Recent Advances in Continuous Rhodium-Catalyzed Hydroformylation

Xiao Wang

Harvard NeuroDiscovery Center, Harvard Medical School and Brigham and Women's Hospital,
65 Landsdowne Street, Cambridge MA 02139, USA; CAS Key Lab of Low-Carbon Conversion Science and Engineering,
Shanghai Advance Research Institute, Chinese Academy of Science, 100 Haike Road, Pudong, Shanghai 201210, P. R. China

This review focuses on the development of continuous rhodium-catalyzed hydroformylations in the past 15 years. Recent progresses are discussed and compared in detail, based on different types of catalyst handling including single-phase homogeneous system, multiphase system, immobilized catalysts on solid supports, supported ionic liquid phase catalyst, and scCO$_2$–ionic liquid biphasic system.

Keywords: hydroformylation, continuous process, higher olefins, catalyst immobilization, ionic liquid, supercritical carbon dioxide

This paper is dedicated to Prof. Stephen Buchwald on the occasion of his 60th birthday.

1. Introduction

Hydroformylation is one of the mildest and most efficient methods to produce aldehydes [1]. It is considered one of the most important homogeneously catalyzed industrial processes. More than 10 million tons of oxo products are produced worldwide annually using this process. Homogeneous catalysis has unique advantages [2a] in hydroformylation compared to heterogeneous processes [2b–2e], in terms of catalyst activity and selectivity. However, recycling of homogeneous catalysts, especially the rhodium complexes, remains a challenge thus hampering its wide use in industrial production. In addition, rhodium-catalyzed hydroformylation has not yet been commercialized for C6 or longer linear alkenes because separation of the low volatility aldehydes from the thermally unstable Rh catalyst remained a problem [3]. To enhance the efficiency of catalyst recovery, while still keeping the advantage of using a homogeneous catalytic system, researchers made efforts in largely two categories of catalyst modification: (1) heterogenization, which means anchoring the catalyst on a soluble or insoluble support [4, 5]; (2) using a biphasic system [6]. Problems with the latter approach include insufficient catalyst usage and variability in phase separation.

Continuous process has many obvious advantages in the industrial production of chemicals. Continuous hydroformylation of propene has been realized for a long time, utilizing homogeneous Rh catalysts in high boiling solvents [7–9] or using an aqueous biphasic system (Ruhrchemie/Rhône-Poulenc process) [10]. However, for higher olefins, it is more challenging to separate the reaction mixture from the catalyst phase. To achieve this, the catalyst has to be more strongly immobilized. The other challenge for higher olefins is their low immiscibility with the catalyst phase because of the increased lipophilicity, if the catalyst is dissolved in aqueous medium. Moreover, the catalyst has to remain active for a long period of time and has a low leaching effect because of the high cost of rhodium catalysts as compared to the cobalt complexes. Combining these requirements is even more demanding, thus little progress has been made in this area [11]. This review will focus on several recent strategies to address these problems.

Research in continuous hydroformylation has been done only by a few groups worldwide. In general, recent progress in this area can be categorized into five major types, depending on the handling of catalyst: (1) single-phase homogeneous system, (2) multiphase system, (3) catalyst immobilized on a solid support, (4) supported ionic liquid-phase catalysis, and (5) supercritical fluidionic liquid biphasic systems. Among these, the latter two strategies involving ionic liquids are a subset of catalyst immobilization, but will be discussed separately.

2. Single-Phase Homogeneous System

Flow reactors have significant advantages for gas-liquid reaction due to their high surface to volume ratios that will lead to high mass and heat transfer rates [12, 13]. As for hydroformylation, the required high pressure usually results in safety concerns for batch reactors. However, the gas-liquid flow reactor can safely and easily allow for higher overall pressure, which eases material handling and in-line optimization [14]. Ley recently developed a continuous-flow hydroformylation process facilitated by a tube-in-tube gas-liquid reactor, which is based on the semipermeable polymer Teflon AF-2400 [15, 16]. Similar to typical batch hydroformylation that employs homogeneous Rh catalyst, styrene derivatives were dissolved in an organic solvent that also contains Rh(CO)$_2$(acac) and the ligand Ph$_3$P. Reaction of all styrene-type substrates could be completed in 58 min with isolated yields of branched aldehyde from 69% to 94% (conditions: CO/H$_2$ = 1:1, 25 bar, 65 °C, MeOH/PhCH$_3$ = 1:1). The acceleration effect of flow reaction came from the generation of homogeneous solutions of gas in liquid by the tube-in-tube reactor (Figure 1). The authors further tested the utility of this reactor in gas-liquid homogeneously catalyzed reactions, by performing a two-step flow process combining Heck reactions with hydroformylation.

Similar to their previous work on continuous hydroformylation using polyhedral oligomeric silsesquioxanes (POSS) enlarged triphenylphosphine, Vogt and coworkers recently described a continuous homogeneous hydroformylation of cyclooctene, using a jet-loop reactor coupled with membrane nanofiltration [17]. A commercial bulky phosphite was used to form the active catalyst (Rhtris(2,4-di-*tert*-butylphenyl)phosphite) with toluene
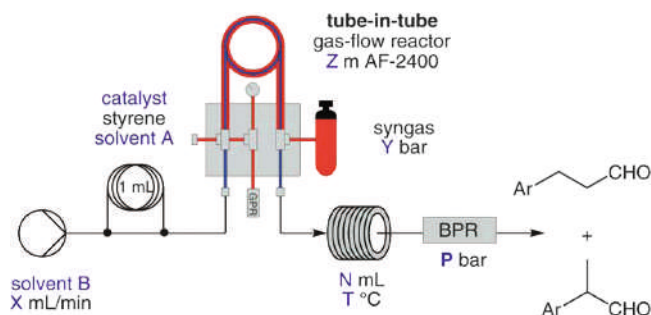

Figure 1. Gas-flow reactor for homogeneous hydroformylation of styrene (ref. [15]; Copyright 2011 Thieme)

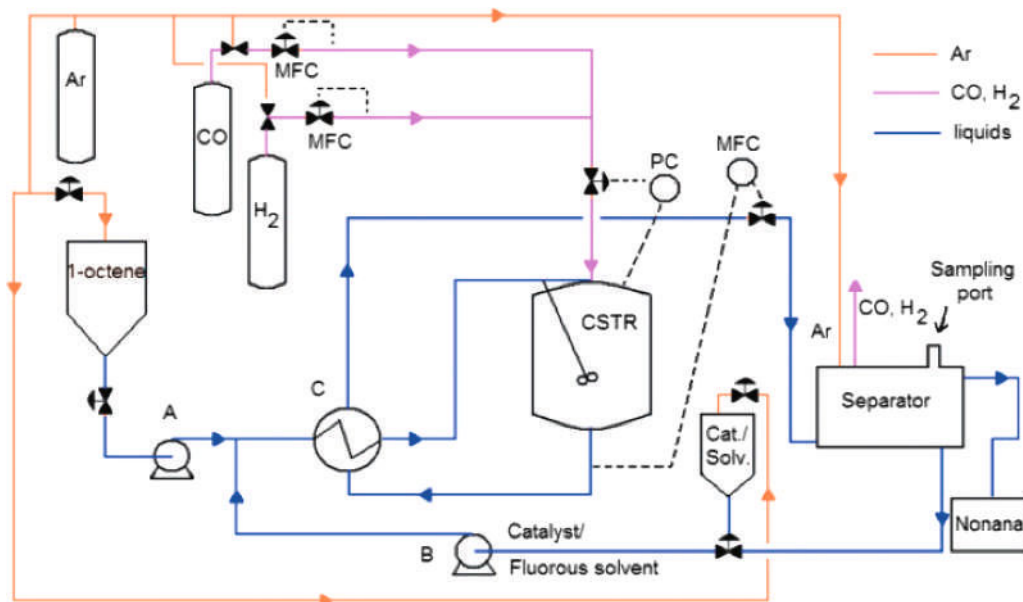* Author for correspondence: xwang21@bics.bwh.harvard.edu

Figure 2. Schematic diagram of a biphasic continuous-flow reactor (Abbreviations: A = 1-octene pump; B = fluorous pump; C = heat exchanger; CSTR = continuously stirred tank reactor) (ref. [20]; Copyright 2004 Royal Society of Chemistry)

as solvent to form a homogeneous reaction medium. Kinetic data showed a high total turnover number (TON) of 44,300 in a total reaction time of 47 h (5 residence times) demonstrating the usefulness of this reactor design, which enables use of a commercially available phosphite ligand without any further molecular weight (MW) enlargement or catalyst immobilization on a solid or soluble support.

3. Multiphase System

Among multiphase catalysis systems, the fluorous biphasic system has unique advantages such as temperature-dependent phase behavior [18, 19]. Many fluorousorganic mixtures remain a single phase at the elevated temperature, allowing homogeneous fluorous catalyst. However, the phases separate upon cooling, allowing feasible separation and recycle of the fluorous catalyst. Manos and Cole-Hamilton developed a fluorous biphasic system, with the fluorous catalyst phase consisting of the precatalyst Rh$(CO)_2$(acac), fluorous ligand $P(p-C_6H_4C_6F_{13})_3$, and perfluoromethylcyclohexane as the fluorocarbon solvent [20]. Syngas, 1-octene, and the fluorous catalyst phase were pumped into a well-stirred continuous-flow reactor, and the reaction mixture was continuously

removed to a gravity separator, where the cool temperature allows phase separation (Figure 2). The nonanal products were removed, and the fluorous catalyst phase was pumped back to the reactor. During the continuous run for 19 h, n-nonanal was obtained with the optimum yield of 20%–40%, with the highest l/b ratio of approximately 9. The fluorous catalyst has a total TON of larger than 15,500, and the average turnover frequency (TOF) was 705/h which equals commercial processes (500–700/h).

Industrial biphasic hydroformylation of olefins of C8 or higher has not been established, due to their low solubility in an aqueous phase. In order to identify an effective multiphase system that could improve solubilization, increase the interfacial area, and improve catalyst recycling, Wozny and Schomäcker did an extensive study on the effect of surfactants, and developed a three-phase medium for the hydroformylation of long-chain olefins with a water-soluble rhodiumSulfoXantPhos catalyst [21]. The selectivity with the bidentate ligands (SulfoXantPhos) was found to be l/b = 49, which was significantly higher than for monodentate ligands (e.g., TPP and TPPTS). Alkylphenol ethoxylates such as Marlophen NP9/Sasol were used as nonionic surfactants (Figure 3).

The authors identified four different phase states within the system, depending on temperature and surfactant concentration
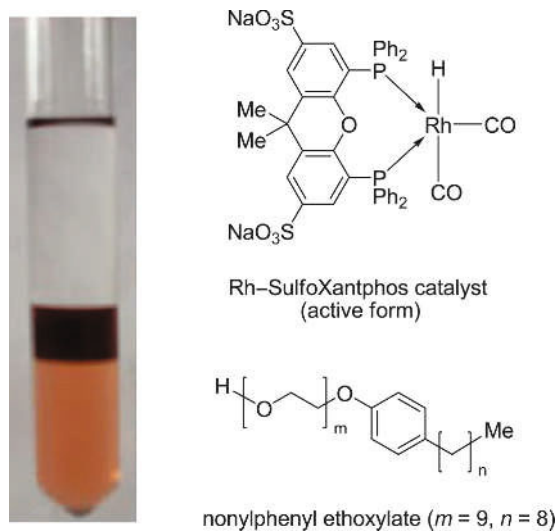

Figure 3. Three-phase system with most of catalyst (Rh—SulfoXantPhos) in the surfactant-rich middle phase (ref. [21]; Copyright 2013 Elsevier)
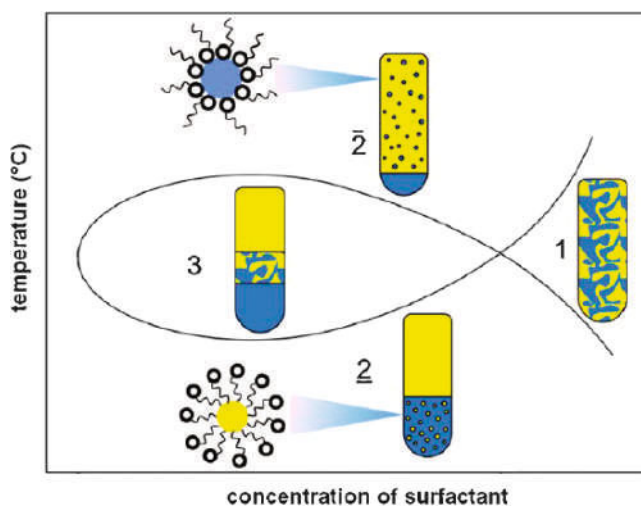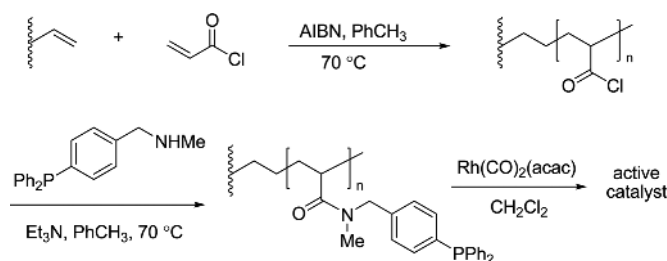

Figure 4. Schematic phase diagram of nonionic surfactant (ref. [21]; Copyright 2013 Elsevier)

Scheme 1. Functionalization of *poly*-TRIM particles containing unreacted double bonds


(Figure 4). At medium temperature and low surfactant concentration, a three-phase system was formed, with most of the Rh–SulfoXantPhos catalyst in the surfactant-rich middle phase. This triphasic state has been identified as the optimal state for reaction and separation, where the conversion of olefins was typically 10%–20% higher than the biphasic region. The hydroformylation took place in a continuous stirred tank reactor (CSTR). Post-reaction phase separation allowed the catalyst phase to be recycled back to the reactor. Based on these results, Muller and Schomäcker also constructed a miniplant for this continuous process [22].

4. Catalyst Immobilized on a Solid Support

Polymer-bound transition metal catalysts, especially when used in continuous flow, are advantageous compared to their homogeneous counterparts because catalyst recovery is simple. However, over a long term, these immobilized catalysts are not sufficiently stable due to metal leaching. In hydroformylation, at higher CO pressures, the phosphorus ligand is often rapidly exchanged with CO, resulting in the leaching of rhodium [23]. This has hampered the wide application of such catalysts in large-scale industrial processes.

In 1993, Hjortkjaer and Andersson reported the continuous hydroformylation with functionalized *poly*-(trimethylolpropanetrimethacrylate) (*poly*-TRIM) [24]. Phosphine-containing support particles were prepared and allowed to react with $Rh(CO)_2(acac)$, and the formed *poly*-TRIM-bound Rh catalyst was used in the continuous liquid-phase hydroformylation of propene (Scheme 1). The influence of particle type, particlephosphine combination, and Rh/P ratio were explored. At 60 °C and a syngas pressure of 6 bar, these catalysts proved highly active with butanal forming rates of between 3×10^6 and 110×10^6 mol/s. The catalysts were found to be highly stable with no loss in activity after 215 h. In follow-up work, the authors described the hydroformylation of 1-hexene using the same catalytic system [25]. At 25 bar and 60–100 °C, high conversions were achieved, with optimal l/b ratio of 3.7 (at 100 °C). However, due to the liquid nature of the starting material and hydroformylation products, the catalyst deactivated with time, due to the elution of rhodium from the support particles.

To overcome the product-catalyst separation problem involved in biphasic hydroformylation of higher olefins, van Leeuwen and Poliakoff [26] reported the first example of a continuous process for the selective hydroformylation of higher olefins in supercritical carbon dioxide (scCO$_2$) using an immobilized homogeneous rhodium catalyst [27]. By immobilizing the rhodium complex derived from *N*-(3-trimethoxysilyl-*n*-propyl)-4,5-bis(diphenylphosphino) phenoxazine (SiloXantPhos, Figure 5) on silica (particle size
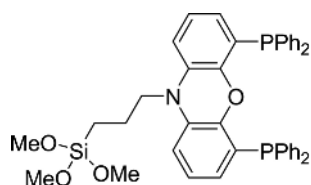
200–500 μm), the authors were able to hydroformylate 1-octene with 14% maximum conversion and 40:1 l/b ratio in a supercritical flow reactor. Up to 90% of the unreacted 1-octene could be recovered from the product by controlling the two-step depressurization of CO$_2$. In addition, the catalyst could be used for six nonconsecutive days with no observable decrease in activity or selectivity. No rhodium leaching was detected by atomic emission spectrometry (AES), the detection limit of which was 0.2% of the total amount of rhodium. Afterwards, the authors tested other ligands, but the results did not improve much [28].

In 2003, after the discovery of (*R,S*)-Binaphos [29], a milestone ligand for asymmetric hydroformylation, Nozaki successfully anchored this ligand to a highly cross-linked polystyrene support [30] (Figure 6). Several organic-solvent-free asymmetric hydroformylations were performed. The reaction of the gaseous *cis*-2-butene provided (*S*)-2-methylbutanal with 100% regioselectivity and 82% ee in a fixed-bed batchwise reactor ($P(H_2) = P(CO) = 12$ bar, 60 °C). This polymer-bound catalyst was used in a continuous vapor-flow column reactor for the reaction of the volatile 3,3,3-trifluoropropene (Figure 7). The product (*S*)-2-trifluoromethylpropanal could be obtained with 90% ee. The branched product predominated (l/b = 5:95) mainly because of electron-withdrawing effect of CF$_3$ group. By employing a scCO$_2$ flow column reactor, nonvolatile olefins such as styrene, vinyl acetate, and 1-octene could be successfully converted into the corresponding branched aldehydes with high ee values.

Siliceous mesostructured cellular foams (MCFs) are hydrothermally robust materials with ultralarge mesopores, which enable MCFs as unique catalyst supports for chemical processes involving large molecules [31]. Ding used a fixed-bed reactor filled with Rh catalyst on a PPh$_3$-modified mesostructured cellular foam (MCF) to perform gas-phase hydroformylation [32]. Transmission electron microscope (TEM) analysis showed small and evenly distributed rhodium particles (Figure 8), whose diameter (1.4 nm) was in accord with the hydrogen chemisorption experiment. Hydroformylation of propylene was studied, and parameters such as conversion, TOF and l/b ratio were compared between the PPh$_3$-Rh/MCF and other fixed-bed catalysts such as the classical heterogeneous Rh/MCF catalyst and the HRh(CO)(PPh$_3$)$_3$/MCF catalyst, in which the new catalyst outperformed the traditional ones.

To expand the scope of the well-known Ruhrchemie/Rhône-Poulenc (RCH/RP) hydroformylation process to include higher olefins, Müller and Vogt used the molecular weight enlargement (MWE) strategy [33], introducing polyhedral oligomeric silsesquioxanes (POSS) as a versatile soluble support and nanofiltration to facilitate catalyst recycling [34] (Scheme 2). In a continuous-flow nanofiltration reactor, the Rh catalyst derived from POSS-modified PPh$_3$ ligand was employed in the hydroformylation of 1-octene (Figure 9). Unprecedented activity, stability, and retention of the POSS-enlarged catalyst system were observed. The highest octene conversion of 99% was obtained after 17 h of operation. Being cubical and rigid in shape, the POSS cages could be efficiently recovered by nanofiltration, and no significant leaching of the catalyst was detected. The conversion remained greater than 90% after continuously operated for almost 2 weeks.
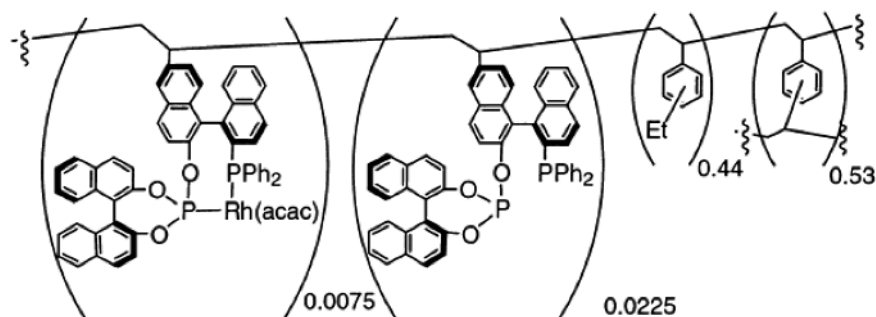

Figure 5. Structure of the SiloXantPhos ligand to be immobilized on silica

Figure 6. Immobilized Rh(Binaphos) catalyst on a highly cross-linked polystyrene support (ref. [30]; Copyright 2003 American Chemical Society)

Subramaniam reported a similar continuous process using different bulky phosphite ligands bound to polymers (average molecular weight from 7000 to 10,000) [35]. In a stirred reactor equipped with a nanofiltration membrane, at optimized conditions (JanaPhos, 50 °C, 30 bar pressure), 1-olefins could be continuously converted to the corresponding linear aldehydes with nearly 50% conversion, and >98% aldehydes selectivity and l/b ratio of 3.5 were observed.

Recently, Haumann et al. used a strategy that did not employ supported ionic liquid-phase (SILP), but just used the long-chain product formed in situ as the solvent for gas-phase hydroformylation [36]. The RhSulfoXantPhos catalyst was deposited on porous Silica 100 by incipient-wetness impregnation, and the catalyst was tested for the gas-phase hydroformylation of 1-butene. The formed high-boiling aldehydes and aldol products fill the pores; thus, the active catalyst dissolved in the condensed phase of products operates in a homogeneous fashion (Figure 10).

The catalyst was stable and active after 70 h, although the conversion was as low as 5%. The l/b ratio of the aldehyde products was as great as 97%, which was in accord with the results obtained with homogeneous liquid phase or SILP. For improving the activity, the SiO_2-supported Rh catalyst using benzopinacol-based phosphite ligands demonstrated much higher activity with a conversion of 47% (Figure 11). This was presumably due to the better π-acceptor ability of the phosphite ligands that strengthens the overall metalligand bonding, thus, facilitating CO disassociation and alkene association which is often the rate-determining step for hydroformylation [37]. A significant weight increase of up to 30% was found by weighing the catalytic material after the reaction, and this mass increase was attributed to the high-boiling compounds mostly consisting of the aldol condensation products.

5. Supported Ionic Liquid-Phase Catalysis

Immobilizing homogeneous catalysts in two-phase catalytic hydroformylation is an effective way to enhance catalyst separation and recycling. For example, the aqueous two-phase Ruhrchemie/
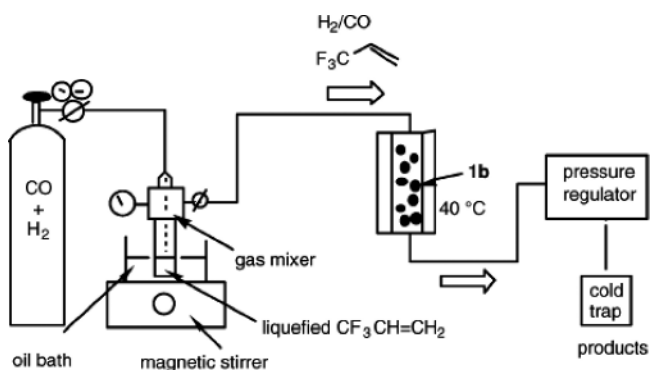
Rhône-Poulenc (RCH/RP) hydroformylation process [10, 38] of lower olefins (C3C5) utilizes aqueous Rh–tris(*m*-sulfonatophenyl) phosphine (TPPTS) complexes and the supported aqueous-phase (SAP) catalysts with water-soluble rhodiumphosphine complexes immobilized on solid supports [39]. However, for higher olefins, reaction rates are often limited by the insolubility of the lipophilic substrate in the catalyst phase. Alternative approaches to aqueous biphasic and SAP catalysis include ionic liquid-phase hydroformylation [40,41], and supported ionic liquid-phase (SILP) hydroformylation [42]. The latter system was established by Mehnert's team in ExxonMobil, by forming a fixed-bed reactor utilizing Rh–phosphine complexes dissolved in a silica-supported ionic liquid film (Figure 12). The SILP catalyst system (HRh(CO)(TPPTI)$_3$ in [BMIM][BF$_4$]; TPPTI = tri(*m*-sulfonyl)triphenylphosphine tris(1-butyl-3-methyl-imidazolium) salt) was tested for the hydroformylation of 1-hexene, with a much lower (but still satisfactory) TOF of 65/min as compared to 400/min when using a homogeneous system.

Fehrmann extended the concept of SILP catalysis to the continuous gas-phase hydroformylation of propene, with TOF of up to 88/h, however, with low selectivities of linear aldehyde (l/b = 2.8) [43a]. The catalyst was prepared by immobilizing Rh coordinated with monophosphines (bis(*m*-phenylguanidinium) phenylphosphine or NORBOS-Cs$_3$, Figure 13) in [BMIM][PF$_6$] on a silica support. The SILP fixed-bed catalyst was installed in a stainless-steel tubular reactor to assemble a microcatalytic flow system [43b] (Figure 14). With the same system, Fehrmann also reported the first example of continuous SILP liquid-phase hydroformylation of 1-octene.

Since halogen-containing ionic liquid such as [BMIM][PF$_6$] are not considered environmentally safe, Fehrmann used the greener [BMIM][*n*-C$_8$H$_{17}$OSO$_3$] as a halogen-free alternative solvent for the catalyst [44]. SulfoXantPhos was selected as optimal ligand because of its ionic nature and the high l/b ratio in previous studies [45]. In the continuous hydroformylation of propene, higher linear aldehyde content (95%, l/b = 19) was
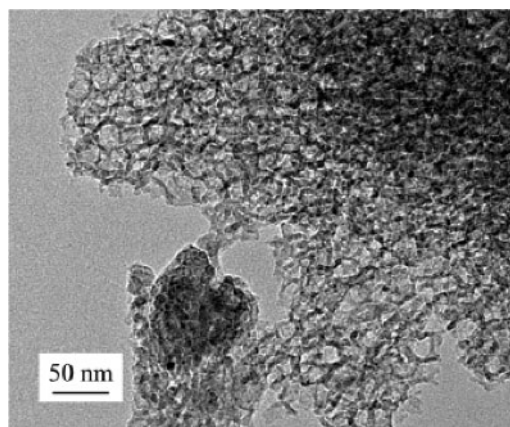

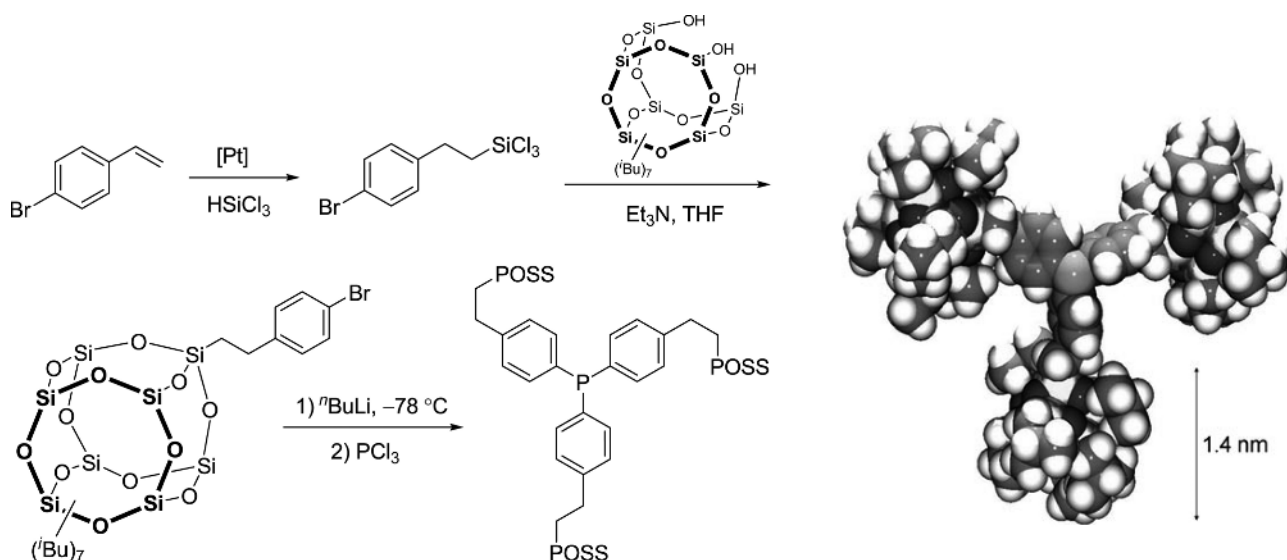**Figure 7.** Continuous asymmetric hydroformylation of 3,3,3-trifluoropropene using a continuous-flow reactor (ref. [30]; Copyright 2003 American Chemical Society)

Figure 8. TEM image of the PPh$_3$-Rh/MCF catalyst (ref. [32]; Copyright 2006 Elsevier)

Scheme 2. Synthesis of POSS-enlarged PPh₃ (ref. [34]; Copyright 2010 John Wiley & Sons)

obtained as compared to the combination of Rh-NORBOS-Cs₃ and [BMIM][PF₆].

Riisager and Wasserscheid carried on this work by exploring the effect of the number of surface silanol groups on the silica support [46]. They found that in the continuous gas-phase hydroformylation of propene, the dehydroxylation of silica surface is crucial for the stability of the catalyst. Meanwhile, the ligand/Rh ratio should remain high to ensure sufficient amount of active catalyst, and to compensate for loss of ligand due to binding irreversibly to surface acidic OH groups. The infrared (IR) data for the Rh–SulfoXantPhos/[BMIM][n-C₈H₁₇OSO₃]/SiO₂ catalyst were very similar to that of Rh–SulfoXantPhos, suggesting that the catalysis in the supported ionic liquid phase was indeed homogeneous.

Haumann and coworkers continued this work by extending the method to the continuous hydroformylation of 1-butene [47]. With [BMIM] [n-C₈H₁₇OSO₃] and Rh–SulfoXantPhos, the catalytic activity was found to be much higher than that in the hydroformylation of propene. The TOF for 1-butene was 2.12.5-fold to that for propene. This could be explained by the solubility difference, since the solubility of 1-butene in [BMIM][n-C₈H₁₇OSO₃] was 2.4 times higher compared to propene as measured by magnetic suspension balance. The authors also studied the effect of replacing the silica gel support with porous glass. However, both propene and 1-butene were much less soluble in the porous glass supported ionic liquid phase (18% of that for silica supported IL).

Haumann further expanded the scope of the system by employing an Rh–diphosphiteSILP catalyst for the continuous hydroformylation of an even more challenging feedstock: the light and non-converted fraction of a typical industrial C4 dimerization plant [48]. The feedstock has low concentration of alkenes (1.5% 1-butene and 28.5% $cis/trans$-2-butene) and 70% inert saturated n-butane (Scheme 3). The authors chose BiphePhos as ligand, which was known to be capable of performing the isomerizationhydroformylation process [49]. The Rh–BiphePhosSILP catalyst was able to convert up to 81% of butenes, providing n-pentanal with selectivity greater than 92%, with a residence time of 155 s. The performance of the catalytic system remained stable for over 500 h on-stream.

6. Supercritical Fluid-Ionic Liquid Biphasic System

Brennecke [50, 51] pointed out that supercritical carbon dioxide (scCO₂) has a unique combination of abilities: (1) highly soluble in certain ionic liquids, (2) able to extract many organics with different functionality from ionic liquids, and (3) able to

transport permanent gases into the ionic liquid. Based on these facts, early work of biphasic scCO₂IL hydroformylation was done by Leitner [52,53] and Erkey [54,55] with windowed batch reactors. Later on, Cole-Hamilton built the first scCO₂ continuous-flow hydroformylation reactor system [56] utilizing ionic rhodium complex derived from Rh₂(OAc)₄ and [PhP(C₆H₄SO₃)₂][PrMIM]₂ (PrMIM = 1-propyl-3-methylimidazolium) in ionic liquid [BMIM][PF₆]. Hydroformylation of 1-octene was carried out using scCO₂ as a transport vector for both gaseous and liquid substrates and products (Figure 15). Approximately 40% conversion could be realized with 85% of the products being aldehydes (l/b = 6.1). Advantages of this supercritical fluidionic liquid (SCFIL) protocol over the traditional liquid-liquid biphasic system include: (1) all of the catalyst remains in its active state during the course of reaction, (2) easy separation of products and unreacted starting material from catalyst phase (less than 1 ppm rhodium
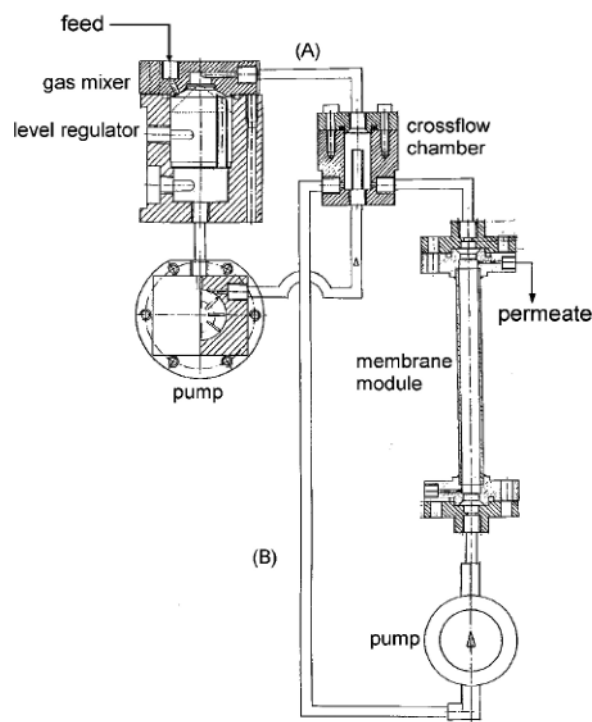
Figure 9. The continuous-flow nanofiltration reactor (ref. [34]; Copyright 2010 John Wiley & Sons)
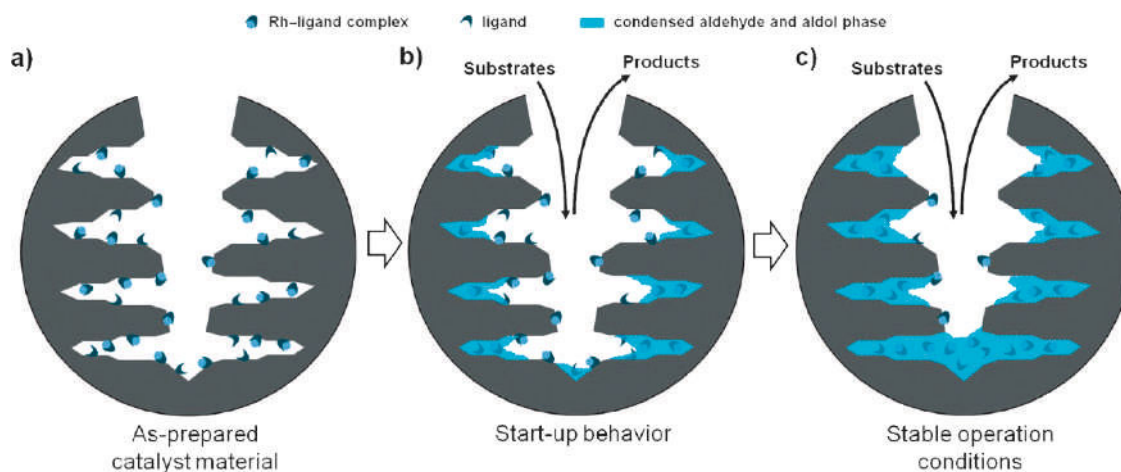
Figure 10. Illustration of pore filling with aldehyde and aldol products during hydroformylation (ref. [36]; Copyright 2013 John Wiley & Sons)
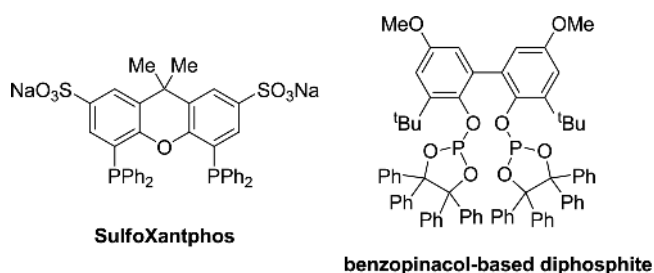

Figure 11. Ligands for the Rh catalysts dispersed on the internal surface of porous silica (ref. [36]; Copyright 2013 John Wiley & Sons)

was leached), and (3) simple removal of gaseous medium/reactant from products by decompressing the mixture at downstream.

In a follow-up report [57], with the same SCF-IL biphasic continuous reaction system ($Rh(CO)_2(acac)$ and [PrMIM][TPPMS] in ionic liquid [BMIM][PF_6]) as in their first report,

Cole-Hamilton and coworkers carried out reactions with more higher alkenes, ranging from 1-octene to 1-dodecene. They studied in detail the effects of temperature, alternative ionic liquids, gas composition, and the long-term stability of the catalyst. The maximum TOF was tested to be 500/h, and the TOF increased with the flow rate of the reactants. Very small rhodium catalyst leaching (0.012 ppm) was observed. However, the linear selectivity of aldehydes in the continuous-flow process was lower than expected. To address this issue, they later switched to the ionic Nixantphos derivatives and significantly improved the l/b ratio from 2 to 40 (Figure 16) [58].

In 2007, the same authors explored ligand effects by trying multiple [TPPMS][X] ionic liquids (TPPMS = $Ph_2P(m-C_6H_4SO_3)$) that differed in counterion [59]. [PrMIM][TPPMS] has relatively poor solubility that caused rhodium leaching in the early stage of the flow reaction. At low catalyst loadings, [PnMIM][TPPMS] led to faster reaction rates with rhodium leaching <1 ppm, but at higher catalyst loadings, it precipitated and lost activities. [OMIM]
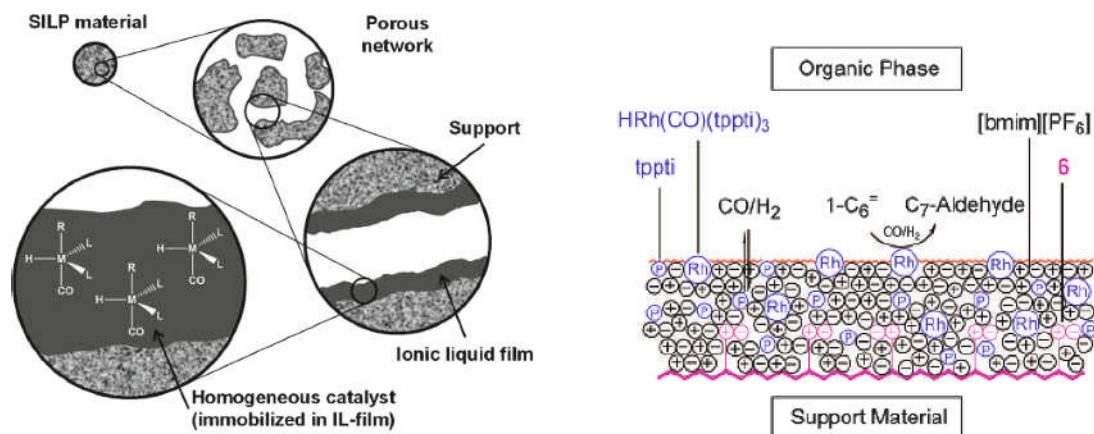

Figure 12. Illustration of supported ionic liquid-phase (SILP) catalyst for hydroformylation (ref. [48]; Copyright 2011 John Wiley & Sons. ref. [42]; Copyright 2002 American Chemical Society)
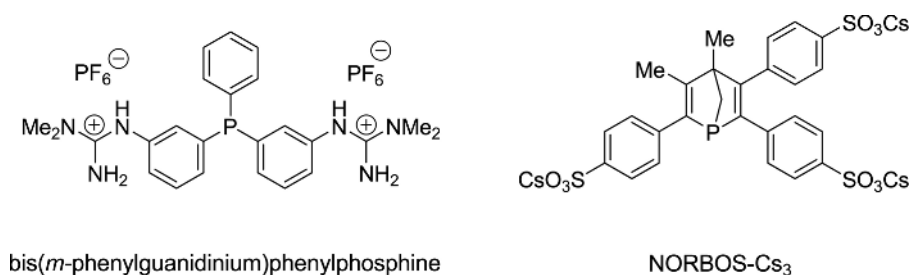

Figure 13. Charged monophosphine ligands (ref. [43a]; Copyright 2003 Springer)
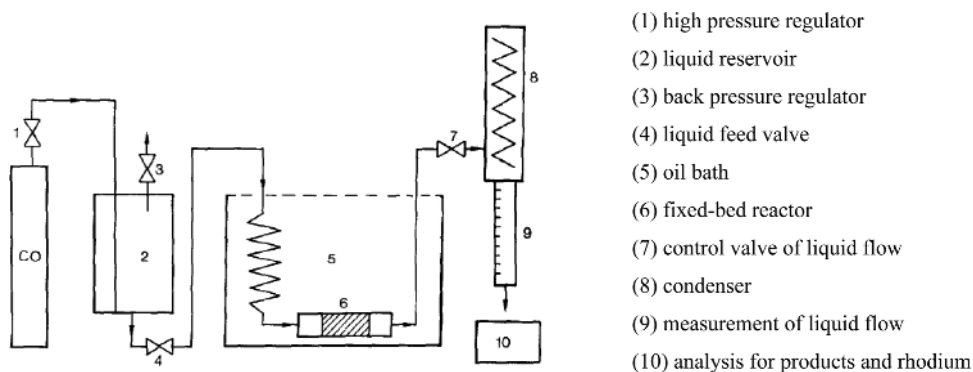
(1) high pressure regulator
(2) liquid reservoir
(3) back pressure regulator
(4) liquid feed valve
(5) oil bath
(6) fixed-bed reactor
(7) control valve of liquid flow
(8) condenser
(9) measurement of liquid flow
(10) analysis for products and rhodium

Figure 14. Fehrmann's continuous reactor for the SILP hydroformylation (ref. [43b]; Copyright 1990 Elsevier)

Scheme 3. SILP-catalyzed hydroformylation of a diluted raffinate 3 feed (ref. [48]; Copyright 2011 John Wiley & Sons)
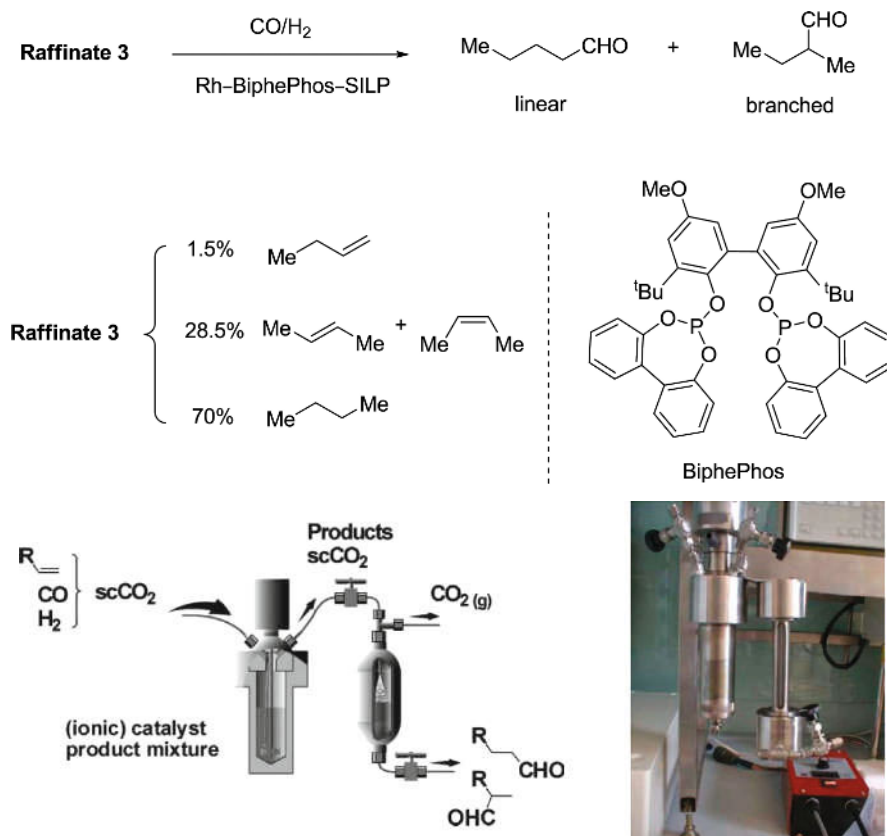

Figure 15. Cole-Hamilton's reactor for the scCO$_2$IL continuous-flow hydroformylation (ref. [59]; Copyright 2007 Royal Society of Chemistry)

[TPPMS] was the most soluble ligand and rendered high reaction rates; however, it led to greater rhodium leaching (510 ppm). In 2010, Cole-Hamilton's team studied several other factors that could effect reaction rates and concluded that: (1) the thickness of the ionic liquid film has little effect on the reaction rate; (2) syngas/substrate ratio has little effect on the overall rate of the reaction; and (3) total system pressure is the most important variable for the reaction rate, which reaches the peak value with increasing pressure up to 100 bar but starts to decrease at higher pressure [60]. At the optimal pressure, the liquid phase was expanded by CO$_2$ with the optimum gas/substrate availability but still not pressurized enough to compress the flowing system to a single homogeneous phase, which would in fact lower the reaction rate. The team also combined the scCO$_2$ and supported ionic liquid-phase (SILP) technologies by depositing the IL catalyst on silica gel support [61]. With the scCO$_2$SILP system, 1-octene was hydroformylated with an increased TOF (800/h) and a decrease in required syngas pressure (100 bar), as compared to those of the scCO$_2$IL system (TOF = 527/h, P = 200 bar).
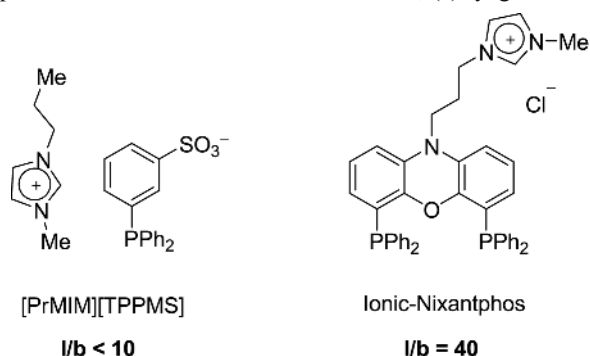
7. Conclusions and Outlook

Progress has been made in the past decade for developing a more efficient catalytic system for rhodium-catalyzed continuous

Figure 16. Effect of ionic ligand on the linear selectivity

hydroformylation, in terms of catalyst activity, recycling, and reaction scope. Attempts for expanding semi-industrial scale reactions to higher olefins were successful in some cases. However, most of the continuous processes still suffer low TOF. The single-solvent homogeneous system was less attractive industrially because of the difficulty of catalyst recovery. Multiphase system normally requires post-reaction separation that is somewhat redundant and lowers the actual amount of functioning catalyst. Catalyst immobilization is still the main-stream in the research of continuous hydroformylation. Leaching has been the major problem for immobilized catalysts, but can be prevented by using novel strategies such as the molecular weight enlargement (MWE) plus nanofiltration. Several reports have also demonstrated the long-term effectiveness of polymer, silica, or ionic liquid-bound rhodium catalysts with low leaching. However, for a mature industrial process, cost is another crucial factor to be considered. The strategies involving ionic liquids as film on a silica support or just as solvent (in combination with the use of scCO$_2$) are extremely expensive. However, further improvements are expected to overcome these challenges to achieve more affordable and sustainable technologies for the development of industrially applicable continuous hydroformylation processes.

References

1. For a recent review, see: Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* **2012**, *112*, 5675–5732.

2. (a) Farnetti, E.; Di Monte, R.; Kaspar, J. *Homogeneous and Heterogeneous Catalysis* in *Inorganic and Bio-inorganic Chemistry*; Bertin, I. Eds., EOLSS, Paris, France, **2009**; vol. 2; (b) Han, D.; Li, X.; Zhang, H.; Liu, Z.; Li, J.; Li, C. *J. Catal.* **2006**, *243*, 318–328; (c) Kainulainen, T. A.; Niemelä, M. K.; Krause, A. O. I. *J. Mol. Catal. A* **1997**, *122*, 39–49; (d) Mukhopadhyay, K.; Chaudhari, R. V. *J. Catal.* **2003**, *213*, 73–77; (e) Nozaki, K.; Itoi, Y.; Shibahara, F.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *J. Am. Chem. Soc.* **1998**, *120*, 4051–4052.

3. Matsumoto, M.; Tamura, M. *J. Mol. Catal.* **1983**, *19*, 365–376.

4. Fraile, J. M.; García, J. I.; Mayoral, J. A. *Chem. Rev.* **2009**, *109*, 360–417.

5. Lu, J.; Toy, P. H. *Chem. Rev.* **2009**, *109*, 815–838.

6. Cornils, B. *Org. Proc. Res. Dev.* **1998**, *2*, 121–127.

7. Hershman, A.; Robinson, K. K.; Craddock, J. H.; Roth, J. F. *Ind. Eng. Chem. Prod. Res. Dev.* **1969**, *8*, 372–375.

8. Claridge, J. B.; Douthwaite, R. E.; Green, M. L. H.; Lago, R. M.; Tsang, S. C.; York, A. P. E. *J. Mol. Catal.* **1994**, *89*, 113–120.

9. Abatjoglou, A. G.; Billig, E.; Bryant, D. R. *Organometallics* **1984**, *3*, 923–926.

10. Kohlpaintner, C. W.; Fischer, R. W.; Cornils, B. *Appl. Catal. A Gen.* **2001**, *221*, 219–225.

11. Herrmann, W. A.; Cornils, B. *Angew. Chem., Int. Ed.* **1997**, *36*, 1048–1067.

12. (a) McQuade, D. T.; Seeberger, P. H. *J. Org. Chem.* **2013**, *78*, 6384–6389; (b) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38–54.

13. Hessel, V.; Kralisch, D.; Kockmann, N.; Noël, T.; Wang; Q. *ChemSusChem*, **2013**, *6*, 746–789.

14. O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2011**, *2*, 1250–1257.

15. Kasinathan, S.; Bourne, S. L.; Tolstoy, P.; Koos, P.; O'Brien, M.; Bates, R. W.; Baxendale, I. R.; Ley, S. V. *Synlett* **2011**, *18*, 2648–2651.

16. Bourne, S.; O'Brien, M.; Kasinathan, S.; Koos, P.; Tolstoy, P.; Hu, D. X.; Bates, R. W.; Martin, B.; Schenkel, B.; Ley, S. V. *ChemCatChem* **2013**, *5*, 159–172.

17. Güven, S.; Hamers, B.; Franke, R.; Priske, M.; Becker, M.; Vogt, D. *Catal. Sci. Technol.* **2014**, *4*, 524–530.

18. Horváth, I. T.; Kiss, G.; Cook, R. A.; Bond, J. E.; Stevens, P. A.; Rabai, J.; Mozeleski, E. J. *J. Am. Chem. Soc.* **1998**, *120*, 3133–3143.

19. Horváth, I. T.; Rabai, J. *Science* **1994**, *266*, 72–75.

20. Perperi, E.; Huang, Y.; Angeli, P.; Manos, G.; Mathison, C. R.; Cole-Hamilton, D. J.; Adams, D. J.; Hope, E. G. *Dalton Trans.* **2004**, 2062–2064.

21. Rost, A.; Müller, M.; Hamerla, T.; Kasaka, Y.; Wozny, G.; Schomäker, R. *Chem. Eng. Process.* **2013**, *67*, 130–135.

22. Müller, M.; Kasaka, Y.; Müller, D.; Schomäcker, R.; Wozny, G. *Ind. Eng. Chem. Res.* **2013**, *52*, 7259–7264.

23. Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpainter, C. W. *J. Mol. Catal. A: Chem.* **1995**, *104*, 17–85.

24. Heinrich, B.; Hjortkjaer, J.; Nikitidis, A.; Andersson, C. *J. Mol. Catal.* **1993**, *81*, 333–347.

25. Andersson, C.; Nikitidis, A.; Hjortkjaer, J.; Heinrich, B. *Appl. Catal. A Gen.* **1993**, *96*, 345–354.

26. Meehan, N. J.; Sandee, A. J.; Reek, J. N. H.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Poliakoff, M. *Chem. Commun.* **2000**, 1497–1498.

27. For reviews on continuous flow processes using scCO$_2$ and supported catalysts, see: (a) Stouten, S. C.; Noël, T.; Wang, Q.; Hessel, V. *Chem. Eng. Process.* **2014**, *83*, 26–32; (b) Burguete, M. I.; García-Verdugo, E.; Luis, S. V. *Beilstein J. Org. Chem.* **2011**, *7*, 1347–1359.

28. Bronger, R. P. J.; Bermon, J. P.; Reek, J. N. H.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Carter, D. N.; Licence, P.; Poliakoff, M. *J. Mol. Catal. A: Chem.* **2004**, *224*, 145–152.

29. Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033–7034.

30. Shibahara, F.; Nozaki, K.; Hiyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8555–8560.

31. Schmidt-Winkel, P.; Lukens, W. W.; Yang, P.-D.; Margolese, D. I.; Lettow, J. S.; Ying, J. Y.; Stucky, G. D. *Chem. Mater.* **2000**, *12*, 686–696.

32. Yan, L.; Ding, Y.-J.; Zhu, H.; Yin, H.-M.; Jiao, G.-P.; Zhao, D.-Y.; Lin, L.-W. *Chin. J. Catal.* **2006**, *27*, 1–3.

33. Janssen, M.; Müller, C.; Vogt, D. *Dalton Trans.* **2010**, *39*, 8403–8411.

34. Janssen, M.; Wilting, J.; Müller, C.; Vogt, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 7738–7741.

35. Fang, J.; Jana, R.; Tunge, J. A.; Subramaniam, B. *Appl. Catal. A Gen.* **2011**, *393*, 294–301.

36. Schönweiz, A.; Debuschewitz, J.; Walter, S.; Wölfel, R.; Hahn, H.; Dyballa, K. M.; Franke, R.; Haumann, M.; Wasserscheid, P. *ChemCatChem* **2013**, *5*, 2955–2963.

37. Kamer, P. C. J.; Reek, J. N. H.; van Leeuwen P. W. N. M. in *Rhodium Catalyzed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C. Eds.; Kluwer Academic Publishers; Dordrecht, **2000**, 35–62.

38. Cornils, B.; Wiebus, E. *Chemtech* **1995**, *25*, 33–38.

39. Arhancet, J. P.; Davis, M. E.; Merola, J. S.; Hanson, B.E. *Nature* **1989**, *339*, 454–455.

40. Wasserscheid, P.; van Hal, R.; Bosmann, A. *Green Chem.* **2002**, *4*, 400–404.

41. Wasserscheid, P.; Waffenschmidt, H.; Machnitzki, P.; Kottsieper; K.W.; Stelzer, O. *Chem. Commun.* **2001**, 451–452.

42. Mehnert, C. P.; Cook, R. A.; Dispenziere, N. C.; Afeworki, M. *J. Am. Chem. Soc.* **2002**, *124*, 12932–12933.

43. (a) Riisager, A.; Eriksen, K. M.; Wasserscheid, P.; Fehrmann, R. *Catal. Lett.* **2003**, *90*, 149–153; (b) Hjortkjaer, J.; Chen, Y.-Y.; Heinrich, B. *Appl. Catal.* **1991**, *67*, 269–278.

44. Riisager, A.; Wasserscheid, P.; van Hal, R.; Fehrmann, R. *J. Catal.* **2003**, *219*, 452–455.

45. Dupont, J.; Silva, S. M.; de Souza, R. F. *Catal. Lett.* **2001**, *77*, 131–133.

46. Riisager, A.; Fehrmann, R.; Flicker, S.; van Hal, R.; Haumann, M.; Wasserscheid, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 815–819.

47. Haumann, M.; Dentler, K.; Joni, J.; Riisager, A.; Wasserscheid, P. *Adv. Synth. Catal.* **2007**, *349*, 425–431.

48. Haumann, M.; Jakuttis, M.; Franke, R.; Schönweiz, A.; Wasserscheid, P. *ChemCatChem* **2011**, *3*, 1822–1827.

49. Behr, A.; Obst, D.; Schulte, C.; Schosser, T. *J. Mol. Catal. A: Chem.* **2003**, *206*, 179–184.

50. Blanchard, L. A.; Hancu, D.; Beckman, E. J.; Brennecke, J. F. *Nature* **1999**, *399*, 28–29.

51. Blanchard, L. A.; Brennecke, J. F. *Ind. Eng. Chem. Res.* **2001**, *40*, 287–292.

52. Kainz, S.; Leitner, W. *Catal. Lett.* **1998**, *55*, 223–225.

53. Koch, D.; Leitner, W. *J. Am. Chem. Soc.* **1998**, *120*, 13398–13404.

54. Palo, D. R.; Erkey, C. *Ind. Eng. Chem. Res.* **1998**, *37*, 4203–4206.

55. Palo, D. R.; Erkey, C. *Organometallics* **2000**, *19*, 81–86.

56. Sellin, M. F.; Webb, P. B.; Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 781–782.

57. Webb, P. B.; Sellin, M. F.; Kunene, T. E.; Williamson, S.; Slawin, A. M. Z.; Cole-Hamilton, D. J. *J. Am. Chem. Soc.* **2003**, *125*, 15577–15588.

58. Kunene, T. E.; Webb, P. B.; Cole-Hamilton, D. J. *Green Chem.* **2011**, *13*, 1476–1481.

59. Frisch, A. C.; Webb, P. B.; Zhao, G.-Y.; Muldoon, M. J.; Pogorzelec, P. J.; Cole-Hamilton, D. J. *Dalton Trans.* **2007**, 5531–5538.

60. Hintermair, U.; Gong, Z.-X.; Serbanovic, A.; Muldoon, M. J.; Santini, C. C.; Cole-Hamilton, D. J. *Dalton Trans.* **2010**, *39*, 8501–8510.

61. Hintermair, U.; Zhao, G.-Y.; Santini, C. C.; Muldoon, M. J.; Cole-Hamilton D. J. *Chem. Commun.* **2007**, 1462–1464.