

Developments in Hydrogenation Technology for Fine-Chemical and Pharmaceutical Applications

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The continuous innovation in hydrogenation technology is testimony to its growing importance in the manufacture of specialty and fine chemicals. New developments in equipment, process intensification and catalysis represent major themes that have undergone recent advances. Developments in chiral catalysis, methods to support and fix homogeneous catalysts, novel reactor and mixing technology, high-throughput screening, supercritical processing, spectroscopic and electrochemical online process monitoring, monolithic and structured catalysts, and sonochemical activation methods illustrate the scope and breadth of evolving technology applied to hydrogenation.

Keywords Catalysis, chiral synthesis, hydrogenation, process equipment, process intensification

Introduction

Catalytic hydrogenation has evolved into a key process technology for the manufacture of pharmaceutical and fine chemicals, replacing chemical reduction methods that generate large quantities of waste. According to Roessler [1•], 10 to 20% of chemical reactions in fine chemical synthesis at Roche are catalytic hydrogenations. Catalytic hydrogenations strike a balance among reaction kinetics, reactor design, catalyst activity and selectivity, process control, mass transfer and mixing. Each of these factors contribute to the performance of hydrogenation processes and their products.

The complexity and diversity of catalytic hydrogenation makes it a rich platform for innovation in equipment design, process monitoring, process engineering and catalysis. For example: (i) the growing need for chiral chemical products for pharmaceutical and fine-chemical applications has promoted the development of new catalysts and hydrogenation techniques to selectively produce these compounds; (ii) a general, applicable method for retaining the properties of homogeneous catalysts in supported systems remains elusive and is driving innovation in physical and chemical fixation methods; (iii) advances in process equipment have improved the mixing and mass transfer performance of traditional reactor technology, facilitating scale-up and efficient manufacturing; (iv) novel reactor technologies that use monolithic catalysts hold the potential to eliminate many of the problems associated with traditional powdered catalysts; (v) online spectroscopic and physical process monitoring instruments create new opportunities to control and characterize processes while improving productivity; and (vi) operations under supercritical conditions eliminate the fluid-phase boundaries that limit traditional hydrogenation processing techniques. These innovations and developments provide the industrial development team with an arsenal of new tools and ideas to create new products and improve processes.

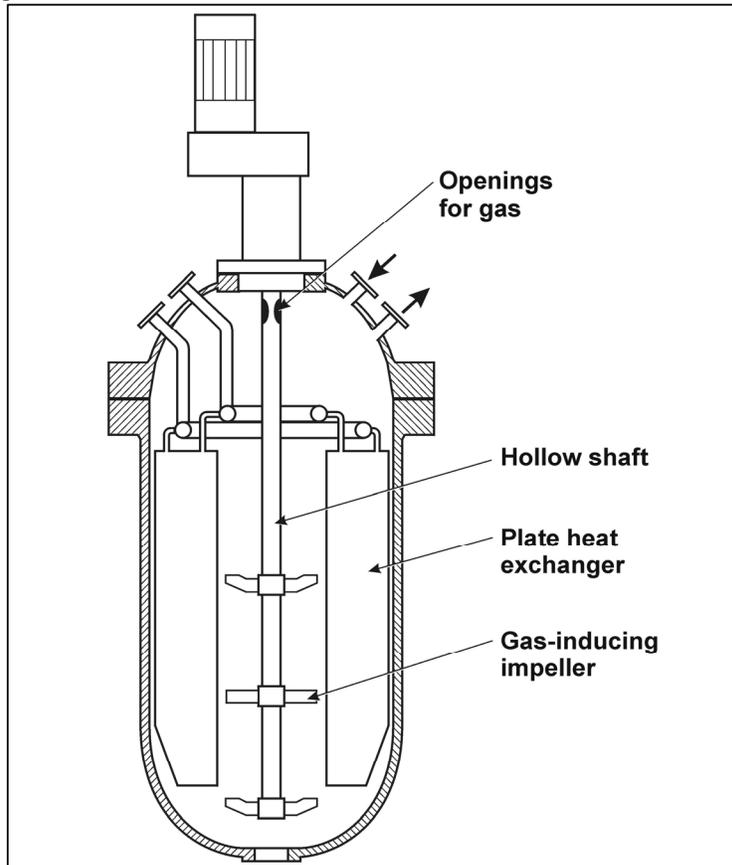
Hydrogenation process and scale-up equipment

Mixing and process equipment

Equipment is the heart of any manufacturing process. In heterogeneous catalytic hydrogenation, the equipment must intimately contact all the physical phases in the process: hydrogen gas, the liquid(s) containing reactants and solvents, and the solid catalyst. As the solubility of hydrogen in most liquids is low, gas-liquid mass transfer is critical to optimal operation. Intensively remixing hydrogen in the reactor headspace back into the liquid phase ensures that the liquid phase does not become depleted of hydrogen, which can degrade catalyst activity and selectivity. An overview of industrial gas-liquid mixing technology by Lee and Tsui illustrates the many reactor types available for hydrogenation and other types of gas-liquid mass transfer [2••]. In traditional, stirred tank reactors, hydrogen is fed through a sparge tube below a flat-blade Rushton turbine; however, the effectiveness of mixing and mass transfer capability is lost in this arrangement as the impeller becomes flooded with gas and power transfer to the liquid is reduced. New asymmetric concave blades in disc turbine design can dramatically improve the efficiency of gas distribution without loss of power transfer [3,101].

Hydrogenation process productivity is often restricted by a combination of mass- and heat-transfer equipment limitations. Subsurface hydrogen spargers and helical, internal cooling coils are often used to overcome these limitations. Unfortunately, current good manufacturing process (cGMP) protocols in the pharmaceutical industry designed to reduce cross-contamination between batches may restrict the use of such equipment. As a result, special reactor designs are required to efficiently disperse hydrogen delivered to the headspace into the liquid for high mass transfer and to provide easy-cleaning heat transfer surfaces for high-heat transfer demands. Biazzi and Ekato have coupled novel mixing and heat transfer technology into a stirred tank reactor [102] to meet these dual requirements. Hydrogen added in the headspace is mixed using a hollow shaft gas-inducing impeller, while heat is removed using efficient vertical plate heat exchangers that simultaneously serve as baffles to enhance mixing (Figure 1). An alternative to the stirred tank reactor design that also meets these requirements is the loop venturi reactor (LVR) such as the Kvaerner Buss Loop Reactor (Figure 2), which uses a gas-liquid ejector to remix hydrogen and create intensive mass transfer. Heat transfer is optimized in an external shell-and-tube heat exchanger. Detailed scale-up correlations for the application of ejectors in this type of reactor have recently been developed [4].

Figure 1. A schematic diagram of a Biazzi reactor.



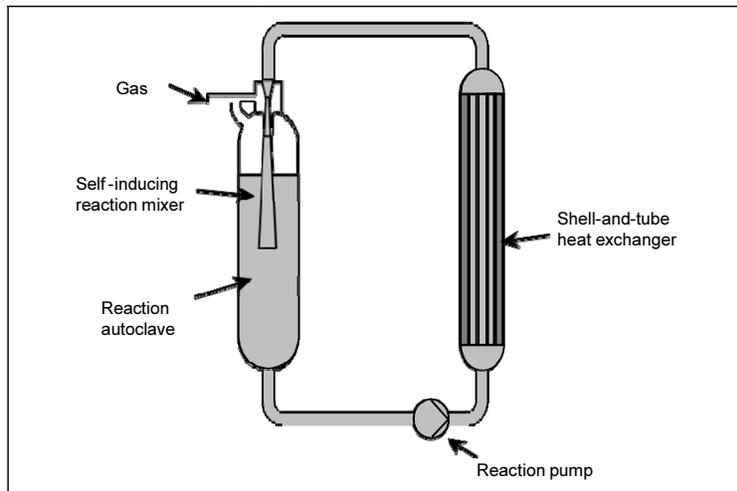
A schematic drawing of the Biazzi reactor, showing vertical plate heat exchangers and multiple impellers. The central impeller is gas inducing and connected via a hollow shaft to the headspace of the reactor. The diagram is adapted from the Biazzi/Ekato patent, US-05478535 [102].

Online process monitoring

Process control is essential for meeting the quality, safety and manufacturing standards in a modern manufacturing process. New spectroscopic analytical instruments that withstand the manufacturing environment in combination with chemometric numerical tools, such as multivariate

statistics, have enabled the movement of analytical tools from the laboratory to the plant. In all online methods, the location of the process monitoring probe needs to be carefully considered. A recirculation loop is often necessary to provide a process interface when access to the liquid contents through the head of the reactor is impractical.

Figure 2. A schematic diagram of Kvaerner Buss Loop Reactor.



Mass transfer scale-up details are given by Cramers and Beenackers [4]. Diagram provided by Kvaerner Process Technology AG.

Pfizer researchers have demonstrated the use of mid-infrared (mid-IR) and near-infrared (NIR) spectroscopy for continuous online monitoring of hydrogenation processes. Using NIR, the endpoint during the hydrogenation of an imine to its corresponding cis and trans isomers was monitored [5]. NIR analytical techniques use fiber optics to transfer spectra and light energy, and a transmittance fiber optic probe placed in the reaction mixture to monitor process chemistry. The use of fiber optics to gather spectra allows the signal processor and instrument electronics to be located remotely. This advantage is also shared by Raman spectroscopy, making it a practical candidate for online monitoring development. Online mid-IR spectroscopy yields a rich dataset that can be used to track the formation of products and depletion of reactants by identifying fundamental vibrational frequencies of functional groups, and has been employed for online hydrogenation of nitro groups, catalytic debenzoylation and double-bond saturation [6]. Unlike NIR, mid-IR spectroscopy requires the use of optical pipes to transmit light energy and collect spectra, and attenuated total reflectance (ATR) probes to monitor process chemistry. Diamond windows over an ATR probe, commercially available as DiComp™ probes, form an impervious barrier to the challenging process environment and expand the use of online mid-IR to a broad range of applications and process conditions [7]. Even with advanced chemometric techniques, spectrophotometric methods are limited in their ability to identify a large number of individual species in a process and characterize complex kinetic problems. Nevertheless, these techniques are well suited for simple systems and process end-point determination.

Continuous online spectroscopic monitoring can also characterize short-lived or unstable intermediates. For example, the formation of unstable intermediates such as hydroxylamines during the heterogeneous hydrogenation of nitroaromatic compounds is a common problem in fine-chemical synthesis. LeBlond *et al* [8] demonstrated the use of online mid-IR with DiComp™ probes to quantitatively identify hydroxylamine intermediates that appeared during a hydrogenation step in the production of Maxalt® (Merck). This is especially useful since hydroxylamines are generally not stable enough to be characterized by traditional gas chromatography (GC) or liquid chromatography (LC) methods. Process productivity and, importantly, process safety both benefit from this type of online monitor.

Heterogeneous catalytic hydrogenations of nitro, carbonyl and unsaturated compounds are essentially electrochemical redox processes. Under the appropriate conditions, electrochemical methods can be used to track the progress of hydrogenation reactions [9]. The catalytic metal acts as a short-circuited electrochemical cell and a simple redox probe placed into a slurry hydrogenation can measure the steady-state mixed potential on the catalyst particles as they contact the electrode. As the reaction progresses and the reactant-product profile changes, the mixed potential changes in a manner characteristic of the particular process. This type of process probe can effectively serve to characterize batch reaction end points and catalyst activity.

Novel physical measurement methods such as acoustic monitoring can be used to characterize the operation of a

gas-liquid reaction system [10]. When gas bubbles form and collapse, they generate sound that can be used to diagnose bubble size, mixing and mass transfer. Bubble oscillation frequency is inversely proportional to bubble size and the sound generated can be used to estimate bubble size. Non-invasive instruments can be applied to a wide variety of gas-liquid processing equipment to track the characteristic acoustic signature of a process and can be used for process control. While acoustic analysis is advanced in areas such as oceanography, it remains to be fully exploited in the chemical processing industry.

High-throughput experimentation

The use of high-throughput experimentation (HTE) in process development has attracted much interest. Besides the most frequently described applications of HTE, ie, in preparation and screening of catalysts and combinatorial synthesis, the concept can also be effectively applied to process development. In this case, along with the catalyst, reaction conditions such as temperature, pressure and solvent are varied in a pre-programmed sequence of automated reaction cycles. Cannarsa *et al* [11] recently reviewed this topic and included examples of many reaction types besides hydrogenations. However, because of the large number of parameters involved in their design and scale-up, hydrogenation processes are particularly amenable, and have been among the most frequently studied with HTE methodologies. Examples include automated catalyst synthesis with subsequent screening for activity toward hydrogenation of 3,4-dichloronitrobenzene [12], selective hydrogenation of 4-nitroacetophenone [13] and complete hydrogenation of dinitrotoluene [14].

To effectively apply HTE to hydrogenation processes, the equipment must be able to screen the entire window of operating parameters (eg, pressure, temperature, solvent) practical for the commercial process. Although some preliminary information can be gained from screening at atmospheric pressure [12] and many fine-chemical reactions are carried out under moderate pressures (eg, [13]), many hydrogenations benefit from high-pressure conditions. Equipment accommodating such conditions will provide the greatest degree of flexibility and the greatest amount of process information. Microreactor technology may soon provide new opportunities for HTE at a very small scale, minimizing waste generation and allowing process developers to take advantage of the latest developments in miniaturized control and micro-analytical sensor technologies. It remains to be demonstrated whether information gained from microreactors, which are typically operated in a continuous flow-through mode, can be applied to scale-up of batch hydrogenation processes.

Process intensification

A common theme in current chemical reaction engineering literature and discourse is process intensification. While this term has been defined in many ways, a definition proposed by Stankiewicz and Moulijn [15] is appealingly broad: 'Any chemical engineering development that leads to a substantially smaller, cleaner or more energy-efficient technology'. In many approaches to process intensification, several unit operations are combined in a single piece of equipment in novel ways, often made possible by new developments both within and outside of the field of

chemical engineering. Several successful and promising approaches are reviewed below: structured catalytic reactors, supercritical processing, microreaction technology and sonochemistry. Others will be discussed in the context of homogeneous and enantioselective hydrogenations.

Structured catalysts

The topic of structured catalysts encompasses many diverse ideas and implementations designed to overcome the limitations of reactors with randomly distributed catalyst-particles (slurry catalyst reactors, dumped fixed catalyst bed reactors). Many drawbacks of slurry reactors are directly related to problematic catalyst-handling procedures (solids charging, filtration, discharge) that often pose safety and environmental problems, and can lead to significant catalyst losses. Traditional fixed-bed reactors (typically trickle-bed reactors in the case of hydrogenations) suffer from low mass transfer rates and high pressure drops. Many means of introducing more structure into the catalytic reactor have been proposed, including bead-string reactors, polyoliths, ceramic foams, corrugated packings (eg, Sulzer's KATAPAK) and spinning disk reactors [15••]. To date, monolithic catalysts have shown the most success.

Monolithic catalysts, best known for their application in automotive catalytic converters, feature a honeycomb channel structure to which a catalytic material is applied. Their application in gas-liquid reactions (especially hydrogenations) has been the subject of much research since the 1980s, when the first production-scale process (the hydrogenation step in the manufacture of hydrogen peroxide) was commercialized. Since then, both scientific literature [16•,17] and patent literature [103,104] have proposed many new potential monolith applications. Advantages of monoliths relative to slurry reactors include simplified catalyst handling and, thus, minimization of catalyst losses. Relative to trickle-bed reactors, advantages include lower pressure drop through the straight monolith channels, allowing high-throughputs, fast mass transfer rates and making liquid recycle a feasible strategy. Until now, most proposed applications have been in medium-to-large-scale continuous chemical processes, but developments such as the monolith loop reactor concept described by Heiszwolf *et al* [18•] indicate that monolith catalysis is ready to make an impact on smaller-scale batch hydrogenation processes. The advantages of higher selectivity and reduced catalyst losses are particularly significant at this smaller scale, which is characterized not only by higher-value products but also higher-cost catalysts.

Supercritical hydrogenation

Although chemical processing under supercritical conditions has been a topic of great interest for many years, the application of supercritical fluids (SCFs) in hetero-geneous catalysis, including hydrogenations, is a relatively recent development with most progress made in the past ten years. Baiker [19••] reviewed the progress and potential for various categories of catalytic reactions. Although processes in which the reaction medium is at supercritical conditions have been used for many years (eg, ammonia synthesis), newer developments deliberately exploit the unique properties of fluids near their critical point. These properties include solubility of

organic substrates, density, diffusivity and viscosity. Frequently used solvents include CO₂, water, low-mass hydrocarbons (such as ethane and propane) and other small-molecule organics.

In hydrogenations, the primary benefit of supercritical processing is the capacity for greatly enhanced reaction rates. Hydrogen solubility in a SCF is much higher than in organic liquids, and mass transfer rates benefit from the absence of gas-liquid interfaces and fast diffusion rates. Another potential benefit is that different selectivity and catalyst stability can arise from different reactant concentrations at the active catalyst site. Hydrogen is typically the limiting reagent in fast hydrogenation reactions in conventional solvents. However, the greater solubility of hydrogen and more limited solubility of organic substrates in SCFs means that the substrate is more likely to be the limiting reagent. In addition, many SCFs are good solvents for high-molecular-weight by-products that lead to catalyst deactivation and can effectively remove such tars from the catalyst surface to maintain activity.

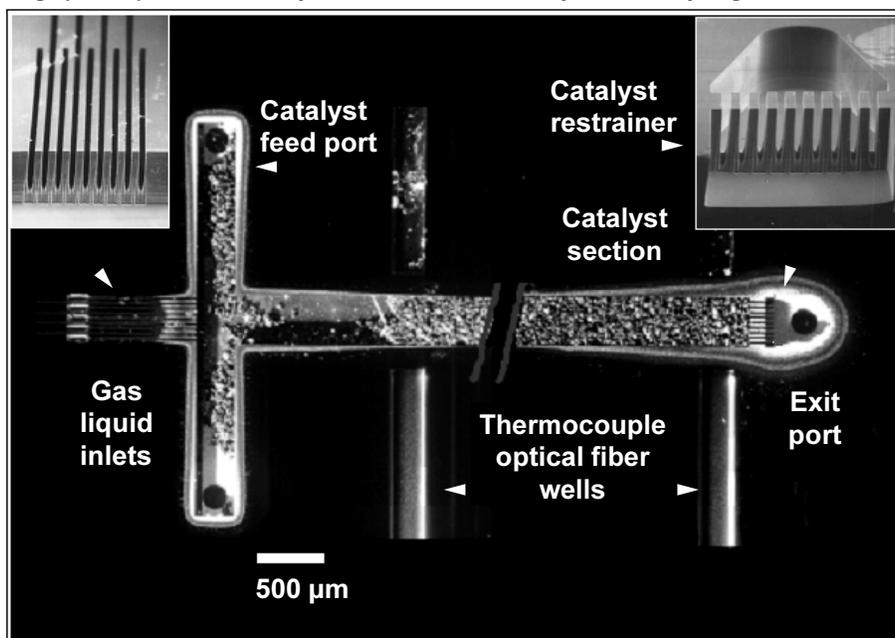
Supercritical hydrogenation is not yet applied commercially, but two patents, US-05750806 [106] and WO-09738955 [107], broadly cover its application. Many other patents and publications describe examples of specific chemistries, including some that are relevant to fine-chemical production. Of particular interest are enantioselective hydrogenations carried out at supercritical conditions. Compared with liquid-phase hydrogenation, supercritical operation may increase or decrease enantioselectivity [20•] depending on the mass-transport and chemical mechanisms of the reaction. Wandeler *et al* [21•] described the continuous enantioselective hydrogenation of ethyl pyruvate over cinchonidine-modified Pt/Al₂O₃ in supercritical ethane at moderate temperatures (15 to 50°C) and pressures ranging from 45 to 130 bar. Continuous operation holds significant promise in this area if the chirally modified catalysts maintain their activity and selectivity for an extended period.

Clearly, supercritical operation has the potential to dramatically change the way many hydrogenation reactions are conducted. High-pressure equipment for attaining and maintaining supercritical conditions is expensive, but the cost can be offset by the reduced reactor size required for the desired production rate. For optimum benefits, reactions that are now carried out in batch equipment may need to be conducted continuously.

Microreactor technology

Advances in microfabrication, integrated micro-analytical techniques and microfluidic design have given rise to microreaction technology, an emerging and promising field of development. Besides its previously mentioned benefits in the area of HTE, it also holds promise as a step-out change in chemical production technology. Whereas the traditional chemical engineering approach to convert laboratory-scale results to production-scale has been through engineered scale-up (applying engineering correlations, heuristics and experience to achieve the desired balance of reaction rate, heat and mass transfer, and mixing), the microreaction approach requires scale-down to achieve the

Figure 3. Photomicrograph of a packed-bed catalytic microreactor used for cyclohexene hydrogenation.



(Reprinted with permission from Elsevier Science and Jensen KF: *Microreaction engineering - is small better?* Chem Eng Sci 56 (2001) 56:293-303. © 2001 Chemical Engineering Science.)

same criteria. After successful scale-down of the reactor size, process scale-up is attained by replication. Benefiting from mass production techniques developed for the electronics industry, such replication may be a cost-effective alternative to traditional processing, especially for the production of high-value chemicals such as pharmaceuticals.

A perspective paper by Jensen [22••] reviews general trends and opportunities in microchemical systems. While most designs are for either liquid- or gas-phase reactors, a recent publication by Jensen *et al* [23•] describes the hydrogenation of cyclohexane over packed beds of catalyst arranged in a multi-channel configuration (Figure 3). Gas and liquid are forced through the packed channels in a bubbly or pulsing flow mode. The mass transfer coefficient for hydrogen transfer to the catalyst surface was two orders of magnitude larger than for a conventional trickle-bed reactor.

Micro-reactor technology development is proceeding at a rapid pace, but has not yet resulted in production-scale applications. The most fruitful areas of initial application will be those where operation at conventional scale is impossible or impractical, for example, where extremely fast mass or heat transfer is required for reasons of safety or selectivity.

Sonochemistry

The chemical and mechanical effects of microbubble creation and subsequent collapse (cavitation) as low- and high-pressure periods of sound waves alternate in a reaction medium are known collectively as sonochemistry. Cavitation results in highly localized energy releases that can be in the form of microjets or fleeting high-temperature/high-pressure conditions. In a reactive system, this can enhance reaction and mass transfer rates. Two recently published reviews cover chemical ultrasound effects [24]

and chemical/mechanical effects in heterogeneously catalyzed systems [25•]. The mechanical effects, which include catalyst particle scouring and break-up as well as mass transfer enhancement, are likely to be more important for hydrogenation.

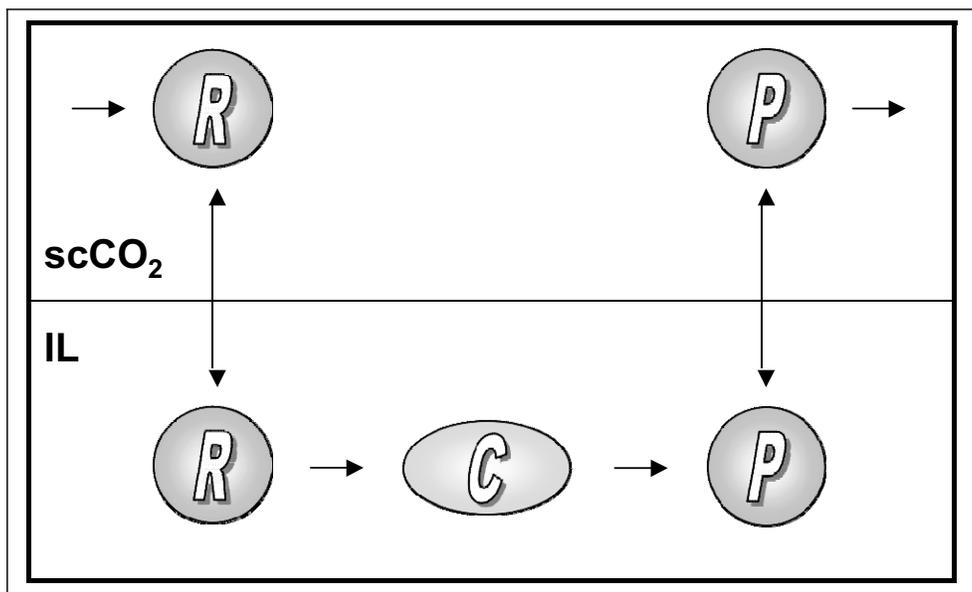
Catalysis

Homogeneous catalysts

Despite the inherent advantage that catalytic hydrogenation has over chemical reduction, there remains room for improvement in chemoselectivity and enantioselectivity while retaining high catalytic activity. Improved catalysts dramatically affect these reaction properties and the search for new catalysts remains an active research area. Homogeneous catalysts are particularly appealing since their well-defined active sites are readily optimized for reactivity and selectivity. For example, homogeneous hydrogenation catalysts from ChiroTech combine high activity with good enantioselectivity. These 1,1'-diphosphanylferrocene ligands (FerroTANE™) have demonstrated superiority over previous systems in the rhodium-catalyzed asymmetric hydrogenation of itaconates to succinate derivatives [26]. Full conversion was demonstrated at a high substrate-to-catalyst ratio of 20,000:1, which compensates for high metal cost.

The high activity and selectivity attainable with homogeneous catalysts make them attractive for small-scale syntheses, but separation and cost issues limit their use in large-scale production. Bulliard *et al* [27•] report the successful scale-up of an asymmetric olefin acid hydrogenation to a 4000-l reactor using a homogeneous ruthenium catalyst with the MeOBiphep ligand (2',6'-methoxy-1,1'-biphenyl-2,6'-diphenylphosphane; Roche). After crystallization, the product was obtained in a yield of

Figure 4. Schematic illustration of the scCO₂/IL biphasic system.



The reactant (R) supplied by the scCO₂ phase dissolves in the ionic liquid (IL) phase and interacts with the catalyst (C) to form the product (P), which is extracted by the scCO₂ phase for recovery.

70%, and > 99% purity and enantiomeric excess (ee). No attempt was made to reuse the catalyst (metal or ligand) for more than one batch. The 14 batches required to produce 2 tons of the pharmaceutical precursor product used a total of ~ 1 kg of ruthenium. This example illustrates the potential (high purity and ee) and the problems (expense and separation) of homogeneous catalysts.

Immiscible liquid phase

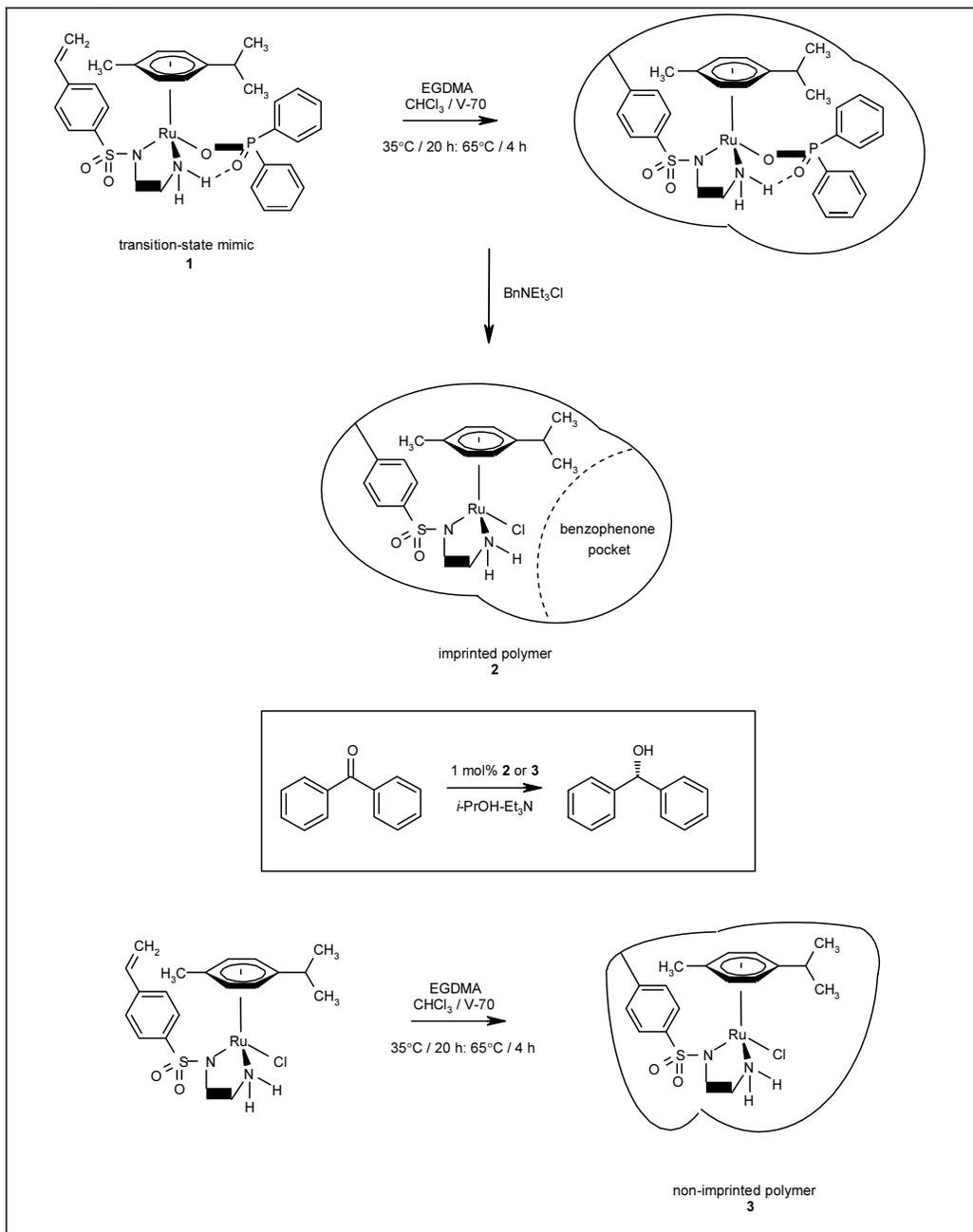
The well-documented difficulty with homogeneous catalyst separation has spurred on a tremendous amount of research into the immobilization of homogeneous catalysts either on heterogeneous supports or in immiscible liquid phases. Immobilization of homogeneous catalysts in immiscible liquid phases has been demonstrated with aqueous/organic, fluorinated/organic and aqueous/supercritical CO₂ biphasic systems. Ideally, the catalyst remains dissolved in the lower liquid phase while the upper liquid phase supplies reactants and removes products (Figure 4). This method provides for facile catalyst reuse or recovery. A new concept is under development using room-temperature ionic liquids (ILs) and supercritical CO₂ (scCO₂) in biphasic systems. This has gained momentum from the discovery that scCO₂ dissolves in the IL 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF₆]) but the IL is insoluble in scCO₂. This may be the ideal biphasic system, with an immobilized homogeneous catalyst in the IL phase and a scCO₂ phase that recovers products without solvent or catalyst contamination by simply venting CO₂. In addition, ILs have no detectable vapor pressure, which eliminates volatile organic compound (VOC) emissions and allows multiple solvent recycles. Jessop and co-workers [28••] have demonstrated good ee and conversion for trans-2-methyl-2-butenic acid hydrogenation over several catalyst recycles in the scCO₂/[bmim][PF₆] biphasic system. Liu *et al* [29] demonstrated the recycle of Wilkinson's and other rhodium-based catalysts in the same system for olefin hydrogenation and for CO₂ hydrogenation. Work is still being carried out on

solubility rules for ILs, but systems in which catalyst and starting material are soluble in the IL (while the product is insoluble and simply floats to the top to be skimmed off) are conceivable.

Heterogenization of homogeneous catalysts

A generally applicable method for retaining the properties of homogeneous catalysts in supported systems remains elusive. Usually, the strategy involves modifying a polymer or inorganic oxide support with a functional group that acts as a ligand for the subsequently added catalytic metal. This strategy has been used recently with polyethylene-based graft copolymer fiber supports (FibreCat™) in place of more traditional polystyrene beads [30]. The fibers show less attrition under intense mixing conditions and also provide greater external surface, resulting in catalysis being less hindered by intra-particle diffusion limitations. A different strategy involves incorporation of pre-assembled catalytic metal complexes with polymerizable ligands (metallomonomers) during polymerization of the support [31••]. This direct catalyst incorporation eliminates the often difficult task of cleanly reacting a metal with an immobilized ligand. The most interesting aspect of this method is the ability to tailor the support around the active catalyst site. Severin *et al* [32•,33•] co-polymerized a ruthenium-based catalyst containing a phosphinato ligand that mimics the target benzophenone substrate in size and orientation when coordinated to the catalyst during hydrogenation (Figure 5). The ligand is removed prior to catalysis, leaving behind a cavity intended to direct the substrate to the active site with the proper orientation. A 3-fold increase in activity versus the same catalyst polymerized without the phosphinato ligand and a 2-fold increase in selectivity for benzophenone over various co-substrates such as acetophenone and cyclohexyl methyl ketone were noted.

Figure 5. Molecular imprinting of a transition metal catalyst.



The phosphinato ligand acts as a template during support polymerization. Upon removal, it leaves behind a cavity that directs the benzophenone substrate to the active site with the proper orientation.

(This figure is adapted from Santora BP, Gagné MR: **A Wolf in sheep's clothing**. *Chem Innov* (2000) **30**:22-29.)

Polymeric heterogeneous substrates have the advantage of simple metal recovery through combustion of the organic material and workup of the ash. However, inorganic substrates are preferable for certain chemistries. Cruden's group used bidentate phosphine groups to anchor a cationic rhodium catalyst to a mesoporous silica substrate (MCM-41) [34]. The bidentate phosphine reduces catalyst leaching and the cationic rhodium complex discourages catalyst-deactivating dimerization. The resulting heterogeneous material catalyzed the olefin hydrogenation of isosafrole more efficiently than the corresponding homogeneous catalyst.

Engelhard Corporation has recently reported a novel immobilization technology for cationic catalysts (Rh, Ru, Ir, Pd, etc) on γ -alumina, carbon, clay or silica supports through acid-base interactions [35]. Heteropoly acids (eg, phosphotungstic acid H₃PW₁₂O₄₀·(H₂O)_x) attached to the substrate give up protons to the catalyst counter-anions and the resulting negatively charged conjugate bases bind the cationic catalysts to the substrate. A cationic rhodium complex with the chiral bisphosphine DuPHOS ligand (ChiroTech) tethered to a γ -alumina substrate via

phosphotungstic acid hydrogenated methyl-2-acetamidoacrylate with no loss of enantioselectivity during nine recycles. The supported catalyst gave the same ee (~ 94%) produced by the homogeneous catalyst, confirming that this tethering strategy causes minimal disturbance to the catalytic metal environment.

Modified heterogeneous catalysts

An alternative to tethering homogeneous catalysts to solid supports is to modify a conventional heterogeneous catalyst for improved enantio- or chemoselectivity. The two most generally successful systems are supported platinum catalysts modified by chinchonidine, and Raney nickel modified by tartaric acid. Comprehensive reviews in these areas have been published [36••,37••].

Bimetallics

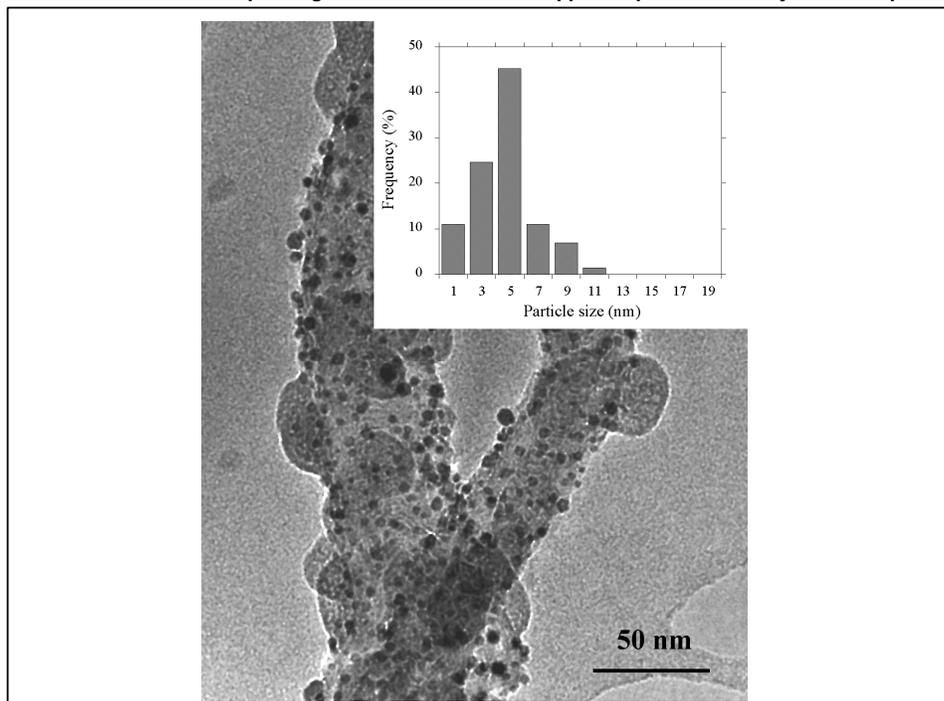
Catalysts comprising more than one metal type often exceed the performance of traditional single-metal catalysts in activity, selectivity and/or stability. Toshima and co-workers reported the use of bimetallic Ni/Pd nanoclusters as homogeneous catalysts [38]. The metal particles (~ 20 Å) are polymer-coated to prevent agglomeration and allow stable colloidal dispersion in organic media. The authors synthesized Ni/Pd nanoclusters that contained varying amounts of Pd (ranging from 0 to 100%) and found the bimetallic composition Ni₂Pd₃ is > 3-fold more active than pure Pd clusters for nitrobenzene hydrogenation. Chaudhari's group found increased activity with addition of Pt to a zeolite-supported Ni catalyst in the hydrogenation of acetophenone [39]. More importantly, a striking improvement in the stability of the catalyst was observed through three recycles. The initial turnover frequency for a 10% Ni/1% Pt catalyst only dropped from 30.5 to 28.7 by the fourth run, compared to a drop from

19.7 to 3.3 for the 10% Ni catalyst. The presented evidence suggests that platinum facilitates complete reduction of nickel, thus keeping catalyst activity high over multiple runs. Finally, Steiner *et al* [40••] developed a bimetallic Pd/Rh catalyst for the ring hydrogenation of 4-(phosphonomethyl)-2-pyridine-carboxylic acid. The required > 95% direct conversion to the cis-isomer could not be accomplished with commercially available monometallic rhodium catalysts. However, the authors discovered that activity and selectivity improved with increasing palladium substitution for rhodium up to 90% palladium, after which they both dropped dramatically. This is a powerful example of the potential of bimetallic catalysts where improved performance comes with lower cost.

New catalyst supports

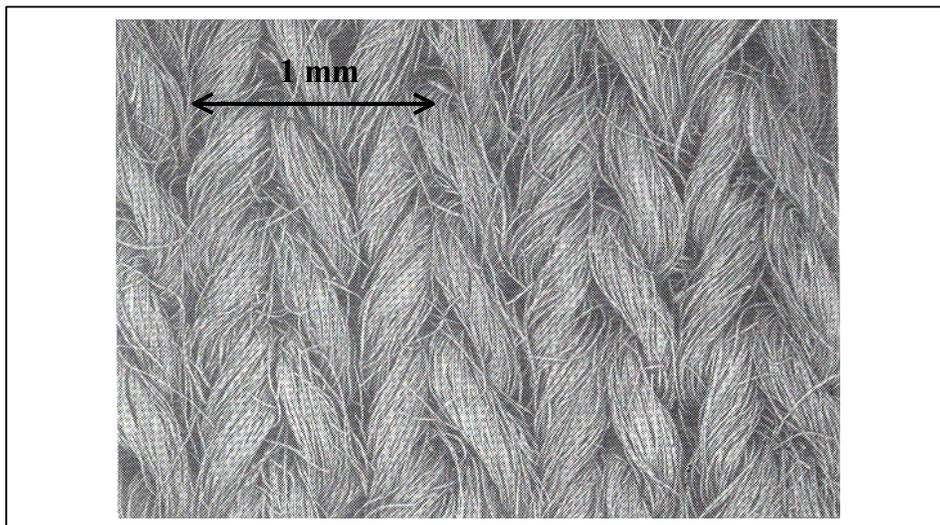
The support material is sometimes overlooked in heterogeneous catalyst selection, but it can have as much influence on performance as the metal. Some examples of new heterogeneous supports have already been described above (FibreCat™ [30], MCM-41 [34]). Fibrous supports are a popular new technology owing mainly to their high external surface area and robust mechanical properties. In addition to the polymeric fibers mentioned earlier, carbon nanofibers are also under investigation as catalyst supports [41]. Ledoux *et al* prepared a catalyst with well-dispersed palladium supported on carbon fibers of ~ 50-nm diameter by several microns in length (Figure 6). The catalyst was active for the hydrogenation of cinnamaldehyde to hydrocinnamaldehyde with > 90% selectivity. An activated charcoal-supported palladium catalyst produced only ~ 40% selectivity in the same reaction in twice the time on stream. The favorable result with the carbon fibers was attributed to a lack of internal diffusion limitations.

Figure 6. Transmission electron microscope image of carbon nanofiber-supported palladium catalyst and the particle distribution.



(Reproduced by permission of the Royal Society of Chemistry and Pham-Huu C, Keller N, Charbonniere LJ, Ziessel R, Ledoux MJ: **Carbon nanofiber supported palladium catalyst for liquid-phase reactions. An active and selective catalyst for hydrogenation of C=C bonds.** *Chem Commun* (2000) **19**:1871-1872. © 2000 Chemical Communications.)

Figure 7. Scanning electron microscope image of knitted silica fiber catalyst support.



(Reprinted with permission from Elsevier Science and Toukoniitty E, Mäki-Arvela P, Neyestanaki AK, Salmi T, Sjöholm R, Leino R, Laine E, Kooyman PJ, Ollonqvist T, Väyrynen J: **Batchwise and continuous enantioselective hydrogenations of 1-phenyl-1,2-propanedione catalyzed by new Pt/SiO₂ fibers.** *Appl Catal A* (2001) **216**: 73-83. © 2001 Applied Catalysis A – General.)

A third form of fibrous support material reported by Toukoniitty *et al* [42,43] is referred to as knitted silica fiber (Figure 7). Knitting the fibers together into a fixed bed allows for continuous rather than batch reaction. Chinchonidine-modified platinum dispersed on the fibers produced ~ 55% ee in the hydrogenation of 1-phenyl-1,2-propanedione to (R)-1-hydroxy-1-phenylpropanone. A nickel-based catalyst gave > 90% selectivity to citronellol in the hydrogenation of citral.

Biotechnology methods

The majority of this review focuses on hydrogenations conducted using synthetic heterogeneous or homogeneous catalysts. An alternative to these methods is provided by bioreductions, ie, hydrogenations conducted using either microorganisms or isolated enzymes. These biocatalysts have the potential to displace traditional catalysts, especially where biologically favored enantioselectivity is important. In traditional catalysis, hydrogenations represent a clearly defined area of reaction engineering owing to the specific issues surrounding the use of molecular hydrogen in the process. With biocatalysis, this distinction is not as clear, since the hydrogen source is not molecular hydrogen but a reduced organic molecule that is simultaneously oxidized. The hydrogen (ie, the reductive ability) from this molecule is typically transferred to the substrate via a biochemical cofactor such as NAD(P): applications of NAD(P)-dependent oxidoreductases have been reviewed by Hummel [44]. The need for a cofactor often makes whole-cell biocatalysis, rather than enzymatic catalysis, the most cost-effective approach [45]. Progress in the field of bioreduction has been steady, paralleling similar developments with other biochemical reactions.

Conclusions

Catalytic hydrogenation is a technology firmly anchored in the manufacture of traditional and new fine- and specialty chemical products. The versatility and complexity of hydrogenation will continue to make it a target of innovation

across many fields: catalysis, process engineering, equipment design and analytical chemistry. Process intensification coupled with new equipment technology, new online monitoring instruments and novel approaches to catalysis allow new industrial hydrogenation processes to be engineered quickly with low capital to meet the growing demands of the fine-chemical marketplace.

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