. In addition, immobilization techniques have to be developed that allow facile regeneration of the active species in the reactor.

Keywords: automated synthesis · combinatorial chemistry · flow-through processes · monolithic materials · polymers · reactors

Introduction

Despite the rapid developments in synthetic methodology during the last ten years, whether they have been achieved in catalysis, asymmetric synthesis, combinatorial chemistry and other fields, organic synthesis is still being carried out in a very traditional way. In fact, reactions are typically performed in standardized glassware, which in essence have been known since Justus Liebig's time and even in the age of the alchemists. Due to this very characteristic equipment compounds are synthesized batchwise regardless of the kind of chemistry to be chosen. Until recently, the keywords "industrialization and automation"—which can be considered as major driving forces in most of the modern branches of industry—did not belong to the chemist's dictionary. As combinatorial chemistry started its triumphant progress in drug discovery, a bit more than ten years ago,[1] chemists learned new ways of thinking as time and costs determined daily laboratory work more and more. Today combinatorial and parallel-synthetic methods are a widely accepted tool in organic chemistry. However, in terms of automation there is a strong discrepancy between laboratories in pharmaceutical industry and more common research laboratories. Despite this strong trend for automation in pharmaceutical research, high-throughput chemistry is still carried out in batches, whereas flow-through processes are restricted to production processes. This is a curious fact, since the main advantages of that approach are facile automation, reproducibility, safety, and process reliability, because constant reaction parameters (temperature, time, amount of reagents, solvent, etc.) can be assured. Moreover, continuous-flow processes are paralleled by current trends in modern synthetic chemis-

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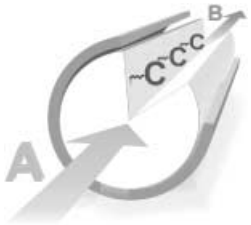


Figure 1. Concept of flow-through reactors that contain a functionalized solid phase. A: starting material B: product C: immobilized reagent or catalyst.

try as they can be performed most advantageously by using immobilized reagents or catalysts (Figure 1).[2] Indeed, these insoluble materials can be adopted to continuous-flow processes by using fixed beds. Concerning large-scale processes the door is particularly opened for repeated use of the reagents and catalysts. Ideally, the flow rates are slow enough to guarantee full conversion of the starting material, and only the desired product(s) are gained at the end of the reactor. Thus, reaction and filtration operations are carried out simultaneously, whereas in corresponding batch reactions both processes have to be performed separately. Simplified reaction workup is the result, and in some cases only the evaporation of the solvent is needed as a single work up step.

Regardless of the discussions whether automation in drug discovery has really led to more efficiency and quality of compound libraries, including the chemistry that has been employed to obtain these libraries, it is sensible to note that automation is still in its infancy. In particular, methods and technologies are missing that allow rapid transfer from the research level to process development without time-consuming adaptation and optimization of methods from laboratory scale to production plant scale. Continuous-flow processes are considered as a universal lever to overcome these restrictions.

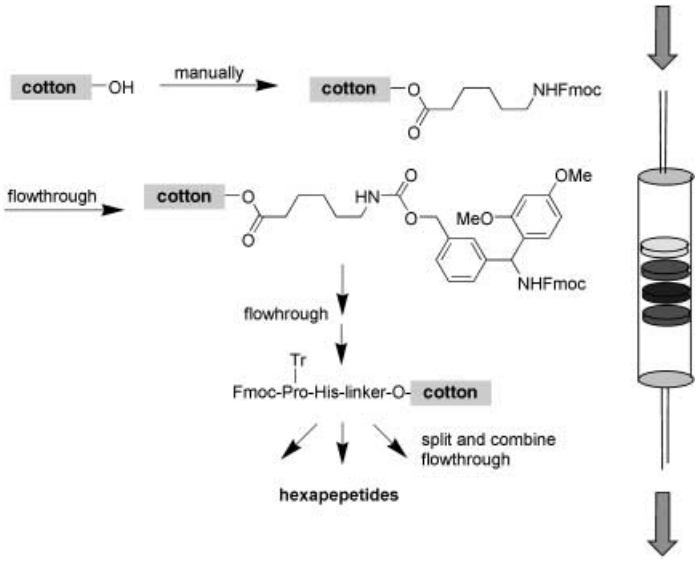
The goal of this literature survey is to give an almost comprehensive and critical overview on the concept of continuous-flow processes that have already been established in modern synthetic chemistry and to direct the reader's interest to recent developments that add new facets to flow-through processes. The latter include microwave-assistance and the use of immobilized reagents and catalysts. Times are changing dramatically and the future of chemistry might lie in flow-through processes as was recently stated by S. Ley.[2]

First Flow-Through Processes Based on Merrifield's Original Concept

Evidently, the work of Merrifield set the stage for solid-phase-assisted synthesis and thus had a strong impact on laboratory automation. The highly repetitive character of coupling reactions and protecting groups, and the small amounts of product required in peptide and oligonucleotide synthesis ideally fit the demands of automation. Not surprisingly the first synthesis machines were developed for the synthesis of these biomolecules. Due to a much higher complexity of chemistry and the need for carefully optimized reaction protocols, only recently a standardized methodology for the automated synthesis of oligosaccharides has been developed.[3]

At first glance, solid-phase-supported peptide synthesis might not be considered as a typical process that takes advantage from continuous-flow methods. However, it is forgotten that Merrifield originally envisaged a flow-through system for peptide synthesis as can be read in his autobiography from 1993.[4] Nevertheless, it took another 20 years until a reliable continuous-flow protocol for peptides was at hand.[5] The intrinsic disadvantages (particularly swelling of the support) were overcome by polymerizing the support within the pores of a rigid macroporous matrix. In a comparative study it was shown that peptides can be synthesized quicker and easier by a flow-through approach,[6] reducing the time for the whole process by a maximum factor of ten.[7]

Surprisingly, even well-established methods give rise to new exciting developments. Recently, Wikberg[8] et al. reported on the synthesis of a library of hexapeptides by means of continuous-flow methods. They employed common peptide synthesizers and varied their use according to the original approach of Frank and Doering.[9] The authors presented the simultaneous, multiple peptide synthesis on paper disks by a continuous-flow approach (Scheme 1).

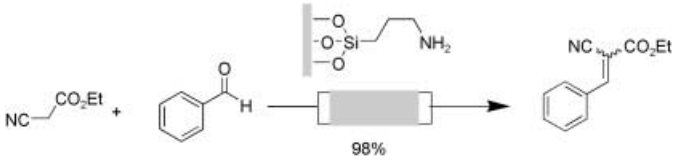


Scheme 1. Wikberg's approach for continuous-flow synthesis of peptides using cotton disks in a split and pool strategy.

This new technique is based on labeled cotton-disks as supporting material, which was manually premanipulated and preactivated for introduction of an Fmoc-protected linker. Piled up in a common synthesis column, the disks were used for the synthesis of a library of hexapeptides according to the Merrifield protocol (Fmoc-strategy). They took advantage of a split and pool strategy, which was realized through individual labeling and spatial encoding of the disks by their assembly in the column.

Starting with the C-terminal amino acid, 16 peptides were synthesized (3 to 4 mg scale; about 30% yield and 80% purity). Washing steps as well as individual reactions were carried out at flow rates of about 30 mL min^{-1} and the reaction times were found to be between 30 and 60 min. The authors estimated that with a typical commercial continuous-flow peptide synthesizer, it should be possible to accomplish six different amino acid couplings per day on 50 disks resulting in 300 amino acid couplings per day. This rather classical but very straightforward and efficient approach can be envisioned to be utilized in conventional synthesis of compound libraries by using other supports. This would combine continuous-flow techniques with traditional solid-phase-supported chemistry.

Peptide-synthesis continuous-flow approaches for conventional synthesis were neglected for a long time. Only in 1988 did Venturello and co-workers report the use of aminopropyl-functionalized silica gel as a suitable catalyst in Knoevenagel condensations under continuous-flow conditions (Scheme 2). Good yields were obtained when aromatic



Scheme 2. Venturello's concept of a Knoevenagel condensations in a flow-through reactor.

aldehydes, cyclohexanone, and acetophenone were condensed with ethylacetoacetate, ethyl cyanoacetate, or malononitrile.[11,12] The concept was based on a conventional column strategy and the reactor consisted of a vertical double-jacket-thermostated glass column, which was loaded with the catalysts. The reactants were placed on the top of the column, toluene was passed through the column, and the products were conveniently obtained by evaporation of the solvent.

The Quest for Monolithic Materials in Flow-Through Processes

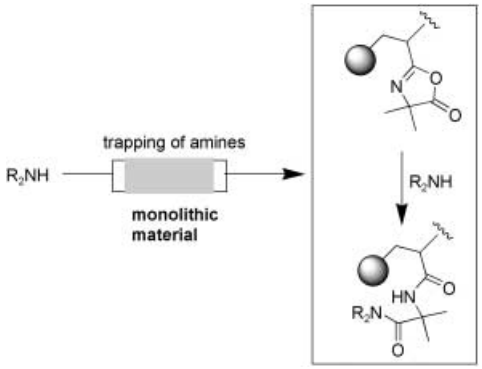
Flow-through processes relying on solid phases that are functionalized with reagents or catalysts are commonly designed by adapting the reaction conditions to the equipment available. Commonly, reactors are equipped with randomly packed catalytic beds and thus have uncontrolled fluid dynamics. This concept results in various disadvantages from a chemical-reaction-engineering standpoint. These can be stagnation zones and hot-spot formation, broad residence time distribution, low selectivity, and in essence low process efficiency. The development of structured beds that are designed on a nanoscale up to the macro-geometry is highly desirable for overcoming these drawbacks. A monolith is the best structured material known for this purpose and in a broad sense is defined as a block of structured material that consists of continuous substructures, or regular or irregular channels.[13] To date, these materials have found wide use in automobile business as supports for catalysts. In addition, they have been most often used as separation media in various chromatographic modes, in solid-phase extraction, and for the fabrication of thermally controlled valve- or gatelike devices.

Monolithic materials have a high void volume and a large geometric surface area. This results in a low pressure drop during the passage of a fluid and a large contact area of the reagent or the catalyst with the fluid.[14]

Therefore, various groups have been involved in designing novel monolithic materials for flow-through reactor systems. In many cases, these developments were directed towards polymeric phases. Among others, three important concepts towards monolithic polymers with regular or irregular channels and which are incorporated into a flow system can be listed:

1. Copolymerization of different monomers in the presence of porogens.
2. Preparation of diblock copolymers, in which a well-defined cylindrical and degradable polymer is embedded inside the second polymer. After selective removal of the degradable polymer, nanotubes are regenerated within the stable matrix.
3. Polymerization of a monolithic polymeric phase wedged inside the microchannel pore system of an inert support, such as glass and other preformed inorganic materials.

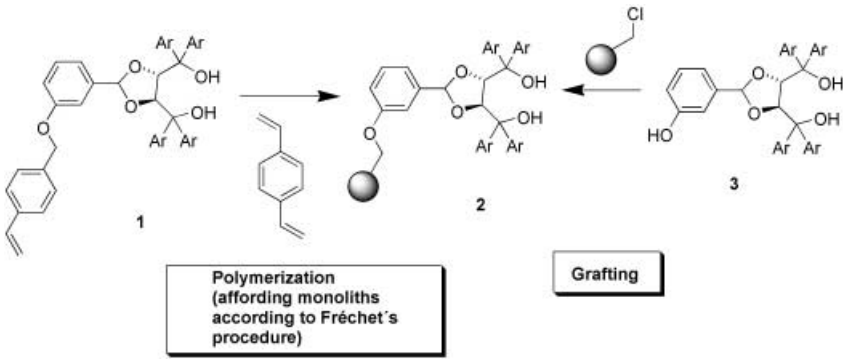
The first concept is particularly associated with the names of Fréchet, Svec, and Sherrington.[15,16] These groups prepared monolithic porous polymers of virtually any shape within a column housing or mold by copolymerization of polystyrene, divinyl benzene, and polymethylacrylate in the presence of a porogen. No suspending medium, as is normally required in suspension polymerization processes, is needed. The resulting rod can be used as a reactor or may be cut into disks. This material was functionalized with an azlactone moiety, which allows the scavenging of amines from solution as depicted Scheme 3. The authors note that this monolithic porous structure shows superior properties to conventional beads because of improved diffusion rates. In addition, they found that in contrast to the direct copolymerization of reactive monomers, grafting increases the accessibility of the reactive groups.



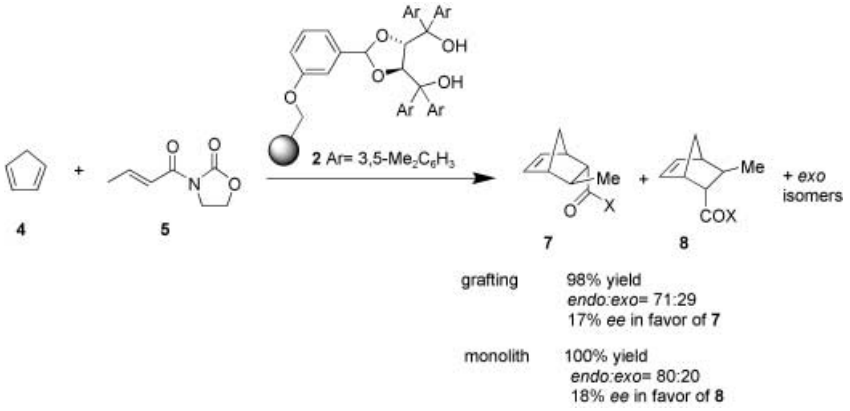
Scheme 3. Scavenging of amines with monolithic materials inside a flow system.

Luis and co-workers[17] used the monolithic Fréchet materials[18] and studied the influence of the mode of preparation of the polystyrene backbone functionalized with TADDOL (α,α,α′α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) and loaded with Ti (**2**) on the topicity of an asymmetric transformation. In their case, the Diels–Alder reaction of cyclopentadiene (**4**) with 3-crotonyl-1,3-oxazolidin-2-one (**5**) was chosen as model reaction. The TADDOL-ligands were incorporated into the polymeric backbone either by polymerization with a functionalized styrene derivative (**1**) or by grafting and coupling of phenol **3** to Merrifield-type resins (Scheme 4).

Although the diastereo- and enantioselectivities observed for this model reaction were poor, a remarkable observation was made by the authors (Scheme 5). The topicity of this process was reversed when changing from the grafted polymer (which equals soluble catalysts) to the monolithic material (prepared from **1**). At this point a rationale can not be given, but it is a clear indication that the nature of the matrix has an influence on the course of metal-catalyzed reactions.



Scheme 4. Preparation of monolithic and grafted materials functionalized with TADDOL ligands.



Scheme 5. Applications of Ti-TADDOL catalysts **2** in Diels–Alder cycloadditions.

The so-called convective interaction media (CIM) are related monolithic supports. They are block polymers prepared by radical copolymerization of glycidyl methacrylate and ethylene dimethylacrylate in the presence of a porogen.[19] These monolithic materials are rigid, macroporous materials which contain epoxy groups as functional groups that can be activated to allow immobilization of various ligands. They have been used as chromatographic supports[20] and in biocatalysis.[21] For example, it was shown that these monolithic materials can also be applied as matrixes in applications of affinity chromatography. Solid-phase peptide synthesis was performed on a glycidyl methacrylate-*co*-ethylene dimethacrylate monolithic column.[22] The resulting immobilized peptide (directed against human blood coagulation factor VIII) showed good properties as a peptide affinity chromatography matrix and did not adsorb proteins unspecifically.

Buchmeiser and co-workers[23] followed a transition-metal-based approach to yield monolithic materials. The continuous matrix was prepared by ring-opening metathesis copolymerization of norbornen in the presence of a porogen within a glass column. The "living" ruthenium–carbene termini were treated in situ with norbornene. which itself had been functionalized with a modified second-generation Grubbs catalyst to yield a porous monolithic metathesis catalyst **9** (Figure 2).

The second concept for the generation of monolithic polymers was recently disclosed by the Hillmyer group.[24] They prepared a diblock copolymer containing oriented nanoscopic cylinders of the degradable polymer polylactide (PLA) embedded in polystyrene. Polystyrene served as an inert thermoplastic matrix, while PLA was selectively removed under well-defined conditions by using sodium hydroxide in aqueous methanol. This treatment resulted in a mesoporous monolithic polystyrene containing nanochannels with defined pore size. However, the polystyrene material shows reduced me-

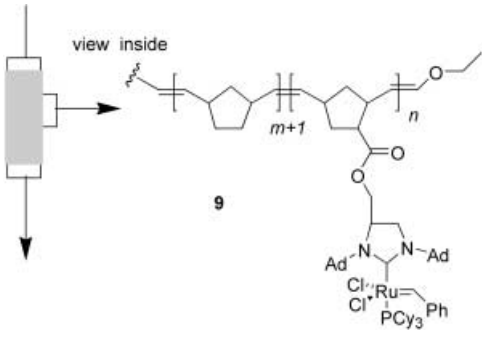


Figure 2. Buchmeiser's concept of monolithic Grubbs catalysts.

chanic and chemical stability as no cross-linker was employed.

The third solution to the design of monolithic matrices was developed by Kunz and Kirschning. The concept is based on the design of a novel type of monolithic block that contains a chemically functionalized highly porous polymer/glass composite. It was prepared by precipitation polymerization of vinyl benzene or other monomers in the pore volume of highly porous glass rods to yield a polymeric matrix inside the rod.[25,26] The polymeric structures obtained consist of small beads (1–5 μm diameter) that are cross-linked with polymeric bridges (Figure 3). This results in a monolithic polymeric phase, with a high surface area, that is wedged inside the microchannel pore system of the inert, inorganic support. As will be shown later these materials can be functionalized and become part of a flow-through reactor system.

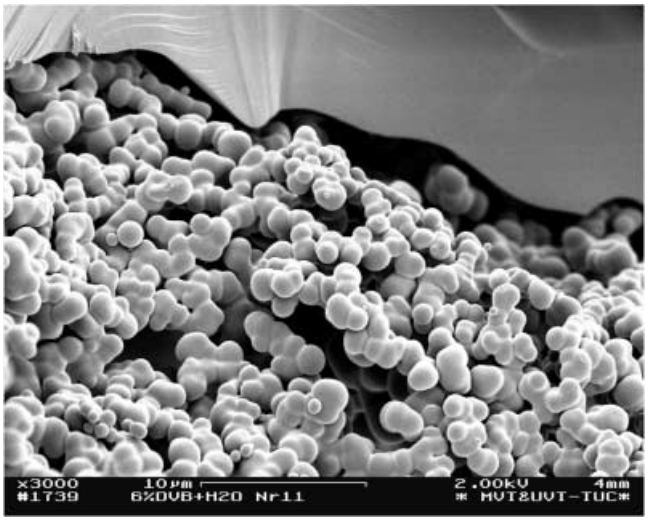
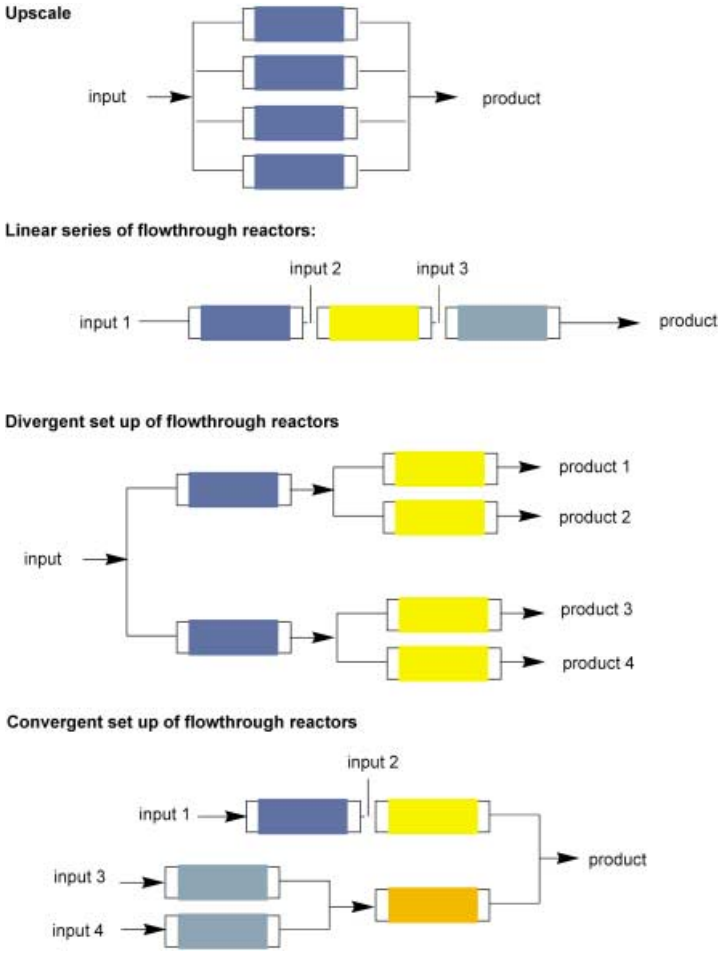


Figure 3. REM view into the monolithic glass/polymer composite material.

Finally, it should not be forgotten that inorganic materials based on silica gel or carbon can ideally be prepared as monoliths with uniform mesopores and tunable microchannels.[27]

Applications of Reactions and Multistep Syntheses in Flow-Through Modes

The switch from a synthetic batch-mode protocol to a flow-through concept has various consequences. It opens opportunities that rarely can be achieved with similar simplicity in batch reactors. Scale-up can be conducted by use of parallel reactors. By assembling a line of reactors multistep syntheses can be achieved with minimum or no purification in between two reaction steps. Divergent as well as convergent multistep syntheses, which either create compound libraries or complex target molecules, are also feasible with flow systems (Scheme 6). The concept can beneficially be extended by incorporating separation and analytical techniques into

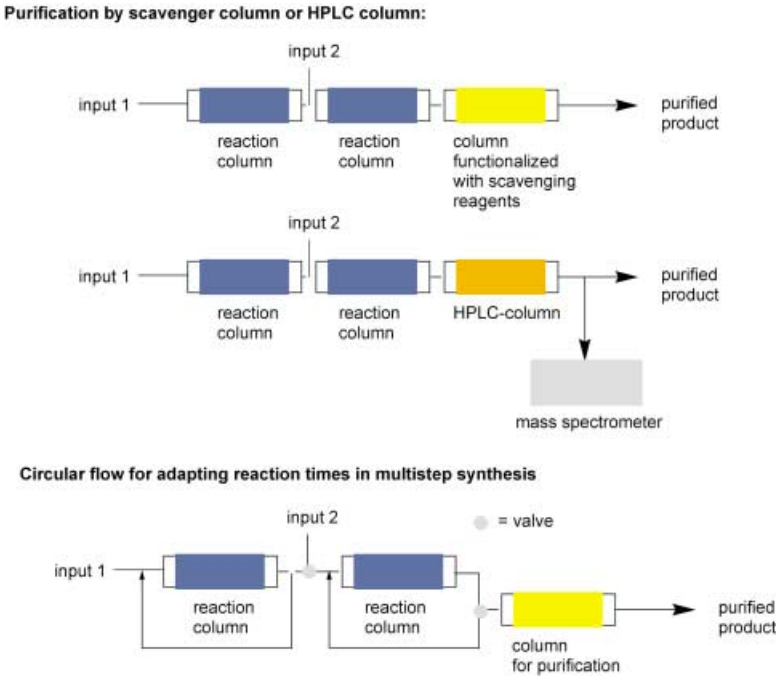


Scheme 6. Concepts for assembling flow-through reactors for different synthetic demands.

the flow system (which is also important if metal-based catalysts are employed that tend to release traces of metals into solution). This demand is easily achieved with HPLC equipment in conjunction with detector devices like mass spectrometry or diode-array detection (Scheme 7).

However, a critical look on flow systems reveals that various difficulties must be encountered. Thus, the realization of reaction sequences by flow-through processes is hampered by some general difficulties. These include a) limitations in the maximum number of sequential reaction steps, b) inert properties of all materials in the flow-through system towards a large variety of different organic solvents, c) the necessity to switch the solvent for selected reaction steps, d) efficient regeneration of reaction columns, and e) facilities to purify intermediates.

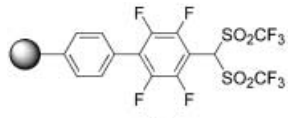
In addition, the reaction times for transformation should be similar in order to avoid complex valve technique for controlling flow rates. If reaction times are too long to achieve complete transformation of the reactants by a single pass through the chemically functionalized reactor, the reaction stream will have to be led in a circular mode through the flow system until a valve directs the products into the next reactor system. From this brief discussion it is already evident that even on a laboratory scale, technical aspects have to be considered besides chemical considerations.



Scheme 7. Combinations of synthetic flow systems with purification and analytical components.

Lately, the utility of flow-through processes has extensively been studied in the field of asymmetric transformations by using immobilized chiral ligands or enzymes (see also previous section). The demand for enantiopure building blocks in fine chemical and pharmaceutical industries is still hampered by the need for simple asymmetric processes that can be scaled up, as well as by the stability, recyclability, and, hence, the price of most chiral catalysts. Immobilization of effective and robust catalytic systems and their application in flow-through reactor systems is regarded to be a key for success in this field.

In a simple example, Yamamoto and co-workers studied the use of super Brønsted acids loaded on polystyrene beads **10** for use in a single-pass column system.[28] It was shown



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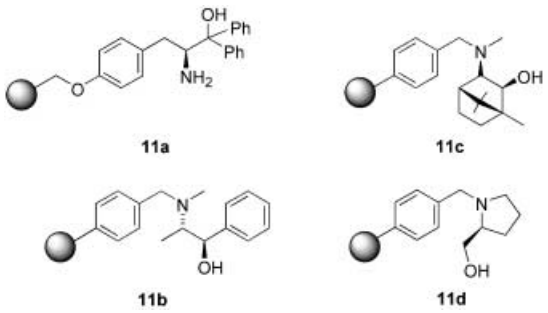
that these columns are suited for the acetylation of alcohols, acetalization of carbonyl compounds, Sakurai–Hosomi allylation reactions, and Mukaiyama aldol reactions.

By immobilization of optically active α or β-amino acohols on cross-linked polystyrenes as in **11a–d**, access to chiral borane complexes is possible; these can be employed in enantioselective reductions of aldehydes and ketones. For example, reduction of acetophenone with a borane complex prepared from **11d** yielded optical active (−)1-phenyl-2-propanol in optical yields up to 100%.[29] Based on this encouraging result a flow system was developed with continuous regeneration of the immobilized complex. In a typical procedure borane and valerophenone were injected in a column loaded with polymer **11a**. Fractions were collected every 30 minutes leading to 1-phenylpentanol batches with enantiomeric excess of 87, 93, and 91%, respectively.[30]

Similarly, diethylzinc was immobilized on resins containing amino alcohol groups and were used in continuous-flow additions to aromatic aldehydes.[31] Thus, diethylzinc and *p*-chlorobenzaldehyde were added simultaneously with slow rate under nitrogen into an ice-cooled column containing the chiral polymer **11a** and 1-(*p*-chlorophenyl)propanol was isolated in 94% *ee*. The authors

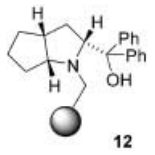


11a **11c** **11b** **11d**

note that 58 mmol of the optically active alcohol were prepared in a continuous process by employing only 0.7 mmol of the polymer-attached catalyst. In view of similar results obtained with immobilized ephedrine the conclusion can be drawn that continuous flow processes are often superior in efficiency and practicability to batch processes. In a closely related approach the polystyrene ephedrine- or polystyrene camphor-catalyzed diethyl zinc addition to benzaldehyde was carried out in a simple bench-top flow system.[32] A round-bottomed tube sealed with a septum cap and filled with low cross-linked polymeric beads **11b** or **11c** was flushed with an aldehyde and a solution of diethylzinc in toluene under nitrogen. Peristaltic pumps were employed to accomplish a flow of the two solutions through the reactor. For this purpose long syringe needles were positioned close to the bottom of the tubes before the solutions containing the reactants passed through the catalyst bed and were released into a flask containing a biphasic solvent system (toluene, dil. HCl) for workup. Yields were commonly good, while the enantiomeric excess was determined to be moderate to very good. It is worth noting that the latter values were found to be higher for the flow-through mode relative to the

corresponding batch systems. The authors ascribed this result to the fact that the flow system principally creates the effect of a high molar concentration of the catalyst, because the initial alkoxide reaction product, which also can act as a catalyst and which would lead to low enantiomeric excess, is continuously removed from the reaction system.

A closely related flow-through approach was pursued by Luis, Martens, and co-workers.[33] Here, polymeric monoliths were prepared according to the work originally disclosed by Fréchet and Svec,[34] and azabicyclo[3.3.0]octane-3-carboxylic acid **12** was immobilized by grafting and polymerization.



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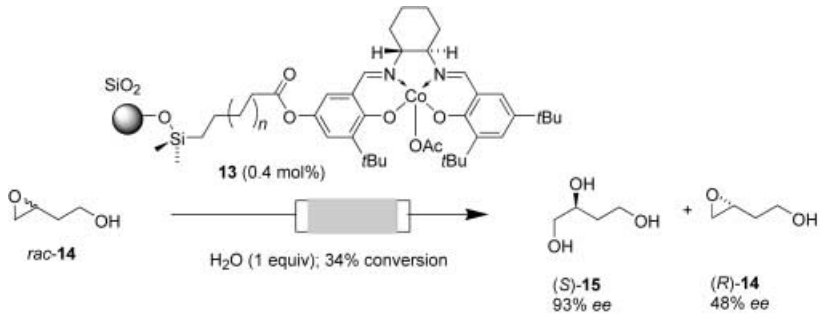
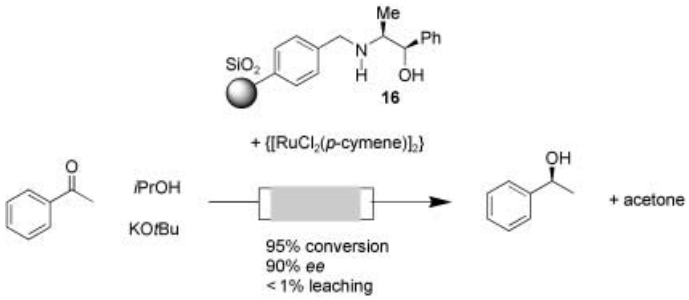
The column was incorporated into a flow system in which it was attached to a pump, and the addition of diethylzinc to benzaldehyde was studied. The monolithic catalyst prepared by polymerization proved to be superior to a catalyst prepared by grafting (compare Schemes 4 and 5) and even to the homogeneous case. High *ee* values up to 99% were obtained, and the authors claimed to have the best supported catalyst to date for this reaction. Differences in appropriate chiral cavities in the polymer is one of the possible explanations for this result, the other one being differences in reaction conditions and most probably the avoidance of diffusional problems in the monolithic catalyst at high flow rates.

From an industrial point of view, particularly in pharmaceutical research and fine chemical synthesis, chiral salen-based catalysts are among the most appealing ones. Indeed, they are useful in synthesis of a plethora of chiral intermediates starting from easy accessable epoxides and they have proven to efficiently work even in large scale. Jacobsen and co-workers[35] developed a synthetic protocol for the immobilization of salen complexes on polystyrene and silica resins by employing unsymmetrically substituted salen ligands **13**. The work opened the door for the application of these catalysts in continuous-flow processes (Scheme 8). The driving force was to ease catalyst recovery. In a model reaction—the hydrolytic kinetic resolution of racemic 4-hydroxy-1-butene oxide (**14**)—it was demonstrated that the reaction mixture can simply be pumped through a HPLC column that was loaded with the catalyst. This setup generated the triol **15** with high enantiomeric excess. In this approach, advantage was taken from the fact that complete conversion of the starting material was not required and a single pass through the column was sufficient to generate the enantiomerically pure ring-opened triol.



Scheme 8. Kinetic resolution of butane oxide **14** in the flow mode.

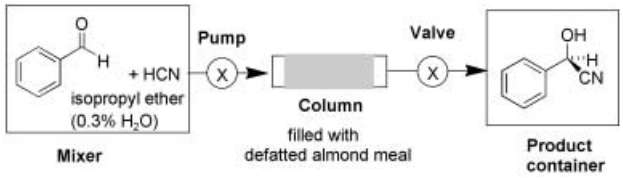
As was demonstrated in this example, inorganic materials are ideally suited for flow-through processes in column-like reactors. Another illustrative example is the covalent immobilization of NH-benzyl-(1*R*,2*S*)-(−)-norephedrine (**16**) onto silica, which after incorporation into a column and doping with ruthenium can take part in continuous asymmetric transfer hydrogenation reactions (Scheme 9).[36] Remarkably, no catalyst deactivation occurred over a period of one week; the authors ascribed this to the successful site isolation on the support.



Scheme 9. Asymmetric transfer hydrogenation in the flow mode.

Continuous-flow processes have traditionally been applied in enzyme-mediated transformations. Particularly when the enzymes are available in an immobilized form, enzymatic transformation can be efficiently performed in a continuous way in a tubular reaction vessel. Other intrinsic advantages are simplified isolation of the enzymes from the reaction mixture, stability and reuse of the enzymes, and, in some cases, improved reaction kinetics.[37]

Based on this knowledge, a solution of aldehydes and HCN in isopropyl ether doped with water were pumped through columns filled with defatted almond meal (Scheme 10). The cyanohydrins were isolated in yields above 90% and stereochemical purity between 97 to >99% *ee* with high substrate/catalyst ratio.[38] The output of 3.653 g of product per liter of almond meal per day could be achieved, and an equivalent to 66.7 mol g^{-1} pure enzyme was produced. Remarkably, the column retained its high catalytic activity after 2 mol of substrates had been passed through. The authors emphasize that no purification step was needed and the crude products could be used for further transformations. Flow rates do have an influence on yields and enantioselectivity of



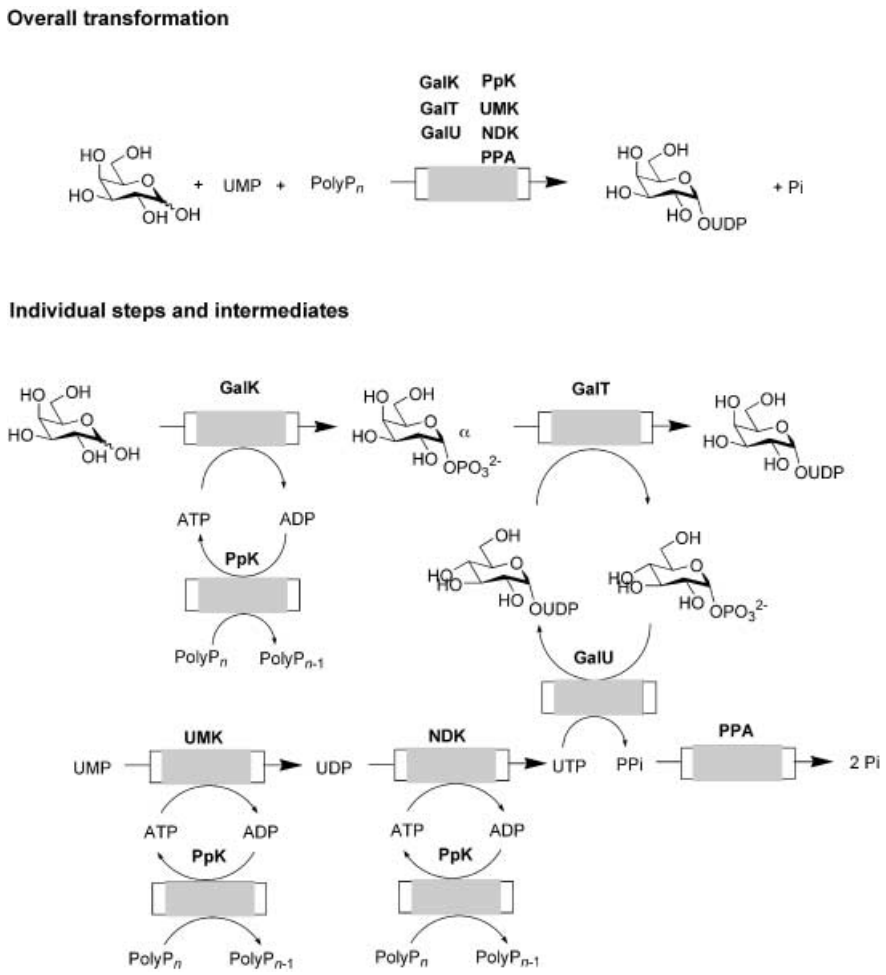
Scheme 10. Enzymatic cyanhydrine formation in a flow-through reactor.

the process. A simple rule of thumbs was presented by the authors for calculating optimized flow rates for this process.

Recently, Wang and co-workers[39] reported a flow-through approach for the efficient and practical gram-scale synthesis of UDP-galactose from inexpensive starting materials. The synthesis was guided by a proposed biosynthetic pathway. Remarkably, they applied no less than seven overexpressed enzymes, each of them immobilized by histidine tags on nickel agarose beads (Scheme 11). The reaction mixture, which contained all starting materials, was continually circulated through a column loaded with all enzyme-charged beads. The space/time yield of the on-column reaction was superior to the classical solution-phase approach, although the reactions proceeded with slower kinetics than in solution. The immobilized enzymes could be reused at least four times with only slight loss of activity. The authors noted that this approach allows the production of UDP-galactose at very attractive costs in gram amounts compared to very expensive commercially available material.

New Trends in Continuous-Flow Processes by Combining Different Technologies

The examples listed in the previous section concentrate on the immobilized catalytic system and its performance in synthetic applications. Little attention, however, has been devoted to the optimization of the solid support in these applications, the ideal linkage which allows easy regeneration, and the reactor design necessary to promote continuous-flow processes. In addition, reaction parameters can be improved by implementing new technologies such as microwave assistance, which will be discussed in this section, or new solvent systems (ionic liquids, and super critical CO_2) into the flow process.



Scheme 11. Multistep enzymatic preparation of UDP-galactose in the flow-through mode. GalK (Galactokinase; EC2.7.7.6), GalT (galactose-1-phosphate uridylyl transferase; EC 2.7.7.12), GalU (UDP-glucose pyrophosphorylase; EC 2.7.7.9); PPA (inorganic pyrophosphatase; EC3.6.1.1), UMK (UMP kinase; EC2.7.4.14), NDK (nucleotide diphosphate kinase; EC2.7.4.6), PpK (polyphosphate kinase; EC2.7.4.1).

As described above, we were the first to develop a chemically functionalized monolithic material based on a glass/polymer composite.[25,26] After its chemical functionalization (e.g., substitution of the benzylic chlorine by trimethyl amine) these rods were first embedded in a solvent resistant and shrinkable PTFE tube. This was followed by encapsulation with a pressure-resistant, fiber-reinforced, epoxy-resin housing with two standard HPLC-fittings which created a microreactor (Figure 4). This PASS-flow reactor (about 110 mm in length, about 5 mm diameter) loaded with the strongly basic ion exchange resin (about 10 to 20 mass % polymer) can be functionalized with various anions. The synthetic properties of these chemically functionalized flow-through reactors **17**–**20** were first tested for basic transformations, such as substitution, oxidation,[40] reduction, and Horner–Wadsworth–Emmons (HWE) olefination (Scheme 12).[25,41] Due to general slow reaction kinetics the reactor was operated with external recycle loop and no optimization was done towards single pass operations (Figure 4). In

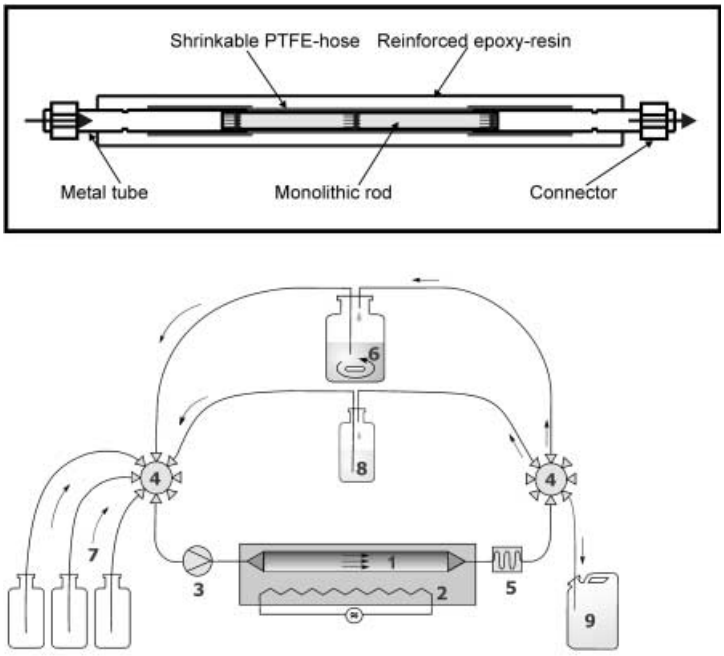


Figure 4. Cross-sectional view through the PASSflow reactor (PTFE = polytetrafluoroethylene) and setup of the flow system. PASSflow reactor Flow system: 1 microreactor, 2 oven, 3 pump, 4 valve unit, 5 chiller, 6 flask used for circulating the reaction components, 7 solvents/reagents, 8 reagent for loading the microreactor, 9 waste.

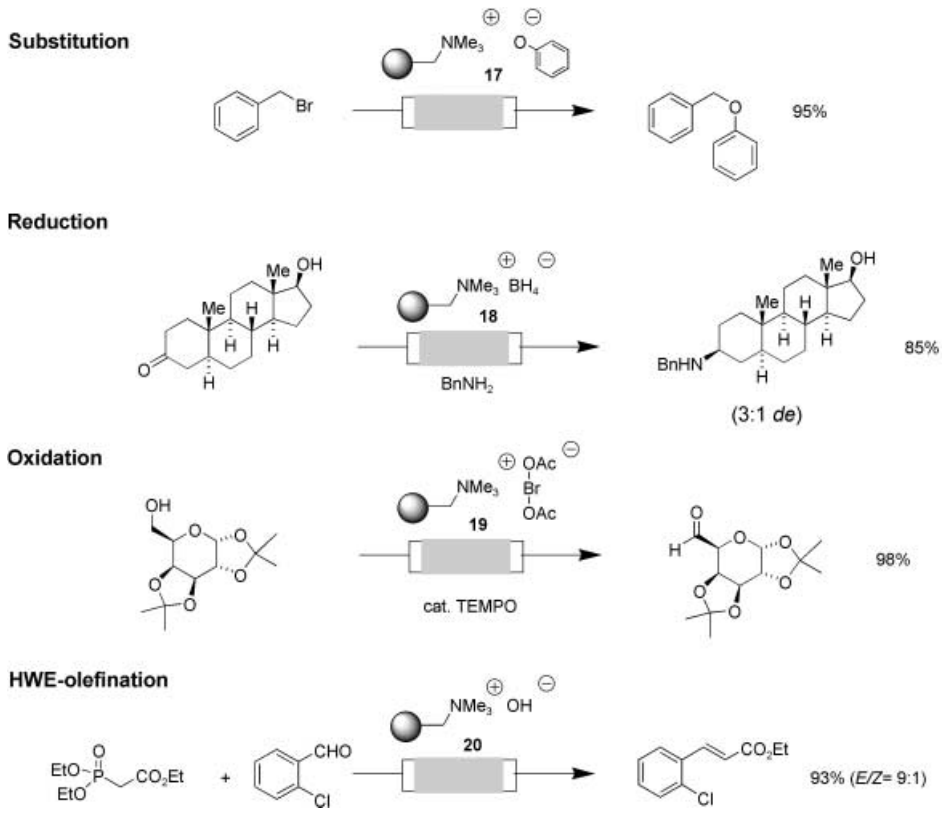
all cases, complete transformation of the starting material was observed; byproducts and excess of immobilized reagents, such as bromide, phenolate, phosphonate, and others, remained ionically bound to the polymeric phase. The products were isolated in excellent yield by simple removal of the solvent.

In addition, catalytic transformations like transfer hydrogenations,[42] Suzuki cross-coupling reactions and the Heck reaction can routinely be conducted in these PASSflow reactors as summarized in Scheme 13.

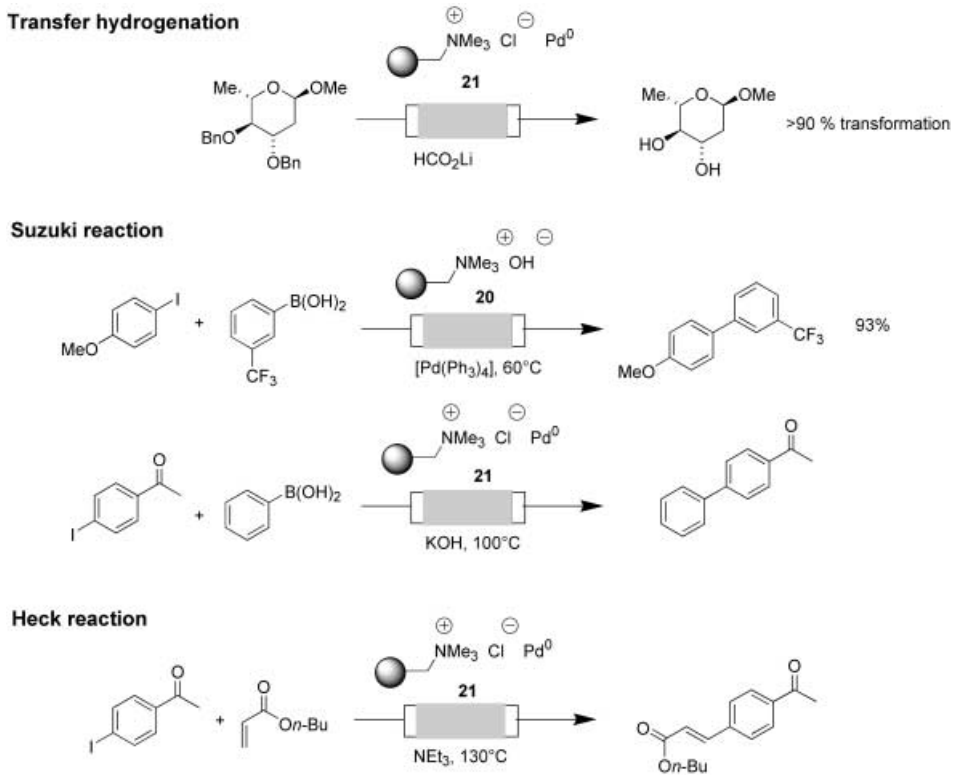
All these reactions were conducted in the flow-through mode by immobilizing microdispersed palladium (**21**) next to polymer-bound ammonium cations. This was achieved after ionic attachment of Pd as palladate, followed by reduction to Pd^0 by pumping a solution of borohydride or hydrazine through the reactor. Besides benzyl ether cleavage, transfer hydrogenations were utilized for the reduction of alkenes, alkynes, and aromatic nitro groups. According to the protocol developed by Vaultier and co-workers, the Suzuki reaction can alternatively be conducted by in situ immobilization of an excess of boronic acid to a strongly ionic exchange resin **20** in the presence of the aryl halide and a homogeneous palladium catalyst.[43] All three components are pumped through the PASSflow reactor, and the boronic acid is spontaneously transformed into the boronate anion and bound to the solid phase.

The first example of an asymmetric transformation in a PASSflow reactor was achieved with the known dynamic kinetic resolution of racemic bromohydrine in the presence of water and an unsymmetrical salen–cobalt complex **22** (Scheme 14).[44] This complex was bound to a Merrifield surface through a glutaric acid linker. The yield and the enantiopurity of the resulting 1,2-diol are similar to those reported for the solution phase.[45] However, workup and isolation of the product are highly simplified, which makes this approach attractive for use in fine chemical synthesis of enantiomerically pure building blocks.

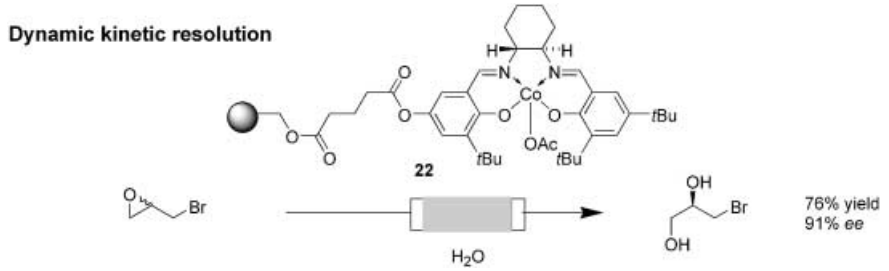
Reaction rates for the flow-through processes were compared with analogous batch-mode reactions by using the commercial resin IRA-900. In general, these rates were considerably higher when the reaction mixture was pumped through the irregular microchannels of the monolithic structured reactor. This clearly indicates that the monolithic and functionalized material guarantees short diffusion path lengths for the



Scheme 12. PASSflow syntheses with immobilized stoichiometric reagents.



Scheme 13. PASSflow syntheses with immobilized palladium catalysts.

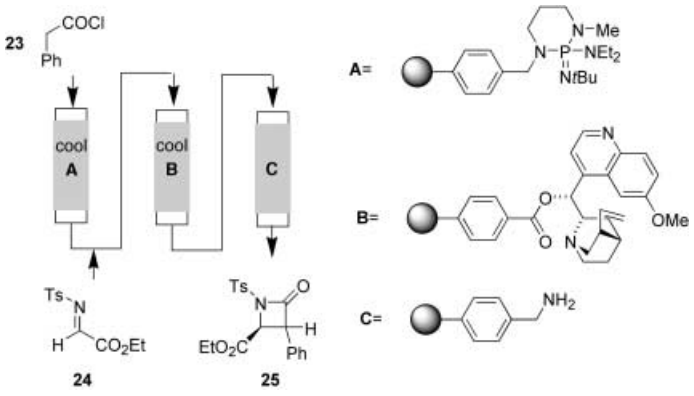


Scheme 14. Application in asymmetric PASSflow synthesis.

soluble organic reactants and products and, in addition, enables good convective flow.[46]

The power of columnlike reactors that are employed in a flow-through environment lies in the possibility to sequentially link them up in order to carry out multistep syntheses in solution in one run (see also Schemes 6 and 7). Lectka and co-workers employed conventional fritted and jacketed columns and filled them with conventional functionalized polymer beads.[47] The continuous flow was forced by gravity. En route to β-lactams like **25**, polymer beads were employed that were functionalized (Scheme 15) either with 1) the Schwesinger base **A** for the generation of phenyl ketene from phenylacetyl chloride **23**, 2) a cinchona alkaloid derivative **B** as a chiral catalysts for achieving the [2+2] cycloaddition in the presence of imine **24**, or 3) a primary amine **C** to scavenge traces of intermediate ketene and phenyl acetyl chloride **23**.[48] β-Lactam **25** was isolated in 65% yield (91% *ee*). It has to be noted that this single pass concept is only feasible when fast reactions are chosen; this is not necessarily guaranteed when employing immobilized reagents and catalysts. Furthermore, each of the three reactions has to proceed with similar rate.

First introduced by Giguere in 1986[49] microwave-assisted synthesis has evolved as a versatile tool in organic chemistry. Particularly, in the drug discovery approach it has found widespread acceptance due to dramatic shortening of reaction times.[50] With the current microwave equipment, scale-up of a batch reaction in a microwave field is restricted to volumes well below one liter, due to safety reasons. However, reactions that are carried out in a flow-through mode with immobilized reagents or catalysts may be an option to scale up reactions under microwave irradiation. Hence, this concept was first tested by Strauss and co-workers, who developed a continuous microwave reactor (CMR; Table 1).[51] It operates by passing a reaction mixture through a pressurized, microwave-transparent coil that is held in a microwave cavity. The laboratory-scale reactor can be run rapidly and safely in various solvents. Numerous reactions have been carried out which include nucleophilic substitutions, 1,2-additions, esterifications, transesterifications, acetalizations, amidations, base- and acid-catalyzed hydrolyses, isomerizations, decarboxylations, eliminations, Michael additions, Hofmann degradations, Williamson ether syntheses, and Mannich, Finkelstein, Baylis–Hillman, and Knoevenagel



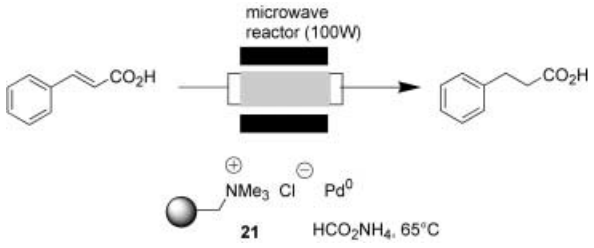
Scheme 15. Three-step preparation of β-lactams in the flow mode.

Table 1. Selected microwave reactions under flow conditions according to Strauss and co-workers.[51]

Reaction	T [°C]	P [kPa]	t [min]	Product	Yield [%]
HOAc + *i*PrOH/H^+	152–5	1200	1.3	*i*-PrOAc	98
PHCOOEt + 5% NaOH	166–8	700	1.0	PhCOOH	100
PhMe + $KMnO_4$/KOH	180	1050	1.3	PhCOOH	41
Ph(CO)Ph + NH_2OH*x*HCl/pyr., EtOH	164	500	1.5	benzophenone oxime	93
$[PhCOCH_2CH_2NMe_3]^+I^-/H_2O$	90–5	100	1.6	$PhCH{=}CH_2$	96

reactions. Technical details include polymerized fluorinated alkanes (PFA; Teflon) or quartz tubing (3 m length), which allow flow rates of approximately 15 mL min^{-1} and residence times of 1–2 min. The processing rates were reported to be around 1 L h^{-1} with a void volume of approximately 25 mL.

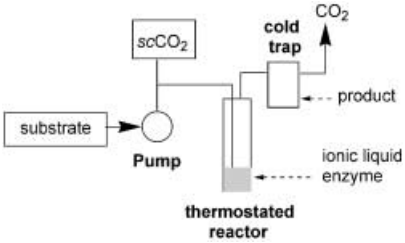
Microwave conditions can also be successfully adapted to solid-phase synthesis,[52] but continuous methods are hardly known. Only very recently the PASSflow approach was applied to microwave reactions under flow-through conditions for the first time (Scheme 16).[53] Thus, cinnamic acid



Scheme 16. Microwave-assisted, flow-through transfer hydrogenation with microdispersed Pd^0.

was reduced under transfer hydrogenation conditions with microdispersed Pd^0 as catalyst (see also Scheme 13). The transparent flow-through reactor was incorporated into a microwave field; this resulted in the acceleration of the process. Indeed, after five minutes 97% of the hydrogenated product was formed and after ten minutes only the product could be detected.

A technologically new and interesting flow-through process for enzymatic reactions was disclosed by Reetz and Leitner.[54] The group designed a protocol for enzymatic reactions, namely the lipase-catalyzed acylation (CAL B) of octan-1-ol by vinyl acetate in ionic liquids {1-butyl-3-methylimidazolium bis(trifluoromethanesulfonimide) [BMIM][BTA]} by using supercritical CO_2 as the mobile phase (Scheme 17). The alcohol is pumped through the biphasic



Scheme 17. Enzymatic transformation in the flow-through mode using ionic liquids for the immobilization of the enzyme and supercritical CO_2 as fluid.

system, and the products are obtained in solvent-free form in a cold trap. The enzyme/ionic liquid mixture can be recycled in batchwise or continuous-flow operations.

An interesting approach towards continuous-flow processes is membrane technology, which has great potential in catalyst recovery. It can be considered as a particular heterogenization method of soluble catalysts and reflects the fact that recycling of homogeneous transition-metal catalysts is very expensive or even impossible.[55,56] Catalysts are separated from the reactants and products by a polydimethylsiloxane (PDMS) membrane prepared such that the catalyst is not able to pass the membrane. In very recent publications the coupling of catalysis to dialysis was reported.[57] Homogeneous (1,1′-binaphtalene)-2,2-diyl-bis(diphenylphosphane) (BINAP) or tosyl-*N*,*N*′-diphenyl-1,2-ethanediamine (TsDPEN) catalysts applied in transfer hydrogenations could be recovered efficiently and reused several times without loss of activity.Figure 5

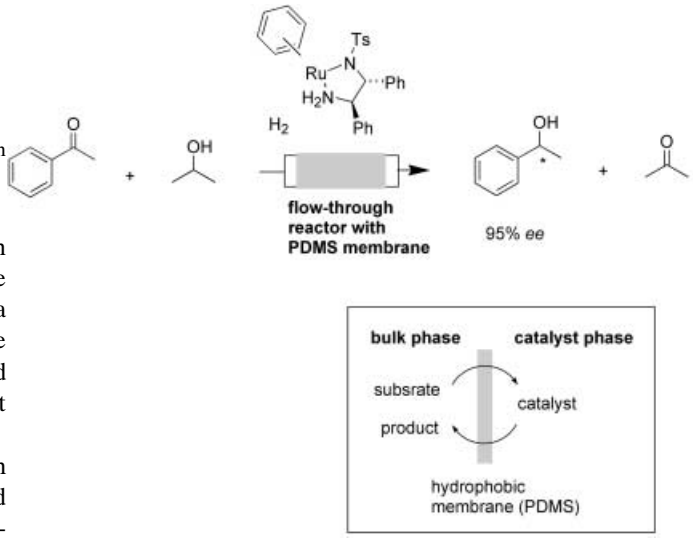


Figure 5. Enantioselective reduction of acetophenon by dialysis coupled catalyis.

Concepts from Microreaction Technology

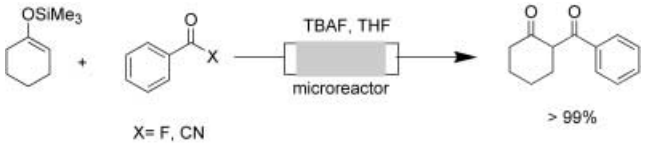
Since their birth more than a decade ago microreactors have been considered as an innovative and revolutionary tool in chemical synthesis.[58] Microreactors generally consist of a series of interconnecting channels (10–300 microns in diameter) in a planar surface in which small quantities of reagents can be manipulated. The reagents are brought together in a specified sequence, mixed, and allowed to react for a specified period of time in a defined region. Evidently, the continuous-flow approach is inherent for microreactors, whether it is based on the (computer-controlled) usage of syringe pumps, HPLC pumps, peristaltic pumps, individually de-

signed membrane pumps, or induced by electroosmotic flow without using any moving part. It is worth noting that the synthesis itself must not be performed under continuous flow, often a continuous mixing of reactants is sufficient. Basic options are scale-up achieved by massive parallelization and spatial and temporal control of chemical reactions, coupled with the typical features of very small reaction volumes and high surface interactions. They can advantageously been exploited in reactions that are hard to control, and interesting applications were found in the fluorination of aromatics and gas-phase reactions with elemental fluorine, which is a strongly exothermic process. Here, microreaction technology is superior to standard chemistry due to the very efficient mixing and reaction control.

Despite some success regarding industrial production processes only very little attention was paid to applications in standard laboratories up to now. This might be due to the high costs of equipment concomitant with that technology. The application of microreactors in organic synthesis has been reviewed recently,[59] focusing on the fabrication and applications of microreactor devices mainly made out of quartz, glass, metals, and polymers.

Recently, remarkable progress has been achieved by the group of Haswell. They expanded and simplified continuous-flow processes to routine laboratory applications including high-throughput chemistry.[60]

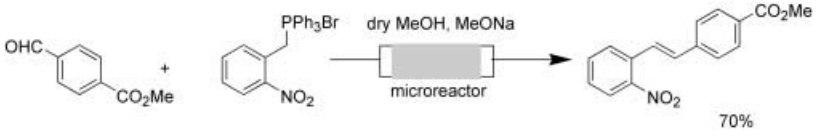
Two significant advantages of microreaction technology are dramatically reduced reaction times combined with increased degree of purity of reaction products. This was demonstrated in the synthesis of 1,3-diketones from a silylenol ether and an acyl fluoride in the presence of a solution of tetrabutylammonium fluoride (TBAF) (Scheme 18). This reaction mixture was passed through a borosilicate glass micro reactor passed by electroosmotic flow (EOF).[61] The conversion of the silylenol ether proceeded quantitatively and formation of byproducts was not observed, whereas the batch process required reaction times of about 24 hrs.



Scheme 18. Acylation of a silyl enol ether in a microreactor device by electroosmotic flow.

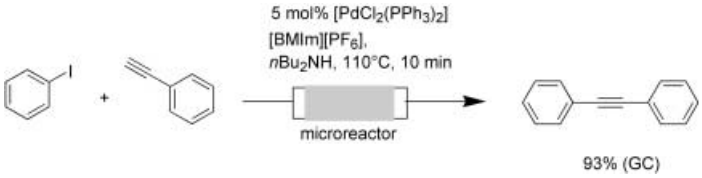
The EOF protocol has been expanded to the multistep, solution-phase synthesis of β-peptides by using a borosilicate glass microreactor.[62,63] Routinely, dipeptides could be synthesized by the well-known carbodiimide coupling procedure or the activation by pentafluorophenyl esters, but, principally, access to longer chain peptides such as tripeptides was demonstrated.

In a similar reactor device the group prepared nitrostilbene esters under Wittig olefination conditions by means of EOF for transport of reagents and products in conventional solution-phase chemistry (Scheme 19). In order to avoid too many byproducts an injection profile was developed that even allowed a 1:1 stoichiometry for aldehyde and triphenylphosphonium bromide.[64] Under optimized conditions the product of 2-nitrobenzyltriphenylphosphonium bromide and 4-formylbenzoate gave a 10% better yield than in the corresponding batch reaction. Three additional examples showed that the yields are generally comparable to batch processes. The authors emphasized that the reactor could not only be used for rapid reaction development and optimization, but has some potential for the preparation of combinatorial libraries.



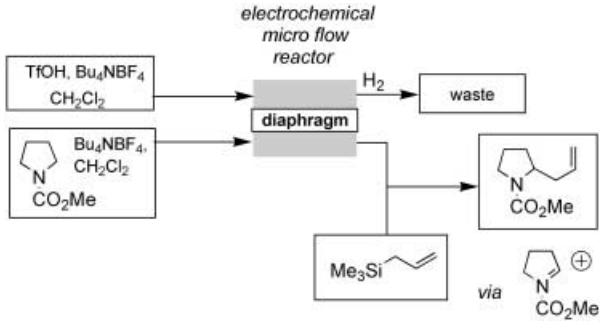
Scheme 19. Wittig olefination in a microreactor device according to Haswell et al.

Ryu et al.[65] described the first successful example of a Sonogashira cross-coupling reaction in a microflow reaction device. This example is one of the first homogeneous metal-catalyzed reactions performed in a microeactor (Scheme 20).[66] A mixture of iodobenzene, phenylacetylene, and *n*-dibutylamine was introduced at one inlet of a micromixer.[67] The catalyst $[PdCl_2(PPh_3)_2]$ in the ionic liquid [BMIm][PF_6] (*N*-butyl-*N*′-methyl-imidazolium hexafluorophosphate) was introduced at 110 °C through a second inlet by means of syringe pumps at flow rates of 0.1 mL h^{-1} (Scheme 20). After homogenizing the reagents in the micromixer the reaction mixture was removed from the outlet after 10 min. The product could be easily separated by extraction with hexane/water leaving the catalyst in the ionic liquid allowing efficient recycling and reuse of the catalyst.



Scheme 20. Sonogashira reaction in a microreactor.

In an interesting approach demonstrating the versatility of microreaction technologies for manipulations of reactive intermediates, Yoshida and co-workers[68] used a low-temperature electrochemical microflow system[69,70] for continuously generating carbocation intermediates (called "cation flow"). These species reacted in C–C bond formations with allylsilanes and silyl enol ethers as carbon nucleophiles. The microreactor was mechanically manufactured and made of diflone and stainless steel bodies with a diaphragm made of

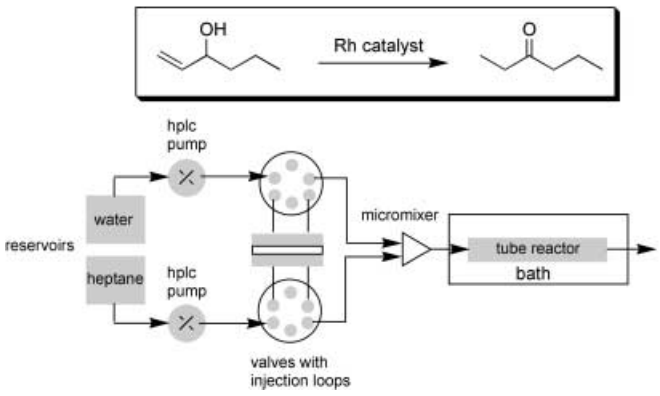


Scheme 21. "Cation flow" method for the handling of reactive intermediates.

PTFE (Scheme 21). The electrodes required for the cation flow consisted of a carbon felt anode and a platinum wire electrode. In a typical experiment a 0.05 M solution of methyl pyrrolidine carboxylate in dichloromethane, containing a supporting electrolyte (Bu_4NBF_4, 0.3 M), was introduced by a syringe pump to the anode chamber with cooling (−72 °C, flow 2.1 mL h^{-1}). A solution of the supporting electrolyte and trifluoromethanesulfonic acid as a proton source was introduced to the cathodic chamber. The cationic intermediate was generated by low-temperature electrolysis with subsequent transport in a usual reaction vessel containing the carbon nuleophile.

Finally, de Bellefon and co-workers[71] described a new approach to achieve high-throughput screening of polyphasic fluid reactions and applied microreaction technology to liquid–liquid isomerization of allyl alcohols and gas–liquid asymmetric hydrogenation. Both processes are of considerable industrial interest. The apparatus is depicted in Scheme 22.

While the carrier liquid phases were continuously pumped through the apparatus a pulse injection of catalyst and substrate was used for mixing both in a static micromixer. Noteworthy, the heptane/water emulsion remained stable for a couple of minutes. The reaction itself proceeded in a thermostated tube reactor (80 × 0.4 cm) with a mean residence time of the mixture of 100 s. Due to the pulse injection protocol a library of various catalysts could be screened towards their potential for the isomerization of 3-hydroxy-



Scheme 22. Dynamic screening of catalysts in polyphasic fluid reactions according to Bellefon.[71]

hexene to 3-hexanone. The concept could successfully be transferred to the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic methyl ester. As was demonstrated by parallel investigations both processes were fully equivalent to the reactions performed in batch reactors.

From these studies it is evident, that the final goal of microreaction technology is to enable combinatorial (parallel) chemistry on a chip containing multiparallel channels.

Perspectives and Outlook

A plethora of chemical methods available at the end of the 20th century creates the impression that every possible molecule can be prepared regardless of its structural complexity. It seems to be only a question of manpower to reach a synthetic goal in a reasonable amount of time. This impression, however, denies the fact that many synthetic routes and chemical methods are far from being highly efficient, particularly when multistep sequences are envisaged. Moreover, despite the tremendous efforts in automation and the development of new chemical methodologies in the past ten years there is an overall deficiency for new chemical technologies. Flow-through processes can be considered to be a significant breakthrough towards more efficient syntheses including mutlistep sequences.

It is our utmost belief that the time has come to include technological questions into chemical research; this is especially important in the consideration of new chemical methods in organic synthesis. The examples given in this overview show that is fruitful to leave classical thinking behind and to combine and merge new methodologies and technologies to create new platforms for conducting synthesis. Indeed, as we tried to show, flow-through processes can already be combined with functionalized solid phases, with ionic liquids, supercritical CO_2, and microwave irradiation. Nevertheless, the number of examples of flow-through processes performed in the laboratory is still small, but we predict a bright future for this approach. Times will soon come when many chemists will be able to perform flow-through processes with standard laboratory equipment at reasonable prices and take advantage of this new approach. Whatever chemists require—synthesis of few milligrams of a compound in drug discovery, the synthesis of building blocks in multigram scale for parallel synthesis, the preparation of kilogram quantities for clinical research, or even the production of fine chemicals—flow-through processes are a universal lever and a crucial link between differently scaled reactions. The door has opened for a similar development in chemical synthesis that happened in analytical chemistry when HPLC conquered the laboratories and took them by storm.

Acknowledgments

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contributions in the field of PASSflow technology. Furthermore, we thank Solvay Pharmaceuticals (Hannover, Germany), Bayer AG (Leverkusen, Germany) as well as Novabiochem (Switzerland) for financial and technical assistance.

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