

Membrane-assisted catalysis in organic media

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Abstract

In the last decades, the rapid advancement of solvent-resistant membranes and catalysis led to the development of more efficient and sustainable materials and processes. The present article critically assesses membrane-assisted catalysis in organic media, which is a multidisciplinary field combining materials science, reaction engineering, organic chemistry, and membrane science and technology. The membranes act either as catalysts directly accelerating the rate of the reaction or as selective barriers for separating homogeneous catalysts from the reaction mixture. The discussions are grouped based on the catalyst type, and introductory tables given for each group allow direct comparison of the literature with regards to reaction type, solvent(s) employed, type of membrane, catalyst rejection, highest conversion and volumetric productivity. Major achievements, limitations and inconsistencies in the field are presented along with future research directions and requirements. Copyright © 2017 VBRI Press.

Keywords: Nanofiltration, catalysis, microfluidics, catalyst recovery, pharmaceuticals, biocatalysis, membrane reactors.

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1. Introduction

Despite the physicochemical basis of membrane processes had been laid in the 19th century, it was a long way until the first industrial applications (**Fig. 1**). The development of scalable membrane fabrication invented by Loeb and Sourirajan in the 1960s was an important step forward [1]. Soon after the new opportunities provided by membrane separations drew the attention of chemical industries, although, the early synthetic membranes suffered from

poor stability in organic solvents. Membranes stable in certain organic solvents followed soon after. In parallel, the revolution of homogeneous catalysis in the chemical synthesis began [2]. The higher selectivity and activity as well as the mild reaction conditions compared to heterogeneous catalysis opened up new possibilities. The first attempt to synergistically combine membrane separations and homogeneous catalysis in organic media was reported by Schurig *et al.* in 1975 [3–4]. However, insufficient catalyst rejection leading to low catalyst

recovery was recognised early as the drawback of membrane-assisted homogeneous catalysis.

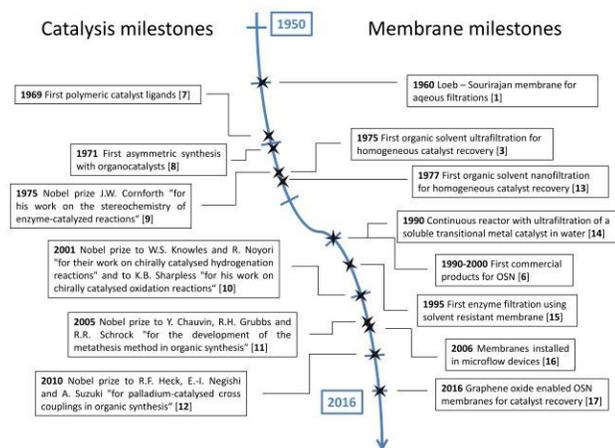


Fig. 1. Visualisation of the milestones and developments in the fields of catalysis and membranes over time.

Laborious catalyst enlargement via polymer anchoring was proposed to overcome this bottleneck but no significant breakthrough was achieved until the 1990s when the first commercial solvent-resistant nanofiltration membranes with relatively low molecular weight cut-off (MWCO) [5] values became available [6]. By 2000,

several organic solvent nanofiltration (OSN) membranes were available which boosted the research in this area. Since then membrane processes have been frequently studied for catalyst recycling. Novel materials and systems have been developed to deal with the growing expectations for processes. Nowadays, the clear majority of industrial synthetic processes are catalysed thanks to the research aimed to find new manners of catalysis. Applying membranes to recycle the catalysts is an attractive approach to sustainable synthesis. In the last decades, a plethora of materials and processes have been developed to synergistically combine membranes and catalysis in organic media, covering various disciplines from microfluidics to enzymes. The next sections will critically review these attempts grouped around the type of catalysts: metals, organic catalysts and enzymes.

Membrane-assisted catalytic reactors can be evaluated from many different approaches (**Fig. 2**). The type of catalyst, the system configuration, the membrane material, the number of phases, the role of the membrane and the catalyst lifetime, can all serve as a ground for categorisation. However, the catalyst is usually not free of choice, rather determined by the genre of the reaction needed to be accomplished. Consequently, the main sorting principle is the type of catalyst allowing direct comparison of the similar reactions and similar purposes. The other factors shown in **Fig. 2** are discussed

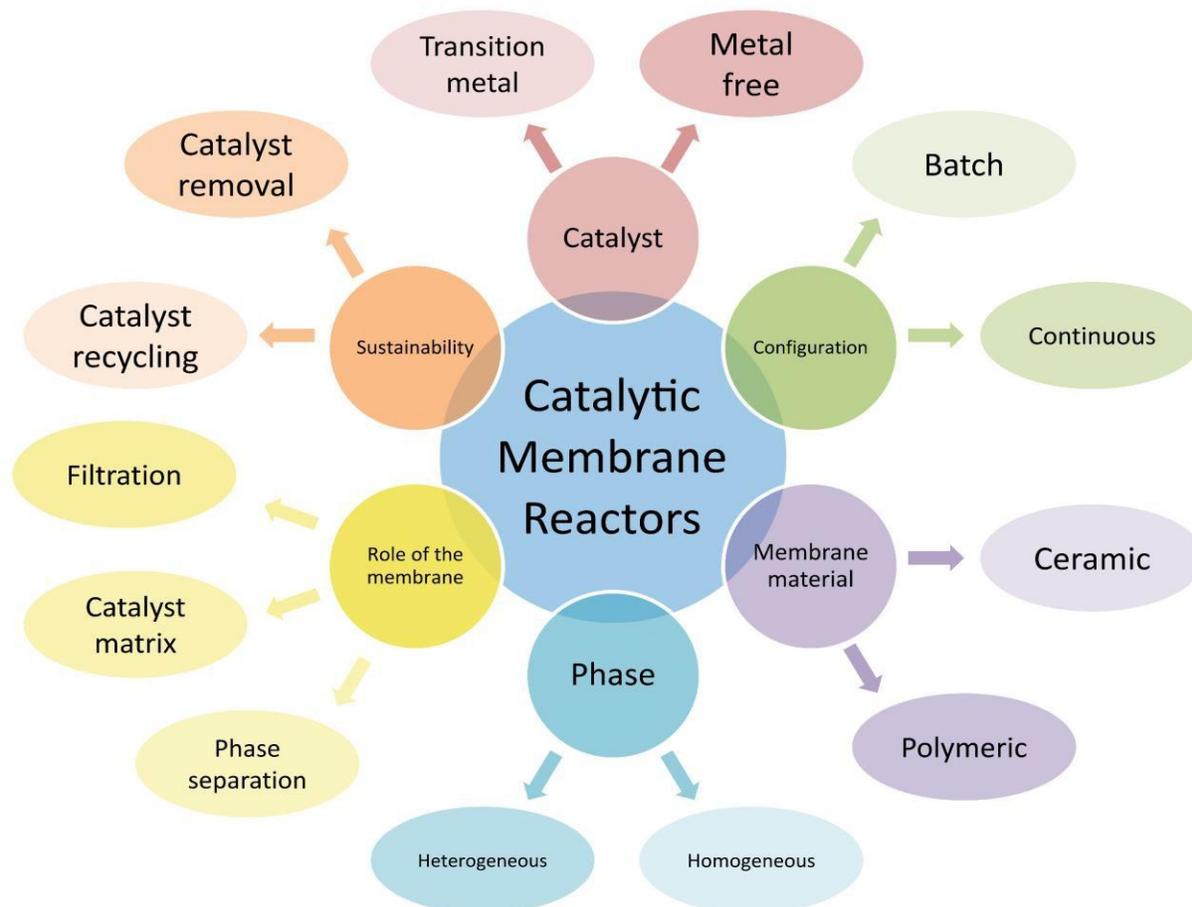


Fig. 2. Different aspects of catalytic membrane reactors in organic media. The various categories also imply that the design of membrane-assisted catalytic reactors requires multidisciplinary skills in organic chemistry, physical chemistry, process engineering and material science.

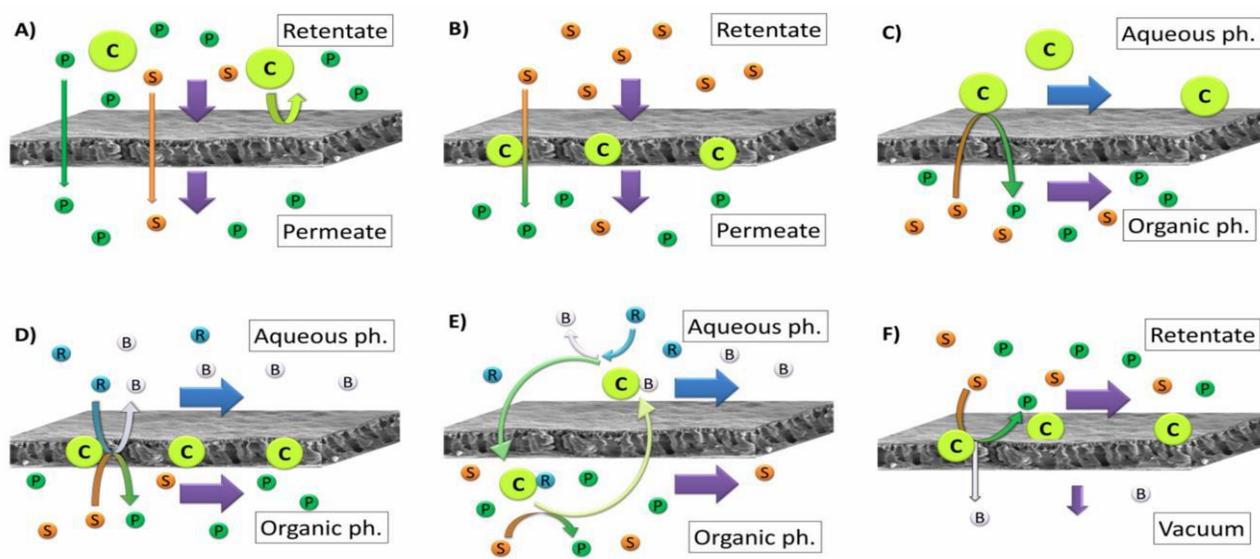


Fig. 3. Different scenarios for membranes applied in membrane-assisted synthesis; **A)** Filtration of the reaction mixture with homogeneous catalyst rejection; **B)** Flow through a catalyst containing membrane; **C)** Phase contact between an aqueous solution of the catalyst and organic solution of the substrates; **D)** Synthesis in a biphasic system separated by a catalytic membrane; **E)** Membrane-assisted phase transfer catalysis; **F)** Removal of the by-product water from an organic reaction by pervaporation. (S: substrate, P: product, C: catalysts, R: reactant, B: by-product; The bulky arrows represent the flows).

individually for each section of the review, and a short overview is given in the following paragraphs about general considerations.

1.1. Membranes for catalytic applications

The definition of membranes is ambiguous even in the scientific literature. The IUPAC Gold Book gives a rather general explanation: “structure, having lateral dimensions much greater than its thickness, through which transfer may occur under a variety of driving forces” [18]. According to this, any film or thin surface is a membrane as the mass transfer and selectivity is not strictly included in the definition. In this work the scope is narrowed down mainly on applications where the membrane was used as a selective barrier hindering the bulk flow but allowing the regulated transfer. The emphasis has been put mainly on ultra- and nanofiltration but other applications will be also mentioned to give an overview about possibilities in membranes in terms of catalytic synthesis. The different roles of the membrane in the membrane-assisted synthetic technologies is summarised in Fig. 3. The arrangement in Fig. 3A is by far the most common in the articles discussed in this review. The filtration of the reaction mixture through a membrane retaining the catalyst is a quite simple process and allows the use of commercial membranes and catalysts. The only requirement is the sufficient molecular weight difference of the catalyst and the product. The retentate containing the catalyst can be partially or completely reused in synthesis. The main drawbacks of this arrangement are the possible high product rejection or residual catalyst content. In contrast, the setup presented in Fig. 3(B) the catalyst contamination of the product can be decreased to zero practically as the catalytic species is incorporated in or bound to the membrane. The regular deactivation of the catalyst is a major limitation since it implies the replacing

of the special and valuable membrane. The process shown in Fig. 3(C) is usually applied in enzymatic reactors. The membrane acts as a phase contactor separating the enzyme containing aqueous phase and the substrate containing organic media. Processes shown in Fig. 3 (C-E) all prevent the risk of slow separation or emulsion formation which often occurs in biphasic reactions. However, the arrangement in Fig. 3(D) is mainly applied in microscale reactors containing membrane catalyst, while Fig. 3(E) shows a typical phase transfer catalytic reactor. Pervaporation coupled membrane reactors, shown by setup in Fig. 3(F), can be used to remove the water by-product from reactions such as esterification or oxidation.

Various membranes are applied in different system arrangement. The catalytic modification is always an in-house procedure resulting in greatly unique membranes. For their productions, mostly polymers are used due to their easy modifiability. The phase contactor membranes are usually of macroporous (pore size >50 nm) hydrophilic membranes, such as polytetrafluoroethylene (PTFE). This way the aqueous phase is prevented to enter the organic solvent, whilst a small overpressure in its side hinders the infiltration of the organic solvent. Ultra- and nanofiltration, as well as pervaporation membranes has been paid much attention in the recent years. Several industrial processes rely on them in the fields of water treatment, sterilisation, purification and separation. Still, there are many opportunities for utilising these membranes waiting for to be accomplished. These membranes can be divided into two major categories per their materials.

Polymeric starting materials offer easy processability and readily tuneable membrane characteristics. There is a big variety in polymeric materials available, moreover there has been many strategies established for further modification. Structurally, two types of polymeric

membranes can be distinguished (**Fig. 4**) [19]. Integrally skinned asymmetric (ISA) membranes are usually made by casting a layer of polymer solution onto a porous support. The polymer gets precipitated by the evaporation of the solvent or by immersing the formed film in a co-solvent (immersion precipitation). During this procedure, a skin layer on the top and a porous sublayer are simultaneously formed. The non-porous or microporous skin layer attributes to the actual performance of the

reaction mixture is transferred to a dead-end filtration unit. This arrangement is used the most frequently on a laboratory scale since it does not require expensive instrumentation and allows easy operation. However, continuous processes gained considerable attention in recent years and thus efforts have been made to develop continuous membrane reactors. The addition of the reagent and the permeate flow occurs at the same flow rate. Consequently, steady-state production is reached in a

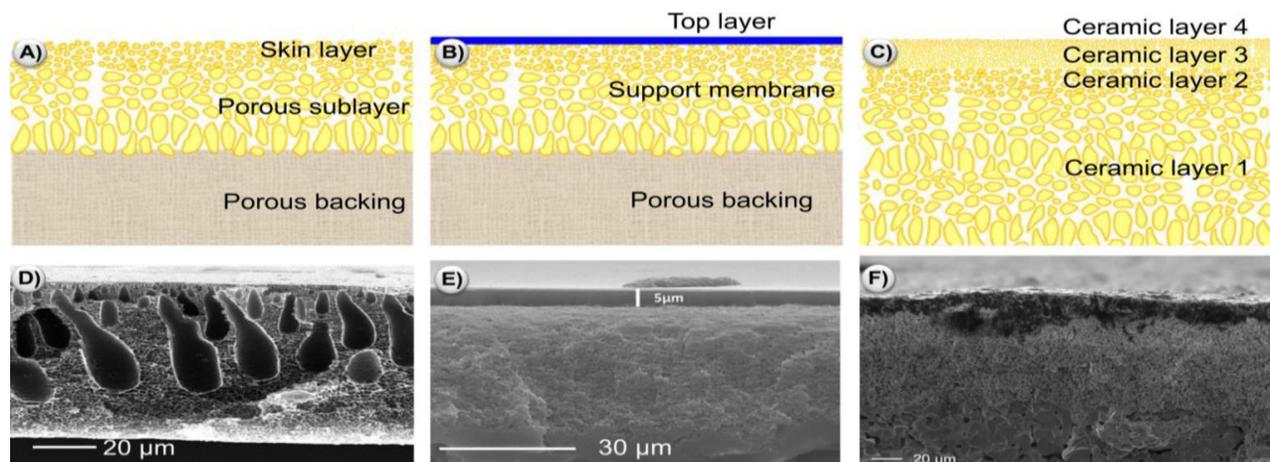


Fig. 4. Structures of different polymeric membranes for filtration purposes; Schematic illustration of **A**) an integrally skinned asymmetric (ISA) membrane; **B**) a thin film composite (TFC); **C**) ceramic membrane; Cross section SEM images of **D**) an ISA membrane; **E**) a TFC; **F**) a ceramic membrane [19–22].

membrane. Often a thin top layer of a different polymer is applied to improve the membrane separation. Thin film composites (TFCs) are usually produced by the coating and curing of an ISA membrane. Highly crosslinked thus very stable TFCs can be obtained by surface polymerisation. The recently developed plasma enhanced vapour deposition offers the production of a very thin (10–40 nm) but selective and durable top layer. One of the main problems with polymeric membranes is the flux decline appearing by aging and compaction of the membrane.

On the other hand, ceramic membranes have the advantage of superior mechanical, chemical and thermal stability [23]. They have high performance even at higher temperature, do not swell in organic solvents and are easy to clean. Ceramic membranes usually require lower pressures and they do not compact. However, they are more brittle and consequently they can be difficult to handle and scale up. Ceramic membranes usually consist of several layers with hierarchical pore sizes (**Fig. 4**). The active top layer evolves in a sol-gel coating process followed by calcination. The temperature of this step has a crucial effect on the final MWCO of the resulting membrane. The tightest commercially available ceramic membrane at the time is Inopor TiO₂ 0.9 nm and has a MWCO of 450 Da [24]. In contrast, commercial polymeric membranes with MWCO as low as 150 are available [25].

1.2. Process configurations

Many different process configurations have been explored when it comes to membrane-assisted reactors. The simplest setup is a batch reactor from which the post

relatively long time. Flow chemistry and flow reactors are gaining more and more interest.

In general, flow reactors are operating units in which the reaction mixture moves through channels or coils having diameters of about 0.01–5 mm in a plug-flow [26]. Another approach applies packed-bed reactors as flow reactors, where a column is filled with a solid reagent or catalyst. Among numerous advantages the most attractive ones are facile automation, reproducibility, safety and process reliability due to constant reaction parameters (efficient mixing, temperature, time, amount of reagents, and solvent) [27]. Since flow reactors operate in a continuous mode, they can be conveniently coupled with further unit operations such as membrane separations [28–29].

1.3. Description of catalytic membrane reactors

Due to the interdisciplinary nature of the field the authors report different parameters to describe process performance which hinders direct comparison of the literature. Hence, we have calculated volumetric productivity (P_V) for all the 60 articles on membrane reactors reported in this review, and they are presented in the introductory tables for each section. The P_V value does not describe the performance of the catalyst or the membrane but the efficiency of the reactor itself by showing the mass of product in grams produced in 1 liter reactor volume (V_r) in 1 hour (**Eq. 1**).

$$P_V = m_{\text{product}} \cdot V_r^{-1} \cdot t^{-1} \quad (\text{Eq. 1})$$

This means that processes which produce large amounts of product in a short time using small reactors have the highest productivity values. The volumetric productivity

they are used as heterogeneous catalysts in their metallic form. Nevertheless, homogeneous catalysis where compounds of metals are used have much more significance in chemical synthesis.

Transition metal ions have low energy unoccupied atomic orbitals therefore they can bind ligands to give coordination compounds, or complexes. This type of bond is known variously as coordination, dative covalent or donor-acceptor bond. Transition metals can have a number of ligands attached to them and ligands can be attached at more than one site. Their complexes may gain or lose ligands to change geometry. This affects their reactivity as complexes with various number of ligands or special arrangement have different affinity for the substrate. Consequently, ligands play a key role in the catalytic performance as well as stability.

Various sophisticated catalytic reactions using transitional metals have been developed. Among these reactions the C–C cross couplings are of special interest, as they could not be carried out efficiently (or sometimes at all) without transitional metal catalysis. Especially the late transition metals, such as palladium, platinum, ruthenium, and rhodium have been shown to be very useful in such reactions. **Scheme 1** summarizes some important named homogeneous transitional metal catalyst used in chemical synthesis. The catalysts are not shown in the order of their significance; the purpose is rather to give an insight in the diversity of catalysts and ligands. Some important ligands applied mostly for palladium are listed in **Scheme 2**.

Table 1. Cost of the most commonly employed transition metals in November 2016 [34–35].

Metal	MW (g·mol ⁻¹)	Price per mol (USD)
Zr	91.22	2.21
Mo	95.96	1.82
W	183.84	6.08
Mn	54.94	0.09
Fe	55.85	0.01
Co	58.93	1.92
Cu	63.55	0.29
Ru	101.07	136
Rh	102.91	2250
Pd	106.42	2160
Au	196.97	8160

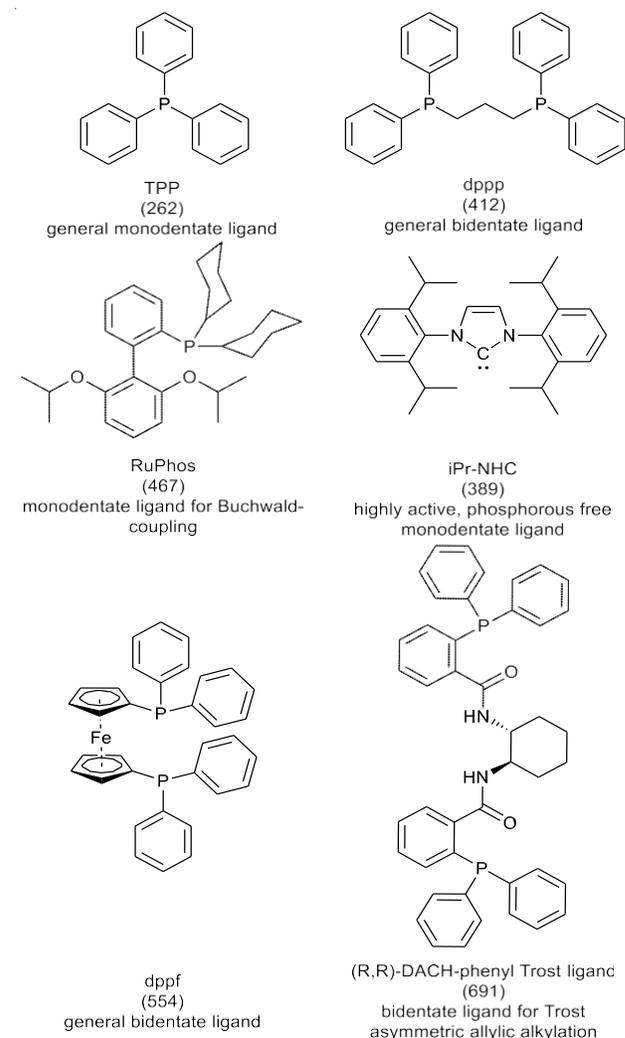
A burden for the up-scaled application of transition metals is their high price (**Table 1**). This is especially true for the catalytically important late metals which can be attributed to the fact that they are rare in the Earth's core [30]. In the recent years, significant effort has been made to replace palladium with cheaper metals like Ni, Ru or Cu [31–33].

Beside the high price another main disadvantage of transition metal catalysts is the possible toxicity [36–37]. A consequence of implementing transition metal catalysed process in production is indeed the need to purge residual metals from product especially the case for transformations used within the pharmaceutical industry. Due to the high costs and possible toxicity, for industrial application of transition metals in environmentally

friendly way, plenty of different methods for reusing and recycling are developed. For instance, the use of insoluble or water soluble ligands, different extractions, precipitation of the catalyst and chromatography was considered [38]. However, the efficient removal and recycling of the homogeneous transitional metal catalysts is still a major challenge. The application of membrane reactors is a possible technique to deal with this problem.

Earlier the laborious enlargement of the ligands was deemed to be essential for the effective use of membrane filtration for catalyst removal. Nevertheless, already in 1977, organic solvent nanofiltration was proved to be an efficient tool to remove off-the-shelf transitional metal catalysts from post reaction mixtures [13]. In this pioneering work palladium, rhodium, ruthenium and cobalt catalysts were tested and the metal content of the filtered product was decreased by roughly 90%. Nonetheless, in the following two decades little attention was paid to this field. Starting from around 2000, the interest has been growing in membrane-assisted processes mostly because of the increasing quality of membranes available.

In the following section of the review, the Pd, Rh, Ru and other transitional metal catalysed examples of membrane-assisted syntheses will be discussed.



Scheme 2. Different ligands and their application in palladium catalysed synthesis.

can be applied for both batch and continuous operation allowing direct comparison.

However, membrane reactors operating in reaction–filtration–refill mode, only the cumulated reaction times are taken into account for the calculation because the duration of shut-downs are seldom reported. Consequently, batch processes even with regular shut-downs can have high volumetric productivity values. Another limitation is that the calculation does not take in account the consumed catalyst, although processes with high consumption of a precious catalyst are unlikely to be efficient.

There are well known indicators of catalytic performance, such as the turnover number (TON) for durability or the turnover frequency (TOF) for activity. The TON indicates the moles of catalytic transformations per the moles of catalyst (Eq. 2), while the TOF is the time derivative of the TON, but usually calculated as an average in time (Eq. 3). Despite their obvious importance, these values are often not reported in the literature.

$$\text{TON} = n_{\text{product}} \cdot n_{\text{catalyst}}^{-1} \quad (\text{Eq. 2})$$

$$\text{TOF} = d\text{TON} \cdot (dt)^{-1} \approx \text{TON} \cdot t^{-1} \quad (\text{Eq. 3})$$

With regards to membrane performance, flux (J) indicates the volume of liquid in litres permeated through 1 square metre of membrane area (A) in 1 hour (Eq. 4), whilst permeability (P) is the flux divided by the

transmembrane pressure (TMP) (Eq. 5). The separation is usually described by rejection, also called retention which is calculated as the proportion of a solute concentration in the permeate and in the feed (Eq. 6).

$$J = V_{\text{permeate}} \cdot m^{-2} \cdot t^{-1} \quad (\text{Eq. 4})$$

$$P = F \cdot \text{TMP}^{-1} \quad (\text{Eq. 5})$$

$$R_x = C_{x,\text{permeate}} \cdot C_{x,\text{feed}}^{-1} \quad (\text{Eq. 6})$$

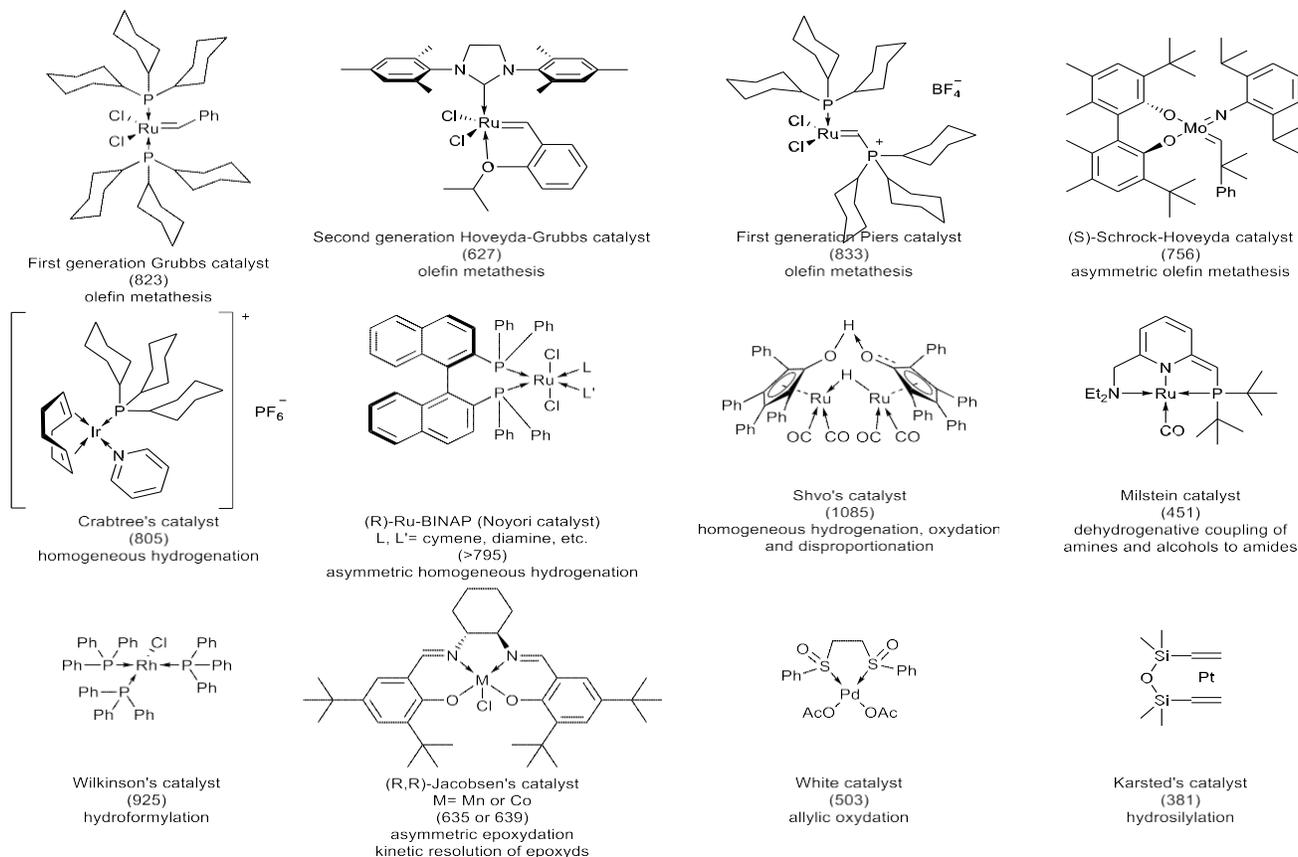
The reaction schemes in this review indicate the molecular weights in parenthesis (MW) under reactants, products and catalysts.

The rejection values for these solutes are given in brackets [R]. Although the reagent and product rejections are important parameters of a membrane procedure, they are not presented in many articles.

2. Applied catalysis

2.1. Transition metal catalysis

The transition elements comprise groups 3 to 12 and are found in the central region of the periodic table. The elements occur at that point in the periodic table where the d atomic orbitals are being filled. One obvious general feature of transition-metal chemistry is the occurrence of a number of characteristic oxidation states for a particular metal species. In general, these oxidation states can be readily interconverted which contributes to their catalytic activity. The largest demand for transition metal catalysts come from the oil and the automotive industry, where



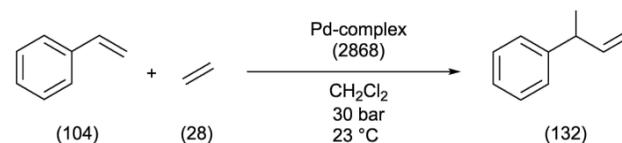
Scheme 1. Overview of the named transitional metal catalysts and their application fields. Molecular weights are indicated in parenthesis (MW: g·mol⁻¹).

2.1.1. Palladium catalysed reactions

Carbon-carbon bonds form the backbone of most of the organic molecules and consequently C-C bond formation is one of the key transformations in organic synthesis. In particular the role of Pd has become preponderant for several transition metal catalysed reactions since Pd allows reactions at low temperature, provides high turnover number, and can promote the couplings of a wide array of substrates with high tolerance to many functional groups. As palladium has been applied to various reactions, many different ligands have been developed. **Scheme 2** gives an insight to the variety of different Pd ligands.

About 22% of all reactions in the pharmaceutical industry are Pd-catalysed Heck, Suzuki and Sonogashira couplings of aryl halides to an olefin, arylboronic acid or an alkyne, respectively [39–40]. The most effective cross-coupling catalysts are supported by strongly electron-donating and sterically bulky phosphine or N-heterocyclic carbene (NHC) ancillary ligands [41]. The enhanced reactivity of these ligands is attributed to the formation of highly reactive monoligated Pd(0) species [42]. Despite the remarkable options provided by Pd-complexes, separation of these catalysts from the reaction products and solvents is often cumbersome, requiring the use of

energy intensive and waste-generating downstream processing [43]. Moreover, few if any of the industrially employed separations are aimed at recovering the catalyst in an active form. Instead, they focus on obtaining a pure (metal-free) product stream by removing any residual catalyst and catalyst decomposition fragments due to the strict guidelines on transition metal contamination of active pharmaceutical ingredient (API) set by the regulatory authorities such as U.S. Drug & Food Administration (FDA) and European Medicines Agency (EMA).



Scheme 3. Continuous hydrovinylation of styrene (1.8 M, 1.0 equiv.) with ethylene (10 M, 5.56 equiv.) catalysed by a dendrimeric Pd-complex (1.4%) in dichloromethane at 23 °C [45].

For instance, the EMA requires the residual Pd concentration of a drug product to be less than 10 ppm [44]. Hybrid materials and processes combining catalysis with membrane separations seem promising to overcome the recycling and purification drawbacks of transition

Table 2. Comparison of different process configurations applying palladium catalyst published in literature in terms of reaction type, solvent(s) employed for reaction and filtration, type of membrane, catalyst rejection (%), highest conversion (%) and volumetric productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$).

Reference	Reaction	Solvent	Membrane	Catalyst rejection (%)	Highest Conversion (%)	Productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$)
Parshall <i>et al.</i> [13]	alkoxylation	benzene	polyimide	96	n.d.	n.d.
Vogt <i>et al.</i> [45]	hydro-vinylation	CH ₂ Cl ₂	PDMS (MPF-60)	n.d.	7.6	2.26
Livingston <i>et al.</i> [46]	Heck coupling	EtOAc, MTBE, THF	polyimide	90, 96, 97	100	53.8
Livingston <i>et al.</i> [47]	Heck coupling	EtOAc-Hexane	Starmem 122	90	100	53.8
Livingston <i>et al.</i> [48]	Heck coupling	MeCN, THF/H ₂ O	Starmem 122, MPF-60	92–96	100	1.80
Plenio <i>et al.</i> [49]	Sonogashira-, Suzuki-, Heck coupling	toluene, NMP	PDMS	>99.95	98	3.0–8.4,
					99	0.6–18.9,
					87	0.2
Livingston <i>et al.</i> [50]	Suzuki coupling	EtOAc, IL	Starmem 122	>99.95	80	38.8–47.0
Uozumi <i>et al.</i> [16,51]	Suzuki coupling	EtOAc:IPA 2:5 / H ₂ O	poly(acrylamide)-triarylphosphine	n/a ^a	100	318–484
Uozumi <i>et al.</i> [52]	Suzuki coupling	IPA / H ₂ O	poly(acrylamide)-triarylphosphine	n/a ^a	99	2030–2220
Dong <i>et al.</i> [53]	Heck coupling	DMF, H ₂ O	PVA-PAM	n/a ^a	92, 96	13.7
Uozumi <i>et al.</i> [54]	hydro-dehalogenation	IPA, H ₂ O	polyvinyl-pyridine	n/a ^a	99	154–573
Bjorsvik <i>et al.</i> [55]	Heck coupling	THF, acetone ^b	Duramem 150, 200, 300	100	67	596
Livingston <i>et al.</i> [56]	Heck coupling	DMF	PEEK	90	98	19.1
Livingston <i>et al.</i> [57]	Heck coupling	DMF	PBI, PI, PEEK, Duramem 300	93	100	0.2–0.5
Ormerod <i>et al.</i> [29]	Suzuki coupling	EtOH, IPA	Inopor TiO ₂	99	92	9.0–23.5

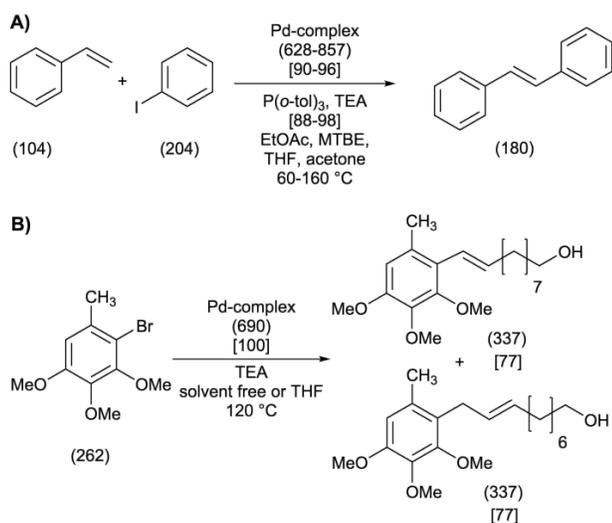
^a Supported catalyst; ^b Reaction solvent: THF, filtration solvent: acetone
^{n.d.} not determined; ^{n/a} not applicable

metal catalysis. The very first results applying homogeneous catalytic reactions combined with membrane separation in organic solvents were reported by Parshall *et al.* in 1977 (Table 2) [13]. They used polyimide membranes in order to remove Pd from the post reaction mixture after the carboethoxylation of 1-pentene catalysed by dichlorobis(tri-*p*-tolylphosphine) palladium under 100 bar carbon monoxide in benzene. The permeate contained 4% of the original amount of palladium.

The first continuous membrane assisted catalytic process was reported by Vogt *et al.* in 1999 for the hydrovinylation of styrene (Scheme 3) [45]. During the continuous operation (up to 80 h), an initial activation phase of about 9 hours was observed before the system reached its maximum productivity of $2.26 \text{ g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$.

The need for activation can be attributed to the fact that some of the transition metal catalysts are in fact pre-catalysts enabling easy storage, which convert to the active catalysts *in situ* in the reaction mixture. For instance, Wilkinson's catalyst $\text{RhCl}(\text{PPh}_3)_3$ (see Scheme 1) loses one PPh_3 ligand before entering the catalytic cycle. After the appearance of commercial solvent-resistant nanofiltration membranes the first step was exploring the rejection of palladium, rhodium and manganese containing homogeneous organometallic catalysts without performing any model reaction [58].

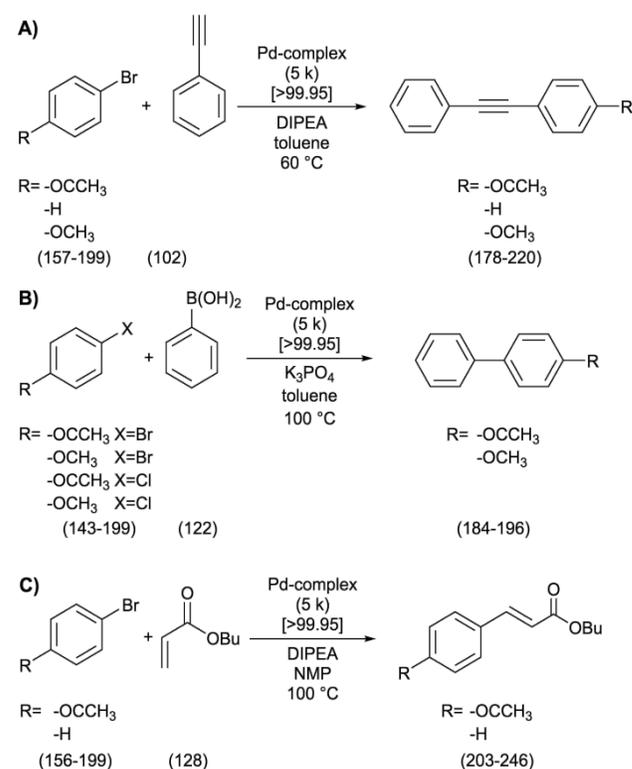
Pioneering work in the field of nanofiltration-coupled palladium catalysis was done by Livingston *et al.* at the turn of the century. In three subsequent publications, a Heck catalyst recycle and reuse by means of organic solvent nanofiltration (OSN) was demonstrated in various solvents (Scheme 4. A-B) [46–48].



Scheme 4. Heck coupling reactions of **A)** styrene (0.72–0.75 M, 1 equiv.) and iodobenzene (0.9 M, 1.2 equiv.) forming *trans*-stilbene catalysed by $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$ (0.04%) [46], Pd-imidazoline (0.01%) [47] or $\text{Pd}(\text{OAc})_2(\text{PPh}_4)^+\text{Br}^-$ (0.01%) [48] in the presence of trimethylamine base (0.72–0.75 M, 1 equiv.) and catalyst stabilising agent (0.009 M 0.012 equiv.) in various solvents at 60 °C; **B)** (1.32 M, 1.0 equiv.) and 9-decen-1-ol (2.15 M, 1.63 equiv.) catalysed by $\text{Pd}(\text{OAc})_2$ (2.61%) in the presence of triphenylphosphine ligand (0.13 M, 0.1 equiv.) and trimethylamine base (2.64 M, 2 equiv.) in THF at 120 °C [55].

The model system comprised of styrene and iodobenzene forming *trans*-stilbene at 60 °C in ethyl

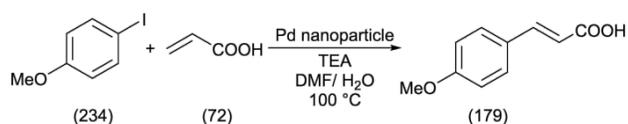
acetate, MTBE and THF. Although the catalyst rejection values of 88–98% were relatively low, this new technique demonstrated potential for general applicability to homogeneously catalysed organic syntheses with productivity as high as $53.8 \text{ g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$. These studies used in-house fabricated polyimide based membranes, and the first commercial membranes for OSN applications, namely MPF®-60 polydimethylsiloxane (PDMS) coated polyacrylonitrile (PAN) membrane from Koch Industries Inc. and Starmem® 122 polyimide based membrane from W. R. Grace & Co. Further studies on OSN assisted Heck coupling reactions already used the next generation of OSN membranes from the Duramem® series which are based on polyimide and distributed by Evonik Industries AG [25, 55]. These studies employed large catalysts having molecular weights of $690 \text{ g} \cdot \text{mol}^{-1}$ to be retained by the membrane whilst the products are isolated via purging them through the membrane using acetone.



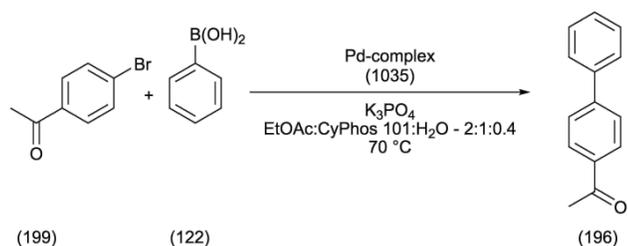
Scheme 5. Soluble polymer-supported palladium catalysis of aryl halides: **A)** Sonogashira coupling of aryl bromides (0.1 M, 1 equiv.) with acetylenes (0.15 M, 1.5 equiv.) catalysed by $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ (1%), polymeric phosphine ligand (2 L/Pd) (1%) and CuI (1.5%) in the presence of diisopropylamine base (0.35 M, 3.5 equiv.); **B)** Suzuki coupling of aryl bromides or chlorides (0.1 M, 1 equiv.) and boronic acid (0.15 M, 1.5 equiv.) catalysed by $\text{Pd}(\text{OAc})_2$ (0.5%), polymeric phosphine ligand (2 L/Pd) (1%) in the presence of potassium phosphate base (0.2 M, 2 equiv.); **C)** Heck coupling of aryl bromides (0.75 M, 1 equiv.) with *n*-butyl acrylate (0.9 M, 1.2 equiv.) catalysed by $\text{Pd}(\text{dba})_2$ (0.5%), polymeric phosphine ligand (2 L/Pd) (1%) in the presence of diisopropylamine base (1.42 M, 1.9 equiv.) [49].

Insufficient rejection and low stability of transition metal catalysts reflected in fragmentation and charge losses were reported as main drawbacks of OSN-coupled catalytic systems. In order to improve the rejection of the catalysts Datta *et al.* developed soluble polymer-supported palladium catalysts for Heck, Sonogashira, and

Suzuki coupling of aryl halides (**Scheme 5**) [49]. By increasing the catalyst's molecular weight to about $5,000 \text{ g}\cdot\text{mol}^{-1}$ virtually quantitative rejection was achieved in toluene using a PDMS membrane. An alternative methodology to address the challenge of insufficient catalyst rejection is the encapsulation of catalytic nanoparticles in the membrane material. A Heck reaction catalyst composed of hydrophilic interpenetrating polymer networks (IPNs) and colloidal palladium nanoparticles were prepared by simultaneous crosslinking of polyvinyl alcohol and polyacrylamide [53]. The nanopores of the IPNs were designed to be one order of magnitude smaller than the average size (33 nm) of the uniformly dispersed catalytic nanoparticles in order to prevent their aggregation and loss. The Heck coupling reaction of aryl halides and alkenes (**Scheme 6**) was carried out in water and DMF achieving yields and TOFs as high as 96% and 321, respectively. In this application the membrane was used only as a matrix for the heterogeneous catalyst; no filtration or flow through the membrane occurred. Nonetheless, the study can be a starting point for further catalytic membrane development.



Scheme 6. Heck coupling of 4-iodoanisole (0.25 M, 1 equiv.) and acrylic acid (0.75 M, 3 equiv.) catalysed by encaged Pd (0.03%) nanoparticles in interpenetrating PVA/PAM polymer networks (IPN) in a presence of TEA base (1.0 M, 4 equiv.) in DMF at $100 \text{ }^\circ\text{C}$ [53].



Scheme 7. Suzuki reaction of 4-bromoacetophenone (0.28 M, 1 equiv.) and phenylboronic acid (0.31 M, 1.1 equiv.) catalysed by Pd(dba)₂ (5%) in the presence of triphenylphosphine (0.14 M, 0.5 equiv.) and potassium phosphate base (0.91 M, 3.3 equiv.) in a solvent mixture of EtOAc, CyPhos[®]101 ionic liquid and water 2:1:0.4 at $70 \text{ }^\circ\text{C}$ [50].

Ionic liquids have been recognized as environmental benign alternative to volatile organic solvents, and consequently, they are often referred to as green solvents [59]. Ionic liquids can have positive effects on catalytic stability through the reduction of palladium black formation and thus ensuring high reaction yields over consecutive recycles. Although challenging, the post-reaction separation of ionic liquids, catalysts and products can be addressed by membrane technology. A Suzuki post-reaction stream of the 4-acetyl-biphenyl product in 50:50 wt% ethyl acetate and trihexyl(tetradecyl)phosphonium chloride (CyPhos[®]101) ionic liquid solvent mixture was successfully separated using Starmem[®] 122 membrane (**Scheme 7**) [50]. Due to the small, $196 \text{ g}\cdot\text{mol}^{-1}$ molecular weight, the product was recovered in the nanofiltration permeate, whilst the

$519 \text{ g}\cdot\text{mol}^{-1}$ ionic liquid and the $1035 \text{ g}\cdot\text{mol}^{-1}$ palladium catalyst were retained by the membrane, and recycled into subsequent consecutive reactions.

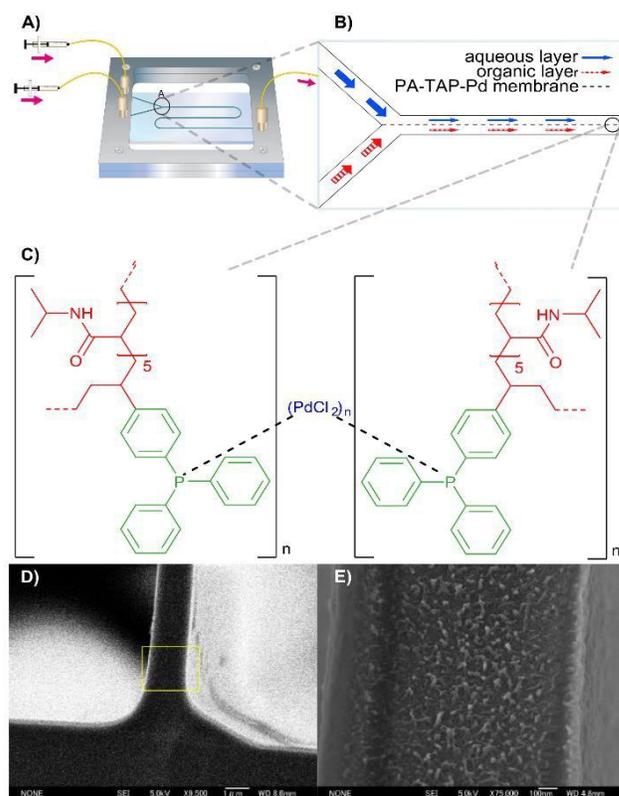
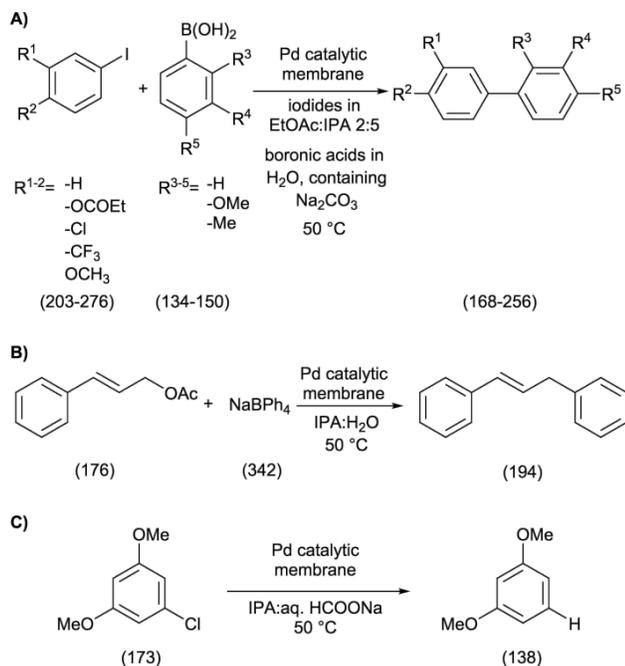


Fig. 5. A) Schematic of a microreactor setup; B) Flow courses around the Pd-crosslinked poly(acrylamide)-triarylphosphine (PA-TAP-Pd) “ship-in-a-bottle” membrane; C) Chemical structure of the PA-TAP-Pd catalytic membrane; SEM images of the membrane at the interface of the aqueous and organic media at D) magnification of $\times 9,500$; E) magnification of $\times 75,000$. Figure adapted with permission from ref. [16]. Copyright 2006 American Chemical Society.

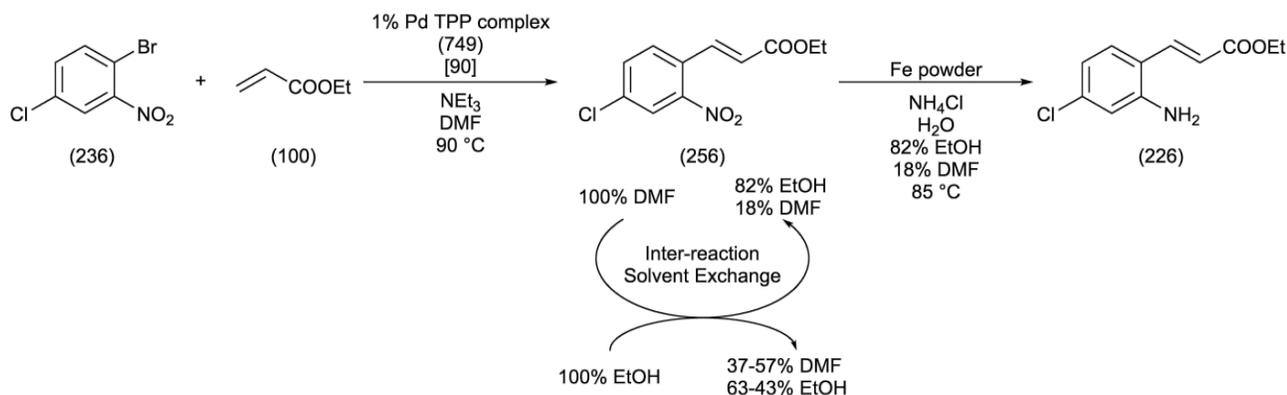
The best performance was observed for the CyPhos1101 system. Additional investigations employing this ionic liquid showed that the reaction–recycle process can be successfully performed at lower catalyst–substrate ratios, leading to higher TON. The miniaturisation of chemical reactors provides various fundamental and practical advantages to the fine chemicals industry such as safety, controllability, high productivity and sustainability [60]. Due to the small reactor volume and short residence times, significantly higher productivities can be achieved compared to batch operation in stirred tank reactors (**Table 2**). Combination of microreactor and membrane technology can result in improved catalytic reactions. In the centre of a microchannel poly(acrylamide) was modified with triarylphosphine ligand followed by palladium-crosslinking which resulted in the formation of a catalytic palladium-complex membrane (**Fig. 5**) [16]. The aryl iodide and arylboronic acid reactants were loaded onto the opposite sides and throughout the microchannel they are in contact with the vast interfacial surface of the catalytic membrane from both front and back sides, thereby realizing an instantaneous chemical reaction (**Scheme 8. A-B**). Catalytic membrane microreactors were also developed for

hydrodehalogenation of aryl halide substrates in IPA/EtOAc mixtures loaded on one side of the membrane and aqueous HCO_2Na in the opposite side (**Scheme 8. C**) [54]. Residence times as low as 2 seconds at 50–90 °C quantitatively afforded the corresponding hydrodehalogenated products.



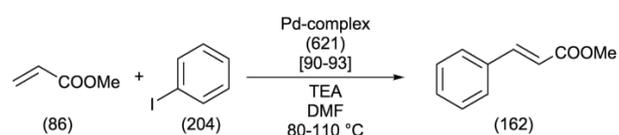
Scheme 8. Carbon-carbon coupling reactions in microchannel devices equipped with palladium containing poly(acrylamide)-triarylphosphine based catalysts: **A)** Suzuki reactions of aryl iodides (6.3 mM, 1 equiv.) in EtOAc/IPA (2:5) (flow rate: 2.5 $\mu\text{L}\cdot\text{min}^{-1}$) and arylboronic acids (9.4 mM, 1.5 equiv.) in 18.3 mM aqueous Na_2CO_3 (flow rate: 5.0 $\mu\text{L}\cdot\text{min}^{-1}$); [16], **B)** allylic arylation of cinnamyl acetate (5.8 mM, 1 equiv.) in IPA by sodium tetraphenylborate (58 mM, 1 equiv.) in water (flow rate: 6 $\mu\text{L}\cdot\text{min}^{-1}$); [52] **C)** hydrodehalogenation of 1-chloro-3,5-dimethoxybenzene (5.0 mM, 1 equiv.) in IPA with HCO_2Na in saturated aqueous solution (flow rate of both solutions: 5.0 $\mu\text{L}\cdot\text{min}^{-1}$) [54].

Apart from the miniaturisation of chemical reactors, continuous processing can in general offer many ways to turn synthesis into a more sustainable practice with regards to reproducibility, scalability, safety, efficiency and productivity [61]. Peeva *et al.* demonstrated the long-term feasibility of OSN-assisted catalytic reactions at high temperatures in aggressive solvents through a continuous



Scheme 10. Heck coupling of 1-bromo-4-chloro-2-nitrobenzene (0.1 M, 1.0 equiv.) and ethyl acrylate (1 M, 10 equiv.) catalysed by $\text{Pd}(\text{OAc})_2$ (1%) in the presence of triphenylphosphine ligand (0.002 M, 0.02 equiv.) and TEA base (0.14 M, 1.4 equiv.) [62].

Heck coupling reaction performed in 1 M triethyl amine in DMF at 80 °C (**Scheme 9**) [57]. The in-house fabricated 3-aminopropyltriethoxysilane (APTS) cross-linked polyimide, polybenzimidazole and polyether ether ketone based membranes were screened and the latter one was selected for the continuous process due to its superior performance with regards to stability and catalyst rejection. The process achieved stable performance for over a month at 85% conversion rates and 20 times higher product purity than in the conventional batch process utilising the same catalyst loading. The achieved TON for the catalyst was about 1772. Using the same model system two reactor configurations were further investigated: a continuous single stirred tank reactor/membrane separator (*m*-CSTR) and a plug flow reactor (PFR) coupled with *m*-CSTR (PFR-*m*-CSTR) [56]. The latter configuration demonstrated the highest potential with 98% conversion and TONs of about 20k.

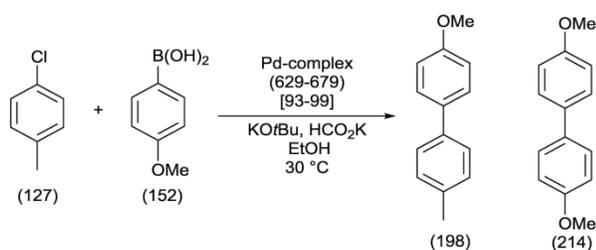


Scheme 9. Heck coupling of iodobenzene (0.6 M, 1.0 equiv.) and methyl acrylate (1 M, 1.67 equiv.) catalysed by $\text{Pd}(\text{OAc})_2$ (0.033% or 1%) in the presence of 1,3-bis(diphenylphosphino)propane (dppp) ligand ($3.88\cdot 10^{-4}$ M, $6.45\cdot 10^{-4}$ equiv. or 0.012 M, 0.02 equiv.) and TEA base (1.3 M, 2.2 equiv.) [56–57].

Two consecutive reactions in the total-synthesis of cyclooxygenase 2 (COX-2) inhibitor are performed in a hybrid process combining catalyst separation and inter-reaction solvent exchange from DMF to ethanol in a continuous process (**Scheme 10**) [62]. Firstly, a Heck coupling reaction is performed in DMF in a continuous membrane reactor employing Duramem® 150 nanofiltration membrane which retains the palladium catalyst. A 10-hour long residence time resulted in 95% conversion with 1880 mg palladium contamination per kilogram product. The solvent exchange in a counter-current membrane system allowed the 100% DMF to be replaced by 82% ethanol at a cost of 1% API loss. The ethanol solution passed through a column packed with iron powder to catalyse the reduction of an aromatic nitro group to aniline with a yield greater than 99%.

Besides the PFR-*m*-CSTR configurations, the coupling

of continuous flow coil reactors with membrane separation can also be found in the literature. Ormerod *et al.* developed a membrane process for the separation of NHC complexes of palladium catalysts from reaction mixtures using highly stable ceramic membranes [29]. Titanium dioxide based membranes with MWCO in the range of 450–1500 were screened. Besides the conventional batch reactions, the membrane separation was also coupled with a continuous flow reactor featuring a coil up to 30 meters. Online, at-line, and off-line methodologies were rigorously compared and contrasted. The model reaction selected for the comparison of different processing methodologies was the Suzuki cross-coupling of 4-chlorotoluene and (*p*-methoxyphenyl)boronic acid (Scheme 11). The organic solvent nanofiltration process resulted in ultra- low palladium contamination of reaction products (<10 ppm palladium in the permeate stream) corresponding to about 99.9% catalyst recovery in the retentate stream.



Scheme 11. Online Suzuki coupling of 4-chlorotoluene (0.067 M, 1.0 equiv.) and (*p*-methoxyphenyl)boronic acid (0.073 M, 1.1 equiv.) catalysed by Pd(OAc)₂ (0.5%) in the presence of potassium formate (0.033 M, 0.5 equiv.) and potassium *tert*-butoxide base (0.087 M, 1.3 equiv.) [29].

2.1.2. Rhodium catalysed reactions

Hydrogen is considered to be the greenest reducing agent and hydrogenation is one of the most frequently used

reactions both on laboratory and industrial scale. A wide range of functional groups can readily undergo hydrogenation. Usually high yields can be obtained even under mild conditions in liquid phase, and high selectivity can be achieved by the adequate selection of the catalyst and the reaction parameters [63]. In most processes, heterogeneous catalysts (such as palladium on activated carbon, or Raney-nickel) are used as the catalyst can be separated by a simple filtration after the reaction. However, homogeneously catalysed hydrogenations offer higher chemo- and stereoselectivity [64]. The organic complexes of platinum group metals, mostly rhodium, ruthenium, iridium and palladium are applied in homogeneous hydrogenations. The growing interest for stereoselective hydrogenation procedures is also demonstrated through the 2001 Nobel Prize in Chemistry awarded to W. S. Knowles and R. Noyori for enantioselective hydrogenations [10].

Hydroformylation, also known as “oxo process” or “Roelen reaction” is the metal catalysed addition of hydrogen and carbon monoxide on 1-alkenes forming the corresponding homologous aldehydes. Since the discovery of hydroformylation by Roelen in 1938 [65], this reaction has become one of the major industrial homogeneously catalysed reactions. In particular, hydroformylation is a valuable reaction in organic chemistry because (i) the resulting aldehydes are highly versatile chemical intermediates, (ii) uses readily available syngas as the primary reagent, (iii) tolerant of many functional groups, i.e. chemoselective, and (iv) atom efficient [66]. Due to the mechanism of the reaction, two isomeric aldehydes can be produced as the new C–C bond can be formed between the CO and either the first or second carbon of the alkene. Linear aldehydes are industrially more sought-after than branched aldehydes. Therefore, hydroformylation processes aim to obtain high linear/branched ratio (*l/b*) resulting in lower separation

Table 3. Comparison of different process configurations applying rhodium catalyst published in literature in terms of reaction type, solvent(s) employed, type of membrane, catalyst rejection (%), highest conversion (%) and volumetric productivity ($g_{\text{product}} \cdot L^{-1} \cdot h^{-1}$).

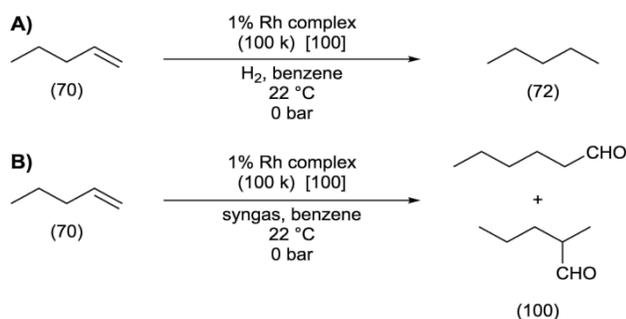
Reference	Reaction	Solvent	Membrane	Catalyst retention (%)	Highest Conversion (%)	Productivity ($g_{\text{product}} \cdot L^{-1} \cdot h^{-1}$)
Schurig <i>et al.</i> [3–4]	hydrogenation, hydroformylation	benzene	polyamid (MWCO: 10,000)	100	100	0.157 (hydrogenation), 0.436 (hydroformylation)
Parshall <i>et al.</i> [13]	hydrogenation, hydroformylation	neat, benzene	self-made polyimide	69–92	100	n.d.
Vankelecom <i>et al.</i> [71]	asymmetric hydrogenation	MeOH	MPF-60	97	100	4.21
van den Broeke <i>et al.</i> [72]	hydrogenation	scCO ₂	tubular microporous (0.5–0.8 nm) silica	>99.9	100 (batch), 40 (continuous)	5.45 (batch), 2.18 (continuous)
Vogt <i>et al.</i> [73]	hydroformylation	toluene	Inopor ceramics (MWCO: 450)	99.96	99	13.8
Subramaniam <i>et al.</i> [74]	hydroformylation	toluene	Starmem 120, 122, 240 GMT-oNF-2	94–99.9	50	19.5
Vorholt <i>et al.</i> [67,75]	hydroformylation	toluene	PDMS (MWCO: 400–450)	66–98	80	23.7

^{n.d.}not determined

costs, and subsequently higher profit. Application of bulky, bidentate ligands is a frequently developed technique to gain high l/b ratio [67]. Nowadays, two distinct types of catalysts are applied in hydroformylations. First, the gaseous phase cobalt carbonyl catalyst offer high activity with medium selectivity and is readily removable from the reaction mixture. However, it requires high temperature (120–170 °C) and pressure (200–300 bar) [68]. Second, the rhodium containing Wilkinson's catalyst [69]. (see Scheme 1) exhibit lower activity in favour of high selectivity under mild conditions requiring temperatures of 25–80 °C and pressures of 1–50 bar [68,70].

Both homogeneous hydrogenation and hydroformylation feature high selectivity under mild conditions, which are very attractive from an industrial point of view. However, both processes suffer from the difficult catalyst removal and recycling which is a major obstacle to economic production, regarding the high price of rhodium (or other noble metal) applied. The different membrane applications discussed in this section can tackle this problem and facilitate the expansion of these rhodium catalysed processes in the chemical industry (Table 3).

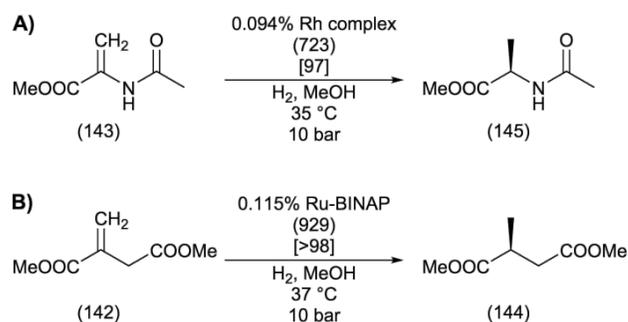
The idea of developing soluble polymer-supported rhodium based catalysts for hydrogenation and hydroformylation dates back to the mid-1970s. Soluble, linear polystyrenes, polyethylene glycols, polyvinylpyrrolidones and polyvinyl chlorides with average molecular weights of about 100k g·mol⁻¹ were used as catalyst carriers in early experiments [3–4]. 1-Pentene was either reduced to pentane using hydrogen, or hydroformylated to C₆-aldehydes using syngas, both with 100% conversion rate (Scheme 12). An l/b isomeric ratio of about 4:1 for *n*-hexanal:methylpentanal was obtained. Berghof GmbH's polyamide based membranes with MWCO value of 10k was used to quantitatively recover the catalysts in benzene.



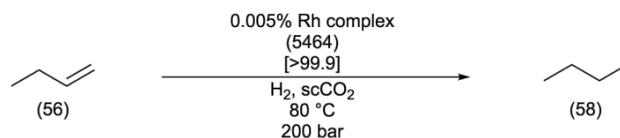
Scheme 12. Soluble polymer bound rhodium complex catalysed homogeneous reactions of 1-pentene: **A)** atmospheric hydrogenation of 1-pentene (0.05 M) in benzene at 22 °C; **B)** atmospheric hydroformylation of 1-pentene (0.10 M) in benzene at 22 °C using syngas (H₂/CO 1:1) [3–4].

Only two years later, in 1977 Parshall *et al.* published their experiments about the first organic solvent nanofiltration of commonly used rhodium catalysts [13]. Despite their promising results, this field of rhodium catalysis recovery remained silent for almost a quarter-century.

Due to the development of nanofiltration membranes the later studies on homogeneous catalyst recovery did not require catalyst enlargement via anchoring metal catalysts to soluble polymer backbone chains. Vankelecom *et al.* demonstrated the MPF®-60 membrane-assisted recovery of Ru–BINAP (See Scheme 1) and a Rh catalysts in the chemo- and enantioselective hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate, respectively (Scheme 13) [71]. The continuous process was carried out in methanol achieving as high as 99% enantiomeric excess and 2000 TOF values.



Scheme 13. Homogeneous hydrogenations carried out in continuous process in methanol at 10 bar hydrogen pressure: **A)** rhodium complex catalysed hydrogenation of methyl 2-acetamidoacrylate (0.13 M) at 35 °C yielding the *R* isomer of methyl *N*-acetylalaninate; **B)** (*S*)-Ru-BINAP catalysed hydrogenation of methyl 2-acetamidoacrylate (0.4 M) at 37 °C yielding the *S* isomer of dimethyl 2-methylsuccinate [71].

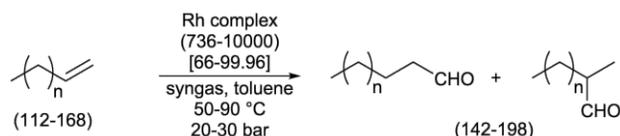


Scheme 14. Homogeneous hydrogenation of 1-butene (0.02 M) in the presence of an enlarged fluororous rhodium complex using supercritical carbon dioxide as solvent at 80 °C and 200 bar [72].

Carbon dioxide in its liquid or supercritical state (scCO₂) has a remarkable potential as an environmentally benign reaction medium for sustainable reaction and separation processes [76]. scCO₂ has been successfully used to replace conventional and potentially hazardous and toxic solvents in a wide range of processes. In particular, development of homogeneous metal-based catalytic processes in scCO₂ has gained increasing attention in recent years [77]. The usual strategy to increase the solubility of catalysts in scCO₂ consists of the introduction of CO₂-philic groups such as fluorinated moieties allowing the necessary interaction between CO₂ molecules of the fluid and the catalyst with its consequent solubilisation [78]. For such purpose a fluororous derivative of the Wilkinson's catalyst (see Scheme 1) was designed and applied in the hydrogenation of 1-butene coupled with *in situ* catalyst recovery (Scheme 14) [72]. This concept demonstrated the advantages of benign high-density gases through obtaining a high concentration of gaseous reactants in the same phase as the substrates and catalyst as well as facile catalyst localization by means of a membrane. The size of the catalyst was estimated to be 2–4 nm which was quantitatively retained by the ceramic membrane having pore diameter in the range of 0.5–0.8

nm. Both batch and continuous operation were evaluated, but the latter one resulted in half as high productivity due to the significantly lower conversion (**Table 3**). Owing to the increasing endeavour to use green solvents in chemical synthesis in the recent years, studies about hydrogenation in *scCO*₂ employing more complex compounds than butene could gain high significance in the future.

Although the recent advancement in membrane science enabled the use of low MWCO membranes, polymeric enlargement of catalysts has still remained in use in some studies. The enlarged catalysts have much higher rejection which allows the application of looser membranes. In turn, looser membranes contribute to the sought-after higher flow and lower product rejection.



Scheme 15. Liquid phase hydroformylation of 1-octene ($n=6$, 1.92 M) and 1-dodecene ($n=8$, 1.25 M) in toluene in the presence of a cubic silsesquioxane enlarged rhodium catalyst (80 °C, 20 bar) [73] or a soluble polymeric-bound rhodium catalyst (50 °C, 30 bar) [74] or rhodium catalyst with various ligands (90 °C, 20 bar) [67] producing a mixture of the corresponding aldehydes with l/b ratio of $2/1$, $3/2$ and $2-30$, respectively.

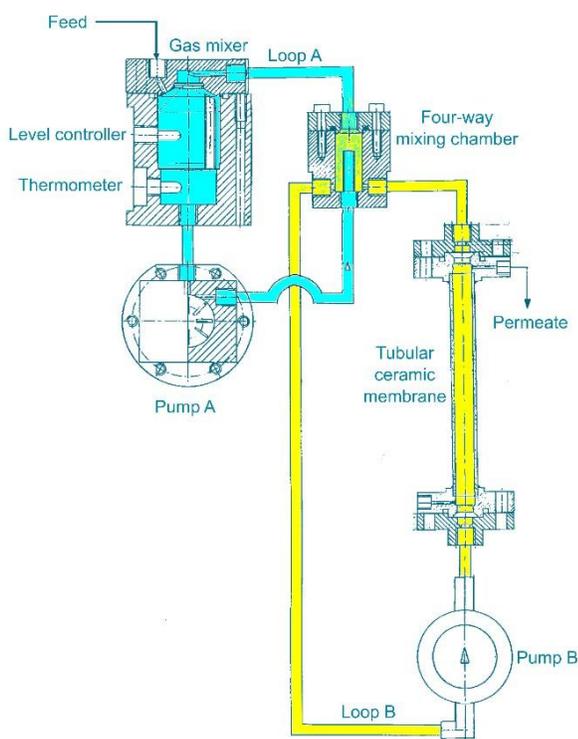


Fig. 6. Schematic diagram of the continuous-flow nanofiltration reactor used for the hydroformylation of 1-octene under reaction conditions shown in **Scheme 15**. Loop A (filled with blue) is the gas-saturation/reaction loop while Loop B (filled with yellow) membrane filtration loop. Both streams were mixed in the four-way mixing chamber [73].

Vogt *et al.* prepared a cubic silsesquioxane enlarged analogue of the TPP ligand (see **Scheme 2**) [73]. This way a high molecular weight (2791 $\text{g}\cdot\text{mol}^{-1}$) but still well-defined ligand structure was obtained. The rhodium

complex catalyst was prepared *in situ* from the ligand and rhodium source in the reaction vessel and used for continuous hydroformylation (**Scheme 15**). The continuous reactor set up consisted of two loops: a gas-saturation/reaction loop and a membrane filtration loop (**Fig. 6**) [73]. Loop A contained the reaction vessel and the gas mixer, in which the reaction mixture was injected into the gas phase for gas saturation. Both loops met and were mixed in the mixing chamber. The reaction mixture subsequently flowed through the tubular cross-flow membrane cell containing an Inopor ceramic membrane (MWCO: 450) and the product containing permeate was continuously collected. In the continuous hydroformylation reaction, an equilibration time of 17 hours was required to reach steady state. At steady state conversion above 95% was maintained for more than 7 days. After 8 days of operation time, a slight decrease to 80% in the conversion was observed followed by a sharp decline after 12 days operation. The results revealed that TON as high as 120,000 was reached while the overall leaching of rhodium and phosphorous remained below 1% [73].

The use of polymeric bound rhodium complexes was demonstrated in 1-octene hydroformylation (**Scheme 15**) [74]. The Starmem® 120 nanofiltration membrane having MWCO of 200 virtually completely retained the catalyst, resulting in residual rhodium levels at ppb level. The continuous operation resulted in 0.004 \$/lb linear aldehyde rhodium loss which is $3/4$ fold lower than the upper limit of economic viability [79]. An increase in the syngas pressure from 6 to 30 bar raised the conversion from 30% to 50% and the aldehyde selectivity from 70% to more than 98%, at a cost of a slight decrease in the l/b ratio. Moreover, the higher pressure could prevent rhodium dimer formation which happens in syngas starved environment leading to the leach of the catalyst metal.

The catalyst ligand can have significant impact on the rhodium catalysed reactions. Having batch preliminary studies in hand [75]. Dreimann *et al.* performed continuous hydroformylation of 1-dodecene (**Scheme 15**) using different phosphine and phosphite ligands such as TPP (see **Scheme 2**) [67]. Bidentate ligands showed high regioselectivity with l/b ratio more than 30. However, after a few hours of run time, the performance declined significantly in both cases. By using the monodentate TPP a steady state with low l/b ratio was reached during the continuous experiment, only a slight decrease in activity emerged after several hours. This can be mainly attributed to the incomplete rejection of the low molecular weight (262 $\text{g}\cdot\text{mol}^{-1}$) ligand on GMT-oNF-2 membrane (MWCO: 400–450), resulting in consistent leaching of the catalyst. This bottleneck was mitigated by the continuous replenishment of the catalyst enabling steady production of the product over 100 hours with 90% yield but with low l/b ratio of about 2 [67].

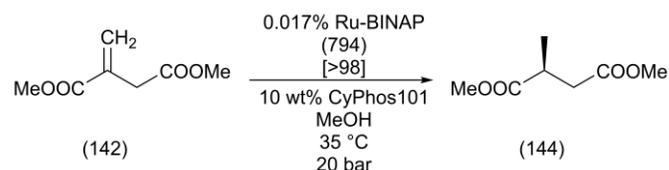
Organorhodium chemistry is now gaining even more significance in chemical synthesis. Several new types of cycloadditions and other rhodium catalysed reactions have been recently discovered, offering unique synthetic pathways, often complimentary to those of ruthenium or palladium. A new synthesis to afford cyclopropanes and

other derivatives has been developed through rhodium-catalysed decomposition of diazo compounds generating metal carbenoids [80]. The increasing portfolio for homogeneous rhodium catalysis calls for further research work on their recovery and recycling to ensure profitable and sustainable processes.

2.1.3. Ruthenium catalysed reactions

The wide scopes of oxidation states and the variety of coordination geometry make ruthenium particularly suitable for catalytic applications. Nonetheless, it was barely applied in chemical syntheses except oxidation and hydrogenation until the 1980s [81]. Since then numerous synthetic methods have been developed exploiting the advantageous nature of ruthenium to create new C–C bonds [32]. However, no other reaction gained as much attention as olefin metathesis, an intra- or intermolecular rearrangement of C–C double bonds. Early transition metal catalysed metathesis has been known since the 1960s but breakthrough came with the high affinity, stable ruthenium catalysts. Today, metathesis is applied on an industrial scale in the oil and polymer industry [82]. At the same time, scientific interests are not dwindling indicated by the recent developments in pharmaceutical and fine chemical applications. Simultaneously, catalyst removal methods using mostly high amount of auxiliary compounds were developed to mitigate concerns about residual ruthenium content [83]. The potential of membrane-assisted ruthenium catalysis in synthetic processes has also been recognised and studied since 2001 (Table 4). However, only metathesis and asymmetric hydrogenation processes have been developed. For

detailed introduction of homogeneous hydrogenation see Section 2.1.2. In the following paragraphs, we will discuss the achievements of membrane-assisted reactors regarding ruthenium catalysis.



Scheme 16. Asymmetric hydrogenation of dimethyl itaconate (50 mM) to dimethyl methylsuccinate employing Ru-BINAP catalyst in a mixed solvent of 10 wt% CyPhos 101 ionic liquid in methanol at 35 °C and 20 bar hydrogen pressure [84].

The continuous homogeneous hydrogenation process of methyl 2-acetaminoacrylate yielding the *S* isomer of dimethyl 2-methylsuccinate developed by Vankelecom *et al.* employed both rhodium and ruthenium catalyst, and it is described in detail in Section 2.1.2 (see Scheme 13) [71]. Using the opposite enantiomer of the off-the-shelf (*R*)-Ru-BINAP catalyst (see Scheme 1), Livingston *et al.* employed ionic liquids as co-solvents in order to enhance the lifetime and selectivity of the catalyst in the homogeneous hydrogenation of dimethyl itaconate (Scheme 16) [84]. A batch membrane reactor employing Starmem® 122 nanofiltration membrane was operated in 4–8 reaction–filtration–substrate reload cycles. The membrane was able to reject the catalyst quantitatively and the CyPhos 101 ionic liquid at 98%. The addition of the ionic liquid resulted in prolonged catalytic activity. The original 4 reaction–filtration–substrate reload cycles

Table 4. Comparison of different process configurations applying ruthenium catalyst published in literature in terms of reaction type, solvent(s) employed, type of membrane, catalyst rejection (%), highest conversion (%) and volumetric productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$).

Reference	Reaction	Solvent	Membrane	Catalyst retention (%)	Highest Conversion (%)	Productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$)
Vankelecom <i>et al.</i> [71]	asymmetric hydrogenation	MeOH	MPF-60	>98	100	17.0
Livingston <i>et al.</i> [84]	asymmetric hydrogenation	MeOH with 10% CyPhos 101	Starmem 122	>98	112 ^a	11.9
Rabiller-Baudry <i>et al.</i> [85]	metathesis	dimethyl carbonate, toluene	Starmem 228	92	100	10.5
Plenio <i>et al.</i> [86]	metathesis	toluene	PAN/PDMS	>99	100 (batch), 37 (continuous)	1.50 (batch), 0.318 (continuous)
van der Gryp <i>et al.</i> [87]	metathesis	neat	Starmem 120, 122, 228, 240	>99.4	75	17.5
Rabiller-Baudry <i>et al.</i> [88]	metathesis	toluene	Starmem 122	86–95	97 (semi-continuous), 92 (continuous)	15.4 (semi-continuous), 16.2 (continuous)
Ormerod <i>et al.</i> [89]	metathesis	DCM, acetone	Duramem 200, Inopor TiO ₂ 0.9 nm, 1 nm (C ₈ modified) (MWCO: 200, 450, 1500)	80–99	98 (batch), 60 (continuous)	1.0865 (batch), 2.1200 (continuous loop)

^a Process yield

were increased to 8 cycles as a demonstrated result of the presence of ionic liquids. The enantiomeric excess also increased from about 70% to more than 95%. However, the theoretical explanation for the role of the ionic liquid in the improved selectivity and elongated catalyst lifetime remained unveiled in the article.

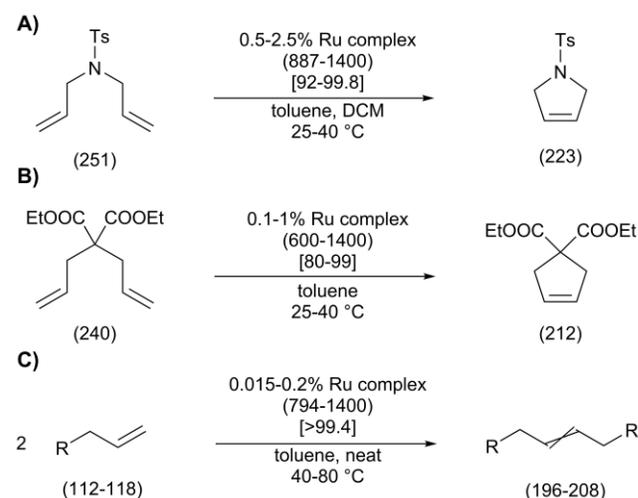
The ruthenium catalysed ring-closing metathesis of diallyllysylamide (**Scheme 17.A–C**) was performed in a membrane assisted reactor using commercially available Hoveyda–Grubbs II catalysts (see **Scheme 1**). Although no degradation of catalyst took place during the filtration process, their rejection on Starmem® 228 having an MWCO of 280 was not sufficient. Consequently, bulkier catalyst complexes in the molecular weight range of 717–2195 g·mol⁻¹ were synthesized [85]. The screening of the catalyst rejections revealed that the recovery as the function of molecular weight has a maximum at 887 g·mol⁻¹, presumably due to the increased adsorption of the bulky catalysts onto the membrane surface. The catalyst with the highest rejection was used in batch reaction-filtration-substrate reload cycles using toluene and dimethyl carbonate (DMC) as solvents. The catalytic activity declined significantly over the cycles resulting in an almost 40 times longer reaction time for the fifth cycle. As a consequence, the productivity value of 133 obtained at the 1st cycle was reduced to 3.4 by the 5th catalytic cycle.

Similarly, an enlarged Hoveyda–Grubbs catalyst with molecular weight of 1400 g·mol⁻¹ was employed in a nanofiltration-coupled homogeneously catalysed metathesis reaction (**Scheme 17.A**) [86]. The enlarged catalyst exhibited retained catalytic activity compared to a commercial Hoveyda–Grubbs II catalyst. The applied PAN/PMDS composite membrane was able to reduce the ruthenium level under the limit of detection in the subsequent nanofiltration step achieving a rejection of more than 99%. The nanofiltration-coupled stirred-tank reactor was also investigated in continuous operation mode but the catalyst activity rapidly decreased indicated by the permeate conversion peaking at only 37%. The cumulated TON of the continuous process was about 13% lower than that of the batch reaction. In a subsequent study a first generation Grubbs catalyst was used for the metathesis of 1-octene in a neat reaction coupled with catalyst recovery using Starmem® 228 (**Scheme 17.C**) [87]. Quantitative catalyst rejection was achieved whilst the product was not retained at all. Despite the high rejection of the catalyst the coupling reaction completely stopped by the fifth batch reaction-filtration-substrate reload cycle. Consequently, the productivity value of 64.9 in the 1st cycle decreased to zero.

Rabiller-Baudry *et al.* focused on the integration of organic solvent nanofiltration in a homogeneously catalysed ring closing metathesis reaction to increase the productivity of a Hoveyda–Grubbs II catalyst (**Scheme 17.B**) [88]. Starmem® 122 membrane resulted in high rejections for both the catalyst (>95%) and the product (80–90%). The semi-continuous process comprised of four reaction-filtration-substrate reload cycles followed by two solvent addition–diafiltration cycles. The initial 97% conversion corresponding to productivity value of 26.3 rapidly decreased to zero by the

fourth cycle. The high rejection of the product resulted in less than 50% and 35% product recovery in the permeate stream after diafiltration at the end of the semi-continuous (40 bar) and continuous (10 bar) processes, respectively. Both processes achieved TON of about 170 with 0.5% catalyst load, whilst the continuous process consumed four times less solvent.

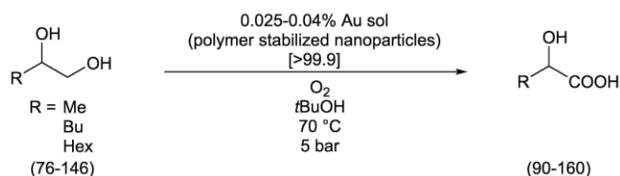
The same reaction (**Scheme 17.B**) was performed by Ormerod *et al.* in a reaction–filter–refill mode and in a nanofiltration-coupled continuous loop reactor examining the performance of different solvent–catalyst–membrane systems [89]. Replacing both dichloromethane with acetone solvent and Umicore with Hoveyda-Grubbs I catalyst had positive effect on the catalyst lifetime and subsequently on the conversion. On the other hand, Umicore catalysts exhibited higher rejection. Three membranes, namely Duramem® 200, Inopor 0.9 and 1 nm (C₈ alkane group modified) were used. Despite the difference in their MWCO (200, 450 and 1500 g·mol⁻¹), all membranes had good rejections (80–96%) for the catalysts in different solvents. The top performing Inopor 0.9 membrane showed high rejection for the catalyst (95%) and sufficiently low for the product (55%) in acetone, however, it had the lowest permeability of 0.3 L·m⁻²·h⁻¹·bar⁻¹. This work also revealed a limitation of membrane reactors in metathesis. If the ethylene by-product cannot leave the system, the final conversion of the metathesis is observed to be far lower than usual.



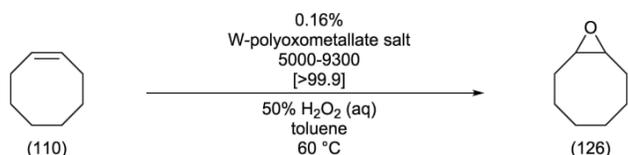
Scheme 17. Alkene metathesis reactions with ruthenium containing Grubbs or Hoveyda-Grubbs catalysts: **A)** Ring closing metathesis of N, N-diallyllysylamide (25–100 mM) in toluene or dimethyl carbonate at 25–40 °C; [85–86]. **B)** Ring closing metathesis of diethyl diallylmalonate (10–106 mM) in toluene at 25–40 °C; [86,88–89]. **C)** Cross-metathesis of allylbenzene (R = phenyl group, 60 mM) [86] or 1-octene (R = *n*-pentyl group) [87] either in toluene or under neat conditions at 40 or 80 °C.

As the examples showed in this section, even if the ruthenium catalyst is recycled effectively by the membrane module, the metathesis reaction rates decline rapidly. This indicates that the ruthenium catalyst deactivates readily under the conditions of the metathesis. Several studies aimed to find the pathways by which this phenomenon takes place. Dimerisation proved to be a major issue in the deactivation of phosphine containing

In another study, PVA was used to prepare and stabilize gold nanocolloid which was applied as catalyst in the oxidation of 1,2-diols to α -hydroxycarboxylic acids (Scheme 19) [101]. The polymer stabilized gold nanoparticles exhibited good activity in water and also in *tert*-butanol. Moreover, the catalyst preserved the 60–80% of its original activity in 3 refill-reaction-filtration cycles. Usage of an organic solvent allowed the application of the process for water insoluble substrates. Moreover, the PDMS membrane were used for the organic solvent nanofiltration showed higher rejection and flux than the membranes (Matrimid 5218, CA, Desal-5 DK) applied for the aqueous filtration.

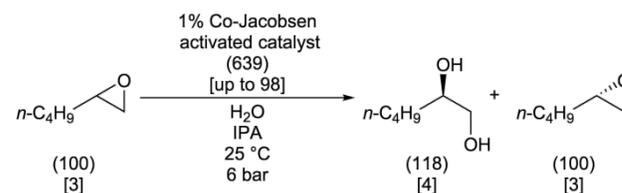


Scheme 19. Oxidation of 1,2-diols to α -hydroxycarboxylic acids (0.8 M, 1.0 equiv.) with oxygen (5 bar) catalysed by an Au sol (1.0 or 1.6 μ mol, 0.0025-0.004 equiv.) in presence of NaOH (0.8 M, 1.0 equiv.) in *tert*-butanol at 70 °C [101].



Scheme 20. Epoxidation of cyclooctene (0.43 M, 1.0 equiv.) in a biphasic mixture of toluene and aqueous hydrogen peroxide (50%) at 60 °C [102–103].

Alsters *et al.* [102–103] used W and Zn containing “sandwich”-type polyoxometalate for cyclooctene epoxidation (Scheme 20). As the substrate is insoluble in water, a toluene soluble catalyst was made by exchanging the Na^+ ions with lipophilic $[\text{MeN}(\text{n-C}_8\text{H}_{17})_3]^+$ moieties. The prepared catalyst was quantitatively retained by the mesoporous (1.8–3.0 nm) γ -alumina membrane. The oxidation was carried out in a reaction-filtration-refill process. Surprisingly the catalytic activity was not only preserved, moreover it increased steadily by each cycle from 70% in the first run to 90% in the sixth run. This can be attributed to the removal of low molecular weight impurities present in the catalyst stock solution which was prepared *in situ* and used without further purification. The mechanism of this reaction is also a type of phase transfer catalysis. The catalyst is in exchange between the two phases; it is oxidized by the hydrogen peroxide in the aqueous phase, then transfers the active oxygen species to the organic phase where it can react with the substrate cyclooctene. The phase transfer catalysts are discussed in detailed in the Section 2.2.2.



Scheme 21. Hydrolytic kinetic resolution of epoxides (1.6 M, 1.0 equiv.) with water (0.9 M, 0.56 equiv.) catalysed by a Co-Jacobsen catalyst (1%) in a presence of 4-nitrobenzoic acid (0.035 M, 0.022 equiv.) under 6 bar pressure in IPA at 25 °C [104–105].

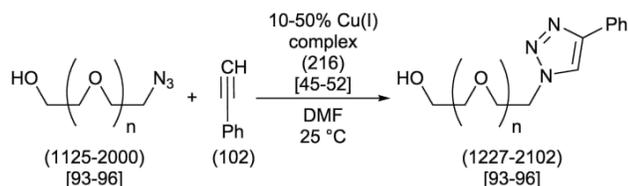
The separation of enantiomers has always been a major challenge in chemical synthesis. Kinetic resolution, the

Table 5. Comparison of different process configurations applying transition metal catalyst other than palladium, rhodium or ruthenium published in the literature in terms of reaction type, solvent(s) employed, type of membrane, catalyst rejection (%), highest conversion (%) and the volumetric productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$).

Reference	Reaction	Solvent	Catalyst metal	Membrane	Catalyst retention (%)	Highest Conversion (%)	Productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$)
Zhu <i>et al.</i> [100]	esterification	neat	Zr	catalytic PVA or PVA/PAA on ceramic support	100	95	68.5
De Vos <i>et al.</i> [101]	oxidation	<i>tert</i> -butanol	Au	Matrimid 5218, CA, Desal-5 DK, PDMS	90–100	43	8.84
Alsters <i>et al.</i> [102–103]	oxidation	toluene	W, Zn	γ -alumina (1.8-3.0 nm)	>99.9	90	20.2
Vankelecom <i>et al.</i> [104–105]	hydrolytic kinetic resolution	diethyl ether, IPA	Co	COK M2, Nadir N30F, VITO FS Ti 139	83–98	100	5.69
Vankelecom <i>et al.</i> [106]	Huisgen cycloaddition	DMF	Cu	crosslinked Lenzing P84 polyimide	93–96	n.d.	n/a
Uozumi <i>et al.</i> [107]	Huisgen cycloaddition	acetone/water 3:1, IPA /water 1:1	Cu	poly-(vinylpyridine)	n/a	99	1050
Kovačić <i>et al.</i> [108]	Friedel-Crafts alkylation	<i>p</i> -xylene	Fe	MOF-PDCPD hybriide	n/a	7	12300

^{n.d.} not determined, ^{n/a} not applicable

selective transformation of one of the enantiomers is a possible option. Metals of the fourth period, such as Ti [110], Fe [111], Co [112], or Cr [113] are frequently applied in such reactions. In the study of Aerts *et al.* [104–105] a recyclable Co-Jacobsen catalyst was used in hydrolytic kinetic resolution of epoxides (**Scheme 21**). Several nanofiltration membranes were subjected to tests concerning the retention of the Co-Jacobsen catalyst in diethyl ether, isopropyl alcohol and under neat conditions. The silicon based COK M2 membrane afforded the best results in the diethyl ether filtration tests and it was applied in the development of a membrane reactor for the kinetic resolution of 1,2-epoxyhexane. A slight decrease in conversion and enantiomeric excess was observed over the four cycles, due to the incomplete retention (98%) of the membrane and the partial deactivation of the Co-Jacobsen catalyst. All in all, the enantiomeric excess of the product and the conversion were above 95% and 75%, respectively during the whole experiment. The commercially available polyethersulfone N30F membrane and the ceramic FS Ti 139 membrane were chosen to recycle the catalyst from isopropyl alcohol solution. In this solvent, the Co-Jacobsen catalyst exhibited higher activity and preserved selectivity compared to the diethyl ether system. The N30F and the FS Ti 139 membranes were used during two and one filtration cycles in which they retained the catalyst for 93% and 89%, respectively. The recycling of the Co-Jacobsen catalyst under solvent-free conditions in the substrate 1,2-epoxyhexane was found to be impossible with the tested membranes to combine a good retention for the catalyst with an acceptable permeability because of the high viscosity of the mixture.



Scheme 22. Huisgen cycloaddition (“click reaction”) of an azidopolyethyleneglycol (1.0 equiv.) and phenylacetylene (2.0 equiv.) catalysed by a Cu(I)Br in a presence of PMDTA in DMF at 25 °C [106].

Vankelecom *et al.* [106] reported the first solvent resistant nanofiltration in which the catalyst is the permeating species and the product is retained. In this approach a polymeric substrate went under Cu(I) catalysed “click reaction” and then the complex of *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDTA) and Cu(I)Br was removed by several discontinuous diafiltration steps (**Scheme 22**). As mostly DMF was used as the reaction media crosslinked polyimide membranes were applied. In five diafiltration steps the residual Cu content decreased to 1.2% of the original concentration. However, the process suffers from many limitations. The applied substrate is needed to be very high molecular weight at around 2000 g·mol⁻¹, as the rejection proved to be inefficient even for a substrate of 1125 g·mol⁻¹. Moreover, the process produces a large amount of diluted DMF solution containing the Cu catalyst, the ligand, the

excess of the small molecule reactant and possible by-products.

An instantaneous Huisgen cycloaddition (“click reaction”) has been developed by Uozumi *et al.* [107] that uses a novel catalytic dinuclear copper complex-containing polymeric membrane to promote the reaction. The catalytic membrane was created inside a microchannel by a laminar flow of a solution of a poly(4-vinylpyridine) (PVPy) polymeric ligand and the solution of CuSO₄ followed by a reduction to Cu(I) by sodium ascorbate (NaAsc). Structure elucidation of polymer catalysts were implemented by Cu K-edge XANES (**Fig. 8**). The positions of the rising-edge of microdevices **A** and **B** were considerably like that of Cu₂O, although the absorption peaks at rising-edge, which were represented by 1s-4p transitions, were shifted toward higher energy compared with Cu₂O. It is noteworthy that no pre-edge peak appeared in the spectra of microdevices **A** and **B**. These results strongly suggested that the oxidation states of Cu centre in both microdevices **A** and **B** were +1, while their coordination structures were different from Cu₂O, which has a tetrahedral structure in crystal state.

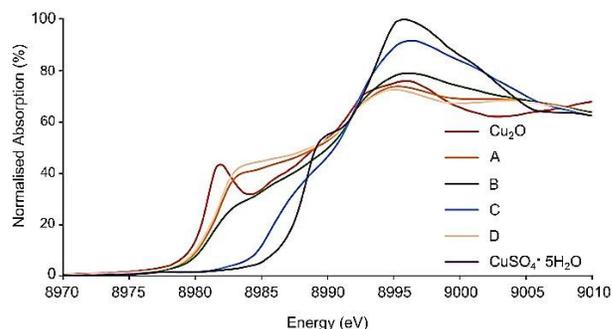
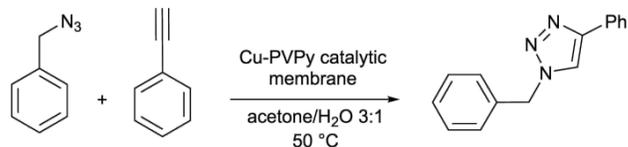


Fig. 8. Cu K-edge XANES spectra of samples corresponding to microdevices: **A** (PVPy + CuSO₄ + NaAsc + NaCl), **B** (PVPy + CuSO₄ + NaAsc), **C** (PVPy + CuSO₄), **D** (PVPy + CuCl₂) and reference compounds (Cu₂O and CuSO₄·5H₂O) [107].

Variety of alkynes and organic azides were tested in microdevice **A** to afford the corresponding triazoles in quantitative yield within 8-38 second residence time (**Scheme 23**). The small reactor volume and the fast reaction resulting excellent reactor productivity (**Table 5**). Microscopic evaluation of the membrane in the microchannel exhibited the stability after 24 h. Furthermore, ICP-MS measurements showed less than 50 ppb Cu content in the outflow.



Scheme 23. Huisgen 1,3-dipolar cycloaddition (“click reaction”) of benzyl azide (20 mM, 1.0 equiv.) and phenylacetylene (22 mM, 1.1 equiv.) catalysed by a Cu-PVPy membrane in acetone/water (3:1) at 50 °C [107].

Metal-organic frameworks (MOFs) are a class of nanoporous materials that primarily consist of metal centres connected through organic molecules leading to an extended network. Among many interesting properties,

the high internal surface and the ability to easily tune their structures makes them particularly attractive for membrane fabrication [114] or applying them as a heterogeneous catalyst [115].

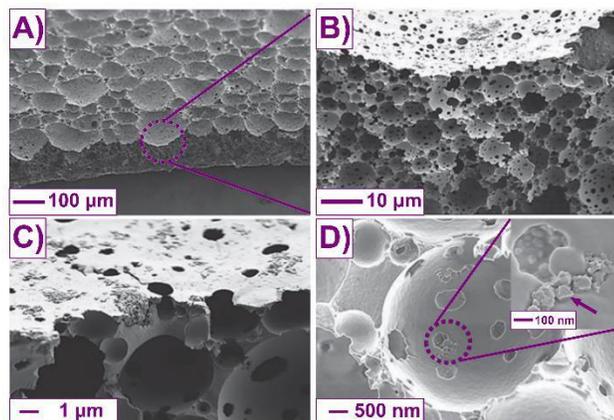
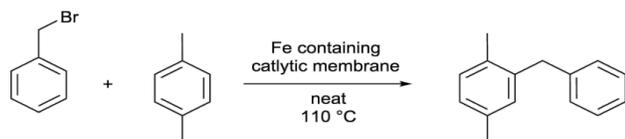


Fig. 9. Scanning electron micrographs of the MIL-100(Fe)@pDCPD polyHIPE membrane; **A)** membrane surface, **B)** interior, **C)** embedded MIL-100(Fe), **D)** High-magnification image of macropore surface with inset image showing MIL-100(Fe) morphology [108].

Synthesis of an iron containing hybrid membrane and application in Friedel-Crafts alkylation were reported by Kovačič *et al.* [108]. The membrane was prepared by curing of a MOF nanoparticle (MIL-100(Fe)) [116] and non-ionic surfactant stabilized dicyclopentadiene (DCPD)-in-water high internal phase emulsion (HIPE). The obtained material is a hierarchically porous, fully opened hybrid membrane consisting of microporous MIL-100(Fe) MOF-nanoparticles embedded into a dicyclopentadiene based macroporous polymer scaffold (**Fig. 9**). Alkylation of *p*-xylene with benzyl bromide was performed in a flow through reactor equipped with a catalytic membrane (**Scheme 24**). The membrane provided 7% conversion applying 0.01 mL·m⁻¹ flow rate, which represents approximately 2 second residence time. The presented setup provided extremely high reactor productivity due to the particularly small reaction volume and the high concentration of the substrate (**Table 5**). However, it needs to be mentioned that this process cannot be categorised as a classical membrane process as no separation occurred.



Scheme 24. Alkylation of *p*-xylene with benzyl bromide (0.5 M in xylene) catalysed by MIL-100(Fe)@pDCPD polyHIPE membrane at 50 °C [108].

2.2. Metal free catalysis

Despite the outstanding activities of metal catalysts, their utilisation on industrial scale is of some concern. Namely, most of these heavy metals considered toxic as well as environmentally harmful. Consequently, the residual metal content of pharmaceutical products is subject of strict regulations (**Table 6**). As a result of this and the

increasing green intentions, efforts have been made to replace metal catalysis in many fields of synthesis.

The oldest and most common genre of metal free catalysis is acid-base catalysis. This field has not been paid much attention regarding membrane processes as most of these catalysts are cheap, easily removable or can be immobilised without the loss of activity.

Table 6. Permitted daily exposure (PDE) limits of the most important transition metals [44].

Classification		Oral Exposure		Parenteral Exposure	
		PDE (μg.day ⁻¹)	Conc. (ppm)	PDE (μg.day ⁻¹)	Conc. (ppm)
Metals of significant safety concern	Pt, Pd, Ir, Rh, Ru, Os	100	10	10	1
	Mo, Ni, Cr, V	250	25	25	2.5
Metals with low safety concern	Cu, Mn	2500	250	250	25
Metals with minimal safety concern	Fe, Zn	13000	1300	1300	130

In this section, the achievements of enzymatic, organocatalytic and phase transfer catalytic reactions combined with membranes will be discussed. Catalysis of biochemical reactions in a living cell is vital due to the very low reaction rates of the non-catalytic reactions at room temperature and pressure in an aqueous solution. Despite these mild conditions natural enzymes are able to enhance a huge variety of reactions. These powerful abilities of biocatalysts are widely used in organic syntheses both in aqueous and organic media. Phase transfer catalysts (PTC) facilitate the mass transfer between two immiscible liquid phases or between solid and liquid phase. Applying PTC catalysts in heterogeneous reactions provides numerous advantages, such as faster reactions, therefore less by-product formation, which allow to use less solvent with lower toxicity and price. Owing to these beneficial properties PTC catalyst are considered as a tool for green chemistry. Organocatalysis considered also an environmental friendly technique for chemical transformations in which metal-free molecules are active, and able to catalyse reactions enantioselectively.

2.2.1. Enzymatic membrane reactors

The potential of enzymes as practical catalysts has gained considerable recognition in the last decades [117]. However, as long as the use of enzymes is restricted to their natural, aqueous reaction media, the scope of industrial bioconversions, especially for the production of special chemicals and polymers, is limited.

Since the discovery of catalytically active enzymes in organic solvents [118] the selection of the appropriate solvent for a specific enzymatic conversion has been widely studied [119]. The solvent can influence an enzymatic reaction both by direct interaction with the enzyme and by influencing the solvation of the substrates and products in the reaction medium [120–121].

Enzymatic reactions in organic solvents provide numerous industrially attractive advantages, such as

increased solubility of non-polar substrates, reversal of the thermodynamic equilibrium of hydrolysis reactions, suppression of water-dependent side reactions, alternation of substrate specificity and enantioselectivity, and elimination of microbial contamination [122]. However, the application of enzymes in organic media is restricted because most enzymes exhibit low activity in pure organic solvents. Therefore, often biphasic systems are used to avoid enzyme dehydration and deactivation. For instance the use of matrix immobilized enzymes or hydrophobic membranes allows the substrates and/or product to be in an organic phase, whilst the biocatalyst remains in the aqueous solution [123–124]. Enzymes can also be encapsulated in reverse micelles in a water/surfactant/organic solvent system [125].

Hydrophobic solvents are usually superior to hydrophilic ones as enzymatic reaction media because the latter have a greater tendency to strip tightly bound water (which is essential for catalytic activity) from the enzyme molecules. Dehydration changes the enzyme structure and results in reduced enzymatic activity in organic solvents [126]. In aqueous media one of the most influential factors of enzyme activity is pH, which has no direct meaning in organic solvents. Consequently, in such media enzymes possess a ‘pH memory’ and their catalytic activity reflects to the pH of the last aqueous solution to which they were exposed. Therefore, the enzymatic activity in organic media can be enhanced several orders

of magnitudes if enzyme is lyophilized from aqueous solutions having optimal pH for catalysis [127].

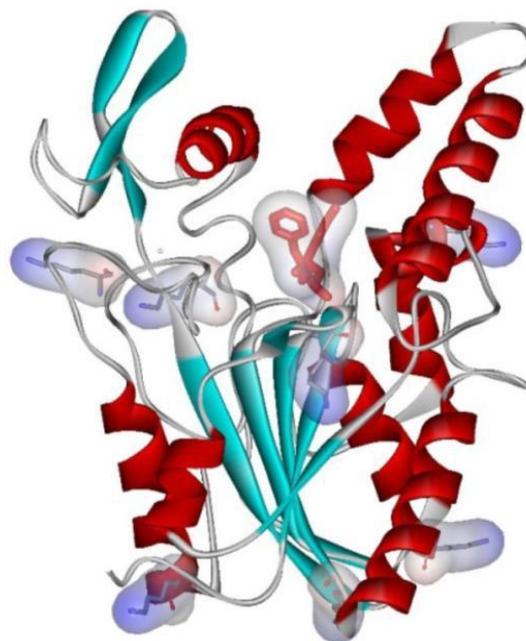


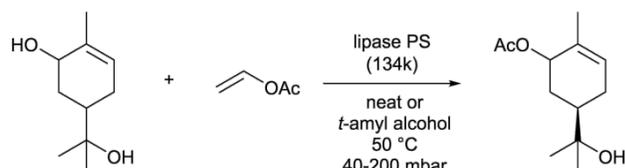
Fig. 10. The catalytically active open conformation of lipase from *Burkholderia cepacia* [136].

Table 7. Comparison of different process configurations applying enzyme catalyst published in literature in terms of reaction type, solvent(s) employed, type of membrane, catalyst, highest conversion (%) and volumetric productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$).

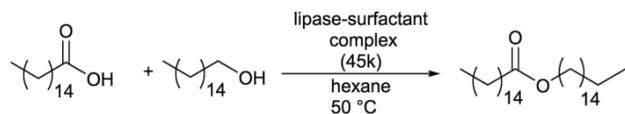
Reference	Reaction	Solvent	Membrane	Catalyst	Highest Conversion (%)	Productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$)
Reuss <i>et al.</i> [15]	transesterification	vinyl acetate, <i>tert</i> -amyl alcohol	polypropylene microfiltration (pores size of 0.1 μm)	lipase PS (134k $\text{g} \cdot \text{mol}^{-1}$)	48	0.0581
Nakajima <i>et al.</i> [125]	esterification	hexane	polyimide MWCO: 8000	lipase (45k $\text{g} \cdot \text{mol}^{-1}$)	96	23.0
Cabral <i>et al.</i> [129]	transesterification oxidation	BuOAc/(AOT)/isooctane reversed micelles	ceramic Carbosep® MWCO: 10000	cutinase (22k $\text{g} \cdot \text{mol}^{-1}$), whole cell	85	8.18, 8.9
Trusek-Holownia <i>et al.</i> [130]	peptide synthesis	ethylacetate	polypropylene capillaries (pores size of 0.2 μm)	termolysin (34.6k $\text{g} \cdot \text{mol}^{-1}$)	80	0.815
Iborra <i>et al.</i> [131]	peptide synthesis	H ₂ O/DMSO or HEX/EtOH/H ₂ O	gelatin- α -alumina dynamic	chymotrypsin (25k $\text{g} \cdot \text{mol}^{-1}$)	98	5.49
Cabral <i>et al.</i> [132–133]	ester synthesis	(AOT)/isooctane reversed micelles	ceramic Carbosep® MWCO: 15000	cutinase (22k $\text{g} \cdot \text{mol}^{-1}$)	60	0.170–1.23
Kumar <i>et al.</i> [134]	hydrolysis	olive oil, heptane/ NaOH buffer	PMMA-EDGM	immobilized lipase	n.d.	18.5
Trusek-Holownia <i>et al.</i> [124]	esterification	isooctane	polyamide	immobilized lipase	98	19.6
Cabral <i>et al.</i> [135]	transesterification	MeOH, EtOH, BuOH/ isooctane	ceramic Carbosep® MWCO: 15000	cutinase (22k $\text{g} \cdot \text{mol}^{-1}$)	80	2.70–3.90

^{n.d.}not determined

The absence of water often leads to a new enzymatic reaction. For instance, in water numerous lipases (**Fig. 10**), esterases and proteases catalyse the hydrolysis of esters to the corresponding acids and alcohols. However, the addition of nucleophiles such as alcohols, amines and thiols to anhydrous solvents, leads to enantioselective transesterification, aminolysis and thioesterification, respectively [128]. The application of enzymatic membrane reactors in organic media are summarized in **Table 7**. The molecular weights of the enzymes are in the range of 20k–130k g·mol⁻¹ which are one or two orders of magnitude higher than that of the substrates and the products of the catalysed reactions. Therefore, mainly more open microfiltration or ultrafiltration membranes are used to retain the enzymes whilst the smaller organic molecules are readily purged through the membrane. Reuss *et al.* in 1995 reported the concept of biocatalytic membrane process in organic media for the first time [15]. Lipase PS from *Pseudomonas sp.* was used for the optical resolution of racemic *trans*-sorbrol by enantioselective transesterification with vinyl acetate (**Scheme 25**). This mucolytic drug were produced and marketed originally in racemic form, in spite of differences in the pharmacological activity between the two enantiomers. The experimental setup for continuous enantioselective transesterification employed a CSTR with a polypropylene microfiltration membrane (pore size 0.1 μm) to retain the enzyme. The system remained stable during the 600 h operation and provided an acetylated product in a steady state with 48% conversion and with ~80% enantiomeric excess.



Scheme 25. Enantioselective transesterification of racemic *trans*-sorbrol (0.04 M, 1 equiv.) with vinyl acetate (0.1 M, 2.5 equiv.) catalysed by a lipase PS enzyme (40 mg/mL) in *tert*-amyl alcohol or neat under reduced pressure at 50 °C [15].

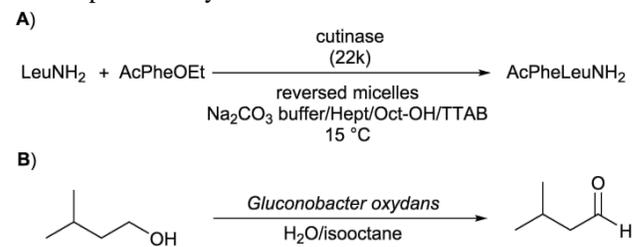


Scheme 26. Esterification of cetyl alcohol (25 mM, 1.0 equiv.) and palmitic acid (25 mM, 1.0 equiv.) catalysed by a lipase (1.06 mg/mL) sorbitol monostearate surfactant (0.53 mg/mL) complex in hexane at 50 °C [125].

Cetyl palmitate is known as a principal ingredient of whale oil [125]. This wax ester has potential applications as premium lubricant, parting agent, and antifoaming agent, as well as in cosmetics. Enzymatic esterification of cetyl alcohol and palmitic acid were carried out in a polyimide membrane (MWCO: 8000) reactor applying a lipase-surfactant complex (Lipase MF-30 from *Pseudomonas sp.*) in hexane (**Scheme 26**). After 1 h the reaction reached a conversion maximum at 96% followed by the filtration of the reaction mixture in the same batch

membrane reactor equipment by supplying pressure with nitrogen gas. After ten cycles the complex was still able to provide conversion above 80%.

Short chain peptides and their derivatives are important compounds in areas such as biomedical research, the development of pharmaceuticals and the food industry. Biotransformations, like enzymatic synthesis of dipeptide derivatives were carried out in a continuous membrane reactor by Cabral *et al.* in reversed micelles of tetradecyl trimethyl ammonium bromide (TTAB) in heptane-octanol mixture (**Scheme 27.A**) [129]. The use of an organic solvent with low water content enables the shift of the thermodynamic behaviour in the direction of the formation of the peptide bond. On the other hand, the presence of the reversed micelles creates a microenvironment that maintains the stability and enzymatic activity of α -chymotrypsin in the organic solvent. The presented membrane reactor was able to produce the dipeptide derivative with 66% yield in high purity due product precipitation. Continuous extractive bioconversion of isoamyl alcohol to isovaleraldehyde using a *Gluconobacter oxydans* strain was also investigated. Solvent extraction effectively utilized the partitioning of components between two immiscible solvents (water, isooctane), while the insertion of a polypropylene hollow fibre membrane avoids the contact between the biocatalyst and the extractant (**Scheme 27.B**) [129]. After 24 h the cells still showed 72% relative activity with overall 8.9 g_{product}·L⁻¹·h⁻¹ reactor productivity.

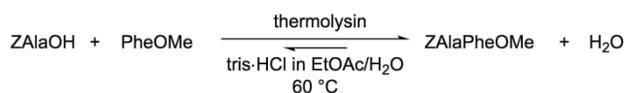


Scheme 27. **A)** Enzymatic esterification of protected amino acid AcPheOEt (6 mM, 1.0 equiv.) L-leucine amide (9 mM, 1.5 equiv.) catalysed by α -chymotrypsin in reversed micelles of tetradecyl trimethyl ammonium bromide (TTAB) (0.2 M) in heptane-octanol 80:20 at 15 °C; **B)** Bioconversion of isoamyl alcohol (0.03 M) to isovaleraldehyde by *Gluconobacter oxydans* strain [129].

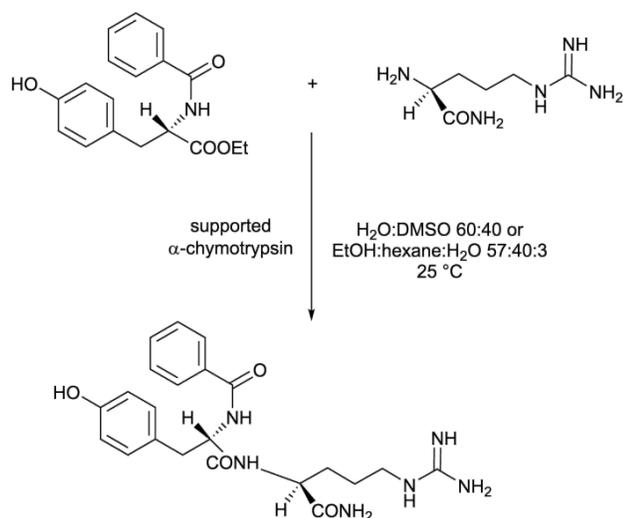
Biphasic enzymatic synthesis of dipeptide ZAlaPheOMe applying also a membrane contractor was reported by Trusek-Holownia *et al.* [130]. The esterification of carboxybenzyl protected alanine (ZAlaOH) with phenylalanine methyl ester (PheOMe) were catalysed by thermolysin which were dissolved in aqueous tris·HCl (tris(hydroxymethyl)aminomethane hydrochloride) buffer (**Scheme 28**). As organic phase ethyl acetate was utilized in the phase contractor to facilitate higher substrate and product concentrations in the process.

α -Chymotrypsin was covalently attached to an α -alumina ultrafiltration membrane by glutaraldehyde coated with an inert protein (gelatin) [131]. This derivative was used as catalyst for the continuous kinetically controlled synthesis the analgesic dipeptide kyotorphin in both membrane and packed bed reactors,

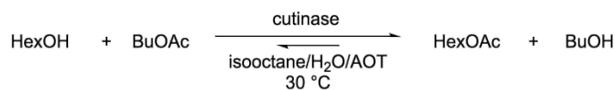
using aqueous (water/dimethyl sulfoxide, 60:40, v/v) and nearly-dry (hexane/ethanol/water, 57:40:3, v/v.) organic media (**Scheme 29**). In both media, the synthetic activity and operational stability of the enzyme-membrane derivative was compared with an adsorbed α -chymotrypsin Celite derivative, being two times and four times higher than the Celite one, respectively. The enzyme-membrane derivative has a half-life time higher than 36 days, with a virtually 100% selectivity.



Scheme 28. Esterification of carboxybenzyl protected alanine (ZAlaOH) (0.12 M, 1.0 equiv.) with phenylalanine methyl ester (PheOMe) (0.15 M, 1.25 equiv.) catalysed by thermolysin (5–25 μM) in EtOAc/H₂O in a membrane reactor at 60 °C [130].



Scheme 29. Enzymatic synthesis of kyotorphin starting from *N*-benzoyl-L-tyrosine ethyl ester (5 mM, 1.0 equiv.) and L-argininamide (10 mM, 2.0 equiv.) catalysed by covalently attached α -chymotrypsin (0.4 $\text{mg}\cdot\text{g}_{\text{support}}^{-1}$) in aqueous (water/dimethyl sulfoxide, 60:40, v/v) and nearly-dry (hexane/ethanol/water, 57:40:3, v/v) organic media at 25 °C [131].



Scheme 30. Continuous enzymatic transesterification of butyl acetate (0.1 M, 1 equiv.) with hexanol (1 M, 10 equiv.) catalysed by a cutinase (0.1 mg/mL) in reversed micelles (isooctane/H₂O and 0.15 M AOT) at 25 °C [132–133].

Enzymatic ester synthesis in a continuous membrane bioreactor (MBR) applying a ceramic membrane and reversed micelles was investigated by Cabral *et al.* (**Scheme 30**) [132–133]. A recombinant cutinase from *Fusarium solani pisi* was microencapsulated in reversed micelles using sodium bis(2-ethylhexyl) sulfosuccinate (AOT) surfactant in isooctane, followed by recirculation in the MBR with a continuous feed, and retentate collection. The calculation of the single-pass conversion confirmed the assumption of MBR acting as a CSTR. The main drawback of the process was the low 0.006% conversion per single pass of the reaction mixture through

the membrane module. On the contrary, the high stability of the system allowed the continuous operation to run more than 900 h without observed deactivation achieving reactor productivity up to $1.23 \text{ g}_{\text{product}}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$.

The synthesis of geranyl acetate, which is a well-known terpene derivative, was carried out in the presence of a supported lipase B from *Candida Antarctica* (CAL-B) (**Scheme 31**) [124]. Two immobilization approaches were investigated: (i) chemical binding to the membrane surface via glutaraldehyde, and (ii) physical sorption fixing a layer of gel protein to the membrane surface. The highest lipase activity was observed in solvents of high logP value, such as pentane, hexane and isooctane. By-product (water) sorption was implemented in the column with an adsorbent bed filled with 3 Å molecular sieves to avoid the formation of a biphasic reaction mixture. Selection of the operating temperature requires a trade-off between enzyme stability and activity (**Fig. 11**). Due to the losses of the catalyst activity during immobilization, it was concluded that it is more advantageous to apply the membrane for separation only and to suspend the enzyme in the bioreactor.

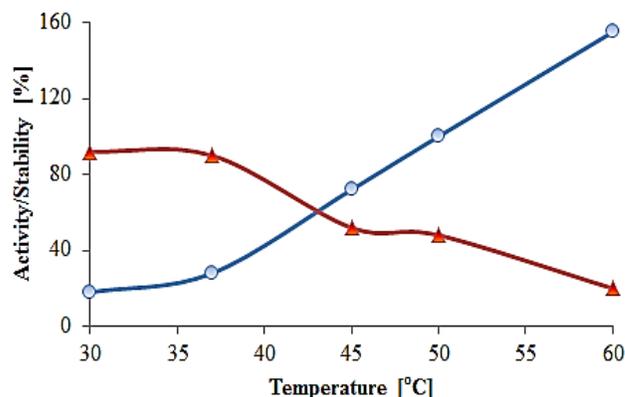
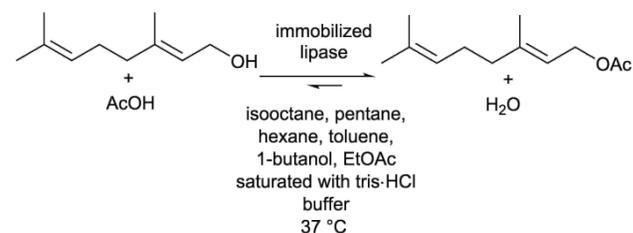


Fig. 11. The effect of temperature on the activity (O) and stability (Δ) of lipase CAL-B. A 100% activity was assumed to be the activity determined at 50 °C. Stability was determined in relation to the activity specified at given temperature prior to the incubation process which for each temperature was assumed to be 100% [124].

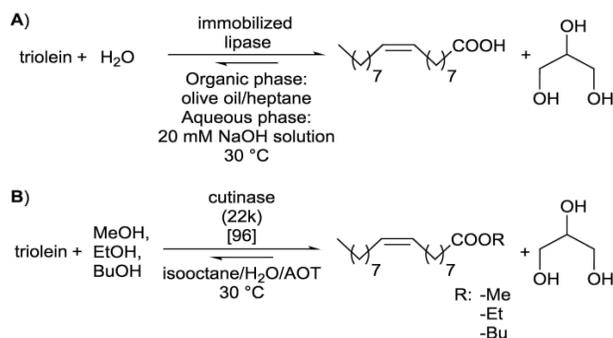


Scheme 31. Enzymatic ester synthesis starting from geraniol (0.25 M, 1.0 equiv.) and acetic acid (0.25 M, 1.0 equiv.) catalysed by membrane supported CAL-B (0.26 g/L) in various solvents saturated with tris.HCl buffer at 37 °C [124].

Random immobilization of pancreatic lipase by covalently linking it onto the surface of chemically modified poly(methyl methacrylate-ethylene glycol dimethacrylate) (PMMA-EGDM) clay composite membrane resulted in 39% increase in enzymatic activity.[134] The functionalization of the polymer attained by a mixture of NO and NO₂, followed by a reduction with hydrazine hydrate to NH₂ functional

groups. The aminated membrane was reacted with glutaraldehyde to get free aldehyde group on the membrane surface, which were suitable for chemical immobilization of the lipase. The biphasic MBR was used for the hydrolysis of olive oil, which contains 75% oleic acid (**Scheme 32. A**) [137]. The supported enzyme was highly stable and has been used for more than 50 h of reaction over a period of 25 days with negligible change (~3%) in the activity.

Enzymatic transesterification of vegetable oils is a promising alternative route for biodiesel production due to their high selectivity, mild operative conditions, easy product recovery, and catalyst recycling. Enzymatic transesterification of triolein with methanol, ethanol and *n*-butanol using recombinant cutinase of *Fusarium solanipisi* ($22\text{ k g}\cdot\text{mol}^{-1}$) microencapsulated in AOT/isooctane reversed micelles (**Scheme 32.B**) [135]. The process was performed in an MBR with a tubular ceramic membrane (MWCO: 15000) achieving as high as $500\text{ g}_{\text{product}}\cdot\text{day}^{-1}\cdot\text{g}_{\text{enzyme}}^{-1}$ specific enzyme productivity over one month.



Scheme 32. A) Enzymatic hydrolysis of olive oil catalysed by immobilized pancreatic lipase (1.72 mg) on a membrane surface in a biphasic MBR, applying heptane (50:50 v/v%) or solvent free conditions as an organic phase and NaOH (20 mM) aqueous solution at 30 °C; [134] **B)** Enzymatic transesterification of natural triolein (81 mM, 1 equiv.) with short chain alcohols (390 mM, 4.8 equiv.) catalysed by recombinant cutinase of *Fusarium solanipisi* (0.56-1 mg/mL) in water/sodium bis(2-ethylhexyl) sulfo-succinate (AOT)/isooctane reversed micelles at 30 °C [135].

Despite the limited stability, resistance and lifetime of biocatalysts in organic solvents, most of the enzymatic membrane reactors presented in the literature have average or good reactor productivity (see **Table 7**). To achieve these results one of the key factors was the application of the organic solvents providing higher solubility of non-polar products. Enzymes catalyse reactions in biological systems such as the human body with superb performance under mild conditions. Consequently, enzymes have always been a source of inspiration and a stimulus to scientists and engineers by exhibiting what could be realized through a deeper understanding of the underlying principles of host-guest interactions in supramolecular systems. Despite the fact that artificial enzymes cannot rival real enzymes in catalytic reaction rate, turnover, enantio-, regio- and stereoselectivity, significant advances in the field have shown the potential of these materials in various applications in the last decades [138–139]. Notably, the inherent limitations of enzymes such as limited stability,

resistance and lifetime in harsh conditions (organic solvents, extreme pH and temperature) have prompted extensive studies on the development of synthetic equivalents that are more robust [140]. Significant progress in the field has been achieved over the last two decades, with scientists developing novel strategies derived from both chemistry and biology areas, such as supramolecular chemistry, molecular imprinting and nanotechnology to name a few.

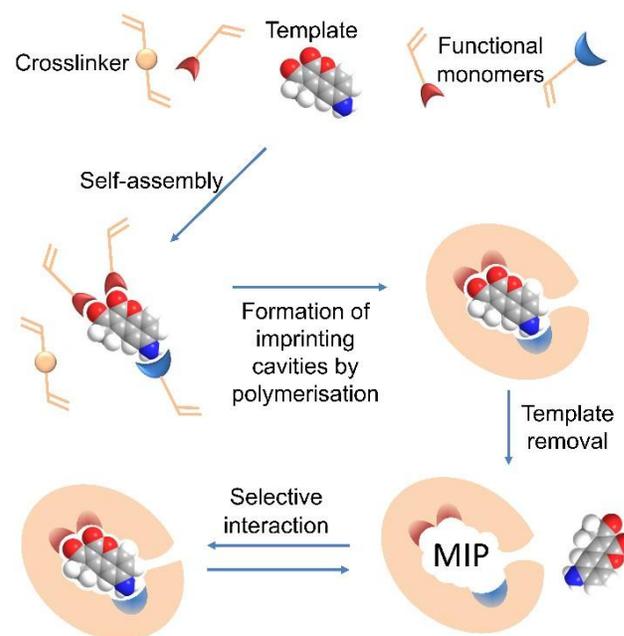


Fig. 12. The concept of molecular imprinting. Self-assembly of the functional monomer, the template, and the crosslinker is followed by polymerization. The template is removed from the polymer leaving a complementary cavity behind. The application of transition state analogues as templates results in materials with catalytic activities [149].

Molecular imprinting is a technique to obtain robust molecular recognition materials able to mimic natural recognition entities in a similar way as biological receptors which can be used in catalysis among others [141]. Consequently, molecularly imprinted polymers (MIPs) are often referred to as artificial enzymes. A target compound is present during the polymerisation process acting as a molecular template (**Fig. 12**). The functional groups of the carefully selected monomers self-assemble with the template, and the resulting complex is held in position via crosslinking polymerisation. Subsequent removal of the template by solvent extraction or chemical cleavage leads to the formation of binding sites that are complementary to the template in terms of both topography and chemical functionality. The application of transition state analogues as templates results in materials with catalytic activities [142]. MIPs demonstrate both high selectivity, stability and reusability over the long-term making them appealing in molecular recognition and catalytic processes with challenging conditions such as high temperature and pressure, extreme pH and organic solvents [143]. The focal point of recent research in the field was on the development of systems able to show enzyme-like activities for reactions for which no enzyme exists, such as the Diels–Alder reaction [144], the hetero

Diels–Alder reaction [145] and Kemp elimination [146], or to improve the activity of the already existing ones in terms of robustness, selectivity or efficiency [147]. The literature on molecularly imprinted membranes with catalytic activity in organic media is limited to a single example, Kalim *et al.* fabricated a polyvinyl alcohol based mixed matrix membranes having catalytic imprinted sites for a model β -elimination reaction [148]. The dehydrofluorination of 4-fluoro-4-(*p*-nitrophenyl)-2-butanone in acetonitrile:water (1:1) mixture at 55 °C with was successfully achieved. The potential of catalytic molecularly imprinted membranes has yet to be fully exploited, especially in the context of developing biomimetic catalytic membranes.

2.2.2. Organocatalysis and phase transfer catalysis

Small organic molecules have been used as catalysts for more than a century, but the term of organocatalysis is relatively new. It originated from MacMillan in 2008 who gave the first exact definition: “organocatalysis, or the use of small organic molecules to catalyse organic transformations, is a field within the domain of enantioselective synthesis” [150]. Historically, the rise of organocatalysis was induced by the tightening regulations in the pharmaceutical sector. As a result of the tragic case of the drug thalidomide [151], the licensing of chiral APIs became more cumbersome and the commercialisation of pure enantiomers became preferred [152]. The need for the simple production of enantiomers and the disadvantages of the applied resolution process, such as

the large demand for chiral auxiliary compounds and high waste production urged the researchers to find alternatives. The first organocatalytic studies were published in the early 1970s [8,153], but the rocketing in research articles only happened nearly thirty years later. Since then, organocatalysts have been used successfully in a plethora of different asymmetric reactions [150]. The most frequently mentioned disadvantages of organocatalysts are their high price, the high catalyst loading needed and the difficulty to separate them from product after the reaction. The latter drawback can be overcome by catalytic membrane reactors through either the immobilization of the catalyst on a membrane (heterogeneous catalysis) or its filtration assisted recovery (homogeneous catalysis).

Parallel to organocatalysis, phase transfer catalysts (PTCs) also gained considerable attention in the last century. PTCs are substances that facilitate the migration of a reactant from one phase into another phase where reaction occurs. They are used in many well-established industrial processes such as polycondensation of bisphenol A, esterification of penicillin or chloroprene production [154]. Quaterner ammonium or phosphonium salts are usually applied as phase transfer catalysts but polyethylene glycols are also recognised. Macrocycles, in particular crown ethers were one of the major inventions of the previous century in the PTC field which resulted in a Nobel Prize in Chemistry [155]. The classic example of phase transfer catalysis is the nucleophilic substitution where the nucleophilic reactant is an anion dissolved in

Table 8. Comparison of different process configurations applying organocatalyst or phase transfer catalyst published in literature in terms of reaction type, solvent(s) employed for reaction and filtration, type of membrane, catalyst rejection (%), highest conversion (%), highest enantiomeric excess and productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$).

Reference	Reaction	Solvent	Membrane	Catalyst retention (%)	Highest Conversion (%)	Highest ee (%)	Productivity ($\text{g}_{\text{product}} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$)
Kragl <i>et al.</i> [163–164]	asymmetric addition of diethyl zinc to aldehydes	hexane	Nadir UF PA20 (MWCO: 20k)	>99.8	30	50 (S), 20 (R) ^a	0.212
Kragl <i>et al.</i> [165]	asymmetric hydrogenation	hexane	MPF-50	100	>98	99	58.3
Clark <i>et al.</i> [157]	oxidation	DCM	PTFE (0.2 μm)	n/a	99	n/a	5.04
Livingston <i>et al.</i> [47, 166–167]	nucleophilic substitution	toluene	Starmem 122 (MWCO: 220)	>99	98	n/a	8.77
Livingston <i>et al.</i> [168]	asymmetric Michael addition	THF	Duramem 500, 300	>99	100	96	9.15
Kragl <i>et al.</i> [169]	asymmetric Henry reaction	THF	Duramem 200	99.6	81	89	4.72
Kragl <i>et al.</i> [170]	CO ₂ addition to epoxides	neat, EtOH ^b	Duramem 300	96	>99	n/a	19.3

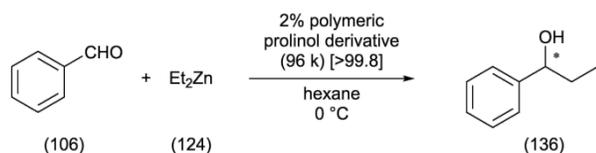
^aThe major enantiomer is dependent on the reactant ratio

^bReaction: neat, Filtration: EtOH

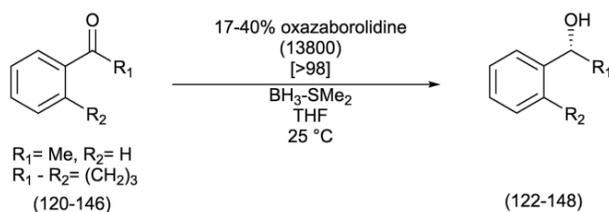
^{n/a}not applicable

water, while the substrate is a hydrophobic substance dissolved in an organic solvent. In the absence of a PTC even the thermodynamically favoured reactions have low reaction rate because (i) the substrates can only react at the interphase and (ii) the hydrated anion has a decreased reactivity. PTCs have amphiphilic nature enabling them to freely move between phases and carry the 'naked' anion into the organic phase where it can readily react with the substrate. Besides nucleophilic substitutions PTCs have been used for oxidations [156–157], dehydrohalogenations [158], and carbonylations [159] among others. Furthermore, PTCs applied with cheap, inorganic bases have become usual substitutes for expensive and toxic organic bases.

The most rapidly growing area in phase transfer catalysis is the enantioselective synthesis [160]. Consequently, the boundaries between the two types of catalysts are blurring. The recovery and reuse of these catalysts have gained increasing attention in this field as well. However, it has been proved that immobilization of these catalysts to a solid support significantly decreases their activity and selectivity [161–162]. Little attention has been paid to membrane-assisted organocatalytic and PTC processes, except by the Livingston and Kragl research groups (Table 8). This section discusses the accomplishments and the potential in this field of membrane reactors.



Scheme 33. Addition of diethylzinc (36–7 mM) to benzaldehyde (14–43 mM) in the presence of a soluble polymeric bound organocatalyst (10 g·L⁻¹) in hexane at 0 °C. In excess of the benzaldehyde, the (*S*) enantiomer, while in excess of diethyl zinc the (*R*) enantiomer was the main product [163–164].



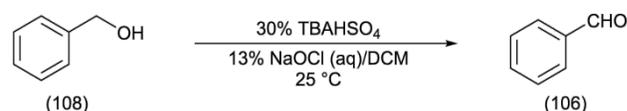
Scheme 34. Polymeric bound oxazaboroline catalysed CBS reduction of aromatic ketones (100–250 mM) with borane dimethyl sulphide complex (100–200 mM) in THF at 25 °C [165].

The first organocatalytic membrane reactors appeared already in the early days of the modern organocatalysis, in the late 1990s. Proline, and natural amino acids in general were the first wave of catalysts, as they are stable, easily modifiable and readily available in an enantiomeric form [171]. A soluble polymeric bound prolinol catalyst was applied in the asymmetric addition of diethyl zinc to benzaldehyde (Scheme 33) [163–164]. In a continuous membrane reactor, the enlarged catalyst (MW: 96k g·mol⁻¹) was successfully rejected by a polyamide ultrafiltration membrane (MWCO: 20k). The enlarged catalyst had preserved activity over a week of

continuous operation, however because of solubility issues, the achieved conversions were low (12–30%). Surprisingly, the configuration of the major enantiomer was found to be dependent on the molar ratio of the reactants. In excess of the benzaldehyde, the (*S*) enantiomer, while with excessive amounts of diethylzinc the (*R*) enantiomer formed with 50% and 20% enantiomeric excesses, respectively.

Similar polymer-bound catalysts were prepared [172], then used in Corey–Bakshi–Shibata (CBS) [173] reduction (Scheme 34) [165]. The spreading of solvent-resistant nanofiltration membranes allowed more efficient synthesis techniques. With Koch's PDMS-based MPF-50 membrane, THF could be used as reaction media and quantitative catalyst rejection was achieved.

High enantiomeric excess values up to 99% and almost quantitative yield were obtained in the continuous membrane reactor. Outstanding productivity as high as 58 was achieved during the 65 hours operation time which is about 3–10 times higher than observed with rhodium or ruthenium catalysts (see Table 3 and Table 4). However, the process is less atom efficient than hydrogenation since stoichiometric amounts of boronic esters and dimethyl sulfide are formed.

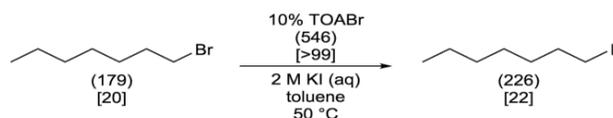


Scheme 35. Selective oxidation of benzyl alcohol (0.12 M) to benzaldehyde in a biphasic system of DCM and 13% aqueous NaOCl solution at 25 °C using tetrabutylammonium bisulfate (TBAHSO₄) as the phase transfer catalyst. The phases were contacted by a hydrophobic PTFE membrane [157].

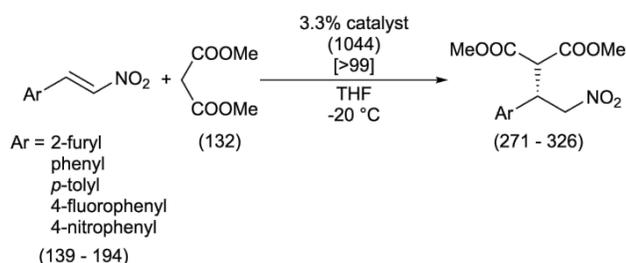
The biphasic reactions usually require good phase contact which can be obtained by vigorous stirring. However, this can favour emulsion formation in the presence of PTCs and can cause slow phase separation. The application of membranes as phase contactors can overcome this problem. The use of a membrane reactor under phase transfer conditions was theoretically modelled and tested in a simple anion displacement reaction [174]. A similar approach was presented by Clark *et al.* who used the selective oxidation of benzyl alcohol to benzaldehyde as a model reaction (Scheme 35) [157]. The substrate and the PTC were introduced in DCM solution while the aqueous phase contained the inexpensive hypochlorite oxidant. A hydrophobic microporous PTFE membrane (0.2 μm) was used and a small overpressure was applied to the inorganic side to prevent any migration of the organic phase. Good yield, selectivity and reaction rates were achieved without any emulsification. However, this approach does not deal with the removal or recycling of the PTC. Some attempts have been made to incorporate the PTCs in membrane contactors [175–176]. Nonetheless, in those reactions only low conversion was reached as the reaction rate suffered from low mass transfer across the membrane.

Recycling PTCs from the post-reaction mixtures using membrane separation has also been investigated. The simple anion exchange reaction of 1-bromoheptane and

potassium iodide was used as a model reaction (Scheme 36) [47,166–167]. After the reaction, the organic phase was separated and went under solvent-resistant nanofiltration. The applied Starmem® 122 membrane rejected the tetraoctylammonium bromide (TOABr) catalyst effectively therefore it could be reused in another two cycles with preserved activity. During the dead-end filtration, a steady decline was observed in the flux from around 40 to 10 L·m⁻²·h⁻¹. Increased adsorption of the PTC on the membrane surface near its maximum solubility, concentration polarisation and osmotic pressure were identified as the reasons for this phenomenon. However, a simple washing step after the filtration allowed the efficient regeneration of the membrane [167].



Scheme 36. Phase transfer catalyzed substitution reaction of 1-bromoheptane (0.5 M) in a biphasic system of toluene and aqueous KI solution at 50 °C in the presence of tetraoctylammonium bromide (TOABr) [167].

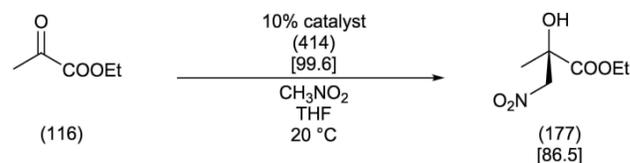


Scheme 37. Asymmetric Michael addition of dimethyl malonate (3 M) to β -nitrostyrenes (1 M) in THF at -20 °C in the presence of an enlarged quinidine-based organocatalysts [168].

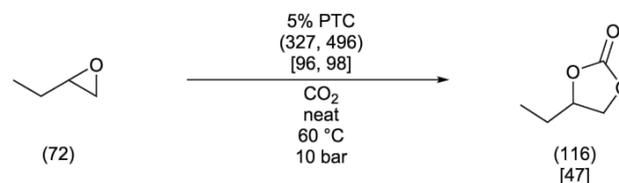
Bifunctional organocatalysis is a useful tool to produce new carbon-carbon bonds enantioselectively using CH-acidic compounds. The chiral organocatalyst needs to contain both a Brønsted basic group to activate the CH-acidic reactant and a hydrogen bond donor group to coordinate the substrate in the right position for the enantioselective addition. Bifunctional catalysts have been used successfully in aldol addition, Michael reaction and Henry reaction. Quinine and its derivatives often serve as a starting material for the catalyst synthesis for these reactions. The choice is obvious as quinine and other cinchona alkaloids are readily available, densely chiral thanks to the four chiral centres and have a basic tertiary amino group. Enlarged quinidine trimers were used in membrane-assisted asymmetric Michael addition (Scheme 37) [168]. In the presence of catalysts lacking basicity no reaction occurred, however, catalysts having basic groups but without hydrogen bond donor sites exhibited negligible enantioselectivity.

The catalyst possessing basic nature and hydrogen bonding sites showed good activity and enantioselectivity. The different catalytic performance of the quinidine based enlarged catalysts confirmed the mentioned theory of bifunctional catalysis [168]. Another promising catalyst candidate was synthesized, but unfortunately it was

neither characterized nor tested in the model reaction or membrane experiment. The membrane separation suffered from high product rejection. However, because the rejection of the catalyst was complete, the separation could be accomplished. Another bifunctional quinine derivative was used in enantioselective Henry reaction (Scheme 38) [169]. Despite the small molecular weight difference between the catalyst and the product (414 and 177 g·mol⁻¹, respectively), good flux and rejection for the catalyst was achieved with a Duramem® 200 nanofiltration membrane. The catalyst was used in four cycles of batch reaction and filtration. High enantiomeric excess of about 88% and 80% yield was observed in the first three cycles. In the fourth batch the yield was less than 40%, however the enantiomeric excess remained high (89%). The performance decline was attributed to the incomplete catalyst rejection and to the retentate sampling during the experiment rather than to catalyst deactivation.



Scheme 38. Asymmetric Henry reaction of ethyl pyruvate (0.5 M) and nitromethane (5 M) in THF at 20 °C in the presence of a quinine-based organocatalysts [169].



Scheme 39. Carbon dioxide addition to solvent-free butylene oxide catalysed by 2-hydroxyethyltributylphosphonium iodide (HETBPI) or 2-hydroxyethyltrioctylphosphonium iodide (HETOPI) at 60 °C and 10 bar [170].

Recently, CO₂ as a renewable C1 building block have gained significant attention. The thermodynamic stability and kinetic inertia hinder the utilization of CO₂ as a feedstock in chemical processes. Therefore, usually high-energy starting materials, elevated reaction temperatures, and highly active catalysts are needed. The addition of CO₂ to epoxides yielding cyclic carbonates has been intensively studied. The obtained products can have various applications as synthesis building blocks, plasticizers or green solvents as well as for the synthesis of polymers. The PTC catalysed production of butylene carbonate coupled with catalyst recovery was investigated (Scheme 39) [170]. PTCs containing hydroxyl groups outperformed others featuring up to 99% product yield. High volumetric productivity of 19.3 g·L⁻¹·h⁻¹ was achieved because no solvent was used in the reaction. However, a large amount of ethanol (440 mL per 7 g_{product}) was used for the 11 steps of the stepwise diafiltration process after each reaction cycle. As a considerable amount of catalyst was lost in the 11 diafiltration steps (20%), the addition of fresh catalyst

was necessary in each subsequent run to maintain the catalyst/substrate ratio. Nonetheless, the catalytic activity was preserved throughout all the runs.

Organocatalysts and PTCs do not contain sensitive functional groups, they have low reactivity, and consequently they are robust catalysts with minimal or no degradation. On the contrary, most of the transitional metal catalysts tend to partially or completely lose their activity. Hence, organocatalysts and PTCs are especially suitable for recycling and long-term applications. There are many future possibilities in the field of organocatalytic and phase transfer catalytic membrane reactors. Catalysts are usually required to have high degree of purity otherwise the impurities can cause undesired side reactions or they can contaminate the product. As the commonly used chromatography is difficult to scale up, nanofiltration has also been studied as an alternative tool in the purification of organocatalysts and PTCs [177–178].

Despite continuous processes have been gaining even more ground in the past few years, there is no recent example in the literature for using organocatalyst or PTC in continuous membrane reactors. Similarly, the recently developed flow chemistry has not yet been combined with downstream membrane separations. However, there are developments which indicate that this field might get more attention in the near future. PTC catalysed synthesis [179] and phase separation [180] have already been executed in flow systems separately, but the conjuncture of these processes has not been realized yet. Phase transfer catalytic processes combining two membrane modules with different aims (phase contactor and catalyst filter) can be another direction of future development.

Conclusions

Ever since catalysts as non-consumable promoters of chemical reactions are in use, recycling of these valuable materials is a major environmental and economical challenge. Catalyst enlargement deemed to be essential to achieve high rejection and consequently good recovery for many years. Various catalysts were enlarged through polymer anchoring which was followed by the atom-efficient hub approaches in which the catalysts were attached as side arms to a low molecular weight reactive core molecule. Thanks to the latest improvement in membrane materials, catalyst enlargement is less necessary as the new generation of membranes can have as low MWCO as 150. Numerous examples showed quantitative recovery of organocatalysts and phase transfer catalysts. Nevertheless, recycling of transition metal complexes is still limited due to their lower stability.

Despite every effort, reused ruthenium metathesis catalysts showed significant activity decline. On the contrary, recycling of palladium and rhodium complexes is more feasible with acceptable loss of activity over several cycle. Besides the recovery of catalysts, membranes also assist in the elimination of toxic catalysts and degradation products from the postreaction mixtures ensuring clean products. However, challenges to be solved include catalyst fouling on the membrane surface

and long-term membranes stability in the presence of harsh solvent and reactive reagents.

Significant time and cost saving can be realised by continuous processes due to higher throughput and single catalyst pre-activation. Furthermore, microfluidic devices as flow reactors combined with catalytic membranes can provide selective production for a variety of desired products with as short residence time as one second. These devices demonstrated excellent reactor productivity, whereas only small scale production can be achieved. Retention of biotransformation catalysts in continuous processes by membranes seems to be a straightforward approach for improving turnover numbers. However, stability and solubility, particularly in organic media are limiting factors. Some enzymes, namely immobilized lipases and α -chymotrypsin, showed improved activity and good stability in highly lipophilic media. Encapsulation of enzymes in reverse micelles provides a versatile tool to avoid enzyme deactivation during long-term operation. Biphasic approaches applying hydrophobic membranes suffer from mass transfer limitations.

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