Heterogeneous catalytic synthesis using microreactor technology

Christopher G. Frost* and Lynsey Mutton

Received 21st May 2010, Accepted 20th July 2010
DOI: 10.1039/c0gc00133c

The application of heterogeneous catalysis in conjunction with microreactor technology can facilitate a cleaner and scalable flow methodology for organic synthesis. In this tutorial review we present recent advances in the design of supported catalysts for emerging synthetic applications within microreactor technology. Specifically, transition metal catalysts such as palladium, copper, ruthenium, and nickel are described on silica, monolithic, magnetic nanoparticles and polymer supports. These catalysts have been utilised to promote a range of reactions including Heck, Sonogashira, Suzuki, Kumada, olefin metathesis, hydrogenation and benzannulation reactions.

Introduction

Traditionally organic chemistry has been conducted utilising techniques and equipment that dates back to the 19th century, allowing for transformations on scales ranging from several milligrams to multi grams. Optimisation of reaction conditions can be time consuming with process scale up providing additional challenges and further adjustments.[2] It is apparent that traditional methods for carrying out organic chemistry are not sustainable in the longer term and alternative techniques need to be sought.[3] This has led to an increasing interest in harnessing microreactor technology to carry out reactions under flow conditions. The term microreactor technology is used to describe the continuous processing of reactions within defined channels whose dimensions are less than 1000 µm.[4] One of the major benefits of conducting reactions under flow conditions is the rapid early-stage reaction optimisation and direct scale-up.[5] This can be achieved by either increasing the running time of the reactor (scaling up), or by running numerous reactors simultaneously (numbering up).[2] This leads to reaction miniaturisation and incorporates the philosophy of process intensification, as well as reducing the financial burden associated with scaling up a process.[4]

Microreactors consist of narrow channels formed from materials such as silicon, glass, stainless steel, ceramics or polymers.[6] For synthetic applications these channels are connected to a series of reservoirs containing reagents or solvent. These regents are pumped together in a specific sequence, with laminar flow dominating and mixing occurring *via* diffusion.[7] The reagents are then allowed to react under controlled conditions for specified reaction times, thus minimising side reactions.[8] Microreactors exhibit large surface area-to-volume ratios which leads to high heat and mass transfer properties.[9] This allows more control over reaction conditions and the ability to rapidly change reaction temperature to afford greater yields of products and higher purities. The nature of these systems also allows for novel thermal conditions that are not accessible when utilising conventional apparatus.[10]

Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK. E-mail: c.g.frost@bath.ac.uk; Fax: 01225 386231; Tel: 01225 386142

Christopher G. Frost

Christopher G. Frost completed his BSc(Hons) and PhD (with Jonathan M. J. Williams) at the University of Loughborough. After a postdoctoral fellowship with Prof. Philip D. Magnus at the University of Texas at Austin, he joined the Chemistry Department at the University of Bath and in 2007 was promoted to Reader in Organic Chemistry. His interests are in the development of new catalytic synthetic methodology, continuous flow synthesis and occasionally playing the saxophone.

Lynsey Mutton

Lynsey Mutton (nee Lobedan) completed her first degree in Chemistry at the University of Leeds in 2004. She then embarked on a PhD for Professor Christopher Rayner into continuous synthetic organic photochemistry. After her PhD she went to work for Peakdale Molecular for 18 months before moving to the University of Bath to carry out research into heterogeneous catalysis for use within microreactor technology.

There are also intrinsic safety benefits with carrying out reactions under flow conditions as highly toxic, hazardous and explosive intermediates can be synthesised in limited quantities and used *in situ* minimising exposure.[8] For example fluorinations[11,12] and diazo transfer reactions.[5] The quantity of volatile organic compounds (VOCs) can also be reduced, which intrinsically allows the screen of a wide array of reaction conditions from small quantities of reagents and catalysts. These systems also have the potential for automation and continuous 24 h processing leading to an increase in throughput.[4]

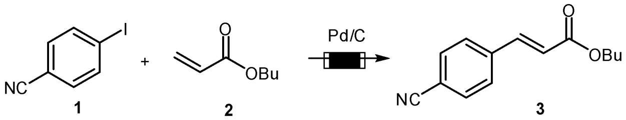
Metal catalysed reactions have a wide utility within the synthetic community, providing access to a variety of reactions and novel chemical entities. Many studies in this field have examined the use of homogeneous catalysis which provides excellent activity and selectivity. Despite its usefulness, homogeneous catalysis has several drawbacks including metal contamination within the final product.[13] For pharmaceutically active compounds this could be a major problem as there are strict guidelines that limit the level of heavy metals.[14] This can potentially be overcome by employing heterogeneous catalysts. After a reaction is complete these catalysts can be filtered from the reaction media, and as most of the metal remains bound to the support, contamination in the final product is reduced.[15] A further advantage is recyclability of these catalysts, which provides both environmental and economical benefits. A broad range of solid supports can be employed including SiO_2,[16] magnetic nanoparticles,[17] MCM-41,[18] polymer beads,[19] molecular sieves[20] and monoliths.[21] Heterogeneous catalysis provides a useful addition to microreactor technology allowing expansion in the use of catalysis under flow conditions. In many cases small amounts of catalyst can be employed, and potentially recycled over numerous runs. A number of the most prominent recent studies concerning the combination of these two emerging technologies have been reviewed in this text.

The potential advantages of heterogeneous catalysis in conjunction with microreactor technology include:

- Continuous product formation
- Simple product/catalyst separation and re-use of catalyst
- Increased reaction rates
- Improved heat transfer and precise temperature control
- Improved mass transfer of a mass transfer limited reaction
- Safer synthesis due to the continuous generation/consumption of unstable or toxic intermediates
- Easier scale-up
- Operation at more severe reaction conditions
- More efficient use of resources and generation of less waste
- Integration of reaction monitoring and processing steps
- Low cost reactors

Palladium on charcoal

Palladium on charcoal (Pd/C) is one of the cheapest and most widely available palladium catalysts for heterogeneous catalysis. It has been utilised by Kappe *et al.* to promote Heck couplings under continuous flow conditions as illustrated between aryl iodide **1** and butyl acrylate **2** (Scheme 1).[22] The Pd/C catalyst was immobilised in a replaceable, pre-packed stainless steel cartridge (60 × 4 mm i.d., *ca.* 310 mg Pd/C) within a high pressure flow reactor (X-Cube).[23] This system allowed flow rates of between 0.1 and 3.0 mL min^{-1} at temperatures of up to 200 °C and pressures of 150 bar to be achieved.



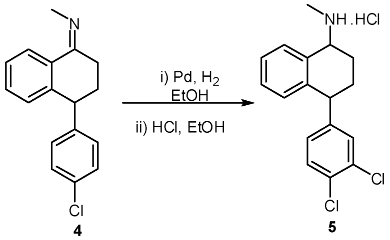
Scheme 1

Complete consumption of **1** was observed at 150 °C employing a 0.5 mL min^{-1} flow rate in the presence of NEt_3, which equates to a 30 s residence time. Under flow conditions it was found that product **3** was accompanied by a significant amount of homocoupling (9%) and dehalogenated (7%) by-products. Varying the temperature, pressure, flow rate or solvent had no impact on the by-products formed. The large amount of dehalogenation was due to the high catalyst loading employed under continuous flow conditions, which can also be observed with high catalyst loading under batch conditions. This, however, did not account for the homocoupling which was attributed to a locally induced chromatographic separation of the reagents as they pass through the column. In particular it was found that the charcoal phase strongly absorbs the aryl iodide **1**, which could be suppressed by employing 2.0 equivalents of the butyl acrylate.

The degree of leaching from the Pd/C catalyst was investigated after conducting twelve consecutive reactions utilising the same solid support. ICP-MS analysis of the used cartridge indicated that 89% of the palladium had leached into the solution. It was felt that a quasi-homogeneous reaction mechanism was occurring in which the Pd/C was acting as a reservoir for soluble, active Pd species which is constantly undergoing absorption/dissolution.[24–26]

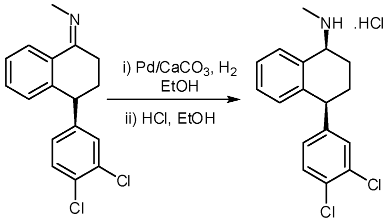
An investigation into the use of aryl bromides was conducted, but it was found that the cartridge size available for the X-Cube system was too short to allow for the high residence times required. Switching to a homogeneous system utilising $Pd(OAc)_2$ and a long stainless steel coil afforded complete conversion to product at 170 °C at 0.4 mL min^{-1} (10 min residence time).

The use of Pd/C under flow conditions has also been reported by Poliakoff *et al.*,[27] where they describe the hydrogenation of the *rac*-imine **4** in supercritical CO_2 ($scCO_2$) to afford the amine **5** (Scheme 2). The optically pure (4*S*)-imine **6** is an intermediate in the synthesis of the Pfizer compound Zoloft® (*cis*-(1*S*,4*S*)-sertraline hydrochloride **7**) (Scheme 3).[28]



Scheme 2

Excellent diastereoselectivity was observed by Pfizer when $Pd/CaCO_3$ was employed to reduce the imine **6**, and only trace amounts of the dehalogenation by-products were observed. Poliakoff developed a continuous flow system to catalyse the



6 **7**

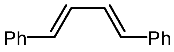
Scheme 3

reaction in Scheme 2, which allowed mixing of the two gases and the substrate at high pressure before pumping over a fixed bed heterogeneous catalyst. Releasing the pressure at the end of the reaction vents off the gases and allows easy recovery of product. Three different catalysts were examined, namely Pt/C, Pd/C and Pd/CaCO$_3$. The Pd/CaCO$_3$ catalyst afforded an excellent conversion (98%) with a *cis*:*trans* ratio of 95 : 5 and only a trace of the dehalogenated by-product. This was deemed to be the optimum heterogeneous catalyst under these conditions, 80 °C with a 1.0 mL min^{-1} flow rate of CO$_2$ and 0.4 mL min^{-1} of substrate.

Hydrogenations utilising the H-Cube reactor

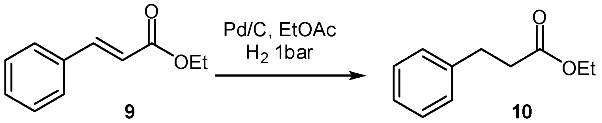
One of the most popular methods for achieving high throughput catalytic hydrogenations under flow conditions is utilising the H-Cube reactor, which was developed by Thales Nanotechnology.[29] This generates the required amount of hydrogen *in situ* by the electrolysis of deionised water, which exhibits numerous safety advantages and does not require the use of a high pressure cylinder. Hydrogen is fed into the reagent system as a series of bubbles, which ensures mixing between the two phases. The reagent/hydrogen stream is then fed through a heating block (max 100 °C) containing a catalyst cartridge. This cartridge can be packed with Pd/C, Pt/C, Pearlman's catalyst, Rh/C, RANEY® Nickel or RANEY® Cobalt, and can hold approximately 140 mg of catalyst.

Numerous substrates have been reduced utilising this equipment, including *trans*,*trans*-1,4-diphenyl-1,3-butadiene (**8**). Reduction utilising the H-Cube occurred in 20 min with 10% Pd/C at 1 bar pressure, to afford a 82% yield and 96% conversion.



8

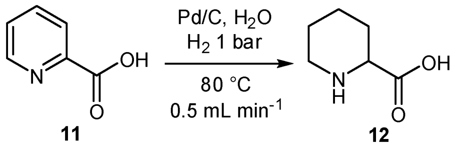
Kappe *et al.* have described the use of the H-Cube reactor to reduce ethyl cinnamate **9** to propanoate **10** under flow conditions (Scheme 4).[30] For a 0.1 M solution of **9** in ethyl acetate complete conversion to **10** was achieved utilising Pd/C (10% w/w) at room temperature at 2 mL min^{-1}. ICP-MS analysis indicated the presence of <0.1 µg of Pd in the eluent, proving only minimal Pd leaching was occurring. Increasing the concentration of **9** afforded a decrease in the conversion to product. This could be counteracted by increasing the temperature to ≥80 °C, which afforded complete conversion of a 0.2 M solution of **9** at 3.0 mL min^{-1}.



9 **10**

Scheme 4

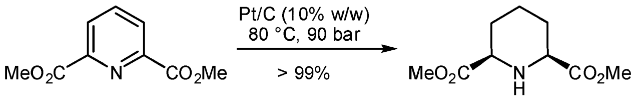
This account also describes the hydrogenation of pyridine utilising the H-Cube reactor. Under normal conditions this requires significant hydrogen pressures, elevated temperatures and long reaction times. It was found that picolinic acid **11** could be hydrogenated to pipecolic acid **12** within the H-Cube reactor employing a Pd/C heterogeneous catalyst (Scheme 5). At 80 °C with a 0.5 mL min^{-1} flow rate in water, complete conversion to **12** was achieved with a 97% isolated yield.



11 **12**

Scheme 5

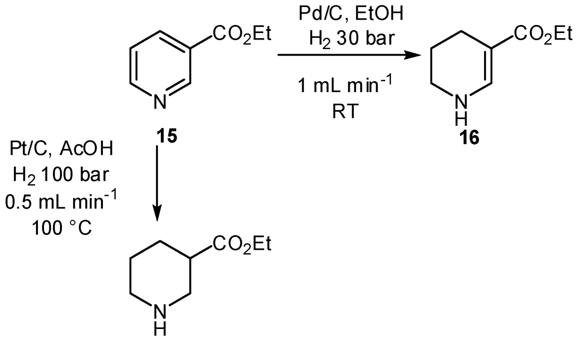
An investigation was conducted into the flow hydrogenation of various substituted pyridines with different solid supported metal catalysts. This was carried out using acidic media (acetic acid), which activated the pyridines and reduced catalyst poisoning from the resultant secondary amines. Full conversions were achieved at hydrogen pressures between 30 and 80 bar at 0.5 mL min^{-1} regardless of whether Pd/C, Pt/C or Rh/C was used. It was found that some hydrogenations occurred stereoselectively, for instance pyridine-2,5-dicarboxylate **13** afforded only the *cis* isomer **14** (99%, Scheme 6).



13 **14**

Scheme 6

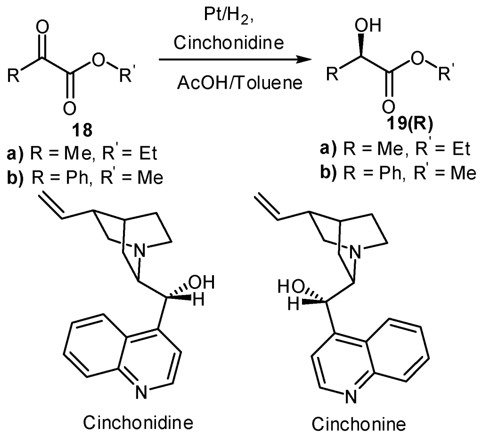
Partial hydrogenations under flow conditions were also investigated using ethyl nicotinate **15**, which afforded vinylogous carbamate **16** (Scheme 7). The stabilised carbamate **16** was formed with a 95% selectivity utilising a Pd/C catalyst in ethanol at 1.0 mL min^{-1}. Complete hydrogenation to **17** could be achieved by switching to a Pt/C catalyst at higher H$_2$ pressures (100 bar) and temperatures (100 °C) in AcOH.



15 **16** **17**

Scheme 7

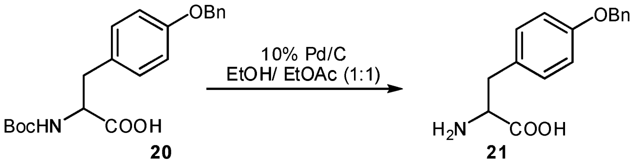
Bartók *et al.* demonstrated that the H-Cube could be employed to carry out enantioselective hydrogenations of α-ketoesters.[31] This was achieved utilising a 5% Pt/Al_2O_3 catalyst in conjunction with cinchonidine, which acts as a chiral modifier. High enantiomeric excess (ee) could only be achieved in the presence of cinchonidine. The enantioselective hydrogenation of ethyl pyruvate was investigated under continuous flow conditions at 1 mL min^{-1} in acetic acid (AcOH) and toluene (Scheme 8), which afforded **19a** in an 89% ee. Synthesis of the *S* enantiomer of **19** could be achieved utilising cinchonine as the chiral modifier.



Scheme 8

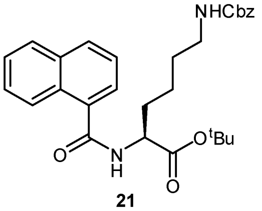
This protocol could be extended further to the enantioselective hydrogenation of methyl benzozoylformate **18b**. It was found that ketones containing aromatic moieties required a higher concentration of modifier (by an order of magnitude) to obtain comparable ee values. For the hydrogenation of **18b** in the presence of cinchonidine the product **19b** was synthesised in an 81% ee.

Ley *et al.* have utilised the H-Cube reactor with a robotic liquid handler in conjunction with Hydromate™ (user interface).[32] This allowed excellent deprotection of N-Boc tyrosine **20** (0.1 M) with 10% Pd/C in EtOH–EtOAc (1 : 1) at 0.5 mL min^{-1} at 30 °C (Scheme 9). The conversion decreased with each subsequent run through the reactor due to catalyst deterioration, which was more pronounced at faster flow rates. It was found that after catalyst deterioration increasing the temperature to 60 °C led to immediate catalyst recovery and sustained activity with subsequent running. This phenomenon was thought to be due to more effective surface cleaning of the catalyst, or an increase in the catalytic off-rate. It was also found that preservation of the catalyst could be achieved by allowing a period of catalyst recovery between runs.



Scheme 9

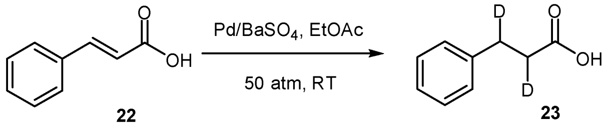
This procedure was further extended to the hydrogenolysis of *N*-Cbz derivatives such as ε-[*N*-Cbz] lysine *tert*-butyl ester **21**.



21

These derivatives were deprotected sequentially employing automation to afford products in good yields and high purities. In one instance both Cbz and benzyl deprotection was carried out successfully on one substrate.

The utility of the H-Cube reactor can be extended to carry out electrolysis of D_2O to simultaneously reduce and deuterate reagents under flow conditions.[33] The reduction and deuteration of cinnamic acid **22** was investigated (Scheme 10) employing $Pd/BaSO_4$, as any more active catalysts led to deuteration of the aromatic ring.

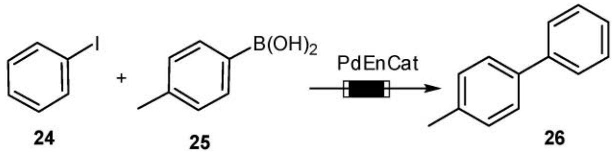


Scheme 10

In ethyl acetate (EtOAc) at 50 atm 95% deuteration was achieved at flow rates between 0.7 and 2.0 mL min^{-1}. For all substrates investigated high deuterated content and yields were achieved with an excellent degree of functional group tolerance. This method was also utilised to deuterate nitriles, although the amine reacted with the nitrile to afford by-products thus reducing overall yields. Despite this it was demonstrated that by utilising this method, deuteration of substrates could be achieved faster (1 mg min^{-1}) than conventional methods and exhibiting excellent purities (99%).

Pd EnCat™

Ley *et al.* were pioneers in the development of polyurea-encapsulated $Pd(OAc)_2$ catalyst, which is commonly known as Pd EnCat™.[34] This is a popular, commercially available heterogeneous palladium catalyst that has been employed in a wide variety of batch applications.[35–36] Packing Pd EnCat™ within a HPLC column allows it to be exploited for continuous flow reactions, which was first demonstrated by Ley *et al.* for the Suzuki coupling of iodobenzene (**24**) and *p*-tolylboronic (**25**) acid in the presence of $^{n}Bu_4NOMe$ (Scheme 11).[37] A quantitative yield of **26** was obtained in toluene–methanol (9 : 1) at 70 °C



Scheme 11

using a single pass over the packed Pd EnCat™ at 0.2 mL min^{-1} (4 min residence time).

Various $^{n}Bu_4NX$ (X = OH, F, OMe and OAc) were examined, but $^{n}Bu_4NOMe$ afforded the best results as a homogeneous reaction mixture was observed to allow maximum interaction between reagents and catalyst. There are three commercially available forms of Pd EnCat™: 30, 40, TPP 30 and TOTP30. Pd EnCat™ 30 and 40 are composed of palladium(II) ligated to a polyurea encapsulation matrix and they differ in the percentage of their matrix content. Pd EnCat™ TPP30 involves Pd(II) ligation to a triphenylphosphine moiety and Pd EnCat™ TOTP30 to a tri-*o*-tolylphosphine. It was initially thought that very little palladium leaching was occurring for these Pd EnCat™ species, with ICP-MS analysis indicating palladium levels of 10 ppm (0.025% metal loss) in the filtered reagent solution.[38] However, by conducting a more complex 3-phase test it was found that significant leaching of a soluble active Pd species was occurring, thus the Pd EnCat™ was serving as a Pd reservoir.[39] It was felt that a significant amount of the reaction was occurring in solution, but a true heterogeneous catalytic system could also be occurring.

Ley *et al.* have also examined the use of Pd EnCat™ for the Suzuki-Miyaura reaction under continuous flow microwave conditions.[40] The reactor utilised comprised of catalyst packed within a U-tube, which was inserted into the cavity of a microwave reactor (Fig. 1). Flow could be induced by a pump, and at the end of the reaction reagents were directed through a column of Amberlyst resin to remove any residual base and boronic acid salts. A solution of boronic acid (0.28 mmol), aryl halide (0.28 mmol) and tetrabutylammonium acetate in ethanol was pumped around the reactor at 0.1 mL min^{-1}. This equated to a total residence time of 225 s with the reagents being subjected to microwave irradiation for 65 s. Initially the reagents were exposed to a constant power of 50 Watts, which proved detrimental as the super heating caused the polymer matrix of the EnCat™ to melt and impede the flow, eventually completely blocking the tubing. Pulsing the microwave irradiation by applying a 50 Watt power for 30 s and then allowing 18 s for cooling prevented this problem from occurring.

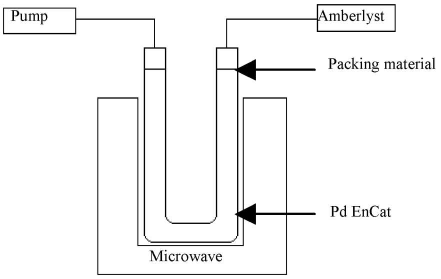


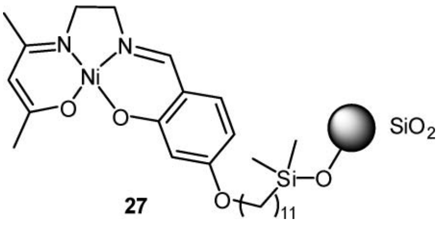
Fig. 1 Schematic of the Pd EnCat™ continuous flow microwave reactor.

For all reactions examined the flow process afforded comparable, and sometimes higher yields of product at greater purity. Several reactions were carried out sequentially by passing equal volumes of ethanol between each reaction allowing the system to run in a truly continuous fashion. It was also ascertained that these reactions could be carried out over extended periods of time so that large quantities of products could be generated. Only after several hours' operation did the conversion drop dramatically, but large quantities of product had been synthesised that were greater than could have been achieved by a single batch reaction.

Another example of the use of Pd EnCat™ under continuous flow conditions has been demonstrated by Leeke *et al.*[41] They investigated the Suzuki-Miyaura reaction under flow conditions with conventional solvents and $scCO_2$. A 9 : 1 mixture of toluene and methanol was utilised as the conventional solvent, with 45 g of Pd EnCat™ being packed into a ModCol column (10.0 cm × 25.4 cm). The Suzuki-Miyaura reaction between *p*-tolylboronic acid **25** and iodobenzene **24** in the presence of tetrabutylammonium methoxide (Scheme 11) was investigated. It was found that higher temperatures afforded higher conversions, but after 100 °C this effect was less pronounced. The optimum flow rate was 6.4 mL min^{-1}, which afforded a 74% conversion to **26**. Any attempt to lower the flow rate, hence increase residence time, resulted in a lower conversion. This was thought to be due to a lower solid/liquid ratio and poorer mixing. To improve conversion further the reagent solution was passed three times over the column, but this only afforded a slight increase in conversion. Addition of a further portion of Bu_4NOMe to pH 13.4 (initial pH) afforded complete conversion to **26** after the second pass. The same reaction was examined under $scCO_2$ conditions, with MeOH as a co-solvent to increase the solubility of the Bu_4NOMe. An optimum conversion of 81% was achieved at 166 bar at 100 °C and 5.5 g min^{-1}, which was under supercritical conditions. Higher pressures afforded a decrease in conversion, and lower pressures afforded satisfactory conversion under a two-phase system. Lower pressures could afford an advantage in process economics.

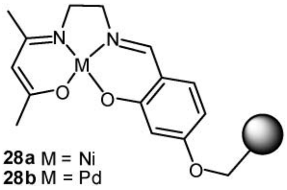
Silicon dioxide support

Another popular choice for supporting metal catalysts is silica dioxide (SiO_2). Styring *et al.* described the synthesis of two types of nickel functionalised silica supports for the catalysis of the Kumada reaction.[42,43] The first catalyst is a silicon hydride functionalised silica which incorporates an extended hydrocarbon tether (**27**). In this sense the catalyst can be described as androgynous, possessing a heterogeneous silica core with a homogeneous tether.

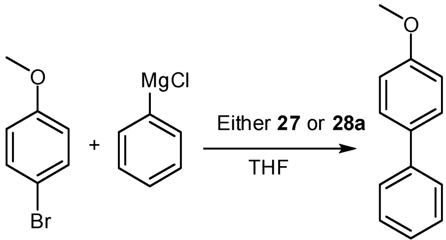


27

Inductively coupled plasma-atomic emission (ICP-AE) analysis of **27** showed there to be *ca.* 1.5% (wt/wt) nickel on silica, corresponding to a complex loading of 0.25 mmol nickel g^{-1} silica. This salen-type nickel complex was also immobilised on to 4-benzyl chloride functionalised silica, which is analogous to Merrifield resin (**28a**).



ICP-AE showed there to be 1% (wt/wt) nickel on silica, corresponding to a catalyst loading of 0.15 mmol nickel g^{-1} silica. Under batch conditions the reaction between 4-bromoanisole **29** and phenyl magnesium chloride **30** in THF at room temperature after 24 h afforded 4-methoxybiphenyl **31** in 67% yield for **27** and 49% yield for **28a** (Scheme 12). It was found that the optimum catalyst loading was 0.5 mol%, and utilising the magnesium chloride in preference to the bromide prevented salt deposition on the catalyst. The higher reactivity of catalyst **27** was attributed to its flexible structure and the greater availability of active sites.



29 **30** **31**

Scheme 12

This reaction was also carried out under flow conditions using a pressure driven microflow reactor constructed from a syringe pump and Omnifit glassware (bed size = 25 mm × 3 mm).[44] The syringe pump directed equimolar amounts of the two reagents (0.5 mol L^{-1}) through the reactor containing catalyst **28a** at different flow rates for 1 h. Optimum results were achieved at a 13 μL min^{-1} flow rate to afford a 64% conversion to **31**. Any further decrease in the flow rate did not afford an increase in the conversion to product. It should be noted that 4,4′-dimethoxybiphenyl (10%) and anisole (20%) were also formed as by-products during the reaction. In THF, the catalyst **28a** exhibits significant swelling causing a pressure drop and reactor blockage when fully packed. This was overcome by packing the catalyst bed to account for the swelling, which is not trivial due to the range of particle sizes and differing amounts of swelling. Switching to a solvent that does not induce swelling also had issues as the majority of active sites in this catalyst are embedded inside the solid support with swelling allowing their accessibility. These problems were not an issue with catalyst **27**, which under the same conditions afforded a 62% conversion to product contaminated with 25% anisole and 7% 4,4′-dimethoxybiphenyl. The continuous flow reactor showed continual degradation in performance with a 30% conversion to product being achieved after 5 h continual operation. After removal of the catalyst and washing with THF and water a conversion of 65% was then achieved in the microflow reactor. It was felt that MgBrCl salt was being deposited on the surface on the catalyst rendering it inactive. This could be prevented by incorporating a wash step between reactions.

Utilising flow technology for the catalyst **27** offered significant advantages over the batch process, allowing the product to be synthesised in minutes compared to 24 h. This was rationalised in terms of the effective ratio of catalyst to substrate, which in this case is 70 mol%. Therefore, under flow conditions at any one time there is a small amount of substrate being forced in close proximity to a large amount of catalyst. When the turn over frequency (TOF) was calculated for the catalyst it was found to be comparable under batch and flow conditions.

The reaction in Scheme 12 has also been carried out by Styring *et al.* in a pressure driven microflow reactor utilising catalyst **28a** supported onto Merrifield resin.[43] It was found that at a flow rate of 13.3 μL min^{-1}, a consistent conversion of 60% was observed with biphenyl (20%) also being formed. Interestingly it was reported that this conversion was found to be independent of flow rate.

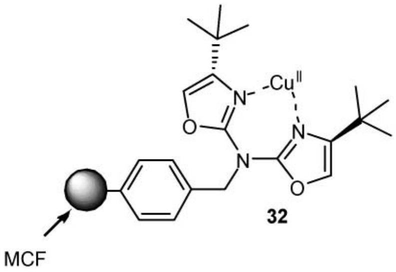
Analysis of the rate of reaction under flow and batch conditions found that flow reactions exhibited a rate enhancement of 3.4 × 10^3. This was rationalised by the availability of catalytic sites. Under flow conditions the beads are packed tightly together and reagents are forced through the beads' pores under high pressure. Hence the number of catalytic sites available for reaction is higher. Under batch conditions a slow diffusion process means that reagents do not penetrate into the interior catalytic sites and the reaction occurs mainly on the surface.

Styring *et al.* have also reported the immobilisation of a salen-type palladium(II) catalyst (**28b**) onto a polystyrene-divinylbenzene cross-linked Merrifield resin.[45] There was found to be *ca.* 2% (wt/wt) palladium on the Merrifield beads, which corresponded to a catalyst loading of 0.2 mmol palladium g^{-1} of resin. This catalyst was utilised to catalyse Suzuki-Miyaura reactions in a pressure driven mini flow reactor (bed size = 25 mm × 3 mm). The coupling of **29** with phenyl boronic acid in DMF–H_2O (1 : 1) in the presence of *N*,*N*-diisopropylethylamine was investigated. Over 5 h at 100 °C at a 6 μL min^{-1} flow rate, a conversion to **31** of 52% was observed.

It was found that yields of **31** were lower (40%) in the first hour of operation, and over the subsequent 4 h increased to an average of 60%. This was thought to be due to the delay in forming the catalytically active Pd(0) species from the Pd(II) precursor. This system was utilised to carry out Suzuki-Miyaura coupling reactions on various aryl bromides and heteroaryl bromides with phenylboronic acid. Yields ranged from 37–77% with the electron deficient substrates affording the higher reactivity. Interestingly, however, 4-bromonitrobenzene only formed a trace of product despite being strongly electron withdrawing. Studies are on-going to clarify this unexpected behaviour.

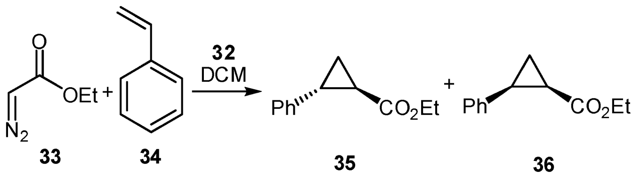
This simple system allowed for the rapid production of small inventories of reagents and the ability to synthesise products on demand very rapidly. The design of this system is economical and allows the user to easily replace catalyst beds and interchange reagents. Another significant advantage is that the product streams are palladium free due to the reduced palladium leaching.

Lim *et al.* utilise mesoporous silica as a support for aza(bisoxazoline) copper catalysts.[46] The silica support was in the form of a siliceous mesocellular foam (MCF) microparticle, which exhibits large pores (29 nm) and interconnecting windows (17 nm). This media is useful for fixating bulky complexes.



32

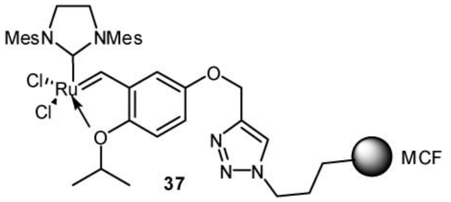
The optimum catalyst for enantioselective cyclopropanation was found to be the MCF supported aza(bisoxazoline) copper catalyst **32**. After immobilisation of the aza(bisoxazoline) ligand, prior to copper ligation, any remaining unreacted silanol groups were postcapped by vapour-phase treatment with hexamethyldisilazane (HMDS). This prevented the copper coordinating to the free silanol groups, and ultimately increased the life time of the catalyst. Copper was added in the form of Cu(II) triflate, which was reduced *in situ* with phenylhydrazine. Under batch conditions it was ascertained that increasing the ligand loading afforded a considerable increase in the enantioselectivity and recyclability of the catalyst. Subsequently, for the continuous flow reactions the ligand loading was 0.245 mmol g^{-1}, and was packed into empty HPLC columns (50 mm × 4.6 mm I.D). After the *in situ* generation of Cu^{I} the reaction between ethyl diazoacetate **33** (0.33 M) and styrene **34** (0.67 M) in DCM was carried out under continuous flow conditions at 0.2 mL min^{-1}, which afforded full consumption of **33** (Scheme 13).



Scheme 13

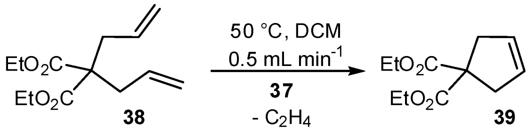
With prolonged reaction time both the enantioselectivity and conversion decreased. This was due to the generated N_2 gas being trapped inside the column for extended periods of time and eventually inhibiting catalytic activity. To overcome this problem a semi-continuous flow system was developed. This comprised of a central reservoir of reagents which were directed thorough the solid supported catalyst, with output being pumped back into the central reservoir. With this system higher flow rates could be achieved and the generated N_2 could be effectively removed. It was found that after 20 cycles the *trans* isomer **35** was afforded in 93% ee and up to 80% yield.

Lim *et al.* also describe a continuous flow metathesis utilising a ruthenium catalyst supported on a siliceous mesocelluar foam microparticle (**37**).[47] Elemental analysis indicated that ruthenium loading was 0.16 mmol g^{-1}, showing that >80% of the immobilised ligand was loaded with ruthenium.



37

n-Propyl was chosen as the linker as this exhibited the greatest activity, with both more rigid (benzyl) or flexible (n-pentyl) linkers affording lower conversions. The metathesis of the diene **38** was investigated under flow conditions at 50 °C at 0.5 mL min^{-1} in DCM (Scheme 14), which afforded complete conversion to **39** in a 30 min residence time.



Scheme 14

It was found that with continuous flow, over time the conversion to **39** decreased rapidly. This was thought to be due to the inhibition of **37** by the generated by-product ethylene, which had previously been observed.[48] In toluene this effect was even more pronounced due to the increase in solubility of ethylene in toluene.[49] To overcome this problem a circulating flow reactor was developed, which allows the *in situ* removal of ethylene. Reagents could be pumped around this reactor at elevated flow rates (5 mL min^{-1}) until complete conversion was attained. For the reaction in Scheme 14 this occurred after 12 runs. ICP-MS analysis of the eluent indicated that under flow conditions 11.3 ppm of ruthenium was present, which decreased to 1.6 ppm after continuous flow for 180 min.

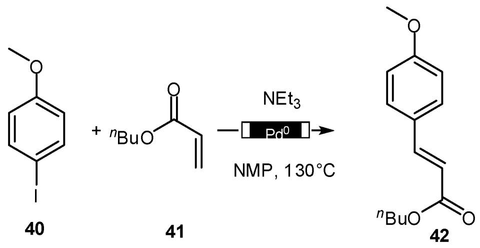
One of the disadvantages to packing columns from solid supports is the intrinsic large void volumes, which is an inevitable result of the particulate character of the packing. In a well packed column about 30% of the total volume is interstitial void, but in most cases it is even larger.[50] This can be more easily controlled by utilising monolithic supports.

Monolithic supports

Monolithic flow reactors are based on a polymer bound reagent encased within a cartridge which exhibit low to moderate pressure drops. These reactors can be synthesised within solvent resistant tubes by precipitation polymerisation of monomers such as polyvinylchlorobenzene, which can be achieved in the absence or presence of a porogen. This affords small polymeric beads (1–5 µm diameter) that are crossed-linked with polymer bridges.[51] As such monolithic supports can be described as uni-body structures composed of interconnected repeating cells or channels.[52] Due to the extensive number of channels within a monolithic composite there is little resistance to flow and hence a low pressure drop. The lower the pressure drop, the lower the resistance to flow or back pressure on the system and hence lower energy loss.[53] They exhibit excellent mass transfer properties, and possess a very stable core structure. The polymer particles can only swell and shrink in the pore volume available, which has no effect on the rigid outer dimensions of the tube. This minimises the technical problems associated with conventional polymer supports, namely high pressure drops or bypassing.[51] Organic monoliths were initially used as stationary phases for chromatographic separations.[54]

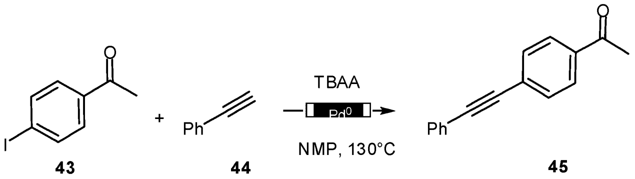
One of the earlier pioneers of this reaction medium was Kirschning who termed this a PASSflow (polymer assisted solution-phase synthesis) technique. The group developed a reactor system consisting of a monolithic block based on a chemically functionalised and highly porous polymer/glass composite material. This is constructed by polymerising vinyl benzyl chloride and divinylbenzene (copolymer) with 2,2′-azobis(2-methylpropionitrile) (AIBN) within porous glass rods. The addition of triethylamine to this vinylbenzyl chloride polymer results in the formation of the quaternary ammonium ion,[55] although other moieties such as sulfonic acid, amino, vinylpyridine and imidazole have also been reported. These functionalised rods were first embedded in a solvent resistant tube before being encapsulated within pressure-resistant fibre reinforced epoxy resin. The termini of these rods were fitted with standard high-pressure liquid chromatography (HPLC) fittings.[51]

Palladium loading was achieved by pumping a solution of sodium tetrachloropalladate (0.5 mol%) in water twice through the reactor, which was reduced *in situ* to Pd^0 utilising sodium borohydride ($NaBH_4$). This reactor has been utilised to perform the Heck reaction between *p*-iodoanisole **40** (1.0 mmol) and n-butylacrylate **41** (1.5 mmol) with NEt_3 (1.4 mmol) as base and 1-methyl-2-pyrrolidinone (NMP) as solvent at 130 °C (Scheme 15).[56] This afforded complete transformation to **42** within 30 min.



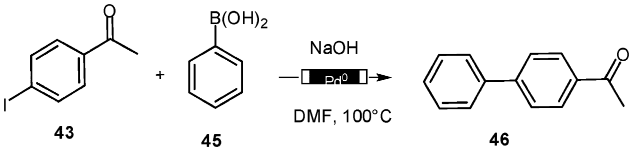
Scheme 15

A copper-free Sonogashira reaction was also reported between *p*-iodoacetophenone **43** (2 mmol) and phenylacetylene **44** (4 mmol) in the presence of tetrabutylammonium acetate (TBAA) in NMP (Scheme 16). These conditions resulted in complete consumption of **43** by GC-MS to afford **45** in 81% yield, with less than 9% homo-coupling by-product.



Scheme 16

The Suzuki-Miyaura reaction between **43** (1 mmol) and phenyl boronic acid **45** (1.2 mmol) in dimethylformamide (DMF) was also investigated (Scheme 17). After three hours **46** was isolated in a 77% yield, with no observable homo-coupling by-product.



Scheme 17

Having established that Heck, Suzuki-Miyaura and Sonogashira reactions could be catalysed utilising Pd supported monoliths, Kirschning *et al.* then established the manufacturing specifications and requirements to improve these solid supports.[57] The conditions chosen were an adaptation of those reported by Kunz for the Horner–Emmons olefination.[58] This utilised the precipitation polymerisation method of the monomer vinylchloromethylbenzene with the cross-linker divinylbenzene in a hydrocarbon based solvent. The polymer was then functionalised by treatment with trimethylamine in toluene.

This modified PASSflow reactor was then employed to immobilise boronic acids as the tetrahedral hydroxyborate for use in the Suzuki-Miyaura reaction. Numerous aryl bromides and iodides were examined in the presence of palladium tetrakis in THF at 60 °C. Residence times ranged from 2 to 18 h with yields between 62 and 91% being achieved.[59]

Ley *et al.* have also prepared palladium supported monoliths to catalyse the Heck reaction.[1] Their monolithic support was constructed using vinyl benzyl chloride (35%) as the monomer, divinyl benzene (20%) as the cross linker and AIBN (1%) as the radical initiator with 1-dodecanol (45%) being employed as the porogen. The polymerisation reactions were performed under 1 bar pressure *in situ* within 6.6 mm i.d × 70 mm Omnifit glass columns.[44] These were temporarily sealed at one end and located within a multichannel convective heating device to allow polymerisation to occur at 80 °C. The solvent THF (1.0 mL min^{-1}; room temperature; 2 h) was then pumped through the monolith to remove residual porogen and nonpolymeric material. Median pore sizes of 3147 nm were determined by mercury intrusion analysis, and nitrogen absorption and BET theory being used to calculate the surface area to be 4.93 m^2 g^{-1}. The quaternary ammonium salt of the monolith was formed by elution with a solution of triethylamine in toluene (1 : 4) at 0.04 mL min^{-1} and 60 °C for 48 h. Washing with toluene at 1.0 mL min^{-1} for 30 min at 60 °C afforded a loading of 2.0 mmol g^{-1}, according to C, H and N analysis.

Derivatisation of the monolith with palladium(0) was achieved by pumping two consecutive freshly prepared solutions of sodium tetrachloropalladate (465 mg, 1.6 mmol) in water (80 mL) through the monolith at 0.3 mL min^{-1}. Initially the solution that exited the column was found to contain only sodium chloride, but after 3 h the outflow was yellow in colour. The palladium(II) grafted onto the monolith was then reduced *in situ* by pumping an aqueous solution of sodium borohydride (625 mg in 50 ml water) at 0.5 mL min^{-1}. Conditioning was then achieved by pumping (1.0 mL min^{-1}) water (20 mL) then 1.0 M HCl (20 mL), water (30 mL) and finally ethanol (20 mL) through the column. HRTEM (Fig. 2a) showed the presence

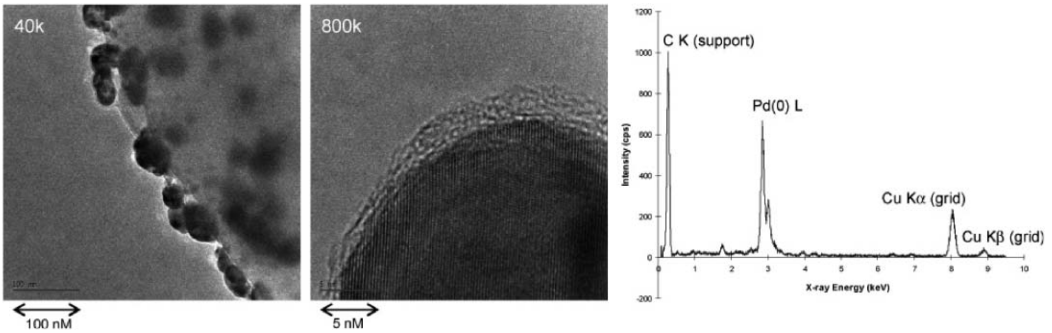
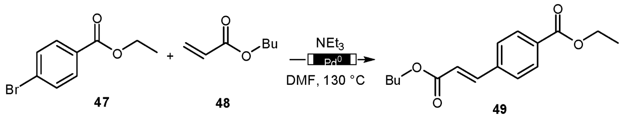


Fig. 2 (a) TEM image of a nanoparticular Pd derivatised monolith. (b) HRTEM image of a Pd nanoparticle showing an ordered lattice structure. (c) EDS spectrum of a nanoparticle showing only Pd(0) to be present.[1] Copyright American Chemical Society. Reproduced with permission.

of Pd nanoparticles attached to a polymer support in the size range 5 to 50 nm. Upon closer inspection it was found that the Pd particles exhibited a very stable ordered lattice arrangement (Fig. 2b), with EDS analysis confirming only Pd^0 nanoparticles were present (Fig. 2c).

Initially a variety of aryl iodides (0.2 mmol) and alkenes (0.3 mmol) were examined utilising DMF as the reaction solvent in the presence of triethylamine (0.3 mmol) at 130 °C. At 0.05 mL min^{-1} each reaction carried out afforded 100% conversion with isolated yields ranging from 82 to 87%. The bromide ethyl 4-bromobenzoate **47** was coupled with butyl acrylate **48** to afford a 51% conversion to **49** (Scheme 18). Unfortunately, aryl chlorides were unreactive under these conditions.



Scheme 18

Due to the toxicity and difficult removal of DMF an alternative solvent was sought that could also carry out the reaction at 130 °C. It was found that superheating EtOH at elevated pressure, by using an in-line 100 psi back pressure regulator, afforded similar results to those obtained using DMF. ICP-MS analysis on the isolate solid products indicated a very high level of Pd contaminate (270 ppm). This was resolved by inserting an on line metal scavenger resin (Quadrapure TU[60]) prior to compound collection. The Pd levels within the solid product was reduced to below 5 ppm.[1]

Kirschning *et al.* expanded the use of monoliths further by incorporating monoliths inside Raschig rings.[61–64] The Raschig ring reactor has the advantage over a rod-type reactor as it can be easily unscrewed and the spent rings removed and replaced with newly functionalised rings.[65] These reactors are adaptable being utilised for small scale reactions (only one ring) as well as larger scales. The reactor design allows the use of one or several rings, so the catalyst amount can be easily varied without the need to alter flow conditions. The rings can be prepared in large quantities, making them more economically viable than rod shaped reactors.[59] Fig. 3 illustrates the separate components of the Raschig ring reactor.

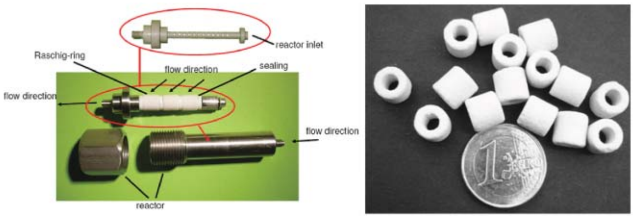
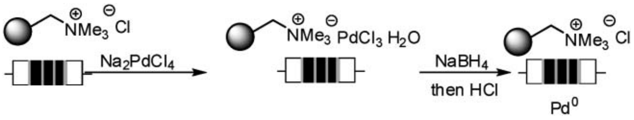


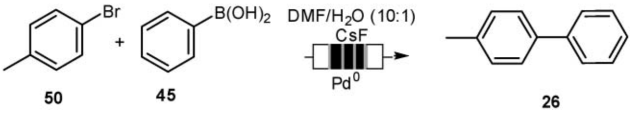
Fig. 3 (a) Reactor with functionalised Raschig rings (rings are aligned on a perforated tube; gaskets between the rings prevent bypass);[64] (b) Raschig rings.[21]

Kirschning *et al.* carried out precipitation polymerisation within Raschig rings utilising styrene, divinylbenzene and vinyl benzyl chloride (2.3%) as monomers. Washing through with triethylamine formed the quaternary ammonium ion, as previously described. Palladium can be anchored onto this solid support by means of ion exchange by pumping sodium tetrachloropalladate through the ring. The active palladium species can then be formed by reduction with sodium borohydride (Scheme 19). This afforded nanoparticles of 7 to 10 nm in size with a palladium content of 0.003 wt%.[21]



Scheme 19

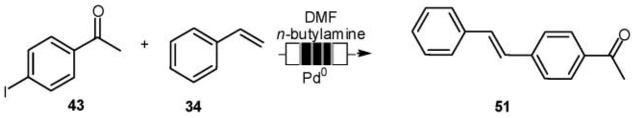
This catalyst was then utilised in both the Suzuki-Miyaura and Heck cross coupling reactions. The Suzuki-Miyaura reaction chosen for analysis involves the coupling between *p*-bromotoluene **50** and phenylboronic acid **45** in DMF–H_2O at 95 °C using CsF as the base (Scheme 20). The reaction was performed in a cyclic mode at 2 mL min^{-1}, and achieved a 99% yield after 10 min residence time. Electron rich and electron deficient aryl bromides with functionalised boronic acids were also examined and exhibited good to excellent yields (60–99%). Aryl chlorides failed to react under these conditions.



Scheme 20

Catalyst reusability was also examined by carrying out this reaction over numerous runs. It was found that the catalyst showed excellent stability without loss of activity even after the tenth run. For each run the palladium leaching was determined to be in the region of 0.7 ppm.

The monolith was also used to promote the Heck coupling of *p*-iodoacetophenone **43** and styrene **34** in DMF using *n*-butylamine as base (Scheme 21). At a flow rate of 2 mL min^{-1} in cyclic mode, full conversion with complete *E*-selectivity within 30 min was observed. Switching to *p*-bromoacetophenone afforded a decrease in conversion to 35%.



Scheme 21

In a further study the Raschig rings were coated in poly(4-vinylpyridine) (PVP) and then cross linked with 5.3% DVB. This can then coordinate to catalyst **52** to create a monolith with irregular microchannels (≤50 μm) (Fig. 4).[65]

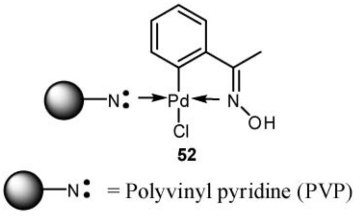
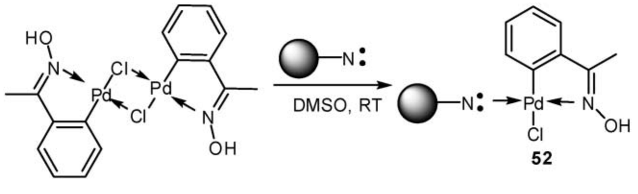


Fig. 4 Catalyst **52** bound to PVP.

It was suggested that catalyst **52** acts as a reservoir for palladium nanoparticles, of an unspecified nature, which are formed after reduction. It was further speculated that the Pd^0 species can either catalyse reactions, or re-coordinate onto the PVP support. This solid supported catalyst was utilised in Suzuki-Miyaura and Heck reactions, and a study on the 'homogeneous' nature of these catalysts was carried out by employing resins with scavenger properties. The catalyst is prepared by coordination of the palladacycle **52** to PVP (Scheme 22). As well as immobilising the catalyst on Raschig rings it was also prepared on powder PVP by precipitation polymerisation and inside a rod-shaped monolith (Fig. 5).



Scheme 22

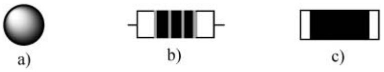
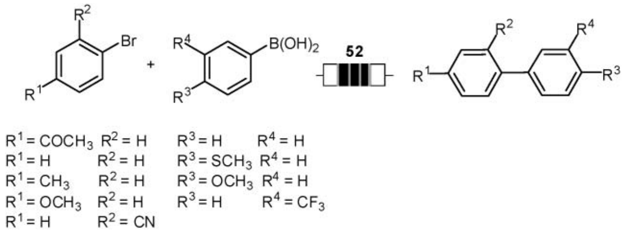


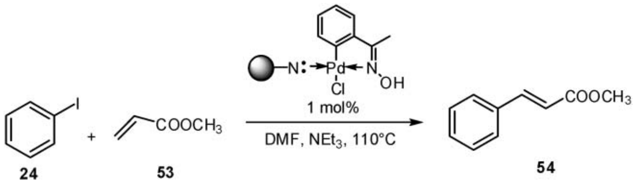
Fig. 5 Types of solid supported catalyst; a) powder prepared by precipitation polymerisation resin (1 mol% immobilized on powder with a loading of 0.8 mmol Pd g^{-1}), b) glass/polymer monolithic composite material shaped as Raschig ring (optimised loading 3.57 × 10–5 mmol Pd mg^{-1} ring as judged by elemental analysis), c) glass/polymer rod shaped monolithic composite material.[63]



Scheme 23

A range of Suzuki-Miyaura reactions have been studied, as illustrated in Scheme 23. The reactions were carried out in the presence of CsF as the base in DMF–H_2O (10 : 1) at 100 °C at 2 mL min^{-1}. For reactions where R^3 was either SCH_3 or OCH_3, DMF–H_2O/amyl alcohol (10 : 1 : 1) was utilised to ensure a complete homogeneous reaction mixture was maintained. In these cases the reaction time had to be increased to between 24 and 30.5 h. This made them unsuitable as cross coupling partners under continuous flow conditions.

All boronic acids tested gave excellent (73–99%) yields when coupled with 4-bromoacetophenone (R^1 = $COCH_3$, R^2 = H). Electron donating aryl bromides coupling to phenylboronic acid afforded only moderate yields (50–89%). This catalyst has also been utilised in the Heck reaction between **24** and methyl acrylate **53** (Scheme 24). In DMF at 110 °C in the presence of NEt_3 under batch conditions complete conversion to product **54** was achieved in 1.5 h.

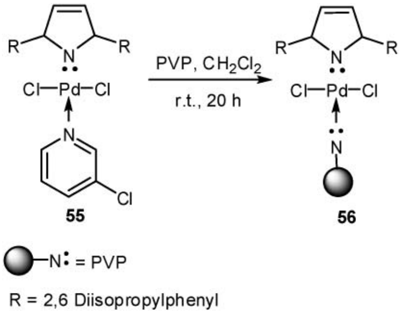


Scheme 24

This reaction was also optimised for use with rod-shaped and Raschig monoliths. Both types of reactors afforded comparable yields of product, and after 24 h under continuous flow conditions at 120 °C in the presence of tributylamine as the base a 76% isolated yield of **54** was achieved. Due to the benefits of the Raschig monolith, all continuous flow reactions were conducted using this reactor type. It was found that all aryl iodides tested afforded reasonable conversions (64–99%), with electron deficient iodides reacting in 2 to 4 h, and electron rich in 24 h.

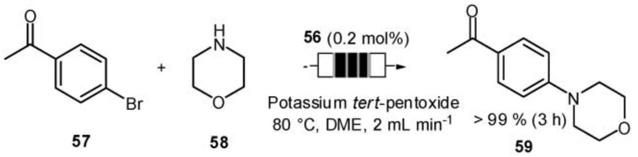
The stability of the Raschig monolith supported **52** was ascertained by carrying out the Heck reaction between *p*-iodoacetophenone **43** and cyclohexyl acrylate over ten runs. It was found that the polymeric material did not erode, and there was no loss in catalytic activity. Due to the high temperature palladium black was deposited on the surface of the glass composite. De Vries had noted that at temperatures between 100 and 150 °C the mechanism of the ligand-free palladium-catalysed Heck reaction changed, which could cause the deposition of Pd black.[66]

It was shown that only a small amount of palladium leaching was observed, with 1.1 to 2.1 ppb being present after the reaction has cooled. It is possible that the PVP is acting as a Pd^0 reservoir, which exerts its reactivity in solution. The low degree of leaching can be attributed to the fact that there are numerous free pyridine sites in PVP that can efficiently scavenge and retard the formation and growth of colloids. When a palladium scavenger is in operation, for example a thiol, then any palladium in solution that becomes trapped in this scavenger is completely deactivated. If, however, the PVP is utilised as the scavenger a palladium species can be created that still exhibits catalytic activity.[65] This idea was extended further to incorporate the PEPPSI™ complex **55** onto a PVP support within a Raschig ring (**56**, Scheme 25).[67]



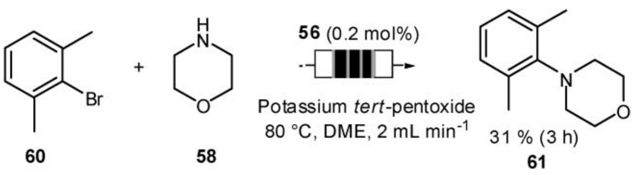
Scheme 25

The Raschig ring catalyst **56** had a loading of 5 × 10^{-6} mmol Pd/mg and was obtained by stirring a solution of PEPPSI™ catalyst **55** in dichloromethane at room temperature for 20 h. This catalyst was utilised under continuous flow conditions to perform the Buchwald–Hartwig reaction between *p*-bromoacetophenone **57** and morpholine **58** (Scheme 26).



Scheme 26

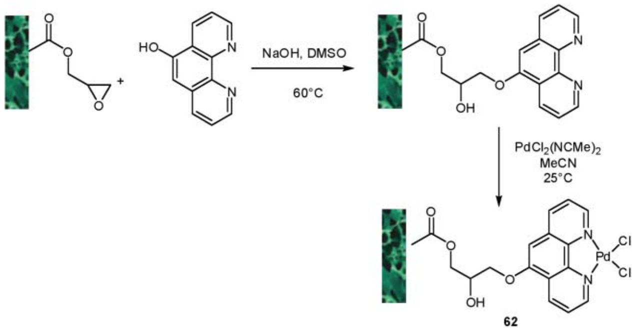
Potassium *tert*-pentoxide was utilised to make the reaction amenable to continuous flow processes. This coupling reaction afforded product **59** at 80 °C in excellent yield. Switching to the more sterically hindered 1-bromo-2,6-dimethylbenzene **60** decreased the yield to 31% (**60**, **58**, **61** Scheme 27).



Scheme 27

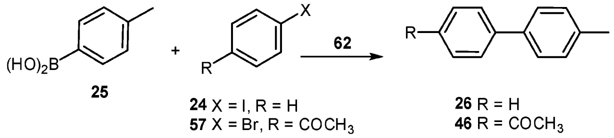
After one run the catalyst **56** lost most of its activity, regardless of the reaction being performed under continuous flow or batch conditions. ICP-MS analysis indicated that 93% of the palladium had remained on the support, but this species turned out to be inactive.[67]

Guijt *et al.* utilised phenanthroline functionalised poly(glycidyl methacrylate-*co*-ethylene dimethacrylate) (GMA-*co*-EDMA) as a solid macroporous monolith to support palladium for the Suzuki-Miyaura reaction. This was synthesised *via* the photografting of the cross linker ethylene glycol dimethacrylate and the reactive monomer glycidyl methacrylate in a commercially available fused silica capillary.[68] The photografting approach enables the polymerisation to be more directly controlled as only those monomers subjected to UV irradiation can be polymerised.[69] On the surface of this monolith is a reactive epoxide, although other functionalities such as azolactone[70] and chloromethyl groups[71] have also been reported. This reactive functionality can then be further functionalised by grafting ligands such as phenanthroline. Palladium loading can be achieved by flushing the monolith with acetonitrile containing $PdCl_2(NCMe)_2$ (Scheme 28).[68]



Scheme 28

Catalyst **62** (in 15 cm capillaries) was used in the Suzuki-Miyaura reaction between iodobenzene (**24**, 50 mM) and *p*-tolylboronic acid (**25**, 75 mM) in the presence of nBu_4NOMe (50 mM) in 9 : 1 toluene to methanol (Scheme 29). At a flow rate of 0.05 μL min^{-1} at 80 °C, equating to a *ca.* 90 min residence time, a conversion of 68% was observed by GC-MS.[68]



Scheme 29

Similar results were also found for the reaction between **25** and the less reactive *p*-bromoacetophenone (**57**), where a conversion to **46** of 59% was observed. After carrying out the reaction for 96 h continuously the conversion achieved remained constant, proving the stability and recyclability of this catalyst. ICP-MS studies of this catalyst found that after four days operation 15 to 20% palladium leaching had occurred, but this was thought to take place in the early stages of reaction.[68] This catalyst was developed further to incorporate a poly(chloromethylstyrene-*co*-divinylbenzene) (CMS/DVB) monolith as it posses a structure similar to that of conventional chloromethylpolystyrene beads.[72] Unlike GMA/EDMA, CMS/DVB does not contain functional groups that could interfere with catalysis.

For this study silica capillaries were used to construct the outer shell, which had an internal diameter of 250 μm. After modification of the inside of the capillary surface,[73] polymeric monoliths were synthesised *in situ* utilising a 6 : 4 porogen/monomer ratio. That is, 60% 1-dodecanol and toluene (porogen), 24% chloromethylstyrene (monovinyl monomer) and 16% divinyl benzene (crosslinking monomer). A porosity and void volume fraction of *ca.* 60% was observed, which was required to achieve good flow-through and high surface area characteristics.[74–76]

The free chloride groups on the benzyl were used to covalently attach 1-methylimidazole (**63**) or 5-amino-1,10-phenanthroline (**64**) (Fig. 6). Palladium loading was achieved by passing $PdCl_2(NCMe)_2$ in MeCN through the monolith at room temperature.

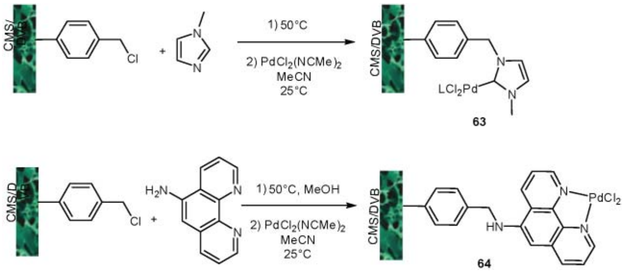
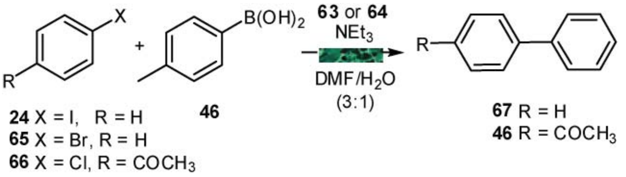


Fig. 6 Ligand and palladium attachment to the CMS/DVB monolith.

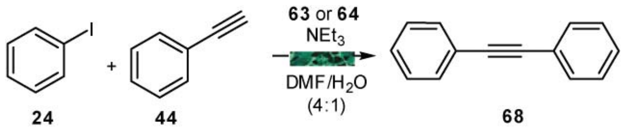
In this monolith the imidazole is thought to be present as the imidazolium group, as previously reported when attached to related polymers.[77–85] The palladium in this material may be present as an anion to balance the imidazolium group, for example $[PdCl_3(NCMe)]^-$, or bonded to the heterocycle as an *N*-heterocyclic carbene (NHC). For the NHC example, an additional ligand would be present to complete the square planar coordination, which in this case was MeCN. With this ligand palladium loadings of *ca.* 0.4% were obtained, and with *ca.* 0.3% with phenanthroline as the ligand. These monolithic catalysts were used to catalyse both Suzuki-Miyaura and Sonogashira reactions. The Suzuki-Miyaura reaction chosen is illustrated in Scheme 30.



Scheme 30

A solution of the aryl halide (0.1 mol), *p*-tolylboronic acid (0.15 mol) and triethylamine (0.15 mol) were pumped through the capillaries at 0.1 μL min^{-1} (45 min) in 20 cm capillaries at 80 °C. For the aryl iodide **24** under flow conditions with the catalyst **64** a 97% yield was obtained, which was comparable to the flow yield of 95% for the NHC catalyst **63**. Utilising the bromide derivative **65** in conjunction with the NHC catalyst **63** afforded a 53% conversion. It was interesting to note that *p*-chloroacetophenone **66** also underwent reaction, although low yields (11%) were obtained.

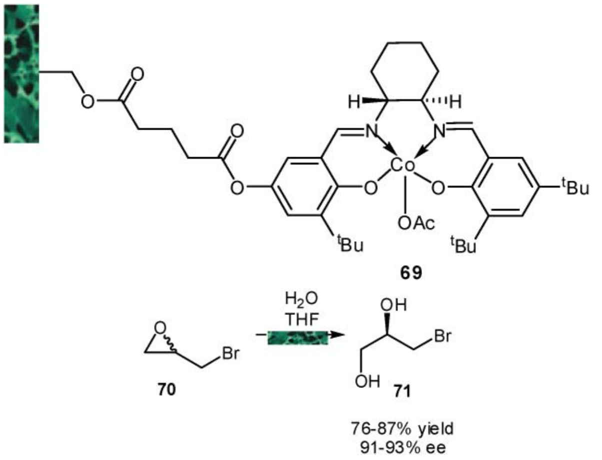
The Sonogashira reaction between **24** and phenylacetylene **44** (Scheme 31) was also examined employing NEt_3 as a base in DMF–H_2O (4 : 1) under copper free reaction conditions.[86]



Scheme 31

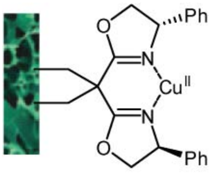
This involved pumping **24** (0.1 mmol), **44** (0.15 mmol) and NEt_3 (0.15 mmol) in DMF–H_2O (4 : 1) though the capillaries at 0.1 μL min^{-1} (45 min) in 20 cm capillaries at 80 °C. For the catalyst **64** a 96% yield of product **68** was observed, and with the catalyst **63** (NHC) a 95% yield was obtained. Comparable yields were observed under batch reaction conditions, but only after a 3 h reaction time. It was found that under flow conditions leaching of the palladium was relatively low, *ca.* 4%, after 8 days' continual operation.

A poly(vinylchlorobenzene-*co*-divinylbenzene) monolith has also been employed as a support for Jacobsen's salen cobalt complex **69**.[59,61,87] This enantioselective catalyst was utilised to conduct a kinetic resolution of racemic epibromohydrin **70** in the presence of water and THF to afford (*R*)-3-bromopropane-1,2-diol **71** (Scheme 32). At a 1 mmol scale reactions were completed within 20 h and afforded (*R*) diol **71** in 76 to 87% yield with a constant enantiomeric purity of 91 to 93% ee.[61] Between each run the column was washed with a mixture of toluene and acetic acid (9 : 1). It was found that no loss of reactivity or enantioselectivity was observed during subsequent runs.



Scheme 32

A monolithic solid support was utilised to immobilise the bisoxazoline copper catalyst **72**.[88] This monolith was prepared by the polymerisation of styrene (0.7 mol) and DVB (80% w/w, 0.2 mol) in the presence of AIBN using toluene and 1-dodecanol (1.25 g) as the porogen at 70 °C. The copper species was immobilised by circulating Cu(II) triflate in methanol through the monolith for 24 h.

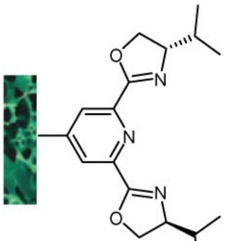


72

This monolith was utilised to carry out the enantioselective cyclopropanation of styrene **34** (2.0 M) and ethyl diazoacetate **33** (0.5 M) in DCM (Scheme 13). At a flow rate of 2 μL min^{-1} total consumption of **33** was observed with an isolated yield of 61% for **35** (*trans* 71% ee) and **36** (*cis* 55% ee). The poor isolated yield was due to the formation of fumarate and maleate by-products. It was ascertained that increasing the flow rate decreased the consumption of **33** and decreased the ee for the *trans* isomer **35**, but had no effect on the ee for the *cis* isomer. This is due to an increase in the amount of **33** per hour per gram of catalyst.

The reaction was repeated under solvent free conditions at 0.02 mL min^{-1}, whilst varying the ratio of **34/33**. It was found that chemoselectivity increased with an increase in **34/33**, with the optimum ratio being 4/1. Under solvent free conditions similar enantioselectivities for the *cis* and *trans* were observed, but the advantage over utilising DCM was that there was a three-fold increase in the amount of product generated per hour per gram of Cu^{II}. This reaction was also examined using scCO$_2$ as the reaction medium, which was achieved at 40 °C and 8 MPa by pumping a solution of VB/EDA (4/1, 1.78 M of EDA) at 0.1 mL min^{-1}and CO$_2$ at 1 mL min^{-1}. The cyclopropanes were afforded in a yield of 63% with reasonable selectivity (59% ee *trans*, 44% ee *cis*). This decrease in ee can be attributed to the greater temperature required during the reaction to reach supercritical conditions. ICP-MS analysis of the eluent indicated that Pd leaching was <1 ppm.

Luis *et al.* also describe the use of a monolithic supported pybox ruthenium catalyst for the cyclopropanation reaction shown in Scheme 13.[89] The monolith **73** was composed of styrene (42%), divinyl benzene (51%) and pybox (7%) with toluene and 1-dodecanol (10 : 50 w/w) as porogens and AIBN as the radical initiator.

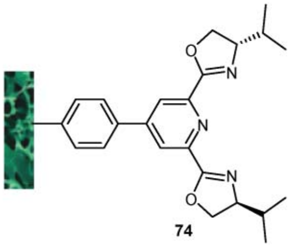


73

A solution of ethyl diazoacetate (**33**, 0.25 mol L^{-1}) and styrene (**34**, 1.5 mol L^{-1}) were pumped through a column of ruthenium supported on **73** (15 cm × $\frac{1}{4}$ in.). When the composition of the monolith was varied it was ascertained that a higher degree of cross-linking afforded better chemoselectivity and an increase in the yields of products. The optimum degree of cross-linking came from utilising 51% divinyl benzene with 42% styrene. This afforded complete consumption of **33** at a 20 μL min^{-1} flow rate (35 min residence time) with a 48 ± 5% ee for the *cis* isomer and 75 ± 5% ee for the *trans*. The isolated yield for product was only 50%, as there was a large degree of dimerisation to ethyl fumarate and maleate. Under these conditions the catalyst achieved a 33 h operation time, with deactivation due to moisture and/or oxygen within the system.

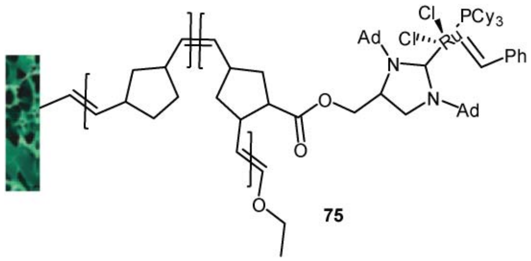
The reaction was also carried out under a solvent free environment, which afforded an improvement in yield due to the increase in the concentration of **33**. At 20 μL min^{-1} flow rate a 92% consumption was observed with a 72% isolated yield of product. In this instance **34** is being utilised as a solvent, which will favour diffusion of reagents into the active site of the catalyst and reduces the level of homocoupling.

To further expand the use of this catalyst scCO$_2$ was used as the reaction medium. At 40 °C at 0.05 mL min^{-1} (1.27 min residence time) afforded a 41% consumption of **33** and a 22% isolated yield, with a 56% ee for the *cis* isomer and 89% ee for the *trans*. In an effort to increase the yield of product, a ruthenium complex of **74** was utilised under scCO$_2$; this catalyst has a higher pybox loading (1.07 × 10^{-3} equiv pybox g^{-1}). At 0.165 mL min^{-1} at 40 °C a 90% consumption of **33** was observed with a 65% isolated yield (77% ee *trans*, 50% ee *cis*). The activity of the catalyst was maintained for over 5 h, with ICP-MS analysis showing >1 ppm Pd in the eluent.



74

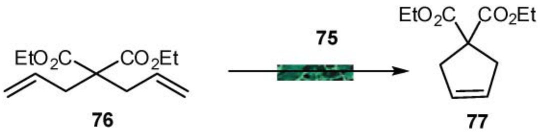
Grubbs' first generation ruthenium olefin metathesis catalyst has also been grafted onto a monolith support for catalysis under flow conditions.[90] The monolith was constructed within a borosilicate column *via* the copolymerisation of 1,4,4*a*,5,8,8*a*-hexahydro-1,4,5,8-*exo*-*endo*-dimethanonaphthalene and norbornene in DCM and 2-propanol. This afforded a monolith with a 1.5 μm diameter and a porosity of 40%. The Grubbs catalyst was immobilised onto the surface by generation of a carbene utilising 4-dimethylaminopyridine (DMAP) to generate the catalyst **75**.



75

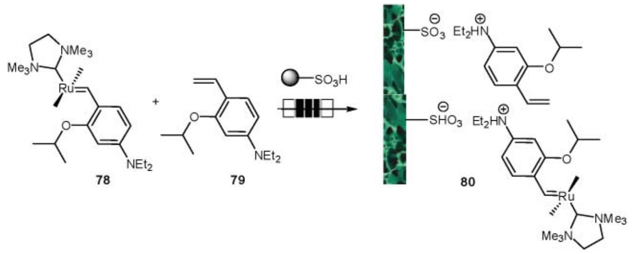
This catalyst was used to promote the ring closing metathesis of **76**, which achieved complete conversion to **77** after 50 min at 56 °C (Scheme 33).

Ring opening metathesis reactions have also been examined at 40 °C with a 3 min residence time, which led to the formation of polymers. The addition of chain transfer agents such as *cis*-2-hexene allows manipulation of the length of the polymers formed. Kirschning *et al.* have also synthesised a solid supported ruthenium catalyst to catalyse Grubbs Metathesis.[62] This was



Scheme 33

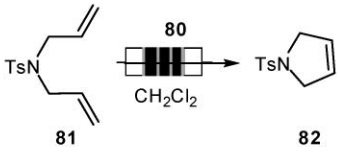
achieved by non-covalent immobilisation of **78** onto a sulfonated styrene DVB monolith within a Raschig ring (Scheme 34).



Scheme 34

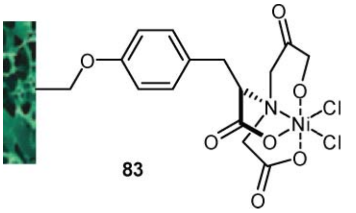
The Raschig rings containing catalyst **80** were encapsulated inside a metal jacket equipped with HPLC fittings. Optimum immobilisation was achieved by passing a solution of **78** and **79** (1 : 19) in CH_2Cl_2 through the reactor, which allows complete saturation of all the SO_3 groups. The excess ligand **79** allows for a boomerang system where any leaching of the ruthenium through the reaction can be simultaneously encapsulated.

The metathesis reaction of diene **81** in Scheme 35 was carried out under flow conditions at 2 mL min^{-1} at 40 °C for 5 h, which afforded complete conversion to **82**. After washing the reactor with CH_2Cl_2 the reaction was repeated to afford a 79% yield, the third run however did not yield any of the desired product. Reactivation of the catalyst can be achieved by pumping 1 N HCl, H_2O (until pH 7), 1 N NaOH, H_2O (until pH 7), 1 N HCl, H_2O (until pH 7), anhydrous methanol, and CH_2Cl_2. The monolith can then be reloaded with a 1/19 mixture of the Ru-complex **78** and ligand **79**.



Scheme 35

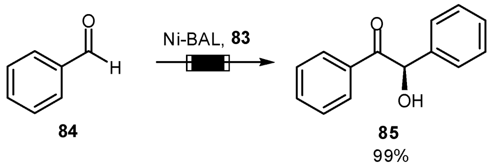
Kirschning *et al.* have utilised immobilised Ni in the form of tyrosine linked Ni-nitrilotriacetic acid (Ni-NTA **83**) to carry out catalytic enzymatic transformations under flow conditions.[63]



83

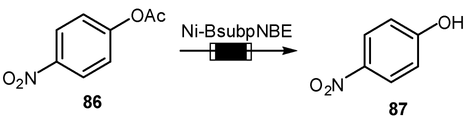
The monolithic polymer utilised was composed of DVB, poly(vinyl benzyl chloride) (VBC) and N-vinylpyrrolidinone (10 : 70 : 20) within a PASSflow reactor. Trapping of the Ni^{2+} species was achieved by pumping an aqueous solution of $NiCl_2$ through the reactor. This system could be utilised to trap His_6-tagged proteins to afford heterogeneous catalysts for enzymatic transformations. The thiamine pyrophosphate dependent enzyme benzaldehyde lyase (BAL) was successfully immobilised onto **83**, with quantification being achieved utilising the Bradford assay.[91]

The Ni-BAL reactor was also used to study the benzoin reaction in Scheme 36. A solution of benzaldehyde (30 µl) in phosphate buffer (5 mL) was pumped (1 mL min^{-1}) around the PASSflow reactor at 37 °C. Complete conversion of benzaldehyde **84** was observed and (*R*)-benzoin **85** was isolated in 99% yield.



Scheme 36

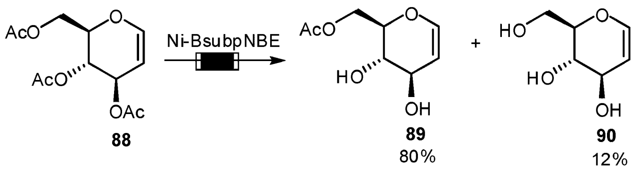
The Ni-NTA system was also employed to immobilise the *p*-nitrobenzyl esterase from *Bacillus subtilis* (BsubpNBE[92–93]), which is commonly used for deacetylation reactions. A study to determine enzymatic leaching was carried out on the deacetylation of *p*-nitrophenyl acetate **86** to afford the phenol **87** (Scheme 37).



Scheme 37

After a single pass through the reactor the reaction mixture was analysed by HPLC before being stored at 37 °C for 1 h to determine if catalysis was still occurring. The sample was then re-analysed to determine the degree of leaching, which was found to be solvent dependant. DMSO led to enzyme leaching, whilst methyl *tert*-butyl ether was fully compatible.

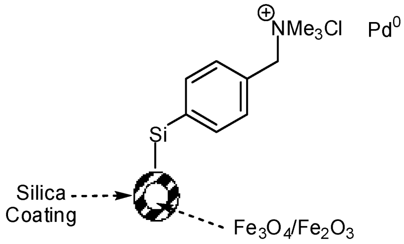
The deacetylation of tri-*O*-acetyl-D-glucal **88** was also investigated (Scheme 38). Complete consumption of **88** was observed after 60 h to afford **89** in good yield contaminated with traces of the impurity **90**.



Scheme 38

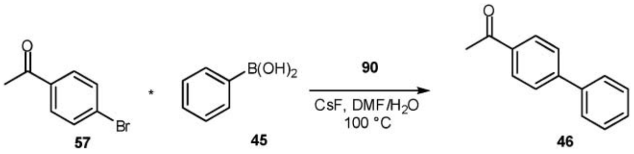
Magnetic nanoparticles

There has been increasing interest in the use of magnetic nanoparticles as solid supports for heterogeneous catalysts.[94] This is due to their ease of separation from a reaction mixture by an external magnetic field.[95] The magnetic nanoparticles can be functionalised to facilitate metal ligation. For palladium containing nanoparticles amine moieties are often used as they prevent aggregation of the Pd nanoparticles reducing the formation of Pd black, and it is recognised that they increase the reactivity of the catalyst.[17] This stems from their easy recovery after reaction by exploitation of their magnetic properties.[95] Kirschning *et al.* disclosed a functionalised silica coated Fe_3O_4/Fe_2O_3 nanoparticle (10 to 40 nm) ligated to Pd° **90**, which could be used under flow conditions.[96] The silica coating on the surface of the magnetic nanoparticles prevents oxidation in air and allows for easy functionalisation and metal loading.



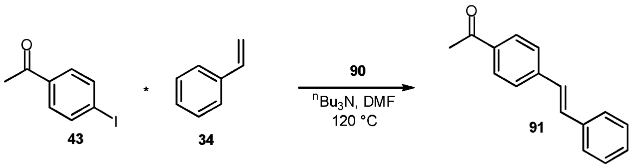
90

The catalyst **90** (2.8 mol%) was utilised in both the Suzuki-Miyaura and Heck coupling reactions. The Suzuki-Miyaura coupling of *p*-bromoacetophenone **57** (1 eq.) and phenyl boronic acid **45** (1.5 eq.) in the presence of CsF (2.4 eq.) in DMF–H_2O afforded a 77% isolated yield of **46** (Scheme 39). This was achieved at a flow rate of 2 mL min^{-1} (1 h residence time) at 100 °C.



Scheme 39

The Heck coupling between *p*-iodoacetophenone **43** (1 eq.) and styrene **34** (3 eq.) in the presence of $^nBu_3N$ (3 eq.) in DMF afforded a 76% isolated yield (Scheme 40). This was achieved at a flow rate of 2 mL min^{-1} (1 h residence time) at 120 °C.



Scheme 40

ICP-MS analysis revealed only low levels of palladium leaching was occurring (34 ppm for the Suzuki-Miyaura coupling and 100 ppm for the Heck), and the catalyst could be reused for more than three runs.

Microreactors under microwave conditions

Microwave-assisted organic chemistry (MAOC) is an important tool to the modern organic chemist, particularly for metal catalysed reactions. The combination of microwave activation with continuous flow techniques offers considerable potential for catalytic applications.

Organ *et al.* described the use of capillaries coated in thin films of Pd for Suzuki-Miyaura and Heck coupling reactions under continuous flow microwave conditions.[97] Palladium films were formed within 1150 μm capped capillaries by flowing a solution of $Pd(OAc)_2$ at 0.1 mmol min^{-1} at 150 °C for 30 min. This afforded a highly porous black film of Pd° over the capillary wall. The porosity could be further increased by calcination at 400 °C, which removes any residual organic matter. A film thickness of 6 μm was determined by scanning electron microscopy (SEM) and energy-dispersive X-ray (EDX) analysis with the palladium nanoparticles being 60 to 140 nm in diameter. These Pd-coated capillaries were utilised in various Suzuki-Miyaura reactions, by lowering the Pd-coated capillary (Fig. 7) into a microwave chamber. Through the capillary a solution of aryl boronic acid, aryl bromide and KOH in DMF–H_2O were pumped under microwave irradiation (power setting ≈ 30 W) at a constant temperature of 200 °C. Good to excellent conversions (97 to 88%) were obtained for the coupling of electron-rich and electron-poor aryl halides with electron-poor boronic acids. The reaction was also conducted in the absence of microwave irradiation at 200 °C, which afforded a decrease in conversion to 58% compared with 97% with microwave irradiation.

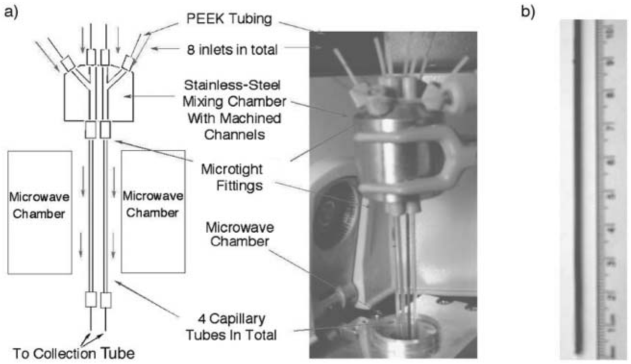
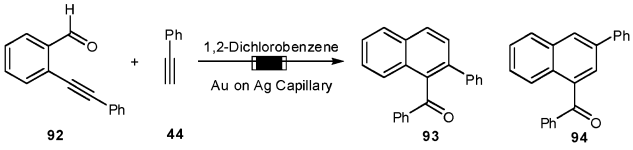


Fig. 7 a) Schematic diagram and photograph of the Pd-coated capillary reactor. b) Pd-coated capillary.[97] Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

Atomic emission spectrometry (ICP-AES) determined 19.2 ppm Pd leaching during the reaction. It was felt that oxidative addition, which was taking place on the surface of the catalyst, liberates Pd atoms into solution where transmetalation and reductive elimination occur. This reactor was also very efficient at promoting various Heck coupling reactions, with conversions between 99 to 58% being achieved.

Organ *et al.* have also described a gold coated capillary (1700 μm) for use within a microreactor to catalyse the benzannulation between aromatic carbonyls and alkynes,[98] with the gold providing heat transfer by convection.[99] It was found that gold exhibits poor adhesive properties onto the glass capillary, but this could be overcome by employing a thin silver coating between the glass and gold.

The benzannulation between **92** and **44** was examined under flow conditions at 240 °C at 25 μL min^{-1} (60 s residence time) to afford **93** and **94** (3 : 1) in a 90% conversion and 78% isolated yield (Scheme 41). Under conventional heating within an oil bath at 190 °C there was a dramatic decrease in yield of product from 60 to 14%. It was postulated that this was due to localised 'hot spots' on the surface of the film that exceed the temperature of the surrounding system. Under conventional heating the system can only achieve temperatures comparable to the oil bath, and at extreme elevated temperatures would cause degradation of the film and decomposition of products.



Scheme 41

With this flow system larger quantities of products could by synthesised by increasing the concentration of starting materials, which afforded 750 mg of product in 90 min under the same conditions. This gold coated capillary could be utilised over several runs, but it was found that the gold film darkens over time and eventually erodes.

Conclusions

Heterogeneous catalysis exhibits significant advantages over traditional homogeneous systems. The need to produce catalysts that are easily recyclable and do not contaminate reaction products has fuelled a drive to develop innovative heterogeneous catalytic systems. Microreactor technology is continually evolving, allowing a reduction in reaction times, greater reaction control, safer working environments and easier scalability. Utilising heterogeneous catalysis in conjunction with microreactor technology and non-thermal activation methods has expanded its potential applications further.[100]

In this review we have examined the immobilisation of selected metal catalysts on different materials. These catalysts have then been employed to promote an array of useful chemical transformations, and in most cases have been recycled over numerous runs. However, there is still a significant opportunity to design catalysts with improved activity and resistance to leaching for flow synthesis. The application of computer simulation techniques to extend our understanding of the structure, stability and reactivity of the catalytic materials could offer significant benefits. This knowledge could be used to guide the design and synthesis of the next generation of catalysts by optimising the size of metal particles and the nature of the microporous support for a chosen reaction. Due to the usefulness and advantages of these emerging technologies they could potentially transform the way chemists and the chemical industry operates in the future.

Notes and references

1 N. Nikbin, M. Ladlow and S. V. Ley, *Org. Process Res. Dev.*, 2007, **11**, 458–462.
2 K. Geyer, J. D. C. Codee and P. H. Seeberger, *Chem.–Eur. J.*, 2006, **12**, 8434–8442.
3 B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan and D. T. McQuade, *Chem. Rev.*, 2007, **107**, 2300–2318.
4 C. Wiles and P. Watts, *Eur. J. Org. Chem.*, 2008, 1655–1671.
5 R. C. Wheeler, O. Benali, M. Deal, E. Farrant, S. J. F. MacDonald and B. H. Warrington, *Org. Process Res. Dev.*, 2007, **11**, 704–710.
6 K. Geyer, T. Gustafsson and P. H. Seeberger, *Synlett*, 2009, **15**, 2382–2392.
7 C. Wiles and P. Watts, *Eur. J. Org. Chem.*, 2008, 1655–1671.
8 P. Watts and S. J. Haswell, *Chem. Soc. Rev.*, 2005, **34**, 235–246.
9 T. Fukuyama, T. Rahman, M. Sato and I. Ryu, *Synlett*, 2008, **2**, 151–163.
10 T. Schwalbe, V. Autze and G. Wille, *Chimia*, 2002, **56**, 636–646.
11 T. Gustafsson, R. Gilmour and P. H. Seeberger, *Chem. Commun.*, 2008, 3022–3024.
12 M. Baumann, I. R. Baxendale and S. V. Ley, *Synlett*, 2008, **14**, 2111–2114.
13 M. Lamblin, L. Nassar-Hardy, J. C. Hierso, E. Fouquet and F. X. Felpin, *Adv. Synth. Catal.*, 2010, **352**, 33–79.
14 C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889–900.
15 S. P. Andrews, A. F. Stepan, H. Tanaka, S. V. Ley and M. D. Smith, *Adv. Synth. Catal.*, 2005, **347**, 647–654.
16 T. Miao and L. Wang, *Tetrahedron Lett.*, 2007, **48**, 95–99.
17 A. J. Amali and R. K. Rana, *Green Chem.*, 2009, **11**, 1781–1786.
18 M. Cai, G. Zheng, L. Zha and J. Peng, *Eur. J. Org. Chem.*, 2009, 1585–1592.
19 A. M. Trzeciak, E. Mieczynska, J. J. Ziolkowski, W. Bukowski, A. Bukowska, J. Noworol and J. Okal, *New J. Chem.*, 2008, **32**, 1124–1130.
20 X. Ma, Y. Zhou, J. Zhang, A. Zhu, T. Jiang and B. Han, *Green Chem.*, 2008, **10**, 59–66.
21 K. Mennecke and A. Kirschning, *Beilstein J. Org. Chem.*, 2009, **5**.
22 T. N. Glasnov, S. Findening and C. O. Kappe, *Chem.–Eur. J.*, 2009, **15**, 1001–1010.
23 C. Csajagi, B. Borcsek, K. Niesz, I. Kovacs, Z. Szekelyhidi, Z. Bajko, L. Urge and F. Darvas, *Org. Lett.*, 2008, **10**, 1589–1592.
24 R. G. Heideneich, K. Kohler, J. G. E. Krauter and J. Pietsch, *Synlett*, 2002, 1118–1122.
25 K. Köhler, R. G. Heidereich, J. G. E. Krauter and J. Pietsch, *Chem.–Eur. J.*, 2002, **8**, 622–631.
26 R. G. Heidenreich, J. G. E. Krauter, J. Pietsch and K. Kohler, *J. Mol. Catal. A: Chem.*, 2002, **182–183**, 499–509.
27 P. Clark, M. Poliakoff and A. Wells, *Adv. Synth. Catal.*, 2007, **349**, 2655–2659.
28 G. P. Taber, D. M. Pfisterer and J. C. Colberg, *Org. Process Res. Dev.*, 2004, **8**, 385–388.
29 R. V. Jones, L. Godorhazy, N. Varga, D. Szalay, L. Urge and F. Darvas, *J. Comb. Chem.*, 2006, **8**, 110–116.
30 M. Irfan, E. Petricci, T. N. Glasnov, M. Taddei and C. O. Kappe, *Eur. J. Org. Chem.*, 2009, 1327–1334.
31 G. Szollosi, B. Herman, F. Fulop and M. Bartók, *React. Kinet. Catal. Lett.*, 2006, **88**, 391–398.
32 K. R. Knudsen, J. Holden, S. V. Ley and M. Ladlow, *Adv. Synth. Catal.*, 2007, **349**, 535–538.
33 I. M. Mandity, T. A. Martinek, F. Darvas and F. Fulop, *Tetrahedron Lett.*, 2009, **50**, 4372–4374.
34 C. Ramarao, S. V. Ley, C. Smith, I. M. Shirley and N. DeAlmedia, *Chem. Commun.*, 2002, 1132–1133.
35 Y. Y. Kuang and F. R. Chen, *Helv. Chim. Acta*, 2009, **92**, 897–903.
36 A. Carpita and A. Ribecai, *Tetrahedron Lett.*, 2009, **50**, 204–207.
37 C. K. Y. Lee, A. B. Holmes, S. V. Ley, I. F. McConvey, B. Al-Duri, G. A. Leeke, R. C. D. Santos and J. P. K. Seville, *Chem. Commun.*, 2005, 2175–2177.
38 N. Bremeyer, S. V. Ley, C. Ramarao, I. M. Shirley and S. C. Smith, *Synlett*, 2002, **11**, 1843–1844.
39 S. J. Broadwater and D. T. McQuade, *J. Org. Chem.*, 2006, **71**, 2131–2134.
40 I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley and G. K. Tranmer, *Chem.–Eur. J.*, 2006, **12**, 4407–4416.
41 G. A. Leeke, R. C. D. Santos, B. Al-Duri, J. P. K. Seville, C. J. Smith, C. K. Y. Lee, A. B. Holmes and I. F. McConvey, *Org. Process Res. Dev.*, 2007, **11**, 144–148.
42 N. T. S. Phan, D. H. Brown and P. Styring, *Green Chem.*, 2004, **6**, 526–532.
43 S. J. Haswell, B. O'Sullivan and P. Styring, *Lab Chip*, 2001, **1**, 164–166.

44 C. P. Omnifit Ltd., Coldhams Lane, Cambridge, UK. CB1 3HD., Website: http://www.omnifit.com.
45 N. T. S. Phan, J. Khan and P. Styring, *Tetrahedron*, 2005, **61**, 12065–12073.
46 J. Lim, S. N. Riduan, S. S. Lee and J. Y. Ying, *Adv. Synth. Catal.*, 2008, **350**, 1295–1308.
47 J. Lim, S. S. Lee and J. Y. Ying, *Chem. Commun.*, 2010, **46**, 806–808.
48 M. Ulman and R. H. Grubbs, *J. Org. Chem.*, 1999, **64**, 7202–7207.
49 N. Intaragamjon, T. Shiono, B. Jongsomjit and P. Praserthdam, *Catal. Commun.*, 2006, **7**, 721–727.
50 F. Svec and C. G. Huber, *Anal. Chem.*, 2006, **78**, 2100–2107.
51 A. Kirschning, C. Altwicker, G. Drager, J. Harders, N. Hoffmann, U. Hoffmann, H. Schonfeld, W. Solodenko and U. Kunz, *Angew. Chem., Int. Ed.*, 2001, **40**, 3995–3999.
52 R. M. Heck, S. Gulati and R. J. Farrauto, *Chem. Eng. J.*, 2001, **82**, 149–156.
53 R. M. Heck, S. Gulati and R. J. Farrauto, *Chem. Eng. J.*, 2001, **82**, 149–156.
54 M. A. Bokari, D. Cherrak and G. Guiochon, *J. Chromatogr., A*, 2002, **975**, 275–284.
55 U. Kunz, H. Schonfeld, A. Kirschning and W. Solodnko, *J. Chromatogr., A*, 2003, **1006**, 241–249.
56 W. Solodenko, H. Wen, S. Leue, F. Stuhlmann, G. Sourkouni-Argirusi, G. Jas, H. Schonfeld, U. Kunz and A. Kirschning, *Eur. J. Org. Chem.*, 2004, 3601–3610.
57 U. Kunz, H. Schonfeld, W. Solodenko, G. Jas and A. Kirschning, *Ind. Eng. Chem. Res.*, 2005, **44**, 8458–8467.
58 W. Solodenko, U. Kunz, G. Jas and A. Kirschning, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1833–1835.
59 U. Kunz, A. Kirschning, H. L. Wen, W. Solodenko, R. Cecilia, C. O. Kappe and T. Turek, *Catal. Today*, 2005, **105**, 318–324.
60 Quadrapure, [655422], a thiourea-based scavenger with high affinity to metal ions. Available from Sigma-Aldrich, Website: http://www.sigmaaldrich.com.
61 W. Solodenko, G. Jas, U. Kunz and A. Kirschning, *Synthesis*, 2007, **4**, 583–589.
62 A. Michrowska, K. Mennecke, U. Kunz, A. Kirschning and K. Grela, *J. Am. Chem. Soc.*, 2006, **128**, 13261–13267.
63 G. Drager, C. Kiss, U. Kunz and A. Kirschning, *Org. Biomol. Chem.*, 2007, **5**, 3657–3664.
64 K. Mennecke, R. Cecilia, T. N. Glasnov, S. Gruhl, C. Vogt, A. Feldhoff, M. A. L. Vargas, C. O. Kappe, U. Kunz and A. Kirschning, *Adv. Synth. Catal.*, 2008, **350**, 717–730.
65 K. Mennecke, W. Solodenko and A. Kirschning, *Synthesis*, 2008, **10**, 1589–1599.
66 A. H. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx and J. G. deVries, *Org. Lett.*, 2003, **5**, 3285–3288.
67 K. Mennecke and A. Kirschning, *Synthesis*, 2008, **20**, 3267–3272.
68 K. F. Bolton, A. J. Cantry, J. A. Deverell, R. M. Guijt, E. F. Hilder, T. Rodemann and J. A. Smith, *Tetrahedron Lett.*, 2006, **47**, 9321–9324.
69 T. Rohr, E. F. Hilder, J. J. Donovan, F. Svec and J. M. J. Frechet, *Macromolecules*, 2003, **36**, 1677–1684.
70 S. Xie, F. Svec and J. M. J. Frechet, *Biotechnol. Bioeng.*, 1999, **62**, 30–35.
71 I. Gusev, X. Huang and C. Horvath, *J. Chromatogr., A*, 1999, **855**, 273–290.
72 A. Gomann, J. A. Deverell, K. F. Munting, R. C. Jones, T. Rodemann, A. J. Canty, J. A. Smith and R. M. Guijt, *Tetrahedron*, 2009, **65**, 1450–1454.
73 T. Rohr, E. F. Hilder and J. J. Donovan, *Macromolecules*, 2003, **36**, 1677–1684.
74 F. Svec and J. M. Frechet, *Chem. Mater.*, 1995, **7**, 707–715.
75 B. Preinerstorfer, W. Bicker, W. Lindner and M. Lammerhofer, *J. Chromatogr., A*, 2004, **1044**, 187–199.
76 M. R. Buchmeiser, *Polymer*, 2007, **48**, 2187–2198.
77 J. Schwarz, V. P. W. Bohm, M. G. Gardiner, M. Grosche, W. A. Hermann, W. Hieringer and G. Raudaschl-Sieber, *Chem.–Eur. J.*, 2000, **6**, 1773–1780.
78 P. G. Steel and C. W. Teasdale, *Tetrahedron Lett.*, 2004, **45**, 8977–8980.
79 J. W. Byun and Y. S. Lee, *Tetrahedron Lett.*, 2004, **45**, 1837–1840.
80 J. H. Kim, B. H. Jun, J. W. Byun and Y. S. Lee, *Tetrahedron Lett.*, 2004, **45**, 5827–5831.
81 J. H. Kim, J. W. Kim, M. Shokouhimehr and Y. S. Lee, *J. Org. Chem.*, 2005, **70**, 6714–6720.
82 D. Schonfelder, O. Nuyken and R. Weberskirch, *J. Organomet. Chem.*, 2005, **690**, 4648–4655.
83 B. Altava, M. I. Burguete, E. Garcia-Verdugo, N. Karbass, S. V. Luis, A. Puzary and V. Sans, *Tetrahedron Lett.*, 2006, **47**, 2311–2314.
84 W. J. Sommer and M. Weck, *Adv. Synth. Catal.*, 2006, **348**, 2101–2113.
85 D. H. Lee, J. H. Kim, B. H. Jun, H. Kang, J. Park and Y. S. Lee, *Org. Lett.*, 2008, **10**, 1609–1612.
86 L. Djakovitch and P. Rollet, *Adv. Synth. Catal.*, 2004, **346**, 1782–1792.
87 U. Kunz, H. Schonfeld, A. Kirschning and W. Solodenk, *J. Chromatogr., A*, 2003, **1006**, 241–249.
88 M. I. Burguete, A. Cornejo, E. Garcia-Verdugo, J. Garcia, M. J. Gil, S. V. Luis, V. Martinez-Merino, J. A. Mayoral and M. Sokolova, *Green Chem.*, 2007, **9**, 1091–1098.
89 M. I. Burguete, A. Cornejo, E. Garcia-Verdugo, M. J. Gil, S. V. Luis, J. A. Mayoral, V. Martinez-Merino and M. Sokolova, *J. Org. Chem.*, 2007, **72**, 4344–4350.
90 M. Mayr, B. Mayr and M. R. Buchmeiser, *Angew. Chem., Int. Ed.*, 2001, **40**, 3839–3842.
91 M. A. Bradford, *Anal. Biochem.*, 1976, **72**, 248–254.
92 J. Zock, C. Cantwell, J. Swartling, R. Hodges, T. Pohl, K. Sutton, P. Rosteck, D. McGilvray and S. Queener, *Gene*, 1994, **151**, 37–43.
93 E. Henke, J. Pleiss and U. T. Bornscheuer, *Angew. Chem., Int. Ed.*, 2002, **41**, 3211–3213.
94 K. M. Yeo, S. I. Lee, Y. T. Lee, Y. K. Chung and I. S. Lee, *Chem. Lett.*, 2008, **37**, 116–117.
95 M. Jin and D. Lee, *Angew. Chem., Int. Ed.*, 2010, **49**, 1119–1122.
96 S. Ceylan, C. Friese, C. Lammel, K. Mazac and A. Kirschning, *Angew. Chem., Int. Ed.*, 2008, **47**, 8950–8953.
97 G. Shore, S. Morin and M. G. Organ, *Angew. Chem., Int. Ed.*, 2006, **45**, 2761–2766.
98 G. Shore, M. Tsimerman and M. G. Organ, *Beilstein Journal of Organic Chemistry*, 2009, **5**.
99 P. He, S. J. Haswell and P. D. I. Fletcher, *Appl. Catal., A*, 2004, **274**, 111–114.
100 B. K. Singh, N. Kaval, S. Tomar, E. VanderEycken and V. S. Parmar, *Org. Process Res. Dev.*, 2008, **12**, 468–474.