Jointly published by
Akadémiai Kiadó, Budapest
and Springer, Dordrecht

React.Kinet.Catal.Lett.
Vol. 93, No. 1, 175–185 (2008)
10.1007/s11144-007-5216-z

RKCL5216

A COMPARISON OF HOMOGENEOUS AND BIPHASIC HYDROGENATION SYSTEMS OF MACROCYCLIC LACTONES WITH *IN SITU* FORMED RHODIUM COMPLEXES

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Received September 18, 2007, in revised form December 7, 2007, accepted December 10, 2007

Abstract

Homogeneous and biphasic hydrogenation of avermectins catalyzed by rhodium complexes *in situ* formed from $[RhCl(COD)]_2$ and triphenylphosphine or sulphonated arylphosphines, respectively, was studied under mild reaction conditions. Effects of adding TBAB and bis-QACs as phase transfer agents, Tween® 80 as non-ionic surfactant, β-cyclodextrin as inverse phase-transfer agent, and triphenylphosphine as co-ligand, are reported for the biphasic system.

Keywords: homogeneous hydrogenation, biphasic hydrogenation, rhodium, avermectins

INTRODUCTION

Macrocyclic lactones (MLs) produced by the fermentation of *Streptomyces avermitilis* have revolutionized the way in which parasites are controlled in the

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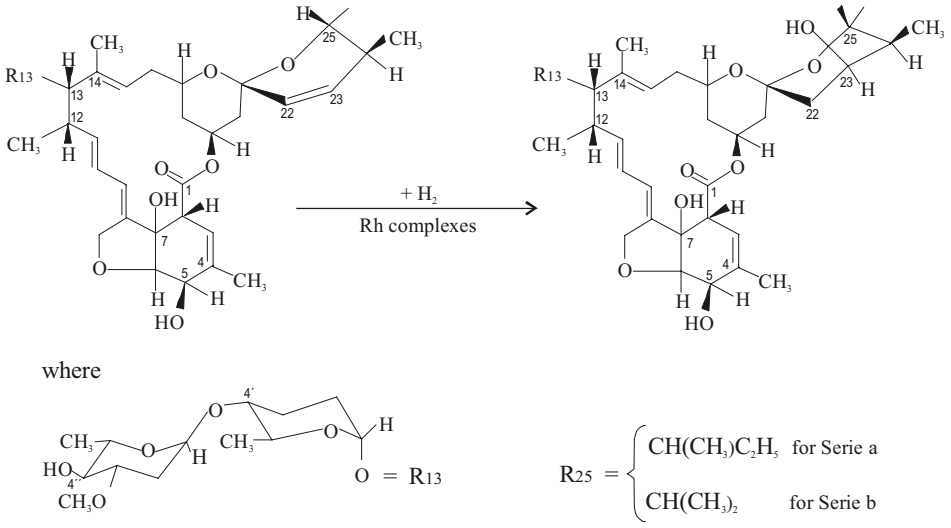
0133-1736/2008/US$ 20.00.

production of animals. Ivermectin (IVM) is the leading product among these compounds specifically formulated for use in animals [1-3]. New applications have also been reported for human medicine [4-9]. The preparation of IVM involves the regioselective hydrogenation of the *cis* 22,23 double bound of avermectins B_{1a} and B_{1b} (AVM), without affecting the remaining four double bonds (see Scheme 1). Wilkinson´s catalyst has been the first rhodium based catalytic system used for this purpose [1]. As the primary patent expired some years ago, a substantial competitiveness has depressed the price of IVM while that of rhodium has continued to rise. Thus, the development of improved hydrogenation processes has gained increasing importance because the production of the costliest ones will be withdrawn from the market.



Scheme 1. Regiospecific hydrogenation of the *cis* 22,23 double bound of avermectin B_{1a} and B_{1b} for preparing ivermectin

Little effort has been given to improve Chabala´s pioneering process. There are only few contributions claimed in patents [10-12]. Unfortunately, they include only scant information on the hydrogenation kinetics. On the other hand, a generalization of results from the catalytic hydrogenation of small olefins to these MLs is not obvious, since the reaction rates can be further influenced by steric hindrances and/or phase-transfer limitations. Therefore, a thorough understanding of the kinetic aspects leading to an enlightened attempt to developing new biphasic systems for the AVM catalytic hydrogenation is still far from being accomplished. In previous contributions we reported the kinetic modeling of the homogeneous hydrogenation of AVM with Wilkinson´s

catalyst [13], and with *in situ* formed catalytic complexes from $[RhCl(COD)]_2$ and triphenylphosphine [14]. Concerning the lack of kinetic information for obtaining IVM in biphasic systems, a comparison of the kinetic behaviors in homogenous and biphasic media under similar conditions might provide more insight into these two alternatives. Therefore, as part of our ongoing studies, results comparing the hydrogenation performances in organic and aqueous/organic media, catalyzed by *in situ* formed catalytic species from $[RhCl(COD)]_2$/triphenylphosphine and $[RhCl(COD)]_2$/ sulfonated arylphosphines, respectively, are herein presented and briefly discussed.

EXPERIMENTAL

Avermectin B_1 (AVM) (purity > 98.75%) was obtained by purification of commercial avermectins as previously reported [13]. Chloro(1,5-cyclooctadiene) rhodium(I) dimer (98%), triphenylphosphine (TPP) (99%); bis(*p*-sulphonatophenyl) phenylphosphine dipotassium salt (BSPP) (97%); tris(*m*-sulphonatophenyl) phosphine (TPPTS) (98%); β-cyclodextrin (β-CD); polyoxyethylene(20) sorbitan monooleate (Tween® 80); and tetrabutyl ammonium bromide (TBAB) (99%) were purchased from Sigma-Aldrich and used as received. The bis-quaternary ammonium compounds (bis-QACs), 2-hydroxi-1,3-(bis) *N,N*-octyldimethylammonium chloride (bis-QAC_1) and 2-hydroxi-1,3-(bis)*N,N*-dodecyl dimethyl ammonium chloride (bis-QAC_2), were synthesized and characterized following procedures reported elsewhere [15]. N_2 gas (AgaGas, 99.999% pure) and H_2 gas (AgaGas, 99.999% pure) were flowed through a Deoxo unit and a drying column before use. Toluene (Cicarelli, puriss. p.a.) and ethylene glycol (Aldrich, 99.8%) were dried and degassed prior to use. Deionized water was used in the biphasic experiments. All air sensitive manipulations were carried out in a reaction device under oxygen-free atmosphere using the experimental setup and techniques reported in our previous works [13,14]. The progress of the reaction was followed by HPLC analyses with the resolution of AVM analogues and hydrogenated derivatives thereof, *i.e.*, series B_{1a} and B_{1b}, as described in our above referenced works.

Homogeneous hydrogenation

Kinetic experiments were carried out in the 313-343 K temperature range, at a hydrogen pressure of 275.7 kNm^{-2}, using 6 (mol/mol) equivalents of TPP/$[RhCl(COD)]_2$, and 1% (mol/mol) $[RhCl(COD)]_2$/AVM. A stirring rate of 750 rpm was found to be enough to ensure a negligible gas-liquid mass transfer

resistance [13,14]. A typical hydrogenation run was as follows: $[RhCl(COD)]_2$ (45.9 mg; 0.093 mmol) and TPP (146.3 mg; 0.558 mmol) were weighed and placed into the cup mounted on the upper part of a cup-and-cap (CAC) holder for powdered catalysts consisting of a fixed cover (cap) and a loose vase (cup) mounted on the reactor shaft [16]. After assemblage, the reaction vessel containing toluene (70 mL) was degassed by mild vacuum, purged three times with hydrogen, and finally pressurized up by hydrogen to the reaction pressure. A stirring speed of 750 rpm was used. Then, by a sudden interruption of the mechanical stirring, the cup containing TPP and $[RhCl(COD)]_2$ was fully immersed into the solvent saturated with dissolved hydrogen. A quick restoring of stirring allowed a good dispersion and fast dissolution of both powdered reagents in the toluene solution, which was heated up to the reaction temperature. On the other hand, a toluene solution of AVM (8.125 g, 93 mmol, 30 mL) was put into a feeder reservoir connected by a simple one-way valve to the reaction vessel head. After vacuum degassing and hydrogen flushing, the reservoir was pressurized by hydrogen and heated up to the reaction temperature. After conditioning for 30 min, the hydrogenation reaction was allowed to start by transferring the AVM solution from the feeder reservoir to the reaction vessel containing the incipient catalytic solution. Zero time was taken just at that moment.

Biphasic hydrogenation

Isothermal reaction experiments were carried out at 343 K and 275.7 kNm^{-2} of hydrogen pressure. Other operating conditions were as follows: 6 (mol/mol) equivalents of BSPP or TPPTS/$[RhCl(COD)]_2$, 1% (mol/mol) $[RhCl(COD)]_2$/AVM, and water/toluene mixtures ranging from 10:90 to 90:10. After increasing the stirring rate, it was found that 850 rpm were enough to produce a well-dispersed biphasic medium. A typical run was as follows. $[RhCl(COD)]_2$ (27.5 mg; 0.0558 mmol) and BSPP (167.0 mg; 0.3348 mmol) were weighed and placed into the cup of the CAC device. An aliquot of the organic solvent (toluene, 35 mL) and the total amount of the water being employed (15 mL) were put into the reaction vessel with the precise amount of the adjuvant agent to be tried, e.g., TBAB (215.9 mg; 0.6697 mmol), bis-QACs (3.9×10^{-5} mol L^{-1}), Tween® 80 (1.6×10^{-5} mol L^{-1}), β-CD (0.3273 mg; 0.2884 mmol), and TPP (8.8 mg; 0.0167 mmol). The reaction vessel was then purged, degassed and pressured by hydrogen. The stirring speed was settled at 850 rpm. On the other hand, a toluene solution of purified AVM (2.1 g; 2.37 mmol; 30 mL toluene) was put into the feeder reservoir. After conditioning for 30 min, the hydrogenation run was allowed to start by adding the AVM solution to the

catalytic aqueous/toluene medium contained in the reaction vessel. All experiments were stopped when no hydrogen gas uptake was noticeable. Further hydrogenation runs were carried out by recycling the catalytic aqueous medium, which separates as a non-miscible phase into a closed loop connected to the reaction vessel and kept under nitrogen atmosphere.

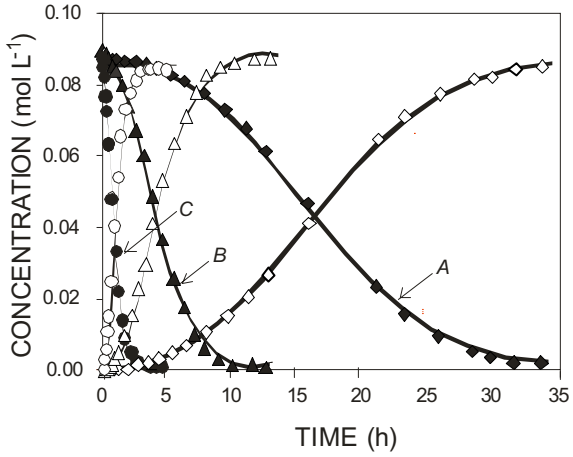


Fig. 1. Concentration profles *vs* reaction time for homogeneous hyddrogenaiton with *in situ* formed catalytic complexes $[RhCl(COD)]_2$ /TPP, at 313 (curve *A*), 328 (curve *B*) and 345 K (curve *C*). Filled symbols denote avvermectin B_1; unfilled symbols denote ivermectin

RESULTS AND DISCUSSION

Figure 1 displays the concentration profiles versus reaction time for the homogeneous hydrogenation with *in situ* formed catalytic complexes from $[RhCl(COD)]_2$/TPP, at 313, 328 and 343 K (curves *A*, *B* and *C*, respectively). The profiles were S-shaped curves revealing an induction phenomenon, which were more marked at lower temperatures. Although this behavior has some precedents in rhodium chemistry, such prolonged initial delays were certainly unexpected. After excluding effects due to a slow dissolution rate of the powdered reagents and/or a reaction medium increasingly saturated with dissolved hydrogen, it was indubitable that the catalytic species demand appreciable time before they are quantitatively synthesized. Two features can be supposed to explain the induction periods, as previously reported [14]. First, the bonds of the bidentate COD ligand to be broken are strong enough to make the barrier of TPP insertion high (about 129 kJ mol^{-1}). This makes the *in situ* generation of the catalytic species hard, and thus being the rate-determining

step (RDS) under mild reaction conditions. Another contributing feature is the ability of AVM to interfere with the course of the synthesis. At the beginning of the hydrogenation run, the significantly greater initial amount of AVM as compared to the COD ligand presumably promotes an undesired competing reaction pathway consisting of COD ligand replacement by AVM. The resulting species $RhCl(TPP)_2(AVM)$ reacts more slowly than $RhCl(TPP)_2(COD)$, producing thereby a delay in the synthesis rate of the catalytic species. The former difficulty could be overcome by using higher temperatures. The latter is unavoidable due to the fact that the synthesis of the catalytic species and AVM hydrogenation take place simultaneously. Therefore, a high temperature was mandatory to achieve a fast enough synthesis rate (curve *C*). Since the induction phenomena were minimized at 343 K, this temperature was chosen for carrying out the study of the biphasic catalysis.

In order to compare the hydrogenation performance in aqueous/organic media with that described above for a homogeneous medium, biphasic catalysis was carried out with the same molar ratios of phosphines, $[RhCl(COD)]_2$, and substrate as used for homogeneous hydrogenation. Hydrogenation runs without adding a phase-transfer agent failed. The concentration of AVM remained practically unchanged for prolonged periods, suggesting significant mass-transfer limitations at the liquid-liquid interface. No attempts were made to increase the interfacial area by increasing the stirring rate above 850 rpm, because the resulting stirring intensity is quite difficult and expensive to be achieved in production reactors. Therefore, the use of adjuvant agents to improve the interfacial mass-transfer rate was unavoidable. Tween® 80 was used as a common non-ionic surfactant. Bis-QACs were used as cationic gemini surfactants characterized by improved surface-active properties, as well as by their capability of acting as phase-transfer agents. TBAB was used as a common phase-transfer agent and β-CD as an inverse phase-transfer agent. TPP was tested for its ability to modulate the hydrophilicity and activity of the catalytic species. On the other hand, a non-significant improvement in the hydrogenation performance was obtained either by changing the aqueous phase by ethylene glycol (a more polar solvent), or by using TPPTS instead of BSPP. The biphasic hydrogenation of AVM was highly selective to the *cis* 22,23 double bound. The selectivity toward IVM was > 99%, which is better than that expected on the basis of the 98% obtained in the homogeneous system. Concentration profiles during the biphasic catalysis by *in situ* formed water-soluble complexes are shown in Figs 2a-d.

As mentioned above, the use of phase-transfer agents was mandatory, and not optional. Results of adding TBAB and bis-QACs are illustrated in Fig. 2a. Catalytic activity was obtained when TBAB, was added to the biphasic medium, in

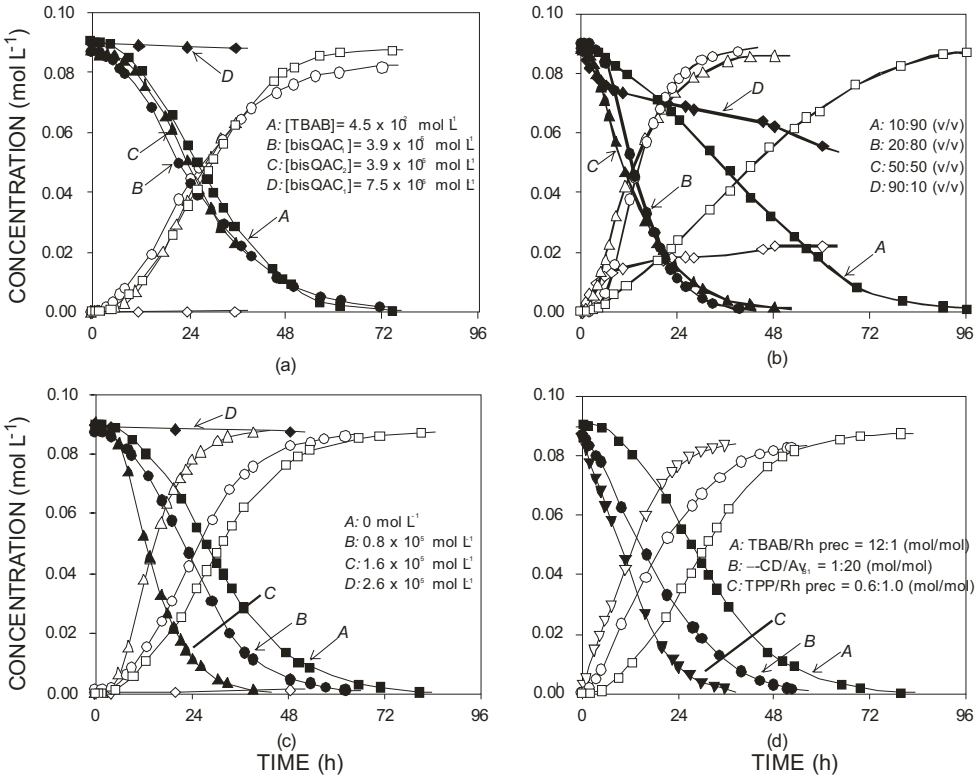


Fig. 2. . Concentration profiles *vs* reaction time in biphasic catalysis by *in situ* formed water-soluble complexes at 343 K. Filled symbols denote avermectin B_1, unfilled symbols denote iverctin. (a) Effect of TBAB and bis-QACs (*) (b) Effect of aqueous phase ratio. (c) Effect of –CD and TPP (*). (*) aqueous/organic phase ratio = 20:80

stoichiometric amount to achieve a full ionic pairing with the sulfonated arylphosphine, for example 2 (mol/mol) equivalents of TBAB/BSPP (curve *A*). 2-hydroxi-1,3-(bis) *N,N*-octyldimethylammonium chloride and 2-hydroxi-1,3-(bis)*N,N*-dodecyldimethyl-ammonium chloride proved to be much more efficient than TBAB, since similar catalytic activity was obtained evenby using quantities about three-orders smaller than that of TBAB (curves *B* and *C*). In addition to the fact that the bis-QAC exhibits better surface-active properties as compared to TBAB, it is likely that the dicationic nature of these bis-QACs plays a significant role in improving the ion pairing effectiveness with the polyanionic phosphines, thus increasing the interfacial activity. However, contrary to our expectations based on the fact that the micelles have been

known to facilitate some reactions, there was an almost no catalytic activity when the critical micellar concentration (CMC) of bis-QACs was surpassed (curve *D*). A plausible explanation for this evidence is that the sulfonated arylphosphines could be partitioned into the micelles remaining in the aqueous phase, thereby reducing their availability to reach the liquid-liquid interface and to react for yielding active catalytic derivatives. Whatever the cause, it was apparent that lower phase-transfer agent concentrations are required than CMC.

The effect of water/toluene ratio was studied within wide limits ranging from 10:90 to 90:10 (v/v), keeping the amount of TBAB constant. Results are illustrated in Fig. 2b. Low catalytic activity was achieved for a 10:90 medium because this ratio promoted a poor generation of liquid-liquid interfacial area under the operating conditions (curve *A*). Ratios of 20:80 and 50:50 gave better hydrogenation performances (curves *B* and *C*). No induction period was practically observed for the 50:50 ratio, but the 20:80 ratio exhibited a slight initial time delay. Nevertheless, the catalytic activity was lower for the former ratio. A plausible explanation for this opposed behavior could be the following: The 50:50 medium afforded a higher interface favoring the synthesis rate, but also provided a greater dilution of the water-soluble Rh complexes slowing down the catalytic hydrogenation rate. By increasing the water/toluene ratio still further, an O/W emulsion was achieved for a 90:10 ratio. Under this condition there were no induction phenomena (curve *D*). Despite the high catalytic activity at the beginning of the hydrogenation process, it was not possible to achieve high conversion to IVM because a breakdown phenomenon caused the rupture of the emulsion. All attempts to keep the stability of the O/W emulsion during the course of hydrogenation failed. Therefore, a water/toluene ratio of about 20:80 yielded the best performance.

The effect of the concentration of Tween® 80 was examined by keeping constant the amount of TBAB, and using an aqueous/organic phase ratio of 20:80. Results are reported in Fig. 2c. As mentioned, without using Tween® 80 the concentration profiles versus reaction time exhibited S-shapes characterized by a significant induction time, and high conversions to IVM came up only after very long reaction times (curve *A*). With increasing addition of Tween® 80 below the CMC, both the induction and reaction times decreased (curves *B* and *C*). This revealed that both the synthesis and hydrogenation rates were favored. As expected, the greater the amount of the non-ionic surfactant, the larger the liquid-liquid interfacial area and thus the faster the reactions. However, there was no catalytic activity when the CMC was surpassed (curve *D*), as also noticed for bis-QACs. This behavior was opposed to that reported for water-soluble Rh complexes interacting with olefinic substrates having linear alkyl chains, which are easily incorporated into the micellar aggregates favoring the catalytic activity above the CMC [17]. This is certainly not the

case for AVM. Although there is no explicit evidence, we think that the presence of micelles prevents the formation of the catalytic species because the arylphosphines and not the AVM are therein partitioned, due to the large molecular size of these MLs. Again, whatever the cause, the convenience of adding Tween® 80 in concentrations lower than the CMC is evident, since the overall hydrogenation time was reduced by half as compared to that obtained without adding this common non-ionic surfactant.

The effects of adding β-CD and TPP, as inverse phase-transfer agent and coligand, respectively, were also analyzed. Results are reported in Fig. 2d. When a 5% (mol/mol) β-CD/AVM was added to the biphasic medium, the catalytic activity significantly improved as compared to that of TBAB (curves *A* and *B*). There is no induction period, as might be expected if the phase-transfer rate is fast enough to compete with the catalytic hydrogenation rate. The transfer was probably mediated by the formation of an inclusion complex due to the capability of β-CD to form this type of inverse phase-transfer agents with an ample variety of organic molecules [18-20]. Concerning the structure of the inclusion complex, no direct information is currently available. At this time, we envisage the formation of a $[RhCl(COD)]_2$-β-CD inclusion complex promoting the transfer of the water-insoluble Rh precursor to the aqueous phase. On the other hand, it was found that the addition of free TPP maximized the performance of the biphasic catalysis (curve *C*). For a 0.6:1.0 (mol/mol) TPP/$[RhCl(COD)]_2$ ratio, the induction period was completely suppressed and a zero-order kinetics governed the hydrogenation reaction until achieving a AVM conversion of about 90%. The water-insoluble TPP could be responsible for a fast cleavage of the $[RhCl(COD)]_2$ being solubilized in toluene [21]. A further substitution of the COD ligand by the sulfonated arylphosphine could also take place since the COD transfer to the organic phase is favored. Therefore, the coexistence of $RhCl[BSPP]_{3-x}[TPP]_x$ (or $RhCl[TPPTS]_{3-x}[TPP]_x$) complexes would not have to be discarded. Mixed ligands would favorably change the intrinsic catalytic activity of the complexes, but this seems quite unlikely to us, given that only a 10 % (mol/mol) of TPP/BSPP was used in the present study. We believe that the better performance is probably due to the less hydrophilic nature of the mixed complexes, which enables these species to prefer being close to the liquid-liquid interface, enhancing thus interfacial catalysis. Despite the fact that TPP was the most effective adjuvant agent to improve biphasic catalysis, the recycling efficiency was quite low since the aqueous phase exhibited a very low catalytic activity. This feature reinforced the assumption of mixed ligand complexes being at the interface.

CONCLUSIONS

The results presented above indicate that IVM yields greater than 98 % are feasible to be reached in both hydrogenation systems, and that biphasic hydrogenation was slightly more selective (99%) than homogeneous hydrogenation (98%). However, the reaction rates in water/toluene medium were found to be much slower than those resulting from the homogeneous system under similar operating conditions. Not unexpectedly, the synthesis and hydrogenation rates in the biphasic system were strongly influenced by the transfer kinetics at the aqueous-organic interface. The addition of TBAB or bis-QACs as phase-transfer agents was mandatory, not optional. Addition of Tween® 80 as interfacial area-promoting agent increased the activity of the biphasic catalysis. Hydrogenation performance was further improved by adding β-CD as inverse phase-transfer agent. Addition of 0.6:1.0 (mol/mol) TPP/$[RhCl(COD)]_2$ as coligand, 6 (mol/mol) BSPP or TPPTS/$[RhCl(COD)]_2$, 1 % (mol/mol) $[RhCl(COD)]_2$/AVM, and a 20:80 water/toluene ratio at 343 K and 275.7 kNm^{-2} of hydrogen pressure, maximized the performance of the biphasic system. It is also noticeable that the better biphasic performances at 343 K roughly approach that resulting in homogeneous hydrogenation at 313 K, as compared to the same amount of catalysts. Therefore, developing a competitive biphasic hydrogenation process remains a challenge, since higher catalytic activity is required to make the process commercially viable. Accordingly, optimization studies are underway, but optimized operating conditions are not yet available.

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