Advanced organic synthesis using microreactor technology

Batoul Ahmed-Omer,[a,b] Johan C. Brandt[a] and Thomas Wirth*[a]

Received 16th October 2006, Accepted 27th November 2006
First published as an Advance Article on the web 18th December 2006
DOI: 10.1039/b615072a

Organic synthesis in microreactors is a novel way of performing reactions in a highly controlled way. The benefits of microreactors result from their physical properties, such as enhanced mass and heat transfer as well as regular flow profiles leading to improved yields with increased selectivities.

Introduction

Microstructured reactors are now finding their way into research laboratories and can offer many advantages to conventional laboratory techniques.[1–5] There are more and more examples where microreactors are integrated into pilot plants or even into large scale production lines.[6] In this short review, we will focus on the various benefits this technology can offer for advanced organic synthesis. The use of microreactors allows the controlled mixing of reagents and the reaction time with a substrate is directly proportional to the length of the microchannel. Furthermore, control over thermal or concentration gradients within the microreactor allows new methods for efficient chemical transformations with high space–time yields. The generation of hazardous intermediates *in situ* is safe as only very small amounts are generated and directly

[a]*School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, UK CF10 3AT. E-mail: wirth@cf.ac.uk; Fax: +44-2920-876968; Tel: +44-2920-876968*
[b]*Laboratory for Applied Microsystems, Cardiff School of Engineering, Cardiff University, Cardiff, UK CF24 3TF*

Batoul Ahmed-Omer graduated from the University of London–King's College with BSc and MSc degrees in Chemistry (2000). She then joined Evotec OAI (Oxfordshire) where she worked as a Research Scientist in R & D for two years on various pharmaceutical chemistry projects using combinatorial and solid phase techniques. She joined the University of Cardiff in 2003, where she is now completing her PhD in microreactor chemistry under the supervision of Professor T. Wirth in the School of Chemistry and Professor D. Barrow in the School of Engineering.

Johan Brandt was born in Berlin, Germany. He attended the Free University Berlin and received his degree (Dipl.-Chem.) in organic and analytical chemistry in 2004 under the guidance of Professor G. Buntkowsky. In 2005, he worked in the SFI Tetrapyrrole Laboratory at Trinity College Dublin on the development of unsymmetric, water soluble photosensitisers. In early 2006, he took up a position as a PhD student in Professor Wirth's group at Cardiff University. His research interests include the investigation and development of efficient consecutive organic reactions in microreactor devices.

Thomas Wirth got a Diploma from the University of Bonn in 1989, and a PhD from the Technical University of Berlin with Professor S. Blechert in 1992. After a postdoctoral stay with Professor K. Fuji at Kyoto University as a JSPS fellow in 1992/93, he started his independent research at the University of Basel. In the group of Professor B. Giese, he obtained his habilitation on stereoselective oxidation reactions supported by various scholarships before taking up his present position at Cardiff University in 2000. He was a visiting professor at the University of Toronto (1999), at Chuo University in Tokyo (2000) and at Osaka University (2004). He was awarded the Werner-Prize from the New Swiss Chemical Society in 2000.

Batoul Ahmed-Omer

Johan C. Brandt

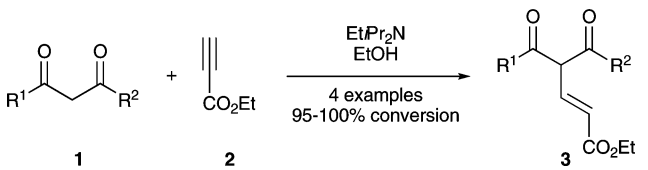
Thomas Wirth

reacted in a closed system. First reports have appeared with the integration of appropriate analytical devices on the microreactor which allow a rapid feedback for optimisation. Even the synthesis of solids has been described using microstructured devices.

Stoichiometric reactions

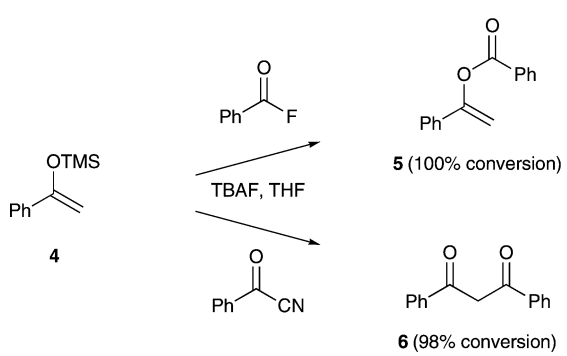
Addition reactions

Reactions involving carbonyl compounds have a long tradition in organic chemistry but there are advantages of microreactor technology over conventional batch procedures using flasks. For example, for 1,4-addition of enolates to α,β-unsaturated carbonyl compounds, it was found that conversions using a glass microreactor are higher compared with those obtained in batch reactions. 1,3-Dicarbonyl compounds **1** were reacted with a mixture of ethyl propiolate **2** and diisopropylethylamine as a base to yield addition products **3** in 95–100% conversion whereas conversions using batch techniques were in the range of 78–91% (Scheme 1).[7]



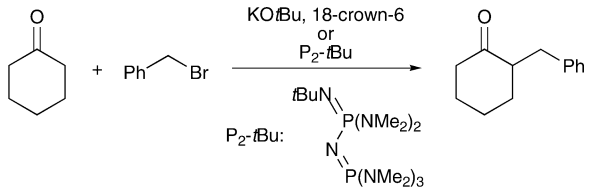
Scheme 1 1,4-Addition of enolates to ethyl propiolate **2**.

Regioselective acylations of enolates can be achieved using microreactor technology. Usually, such reactions can result in the formation of *C*-acylated as well as *O*-acylated products, which are difficult to separate. The formation of unwanted side-products in this acylation can be completely suppressed using microreactor technology. Silyl enol ethers have been treated with an anhydrous fluoride source to generate the corresponding enolates. Depending on the acylation reagent, either *C*-acylated as well as *O*-acylated products can be obtained selectively.[8] Reaction of the silyl enol ether of acetophenone **4** with benzoyl fluoride in a glass microreactor led to an exclusive formation of the *O*-acetylated product **5** with 100% conversion, whereas the use of benzoylcyanide led to the formation of only the *C*-acylated product **6** (98% conversion) (Scheme 2).[9]



Scheme 2 Oxygen *versus* carbon acylation of silyl enol ethers.

The direct generation of enolates from ketones using other soluble bases was investigated as well. Either phosphazene bases such as P_2-*t*Bu or potassium-*tert*-butoxide with 18-crown-6 were used to generate enolates for alkylation reactions in glass microreactors using electroosmotic flow (EOF) to control the flow of solvents (Scheme 3). The conversions were high whereas in the batch reaction, low conversions and considerable amounts of dialkylated product were observed.[10]

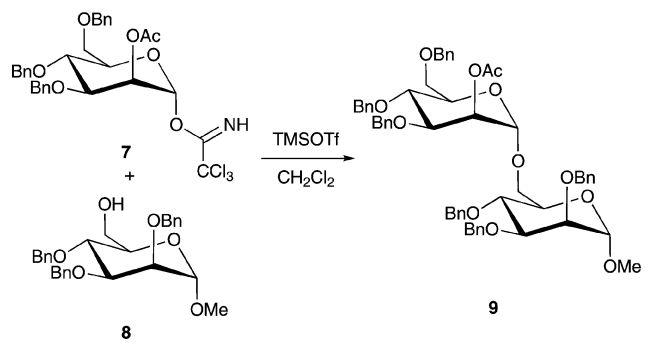


Scheme 3 Direct alkylation of enolates.

Based on these results, stereoselective alkylations of an Evans auxiliary derivative were performed within a pressure-driven glass microreactor. These reactions have also been performed at low temperatures (−100 °C) and better conversions and selectivities than in batch reactions have been observed.[11]

The synthesis of β-peptides was also achieved in microreactors and the increase in reaction efficiency over traditional batch methods is believed to be due to the fact that this reaction is performed in an electric field, as solvents and reagents are controlled by electroosmotic flow (EOF).[12] The peptides synthesized in the microreactor by a conventional carboxylic acid activation with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) or dicyclohexylcarbodiimide (DCC) can be separated from unreacted reagents and byproducts by using the reverse electrokinetic flow technique which demonstrates an on-chip separation protocol.[13] A different highly efficient coupling protocol for β-amino acids using microreactors at elevated temperature (up to 120 °C) was reported recently.[14] A similar increase of reactivity by transferring a reaction from batch to microreactor mode has been observed in a Claisen–Schmidt reaction.[15]

Seeberger *et al.* performed glycosylation reactions in silicon microreactors of 2,3,4-tri-*O*-benzyl-methyl mannoside **8** with mannosyl trichloroacetimidate **7** using the trichloroacetimidate protocol (Scheme 4).[16] Optimisation studies were performed over a wide range of conditions with very small amounts of reagents until maximum conversions to **9** were achieved. Transglycosylation reactions with enzyme catalysis have also been studied using microreactor devices.[17]

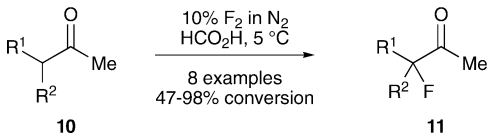


Scheme 4 Glycosylation reactions in microreactors.

Halogenations and metalations

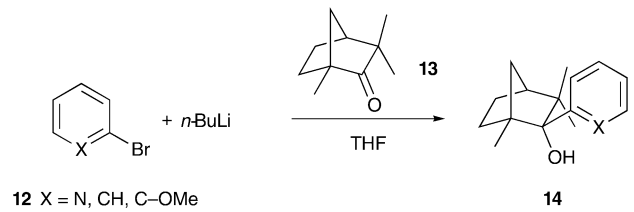
Halogenations using elemental halogens is a fundamental process. Safety considerations are usually severe limitations especially

when handling fluorine as a highly reactive fluorination agent. As fluorine is sparingly soluble in organic solvents, the large volume-to-surface area in biphasic liquid/gas fluorinations together with precise temperature control allows the use of microreactors for halogenations. Special reactors have been designed for these processes, such as micro bubble columns, which can disperse the gaseous halogen in a liquid stream of solvent. A controlled direct fluorination of toluene is possible, but also various carbonyl compounds **10** can be monofluorinated in the α-position to give compounds **11** in high conversions as shown in Scheme 5.[18,19] With compounds **10** (R^2 = H), difluorinated products are observed as minor components.



Scheme 5 Fluorination using elemental fluorine.

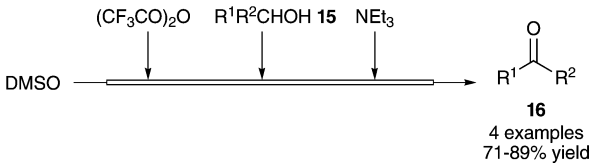
Halogen–lithium exchange reactions and the generation of Grignard reagents are operations routinely performed in a synthetic laboratory. On a large scale, such processes require extensive safety precautions and the temperature control is difficult. The use of microreactor systems for such reactions is therefore highly desirable as they allow a very efficient heat transfer of extremely fast and highly exothermic reactions. Especially advantageous is an *in situ* quench protocol when using organometallic reagents. For example, the generation of aryllithium compounds from **12** using *n*-butyllithium and a subsequent addition to fenchone **13** in a microreactor gave **14** in 93% yield (X = N) which is almost identical to the yield obtained in a batch reaction (92%) (Scheme 6). The reaction can be performed at low temperatures (−17 °C) with a residence time in the microreactor of only 5 minutes.[20]



Scheme 6 *in situ* quench protocol using aryllithium reagents.

Oxidations

The generation of singlet oxygen and its use in an addition reaction to α-terpinene was described using a microreactor device and rose bengal as a sensitiser. The yields of the reaction are higher than in the batch mode and inherent dangers of large quantities of oxygenated solvents are avoided.[21] The selective oxidation of alcohols to aldehydes is an important reaction in organic synthesis and has already been addressed using microreactor technology. A microreactor system for Swern-oxidation has been developed taking advantage of the possibility of the subsequent addition of the reagents to generate first the activated DMSO before adding the alcohol **15** and finally the base (triethylamine) to liberate the ketone **16** as shown in Scheme 7.[22] Different alcohols have been used in the reaction and all show superior yields with less side



Scheme 7 Swern oxidations using a microscale flow system.

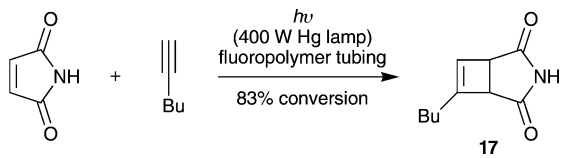
product formation (Pummerer rearrangement or formation of the trifluoroacetylated alcohol) in the microreactor flow system. Furthermore, the microreactor system could be operated at room temperature whereas in the batch mode, a temperature of −50 °C is required.

The use of solid supported reagents has already been featured widely in organic synthesis and the combination of such reagents with microreactor technology allows a high degree of reaction control unattainable in traditional flask reactions. The oxidation of primary alcohols was performed using a silica-supported Jones' reagent. Depending on the flow rates, a selective oxidation to either the aldehyde or the corresponding carboxylic acid could be achieved.[23] The yields obtained are very high, but the amount of solid supported reagent in the reactor obviously limits the amount of alcohol which can be oxidised.

The influence of microwave irradiation on the oxidation of benzyl alcohol to benzaldehyde using iron(III)nitrate was demonstrated using a continuous isothermal reactor consisting of a heat transfer and a reaction zone.[24] The heat generated in the reaction zone is rapidly absorbed by a heat transfer fluid (water), which is circulated through the heat transfer area. The construction materials used for the system were selected carefully in order to allow full transparency to microwave irradiation in the reaction area and no transparency in the heat transfer area. This allows microwave irradiation under isothermal conditions leading to higher conversion rates especially for longer residence times.

Photochemistry

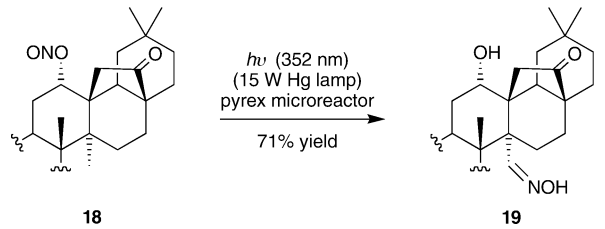
Photochemical reactions are usually performed in solution using immersion well reactors. This equipment therefore requires a batch process and photochemical reactions are not routinely used in synthesis. The development of flow reactors for continuous processes now allows large scale reactions. [2 + 2] Cycloadditions have been performed by combining immersion well equipment with UV transparent fluoropolymer tubing (Scheme 8). The cycloadduct **17** has been formed with 83% conversion on a large (0.7 kg) scale.[25] Although the device used for this reaction is better described as a flow reactor than a microreactor, similar cycloadditions have been performed in a glass microreactor with microchannels of only 500 μm depth with high efficiency.[26]



Scheme 8 [2 + 2] Cycloadditions in fluoropolymer tubing photoreactors.

Further miniaturisation using a microchannel with only 100 μm depth allowed the use of a much less powerful light source as

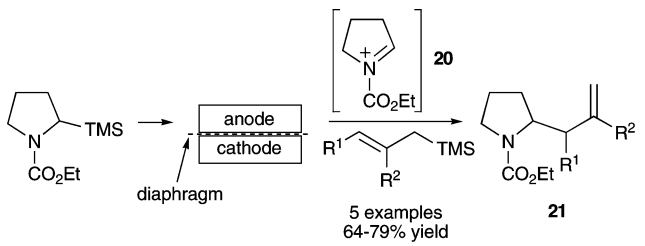
demonstrated in the Barton reaction of **18** to compound **19**, a key intermediate for the synthesis of an endothelin receptor antagonist (Scheme 9).[27] Photochemical chlorinations in microreactors have been developed for the synthesis of chlorinated aromatic compounds.[28]



Scheme 9 Barton reaction under continuous photochemical conditions.

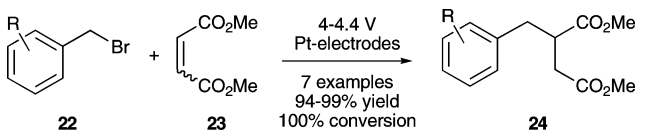
Electrochemistry

Electrosynthesis offers a clean and mild method for the generation of anion and cation radical intermediates. These are usually short-lived intermediates and it is well known that the method of mixing affects product selectivity in such fast reactions. Microreactors have been used for reactions of electrochemically generated intermediates with great success.[29] The formation of *N*-acyliminium ions **20** in the presence of allylsilanes, which can also be generated by using a paired electrochemical flow system, allowed the synthesis of coupling products **21** in high yields (Scheme 10).[30]



Scheme 10 Electrochemical coupling reactions of allylsilanes and *N*-acyliminium ions.

The integration of electrodes in a microreactor device allowed the electrochemical coupling of benzylbromides **22** with dimethylfumarate or dimethylmaleate **23** to the C–C-coupling product **24**.[31] Adjusting the potential as well as the geometry of the electrodes led to an almost complete suppression of the homo-dimerisation as the main side-reaction in this process (Scheme 11).

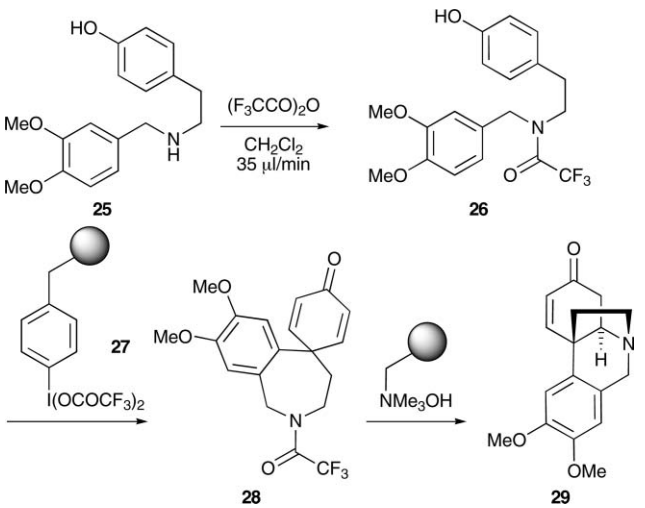


Scheme 11 Electrochemical C–C coupling reactions.

A novel development of electrode arrangement with an electric current flow parallel to the liquid flow results in successful reactions in the absence of supporting electrolytes. Two carbon fibre electrodes were separated with a PTFE membrane by only 75 μm allowing methoxylations of various substrates, which have been investigated as model reactions.[32]

Multistep syntheses

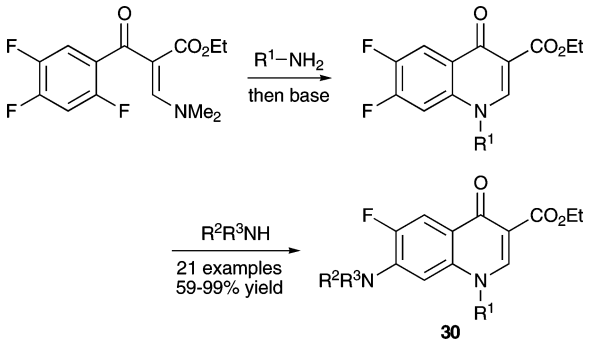
Various impressive natural product syntheses by continuous flow processes have been reported by Ley *et al.* The use of solid-supported reagents is crucial for these syntheses. In the synthesis of (±)-oxomaritidine **29** the precursor **25**, also synthesised in a continuous flow process, is subjected to a trifluoroacetylation reaction in a microreactor (Scheme 12). The product **26** is subsequently cyclised by passing the solution over polymer-supported bis(trifluoroacetoxyiodo)benzene **27** and, after amide cleavage of **28** using a polymer-supported base, (±)-oxomaritidine **29** was obtained.[33] This sequence is only limited by the amount of polymer-supported reagents available in the reagent cartridges within the continuous flow system.



Scheme 12 Multistep continuous flow synthesis of (±)-oxomaritidine **29**.

The optimization of synthetic efficiency with microreactor technology was also used in the development of a rapid synthesis of [^{18}F]fluoride radiolabelled molecular imaging probes. The ^{18}F isotope has a half-life time of only 110 min and rapid synthetic steps are required to obtain the imaging probes. Five steps have been combined on a single reaction circuit unit. Initially, a preconcentration of fluoride using a miniaturized anion-exchange column and a solvent exchange took place, then the reaction with an activated glucose derivative and, after another solvent change, deprotection yielded 2-desoxy-2-fluoro-D-glucose, a widely used radiolabelled molecular probe.[34] The speed of chemical synthesis is even more important when incorporating a [^{11}C]carbon radiolabel as the ^{11}C isotope has a half-life time of only 20 min. Fast esterifications of carboxylic acid derivatives have been investigated.[35]

The synthesis of a library of ciprofloxacin analogues has been achieved by sequential reactions in a microreactor (Scheme 13). A primary amine and a secondary amine have been used in this two-step process and 21 analogues of ciprofloxacin **30** have been prepared in quantities above 110 mg each.[36] Another approach allowed the continuous flow synthesis of gram quantities of 4,5-disubstituted oxazoles from acid chlorides and isocyanides as a rapid on-demand synthesis of valuable building blocks.[37]



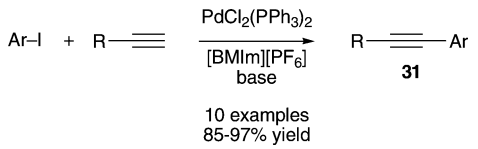
Scheme 13 Synthesis of a library of ciprofloxacin analogues **30**.

Catalytic reactions

Homogeneous catalysis

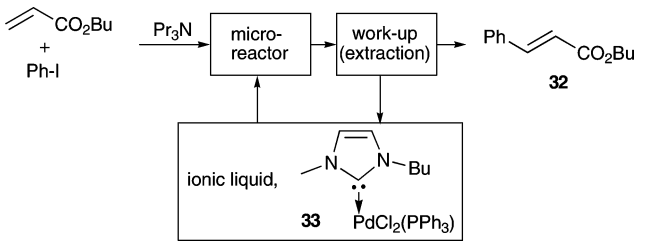
Single phase reactions

Copper-free Sonogashira couplings were performed in ionic liquids using a microflow system. Ryu *et al.* described how the coupling reaction of aryl halides with terminal acetylenes proceeds efficiently without copper salts.[38] The advantage of using an ionic liquid is in catalyst recycling as the organic product can be removed from the catalyst ionic liquid mixture by extraction. The combination of $PdCl_2(PPh_3)_2$ as a catalyst with a base in [BMIm][PF_6] (1-butyl-3-methylimidazolium hexafluorophosphate), gave optimal conditions for the coupling step. Using a micromixer, reaction times were reduced dramatically under continuous flow conditions from 120 min to 10 min to give the product **31** in 93% yield (Scheme 14). After extraction of **31** the ionic liquid–catalyst mixture could be reused in a second run with slightly lower (83% yield) efficiency.



Scheme 14 Sonogashira coupling in microreactors.

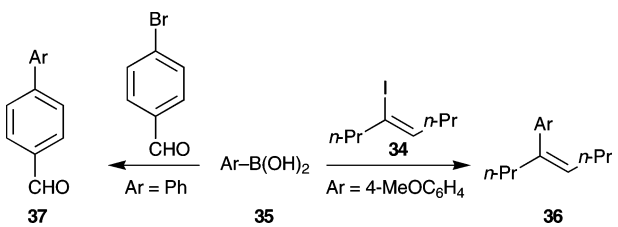
Further development with integrated recycling of the ionic liquid–catalyst solvent was demonstrated with the palladium-catalysed Mizoroki–Heck reaction of iodobenzene with butyl acrylate.[39] The microflow apparatus was combined with a microextraction system. Pd-carbene complex **33** as a catalyst was employed, which is more soluble in ionic liquids than other catalysts such as $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$. The reaction was initially conducted in a micromixer using the highly viscous ionic liquid [BMIm][PF_6] at 130 °C resulting in only poor yields. Increasing the temperature to 150 °C and attaching an additional stainless steel tube resulted in 87% yield of **32** within 50 min. The use of a low viscosity ionic liquid [BMIm][NTf_2] (1-butyl-3-methyllimidazolium bis(trifluoromethylsulfonyl)imide) allowed even higher conversion rates to give 97–99% yield of **32** in a 50 min reaction at 130 °C (Scheme 15). For the continuous reaction, the microdevice was equipped with micromixers and a residence time unit. Additionally, the workup system consisted of T-shaped micromixers attached to the microflow unit to aid the product extraction. After the reaction and extraction, the ionic



Scheme 15 Mizoroki–Heck reaction with continuous work-up–extraction and catalyst recycling.

liquid–catalyst mixture was collected and pumped back into the microflow unit for further reaction. After running the system for 10 h, more than 100 g of *trans*-butyl cinnamate **32** was obtained in 80% yield.

Comer and Organ demonstrated a very simple and practical method to achieve rate enhancement of homogeneous catalysed reactions by combining both microreactor and microwave irradiation.[40] The basic design of the flow reactor consisted of a stainless steel holder with an attached mixing chamber connected to a capillary tube inside a microwave cavity. Suzuki–Miyaura coupling between 4-iodooct-4-ene **34** and 4-methoxyboronic acid **35** (Ar = 4-$MeOC_6H_4$) with $Pd(PPh_3)_4$ as catalyst yielded product **36** with a reaction time of 28 min (Scheme 16). Intriguingly, in the coupling of 4-bromobenzaldehyde with phenylboronic acid **35** (Ar = Ph), the palladium catalyst decomposed and formed a thin metal film coating the inside of the capillary tube. Consequently, a dramatic increase in temperature during irradiation occurred resulting in complete conversion to the biaryl product **37** within 4 min. However, when potassium carbonate was used as a base, no decomposition of the catalyst and hence, no formation of the thin metal film occurred. The reaction therefore proceeded at a lower temperature with lower conversion (38%). External coating of microreactors with a thin gold film to enhance microwave absorption has also been reported.[41]

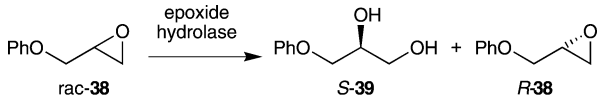


Scheme 16 Suzuki–Miyaura coupling of boronic acids.

A Pd coated microcapillary can also be used in other reactions, such as the metathesis reaction, improving the conversion when compared to a reaction in a non-coated microcapillary even when higher microwave power was applied.

Furthermore, sequential microflow technique combined with microwave irradiation was introduced to produce libraries of compounds using a single capillary, whereby compounds were produced, one after another, through the same reactor channel. An array of Suzuki–Miyaura cross-coupling reactions were conducted to afford a biaryl library with very good conversions. Additionally, flow parallel synthesis was also conducted whereby the reagents were introduced in sequence into a multicapillary reactor while being irradiated with microwaves to provide a library of biaryl compounds in a very efficient way.[42]

A combination of enantioselective catalysis and on-chip analysis has recently been reported by Belder and Reetz.[43] The combination of very fast separations (<1 s) of enantiomers using microchip electrophoresis with enantioselective catalysis allows high-throughput screening of enantioselective catalysts. Various epoxide hydrolase mutants were screened in the hydrolysis of **38** to **39** with direct on-chip analysis of the enantiomeric excess (Scheme 17).



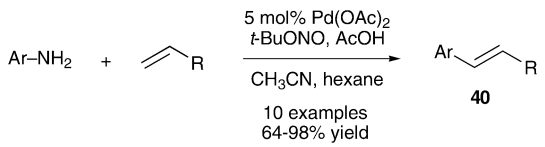
Scheme 17 Enantioselective hydrolysis of epoxide **38** with on-chip analysis of the enantiomeric excess.

The combination of microreactors with online LC-UV-MS systems has also been reported.[44] Such techniques allow a rapid (online) optimisation of reaction conditions. This has recently been taken a step further by altering reaction conditions in each solvent segment of a segmented flow and separate MALDI-MS analysis of the segments.[45]

Multiphase liquid/liquid reactions

The catalytic reactions discussed so far were carried out in a single liquid phase within a microreactor. Recently, an interest in applying microreactors utilizing liquid/liquid multiphase systems has emerged.[46,47] In a microchannel, the contact interface between immiscible liquids can follow various flow patterns, due to the forces generated at the interface. Depending on the geometry of the mixing device, laminar flow or segmented flow can be formed in the microchannel.

We have reported the effect of segmented flow in a fluoropolymer microreactor by demonstrating the increase in the conversion rate of *p*-nitrophenyl acetate hydrolysis as a model study.[48] We applied the same concept to homogeneous catalysed reactions by introducing an immiscible solvent to the flow generating segmented flow instead of a single flow. As a result, not only were we able to enhance the yields of various Heck products **40** compared to conventional methods, but we were also able to further improve the outcome when using segmented flow instead of single flow (Scheme 18).



Scheme 18 Enhancement of Heck reactions using segmented flow.

Okamoto *et al.* demonstrated the use of alternating pumping forming segmented flow to provide a more effective mixing and an increased yield for biphasic organic reactions that use a phase transfer catalyst.[49] The aim was to investigate the rate enhancement in alkylation of a malonic ester with tetrabutylammonium hydrogen sulfate as the phase transfer catalyst. The increase in yield indicates that the alternating pumping method can be useful for such reactions.

Isomerization of allylic alcohols into carbonyl compounds was conducted by using a liquid/liquid process in a micromixer with interdigitated channels.[50] An emulsion was generated between the aqueous layers where the catalyst is soluble and the organic layer where the substrate and the product are soluble. Various complexes of transition metals with a library of water soluble phosphine ligands were screened for the isomerization of 1-hexene-3-ol to ethyl propyl ketone. The results clearly demonstrated the efficiency of the coupled microdevice for discovering new efficient catalysts. Recently, the synthesis of imprinted polymers using segmented flow in a microreactor was reported as well.[51]

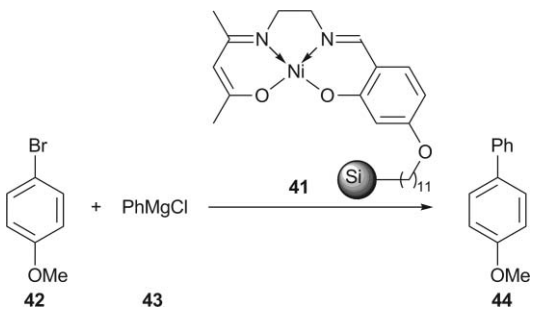
Heterogeneous catalysis

The combination of continuous flow systems along with heterogeneous catalysis is a relatively new idea, and, in the cases of additional microwave irradiation, several modern enabling techniques are applied alongside each other.[52,53]

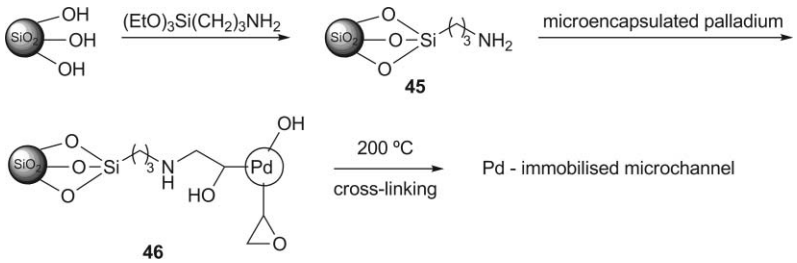
C–C Coupling reactions

Transition metal mediated C–C coupling reactions and heterogeneously catalysed hydrogenations have been the first examples in organic synthesis to transfer this concept into microdevices. The key technical problem is the placement of the catalyst in the reactor and different solutions have been offered.

In initial studies, an unsymmetrical salen-type nickel catalyst was immobilized on Merrifield resin polymer beads (**41**) and inserted into capillary channels, either made of polypropylene or glass, to form the microreactor device. The resin was kept within the channels by glass wool on both ends.[54] The substrates (solutions of 4-bromoanisole **42** and a Grignard reagent **43**) were inserted with syringe pumps and the reaction mixture was quenched immediately after leaving the reactor. The reaction under flow conditions was compared with batch conditions by GC. The greatest benefits compared to the batch process were that reaction rates were found to be enhanced by up to three orders of magnitude in the flow processes and that the Kumada reaction could be carried out without the need of an inert gas atmosphere. The drawback of using Merrifield resin within a microreactor is the constant threat of blockage due to swelling caused by the solvent, one of the common problems in microreactor applications. Hence another approach to immobilize this catalyst on silica was developed.[55] The reactor set-up consisted of a small reactor (25 mm × 3 mm) while the non-swelling catalyst was kept within the reactor by glass frits on both ends. The product **44** was obtained in up to 68% yield (Scheme 19).



Scheme 19 Polymer-supported catalyst **41** for a Kumada reaction.



Scheme 20 Immobilized Pd-catalysts **46** for hydrogenations in microreactors.

The general feasibility of the Suzuki coupling reaction by microwave irradiation using a solid Pd-catalyst in a microreactor was shown in a glass micro reactor provided with a broader catalyst bed and an additional central port.[56] Through this port, the charging and discharging of the reactor with catalyst was possible by manipulation with syringes. The flow was pressure-driven by a syringe pump, which had been charged with the premixed solution of the substrates. The yields were very good to quantitative.

A Suzuki coupling using a salen-type catalyst immobilized on Merrifield resin was carried out.[57] It was found that phosphine ligands were not necessary and convenient conversions were accessible within minutes rather than several hours in the known batch procedures. In another study, borosilicate capillaries had been coated with thin Pd films consisting of nanometre-sized Pd crystallites.[58] Within minutes, excellent conversion rates in Suzuki as well as Heck reactions were achieved by microwave irradiation.

Recently a detailed study was published comparing libraries of Suzuki products that had been synthesized under batch and continuous flow conditions supported by microwave irradiation.[59] In this reaction, microencapsulated palladium catalysts (Pd EnCat) in conjunction with tetrabutylammonium acetate in ethanol were used.

Hydrogenations

The concept of using solid catalysts in microreactors was applied successfully to an important three-phase system, the catalytic hydrogenation.[60] This system takes advantage of the maximized interfacial interaction resulting in excellent conversions in short residence times. Various hydrogenations of alkenes, alkynes or benzyl ethers were performed and showed high reactivities and yields as well as very good chemoselectivities. No leaching of the catalyst was observed and the devices showed constant activity when used repeatedly. The efficient immobilisation of the catalyst on the inner surface of the reactor was performed using the 'polymer incarcerated' (PI) method.[61,62] Firstly, amino groups were introduced to the glass wall of the channel (**45**). A colloidal solution of microencapsulated palladium was passed through the reactor to immobilize the catalyst on the amino groups (**46**). Finally the reactor was heated to 200 °C to cross-link the polymer (Scheme 20). More recently this strategy was successfully applied to fused silica capillaries as microreactors instead of the far more expensive commercial devices, making this application more accessible.[63] Catalyst immobilization with other metals or molecular catalysts like ruthenium,[64] platinum[65,66] or scandium triflate[67] is possible giving this work a high potential for future synthetic research.

Conclusions

Recently, it has become more and more obvious that microreactor technology has begun to influence the concepts of chemical processing on both laboratory and industrial scale. Laboratory researchers have assembled proof during the last few years that microreactor technology can successfully be applied in nearly all fields of organic chemistry. The strongest advantages of this new technology have been identified as being higher yields and selectivities, more effectiveness in the use of resources (friendly to the environment) and much enhanced reaction control (avoiding explosions, makes isothermic reaction control possible). This opens access to elegant combined reactor arrangements including online analytical devices or microchannels coated with heterogeneous catalysts while taking maximum benefit of the enhanced surface-to-volume ratio of the microreactors. As the research in this area is growing, one can expect an increasing interest reflected in the number of successful projects and publications.

References

1 P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong and X. Zhang, *Tetrahedron*, 2002, **58**, 4735–4757.
2 V. Hessel, P. Löb and H. Löwe, *Curr. Org. Chem.*, 2005, **9**, 765–787.
3 P. Watts and S. J. Haswell, *Chem. Soc. Rev.*, 2005, **34**, 235–246.
4 P. Watts and C. Wiles, *Chem. Commun.*, 2007, DOI: 10.1039/b609428g.
5 K. Geyer, J. D. C. Codée and P. H. Seeberger, *Chem.–Eur. J.*, 2006, **12**, 8434–8442.
6 T. Schwalbe, V. Autze and G. Wille, *Chimia*, 2002, **56**, 636–646.
7 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2002, **2**, 62–64.
8 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Tetrahedron Lett.*, 2002, **43**, 2945–2948.
9 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Chem. Commun.*, 2002, 1034–1035.
10 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Tetrahedron*, 2005, **61**, 10757–10773.
11 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2004, **4**, 171–173.
12 P. Watts, C. Wiles, S. J. Haswell and E. Pombo-Villar, *Tetrahedron*, 2002, **58**, 5427–5439.
13 V. George, P. Watts, S. J. Haswell and E. Pombo-Villar, *Chem. Commun.*, 2003, 2886–2887.
14 O. Flögel, J. D. C. Codée, D. Seebach and P. H. Seeberger, *Angew. Chem.*, 2006, **118**, 7157–7160; O. Flögel, J. D. C. Codée, D. Seebach and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7000–7003.
15 J.-X. Mu, X.-F. Yin and Y.-G. Wang, *Synlett*, 2005, 3163–3165.
16 D. M. Ratner, E. R. Murphy, M. Jhunjhunwala, D. A. Snyder, K. F. Jensen and P. H. Seeberger, *Chem. Commun.*, 2005, 578–580.
17 K. Kanno, H. Maeda, S. Izumo, M. Ikuno, K. Takeshita, A. Tashiro and M. Fujii, *Lab Chip*, 2002, **2**, 15–18.
18 R. D. Chambers, D. Holling, R. C. H. Spink and G. Sandford, *Lab Chip*, 2001, **1**, 132–137.
19 P. Lob, H. Löwe and V. Hessel, *J. Fluorine Chem.*, 2004, **125**, 1677–1694.

20 S. El Sheikh and H. G. Schmalz, *Curr. Opin. Drug Discovery Dev.*, 2004, **7**, 882–895.
21 R. C. R. Wootton, R. Fortt and A. J. de Mello, *Org. Process Res. Dev.*, 2002, **6**, 187–189.
22 T. Kawaguchi, H. Miyata, K. Ataka, K. Mae and J.-I. Yoshida, *Angew. Chem.*, 2005, **117**, 2465–2468; T. Kawaguchi, H. Miyata, K. Ataka, K. Mae and J.-I. Yoshida, *Angew. Chem., Int. Ed.*, 2005, **44**, 2413–2416.
23 C. Wiles, P. Watts and S. J. Haswell, *Tetrahedron Lett.*, 2006, **47**, 5261–5264.
24 R. J. J. Jachuck, D. K. Selvaraj and R. S. Varma, *Green Chem.*, 2006, **8**, 29–33.
25 B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry and K. I. Booker-Milburn, *J. Org. Chem.*, 2005, **70**, 7558–7564.
26 T. Fukuyama, Y. Hino, N. Kamata and I. Ryu, *Chem. Lett.*, 2004, **33**, 1430–1431.
27 A. Sugimoto, Y. Sumino, M. Takagi, T. Fukuyama and I. Ryu, *Tetrahedron Lett.*, 2006, **47**, 6197–6200.
28 H. Ehrich, D. Linke, K. Morgenschweis, M. Baerns and K. Jähnisch, *Chimia*, 2002, **56**, 647–653.
29 J. Yoshida, *Chem. Commun.*, 2005, 4509–4516.
30 S. Suga, M. Okajima, K. Fujiwara and J. Yoshida, *QSAR Comb. Sci.*, 2005, **24**, 728–741.
31 P. He, P. Watts, F. Marken and S. J. Haswell, *Angew. Chem.*, 2006, **118**, 4252–4255; P. He, P. Watts, F. Marken and S. J. Haswell, *Angew. Chem., Int. Ed.*, 2006, **45**, 4146–4149.
32 R. Horcajada, M. Okajima, S. Suga and J. Yoshida, *Chem. Commun.*, 2005, 1303–1305.
33 I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby and G. K. Tranmer, *Chem. Commun.*, 2006, 2566–2568.
34 C.-C. Lee, G. Sui, A. Elizarov, C. J. Shu, Y.-S. Shin, A. N. Dooley, J. Huang, A. Daridon, P. Wyatt, D. Stout, H. C. Kolb, O. N. Witte, N. Satyamurthy, J. R. Heath, M. E. Phelps, S. R. Quake and H.-R. Tseng, *Science*, 2005, **310**, 1793–1796.
35 S. Lu, P. Watts, F. T. Chin, J. Hong, J. L. Musachio, E. Briard and V. W. Pike, *Lab Chip*, 2004, **4**, 523–525.
36 T. Schwalbe, D. Kadzimirsz and G. Jas, *QSAR Comb. Sci.*, 2005, **24**, 758–768.
37 M. Baumann, I. R. Baxendale, S. V. Ley, C. D. Smith and G. K. Tranmer, *Org. Lett.*, 2006, **8**, 5231–5234.
38 T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato and I. Ryu, *Org. Lett.*, 2002, **4**, 1691–1694.
39 S. F. Liu, T. Fukuyama, M. Sato and I. Ryu, *Org. Process Res. Dev.*, 2004, **8**, 477–481.
40 E. Comer and M. G. Organ, *J. Am. Chem. Soc.*, 2005, **127**, 8160–8167.
41 P. He, S. J. Haswell and P. D. I. Fletcher, *Sens. Actuators, B*, 2005, **105**, 516–520.
42 E. Comer and M. G. Organ, *Chem.–Eur. J.*, 2005, **11**, 7223–7227.
43 D. Belder, M. Ludwig, L.-W. Wang and M. T. Reetz, *Angew.Chem.*, 2006, **118**, 2523–2526; D. Belder, M. Ludwig, L.-W. Wang and M. T. Reetz, *Angew. Chem., Int. Ed.*, 2006, **45**, 2463–2466.
44 E. Garcia-Egido, V. Spikmans, S. Y. F. Wong and B. H. Warrington, *Lab Chip*, 2003, **3**, 73–76.
45 T. Hatakeyama, D. L. Chen and R. F. Ismagilov, *J. Am. Chem. Soc.*, 2006, **128**, 2518–2519.
46 D. Belder, *Angew. Chem.*, 2005, **117**, 3587–3588; D. Belder, *Angew. Chem., Int. Ed.*, 2005, **44**, 3521–3522.
47 H. Song, D. L. Chen and R. F. Ismagilov, *Angew. Chem.*, 2006, **118**, 7494–7516; H. Song, D. L. Chen and R. F. Ismagilov, *Angew. Chem., Int. Ed.*, 2006, **45**, 7336–7356.
48 B. Ahmed, D. Barrow and T. Wirth, *Adv. Synth. Catal.*, 2006, **348**, 1043–1048.
49 H. Okamoto, *Chem. Eng. Technol.*, 2006, **29**, 504–506.
50 R. Abdallah, T. Ireland and C. de Bellefon, *Chem.-Ing.-Tech.*, 2004, **76**, 633–637.
51 A. Kubo, H. Shinmori and T. Takeuchi, *Chem. Lett.*, 2006, **35**, 588–589.
52 J. C. Schouten, E. V. Rebrov and M. H. J. M. de Croon, *Chimia*, 2002, **56**, 627–635.
53 A. Kirschning, W. Solodenko and K. Mennecke, *Chem.–Eur. J.*, 2006, **12**, 5972–5990.
54 S. J. Haswell, B. O'Sullivan and P. Styring, *Lab Chip*, 2001, **1**, 164–166.
55 N. T. S. Phan, D. H. Brown and P. Styring, *Green Chem.*, 2004, **6**, 526–532.
56 P. He, S. J. Haswell and P. D. I. Fletcher, *Lab Chip*, 2004, **4**, 38–41.
57 N. T. S. Phan, J. Khan and P. Styring, *Tetrahedron*, 2005, **61**, 12065–12073.
58 G. Shore, S. Morin and M. G. Organ, *Angew. Chem.*, 2006, **118**, 2827–2832; G. Shore, S. Morin and M. G. Organ, *Angew. Chem., Int. Ed.*, 2006, **45**, 2761–2766.
59 I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley and G. K. Tranmer, *Chem.–Eur. J.*, 2006, **12**, 4407–4416.
60 J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori and S. Kobayashi, *Science*, 2004, **304**, 1305–1308.
61 R. Akiyama and S. Kobayashi, *J. Am. Chem. Soc.*, 2003, **125**, 3412–3413.
62 K. Okamoto, R. Akiyama, H. Yoshida, T. Yoshida and S. Kobayashi, *J. Am. Chem. Soc.*, 2005, **127**, 2125–2135.
63 J. Kobayashi, Y. Mori and S. Kobayashi, *Adv. Synth. Catal.*, 2005, **347**, 1889–1892.
64 S. Kobayashi, H. Miyamura, R. Akiyama and T. Ishida, *J. Am. Chem. Soc.*, 2005, **127**, 9251–9254.
65 H. Hagio, M. Sugiura and S. Kobayashi, *Synlett*, 2005, 813–816.
66 Y. Miyazaki, H. Hagio and S. Kobayashi, *Org. Biomol. Chem.*, 2006, **4**, 2529–2531.
67 M. Takeuchi, R. Akiyama and S. Kobayashi, *J. Am. Chem. Soc.*, 2005, **127**, 13096–13097.

