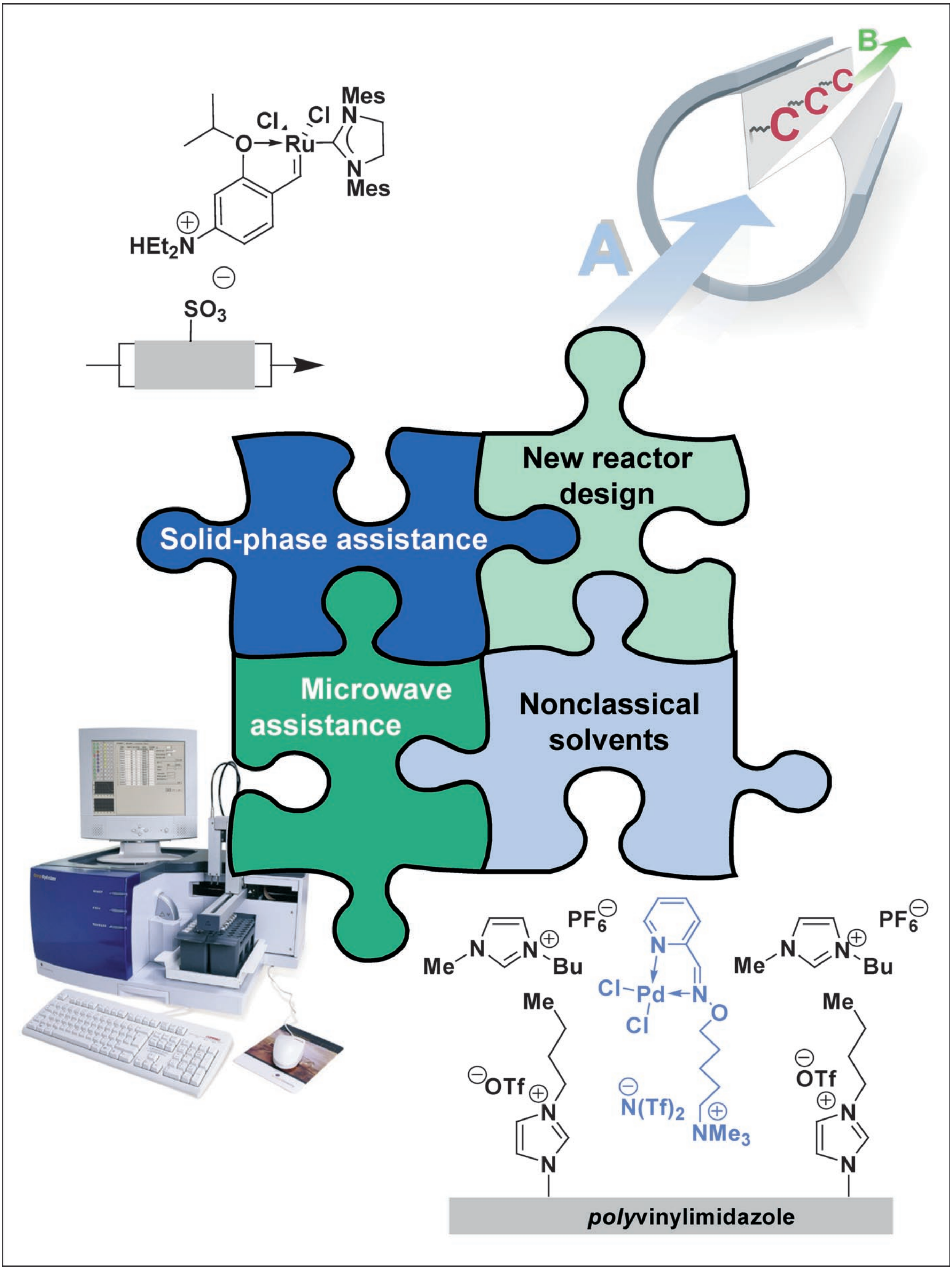
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Combining Enabling Techniques in Organic Synthesis: Continuous Flow Processes with Heterogenized Catalysts

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Abstract: The concepts article describes enabling techniques (solid-phase assisted synthesis, new reactor design, microwave irradiation and new solvents) in organic chemistry and emphasizes the combination of several of them for creating new synthetic technology platforms. Particular focus is put on the combination of immobilized catalysts as well as biocatalysts with continuous flow processes. In this context, the PASSflow continuous flow technique fulfils both chemical as well as chemical engineering requirements. It combines reactor design with optimized, monolithic solid phases as well as reversible immobilization techniques for performing small as well as large scale synthesis with heterogenized catalysts under continuous flow conditions.

Keywords: C–C coupling • heterogeneous catalysis • immobilization • microreactors • organic chemistry

Introduction

Despite the rapid and often underscored developments in synthetic methodology during the last decades—whether they have been achieved in catalysis, asymmetric synthesis, combinatorial chemistry or other areas—organic synthesis is still performed in a very traditional setup mainly focussing on the reactions themselves and improving them artfully in terms of efficiency (yield) and selectivity (chemo-, regio- and stereoselectivity). Indeed, compounds are commonly synthesized batchwise regardless of the kind of chemistry chosen. Aspects of technology are only recently creeping into the chemist's dictionary in a broader sense. Nowadays, with the peak of combinatorial chemistry[1] being in the near past, aspects of automation and the quest for improved technologies in synthesis, workup and isolation still prevail and remain to be of fundamental importance and in fact have even become part of research programmes in academia. Consequently, so-called *enabling techniques* have emerged in the past decade and have influenced the way organic synthesis is conducted to a very large extent.[2] In this overview we shall give a brief introduction into enabling techniques that can be utilized in organic synthesis and demonstrate how combination of different enabling techniques lead to new synthetic technology platforms. In this context, we shall particularly focus on continuous flow processes being part of new synthetic technology platforms.

Definitions

What are enabling techniques in organic synthesis?

Enabling techniques summarize various traditional as well as new techniques which have been developed to speed up synthetic transformations and importantly ease workup as well as isolation of products. While catalysis and solid-phase assistance, electrochemistry and synthesis under high pressure are by now traditional examples for accelerating reactions and/or for workup simplification other techniques have been added to the portfolio of enabling techniques recently. These are briefly summarized.

Catalysis: Although catalysis is an established and powerful concept in modern organic synthesis though not necessarily belonging to the new enabling techniques, its current status is briefly summarized here, because this report mainly focuses on catalysis in the context of enabling techniques. Indeed, catalysis will also undoubtedly play a key role in the future. Biocatalysis is already an established field in terms of industrial application and production while in the field of transition-metal catalysis palladium- and ruthenium-based cata-

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lysts are currently the main focus and are moving into industrial applications in a broader sense.[3] Organocatalysis has only been emerging as a new field of catalysis after an induction time of about 30 years.[4] In the context of enabling techniques, solid-supported catalysts as well as tagged catalysts[5] are already important and applicable for biocatalysts. This technique will become particularly important for chemical catalysis because the realm of newly developed homogeneous transition-metal catalysts including those with chiral ligand systems for asymmetric transformations can be used under heterogeneous conditions. The supported catalysts themselves can easily be separated from a reaction mixture and be reused after regeneration.

Solid-phase assistance: Solid-phase-assisted synthesis, dating back to the seminal work by Merrifield,[6] has become a popular tool for the preparation of peptide and oligonucleic acid libraries with minimum purification. As part of high-performance automation and combinatorial chemistry, reliable synthesis of heterocycles has recently been added to solid-phase applications. An alternative to this classical approach is the solid-phase assisted solution-phase synthesis using immobilized reagents or catalysts.[7,8] The intrinsic advantage of this hybrid solid-/solution-phase technique lies in the simple purification and monitoring of reactions and the possibility to use immobilized reagents in excess to drive the solution-phase reactions to completion. Various subtechniques have emerged which make use of functionalized solid phases such as scavenging reagents[9] and the resin catch-and-release technique.[10]

New solvent systems: Ever since the initial report by Horváth and Rábai,[11] fluorous biphasic systems have received much attention as a tool for the separation and recovery of reagents or catalysts. The concept is based on the temperature-dependent immiscibility of perfluorinated solvents and common organic solvents.[12] Organic compounds are usually not soluble in perfluorinated solvents, but the solubility greatly increases when perfluoroalkyl chains, so called perfluoro tags, are attached to the molecule. These properties can be exploited in separation and workup protocols.

Likewise, ionic liquids (IL's) have attracted attention as alternative reaction media in biphasic media.[13] Because of their highly polar nature they are immiscible with many organic solvents. This forms the basis for biphasic reactions where the catalyst or the reagent is present in the ionic liquid while the substrate stays in the organic phase. Reagents or catalysts that are not polar enough in order to be only miscible in ionic liquids can be tagged with polar or ionic liquid type functional groups, for example, which may become task specific onium salts (TSOS) that in conjunction with ionic liquids afford so called task specific ionic liquids (TSIL).[14]

Finally, supercritical fluids can advantageously be employed for the separation of homogeneous catalysts,[15] a technique that has seen primary applications under continuous flow conditions.[16a] This setup guarantees that the catalyst always stays in its active state inside the reactor. Additionally, comparative small reactors allow high-throughput transformations.[16b–d]

Microwave (μw) acceleration: Over the past decade the use of microwaves has grown exponentially in chemical synthesis. Microwave conditions are applied in many types of chemical transformations and the area of organic synthesis has benefited significantly from this technique. Microwave conditions have been applied to most types of chemical transformations promoted by heat, largely due to the frequently observed acceleration in reaction rates, reduced reaction times and higher yields. Whilst the actual nature of the effect of microwaves remains a subject of intense debate, the heating under microwave conditions is explained by the wave-material interaction (dielectric and conduction losses).[17] This methodology recently finds scope in the more advanced and sophisticated areas such as combinatorial, medicinal chemistry and high-throughput parallel synthesis.[18]

Continuous-flow and microreactors: The environment in which synthesis is conducted has not changed as reactions are still typically performed batchwise in standardized glassware which has commonly been used since Justus Liebig's times. Thus far, flow-through processes are rather restricted to production processes. This is surprising since facile automation, reproducibility, safety and process reliability can be assured due to constant reaction parameters (such as temperature, time, amount of reagents and solvent). Advantageously, continuous-flow processes can be further improved by techniques that originate from high-throughput chemistry laboratories as they can be combined with the use of immobilized reagents or catalysts, or by parallelizing fixed bed reactors. Only recently chemists in industry as well as in academia have begun to focus on the development of flow devices for laboratory use and hence for industrial applications by combining new chemical techniques with flow-reactor devices.[19,20] These techniques include microwave assistance, the use of immobilized reagents and catalysts as well as new fluids such as supercritical CO_2 and ionic liquids.[21] Membrane reactors or nanofiltration devices are commonly required when the reagent or catalyst operates as a size enlarged species in solution[22] by being attached to soluble solid phases, dendrimers or other tags.[23]

However, a critical view on flow system reveals that various aspects must be encountered. Thus, the realization of flow-through processes is hampered by some general difficulties which include a) inert properties of all materials in the flow-through system towards a large variety of different organic solvents, b) efficient regeneration of reaction columns, c) facilities to purify intermediates or final products and d) problems associated with different kinetics of reactions and the necessity of different solvents when performing multistep syntheses in the flow-through mode.

Concepts of combining enabling techniques

In fact, truly new synthetic technology platforms, however, will not be based on the individual use of these enabling techniques but will require the integration of two or more of these enabling techniques. For clarification, four possible overlapping areas between enabling techniques are suggested in this overview (Figure 1). Other combinations are possible or three instead of two techniques can be utilized simultaneously in synthetic applications. For a given reaction, the best combination will have to be determined and optimized. Thus, the setup will vary from one to another reaction. Various successful examples of combining several of these techniques in order to achieve faster synthesis or improved work-up have recently appeared in the literature, particularly in the field of catalysis. Before focussing on new reactor designs the concept of combined enabling techniques is exemplified with three binary combinations.

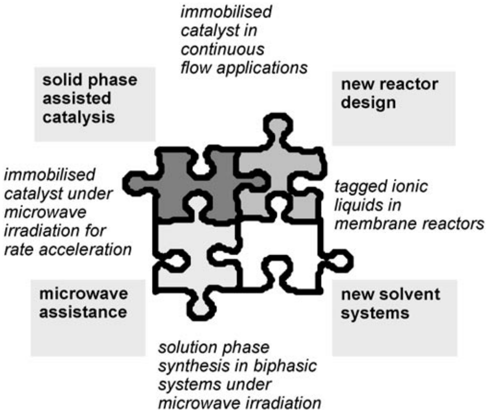
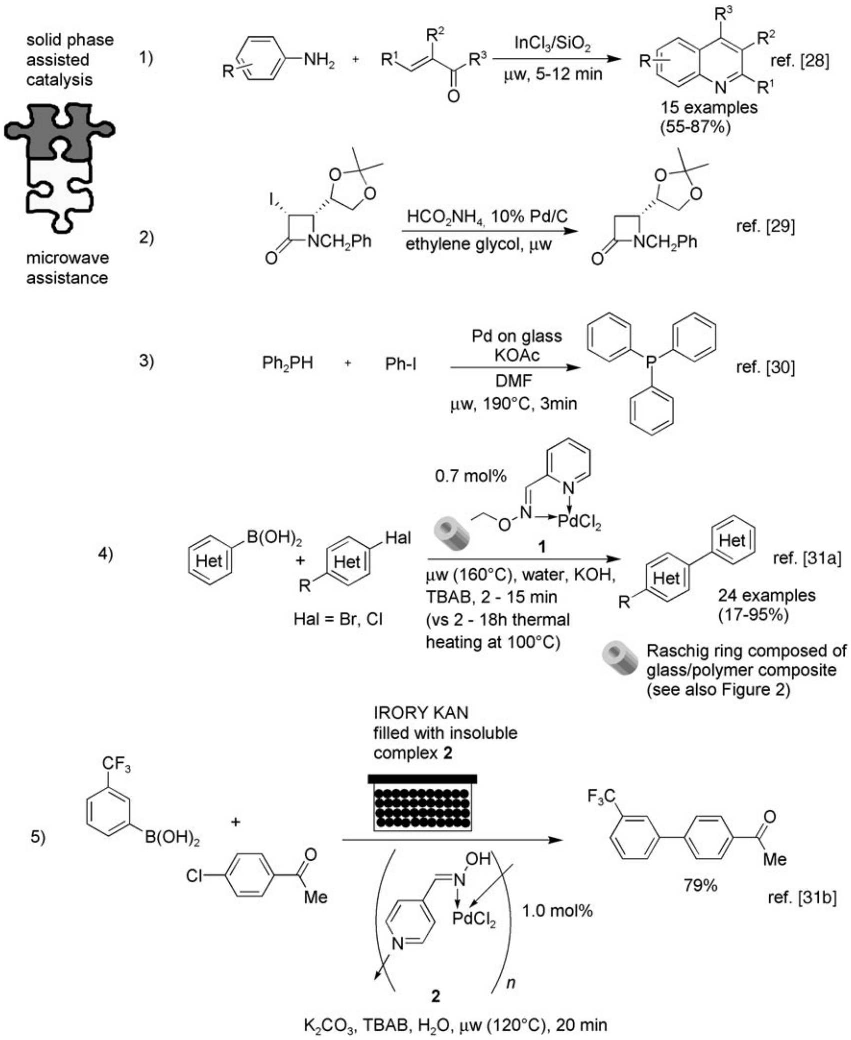


Figure 1. Enabling techniques and selected proposals of possible combinations for developing new synthetic platforms (with special focus on solid-phase assisted catalysis).

Combination of microwave assistance and continuous flow: Thus, microwave-accelerated synthesis under continuous flow conditions[24] was recently achieved in the synthesis of substituted pyridines employing the Bohlmann–Rahtz reaction.[25] In a related study Organ et al. used a capillary to carry out microwave-assisted Pd-catalyzed cross-coupling reactions, olefin metathesis and other reactions in solution under continuous flow conditions.[26] Likewise, continuous flow photochemistry allowed to carry out [2+2] as well as [5+2] cycloadditions.[27]

Combination of microwave assistance and solid-phase-assisted catalysis: Alternatively, the combined microwave-assisted solid-phase technique was applied in the synthesis of several heterocycles[28] and natural product derivatives[29] [Scheme 1; Eqs. (1–2)]. A few publications concerning the use of insoluble Pd catalyst under microwave irradiating conditions have appeared of which selected examples are summarized below.[30,31]

Precatalyst **1** serves as a reservoir for Pd particles and has been immobilized on a Merrifield-type resin which is part of a Raschig-ring shaped glass/polymer composite material [see Scheme 1, Eq. (4) and Figure 3c]. This solid phase has successfully been employed under μw conditions in Suzuki–Miyaura reactions and other



Scheme 1. Catalysis under microwave irradiating conditions using heterogenized catalysts (supports: silica gel, glass, carbon and polymeric-materials; TBAB = tetra-*n*-butylammonium bromide).[32]

C–C cross-coupling reactions.[31a] Additionally, we showed that Pd^{II}-complex **2**, which is insoluble in most solvents, can be incorporated inside an Irory Kan teabag and repeatedly used in μw-accelerated Suzuki–Miyaura cross-coupling reactions [Scheme 1; Eq. (5)]. The temperature had to be kept as low as 120 °C in order to avoid decomposition of the polymeric material of the Irory Kan.[31b]

From the latter examples [Scheme 1; Eq. (4)] it becomes evident that the kinetic restrictions created by heterogenization of the catalysts which lead to longer reaction times as well as reduced activity can be overcome by substituting conventional thermal heating with microwave irradiation. However, it should be kept in mind that the combination of these two enabling techniques not necessarily gives improved procedures, because localized superheated areas (hot spots), for example, Pd^0 nanoparticles or clusters created by the irradiation can lead to the destruction of the catalyst or may impose a higher degree of leaching. Thus, rapidly eroding activity and shorter life times of catalysts would have to be encountered.

Solid-phase-assisted catalysis and new solvent systems: Examples for combining heterogeneous catalysis and new solvent systems in which the solvent system becomes part of the immobilization concept are still rare.[14,33] The advantage of such immobilization concept lies in the possibility of noncovalently loading a solid phase so that it can be regenerated by simple washing procedure and thus are potentially useful for catalysis under continuous flow conditions (see also Section on Immobilization techniques and applications). One of the first examples in this field was disclosed by Mehnert et al., who immobilized the cationic rhodium complex **3** in a very small volume of ionic liquid which itself had been "immobilized" on the polar surface of silica gel [Scheme 2; Eq. (1)].[34] This noncovalently loaded complex exerted good catalytic activity in gas-phase hydrogenations of alkenes. A related approach except that perfluorinated silica gel and phosphane ligand were employed in order to achieve noncovalent immobilization of a Pd^{II}-complex **4** on silica gel was disclosed by Bannwarth et al. [Scheme 2; Eq. (2)].[35]

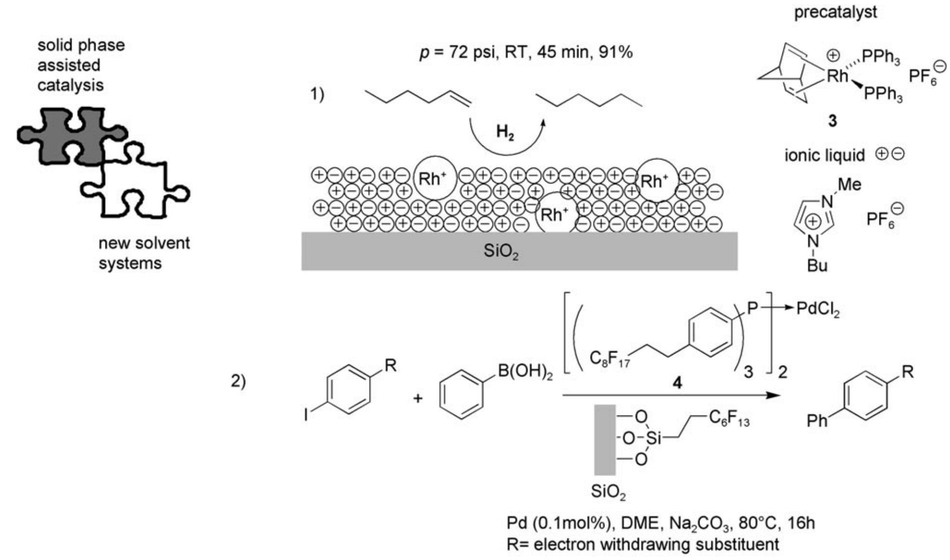
In our laboratories, we developed a Pd^{II} precatalyst which was functionalized with an ionic liquid tag resulting in a task specific onium salt (TSOS) **5**.[36,37] The tag allows for specific interactions with ionic liquids so that the complex was immobilized both on silica gel (SiO_2) according to Mehnert's procedure yielding functionalized solid phase **7** as well as to the newly developed ionic-liquid-type polymer which derives from polyvinyl imidazole (Scheme 3). In order to be able to apply compound **6** under continuous flow conditions we chose glass/polymer composites shaped as Raschig rings (see above). Both functionalized supports were studied in Mizoroki–Heck C–C reactions such as the coupling of 3-iodopyridine with *tert*-butyl acrylate with superior performance of the polymer-bound task specific onium salt **6**.

An additional advantage of ionic liquids is their high polarity which allows strong wave material interactions with microwaves. Therefore many examples can be found in the literature where new solvent systems, namely ionic liquids, are utilized in catalytic transformations accelerated by microwave irradiation.[38]

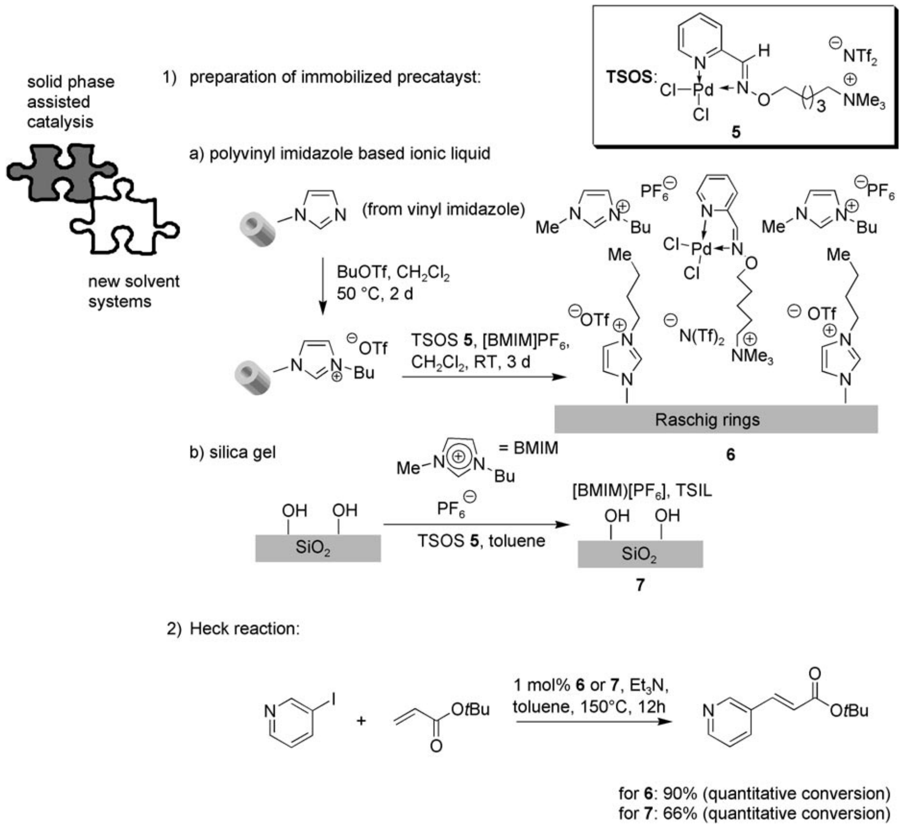
Heterogeneous Catalysis under Continuous Flow Conditions

Only recently, the concepts of microfluidic devices and microreactor technology have become new key issue as part of enabling techniques. Most microfluidic devices for laboratory scale are based on homogeneous fluids.[39] However, an ideal continuous flow process combines novel reactor design with heterogenized reagents[40] or heterogeneous or immobilized homogeneous catalysts.[41] However, biphasic systems often suffer from poor kinetic parameters compared with classical solution-phase chemistry. This can partially be overcome under continuous flow conditions as long as monolithic materials are used as solid phase (see above).

In addition, problems of kinetics of solid-/solution-phase systems can be overcome by speeding up reactions with microwave assistance which in the case of continuous flow devices is subjected at the location where the interactions



Scheme 2. Concepts for the noncovalent immobilization of catalysts using non classical solvents.



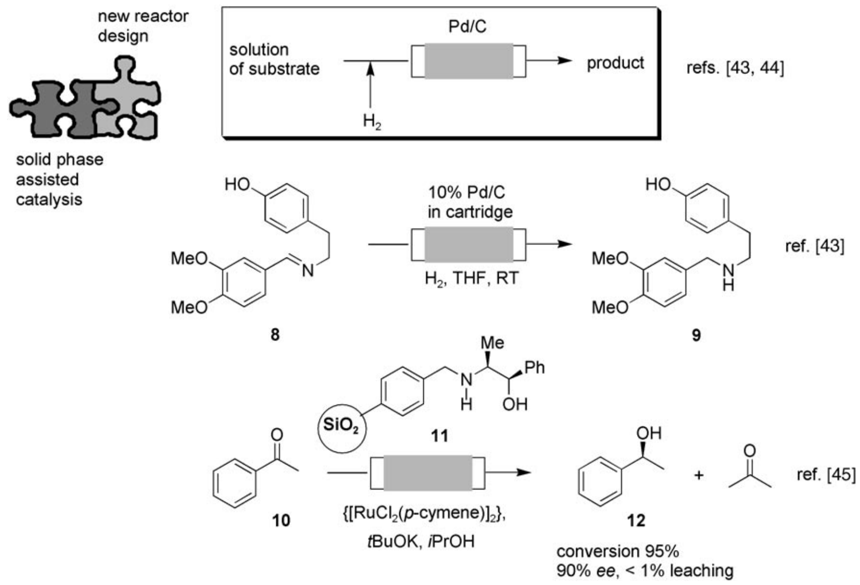
Scheme 3. Noncovalent immobilization of task specific onium salt **5** to polyvinylimidazolium salts and silica, respectively (Raschig rings see Scheme 1 and Figure 2).

between the two phases occur. This is an ideal situation, particularly when microwave-assisted large scale synthesis is envisaged.

Continuous catalysis with packed columns

Chemical catalysis: In recent years, several examples of flow through processes have been reported utilizing immobilized catalysts.[42] Commonly, polymer beads grafted with different ligands and coordinated with metals are filled into a glass column which is attached to a pump or a whole HPLC system.

Typical applications of flow processes with heterogeneous catalysts are hydrogenations for which several examples have recently been published (see also Scheme 12). Thus, continuous flow reactors can be packed with Pd/C for the reduction of organic compounds such as imines to amines with a mixed hydrogen flow stream (Scheme 4).[43]



Scheme 4. Hydrogenations under continuous flow conditions.

Hydrogen gas (provided from an H-Cube flow hydrogenator) was mixed with a flowing substrate stream in a T-piece mixer, and the gas/liquid mixture was pumped through a 10 % Pd/C catalyst packed in a metal cartridge which can be heated up to 100 °C and allows flow hydrogenation to be performed at pressures up to 100 bar. The optimization of the flow conditions for conversion of imine **8** was systematically investigated by varying concentration, flow rate, pressure and temperature (Scheme 4). Using the optimized conditions, the process was readily scaled to provide a preparative quantity of amine **9**. For this purpose, a continuous flow hydrogenation was performed through eluting 0.05 M THF solution of imine **8** at 25 °C and 20 bar at a flow rate of 1.0 mL min^{-1} for 70 min giving 1.0 g of amine **9** (quantitative yield) with high purity (> 95 %). A similar approach was disclosed by Sato and co-workers.[44] They demonstrated the efficient continuous hydrogenation of 4-cyanobenzaldehyde to the corresponding 4-cyanobenzyl alcohol at RT using a similar gas–liquid–solid microflow system. At elevated temperature (95 °C) the cyano group is also reduced. The authors also noted that the flow system performed more efficient hydrogenations compared with the batch system.[44]

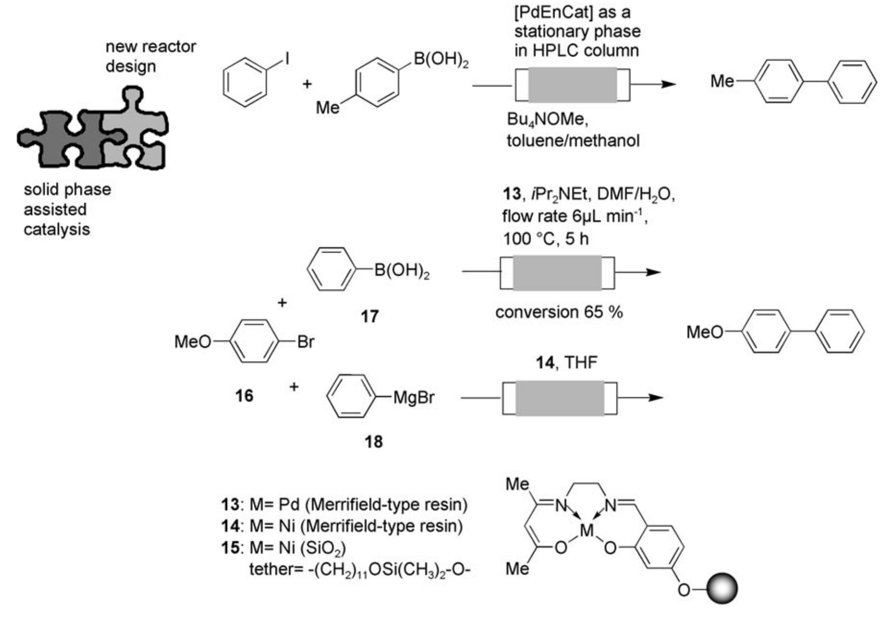
Asymmetric transfer hydrogenation of acetophenone **10** yielding (*S*)-1-phenylethanol (**12**) was also successfully carried out in the flow-through mode (Scheme 4). The column reactor was filled with NH-benzyl-(1*R*,2*S*)-norephedrine **11**, covalently immobilized on silica gel and finally activated ruthenium. In contrast to the analogous homogeneous catalyst, this immobilized catalyst retained high activity in continuous transfer hydrogenation reactions over a period of one week.[45]

Other important applications of continuous flow catalysis are transition metal catalyzed C−C cross-coupling reactions (see also Schemes 12 and 17). Ley and co-workers investigated the use of a polyurea-encapsulated palladium(II) acetate [PdEnCat] precatalyst[46] for the Suzuki cross-coupling under continuous flow conditions (Scheme 5).[47] At 55 °C, low to moderate yields were obtained in the presence of Bu_4NOAc and Bu_4NF as bases. Better results were obtained with Bu_4NOH and Bu_4NOMe affording 70 and 85 %, respectively, after three passes through the column. The best result was observed with Bu_4NOMe at 70 °C after a single pass through the [PdEnCat] column. Noteworthy, Bu_4NOMe was the only base employed that did not lead to phase separation of the reaction mixture. Obviously, the stable homogeneous state of reaction mixture during the whole reaction period is very important for the continuous flow processes allowing maximum interaction between reagents and catalyst.[48]

Styring and co-workers[49] have performed the continuous Suzuki–Miyaura reactions in a pressure driven mini flow reactor packed with Merrifield resin-supported salen-type palladium(II) complex **13**. The Omnifit column for low pressure liquid chromatography was used as a reactor supplied by a standard syringe pump. The system exhibited catalytic activity in the cross-coupling reactions of various aryl and heteroaryl bromides with phenylboronic acid in a continuous flow reactor system at elevated temperatures. Reasonable conversions (37–91 %) could be achieved in a few minutes (under the conditions chosen, the residence time in the reactor was 10.5 min) in a "one-way" process. A 20-fold increase in the rate of model reaction between 4-bromoanisole (**16**) and phenylboronic acid (**17**) (Scheme 5) in the reactor compared with the stirred batch reaction was observed and explained by the increased reagent-catalyst contact in the continuous flow process. Moreover, the minireactor could be used over several cycles in the Suzuki–Miyaura couplings without a significant drop in activity. The enhancements in conversion up to 86 % was achieved for the model reaction through the application of the "stop-flow" technique—the reactants were pumped through the reactor for 10 min and then the pumping was stopped for a designated period of time (5–20 min) prior to re-injecting the solution again into the reactor.

Related salen-type nickel(II) complex immobilized on Merrifield resin **14** was used to perform Kumada–Corriu coupling reactions in continuous flow mode (Scheme 5).[50] A microreactor was constructed by placing a plug of catalyst into the polypropylene tube. Standard HPLC connectors and syringe pump were used to drive a pre-mixed solution of equivalent quantities of the aryl halide **16** and Grignard reagent **18** through the reactor. An enhanced rate of the 4-methoxybiphenyl formation was observed in the microreactor compared with the batch reaction.

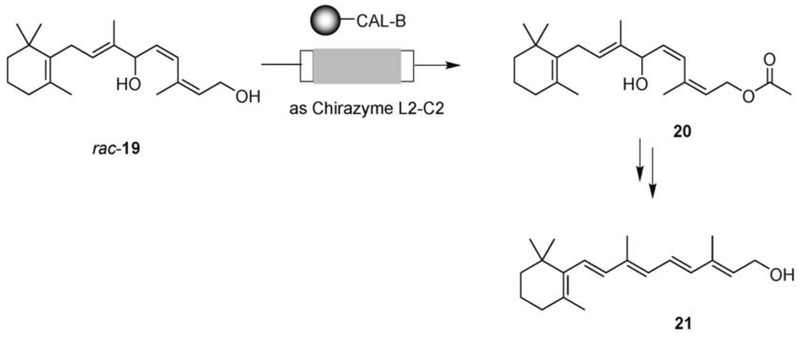
Recently, the same nickel(II) complex was immobilized onto functionalized silica gel using a convenient tethering method.[51] The same Kumada–Corriu coupling reaction was carried out at room temperature in a pressure driven microflow reactor (length 25 mm, inner diameter 3 mm) containing functionalized silica **15** (ca. 0.15 mmol Ni g^{-1} silica gel loading) to yield the coupling product within 5 h. The authors claim negligible leaching of the metal into solution and note that the major advantage of these functionalized inorganic materials are non swelling properties which is a common problem associated with polymeric supports.



Scheme 5. Transition-metal-catalyzed cross-coupling reactions under continuous flow conditions.

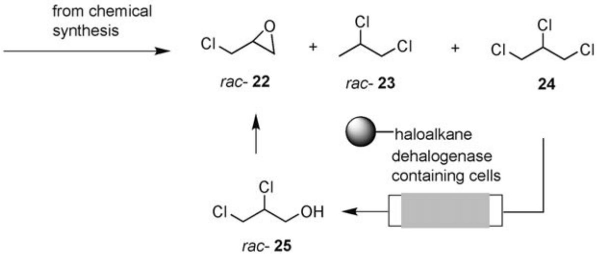
Biocatalysis:[52] Biocatalysts have been extensively studied and used for the industrial production of important intermediates and products such as amino acids, sugars, lipids, acids and pharmaceuticals.[53] Immobilization of biocatalysts as well as resting and living cells which may stem from bacterial, fungal and archaeal origin as well as from higher animals or plants[54] and their use under continuous flow conditions has been particularly relevant in industrial applications, as most biocatalysts are inherently unstable. However, operational stability is a central quest for any bioprocess. The most obvious measures to prolong the lifetime of biological systems are using an organic or inorganic solid support,[53c,55] cross-linking of enzymes,[56] solvent engineering techniques,[57] bio-imprinting[58] as well as reactor design.[59] Additionally, genetic manipulation techniques such as directed evolution have become irreplaceable tools for enzyme modification and stabilization.[60] Methods for immobilization span the range from adsorption and covalent bonding to encapsulation and entrapment.[61]

One example is Chirazyme L2-C2 (CAL-B), which proved to be a very useful enzyme for the development of an acylation process for the large-scale production of vitamin A (retinol **21**) (Scheme 6).[62] The enzymatic approach allows for the selective monoacylation of **19**. Under continuous conditions using a 15 mL fixed-bed reactor containing 5.0–8.0 g of immobilized biocatalyst, 4.9 kg of **20** were prepared within 100 days in 99 % yield and with 97 % selectivity for the primary hydroxyl group. In a miniplant environment 120 g of Chirazyme converted 1.4 kg of **19** into 1.6 kg **20** per day and even after 74 days the conversion efficiency was still 99.4 %. Further development of this transformation led to a modified process, which uses *Thermomyces lanuginosus* lipase immobilized on Accurel MP1001 for the continuous production of **20**.[63]



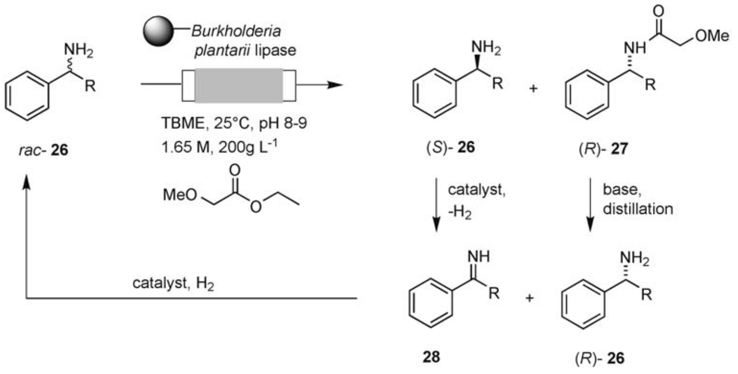
Scheme 6. Continuous acylation in the production of vitamin A.

Dow Chemical[64] developed a continuous process for the enzymatic production of the commodity chemicals propylene oxide and epichlorohydrine (**22**) from a mixture of chlorinated products **23** and **24** that result from a chemical process (Scheme 7). For regenerating trichlorinated byproduct **24** to epichlorohydrine a dehalogenase enzyme from *Rhodococcus sp.* ATCC 55388 recombinant in *E. coli* was immobilized onto a polyethyleneimine/alumina carrier which affords intermediate dichlorinated alcohol **25**.[65]



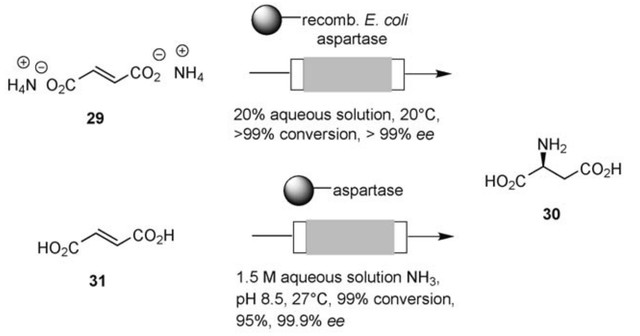
Scheme 7. Continuous formation of 2,3-dichloropropanol **25** in the production of epichlorohydrine **22**.

BASF developed a process based on the enzymatic resolution of racemic amines **26** with *Burkholderia plantarii* lipase immobilized on polyacrylate (Scheme 8).[66] Methoxyacetic acid amides are particularly well suited for the stereospecific enzymatic hydrolysis, giving both the free amine (*S*)-**26** and the acylated product (*R*)-**27** with high *ee* values. A plug-flow reactor (5–7 h residence time) can be used for the enzymatic reaction with several substrates.



Scheme 8. Continuous large scale resolution of chiral amines (TBME = *tert*-butyl methyl ether).

A process developed by BioCatalytics[52] utilizes isolated, immobilized on a silica gel supported L-aspartase for the addition of ammonia to ammonium fumarate which is conducted in a plug flow reactor, which is fed with both fumarate and an ammonia solution **29** (Scheme 9). The immobilized enzyme is stable preserving half of its initial activity



Scheme 9. Continuous production of L-aspartic acid using immobilized aspartase.

for at least half a year which allows to produce up to 100000 kilograms of L-aspartic acid **30** from a single kilogram of immobilized enzyme. In this respect, it is one of the most efficient biocatalytic continuous processes known.[52]

Despite these advances of continuous flow processes in industry using immobilized biocatalysts, academia has begun to add new aspects to this field, particularly new transformations[67] as well as multistep sequences.[68]

The PASSflow technology

Monolithic solid phase and reactor design: Most of the continuous flow processes described so far, utilize reactors with randomly packed catalytic beds. These commonly show uncontrolled fluid dynamics which result in stagnation zones and hot-spot formation, broad residence time distribution, low selectivity and in essence low process efficiency. In contrast, monolithic structures are the best structured material known for this purpose.[69] They have a high void volume and a large geometric surface area. This results in a low pressure drop during the passage of a gas or a fluid and a large contact area of the reagent or the catalyst with the fluid.[70]

Inorganic materials based on silica gel or carbon can ideally be prepared as monoliths with uniform mesopores and tunable microchannels.[71] Additionally, three concepts for creating monolithic materials with regular or irregular channels based on polymeric phases are currently known: a) Copolymerization of different monomers in the presence of porogens, b) preparation of diblock copolymers of which a well defined cylindrical and degradable polymer is embedded inside the second polymer and c) 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[72] and has been used by other groups.[73] All of 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 usually required in suspension polymerization processes, is needed. The resulting rod can be used as a reactor or may be cut into disks.[74] Related monolithic supports created by convective interaction is a transition-metal-based approach which is prepared by ring-opening metathesis copolymerization of norbornene 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.[75]

Hillmyer et al.[76] developed a second approach to copolymeric monolithic material which contain oriented nanoscopic cylinders of the degradable polymer polylactide (PLA) embedded in an inert thermoplastic matrix made of polystyrene. PLA was selectively removed under well defined conditions using sodium hydroxide in aqueous methanol which resulted in a mesoporous monolithic polystyrene containing nanochannels with defined pore size. However, the polystyrene material shows reduced mechanic and chemical stability as no cross-linker was employed.

The third concept was developed by Kunz and in our laboratories which relies on the immobilization of homogeneous catalysts on a newly designed monolithic block.[77] This material consists of a chemically functionalized highly porous polymer/glass composite which is obtained after precipitation polymerisation of styrene, chloromethylvinyl benzene, vinyl pyridine, vinyl imidazole, vinyl pyrrolidinon or other monomers in the pore volume of highly porous glass (see also Schemes 1 and 3). This procedure creates a polymeric matrix inside the glass which consists of small polymer bridged beads (1–5 μm diameter) (Figure 2). Basically, creation of a monolithic polymeric phase with a high surface area, wedged inside the microchannel pore system of the inert, inorganic support is achieved.

This material can be generated in different shapes depending on the type of reactor to be used. Monolithic rod-shaped composites were enclosed in a double layered shrinking hose. The inner layer is made of hot melt glue; the outer layer consists of polytetrafluorethylene which upon heating shrinks and the hot melt glue is pressed firmly onto the outer surface of the rod. Fiber reinforced epoxy resin casing is created to achieve pressure resistance. During the shrinking process metal connectors are integrated. This procedure turned out to be less suited for temperature sensitive functionalities so that partial decomposition caused by thermal treatment during shrinking of the polytetrafluorethylene hose was encountered. Alternatively, a high pressure resistant casing can be made from stainless steel tubes by first inserting the carrier material rod or honeycomb (for large scale) into this metal cartridge followed by closing the gap by precipitation polymerization. After this step functional groups and/or catalysts may be introduced chemically (Figure 3).[78]

A very flexible reactor concept utilizes ring-shaped composites (based on porous Raschig rings) in irregular beds as well as regularly structured arrangements (Figure 4). This

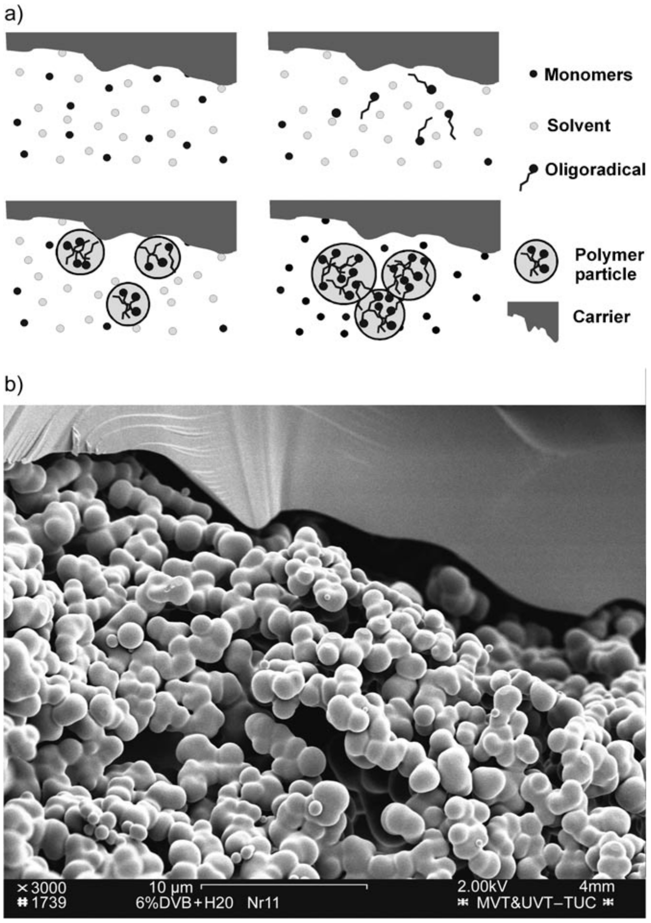


Figure 2. Precipitation polymerization inside megaporous inorganic carriers such as glass. a) From top left to bottom right: $T = 0$ homogeneous solution; $T < 3$ h formation of oligoradicals; $T = 3$ h start of precipitation; $T > 3$ h particle formation and growth. b) REM view into the monolithic glass/polymer composite material.

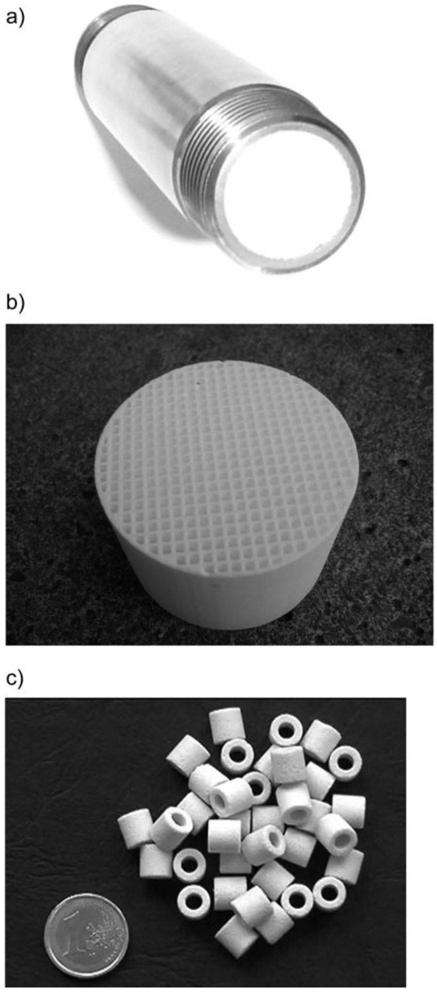


Figure 3. Monolithic porous composite rod inserted into stainless steel tube (a), honeycomb monolithic composite (b) and Raschig rings (c).

reactor concept is well suited both for large as well as small scale (single rings) synthesis. These rings can be prepared in large batches of many litres, making their preparation much cheaper than rod shaped reactors. The design of single ring reactors can handle one or several rings, so variation of catalyst amount by keeping the flow conditions constant can easily be achieved. Just the change of active rings with inert rings is necessary. The casing can be made of stainless steel, glass or of polymers such as polyetheretherketone (PEEK) (Figure 5). Except for metal reactors, they can be used under microwave irradiating conditions in order to speed up reaction rates under continuous flow conditions. When catalysts are immobilized, these reactors can be used for large scale synthesis under microwave irradiating conditions.

Another major advantage of this reactor concept is the possibility of easily reloading the reactor with new glass/polymer composite Raschig rings after use or by incorporation of differently functionalized rings for multistep synthesis.

Immobilization techniques and applications: Irregularly packed or monolithic continuous flow reactors containing functionalized polymeric resins or silica gel require special considerations which are not necessarily of equal relevance in batch reactions. In view of upscaling and economical considerations it does not make sense to exchange the solid phase physically after the catalyst has lost most of its activity. A better concept would be to remove the old, inactive catalyst and regenerate the solid phase by simple washing steps so that the solid-phase architecture remains unaltered.

As a consequence, covalent attachments of ligands have to be avoided. Indeed, support for developing noncovalent methods for immobilization of transition-metal catalyst came from experiences we collected from continuous flow experiments with chiral salen complexes. These catalysts are among the most versatile ones as they can be utilized in a plethora of chiral building blocks and intermediates starting from easy accessible alkenes and epoxides, respectively.[79] They also have proven to efficiently work in large scale transformations. Jacobsen and co-workers[80] developed a synthetic protocol for the immobilization of salen complexes on polystyrene as well as silica gel resins by employing unsymmetrically substituted salen ligands **33**. The hydrolytic kinetic resolution of racemic 4-hydroxy-1-butene oxide **32** generated triol **34** with high enantiomeric excess. The work paved the way for the application of these catalysts under continuous flow conditions as well as in PASSflow reactors (Scheme 10).[19,81] Thus, cobalt–salen-complex **33b** was linked via glutaric acid to a Merrifield-type glass/polystyrene composite material inside the reactor. The first example of an asymmetric transformation inside a microreactor was achieved with the known dynamic kinetic resolution of racemic bromohydrine in the presence of water.[81] The reactor could be used for four cycles without reduced yield or enantiomeric excess. Workup and isolation of the product is highly simplified and make this approach attractive for the synthesis of chiral building blocks in fine chemical industry. In the following, the reactor was used for the ring-opening of 1-hexene oxide with phenols.

Still, the major disadvantage of a covalent attachment of a precious ligand is the limited lifetime of these complexes. Being incorporated inside the PASSflow reactor (rod shaped glass/polymer composite; Figure 3). It was impossible to regenerate the solid phase after the catalyst had lost its activity after several applications or to easily implement new monolithic material inside the column.

As an alternative to covalent immobilization other modes of attachment were envisaged in our group which include a) physisorption, b) immobilization by ionic interactions (ion exchange) and c) immobilization by coordination to metal centers which will be briefly discussed below.

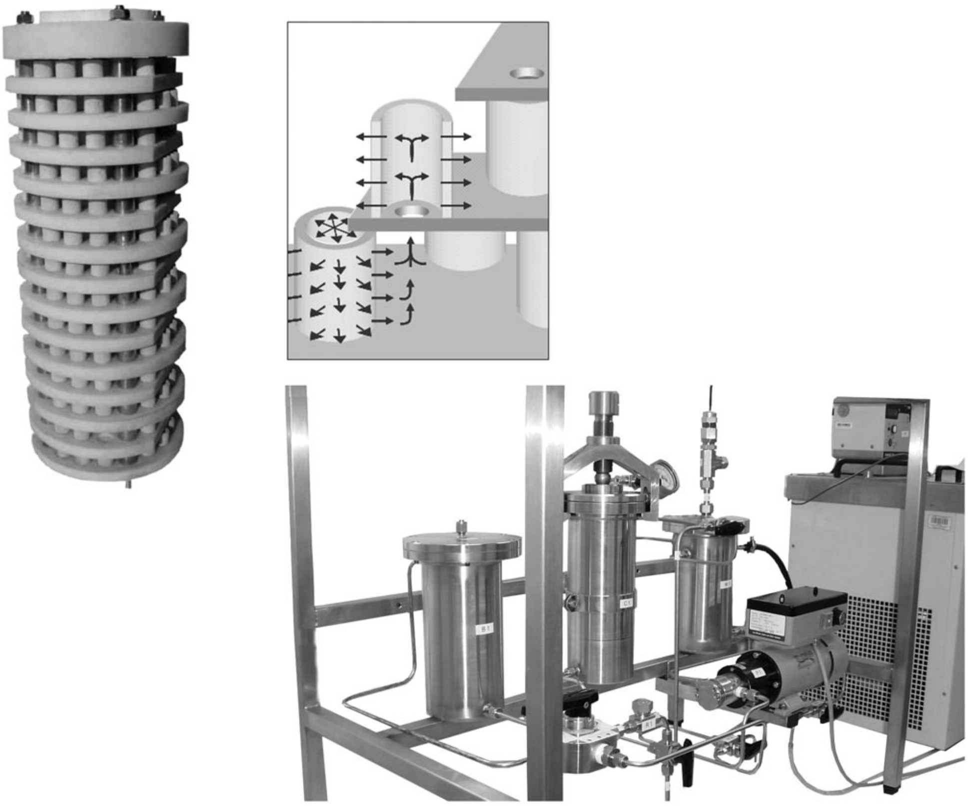


Figure 4. Large scale setup based on Raschig rings: Raschig rings in an arranged ordered column structure in about 20 cm length (left), flow pattern inside arranged rings (top middle) and continuous flow apparatus for large scale production.

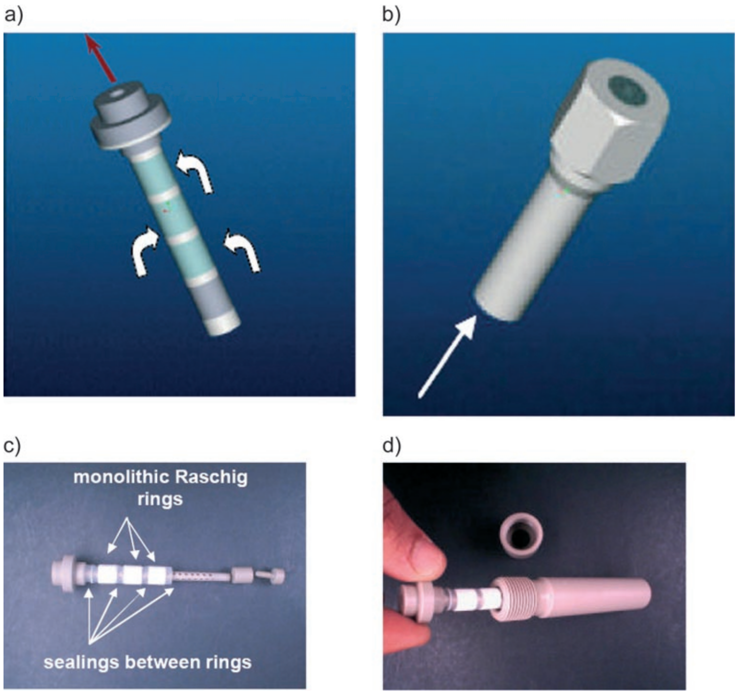
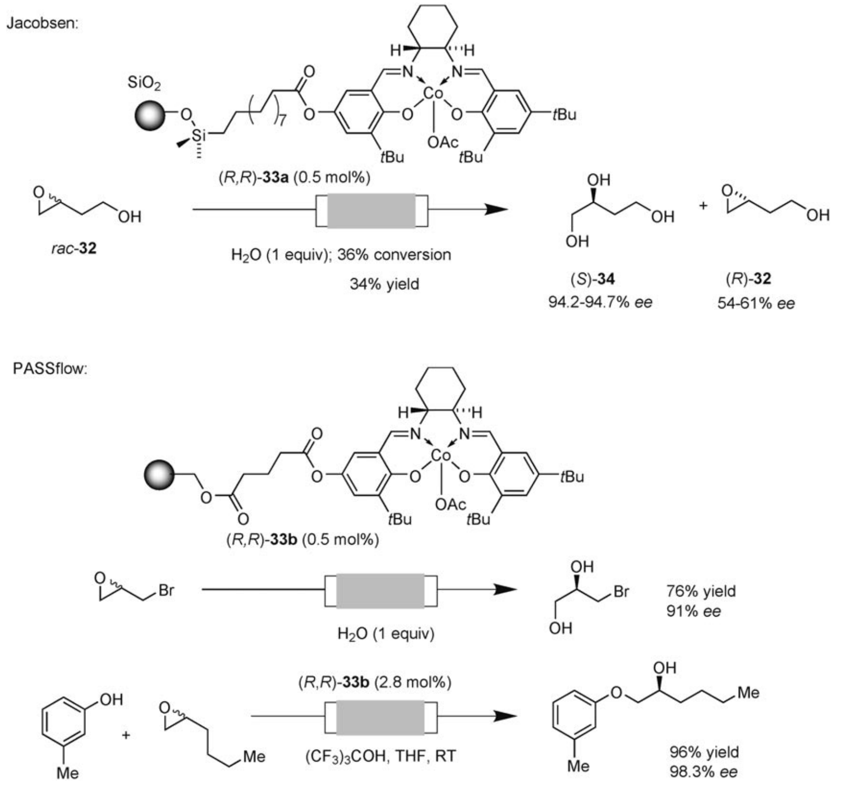


Figure 5. a) and b) The flow streams from an annular gap through the ring walls and irregular microchannels inside the glass/polymer composite and leaves through the perforated inner tube (9 mm ring diameter). c) and d) PASSflow reactors with single ring shaped composites. Rings are aligned on a perforated tube. Gaskets between the rings prevent bypass. Housing is made of PEEK polymer.

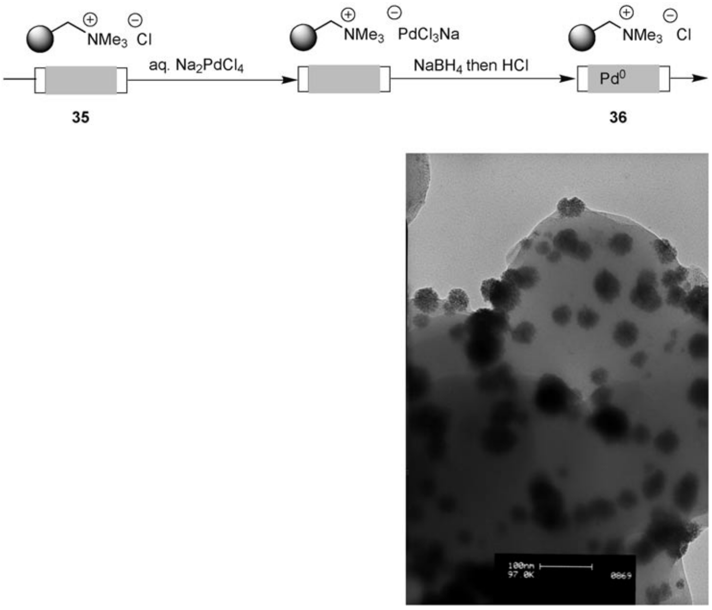


Scheme 10. Kinetic resolution of butane oxide **32** by Jacobsen[80] and PASSflow applications with covalently linked salen catalyst.[81]

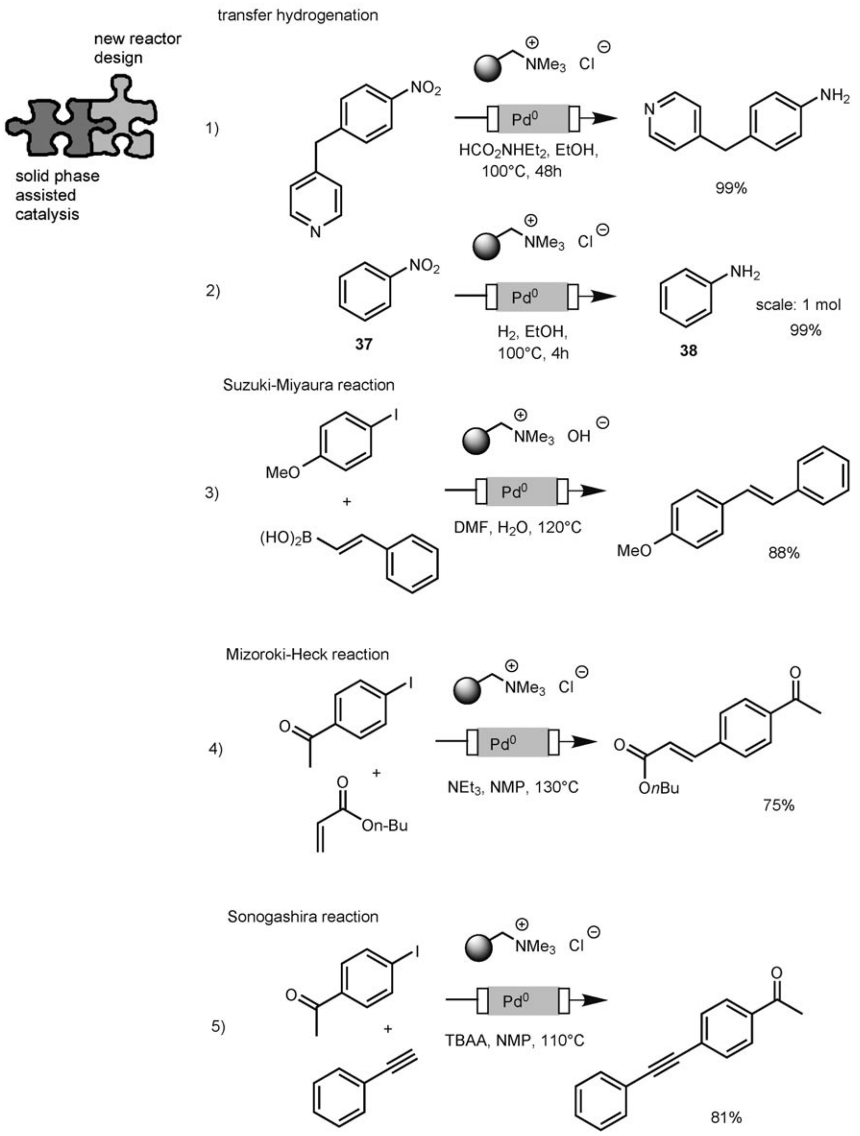
Catalysis under continuous flow conditions using physisorption as mode of immobilization: Pd^0-catalyzed transformations such as transfer hydrogenations, Suzuki- and Mizoroki–Heck C–C cross-coupling reactions can routinely be conducted in PASSflow reactors.[82] These transformation were achieved using microdispersed palladium nanoparticles (25–65 nm) which were positioned by physisorption next to polymer-bound ammonium cations (anion-exchange resin). The preparation of these catalytically highly active palladium particles was carried out by first loading palladate anions to the anion exchange resin **35** inside the PASSflow reactor or Raschig rings which was followed by $NaBH_4$ reduction to yield Pd^0 nanoparticles **36** (Scheme 11). It is possible to conduct transfer hydrogenations of alkenes, alkynes, nitro groups [Scheme 12, Eq. (1)] as well as benzyl ethers.[82] All substrates were circulated through the reactor with external recycle loop to achieve high conversion. Instead of transfer reagents also fluids which are saturated with hydrogen gas can be employed which leads to accelerated hydrogenations. Large scale hydrogenation (1 mol) of nitrobenzene **37** affording aniline **38** was achieved under continuous flow conditions using the apparatus and composite material shown in Figure 4 [Scheme 12; Eq. (2)]. Importantly, scale up did not require additional optimization or process engineering so that conditions collected for laboratory scale could directly be employed.

In addition, Suzuki–Miyaura- [Scheme 12, Eq. (3)], Mizoroki–Heck- [Scheme 12, Eq. (4)] and Sonogashira reaction [Eq. (5)] can be conducted with these Pd^0-nanoparticles **36** as long as homogeneous reaction mixtures are guaranteed. It is noteworthy, that the vacant ion exchange site next to the palladium(0) can serve as an anchor for a second functionality such as a basic anion as was proven for the Suzuki–Miyaura reaction (Scheme 12, Eq. (3)].

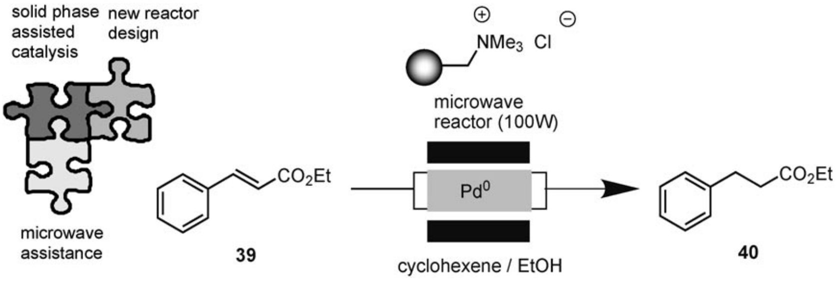
The simultaneous combination of more than two enabling techniques has so far rarely been achieved.[83] In the present case, microwave conditions were also successfully applied to the PASSflow setup using specially designed PEEK reactors (Raschig-ring version; see Figure 5).[84] In these reactors, cinnamyl ethyl ester **39** was quantitatively reduced with cyclohexene to yield 3-phenyl ethyl propionate (**40**) within 30 min (Scheme 13). In this approach, different polymers (variations in cross-linking, different ratios of 4-vinylbenzyl chloride and styrene) and several solvents (differing in µw adsorption properties) were tested under µw irradiating conditions in continuous flow reactors and compared with conventional thermal heating.



Scheme 11. Preparation of Pd^0-nanoparticles by ion exchange and reductive precipitation. TEM view of palladium nanoparticles **36** (25–65 nm) on polymer (5.3 % cross-linking); scale bar: 100 nm.



Scheme 12. Examples of catalytic transformations with precipitated Pd^0 particles **36** in the PASSflow mode (NMP = *N*-methylpyrrolidinone; TBAA = tetra-*n*-butylammonium acetate).

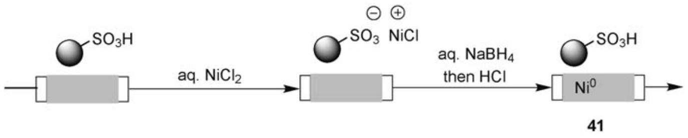


Scheme 13. Microwave accelerated transfer hydrogenation in the PASSflow mode.

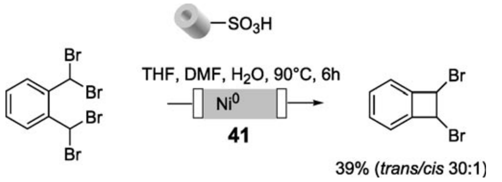
The latter conditions gave particular good results in terms of efficiency the process and stability of the nanoparticles, if the polymeric phase contained 5.3 % cross-linking and a 10-fold excess of vinylbenzene with respect to anion exchange sites. The catalyst shows a six-fold higher reactivity under µw compared with thermal heating in ethanol, while the factor is only two in toluene. In general, the hydrogenation proceeds faster under continuous flow condition than in the batch mode, irrespective whether it was conducted with thermal heating or accelerated by µw irradiation. Most of the functionalized polymers tested could be employed for more than 10 runs without substantial loss of activity.

Related to this procedure is the deposition of Ni^0 on the polymeric phase inside the PASSflow reactor after cation exchange and reduction (Scheme 14).[85] The procedure allows to incorporate the metal inside the PASSflow reactor and showed activity under stoichiometric as well as under catalytic conditions (Scheme 15). Thus it was possible to conduct the nickel mediated **41** synthesis of highly reactive 7,8-dibromocyclobutabenzene under continuous-flow conditions.[86]

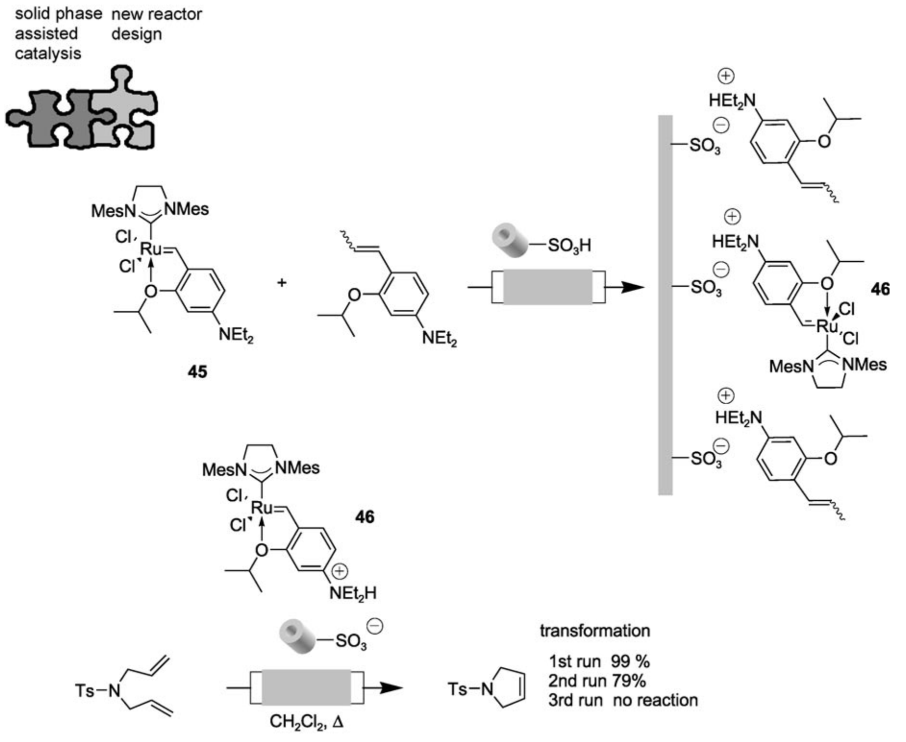
Catalysis under continuous flow conditions using ionically bound catalysts: In alternative to physisorption by means of precipitative desorption is immobilization by ion exchange. In collaboration with K. Grela we developed a Hoveyda-type Ru-catalyst **45** which contains an additional diethylamino group in the aryl–carbene ligand which upon protonation switches from an inactive to an active catalyst **46** (Scheme 16).[87] Treatment of a cation-exchange resin (Raschig ring with SO_3H groups) with complex **45** and the precursor styrene[88] has two effects which are a) immobilization as ammonium salt **46** and b) activation. When the Raschig ring is part of a PASSflow reactor (see Figure 5), cross metathesis, ring-closing metathesis and enyne coupling can be performed under continuous



Scheme 14. Formation of Ni^0 **41** inside the PASSflow reactor by reductive precipitation.



Scheme 15.



Scheme 16. Ionic immobilization of Ru-complex **45** inside PASSflow reactor and ring closing metathesis under continuous flow conditions.

flow conditions although the catalytic system looses more quickly its activity than batch-type reactions (after the 2nd run compared to five runs). Notably, this ionically attached Ru-catalyst shows a very low degree of leaching (<100 ppm) in the crude reaction media, for which scavenging properties of the solid phase can be made responsible.

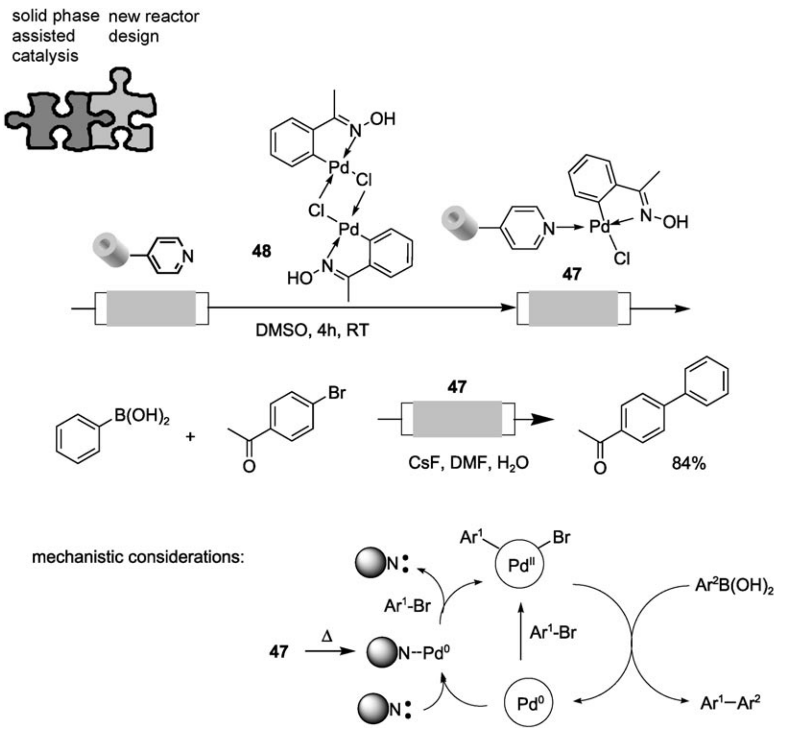
Catalysis under continuous flow conditions using coordination as immobilizing strategy: A third strategy of immobilization relies on direct coordination of a polymeric phase to transition-metal catalysts inside the PASSflow system (rod-type according to Figure 3c) as is first exemplified for palladium(II) complex **47**.[89] This complex was created by treatment of polyvinyl pyridine (PVP) with the dimeric oxime-based palladacycle **48** first described by Najèra et al. (Scheme 17).[90] The resulting precatalyst exerts high activity in Suzuki–Miyaura, Mizoroki–Heck and Sonogashira reactions both in batch as well as in continuous flow processes. We collected evidence that besides serving as an anchor for the precatalyst PVP may also act as a scavenger for Pd particles that are released into solution which is documented by the very low degree of leaching (<2 ppb). The first step of the catalytic process could be expected to involve a reduction step in which precatalyst **47** is reduced to a Pd^0 species still bound to the polymer. This species can then undergo oxidative addition with an aryl halide yielding a soluble catalyst. In the following, the catalyst enters the standard cross-coupling cycle possibly as a nanoparticle of unknown nature. The Pd^0 species can carry on the catalytic cycle or can be recaptured by PVP.

Likewise, PVP can be utilized to immobilize the Grubbs III catalyst **49** by coordination which results in a functionalized composite material **50** (Raschig rings) suitable for PASSflow reactors **50** which were used in RCM, enyne and cross-metathesis reactions (Scheme 18).[91]

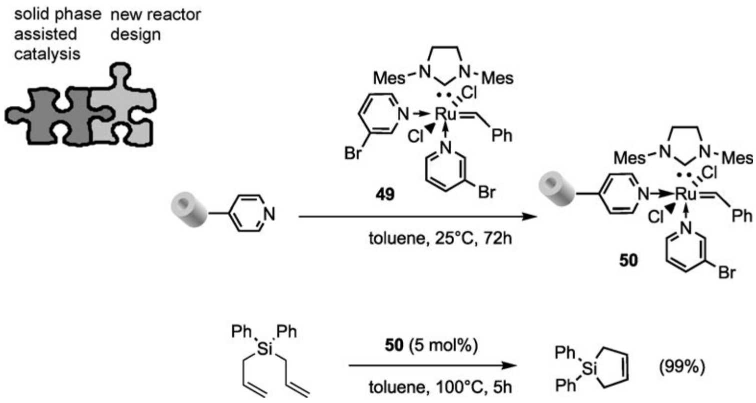
In addition, enzymes can be immobilized inside a PASSflow reactor by means of coordinative attachment. This was achieved by synthesizing a Ni–nitrilotriacetic acid (NTA) matrix on monolithic polyvinyl pyrrolidinone/polyvinyl benzyl chloride which affords a new polymeric phase **51** for automatic purification and immobilization of His$_6$-tagged proteins. As one example, benzaldehyde lyase (BAL, EC 4.1.2.38) was immobilized, purified and utilized as a stable and highly active biocatalyst for the synthesis of (*R*)-benzoin from benzaldehyde in the flow through mode (Scheme 19).[92]

In essence, the combination of an optimized monolithic solid phase inside different types of reactors along with new concepts for the immobilization of active species creates an ideal continuous flow system which can widely used for chemical catalysis as well as biotransformations.

Miscellaneous flow devices: All continuous flow reactions discussed above were performed in column-like reactors filled with tight packed catalyst particles which are truly



Scheme 17. Suzuki–Miyaura cross-coupling under continuous flow conditions (PASSflow) using functionalized polymer **47** and mechanistic considerations.



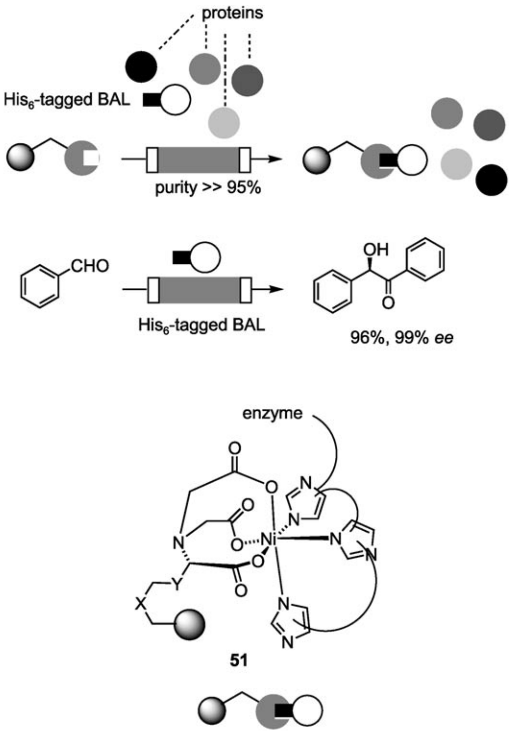
Scheme 18. Preparation of PVP-coordinated Ru-complexes **50** (the exact stereochemistry in the coordination sphere of the Ru centre is unknown).

"immobilized" on a solid phase within the reactor. However, other continuous flow concepts with biphasic systems have been reported. Plenio and Hillerich immobilized the polymer (soluble MeOPEG) tagged palladium catalyst in a stationary solvent (DMSO). A solution of reactants dissolved in another immiscible solvent (*n*-heptane) was pumped through the DMSO phase, during which time the catalytic process occurred (Scheme 20).[93] Using phosphine **52** as a polar phase tag for palladium(II) binding, continuous biphasic Sonogashira cross-couplings between aryl bromides and phenyl acetylene were carried out (conversion > 88 %).

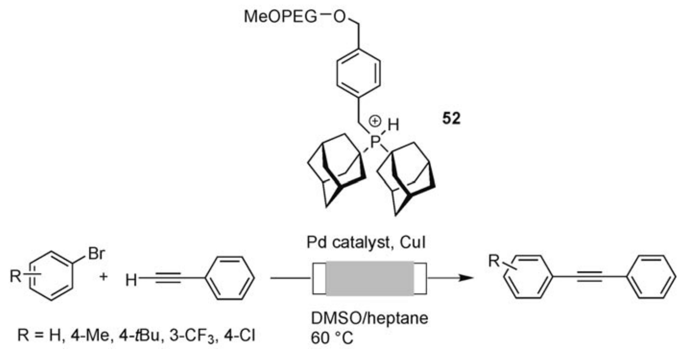
Another variant of non-traditional "compartmentalization" of metal catalysts is represented by continuous-flow membrane reactors (CFMR) (Figure 6). Catalytically active metal complexes are suitably functionalized with dendrimers (dendritic catalysts) which are unable to penetrate a nanomembrane inside the reactor. The nanofiltration of the substrate stream results in product formation under continuous flow conditions. Applications of CFMR for palladium-catalyzed allylic substitutions and hydrovinylation reactions, as well as for nickel-catalyzed Kharasch additions and rhodium-catalyzed hydrogenation reactions were recently reviewed.[94]

In an interesting approach demonstrating the versatility of microreactor technologies for manipulations of reactive intermediates Yoshida and coworkers[95] used a low-temperature electrochemical microflow system[39b] 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 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 containing a supporting electrolyte (Bu_4NBF_4, 0.3 M) in dichloromethane 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 nucleophile.

A technologically new and interesting flow-through process for enzymatic reactions was reported by Reetz and Leitner.[96] The group designed a protocol for enzymatic reactions, namely the lipase-catalyzed acylation (CAL B) of



Scheme 19. Purification of enzymes inside the PASSflow reactor using the His$_6$-tag concept and benzoin reaction under continuous flow conditions.



Scheme 20. Sonogashira cross-coupling under continuous flow conditions using a polar phase tagged Pd catalyst.

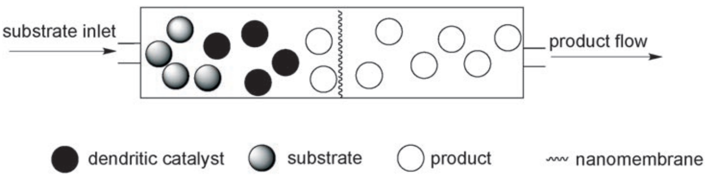
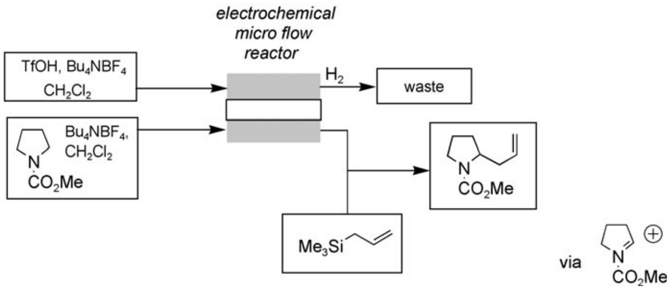


Figure 6. Catalysis with continuous-flow membrane reactors (CFMR).

octan-1-ol by vinyl acetate in ionic liquids [1-butyl-3-methylimidazolium bis(trifluoromethanesulfonimide) [BMIM]-[BTA] using supercritical CO_2 as the mobile phase. The alcohol is pumped through the biphasic 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.



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

Conclusions

It is our utmost belief that technological questions more and more become part of chemical research. The examples given in this overview show that it is fruitful to leave classical thinking behind and combine and merge new methodologies and enabling technologies to create new synthetic platforms for conducting synthesis particularly single as well as multistep catalytic transformations.

Despite the fact that the number of examples of flow-through processes and their combination with solid-phase assistance and microwave acceleration performed in the laboratory is only small today, not only process engineers but recently also industrial medicinal chemists have begun to evaluate flow-through processes with standard laboratory equipment and take advantage of this new approach. Particularly, the combination with heterogeneous or heterogenized catalysts as well as microwave acceleration is an ideal combination for the rapid continuous production of chemicals with minimum purification. 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 is opened for a similar development in chemical synthesis as had to be noted in analytical chemistry when HPLC conquered the laboratories and took them by storm.

Acknowledgements

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