8

UNDERSTANDING RATE PROCESSES IN CATALYTIC HYDROGENATION REACTIONS

YONGKUI SUN

Department of Process Research, Merck & Co., Inc., Rahway, NJ, USA

CARL LeBLOND

Department of Chemistry, Indiana University of Pennsylvania, Indiana, PA, USA

8.1 INTRODUCTION

Hydrogenation is a powerful methodology in synthetic organic chemistry and has been broadly employed by organic chemists in drug synthesis. Heterogeneous-catalyzed hydrogenation has traditionally been very popular and continues to play a critical role in modern organic synthesis [1, 2]. Hydrogenation by homogeneous catalysts, particularly asymmetric hydrogenation, is gaining momentum in applications in the pharmaceutical industry. Since the pioneering work on the development of chiral catalysts for asymmetric hydrogenation by William Knowles in late 1960s and the first commercial application of asymmetric hydrogenation in the early 1970s by Monsanto in the production of the antiparkinsonian drug L-DOPA [3, 4], asymmetric hydrogenation has developed into a powerful chemical transformation, achieving enantioselectivities matching those previously seen only in enzymatic processes. Over the ensuing two to three decades, there has been rapid development in the science and technology of asymmetric hydrogenation. One of the key milestones in the development of this chiral technology was the discovery of BINAP in the 1980s by Ryoji Noyori and coworkers [5], which significantly broadened the scope of utility of asymmetric hydrogenation [6]. A recent special issue of the *Accounts of Chemical Research* documented the growing application of asymmetric hydrogenation in the pharmaceutical industry [7].

Hydrogenation reactions in the liquid phase are complex processes. Even for a homogeneously catalyzed hydrogenation for which the catalyst and the substrate are fully soluble in the solvent, the hydrogenation process is heterogeneous in nature since the dihydrogen reducing reagent H_2 is in a different phase. In addition to the catalytic reaction occurring on the catalyst, there are a number of mass transfer processes that can exert direct influence on the outcome of the catalytic reaction itself.

In the case of heterogeneous catalysis, the mass transfer processes include H_2 transport across the gas/liquid and the liquid/solid interfaces before the molecular H_2 chemisorbs dissociatively on the metal catalyst, as well as H_2 diffusion inside the pore structure of the catalyst particles. A schematic depicting the mass transfer processes (pore diffusion not displayed) is shown in Figure 8.1, along with the corresponding H_2 concentration profile. Among the mass transfer processes, the gas/liquid mass transfer needs significant attention in designing a hydrogenation process because it can have profound impact on the performance of the hydrogenation reaction [8], and it is greatly affected by agitation, reactor design and configuration, solvent properties such as viscosity, and solvent fill level. Mass transfer of H_2 across the liquid/solid interface and through the pore structure in the catalyst particles are often dominated by the physical characteristics of the catalyst, that is, particle size, shape and support material, and density and pore structures. While agitation intensity and reactor design can influence their
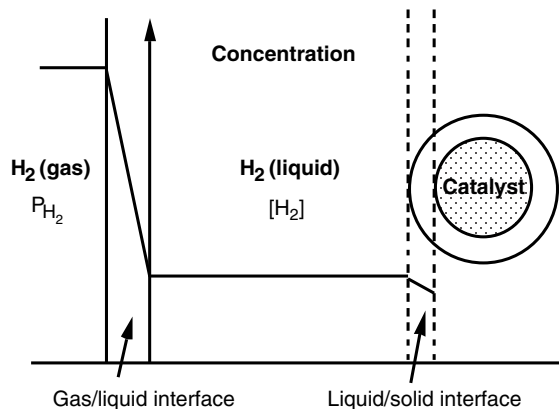
FIGURE 8.1 A schematic of hydrogen mass transfer processes across the gas/liquid and liquid/solid interfaces during a heterogeneously catalyzed hydrogenation reaction. Also plotted is a schematic of the hydrogen concentration profile.

kinetics, for catalytic system in which the diameter of the catalyst particle is <50 μm, the effects become minimal once a uniform catalyst suspension is achieved. All the mass transfer issues encountered in hydrogenation reactions carried out in slurry reactors are not reviewed in this chapter [9]. Instead, this chapter focuses only on the simple but crucial hydrogen gas/liquid mass transfer issue and its impact on the development of hydrogenation processes.

8.2   SOLUTION HYDROGEN CONCENTRATION DURING HYDROGENATION REACTIONS, [H₂]

When gas/liquid delivery is the dominant mass transfer step, the pathway followed by H_2 from the gas phase to its incorporation into the product in catalytic hydrogenation reactions using a homogeneous or a heterogeneous catalyst may be simply described as follows:

$$H_2(g) \xrightarrow{k_L a} H_2(l) \xrightarrow{k_r} \text{Hydrogenation product} \qquad (8.1)$$
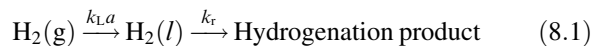
where $k_L a$ is the mass transfer coefficient for the H_2 mass transfer across the gas/liquid interface, and k_r is the rate coefficient of the catalytic reaction. The intrinsic kinetics in the catalytic hydrogenation is a function of concentrations of the substrate, the catalyst, and the dissolved H_2 in addition to other factors such as the temperature. In developing a chem-

ical process, one is normally demanding in the knowledge of the concentration of the substrate and try to follow [substrate] via various means during the course of the reaction. One is frequently, however, less demanding in the knowledge of the solution concentration of hydrogen, [H₂], due, in most part, to an assumption that [H₂] equals the equilibrium solubility of hydrogen, $[H_2]_{sat}$, at the temperature and pressure of the reaction.

The assumption holds, however, only when the rate of H_2 mass transfer is far greater than that of hydrogenation reaction itself. While $[H_2]_{sat}$ is fixed at a constant gas-phase H_2 pressure, [H₂] may vary widely from nearly zero to nearly saturation, depending critically upon the relative magnitude of the rate of H_2 mass transfer from the gas to the liquid phase and the rate of reactive H_2 removal from the liquid phase due to the hydrogenation reaction. This is readily seen from a mass balance of the dissolved H_2 in the following equation:

$$\frac{d[H_2]}{dt} = k_L a([H_2]_{sat} - [H_2]) - k_r f([H_2], [\text{catalyst}], [\text{substrate}])$$

$$(8.2)$$

The first term to the right of equation 8.2 is the rate of H_2 mass transfer from the gas to the liquid phase, and the second term is the rate of reactive removal of the dissolved H_2 from the liquid phase by the catalytic hydrogenation.

The kinetics of H_2 mass transfer resembles that of the familiar first-order chemical reaction and may be characterized by a single parameter, the mass transfer coefficient $k_L a$. A comparison of the characteristics, including the kinetic expression and the maximum rate, between these two processes is given in Table 8.1. The significance of the mass transfer coefficient $k_L a$ is that it is the kinetic factor that dictates the maximum rate of mass transfer of hydrogen across a gas/liquid interface, that is,

$$R_{H_2,g/L}^{max} = k_L a[H_2]_{sat} \qquad (8.3)$$

in conjunction with the thermodynamic factor $[H_2]_{sat}$.

While k_r is an intrinsic kinetic property of the catalytic system, $k_L a$ is strongly affected by characteristics of the reactor vessel, including reactor type, configuration, liquid fill level, viscosity, and particularly agitation speed. At a constant H_2 pressure, the magnitude of [H₂] during the reaction critically depends upon the relative magnitude of these two rate coefficients. In a situation where the kinetics of the mass transfer is much slower than the intrinsic reaction

TABLE 8.1   A Comparison of the Characteristics of Gas–Liquid Mass Transfer and a First-Order Chemical Reaction

	Gas–Liquid H_2 Mass Transfer	First-Order Reaction
Kinetic expression	$-\frac{d[H_2]}{dt} = k_L a([H_2] - [H_2]_{sat})$	$-\frac{d[C]}{dt} = k_r[C]$
First-order rate coefficient (s⁻¹)	$k_L a$	k_r
Maximum rate	$R_{H_2,g/L}^{max} = k_L a[H_2]_{sat}$	$R_{rxn}^{max} = k_r[C]_0$

kinetics, that is,

$$R_{H_2,g/L}^{max} \ll R_{H_2,rxn}^{max}$$

or

$$k_L a[H_2]_{sat} \ll k_r f([H_2]_{sat}, [catalyst], [substrate]) \qquad (8.4)$$

[H$_2$] deviates significantly from [H$_2$]$_{sat}$, and the solution is starved of H$_2$. In other words, the effective H$_2$ pressure, that is, the pressure that the catalyst experiences, is lower than the H$_2$ pressure in the gas phase. Under extreme hydrogen starved conditions, [H$_2$] or the effective H$_2$ pressure may approach zero. In this case, the reaction becomes entirely limited by the mass transfer instead of by the catalytic processes on the catalyst, and the observed reaction rate equals the maximum rate of H$_2$ mass transfer. On the other hand, if the kinetics of mass transfer is much faster than the intrinsic reaction kinetics, that is,

$$R_{H_2,g/L}^{max} \gg R_{H_2,rxn}^{max}$$

or

$$k_L a[H_2]_{sat} \gg k_r f([H_2]_{sat}, [catalyst], [substrate]), \qquad (8.5)$$

[H$_2$] approaches [H$_2$]$_{sat}$, and the effective H$_2$ pressure approaches the pressure in the gas phase.

Assuming that [H$_2$] in equation 8.2 varies slowly with time, the lowest value of [H$_2$] may be expressed as

$$[H_2] \approx [H_2]_{sat} \left(1 - R_{H_2,rxn}^{max}/R_{H_2,g/L}^{max}\right) \qquad (8.6)$$

To ensure that the solution is nearly saturated with H$_2$ throughout the entire course of the reaction and the observed rate is representative of the kinetics intrinsic to the catalytic system under the specified hydrogen pressure, a rule of thumb is that the maximum intrinsic reaction rate should be less than 10% of the maximum H$_2$ delivery rate:

$$R_{H_2,rxn}^{max}/R_{H_2,g/L}^{max} \leq 10\% \qquad (8.7)$$

Equation 8.6 shows

$$[H_2] \geq 90\%[H_2]_{sat} \qquad (8.8)$$

when the 10% rule of thumb is satisfied.

8.3 IMPACT OF $k_L a$ ON REACTION KINETICS AND SELECTIVITY

As shown in Section 8.2, even when the pressure in the gas phase is specified, the reaction conditions could in actuality be unspecified due to uncharacterized deviation of [H$_2$] from [H$_2$]$_{sat}$ as a result of a lack of knowledge of the hydrogen mass transfer coefficient $k_L a$. Under the unspecified conditions, rate measured reflects kinetics at an unknown [H$_2$] instead of the intended constant [H$_2$]$_{sat}$. The

kinetic data obtained under such conditions are not helpful and can even be harmful to the development of scalable processes. Irreproducibility in rate from reactor to reactor may be observed under seemingly identical reaction conditions due to different mass transfer coefficients in different reactors. A process developed under such conditions may both pose safety and selectivity problems in scale-up. In addition, the deviation of [H$_2$] from [H$_2$]$_{sat}$ may cause irreversible alteration of the catalyst properties. The catalyst may be deactivated due to lack of hydrogen atoms on the catalytic surface, which not only reduces the catalytic activity, but also may change the selectivity of the catalyst in undesirable manners.

In addition, selectivity of the hydrogenation reactions may be strongly influenced by mass transfer by virtue of the intrinsic dependence of the selectivity on [H$_2$], the effective pressure that the catalyst experiences. Many reactions exhibit strong dependence of selectivity on hydrogen pressure. Examples include the [Rh(DIPAMP)]$^+$-catalyzed asymmetric hydrogenation of α-acylaminoacrylic acid derivatives [10], asymmetric hydrogenation of γ-geraniol and geraniol catalyzed by Ru(BINAP) [11], and enantioselective hydrogenation of ethyl pyruvate over cinchonidine-modified Pt [12]. In the case of asymmetric hydrogenation of γ-geraniol catalyzed by Ru[(S)-BINAP], the enantioselectivity to (R)-β-citronellol decreases precipitously from 90% ee to nearly racemic with increasing effective H$_2$ pressure from nearly 0 to 100 psia. The case of asymmetric hydrogenation of geraniol is even more dramatic. The enantioselectivity flips from an ee of 93% (R) to 91% (S) when the H$_2$ effective pressure changes from 100 psia to nearly zero due to the presence of the competitive isomerization of geraniol to γ-geraniol under the hydrogenation conditions (Figure 8.2) [13]. In all these cases, even at constant H$_2$ gas-phase pressure, uncharacterized deviation of [H$_2$] from [H$_2$]$_{sat}$ as a result of H$_2$ mass transfer limitations translates into unpredictable selectivity.

It is interesting to note that the mass transfer limitations may work for or against the desired selectivity, depending on how the selectivity is related to [H$_2$]. For instance, at a constant gas-phase pressure, mass transfer limitations help to enhance the enantioselectivity of the Ru[(S)-BINAP]-catalyzed asymmetric hydrogenation of γ-geraniol to (S)-citronellol, in which case the selectivity increases with decreasing pressure.

The effect of the interplay between the mass transfer and the intrinsic rate processes on kinetics and selectivity for reactions carried out at constant H$_2$ pressure is further demonstrated in Figure 8.3, using as an example the enantioselective hydrogenation of ethyl pyruvate over cinchonidine-modified Pt.[8(b)] The effects of the two extreme situations discussed above are graphically illustrated by the difference in the observed kinetics and enantioselectivity. At 400 rpm, the H$_2$ mass transfer is much slower than
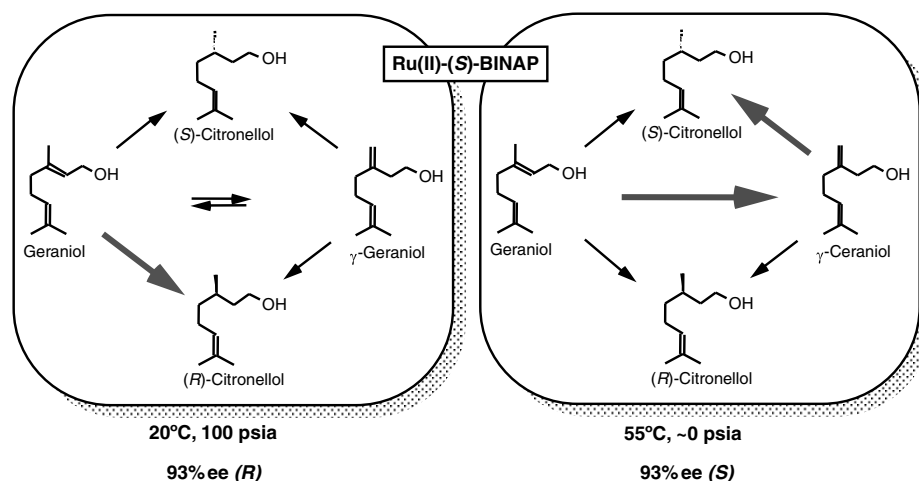
FIGURE 8.2   Striking dependence of enantioselectivity in the asymmetric hydrogenation of geraniol as a result of the interplay of rate processes in the isomerization/hydrogenation network.

the intrinsic hydrogenation rate ($k_La = 4 \times 10^{-3}\,s^{-1}$). [$H_2$] is virtually zero. The kinetics, being completely limited by the rate of the H_2 delivery across the gas/liquid interface instead of by the catalytic hydrogenation of ethyl pyruvate on the Pt surface, is independent of the substrate concentration and therefore exhibits zero-order kinetic behavior. A process developed under these conditions would potentially run into safety issues when scaled up as the hydrogenation rate would change greatly with differences in the mass transfer coefficient k_La associated with large hydrogenators. At 2000 rpm, the mass transfer is no longer limiting the rate ($k_La = 0.7\,s^{-1}$), the solution is saturated with H_2 at all
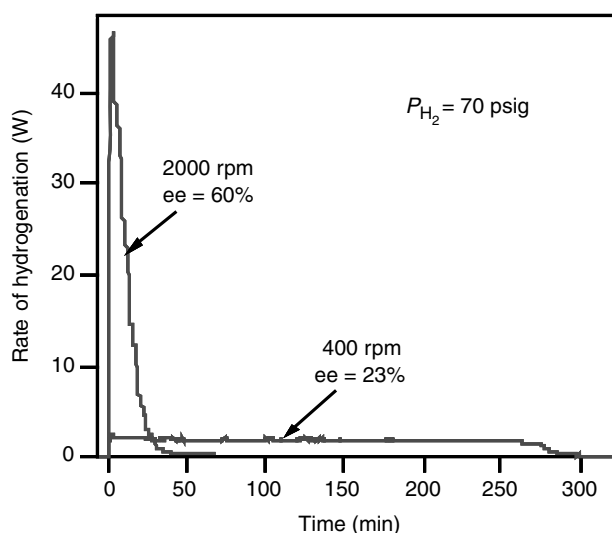

FIGURE 8.3   Effect of hydrogen mass transfer on kinetics and enantioselectivity in the chiral hydrogenation of ethyl pyruvate over cinchonidine-modified Pt. Except for the different stir rates, the two experiments were carried out under otherwise identical conditions (30°C, solvent: 1-propanol).

times during the reaction, that is, [H_2] $\cong$ [H_2]$_{sat}$, and the rate is limited by the catalytic hydrogenation of ethyl pyruvate over Pt. Further increases in the mass transfer coefficient no longer change the rate profile. As a result, a picture of the intrinsic kinetics emerges. In addition to the kinetics, the mass transfer also influences selectivity by virtue of changing the availability of H_2 that the catalyst experiences. Figure 8.3 shows that the enantioselectivity increases from 23% to 60% ee due to a change in [H_2] from starvation to saturation upon increasing the agitation speed from 400 to 2000 rpm.

In developing a hydrogenation process, it is the intrinsic catalyst activity and selectivity, that is, the catalytic behaviors under well-defined conditions, that are of foremost concern, not those convoluted with the hydrogen mass transfer process. Obviously, it is not sufficient to specify H_2 pressure alone to unravel kinetics and selectivity of a catalytic hydrogenation reaction intrinsic to the catalytic system. It is necessary to characterize the mass transfer properties of the hydrogenator and conduct the hydrogenation experiments according to the 10% "rule of thumb" as described by equation 8.7.

8.4   CHARACTERIZATION OF GAS–LIQUID MASS TRANSFER PROCESS

Section 8.3 described how the gas/liquid mass transfer process, characterized by the simple parameter k_La, can exert significant influence on the outcome and robustness of the hydrogenation process. It is not uncommon in the pharmaceutical industry, however, to see chemists and chemical engineers employ hydrogenation vessels for screening, scaling-up, and commercialization of hydrogenation processes without characterizing their mass transfer coefficients.

In this section, a simple practical procedure for measuring k_La is reviewed and examples are given for measuring k_La in a variety of hydrogenators at scales ranging from 100 mL to 760 gal in volume. Given the importance of the mass transfer coefficient, it is recommended that all hydrogenators, including those used for screening, for process development and scaling-up, and for commercialization, be characterized in term of their mass transfer coefficients.

Among the methodologies available, the most straightforward one for measuring the gas/liquid mass transfer coefficient k_La is to measure directly the kinetics of nonreactive hydrogen uptake by the solution at various agitation speeds [14]. In this method, the solution is first degassed thoroughly by vacuum with the agitation on. The agitator is then turned off, and hydrogen gas is introduced to the headspace of the hydrogenator at a pressure close to the hydrogenation pressure at which point the hydrogen line valve to the hydrogenator is closed. When the agitation commences, the pressure in the reactor is recorded as a function of time using a fast-response pressure transducer. A schematic depicting the pressure drop in the headspace of the hydrogenator and the corresponding concentration rise of hydrogen in the liquid phase is shown in Figure 8.4. The rate at which the pressure decreases is directly related to the gas/liquid transfer rate, whereas the extent to which the pressure drops is related to the solubility of the gas in the liquid. The dependence of pressure P as a function of time t is governed by the simple first-order rate equation

$$\frac{P_f - P_0}{P_i - P_0} \ln\left(\frac{P_i - P_f}{P - P_f}\right) = (k_La)t \qquad (8.9)$$

where P_i is the initial pressure, P_f the final pressure, and P_0 the solvent vapor pressure.
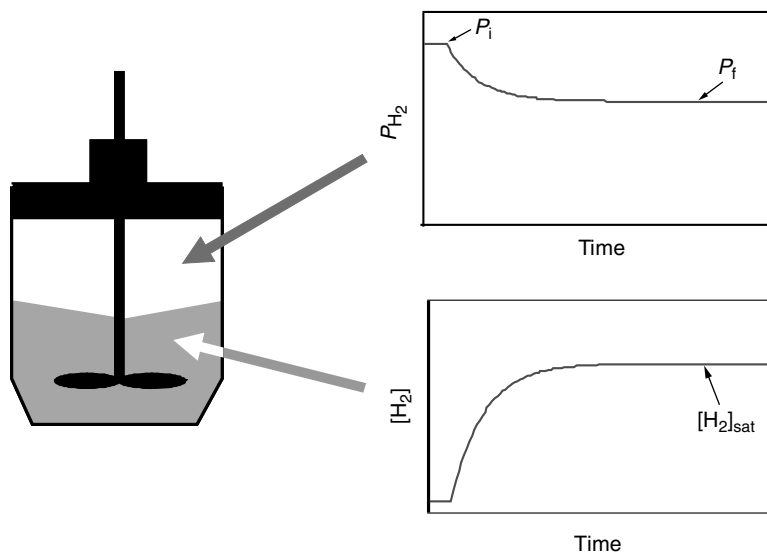
Typical pressure–time curves in Metter Toledo's 1L RC1 MP10 reactor are displayed in Figure 8.5a. They graphically illustrate the difference in mass transfer rates at agitation rates of 400 and 1000 rpm. Figure 8.5b shows the pressure plot obtained using data in Figure 8.5a according to equation 8.9. The slope of the pressure plot yields k_La that is $3.8 \times 10^{-3}\,\text{s}^{-1}$ at 400 rpm and $0.24\,\text{s}^{-1}$ at 1000 rpm. Another way to look at the difference in the mass transfer rates is a comparison of the "half-life", that is, $t_{1/2} = \ln 2/k_La$. While reaching 50% of the hydrogen saturation concentration takes only ~3 s at 1000 rpm, it takes ~3 min at 400 rpm.

The mass transfer coefficient can be strongly influenced by a number of parameters including the agitation rate, the type of reactor, reactor configuration such as reactor size and shape, the type of agitator and its position in the reactor, fill level, temperature, solvent and solute, the use of baffle, and subsurface sparge line. The methodology described here is a convenient and fast way to measure the mass transfer characteristics of the hydrogenator relevant to the specific conditions of the hydrogenation process.

Using the simple methodology described in this section, the full mass transfer characteristics of three different laboratory hydrogenators, the 1L Mettler Toledo's RC1 MP10 reactor, the 250 mL Parr shaker, and a 5 gal stainless steel hydrogenator with mechanical agitation, have been conveniently and rapidly measured. The mass transfer coefficients and their dependence on agitation speed are shown in Figure 8.6.

Taking advantage of its design precision, for example, the reproducible agitation ramp from zero to the desired agitation rate in <0.2 s, we first used the 1L Mettler Toledo's RC1 MP10 system to study the effect of the hydrogen pressure on k_La using methanol as the solvent. The results show that the
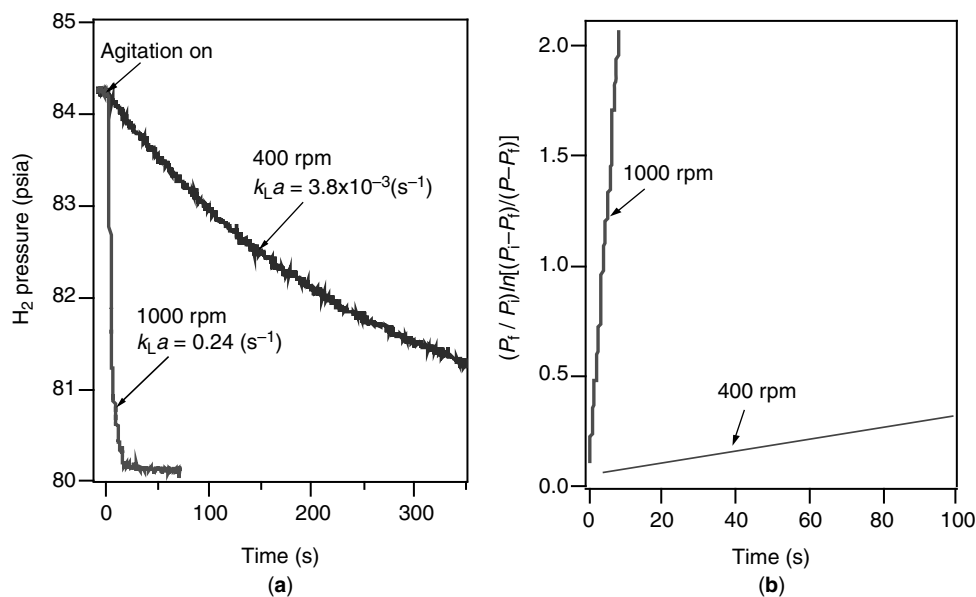

FIGURE 8.4 Schematics of the pressure drop and the corresponding concentration rise in a k_La measurement experiment.

FIGURE 8.5   Measurements of the H_2 uptake kinetics in 1-propanol (0.5 L) in the Mettler Toledo's 1L RC1 MP10 reactor at 30°C. (a) Hydrogen pressure drop as a function of time. (b) Corresponding plots of the pressure function in equation 8.9 versus time. The slope is k_La.

k_La value is rather independent of the hydrogen pressure over the range of 15–100 psig. Given this observation, we simply choose any convenient hydrogen pressure in this pressure range for the k_La measurement.

To the best of our knowledge, mass transfer characteristics of the Parr shaker system, traditionally and frequently employed for development of hydrogenation processes, have not been reported. Figure 8.6 shows that the Parr shaker possesses surprisingly good mass transfer capability rivaling the best achievable in the RC1 system that is known for its good mass transfer capability. At the shaking frequency typically used for process development, the value of k_La is moderate, $0.1\,s^{-1}$ at 130 rpm. Higher k_La values are achievable at higher shaking frequencies. Figure 8.7 shows several pressure curves measured in the Parr shaker. Figure 8.6 also shows that the mass transfer capability of the specific 5 gal
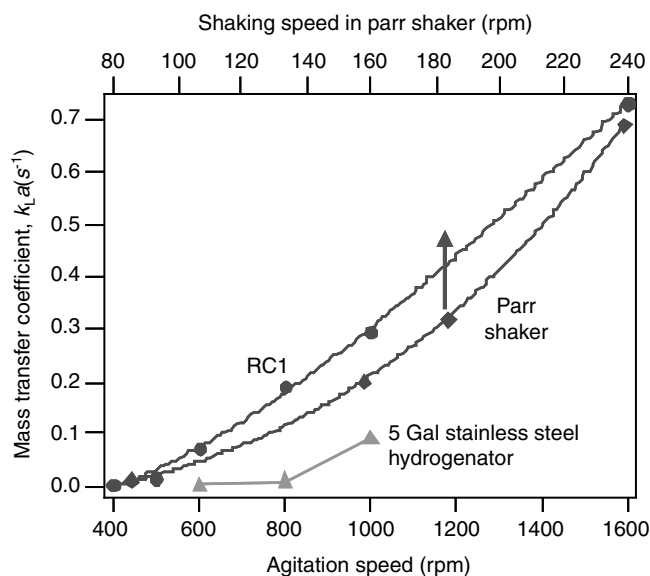

FIGURE 8.6   Hydrogen mass transfer coefficient k_La as a function of the agitation intensity for three types of hydrogenators: the 1L Mettler Toledo's RC1 MP10 reactor (500 mL MeOH), a 5 gal stainless steel hydrogenator with mechanical agitation (2.5 gal MeOH) and the 250 mL Parr shaker (90 mL MeOH).
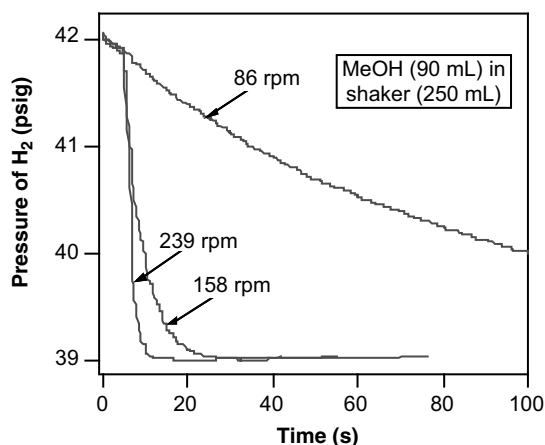
FIGURE 8.7 Decay of pressure in the headspace due to the nonreactive hydrogen uptake by methanol (90 mL) in the Parr shaker (250 mL) parametric in the shaking frequency.

hydrogenator studied even at the highest allowable rpm (1000 rpm) is somewhat limited ($k_L a = 0.1\,\mathrm{s}^{-1}$).

The simple methodology is applicable to $k_L a$ measurement in large hydrogenators in manufacturing facilities. The mass transfer capability of a factory glass-lined hydrogenator with a nominal 750 gal volume (900 gal actual, with a retreat blade impeller, one baffle, subsurface sparging) was characterized. The results revealed a limited gas/liquid mass transfer capability of this specific hydrogenator even with 100% agitation power. For instance, at a 460 gal fill and with the full agitation power, the $k_L a$ value is $0.035\,\mathrm{s}^{-1}$, a mass transfer coefficient equivalent to that in the RC1 reactor at 500 rpm only (Figure 8.6). The low mass transfer ability in this hydrogenator makes it unsuitable for running fast hydrogenation reactions that require $k_L a > 0.035\,\mathrm{s}^{-1}$ at the existing configuration.

8.5 CHARACTERIZATION OF CATALYST REDUCTION PROCESS

For hydrogenation processes in a solvent with a solid-supported metal catalyst, an important process involved is the reduction of the catalyst itself to its metallic state. For example, the Pd in the typical Pd/C catalysts is either in the form of palladium hydroxide or in the form of metallic palladium particles with its surface layers oxidized. Reduction of the surface Pd to its metallic state is necessary for the catalytic hydrogenation processes. While reduction of Pd/C catalysts used in the gas–solid reactions can be conveniently studied, to the best of our knowledge, the kinetics of catalyst reduction under the gas–liquid–solid slurry hydrogenation conditions has not been reported. How long does it take to reduce the catalyst under the slurry hydrogenation conditions? What does the kinetics look like? Is it instantaneous

upon pressurization of the hydrogenator? How do the solvent, the additives, and the substrate influence the kinetics of the catalyst reduction? How do the transient properties of the catalyst during the catalyst reduction process influence reactivity and selectivity of the hydrogenation of the substrate? These questions remain unanswered due to lack of research tools to characterize the kinetics of the catalyst reduction *in situ* under the slurry hydrogenation conditions. In this section, a simple procedure is described that allows one to measure the characteristics of the catalyst reduction process.

The procedure is an extension of the $k_L a$ measurement protocol described in Section 8.4. First, profile of the nonreactive uptake by the solvent is measured. Profile of the sum of the nonreactive and reactive hydrogen uptake due to the catalyst reduction is subsequently measured by repeating the same procedure (under the identical conditions) after addition of the heterogeneous catalysts to the solvent in the batch. The uptake profile due to the catalyst reduction can be extracted by taking the difference of the two uptake profiles.

The methodology is demonstrated in Figure 8.8 for measuring the reduction rate of a Pd/C catalyst in methanol at $-10°C$. The hydrogen uptake curves at 40 psig H_2 and at $-10°C$ upon agitation (1000 rpm) for MeOH (500 mL) only and for MeOH (500 mL) plus the 5% Pd/C catalyst (10 g) were measured consecutively and the results are shown in Figure 8.8a. Because the two uptake curves were measured under the identical conditions except that one is with the Pd/C catalyst added, the nonreactive uptake curve can be directly subtracted from the sum curve to generate the uptake curve associated only with the Pd/C reduction. By subtracting the two curves in Figure 8.8a, the reduction profile of the Pd/C catalyst emerges and is shown in Figure 8.8b.

A few properties of the reduction process become apparent from Figure 8.8b. The reduction is a relatively fast process—it is nearly completed in 2 min at 40 psig H_2 and at $-10°C$. The reduction kinetics exhibits two distinct regimes and can be fitted nearly perfectly by a double exponential function, that is, uptake $= 2.55 - 1.65e^{-0.0177t} - 1.34e^{-0.0864t}$. The fast rate process has a half-life of about 8 s and is likely associated with the reduction of the outside layers of Pd catalyst particles, whereas the slower rate process has a half-life of about 39 s and is likely associated with the reduction of the bulk of the Pd catalyst particles and with the formation of bulk palladium hydrides. Figure 8.8b also shows that the overall stoichiometry of the reactive hydrogen update for this catalyst is $H/Pd = 1.3$.

A closer look at the uptake profile in Figure 8.8b shows that there is a short induction period ($\sim4\,s$) in the catalyst reduction at $-10°C$; that is, there is no appreciable hydrogen uptake in the presence of 40 psig hydrogen for $\sim4\,s$. The induction period virtually disappears at $25°C$ for the catalyst reduction. This temperature effect is more evident when the reduction profiles at the two temperatures are placed in the same graph as shown in Figure 8.9. Interestingly, the kinetics in the fast rate regime at $25°C$ is similar to that at $-10°C$
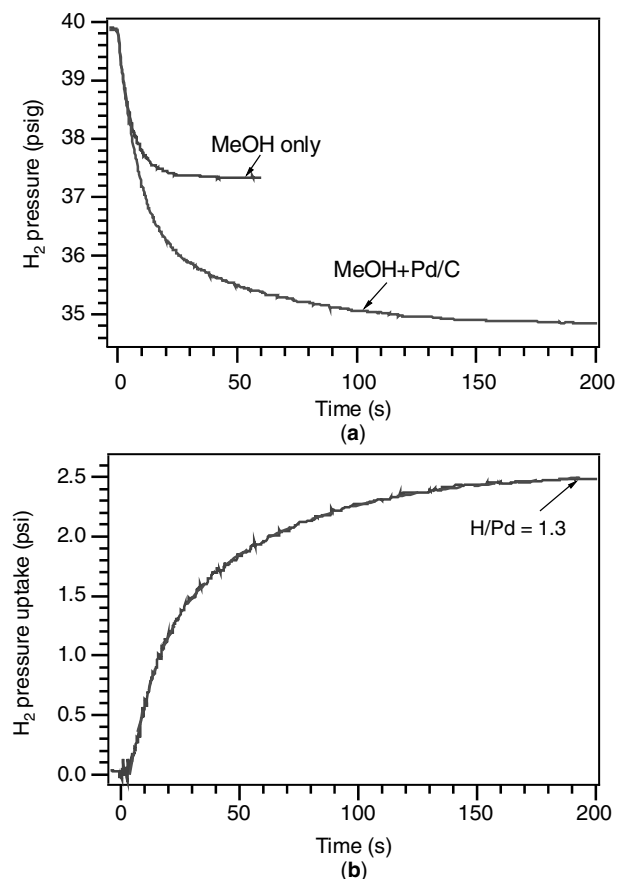
FIGURE 8.8 (a) Hydrogen uptake curves at 40 psig H_2 and at $-10°C$ upon agitation (1000 rpm) for MeOH (500 mL) only and for MeOH (500 mL) plus 5% Pd/C (10 g, Type 21, JM), following the standard $k_L a$ measurement procedure described in Section 8.4. Apparatus: Mettler-Toledo's RC1 with an MP10 reactor. (b) Difference between the two uptake curves in (a), representing the reactive hydrogen uptake by the reduction of the Pd/C catalyst only. The reactive hydrogen uptake curve can be fitted perfectly by a double exponential function. Uptake $= 2.55 - 1.65e^{-0.0177t} - 1.34e^{-0.0864t}$.

(similar slopes of hydrogen uptake at the fast rate regimes). The total reduction in hydrogen uptake at 25°C is however less, presumably due to lower equilibrium surface coverage of the hydrogen atoms on Pd and the bulk concentration of the Pd hydride at higher temperatures.

The methodology provides a convenient way to measure the catalyst reduction kinetics in solvents under the hydrogenation conditions except that the substrate is not present. In the presence of the substrate, the reactive hydrogen uptake would originate from the catalyst reduction and from the substrate hydrogenation. The methodology described here cannot deconvolute the rate of the catalyst reduction from the rate of the substrate hydrogenation. How the presence of the substrate affects the reduction kinetics of the heterogeneous catalysts remains unclear. One thing is clear that the kinetics of the catalyst reduction can be altered by the substrate in the
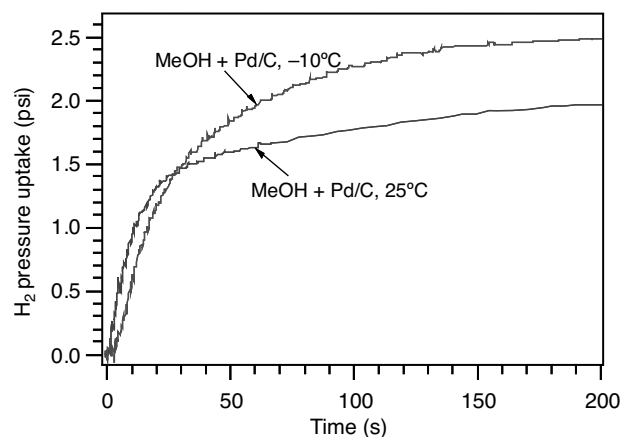

FIGURE 8.9 A comparison of the reduction kinetics of the 5% Pd/C catalyst (Type 21, JM) at -10 and 25°C. The experimental conditions are identical to those described in Figure 8.8.

hydrogenation reaction. Figure 8.10 shows the effect of the addition of ammonia to the methanol solvent on the catalyst reduction at $-10°C$. In this experiment, a small amount of aqueous ammonia (0.78 mol) was added into methanol to a total volume of 500 mL, and the catalyst reduction kinetics was studied following the standard procedure. The two hydrogen uptake curves measured are shown in Figure 8.10a. The catalyst reduction kinetic profile derived from Figure 8.10a is plotted in Figure 8.10b along with the kinetic profile of the catalyst reduction in methanol alone as a reference.

The most striking feature of the reduction kinetics in the presence of ammonia is that there is a significant induction period, $\sim$60 s, much longer than the 4 s induction period in MeOH without the ammonia addition. Over this long induction period, there is virtually no hydrogen uptake. At the end of the induction period, the rate of the Pd catalyst reduction accelerates. This induction period may result from strong chemisorption of ammonia on the surface of the Pd catalyst, inhibiting dissociative chemisorption of dihydrogen on Pd. Adsorption of a small amount of hydrogen on the catalyst surface through competitive adsorption process reduces a small fraction of the surface Pd that conversely facilitates dissociative chemisorption of additional hydrogen, leading to the rate acceleration. The maximum rate of the reduction, however, is slower than that in the absence of ammonia (Figure 8.10b). The long induction period is attributed to the presence of ammonia in the hydrogenation batch. Independent experiments showed that water as a result of the aqueous ammonia addition does not alter the catalyst reduction. Overall, the addition of ammonia extended the catalyst reduction timescale from about 2 to 7 min, suggesting that additives used in hydrogenation reactions and the substrate itself can influence the catalyst reduction kinetics.
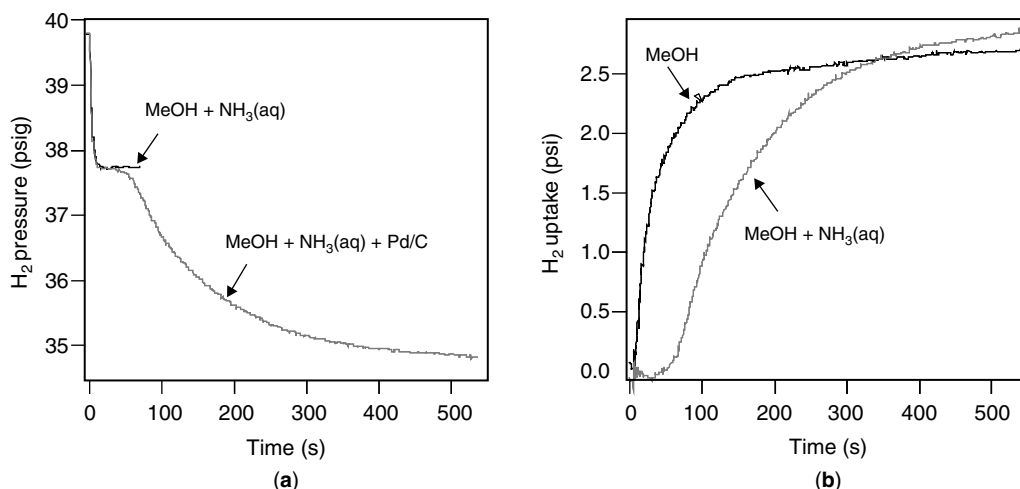
FIGURE 8.10   (a) Hydrogen uptake curves at 40 psig H_2, $-10°C$, 1000 rpm for MeOH $+$ NH_3 (aq)) (500 mL) and for MeOH $+$ NH_3(aq) (500 mL) plus 5% Pd/C (10 g, Type 21, JM), following the standard $k_L a$ measurement procedure described in Section 8.4. (b) Kinetics of the Pd/C catalyst reduction in MeOH $+$ NH_3(aq)) in comparison with the kinetics in MeOH only (reproduced from Figure 8.8b).

8.6   BASIC SCALE-UP STRATEGY FOR HYDROGENATION PROCESSES

When a hydrogenation process is translated from the laboratory to the plant, chemists and chemical engineers sometimes encounter scale-up issues such as problems with reactivity and/or selectivity. Often the scale-up issues can be traced to a lack of characterization or understanding of the various rate processes and an ensemble of key factors that affect the reproducibility and robustness of the hydrogenation process. A successful scale-up necessitates that these factors be identified, measured, and controlled. This section discusses some of the fundamental factors that need to be considered for a successful scale-up. A basic strategy for scaling up hydrogenation processes is described in terms of several quantitative criteria.

The most basic requirement for a successful scale-up is for the chemists and engineers to have at the laboratory development stage a true understanding of reaction kinetics that is intrinsic to the catalytic system, that is, one that is not masked by H_2 mass transfer limitations but is obtained under well-defined conditions, in particular, with a known $[H_2]_{lab}$. The best strategy to achieve this is to characterize the mass transfer capability of the hydrogenation reactor and use the 10% rule of thumb (as described by equation 8.7) in the laboratory developmental work so that the condition

$$[H_2]_{lab} \approx [H_2]_{sat} \qquad (8.10)$$

is also satisfied at all times. Availability of the intrinsic kinetic information allows one to make an intelligent choice of reactors and reaction conditions for reproducible and robust scale-ups.

The hydrogen mass transfer coefficient $k_L a$ of the hydrogenation reactor is one of the primary factors to consider in scale-up because it can have direct impact on kinetics, process safety, and selectivity. It is not uncommon, however, to find hydrogenation process descriptions specifying only the gas-phase H_2 pressure and agitation speed without specifying the requirement for the mass transfer coefficient $k_L a$ of the hydrogenator. To scale up a process in this manner subjects the process to the risk of running under ill-defined conditions; that is, undefined $[H_2]$ that is disengaged from the gas-phase hydrogen pressure. To reproduce in the plant runs the rate and selectivity observed in the laboratory, it is important that $[H_2]$ in the plant runs be the same as the $[H_2]$ used in the laboratory development work, that is,

$$[H_2]_{plant} = [H_2]_{lab} \approx [H_2]_{sat} \qquad (8.11)$$

Using the same pressure as that employed in the laboratory development without specifying $k_L a$ does not necessarily guarantee that this condition (equation 8.11) is satisfied.

When one runs the plant process far from the hydrogen mass transfer-limited situations, the hydrogen concentration $[H_2]$ is known and constant (as long as the gas-phase pressure remains unchanged) over the entire course of reaction. This is particularly important for hydrogenation reactions with $[H_2]$-dependent selectivity. If this type of reactions is operated under hydrogen diffusion limitations, $[H_2]$ deviates from $[H_2]_{sat}$ and becomes disengaged from the gas-phase hydrogen pressure. The solution goes from hydrogen starved at the beginning stage of reaction when the intrinsic hydrogenation rate is fast to hydrogen saturated at the later stage of the reaction when the intrinsic hydrogenation slows down due to depletion of the starting material. The selectivity would vary

throughout the course of the reaction as a result. In addition, rate of a process running under hydrogen mass transfer control is sensitive to slight changes in reaction conditions. For example, the rate can change significantly with changes in rpm due to the commonly observed exponential dependence of $k_L a$ on the agitation rate. The rate would not be affected by changes in the agitation rate, however, for processes running away from hydrogen mass transfer limitations.

To satisfy the scale-up requirement described by equation 8.11, the 10% rule of thumb (equation 8.7) provides a good general guideline for matching the mass transfer capability of the hydrogenation reactor to the kinetics of a process. Given a process with known intrinsic kinetics, the chosen reactor for scale-up needs to have a minimum mass transfer coefficient of

$$k_L a \geq 10 R_{H_2,rxn}^{max}/[H_2]_{sat} \qquad (8.12)$$

In addition, the heat transfer issue also needs to be considered for safe operations in scale-up. The following condition needs to be met

$$R_{H_2,rxn}^{max} \leq q_r^{max}/\Delta H_{H_2} \qquad (8.13)$$

where q_r^{max} is the maximum heat removal capability of the reactor, and ΔH_{H_2} is the heat of hydrogenation per mole of H_2 reacted.

The inherent reaction kinetics and the conditions described by equations 8.12 and 8.13 form some of the basic requirements that need to be considered for successful scale-ups of hydrogenation processes.

8.7 SUMMARY

Dissolution of H_2 into the liquid phase is the first rate process along the H_2 pathway in catalytic hydrogenation reactions. The dissolution kinetics can play a key role in the kinetics and selectivity of catalytic reactions and the outcome of process scale-up. At a given gas-phase H_2 pressure, while thermodynamics determines the solubility $[H_2]_{sat}$, it is *kinetics* that determines the actual solution H_2 concentration $[H_2]$ or the "effective hydrogen pressure" that the catalyst experiences *during* hydrogenation reactions. Depending upon the relative magnitude of the rate of H_2 mass transfer across the gas/liquid interface versus the rate of the reactive removal of the dissolved H_2 from the liquid phase by hydrogenation, $[H_2]$ may vary greatly from saturation to nearly zero, even at a constant pressure in the gas phase. The influence of mass transfer on $[H_2]$ exerts a direct impact not only on rate but also on selectivity for reactions whose selectivity depends on $[H_2]$. It is also often the fundamental cause of irreproducibility in rate and selectivity observed from reactor to reactor (e.g., when scaling up a laboratory process in the manufactur-

ing facility) when the same reaction is carried out under seemingly identical conditions. This is because different mass transfer capabilities of reactors of different types and scales can lead to different "effective pressures" even at a constant gas-phase pressure.

A catalytic hydrogenation process should be carried out under conditions where the intrinsic hydrogenation rate is at least 10 times lower than the maximum rate of H_2 mass transfer across the gas/liquid interface. This ensures that the observed kinetics and catalytic behaviors are not masked by the mass transfer limitations but are intrinsic to the catalytic system under well-defined conditions. This requirement may serve as a general guideline for designing scalable processes, since as long as the 10% rule of thumb is satisfied, the hydrogenation process is "portable"; that is, the same kinetics and catalytic behavior will be reproduced from reactor to reactor at any scale. Strategy for a successful scale-up of hydrogenation processes is formulated in terms of a set of quantitative criteria.

The process of reduction of a Pd/C catalyst under the hydrogenation conditions is characterized using a novel methodology. The results show that the catalyst reduction process can have an induction period, is relatively fast (on the order of <5 min) under typical hydrogenation conditions, and can be significantly influenced by the nature of the additives or the hydrogenation substrates.

REFERENCES

1. (a) Rylander PN. *Hydrogenation Methods*, Academic Press, 1990;(b)Rylander PN. *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, 1979.
2. Augustine, R.L. *Heterogeneous Catalysis for the Synthetic Organic Chemists*, CRC Press, 1995.
3. Knowles, W.S., *Angew. Chem., Int. Ed.* 2002;41:1998.
4. Knowles, W. S., Noyori, R., *Acc. Chem. Res.* 2007;40:1238.
5. Noyori, R., *Angew. Chem., Int. Ed.* 2002;41:2008.
6. Noyori R. *Asymmetric Catalysis in Organic Synthesis*, Wiley, 1994, and references therein.
7. Krische MJ, Sun YK,guest editors. Hydrogenation and transfer hydrogenation, *Acc. Chem. Res.*, 40, 2007.
8. (a) See, for example, Sun, Y.K., Landau, R.N., Wang, J., LeBlond C., Blackmond, D.G., *J. Am. Chem. Soc.*, 1996;118:1348; (b)Sun, Y.K., Wang, J., Landau, R.N., LeBlond C., Blackmond, D.G., *J. Catal.* 1996;161:759.
9. (a) Ramachandran PA, Chaudhari, RV. Three-phase catalytic reactors. In: *Topics in Chemical Engineering 2*, Gordon and

Breach Science Publishers, 1983; (b) Beenackers, A.A.C.M., and Van Swaaij, Mass transfer in gas-liquid slurry reactors. *Chem. Eng. Sci.*, 1993;48:3109; (c) Hines AL Maddox RN. *Mass Transfer: Fundamentals and Applications*, Prentice-Hall, 1985.

10. (a) Landis, C.R.,and Halpern, J., *J. Am. Chem. Soc.* 1987;109:1746; (b) Sun, Y.K., Landau, R.N., Wang, J., Le-Blond, C.,and Blackmond, D.G., *J. Am. Chem. Soc.* 1996;118:1348.

11. Sun YK, LeBlond, C, Wang J, LeBlond C, Blackmond DG, Laquidara J, Sowa J., Jr., *J. Am. Chem. Soc.* 1995;117:12647.

12. Wang, J., Sun, Y.K., LeBlond, C., Landau. R, Blackmond, D.G., *J. Catal.* 1996;161:752.

13. Sun, Y.K., Wang, J., LeBlond, C., Reamer, R.A., Laquidara, J., Sowa, J.R., Blackmond, D.G., *J. Organomet. Chem.*, 1997;581:65.

14. (a) Matsumara, M, Masunaga, H.,and Kobayashi, J., *J. Ferment. Technol.*, 1979;57:107; (b) Deimling, A., Karandikar, B. M.,and Shah, Y.T., Carr, N.L., *Chem. Eng. J.* 1984;29:140; (c) Blaser, H.U., Garland, M., Jallet, H.P., *J. Catal.*, 1993;144: 569.