Homogeneous vs immobilized palladium catalysts for continuous flow cross-coupling chemistry


Abstract
Implementation of continuous flow reactors to organic syntheses, including metal catalyzed cross-coupling chemistry applications, has been growing dramatically during the past decade. Introduction of the metal (typically palladium) into a flow cross-coupling reaction as well as its recycling has been subject to intensive research efforts. Despite the popularity of packed bed reactors and immobilized catalysts during the past 15 years, evidence of metal leaching and catalyst deactivation in most cases makes this technique unpractical on a large scale. Homogeneous (pre)catalysts in combination with an appropriate catalyst recycling technology offers several advantages such as better control of the reactivity and selectivity.

INTRODUCTION
In recent years continuous flow processing, a tool classically associated with the large scale production of commodity chemicals and the oil industry, is becoming increasingly important for the production of more complex substances or materials such as active pharmaceutical ingredients (APIs) or agrochemicals (1). Considering the rapid development of this technology during the past decade, it can be assumed that in the future many industrially important chemicals will be prepared on scale using continuous flow procedures. The main advantages that are attracting both synthetic and process chemists to this enabling technology are their enhanced heat and mass transfer characteristics in microstructured devices (1,2). Reactions involving highly toxic or explosive intermediates or reagents can be safely performed, as only small amounts of the hazardous material is generated and consumed in situ, thus minimizing exposure (3). A particularly attractive feature of continuous flow reactors for pharmaceutical industry is the ease with which several reaction steps can be integrated, including separation and purification, in a single stream process thus enabling automated multi-step synthesis during APIs manufacturing (4).

Catalytic reactions involving homogeneous-, heterogeneous-, and even biocatalysts have also benefited from the advantages of microreactor technology (5). In the case of continuous flow heterogeneous catalysis the solid catalyst is typically placed in a packed bed reactor and the reaction mixture is flown through the solid using appropriate pumping systems (6). The catalytically active material remains located in a specific part of the reactor during processing of the reaction mixture. In this way, reaction and separation of the catalyst from the solution (including the product) take place simultaneously, thus enormously simplifying catalyst re-use and recycling as a catalyst separation/filtration step can be avoided. The reaction mixture flows through the packed catalyst bed, leading to a very high ratio between the active catalyst and the substrates/reagents. This high local concentration of catalyst, combined with the enhanced mass transfer in a microreactor results in increased reaction rates and higher turnover numbers (TONs) as compared to a batch reaction, especially in those cases where the mass transfer has a limiting effect (6). Owing to the key importance of cross-coupling chemistry in modern organic synthesis, a large number of immobilized palladium catalysts have been developed and in many instances employed as heterogeneous catalysts for continuous-flow cross-coupling reactions on the premise that the solid supported active metal could be easily reutilized (7,8). However, when combining cross-coupling chemistry and continuous flow using a packed bed heterogeneous catalyst, substantial amounts of “dissolved” palladium are typically observed in the reaction mixture collected from the reactor output (8). Ultimately, deactivation of the catalyst bed and reduced product formation is inevitable. The leaching phenomena in cross-coupling reactions is ascribed to the fact that the reaction mechanism for these kinds of transformations is (quasi)homogeneous and involves the transformation of Pd0.
IMMOBILIZED PALLADIUM CATALYSTS

Among the wide range of solid supports available for palladium catalysts immobilization, palladium on charcoal arguably is the most widely utilized for cross-coupling reactions (12). It is a comparatively inexpensive and readily available material which can - in addition to cross-coupling reactions - be applied in catalytic hydrogenations or oxidations (13). Pd/C was first utilized in a packed-bed reactor for continuous flow cross-coupling by the group of Seeburger in a modular microreactor system (14). Later on, a detailed investigation on the leaching phenomena during Pd/C catalyzed Mizoroki-Heck reactions in continuous flow was reported (15). A set of microwave batch experiments and continuous-flow reactions demonstrated that, apart from the leaching phenomena, a significantly higher amount of side-products (homocoupling and dehalogenation) were found in the flow reactions compared to the batch experiments.

This was attributed to the very high local concentration of palladium catalyst in the packed bed reactor which resulted in decreased selectivity, which is a known phenomenon. Using as model the reaction of 4-iodobenzonitrile with butyl acrylate in MeCN as solvent, 20 mmol of substrate (40 mL reaction mixture) were processed using the optimized flow conditions (150°C, 20 bar, 0.5 mL min⁻¹). GC-FID monitoring of the reaction mixture revealed that metal leaching/re-adsorption (8). Not surprisingly, the results revealed that the combination of aryl iodide and base resulted in the highest level of metal leaching, as the initial oxidative addition step is supposed to be responsible for the metal leaching (15). This work demonstrated that, at least under the conditions employed, Pd/C packed in a fixed bed reactor is not a suitable catalyst for performing continuous flow cross couplings on scale.

Polyurea encapsulated Pd(OAc)₂ is one of the most popular, commercially available, heterogeneous palladium catalysts. Introduced by the Ley group in 2002 (16), the polyurea matrix provides the material with a good ability to ligate metal species, and has been used in a wide range of applications, including cross-coupling reactions (17). PdEnCat catalyst was packed in a glass U-tube by Ley and coworkers and used for continuous flow Suzuki-Miyaura reactions under microwave conditions (Figure 3a) (18). The reactions were carried out in EOH at 120°C using Bu₄NOAc as base. After a residence time of 10 min good to excellent conversions were obtained for several substrates bearing electron donating and withdrawing groups. Notably, aryl bromides could be successfully used as substrates in this case instead of the more reactive iodides. The amount of Pd leaching from the EnCat packed catalyst was not directly measured in this study. Although metal contamination in the products was observed, contamination

species into soluble Pd⁺⁺ during the oxidative addition step (9,10). Using an immobilized catalyst in a batch cross-coupling reaction the leaching of palladium is not obvious because upon completion the metal re-adsorbs onto the solid support (thus acting as a “reservoir” of soluble, active Pd species). When working in continuous flow the situation is different: in continuous flow mode, the palladium metal will progressively be “chromatographed” through the packed-bed catalyst until eventually all Pd will be removed from the support owing to continuous metal leaching/re-adsorption (8). This effect, which becomes especially relevant when long run experiments are performed, leads to significant amounts of transition metal being leached out of the reactor contaminating the product (Figure 1).

A recent critical assessment of the published literature in the field of transition metal-catalyzed cross-couplings employing immobilized metal catalysts in packed-bed flow devices has shown that in most cases important amounts of catalyst leaching and reduced reaction conversions over time can be observed (8). It appears in many cases more appropriate to perform transition-metal catalyzed cross-couplings in flow using a homogeneous metal (pre)catalyst and –if required– a suitable ligand system. Homogeneous catalytic systems provide increased selectivity and allow careful control and optimization of the required catalyst loading needed for the transformation at hand. In order to recycle the (often expensive) metal catalysts from a flow process recent research has opened up several possibilities, including liquid/liquid phase separation or solvent nanofiltration techniques (11).

Figure 1. Metal leaching phenomena under continuous flow conditions is associated to the fact that the mechanism follows a (quasi)homogeneous pathway.

Figure 2. Drop in conversion during the processing of 20 mmol of aryl iodide using a single Pd/C catalyst cartridge, and (inset) Pd-mirror formed on the walls of the collection vials. Adapted from (8) with permissions.
could be minimized by incorporating a metal scavenging resin into the flow setup. However, attempts to process a larger scale 0.2 M reaction mixture failed after few hours pumping constantly at 0.2 mL min⁻¹. The conversion dropped dramatically thus suggesting that the palladium metal had leached from the support.

More recently a benchmarking study comparing the efficiency, durability and metal leaching resistance of some of the most common immobilized di- and triarylphosphine-based palladium catalysts towards continuous flow cross-coupling reactions was performed (19). Pd Tetrakis (polymer-bound), FiberCat 1001, EnCat TPP30, and SiliaCat DPP-Pd were independently evaluated using two model reactions: the Mizoroki-Heck reaction of 4-iodobenzoazinone with butyl acrylate and the Suzuki-Miyaura reaction of the same halide with phenyl boronic acid. The Suzuki-Miyaura cross-coupling produced a much higher amount of metal leaching and catalyst degradation than the Mizoroki-Heck reaction, except for SiliaCat DPP-Pd which provided comparably good results. In the case of the Pd EnCat TPP30 a constant drop in conversion was observed when EtOH as solvent in combination with TBAOAc as base were utilized for the Suzuki-Miyaura reaction (Figure 3b), using analogous conditions to that utilized by the group of Ley in their study. In this study the choice of an appropriate solvent/base system was shown to be crucial for the durability of the supported catalyst. Importantly, variable amounts of Pd leached from the packed bed reactors were always present in the crude reaction mixtures collected from the reactor output. In this context, SiliaCat DPP-Pd combined with THF/EtOH/H₂O as solvent and K₂CO₃ as base gave the best results regarding catalyst efficiency and cleaning resistance. Yet, significant degradation of the immobilized catalyst was also observable in these cases. Negligible amounts of metal leaching are only achieved when rather diluted reaction mixtures (e.g., 0.05 M) are processed, not being practical for preparative purposes. Although immobilized catalysts which minimize the amount of metal leaching such as SiliaCat DPP-Pd are being developed, it seems difficult that a genuinely “leaching-free” catalyst will appear due to the above mentioned mechanistic implications with (quasi)homogeneous palladium species being involved in the catalytic cycle.

**HOMOGENEOUS PALLADIUM CATALYSTS**

Many transition-metal catalyzed cross-couplings in flow using homogeneous palladium catalysts have also been reported (7). Apart from the better control over the catalyst loading and thus reaction selectivity, the scalability of the process is unproblematic as the problem of metal leaching does not apply in these cases. An interesting example is the two-step continuous-flow synthesis of 2-amino-4'-chlorobiphenyl (3) (20), a key intermediate for the industrial preparation of the fungicide Boscacid and possibly one of the largest scale Suzuki-Miyaura cross-couplings reactions worldwide (Figure 3b). The reaction comprises an initial palladium-catalyzed high-temperature Suzuki-Miyaura cross-coupling of 1-chloro-2-nitrobenzene (1) with 4-chlorophenylboronic acid (2) and a subsequent hydrogenation to the aniline 3. The reported batch procedure for the Suzuki coupling required reaction times of 8 to 18 h at 65–100°C to achieve completion. Preliminary optimization of this reaction in a batch microwave reactor and further tuning in a high pressure microtubular flow reactor reduced the reaction time to 15 min at a reaction temperature of 160°C, affording the desired 4'-chloro-2-nitrobenzophenone in ~90% yield. For the subsequent hydrogenation, the palladium from the Suzuki reaction had to be removed to prevent a palladium-catalyzed reductive dehalogenation. This was achieved by passing the reaction stream from the coupling step directly through a macroporous Quadrupure™ TU (Thioure) resin cartridge to scavenge the Pd metal from the solution. The nitro compound was subsequently hydrogenated over Pt/C at 30°C in a commercial flow hydrogenation device to afford 2-amino-4'-chlorobiphenyl (3) in 77% overall yield (Figure 4a) (20).

An alternative to single, fully homogeneous reaction mixtures is to employ biphasic systems in which two immiscible solvents, containing different reaction partners are used. In this way good solubility of all organic reactants and inorganic compounds (e.g., inorganic base) is ensured. Buchwald and Noël utilized packed bed reactors containing 60-125 μm stainless-steel spheres to enhance the mixing and thus the contact between the immiscible phases. The concept was applied for the continuous flow C-N cross-coupling of aryl chlorides with anilines (21), and for the Suzuki-Miyaura reaction heteroaryl halides with (hetero)aryboronic acids using a biphasic toluene/water system (Figure 4b) (22). In the case of the Suzuki-Miyaura coupling the flow setup consisted of three feeds. The organic feed used NMP/toluene 4:1 as solvent and contained the halide, aryboronic acid, and the palladium catalyst. Two further aqueous solutions with the base (K₂PO₄) and a phase-transfer catalyst [Bu₄NBr] were also fed into the system. The mixture passed through the packed bed reactor, preheated at 90°C, before being diluted with EtOAc/water. The packed bed reactor significantly improved the contact between the phases and hence the efficiency of the reaction. Thus, under analogous conditions...
Quadrapure thiourea resins, which have been frequently utilized in continuous flow in packed bed reactors, efficient separation/recirculation of metal catalyst by liquid/liquid phase separation or nanofiltration are being developed. Using liquid/liquid biphasic conditions in which one of the solvents selectively dissolve the catalyst is an elegant procedure for the facile separation and recycling of the metal catalyst. This concept has been applied for example to Suzuki-Miyaura (24) and Mizoroki-Heck (25) reactions. Continuous separation of liquid phases using semipermeable membranes has also been described thus opening the door to fully automated recycling process (26) (Figure 5a).

Organic solvent nanofiltration techniques for catalyst separation have been more recently developed (27). These methods do not require biphasic systems and are based on the use of membranes with a molecular weight cut-off. Homogeneous catalysts normally present analogous molecular weights as the reagents or products, and thus they typically need to be enlarged. For this purpose dendrimers, polymers, or oligomeric silsesquioxanes have been used. Using this methodology the catalyst can be easily retrieved from the reaction mixture and reutilized, making the continuous flow processes more economical and greener (Figure 5b).

CONCLUSION AND OUTLOOK

An increasing number of chemical processes, including preparation of complex pharmaceutical compounds, are being designed for their implementation using continuous flow technology. In many of the synthetic steps involved in these protocols transition metal (mostly palladium)-catalyzed carbon-carbon or carbon-heteroatom bond forming reactions (“cross-coupling chemistry”) play an important role. Such transformations involve either the use of a homogeneous or of a heterogeneous (immobilized) catalyst/ligand system. In the latter case, the catalyst/ligand system is typically employed in the form of a packed-bed reactor where the reaction mixture is pumped through employing an appropriate temperature regime and residence time. However, using this technique significant leaching of the transition metal out of the packed-bed catalyst almost inevitably will occur, leading to decreased catalyst activity...
and contamination of the product with transition metal. The preferred alternative, in particular for larger scale experiments, therefore is to use a homogeneous (pre) catalyst in combination with an appropriate catalyst recycling technology.

ACKNOWLEDGEMENTS

Research on continuous flow chemistry in our laboratories for the past decade has been generously supported by the Christian Doppler Research Association (CDG) and a variety of industrial partners including Lonza, DPx, Microinova, ThalesNano, Anton Paar, Eli Lilly, BayerPharma, BASF and Clarient.

REFERENCES AND NOTES


Improvement is always on our mind. And in your mouth.

Of course we know that toothpaste is more useful in your mouth than on a mirror, but sometimes we get carried away with the brilliance of our formulas. Our Rhodium or Ruthenium catalyst is used in the production of menthol for toothpaste and chewing gum. Speaking of which, you should see the formulas we pop out with gum.

Employee: Don Zeng/Sales and Business Development Manager

www.chemistry.umicore.com

Innovation made. Easy.