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ARTICLE

Separation/Recycling Methods of Homogeneous Transition Metal Catalysts in Continuous Flow

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Catalytic processes are of paramount importance in the chemical industry. Homogeneous catalysts are of great interest for making fine-chemical/specialty chemical/pharmaceutical products with their advantage of high activity and selectivity. However, their separation from the product remains a challenge. Transition metals and especially platinum group metals are used extensively as catalyst. They are expensive and there are strict regulations on the permitted levels of these metals in pharmaceutical products. Therefore, their effective separation is required. Moreover, we are running short of these and many other valuable metals. This puts more emphasis on the need to separate these homogeneous metal catalysts in their active form and recycle them back to the reactor. This review aims to provide the reader with an overview of the current literature on the separation/recycling methods of homogeneous transition metal catalysts in continuous flow. These include heterogenization, scavenging, use of biphasic systems and organic solvent nanofiltration. There are numerous successful demonstrations on laboratory scale and recently also on an industrial scale.

1. Introduction

Metals are essential for our way of life. We rely on the goods made from metals such as mobile phone, television, laptop or a car to maintain our quality of life. Peak oil is defined as the point in time when the global production of oil reaches it maximum and will subsequently begin to decline until full depletion is ultimately reached [1]. To point out the serious depletion of metals in the Earth, in analogy with the peak oil, recently the term peak metal has emerged [2]. There are a wide range of metals with imminent threat of failing to meet demand. Growth in world population along with continuous developments in technology is predicted to result in some of these metals to run out in about 20 years [1]. In 2013 EU identified twenty critical raw materials that include antimony, beryllium, chromium, cobalt, gallium, germanium, indium, magnesium, niobium, tungsten, platinum group metals (PGMs) and rare earth elements [3]. However, in contrast to fossil fuels, metals can be recycled. But, this can be challenging as they are used in a rather dissipative way, it is hard to collect and channel them together through a recycling chain. Therefore, it is important to improve logistics and efficiency of recycling processes. Also, more efficient use of resources can be very effective. This calls for scientific research so that more can be achieved with less amount of metals.

Another important point is that the reserves of these metal resources are not evenly distributed around the world. More than 90 % of rare earth metals, more than 85 % of tungsten and magnesium are supplied from China and more than 60 % of PGMs are supplied from South Africa [3]. Therefore, it is important for the resource dependent countries such as the EU countries to employ these measures of recycling and resource efficiency to overcome supply risks.

The availability of these critical metals is also important to provide and improve environmental performance. For a car to meet legally mandated emission levels, catalytic converters containing PGMs are required; currently there is no other alternative [3]. Wind turbines use magnets containing rare earth metals [3]. Electric cars also require rare earth metals and solar panels require indium and gallium among others [3].

Accordingly, recycling can be ‘resource’. Recycling can allow a circular economy and would reduce reliance on mining. As an example, efforts for PGM recycling from catalytic converters have already set in and in just three years the total PGM recycled amount has notably increased by almost 600 % to 150 tons per year. This constitutes already 30% of the annual PGM production and about 0.2 % of all PGM resources and reserves on earth [4]. As a matter of fact, Germany has become the largest platinum supplier for the US market, with South Africa as the number 2.

Transition metal catalyst and especially PGMs (palladium, platinum, rhodium, ruthenium, iridium and osmium) are used extensively in the fine-chemical, agrochemical and pharmaceutical industry as catalysts due to these metals’ unique ability to catalyze important synthetic transformations with high selectivity. Catalysis provides access to complex chemical molecules via alternative more direct routes involving fewer chemical steps and with less waste generated, compared to more traditional non-catalyzed alternatives. In particular, cross-coupling reactions have revolutionized the synthesis of target molecules for pharmaceutical synthesis with the use of metal catalysts [5]. The Nobel Prizes to Sharpless, Noyori and Knowles (2001), Schrock, Grubbs and Chauvin (2005) and Heck, Suzuki and Negishi (2010) highlights the importance of homogeneous metal catalysis.

However, despite the extensive application of these metals for homogeneous catalysis at development stages, their commercial application for fine chemical and pharmaceutical production is limited. The major reason for this is the difficulty of their separation. The permitted levels of these metals in pharmaceutical products is strictly regulated. Guidelines from the European Medicines Agency state that the daily permitted oral exposure to these metals in a pharmaceutical ingredient should be typically less than 10 ppm [6]. Also, the majority of these metal catalysts and in most cases the ligands have a high cost. Therefore, the ability to efficiently remove and recycle these homogeneous catalysts in continuous flow is of great importance.

2. Homogeneous Catalysts vs. Heterogeneous Catalysts in Terms of Catalyst Separation/Recycling

In batch reactions, the catalyst, reactants and solvent are stirred together until completion of the reaction after which the liquid is separated from by filtration. The catalyst can then be collected and recycled. In a continuous process, the catalyst can be fixed on a heterogeneous support and the reactants and solvent flow over it. The catalyst remains in the reactor and can be re-used.

Homogeneous catalysis has advantages over heterogeneous catalysis such as higher activity and selectivity and the reaction mechanism is better understood [7]. The use of continuous flow systems with intensified reaction conditions increases the reaction efficiency, allows safe operation and the reactions to be greatly accelerated [8,9]. However, difficulty in separation of the product and recycling of the catalyst are major drawbacks of homogeneous catalysis. So far a comprehensive solution has not been achieved which represents a major hurdle to their large scale application.

2.1. Heterogenization of Homogeneous Catalyst for Separation in Flow

This limitation of homogeneous catalysts led to increasing activity to heterogenize homogeneous catalysts [10]. The aim is to combine the benefits of homogeneous catalysis with the ease of catalyst separation of heterogeneous systems. There are two ways of heterogenization of homogeneous catalyst. First is by immobilizing homogeneous catalysts on solid support. Second is recently studied immobilization of homogeneous catalyst in a stationary liquid phase.

2.1.1. Immobilization of Homogeneous Catalyst on a Solid Support.

The immobilization of homogeneous catalysts can be done on organic (polymer) or inorganic (silica) supports. The major drawback of this modification is the significant leaching and degradation of the catalyst during its use and recycle [7]. However, robust systems have been developed in flow chemistry. Leeuwen and co-workers immobilized a Ru catalyst used in transfer hydrogenation reactions by linking the ligand covalently to silica gel and packed the catalyst in a glass column [11]. They achieved high conversion (95 %) and enantioselectivity (90 %) in flow and they could continuously run it for one week without significant catalyst deactivation.

Lamb et al. successfully achieved immobilization on organic support [12]. They describe the use of Ru catalyst immobilized on a phosphine bound polymer in a continuous flow *N*-alkylation of morpholine with benzyl alcohol. Fixed bed reactor shown in Figure 1 was used. At 150 °C and 0.1 cm^3/min flow rate conversion into the desired tertiary amine was 98 % but dropped with higher flow rates. The reactor could be run continuously for 72 h.

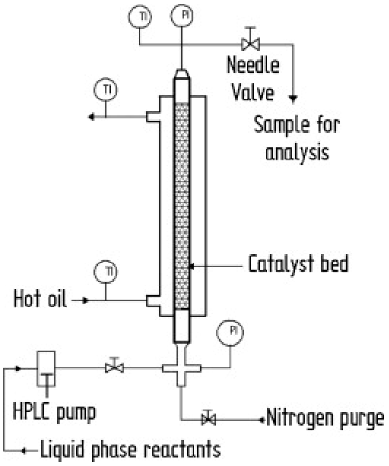

Figure 1. Continuous flow fixed bed reactor for N-alkylation of morpholine with bezyl alcohol using an immobilized ruthenium complex supported on a phosphine bound polymer (Reproduced from ref. 12 with permission from Elsevier)

There are a lot of examples where immobilization of a catalyst on a solid support is done for cross-coupling reactions in continuous flow. These examples can be found elsewhere [9,13–17]. However, in their recent review Cantillo & Kappe pointed out that the use of heterogeneous (immobilized) catalysts for performing cross-coupling chemistry in continuous flow is in fact not appropriate [13]. This is explained with the reaction mechanism of cross-coupling reactions involving the transformation of Pd^0 species into (soluble) Pd^{II} species given as example for the palladium transition metal catalyst used. In continuous flow this results in all metal to be eventually removed from the support. The leaching causes reduced activity and contamination of the product. In a previous paper by Kappe et al. [18] they observed leaching of Cu from the charcoal support in their experiment employing Cu/C catalyst for copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction in continuous flow. Their investigation confirmed a homogeneous mechanism with the charcoal acting as reservoir for Cu.

Therefore, the use of homogeneous catalyst is found more appropriate together with an appropriate catalyst recycling technique [13]. This statement makes it even more important to develop methods for homogeneous catalyst recovery and possibly also recycle in continuous flow.

2.1.2. Immobilization of Homogeneous Catalyst in a Stationary Liquid Phase

A homogeneous catalyst can also be immobilized in a stationary liquid phase. In this system, the catalyst is dissolved in a thin film of liquid which is supported within the pores of silica. This is easy to be prepared compared with the chemical bonding immobilization technique. As such, the homogeneous mechanism is respected and the reactants diffuse into the stationary liquid phase. After reaction, the products leave the stationary liquid phase and are removed with the continuous phase.

A supported aqueous phase catalyst was used for the Mizoroki-Heck reaction[19]. Ionic liquid can also be used as the supported liquid phase. The supported ionic liquid phase (SILP) systems were attractive to be studied with compressed CO_2 as the flowing medium in continuous flow. This concept of SILP catalysis with $scCO_2$ is given in Figure 2 [20]. The catalyst is supported in a thin film of ionic liquid on a porous support. This SILP/$scCO_2$ system is similar to the $scCO_2$/IL biphasic system explained in Section 3.3.1. The SILP/$scCO_2$ system is advantageous because it requires much less ionic liquid which is an expensive material and CO_2 can be used below the critical point allowing lower pressure operation. Hydroformylation [21,22], olefin metathesis[23] and enantioselective hydrogenation[20,24] reactions have been successfully carried out continuously by using SILP/$scCO_2$ systems. Further information can be found in review by Stouten et al.[25]

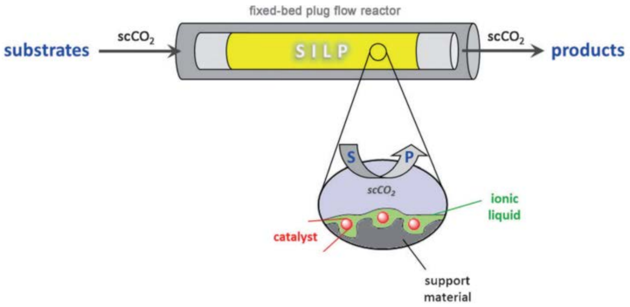

Figure 2. Concept of continuous flow supported ionic liquid phase catalysis with $scCO_2$ (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Adapted with permission from ref. 20)

3. Separation/Recycling Methods of Homogeneous Catalysts in Continuous Flow

There are several methods applied to separate homogeneous catalysts from the reaction mixture in homogeneous form in continuous flow. Most of them involve the use of liquid/liquid biphasic system. It can also be achieved with scavenging which is typically done utilizing solid-supported scavenging resins packed into columns. There is also relatively new method of organic solvent nanofiltration (OSN) to separate the homogeneous catalyst in flow.

3.1. Scavenging

Metal scavenging has been performed for years, particularly in order to remove heavy metal from natural water and sediment due to increased amount of metals discharged into natural environments [26]. It has also been used to recover valuable metals from spent catalyst and soil washing [27–30]. These scavenging agents extract metal by forming a metal-chelate complex which can further be removed from the solution [28]. It enables high extraction efficiency of the metal and is fast, compatible with many solvents and causes no loss of product [31]. It is especially attractive when the amount of metal in solution is very low making it not practical or economical to separate with conventional methods. Therefore, scavengers have also found application in the pharmaceutical industry during the manufacture of active pharmaceutical ingredients (APIs) where the removal of trace amounts of metals from the final product is important [32,33].

3.1.1. Use of Scavenging Columns (Solid-Assisted Purification)

There are numerous examples of the use of solid-supported scavenger resins packed into columns to achieve purification under flow conditions [34,35]. They have also found wide use to get the product free from metal catalyst by capturing trace metals from the reaction mixture. This was done generally for heterogeneous catalysis to scavenge the metal leached out of the reactor. Commercial Quadrapure™ thiourea functionalized polymer (QP-TU)[36,37] , which has high scavenging ability (99 %) to a wide range of metals used in catalysis, has been used in literature frequently [18,38–40].

Glasnov and Kappe used QP-TU column for in-line purification placing between two reactions in the synthesis of a key-intermediate of Boscalid® in continuous flow [41]. In the two-step process, the first step was Suzuki-Miyaura reaction with homogeneous Pd catalyst and second step was heterogeneous Pd/C catalyzed hydrogenation reaction. The Pd in solution adversely affected the second reaction resulting in a significant amount of overreduced product. To solve this problem, Pd was efficiently removed in-line with scavenger column placed between two reactors as shown in Figure 3.

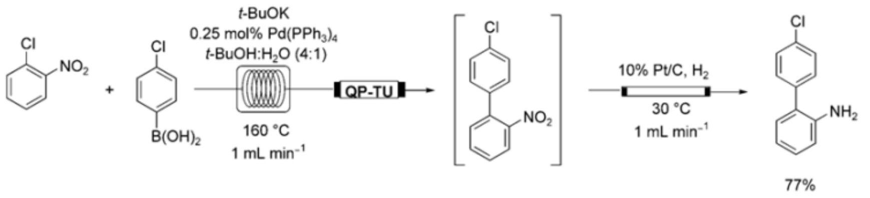

Figure 3. Continuous flow setup for the synthesis of a key-intermediate of Boscalid® with in-line purification using scavenger column of QP-TU (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission from ref. 41)

3.1.2. Use of Scavenging Agents in Solution

Scavenging columns are effective in removing the metal from the product steam but they need to be replaced after saturation interrupting the continuous operation. Also, although they perform well for up to few grams of production, they were not found suitable for larger scale experiments [15,18]. Fuchs et al. found that an off-line washing step with EDTA was suitable for large-scale experiments. However, achieving this separation in flow after the reaction would be a more favorable situation.

This was achieved by realizing scavenging and phase separation in a single unit. After extraction, liquid-liquid phase separation can be achieved using membranes [42]. It can also be performed with branched hydrophobic and hydrophilic outlets [43,44]. In this way metal catalyst can be separated in an uninterrupted continuous flow. The unit developed was based on liquid-liquid extraction with the use of scavenging agents in solution such as aqueous EDTA and phase separation using porous polytetrafluoroethylene membrane[45]. This continuous metal scavenging unit was successfully connected after CuAAC reaction in flow with a setup given in Figure 4. Flow liquid-liquid extraction FLLEX module from Syrris was used to achieve the separation of the organic phase containing product and the aqueous phase containing the catalyst. In initial experiments three stages of separation was required to reduce the copper content of triazole product below the limit for APIs of 15 ppm. Since this was not optimal, more extensive analysis on the microseparation unit was done. Based on this analysis and the optimization of the process parameters, the triazole product was obtained in high yield (92 %) and required purity was achieved in one stage of separation [46].

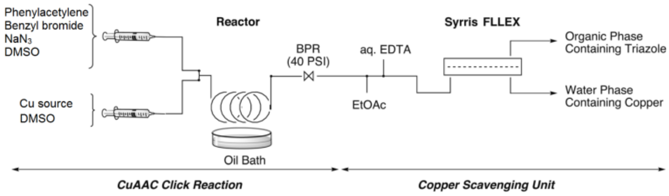

Figure 4. Continuous flow setup of one-pot CuAAC click reaction coupled with metal scavenging unit [46].

Solvent extraction of metal ions without using scavenging agents was also investigated. Aota et al. modified the walls of a glass microchannel enabling one side to be hydrophilic while the other is hydrophobic [47]. Countercurrent laminar microflow was applied to a solvent extraction of cobalt complex from toluene into water. Maruyama et al. demonstrated use of liquid membrane in a microchannel for solvent extraction of metal ions [48]. The liquid membrane consisted of a feed aqueous phase, an organic phase and a receiving aqueous phase. It was utilized for the selection separation of Y^{3+}.

3.2 Use of Liquid-Liquid Biphasic Conditions

Another way of recycling homogeneous catalysts is through the use of liquid-liquid biphasic conditions. This is achieved with one phase selectively dissolving the catalyst while the other dissolving the product. After separation of the phases, the phase containing the catalyst can be recycled to the reactor. Continuous operation with these biphasic systems was achieved where most examples involve the use of aqueous-organic systems but immiscible organic-organic system was also described. They can also be achieved using fluorous solvents, ionic liquids and supercritical fluids.

One example is the use of fluorous solvents and tags within flow systems for the continuous recycle of catalyst. Theberge et al. used fluorous tagged palladium catalyst that was soluble in fluorous solvent for catalyzing the Suzuki-Miyaura reaction [49]. The palladium catalyst remained in the fluorous phase while reagents and products were in aqueous phase forming a slug flow. The polar catalyst was oriented towards the aqueous slug at the interface. At the end of the reaction channel the aqueous and fluorous phases separated by density and the fluorous phase was pumped back to reactor. The fluorous phase was continuously recirculated four times without loss in activity. The amount of palladium in the aqueous phase was measured to be less than 0.5 ppm.

George and co-workers also demonstrated fluorous biphasic catalysis. They achieved automated recycling of the catalyst system for continuous oxidation of citronellol [50]. The reaction was achieved in flow in a single phase system with supercritical CO_2 and high pressure conditions. With release of pressure gaseous CO_2 and biphasic liquid mixture formed as shown in Figure 5. The fluorous phase containing the fluorinated catalyst was separated from the organic phase containing product and continuously recycled by pumping it back to the reactor. The catalyst was recycled 10 times over 20 h of continuous operation producing 240 mL of product using 12 mL of photocatalytic solution. Compared to their single pass continuous experiments with a previous photocatalyst twice the product was obtained with ten times lower amount of photocatalyst.

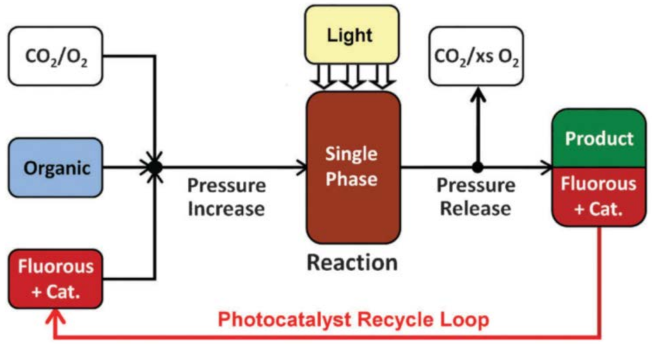

Figure 5. Continuous florous biphasic catalysis for photo-oxidation of citronellol in $scCO_2$ with continuous recycle of photocatalyst (Reproduced from ref. 50 with permission from The Royal Society of Chemistry)

Another example is the use of ionic liquid as the recycling reaction medium. Ryu and co-workers successfully carried out Mizoroki-Heck reaction in an automated microreactor system catalyzed by Pd catalyst immobilized in ionic liquid phase [51]. They were able to combine the microreactor with a flow workup/catalyst recycling system shown in Figure 6. The ionic liquid solution from the reactor was mixed with an aqueous solution to remove the by-product ammonium salt. Then it was mixed with hexane to extract the product. The resulting mixture was separated into three phases after which the ionic liquid phase containing the Pd catalyst was recycled back to inlet. The Pd catalyst could be continuously recycled five times providing 115.3 g of trans-butyl cinnamate product to be produced in an overall yield of 80 %. A similar application of the use of ionic liquid was given for the Sonogashira coupling reaction and 100 g scale synthesis of the precursor for matrix metalloproproteinase inhibitor was achieved with continuous catalyst recycling system [52].

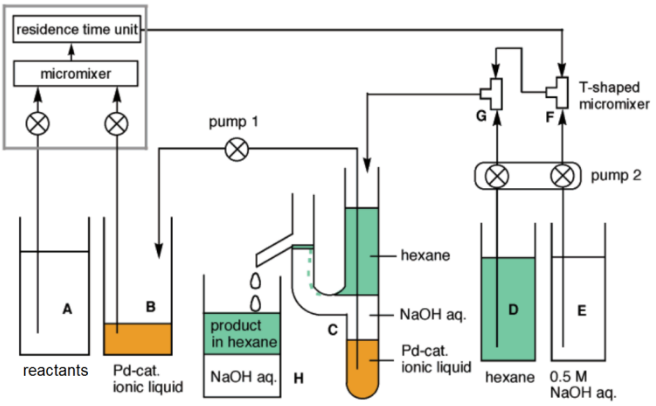

Figure 6. Continuous Pd-catalyzed Mizoroki-Heck reaction in a microflow system with flow workup/catalyst recycling using ionic liquids as the reaction media (Adapted with permission from ref. 51. Copyright 2004 American Chemical Society.)

The combination of supercritical CO_2 ($scCO_2$) with ionic liquid (IL) forms an attractive biphasic system. Brennecke observed that $scCO_2$ is highly soluble in ionic liquids whereas IL does not dissolve in $scCO_2$ [53]. He later demonstrated that organic compounds can be extracted from IL using $scCO_2$ while IL is retained. Therefore, $scCO_2$ is an ideal transport vector for the substrates and products. In the $scCO_2$/IL biphasic system, the catalyst is retained in the IL while the reactants and products are transported in and out of the reactor dissolved in $scCO_2$ as depicted in Figure 7 [54]. The examples of this $scCO_2$/IL biphasic system applied to homogeneous catalysis in continuous flow can be found in the review by Stouten et al. [25].

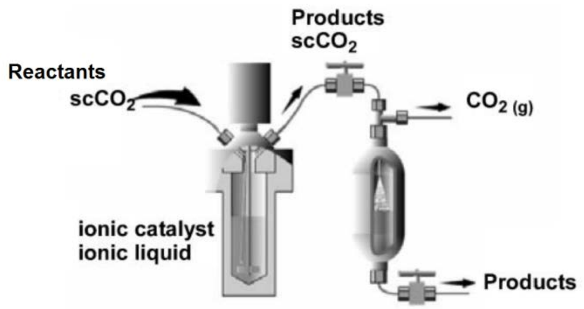

Figure 7. Concept of $scCO_2$/IL biphasic system applied to homogeneous catalysis in continuous flow (Adapted from ref. 54 with permission from The Royal Society of Chemistry)

In previous examples the separation of the phases were achieved by collecting the mixture in a flask and passive separation of the phases based on density difference. Jensen group used a membrane separator to achieve liquid/liquid phase separation [55]. Their flow setup for the continuous Pd catalyzed hydroxylation of aryl halides consisted of a packed-bed reactor and catalyst-recycling loop including the membrane separator and a pump. A highly active bulky phosphine was utilized as the supporting ligand. The reaction proceeded in a mixture of water and toluene with a phase-transfer-catalyst added as promoter. Water-soluble phenolate product was successfully separated from the Pd catalyst containing organic phase. The organic phase was then pumped back to the reactor. The formation of palladium black was avoided by optimizing reaction conditions at 80 % conversion enabling efficient catalyst recycle. The catalyst was reused in four more cycles without significant loss in activity.

Sharma et al. describe the use of thermomorphic multicomponent solvent (TMS) to enable continuous homogeneous catalyst recycling with a system shown in Figure 8 [56]. They chose highly polar DMF solvent for the polymer supported Pd or Cu catalyst. They developed a microfluidic loop system where the DMF and decane biphasic mixture is collected in a reservoir. The decane phase at the top containing the catalyst was continuously recirculated with a pump and the

DMF phase containing the product was collected from the bottom. This system was first tested for isocyanide insertion reaction continuously for 18 h. Quinazolinone was attained with a yield of 81.8 % catalyzed by NHC-Pd catalyst. Then it was expanded to synthesize chemical library of quinazolinone derivatives. The NHC-Pd catalyst was also used for Heck reaction for synthesis of drug intermediate in a 6 h continuous operation. 16.75 g was attained at 82 % overall yield. Finally, the TMS system was tested for Cu catalyst in Huisgen 1,3 dipolar cycloaddition click reaction. 8.26 g of triazole product was collected at 88 % overall yield after continuous operation of 10 h. No metal leaching was observed.

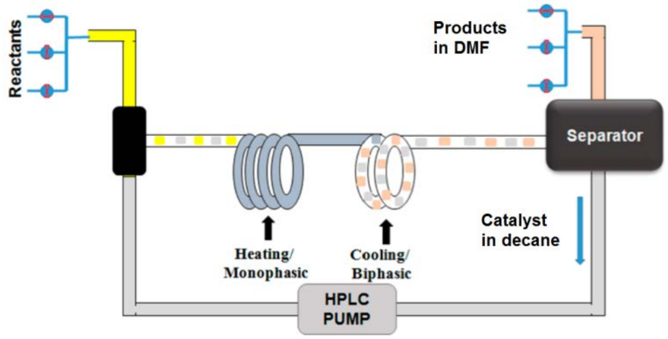

Figure 8. Microfluidic loop system for automated continous recirculation of metal catalyst under thermomorphic multicomponent solvent conditions (Adapted with permission from ref. 56. Copyright 2014 American Chemical Society.)

3.3 Organic Solvent Nanofiltration (OSN)

To recycle homogeneous catalysts organic solvent nanofiltration (OSN) is a recently used separation technique. It has been investigated within the last 10 to 15 years with the development of membranes stable in organic solvents [57]. The advantage of this method is that it does not require presence of biphasic system to separate the catalyst. It also requires low energy compared to other typical separation techniques thus considered green separation [57].

There are mainly two types of continuous membrane reactors. The first type is dead-end filtration where the catalyst stays in the reactor retained by the membrane as the products, solvent and unreacted material pass through [58]. Concentration polarization which is the accumulation of catalyst near the membrane can occur. The second type is loop reactor where the solution is continuously circulated and as it passes through the filtration unit products can cross the membrane and go out [58].

The selection of the membrane is based on the molecular weight difference between the catalyst and other species. The molecular weight cut-off (MWCO) of membrane is selected accordingly [59]. Extensive information about the membrane materials, membrane preparation and transport mechanisms can be found in the review by Vankelecom and coworkers [60].

Homogeneous catalysts are usually about the same size as the reagents and products. Therefore, generally they are molecular weight enlarged (MWE) to facilitate the membrane filtration [59]. For this, homogeneous catalysts are attached to soluble supports. But, use of nonenlarged systems with application of OSN in continuous flow is also studied.

3.3.1. Non-enlarged Catalysts

Continuous OSN was used in a continuous Heck coupling reaction [61]. After 100 h of operation at a conversion higher than 85 %, 1.081 mol of product was produced equivalent to catalyst turnover number (TON) of 1772. The polyether ether ketone (PEEK) membranes used performed stable at reaction temperature of 80 °C throughout the run. The Pd rejection by the OSN membrane was estimated to be 93 %. The $Pd(OAc)_2$ catalyst is converted to high molecular weight Pd complexes with 1,3-bis(diphenylphosphino)propane ligand and therefore rejected better by the membrane. However, the product contamination was still above limits for pharmaceutical product (317 mg Pd per kg of product).

This experiment was performed in a single reactor system which included a continuous stirred-tank reactor (CSTR) with membrane separator having 51 cm^2 membrane area [61]. The stirred tank reactor/membrane separator unit is shown in Figure 9. In a more recent experiment they were able to achieve 95 % conversion resulting in catalyst TON of 17963 with 26 mg Pd per kg product contamination in the product stream [62]. They also made experiments with a reactor configuration with plug flow reactor (PFR) added before the CSTR reactor/separator unit. With this configuration, conversion above 98 % and catalyst TON of about 20000 was attained at a similar Pd contamination of product stream.

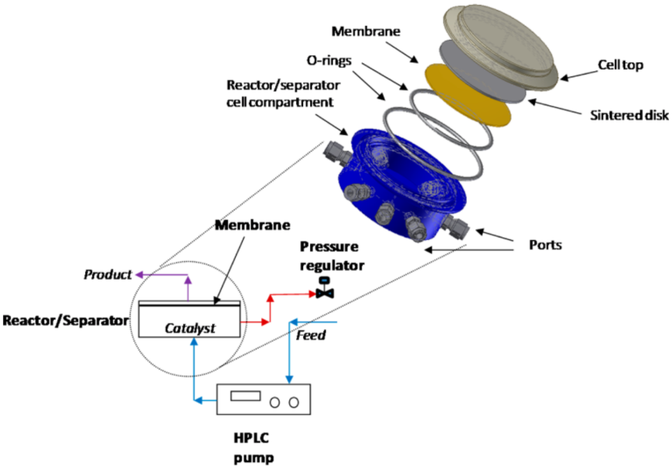

Figure 9. Process scheme for the continuous Heck reaction with in situ separation of the catalyst with the membrane within the reactor/separator unit (Reprinted with permission from ref. 61. Copyright 2013 American Chemical Society.)

Goetheer et al. described the use of a membrane reactor for continuous hydrogenation of 1-butene in supercritical carbon dioxide [63]. A fluorous derivative of Wilkinson's catalyst has been used to achieve better solubility in $scCO_2$. After 32 h of continuous stable operation at 20 MPa and 353 K, catalyst TON of 120000 was obtained. However the conversion at the end of run was 33 %, 60 % lower than batch experiment. The catalyst was completely retained with the inorganic microporous silica membrane used.

The previous examples were from dead-end type filtration. Loop type of membrane reactors was also studied. De Smet et al. developed a continuous reactor system composed of a CSTR and nanofiltration unit that only allows the product to pass through [64]. The rest of the stream containing the catalyst was recycled with a system shown in Figure 10. In a first example, Rh-EtDUPHOS was applied in enantioselective hydrogenation of methyl-2-acetamidoacrylate. Complete conversion was observed initially but decreased to 90 % after 20 h of operation. For the second reaction example of hydrogenation of dimethyl itaconate with Ru-BINAP catalyst, complete conversion was achieved throughout the run. The catalyst TON was 930 for the first and 1950 for the second reaction example. MPF-60 membrane used enabled 97 % retention of the catalyst.

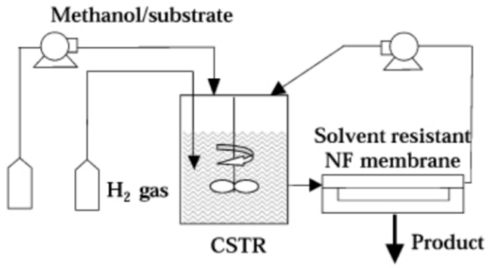

Figure 10. Continuous set-up composed of CSTR and nanofiltration unit with catalyst recycle for enantioselective hydrogenation reactions (Reproduced from ref. 64 with permission from The Royal Society of Chemistry)

Recent application of loop type of membrane reactor was for metathesis reaction [65]. Teflon AF-2400 was used as the flow reactor to achieve efficient ethylene byproduct removal across the membrane. They built a continuous catalyst recycle system with OSN module using polyimide membrane of MWCO of 280 Da, a stirred holding tank with liquid level control system to respond to membrane-flux decline and automated sampling. This system allowed 50 h continuous operation using less than 2 mg of Hoveyda-Grubbs catalyst. Solvent flux declined as the deactivated catalyst accumulated in the system. Therefore the throughput declined as the run proceeded. A total TON of 935 was obtained with Ru contamination in the product stream of less than 1 ppm.

3.3.2. Molecular Weight Enlarged (MWE) Catalysts

As supports for homogeneous catalysts for molecular weight enlargement dendrimers, polymers and polyhedral oligomeric silsesquioxanes (POSS) have often been used [59].

One of the first works with dendrimers used as catalyst support was performed by Brinkmann et al.[66] They reported a continuously operated membrane reactor for an allylic substitution reaction catalyzed by dendritic palladium catalyst (Figure 11). Initially complete conversion was achieved which gradually dropped to 80 % after 100 residence times (50 h). At this point experiment was stopped. A moderate catalyst TON of 95 was achieved. With the MPF-50 membrane used 99.9 % retention of the catalyst was found.

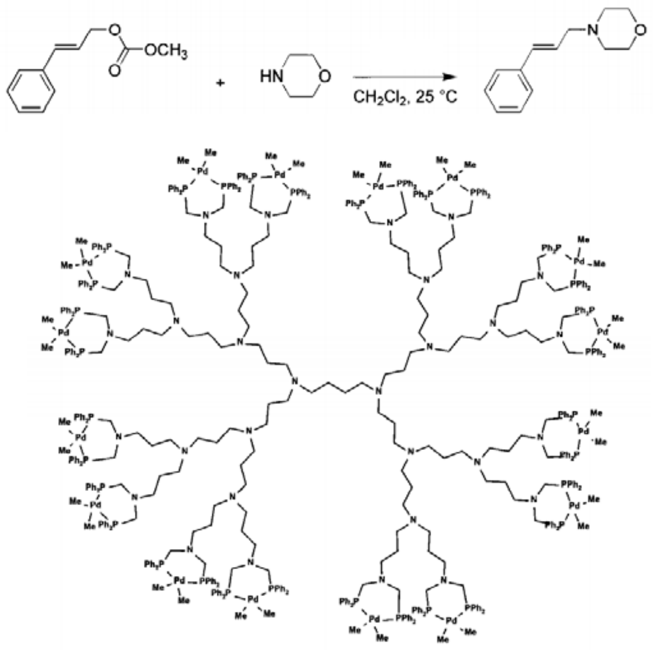

Figure 11. Allylic substitution with dendritic palladium catalyst in a continuous membrane reactor (Adapted from ref. 66 with permission from Elsevier)

Dendritic materials usually have flexible backbones which can affect their retention by the membranes. Therefore, Dijkstra et al. developed shape-persistent pincer-metal complexes and found that with the increase in rigidity of the backbone the retention rate of the membrane increased [67]. They applied the dodecakis (NCN-Pd-aqua) complex as homogeneous catalyst for double Michael reaction in a continuous membrane reactor [68]. The MPF-50 membrane used enabled catalyst retention of 99.5 %. The catalyst showed stable operation throughout the reaction time of 26 h at a conversion of 85 %. Catalyst TON of over 3000 was achieved which is much higher than the TON of 80 obtained in batch.

An example for homogeneous catalysts bound to polymer support for molecular weight enlargement is given by Fang et al.[69] They performed continuous hydroformylation with Rh complexed with polymer bound bidentate ligand (JanaPhos[70]) in a stirred reactor fitted with nanofiltration membrane of Starmem® (Figure 12). 50 % conversion and 98 % aldehyde selectivity was achieved in the 22 h continuous run. The catalyst complex was successfully retained by the polyimide membrane with the Rh concentration in the effluent being steady at approximately 20 ppb.

The use of polyhedral oligomeric silsesquioxane (POSS) was described recently as support for homogeneous catalyst. The rigid, cubical shape of the POSS cages enable them to display high retention[59]. A POSS enlarged triphenylphosphine/Rh

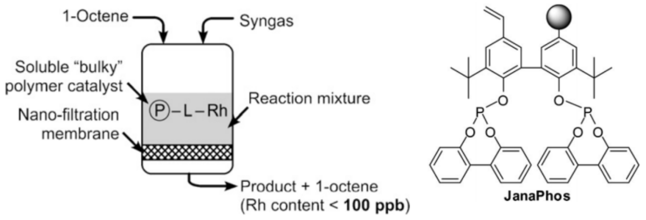

Figure 12. Continuous hydroformylation with Rh complexed with polymer bound bidentate ligand (JanaPhos) in a stirred reactor fitted with nanofiltration membrane (Left: reproduced from ref. 69 with permission from Elsevier, Right: Reprinted with permission from ref. 70. Copyright 2009 American Chemical Society.)

catalyst was used in continuous hydroformylation of 1-octene [71]. From the reaction vessel the reaction mixture flows along ceramic nanofiltration membrane where the product containing phase is separated from the MWE catalyst and continuously collected. The system was operated continuously for almost two weeks with conversion remaining higher than 90 %. No significant deactivation or leaching of catalyst was observed. Catalyst TON of 120000 was achieved. 99.96 % of the Rh was effectively retained by the ceramic nanofiltration membrane.

POSS was also used attached to Ru catalyst for continuous olefin metathesis [72]. MWE catalyst was synthesized by attaching the Grubbs-Huveyda complex to a suitable functionalized POSS. The metathesis reaction of diethyl diallylmalonate was used as a model reaction (Figure 13). The commercial PuraMem280 membrane was used to retain the catalyst and showed about 98 % rejection. Experiments were performed with both CSTR and PFR type reactors. In CSTR mode continuous recycle of the catalyst back to the reactor was also achieved. Nanofiltration cell used had a membrane area of 51 cm^2. Low catalyst TONs (144 and 100) were observed.

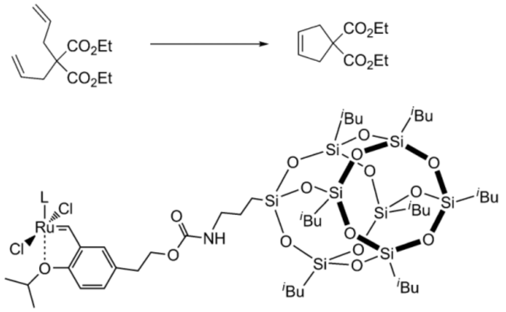

Figure 13. Ring-closing metathesis reaction of diethyl diallylmalonate with POSS-tagged Grubbs-Hoveyda type catalyst (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Adapted with permission from ref. 72)

Schoeps et al. also synthesized MWE catalyst for olefin metathesis [73]. Mass-tagged NHC ligand was used to generate Grubbs type catalysts. In batch experiments for the RCM reaction of diethyl diallylmalonate at 40 °C and 0.1 mol % catalyst loading almost quantitative yields were achieved. In continuous membrane reactor however maximum 37 % conversion was achieved and it decreased during the 500 min run. Still catalyst TON of 866 was attained. 97.6 % of Ru was retained by the composite membrane of PAN/PDMS (poly(acrylonitrile)/poly(dimethyl siloxane)) in the continuous experiment resulting in less than 10 ppm Ru in permeate enabling EMEA threshold for oral exposure to be met.

4. Industrial Applications

For homogeneous catalysis, the difficulty of separating the product from the catalyst is a major hurdle to their application in industry. Therefore, in industry, heterogeneous catalysis is preferred. If homogeneous catalysis is to be applied, cheap catalysts are preferred and they are generally left in the product. If expensive catalysts are used then separation technology is applied. However, industrially used separation generally focuses on attaining the product at high purity rather than recovering the catalyst at its active form. Distillation is generally the first consideration for homogeneous catalyst removal in industry [74]. It requires high energy and also can result in irreversible deactivation of the catalyst system. The recovered metal is generally sent to a catalyst manufacturer instead of trying to be recycled continuously [60] . The catalyst losses result in high costs due to the high cost of the platinum group metals generally used as catalysts. Also, the ligands, used to stabilize the complex, are temperature sensitive and usually expensive as well. In certain examples, the price of the ligand exceeds the cost of the metal catalyst [75,76]. Therefore, their loss is another high cost component. Accordingly, it is estimated that the separation part of production costs accounts for 40 to 70 % when homogeneous catalysts are used [74]. Therefore, more gentle alternatives to distillation to prevent thermal shock were searched. Vacuum distillation has been applied to achieve distillation at lower temperatures to prevent decomposition of the catalyst. However, it requires high cost to generate the reduced pressure. Also, reduced pressure may cause volatilization of the ligand so high ligand losses can occur [77]. Another, method used is adsorption onto an insoluble support such as an acidic ion exchange resin [78]. Extraction method has also been used in the industry either by transferring the catalyst and ligand into another solvent creating a biphasic system [79].

Biphasic systems have found application in the industry. The phase containing catalyst and ligand can be separated from the organic product with minimal effort after the reaction. Recycling can be achieved without any thermal or chemical stress. Since it avoids the costly recycling procedures of classical methods, it is more energy efficient and more economical. Water-organic systems are the most developed. Such a system has been commercialized by Ruhr Chemie/Rhône Poulenc (RCH/RP) for the hydroformylation of propene to butanol. Total production of products worldwide with this process accounts to 800,000 t/y [80]. This process relies on rhodium catalyst and water soluble TPPTS as ligand. The crude product is separated at the top from the aqueous phase containing catalyst. The crude product is then freed of unreacted alkene in the stripper with countercurrent flowing syngas. Since stripping is performed in the absence of catalyst no selectivity and yield reducing secondary reactions occur [80]. Also, catalyst poisoning with the potential catalyst poisons coming with the synthesis gas is avoided [81]. Therefore, typical RCH/RP process have high yields and selectivities (99%) under mild conditions (120°C, 5 MPa) [82]. The process is very energy efficient with the reaction heat from the exothermic hydroformylation is recovered and used in the reboiler of the distillation column that separates the organic phase into *n*- and *iso*-butyraldehyde [77]. The Rh catalyst remains in the reactor. Therefore during its lifetime less than 1 ppb is lost reflecting high economy of the process [83]. Compared with the conventional process which includes thermal separation of reaction products from the catalyst, the process is considerably simplified. The high selectivity and yields and high energy efficiency achieved with this RCH/RP process enables it to have about 10 % lower manufacturing costs compared to other Rh catalyzed hydroformylation processes that do not use aqueous-phase operation [81]. Besides the economic advantages, there are also environmental advantages. The environmental *E* factor for conventional cobalt catalyzed hydroformylation processes is about 0.6-0.9 [77]. This factor falls to below 0.1 for the RCH/RP process due to conservation of resources and minimization of waste [77]. This makes evidence of an environmental benign and green process.

Besides this industrial bulk chemical production via aqueous-biphasic process there is also another bulk process of hydrodimerization of butadiene and water with Pd/TPPMS run by Kuraray company with a capacity of 5,000 t/y [82]. There are also examples fine chemical production in industrial scale using aqueous-organic biphasic conditions such as intermediates for vitamins, phenyl acetic acid [84,85]. There is an example of industrial organic-organic biphasic process as well which is Shell's SHOP (Shell Higher Olefin Process). Oligomeric alkenes are produced with capacity of approximately 900,000 t/y [86]. The biphasic operation is due to catalyst being dissolved in polar solvent and the alkenes being nonpolar is insoluble and can be easily separated.

Biphasic systems can also be created with fluorous solvents, ionic liquids and supercritical carbon dioxide as explained in section 3.2.1. Fluorous solvents and ionic liquids have high initial cost. However, it has been seen that they can be recycled very efficiently. Therefore, despite the high cost of these chemicals it has been estimated that they have small effect on the cost of the process [77]. Also, the commercial availability of ionic liquids has improved over the last few years leading the prices to go down considerably. They can switch from being a curiosity to become a commodity. Ionic liquids are attractive due to their nonvolatile nature and high tunability making them attractive to be used as solvent for biphasic systems as well as for SILP catalysis [87]. Regarding health, safety and environment, some ionic liquids can be flammable and/or toxic [88]. In fluorous biphasic catalysis the catalyst is made soluble in the fluorous phase by attaching to fluorinated ligands. This fluorous biphasic system has the advantage of temperature dependent phase behavior allowing single phase to exist at reaction temperature allowing reagents to have good contact with the catalyst during reaction [89]. Upon cooling the phases separate allowing easy separation of catalyst and product and reuse of the catalyst phase. They are considered as non-toxic and having zero ozone depletion thus considered friendly to environment [87]. For thermally sensitive systems with fluorous biphasic catalysis supercritical CO_2 can be used to affect phase behavior [50]. In these systems, pressure is released to change from single phase to multiphase. Supercritical CO_2 is also attractive to be used in combination with ionic liquid with ILs having no solubility in CO_2 and CO_2 having high affinity to ILs [53]. Therefore, supercritical CO_2 allows rapid mass transfer of reactants and products in and out of the reactor. Supercritical CO_2 is a cheap and non-toxic solvent, however, the high pressure results in high cost for specialized equipment and also energy for compression [88]. In conclusion, provided very good recyclability and long lifetime, it can be economical to use these biphasic systems at industrial scale with the ease of catalyst separation and recycle achieved. Therefore, it can be expected that with the increase in their successful demonstrations, their unique advantages will be exploited in industry especially for fine chemical production in near future.

Nanofiltration is a relatively new method to be applied for organic solvents for homogeneous catalyst separation. It has been vastly applied to water-based process industries for water treatment [90]. From 1970s there has been research to expand their use for non-aqueous applications. From 1980 onward, major oil companies, such as Exxon and Shell, and chemical companies, such as Imperial Chemical Industries and Union Carbide, filed patents on the use of polymeric membranes to separate molecules present in organic solution [91].

From 1990s membranes for organic solvent nanofiltration has become commercially available. Koch Membrane Systems[92], USA was the first to bring the OSN membranes on the market. Their SelRO® MPF-60 and MPF-50 have been the most studied commercial membranes with other membranes not being freely available for a long time [60]. Both of them has been discontinued. Starmem® series, which are polyimide based membranes, then came on the market. It is a trademark of W.R. Grace-Davison Company, USA but then are supplied from Evonik Ind.[93], UK. SolSep BV [94], Netherlands produces nanofiltration membranes for applications in organic solvents. GKSS (renamed Helmholtz-Zentrum Geesthacht - Zentrum für Material- und Küstenforschung GmbH[95]), Germany produced PDMS membranes that are commercially available. DuraMem® and PuraMem® series from Evonik Ind. [93], UK are also commercial membranes that find high number of applications

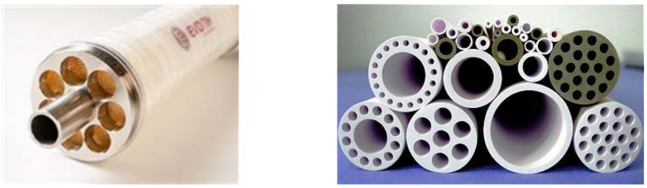

Figure 14. Examples of commercial polymeric (DuraMem® membrane, Evonik) [93] and ceramic (Inopor ®)[96] membranes

for OSN. They are polyimide based. Inopor® company[96], Germany offer a range of ceramic membranes generally with TiO_2 layer. Figure 14 gives examples of commercial polymeric and ceramic membranes available.

Only a few large scale applications of OSN exist. Mobil's MAX-DEWAX™ process installed at Beaumont refinery in 1998 is the largest with a design feed rate of 11500 m^3/day [97]. It is used for solvent recovery from the dewaxed oil filtrate stream. The stream runs through banks of membrane tubes that contain spiral-wound membrane modules. OSN applications in food industry, petrochemistry, catalysis, pharmaceutical manufacturing is reviewed in the paper of Vankelecom and coworkers [60].

Recently, OSN has also been investigated for homogeneous catalyst separation by companies at larger scales. Several patent applications were made by companies on the use of membranes for homogeneous catalyst separation e.g. DSM [98,99], Evonik [100,101], BASF [102]. With reliable membranes with long term resistance to wide range of organic solvents now being commercially available, the industrial applications of OSN is expected to increase fast in the near future. Currently many companies are working on this with selected examples detailed below.

One example of the application of this technique on industrial scale is given by Evonik [74] (Figure 15). In the test plant for OSN, they used as model the Rh-catalyzed hydroformylation of octene and dodecene [90]. The reaction was carried out in 5 L autoclave and then the reaction mixture was pumped over the flat sheet membrane of 80 cm^2 area. The Rh-ligand complex was retained and then concentrated. The catalyst concentrate was then pumped back to the reactor. Nanofiltration with CO blanketing enabled reduced clustering and precipitation of the catalyst. The commercial polyimide membranes used allowed catalyst retention of over 99 %.

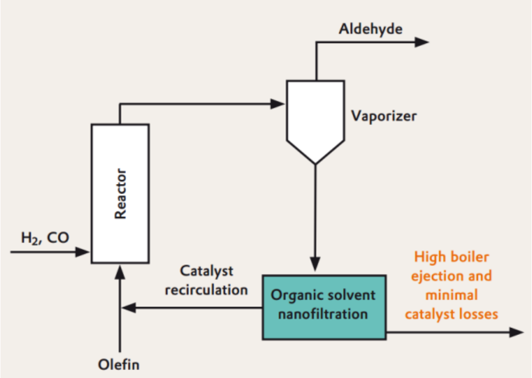

Figure 15. Continuous reaction integrated separation for hydroformylation of higher olefins by OSN (Reproduced from ref. 74)

Evonik has calculated energy savings for homogeneous catalyst recycling [103]. This can be applicable to recycling of homogeneous catalysts for metathesis, Suzuki coupling, palladium catalyzed cross-coupling, hydroformylation and telomerisation reactions. It is found that a switch to membrane process from a thermal separation results in 30% lower investment costs and 75% lower operational costs. This amounts to savings of over € 1 million per year.

Evonik has made a case study of catalyst recycle for catalytic hydrogenation reaction to produce a high-value compound [103]. The process is carried out in 5 m^3 batches containing 20 wt % reactant/product (MW=200 g/mol); 2 batches per day. Catalyst costs amount to € 50k per kg; S/C ratio 20,000. It is estimated that by achieving recycle of catalyst with OSN membranes savings over € 2 million per year in catalyst cost can be achieved.

VITO is coordinating a research project FunMem4Affinity financed by the Flemish IWT [104]. They use an innovative grafting method to produce functionalized ceramic membranes to achieve stability. The membranes can also be tailored to a specific separation based on solvent affinity. They functionalized commercially available 1 nm TiO_2 membranes with a series of alkyl groups in order to generate a more hydrophobic membrane surface [105]. With the increase in the hydrophobicity increase in retention was observed. Both the polar and non-polar solvents were able to be permeated. Also, compared to polymeric membranes, these membranes showed comparable performance and they do not suffer from swelling. In these experiments retention of polyethylene glycol mixture dissolved and polystyrene mixture in water was measured.

VITO tested these functionalized ceramic membranes to separate catalysts. They used readily available commercial catalysts without modification in a continuous flow reactor with in-line catalyst separation using OSN [57] (Figure 16). It was used for ring closing metathesis catalyzed by commercial Hoveyda-Grubbs and Umicore M series catalysts. Nanofiltration membranes of polymeric Duramem200, ceramic Inoper 0.9 nm TiO_2 and in-house surface modified 1 nm TiO_2 were used. They showed that the rejection mechanism of membranes is not only achieved by size but also solubility plays an important role by showing the difference in results obtained with the different solvents used. Moderate to high (40-95 %) catalyst retention was achieved but this is low compared to molecular weight enlarged catalysts. Authors argue that there is a compromise between the higher catalyst cost of the enlarged catalyst and their easier purification.

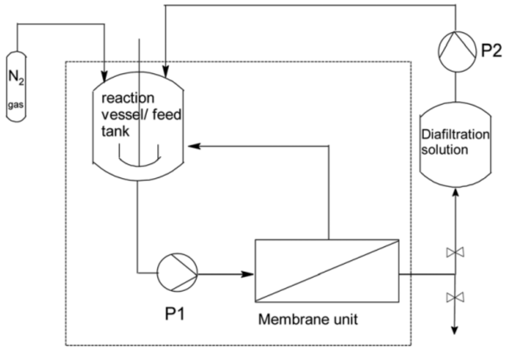

Figure 16. Continuous flow reactor with in-line catalyst separation using OSN for ring-closing metathesis reaction (Reproduced from ref. 57 with permission from The Royal Society of Chemistry)

VITO is also a partner in Chem21 project funded by EU Innovative Medicines Initiative [106]. The Chem21 project is working to evaluate the use of alternative organo-, bio- and base metal catalysts as well as more efficient processes and recovery recycle methods. VITO is working to achieve direct coupling of membrane filtration to chemical reactors to recover catalysts [107].

SP Process Development researchers have developed a palladium-based catalytic system for the Heck reaction where the catalyst can be easily separated and reused a number of times[108]. This is achieved by being able to control the oxidation state of the metal. In a catalytic process there are a series of steps. Depending on the step being fast or slow, stable or unstable intermediates will form with different oxidation state of the metal. SP Process Development researchers were able to tune the rate of the individual steps in the catalytic cycle so that the dominating catalyst is the stable Pd(II) complex. In this way at the end of the reaction the catalyst being in dormant form is easily separated and can be reused without any decrease in catalyst activity. Another advantage of this catalyst system is the catalysts tendency to deposit on the reactor walls is completely suppressed which is a common problem faced with palladium catalyzed reactions.

5. Conclusions

In chemical industry catalytic processes are of paramount importance. Homogeneous catalysis is of great interest with its high activity and selectivity. However, the separation of homogeneous catalysts from the product can be difficult. In industry, classical methods of homogeneous catalyst separation involves thermal or other costly processes. The most common method of distillation requires high energy and also can result in irreversible deactivation of the catalyst system. This has stimulated to look for entirely new processes as more gentle, low energy alternatives to separate/recycle homogeneous catalysts in continuous flow. Several methods have been developed most often at universities on a laboratory scale. However, in recent years there has been implementation in the industry as well. Overview of the methods and their application in lab and industrial scale is provided in this review. The examples provided for the separation methods include most used chemical transformations in industry such as hydroformylation, metathesis, hydrogenation, cross-coupling reactions. These are significant reactions used in bulk chemical, fine chemical and pharmaceutical production. Overall, all these methods have the advantage of ease of separation and low energy requirement compared to classical separation methods such as distillation.

Table 1. Overview of separation/recycling methods of homogeneous metal catalysts in continuous flow

Separation Methods	Advantages	Disadvantages
Heterogenization	o Catalyst is immobilized on support enabling easy reuse	o Lower catalytic activity o Significant problem of leaching in case of homogeneous mechanism o Catalyst deactivation due to deposition of impurities
Scavenging	o High efficiency o No loss of product o Especially advantageous for trace amount of metals	o Need for replacement of scavenging columns after saturation o Use of scavenging columns not suitable at larger scales
Use of Biphasic Conditions	o Phase containing the catalyst can be separated and recycled easily o Applicability at industrial scale	o The chemistry needs to be compatible with the biphasic reaction conditions o Systems with fluorous solvents, ionic liquids and supercritical fluids have high initial cost
Organic Solvent Nanofiltration	o Low energy separation o Catalyst retained enabling easy reuse o Applicability at industrial scale	o Catalysts need to be molecular weight enlarged to achieve high retention performance o Concentration polarization can occur for dead-end filtration

The methods described and the advantages and disadvantages of them are summarized in Table 1. One of the methods is heterogenization of homogeneous catalysts by immobilizing on a solid support. Due to problem of leaching, metal losses can occur. Because of the high catalyst cost this has an economic impact and this is the reason this method has no application at large scale. However, there are successful examples and commercialization in future can be possible. A homogeneous catalyst can also be immobilized in a stationary liquid. With the successful examples of SILP systems, there is potential for their application, especially since only small amount of costly ionic liquid is required. Homogeneous catalyst separation can also be achieved by scavenging which is typically done utilizing solid-supported scavenging resins packed into columns. They are very efficient in capturing very low amounts of metal in metals which is attractive for pharmaceutical production in small scale. As a kind of extension, recently use of scavenging agents in solution has been investigated which holds promise to be applied at large scale. Another method is the use of liquid/liquid biphasic systems which have several commercial applications at very large scale showing economic and environmental benefits. Biphasic systems can also be created with fluorous solvents, ionic liquids and supercritical carbon dioxide which have a number of successful applications on a lab-scale. They have not found commercial application so far, most likely due to their high cost. But with efficient processes, they can be recycled almost totally and with a long lifetime. Then their initial sales price becomes less significant. With the number of successful examples of their application increasing, it can be expected that their advantages will be exploited in industry especially in fine chemical production. Finally, there is the relatively new method of organic solvent nanofiltration. It has been studied in flow for a large range of reactions using also molecular weight enlarged catalysts to achieve better retention. There are currently few examples of its application by industry. The economic potential is seen to be very promising. With the ongoing development, more and better performing commercial membranes are becoming available. The industrial applications are thus expected to increase in the near future.

Acknowledgements

Funding by the Advanced European Research Council Grant "Novel Process Windows –Boosted Micro Process Technology" under grant agreement number 267443 is kindly acknowledged. T.N. would like to acknowledge the support of the Netherlands Organization for Scientific Research (NWO) for a VENI grant (12464). Authors would like to thank Johan Tinge from DSM for the information he provided regarding metal catalyst separation in industry.

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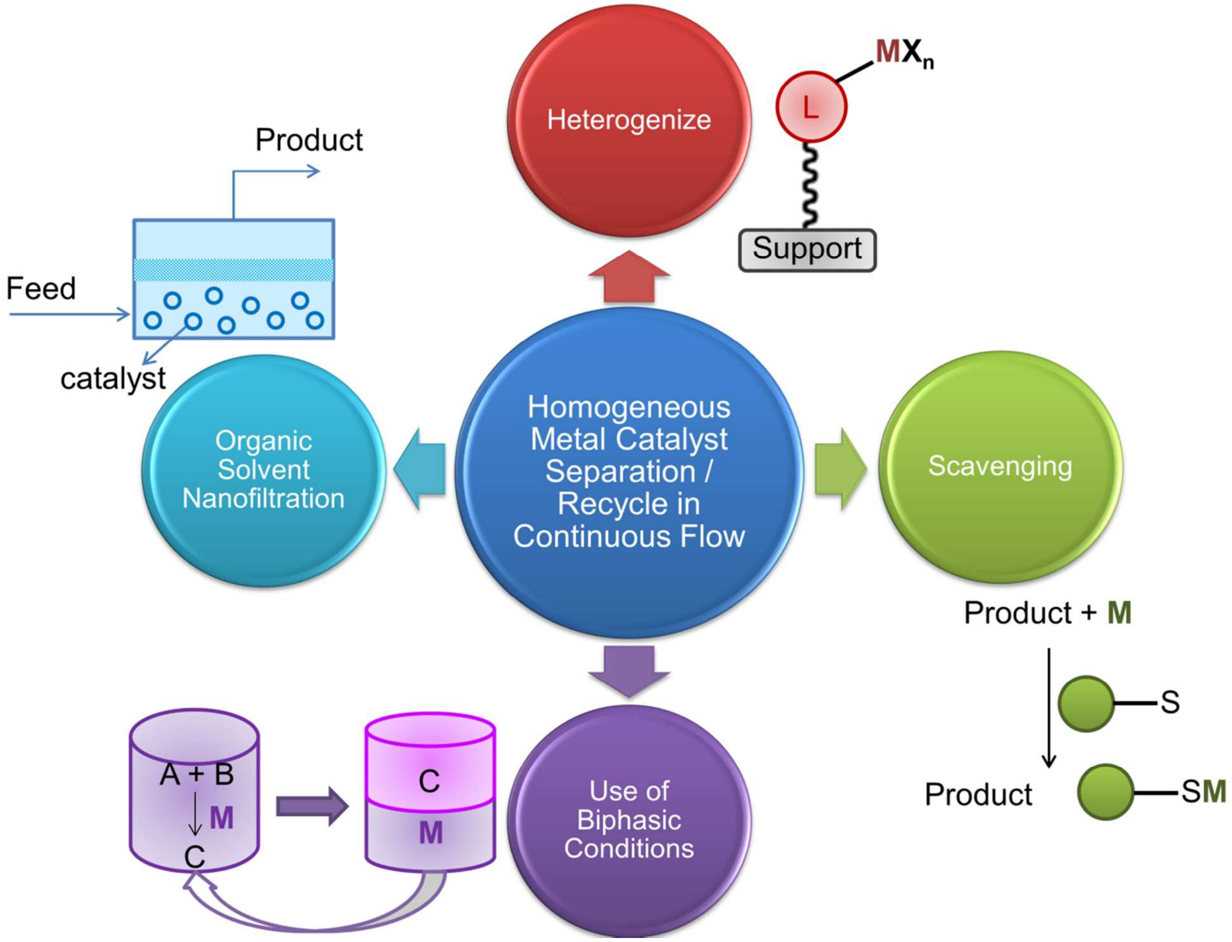
Table of Contents Entry



An overview on the separation/recycling methods of homogeneous transition metal catalysts in continuous flow on lab- and industrial scale is provided.