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ARTICLE TYPE

Rapid Nanoparticle-Catalyzed Hydrogenations in Triphasic Millireactors with Facile Catalyst Recovery

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We report a triphasic segmented flow millireactor for rapid nanoparticle-catalyzed gas-liquid reactions with facile catalyst recovery. Process intensification using a pseudo-biphasic scheme of reactor operation allows order-of-magnitude reduction in reaction times for a variety of substrates and catalysts.

Metal-catalyzed gas-liquid reactions such as hydrogenation, carbonylation and hydroformylation are ubiquitous in pharmaceutical and fine chemical production. Typical gas-liquid reactions are performed in stirred batch reactors, where the gaseous reactant is pressurized in the headspace above the stirred liquid phase containing the substrates and catalysts, and are often hindered by heat and mass transport limitations due to low specific interfacial areas. Such limitations can be mitigated through the use of micro-/milli-reactors as platforms for multiphase organic syntheses due to the tremendous transport acceleration inherent in these small scale flowing systems.[1] In recent years, several biphasic organic synthetic transformations have been demonstrated in various microreactor schemes, such as gas-liquid segmented flow, membrane microreactors and falling film microreactors, with significant improvements in yield, selectivity and reaction times.[2-7] However, despite the various advantages of microreactor technologies, catalyst recovery and recycle remains a challenge, especially in homogeneously catalyzed reactions where the unreacted substrates and products may exist in the same fluid phase as the catalyst. To facilitate catalyst reuse, the immobilization of catalysts on solid supports in packed bed microreactors, or on channel walls in the case of falling film microreactors and wall-coated microchannel reactors has been employed successfully for certain organic transformations.[6, 8-15] However, the deactivation of catalysts limits the long term use of such reactor schemes unless the catalyst can be regenerated easily *in situ*.[16]

Alternatively, a catalyst can be 'immobilized' by containing it within an immiscible liquid phase to aid subsequent, and straightforward, separation from substrates and products; this concept has been demonstrated for a variety of catalysts, including homogeneous transition metal complexes, nanoparticles (NPs) and enzymes.[17-21] Though this technique is ideal for catalyst recovery and recycle, the involvement of three fluid phases – gaseous reactant phase, liquid substrate/product phase and an immiscible catalyst-carrying liquid phase – implies the presence of additional, and potentially severe, mass transport limitations beyond the basic biphasic reaction scheme. Therefore, conducting triphasic reactions even in small-scale batch reactors with poorly controlled interfacial areas typically requires high pressures and/or longer reaction times for reasonable product yields, when compared to homogeneous or biphasic reactions.[2, 20, 21] Here, we present a triphasic millireactor scheme that utilizes the idea of a flowing, immiscible catalyst-carrying liquid phase, and enables tremendous acceleration of multiphase mass transport while also allowing facile catalyst recovery and recycle. The basic idea of our triphasic millireactor, as indicated in Fig. 1, is to first create a liquid-liquid segmented flow of aqueous catalyst-carrying phase and an organic substrate/product phase, into which the gaseous reactant is injected to yield a highly controlled 'pseudo-biphasic' gas-liquid segmented flow. This latter flow involves long gas bubbles completely coated by thin films of the organic phase, flowing alternately with organic segments, each of which contains a plug of aqueous catalyst.

To realize this reactor scheme, a 1 mm ID hydrophobic PTFE tube is chosen as the material for our millireactor to better facilitate the wetting of the wall by the organic phase. Liquid-liquid segmented flow is first formed under ambient conditions by infusing an aqueous catalyst phase at 20 μL/min into a T-junction, together with an organic phase containing the substrate at 10 μL/min. Thereafter, the flow is directed into a second T-junction where hydrogen gas at near atmospheric pressure is introduced to realize the pseudo biphasic flow described above (also see video S1 in ESI). We employ 'soluble' metal nanoparticles as the aqueous-phase catalyst, which circumvents problems of channel fouling or blockage that conventional heterogeneous catalysts would encounter in flowing microfluidic systems.

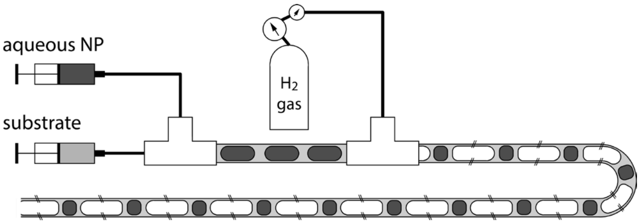

Fig. 1 Illustration of triphasic segmented flow millireactor formed from the simultaneous flow of organic phase containing substrate, nanoparticles suspended in aqueous phase, and hydrogen gas.

Rh is the most active element for C=C bond and aromatic ring hydrogenation; as a result Rh-catalyzed hydrogenations of alkenes and arenes often suffer from mass transfer limitations. The hydrogenation of 1-hexene over a Rh nanoparticle-based catalyst is thus chosen to demonstrate the concept and advantages of our millireactor system. Highly active, stable and water dispersible Rh nanoparticles (RhNPs) with a diameter of ~3 nm were prepared from $RhCl_3$ via a classical ethanol/water reduction method in the presence of polyvinylpyrrolidone (PVP) as the stabilizer.[22] As a first demonstration, we study the hydrogenation of 1-hexene dissolved in cyclohexane catalyzed by RhNPs in our millireactor. The volumetric flow rates of hydrogen and hence flow speeds and residence times in our 2 m long millireactor are adjusted via modifications in gas pressure (101 – 103 kPa) at the inlet of the reactor. Typically, the simultaneous infusion of gas and multiple liquids within small channels is operationally complex due to the many flow regimes that are possible in these systems.[23, 24] Often, even small fluctuations of the liquid volume fraction within the reactor can dramatically amplify, leading to irregular flow patterns, and great care is required in choosing the operating conditions to ensure a stable flow in triphasic systems.[21] The *pseudo-biphasic nature* of our reactor, where the volumetric flow rate of gas far exceeds that of the liquid phases (by a factor of 30 - 100), overcomes these potential challenges, as small flow rate fluctuations in this mode of reactor operation have a minimal effect on the flow pattern and reactor stability.

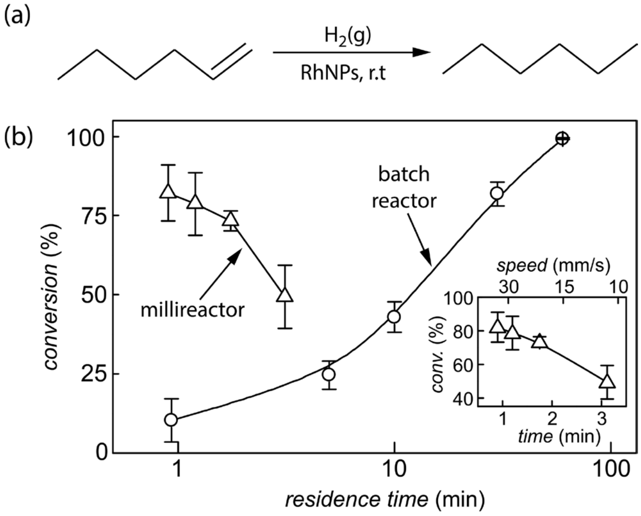

Fig. 2 (a) Reaction scheme for the hydrogenation of 1-hexene. (b) Comparison of 1-hexene conversion between millireactor and batch reactor against residence time. The inset allows a simultaneous comparison of 1-hexene conversion in the millireactor as a function of residence time and flow speed.

The results obtained from the millireactor are compared against a 50 mL small-scale stirred batch reactor. For 80% conversion of 1-hexene, the millireactor requires a mere 1 min compared to 30 min in a batch reactor under ambient conditions (Fig. 2), highlighting the tremendously accelerated mass transport achievable in our pseudo-biphasic system. Interestingly, despite a fall in residence time at higher flow speeds, the conversion of 1-hexene in our millireactor continues to increase with flow speed (inset of Fig. 2), thus highlighting that even after significant intensification, the reaction is still mass transport controlled.

To further explain this observation, we first note that residence time is tuned by varying the inlet pressure (and thus volumetric flow rate) of hydrogen entering the reactor. As shown in Fig. 3, shorter residence times imply longer gas bubbles, at constant aqueous and organic phase flow rate. Further, in this mode of reactor operation, the organic phase wets the reactor wall and deposits an organic film around the gas bubbles. Thus, as depicted in Fig. 3, at a constant organic phase flow rate, the natural redistribution of the organic phase from the organic segment to the organic film coating the bubbles leads to a narrower organic segment width w_{org} at a higher flow speeds. For thin organic segments much smaller than the reactor radius R ($w_{org} \leq 0.25R$), internal convection within these segments is negligible.[25] The acceleration of mass transfer of hydrogen and 1-hexene thus occurs via a reduction in the diffusion distance (w_{org}) the solutes require to reach the catalyst NPs near the aqueous-organic interface. Since the intrinsic rate of the Rh-catalyzed hydrogenation of 1-hexene is still fast compared to diffusive transport under all conditions, a nonlinear increase in transport rates with flow speed can lead to higher conversions at the outlet of the millireactor, even at correspondingly lower residence times. We have developed a simple phenomenological reactor model (see ESI) that fully simulates these trends quantitatively.

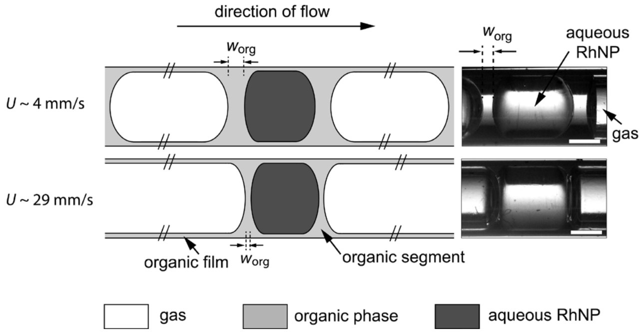

Fig. 3 Stereoscopic images of gas-organic-aqueous segmented flow accompanied by a schematic illustrating the change in the width of the organic segment, w_{org}, at various flow speeds in millireactor. As the flow speed increases, w_{org} decreases. The direction of flow is from left to right. All scale bars represent 500 μm.

A comparative study between the pseudo biphasic millireactor and the stirred batch reactor for a variety of substrates and two different nanoparticle (NP) catalysts (Rh and Pt) is summarized in Table 1. As a consequence of rapid mass transfer rates, in all cases, the millireactor is able to afford a higher reaction conversion within 10 - 100 times smaller residence times than its batch counterpart under the same reaction conditions. Accordingly, the catalyst activity, defined as the moles of substrate converted per mole of metal atoms per minute, is 10 - 50 times higher in the case of pseudo biphasic millireactor. It is worth highlighting that for the selective hydrogenation of styrene to ethylbenzene in our millireactor, a mere ~5 min is sufficient to achieve 71% conversion under near atmospheric conditions, while a pressurized stirred batch reactor at an initial pressure of 10 barg requires 30 min to achieve a conversion of 61%. A quick comparison reveals that for the hydrogenation of C=C, our reactor is able to achieve an activity that is at least 60% higher than that reported for similar hydrogenation reactions conducted in fixed bed microreactors.[11, 26] Similarly, the activity of PtNPs for the hydrogenation of nitrobenzene in our reactor is

110 min^{-1}, which is twice that achieved by PtNPs immobilized on the walls of a microreactor.[16]

In addition to a dramatic reduction in reaction time, we also find that the pseudo-biphasic millireactor allows improved selectivity for the case of multiple series hydrogenation reactions, which is of great significance in fine chemical production. Catalytic hydrogenation is the most promising technique to make industrially important intermediates such as functionalized anilines and alcohols.[27] However, the reaction often suffers from low selectivity in the presence of other functional groups and therefore more effective catalysts have to be carefully (and often laboriously) developed.[28-30] The pseudo-biphasic millireactor offers an alternative and simple way to improve the selectivity by accelerating the desired, mass-transfer limited hydrogenation step. For instance, the hydrogenation of 4-nitrochlorobenzene gave a selectivity of 89% towards 4-chloroaniline for ~80% conversion of the substrate, while a small scale batch reactor gave only a 20% selectivity for similar substrate conversions, as reflected in Table 1.

Table 1 Comparison of hydrogenation of various substrates between the millireactor and batch reactor.[a]

Substrate	Millireactor				Batch Reactor			
	Residence time (min)	Conversion (%)	Selectivity (%)	Activity[b] (min^{-1})	Residence time (min)	Conversion (%)	Selectivity (%)	Activity[b] (min^{-1})
1-hexene[c]	0.9	82	-	634	30	80	-	21
Cyclohexene[d]	1.2	30	-	258	60	14	-	23
Styrene[e]	4.9	71	100	126	60	61	100	9
Styrene[e,f]	-	-	-	-	30	53	100	16
Nitrobenzene[g]	0.9	98	-	110	45	97	-	2
4-nitrochlorobenzene[h]	0.5	76	89	229	60	80	20	2

[a]Reaction at room temperature and pressure using 0.5 mM aqueous NP solution, unless otherwise specified. A 2 m and 20 m long millireactor is used for the hydrogenation of 1-hexene and styrene respectively while a 10 m millireactor is used for the hydrogenation of all other substrates. [b]Activity is calculated based on the moles of substrate converted per mole of Rh atoms per minute. [c]Cyclohexane, 800 mM 1-hexene, RhNP. [d]Neat cyclohexene, RhNP. [e]Cyclohexane, 870 mM styrene, RhNP. [f]10 barg. [g]Diethyl ether, 100 mM nitrobenzene, PtNP. [h]50 vol% diethyl ether, 50 vol% dichloromethane, 150 mM nitrochlorobenzene, PtNP.

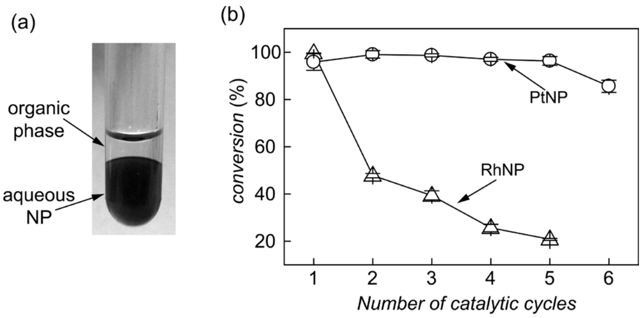

Fig. 4 (a) Photograph of aqueous-organic phase separation of the reaction mixture collected at the outlet of the millireactor highlighting the ease of catalyst recovery. (b) Substrate conversion versus number of catalytic runs for RhNP (hydrogenation of 1-hexene) and PtNP (hydrogenation of nitrobenzene).

Finally, facile catalyst recovery and recycle in our millireactor is demonstrated by collecting the reaction mixture at the outlet of the reactor. Since the aqueous catalyst phase forms an immiscible layer with the organic phase, the aqueous catalyst can be recovered and recycled easily by means of simple decantation (Fig. 4a). Taking the hydrogenation of 1-hexene catalyzed by RhNPs and that of nitrobenzene catalyzed by PtNPs as model reactions, the substrate conversion across multiple catalytic cycles is given in Fig. 4b. To enhance catalyst recyclability in this demonstration, we add more PVP (as a colloidal stabilizer) during NP syntheses. Despite increasing the residence time from 0.9 min to 4.6 min, the conversion of 1-hexene decreased in serial recycle runs due to the limit posed by the total turnover number (TTON) of the RhNPs used – the turnover number (TON) of the RhNPs in the first catalytic run is ~800, more than one-third of the estimated TTON of ~2300. We note here that, while it is not the central point of our work, the TTON of the catalyst can be improved via the adoption of better NP synthetic methods reported in the literature to provide sustained catalytic activity during recycling.[31] Interestingly, for the case of PtNPs which are not limited by the TTON[32] (TON of ~100 per cycle compared to TTON of > 15,000), we measure consistently high catalyst activity across six catalyst cycles under the same reaction conditions reported in Table 1. Further analysis via electron microscopy reveals that the PtNPs remain unchanged even after multiple catalytic cycles (see Fig. S2 in ESI), thus validating the idea of catalyst recovery and recycle in the pseudo-biphasic millireactor.

Conclusions

In this work, a triphasic millireactor has been applied for the rapid NP-catalyzed hydrogenation of various organic substrates, including industrially important chemicals. Despite the involvement of an additional immiscible fluid phase wherein catalysts are ‘immobilized’, the pseudo-biphasic reaction system is able to provide tremendous acceleration in mass transport such that higher yield and selectivity can be achieved within a few minutes – a time-scale not possible in conventional stirred batch reactors. This working principle can be extended to other similar catalytic reactions, incorporating both homogeneous and heterogeneous catalysts, for rapid multiphase reactions with facile catalyst recovery.

Materials and Methods

Nanoparticles (NPs) are synthesized using the ethanol reduction method.[22] Briefly, 5 mM RhNP stock solution is prepared by refluxing 5 mM of $RhCl_3.xH_2O$ (Alfa Aesar Rh 38.5-45.5%) and 0.555 g of Polyvinylpyrrolidone (Alfa Aesar, M.W. 40k) in 30 mL of ethanol and 20 mL of ultrapure water (Milli-Q, 18.2 MΩ.cm at 25°C) at 120°C for 1 h. Thereafter, all solvent is vaporized at 60°C under reduced pressure to afford a black residue before adding 50 mL of ultrapure water to obtain a 5 mM NP stock solution. PtNPs are similarly prepared using 5 mM of $H_2PtCl_6.xH_2O$ (Sigma, ≥ 99.9% trace metal basis), with the addition of 840 μL of 1 M NaOH (Fluka, HPCE) prior to refluxing the solution at 135°C for 30 min (see Fig. S2). RhNPs and PtNPs used for the demonstration of NP recycling is synthesized using 2.775 g of PVP for 50 mL of 5 mM stock solution. The respective 5 mM NP stock solutions are then diluted to their respective concentrations prior to use in both batch and flow experiments. Batch experiments under atmospheric pressure are done by charging a 50 mL round-bottom flask attached to a balloon with hydrogen gas. Thereafter, 5 mL of the organic substrate and 10 mL of the NP solution are introduced into the flask, and the reaction takes place under well-stirred conditions. For batch experiments conducted under pressurized conditions, a 20 mL autoclave filled with 2.5 mL of organic substrate, 5 mL of NP solution and 10 barg of hydrogen gas before leaving to react under well-stirred conditions. The organic phase of both flow and batch experiments are analyzed using gas chromatography (Shimadzu 2010Plus). All experiments are conducted under room temperature and are done in duplicate.

Notes and references

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† Electronic Supplementary Information (ESI) available: The ESI gives photograph of the setup, transmission electron microscope (TEM) images of recycled PtNPs, metal leaching experiments and a brief outline of the reactor model. A video of the setup in operation is also provided. See DOI: 10.1039/b000000x/

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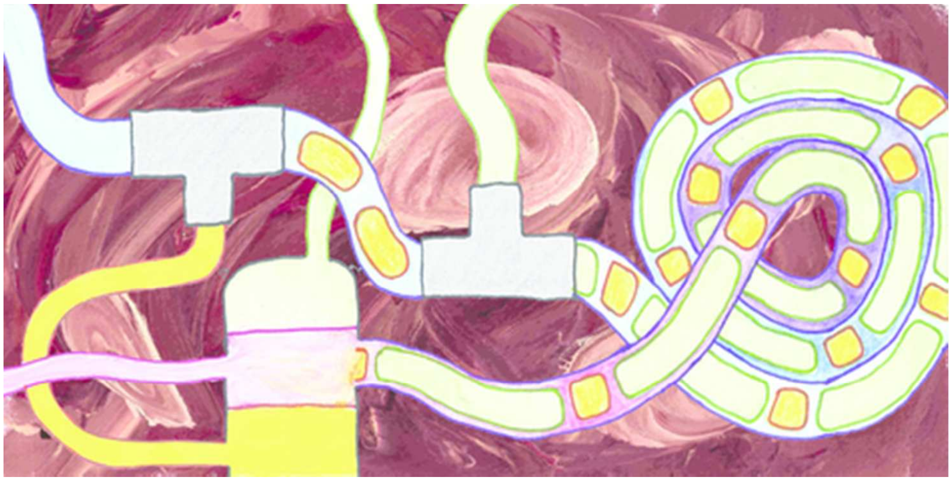

Process intensification in a triphasic millireactor for nanoparticle-catalyzed gas-liquid reactions with facile catalyst recovery and recycle is demonstrated.
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