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Process intensification of continuous-flow imine hydrogenation in catalyst-coated tube reactors

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ABSTRACT

Hydrogenation of an imine (N-Cyclohexyl(benzylidene)imine) into a secondary amine (N-Benzylcyclohexylamine) was studied in catalyst-coated tube reactors to utilize the advantages of continuous-flow processes. Tetrahydrofuran (THF) was found to be an optimal solvent providing high reaction and low catalyst deactivation rates compared to toluene and isopropanol. Even in THF, however, the deactivation was noticeable with the decrease in the imine hydrogenation rate during 20 hours on stream over the Pd/C and Pd/SiO_2 catalyst-coated tubes of 80 and 47%, respectively. After comparing various regeneration methods, we found that washing with isopropanol recovered the catalyst activity. The catalyst support affected regeneration – the Pd/SiO_2 catalyst suffered from a permanent degradation, while the Pd/C was stable over multiple reaction-regeneration cycles. Process intensification study at a range of reaction temperatures allowed to establish the optimal secondary amine production temperature of 110 ^{o}C. The long-term stability test under the optimized conditions allowed reaching a turn-over number (TON) of 150,000 – an unprecedented value in heterogeneous imine hydrogenation. A reductive amination cascade reaction (aldehyde and amine condensation simultaneously with imine hydrogenation) showed the by-product yield below 3%. The cascade reaction, however, decreased the reaction throughput by 45% compared to the direct imine hydrogenation still allowing for a throughput of 0.75 kg of product per day in a single 5 m catalyst-coated reactor opening a way for a multi-kilogram synthesis.

Keywords: hydrogenation, flow chemistry, heterogeneous catalysis, coating, imine.

1. INTRODUCTION

Reduction of organic molecules with hydrogen is commonly used in the manufacture of fragrances and flavors, dyes and fuels, nutraceuticals and pharmaceuticals.[1] Innovations leading to a greater efficiency in the product quality and synthesis process are amplified by the optimization of process parameters. In this respect, continuous-flow chemistry is known to improve over the state-of-the-art batch processes. In a flow process, the reactants are pumped continuously and the reaction takes place while the reaction mixture moves through the reactor. Small reactor dimensions and controllable fluid velocity enhance heat and mass transfer, improve safety, and even allow performance of microsecond reactions impossible in batch reactors.[2–4] Telescoping the processes (connecting several reaction stages in a single unit) improves product quality and decreases the process development time.[5–9]

A combination of flow chemistry with heterogeneous catalysis provides additional benefits. The rates of many heterogeneously catalyzed reactions are limited by interphase mass transfer which are greatly improved in flow.[10,11] The continuous-flow heterogeneously catalyzed reactions simplify product-catalyst separation and thus decrease operational costs. That is why large-scale petrochemical industry relies entirely on the continuous processes.[12,13] In the fine chemicals industry, continuous-flow processes are an exception but demonstrate substantial potential. Structured reactors with their periodic structure allow for an excellent control of the reaction parameters and greatly simplify the process scale-up removing associated market delay costs.[14–16] Smaller structured reactors such as catalyst-coated capillary or tube reactors seem particularly promising for the pharma industry allowing for quick scale-up from gram to kilogram scale in the same reactor.[17,18]

The pharma applications involve synthesis of biologically active molecules that most often contain heterocycles, coming from condensation of aldehydes and amino groups.[19–21] Secondary amines are particularly interesting. Their synthesis commonly includes a primary amine alkylation[22] or imine hydrogenation.[23,24] Alkylation involves application of potentially carcinogenic alkyl halides, while imine hydrogenation stands out as a better alternative with excellent yields and atom economy. Imines, in turn, can be obtained using simple procedures of ketone or aldehyde amination,[25–27] alkylation of amines and aryls,[22,28] or hydrogenation of nitriles.[29–31] Imines subsequently can be hydrogenated to amines via transfer hydrogenation or by molecular hydrogen over homogeneous or heterogeneous catalysts.[32–35]

The possibility of using flow chemistry for imine reduction has been already noted in a previous research.[36] However, the vast majority of the modern research on secondary amine synthesis is carried out in batch reactors and the advantages of continuous-flow might be overlooked. These works mostly report proof-of-principle investigations under the conditions remote from industrial applications with high catalyst loadings and impractical reaction times. In the work presented, we focus on the continuous-flow hydrogenation under relevant kilo-scale conditions, study the catalyst utilization efficiency, and process intensification – major factors for industrial implementation. The amine selected (N-Benzylcyclohexylamine) combines the sterically demanding aryl and cyclohexyl groups and its behavior is often found representative of a wide range of secondary amines.[37]

2. MATERIAL AND METHODS

2.1. Reagents

The following reactants and solvents were used as purchased: cyclohexylamine (99%, Acros Organics), benzaldehyde (99%, Merck Millipore), isopropanol (IPA, 99%, Fisher Scientific),

tetrahydrofuran (THF, 99% Fisher Scientific), toluene (99.8% Sigma-Aldrich). Molecular sieves 4Å from Fluka were dried at 400 °C prior to use. Tetradecane (98%) and dodecane (98%) purchased from Fisher Scientific were used as internal standards for gas chromatograph analysis.

N-Cyclohexyl(benzylidene)imine was obtained by condensation of cyclohexylamine and benzaldehyde as shown in Figure 1. Typically, 74.4 g cyclohexylamine was dissolved in 1 L solvent (toluene, THF, or IPA) and 79.6 g benzaldehyde was added on stirring. After 2 hours, 50 g of molecular sieves were added to absorb water and shift the equilibrium to the imine.[38] The product analysis was performed with a Shimadzu GC-2010 gas chromatograph (GC) equipped with a Restek RTX-1 10m x 0.15 mm x 0.15 µm column and an FID detector. The analysis showed the product yield above 99.5% and NMR analysis confirmed the structure of the imine formed.
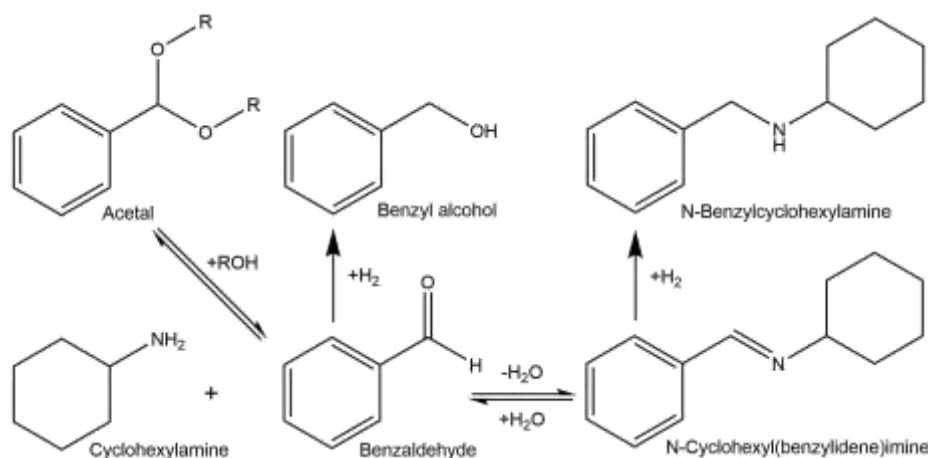

Figure 1. Scheme of the synthesis, side reactions, and hydrogenation of N-cyclohexyl(benzylidene)imine.

2.2. Catalyst characterization

The 2.4 wt% Pd/SiO$_2$ and 2.3 wt% Pd/C catalyst-coated tube reactors were provided by Stoli Catalysts Ltd and used as received. The tube reactors (1.27 mm i.d., 1.60 mm o.d.) were 5 m long coils made of 316L stainless steel. The catalyst coating had been obtained using an improved sol-gel procedure described in reference,[39] where the main challenges in obtaining uniform catalyst coatings inside the reactor tubes are discussed. Once the coating process is established, however, the uniformity of the coating thickness can be assured by controlling all the external parameters (temperature, withdrawal speed, etc.).

The coating thickness was studied with a Carl Zeiss Sigma scanning electron microscope (SEM) equipped with an Oxford instruments energy-dispersive X-ray (EDS) detector observing tube sections taken at various points along the reactor. SEM studies confirmed a uniform coating along the reactor length with the thickness of 28 ± 3 µm for Pd/SiO$_2$ and 21 ± 2.5 µm for Pd/C coatings. The Pd loading was analyzed with EDS from several areas of the coating to be 2.4 wt% for Pd/SiO$_2$ and 2.3 wt% for Pd/C. For the TEM analysis, the catalyst from the tubes was removed mechanically, dispersed in acetone, and applied on a carbon-coated copper grid. The analysis was performed with a Jeol 2000FX transmission electron microscope. The images were processed with an ImageJ software to obtain particle size distribution data. The mean Pd size was 4.3 ± 1.2 nm in the Pd/SiO$_2$ and 4.0 ± 1.3 nm in the Pd/C catalyst.

A piece of the Pd/SiO$_2$ tube deactivated in the imine hydrogenation reaction had been studied by temperature-programmed oxidation in a system containing several mass flow controllers, an oven

for the sample, and a quadrupole mass spectrometer. The piece of the stainless tube was placed into a quartz tube into the oven and heated to 550 °C at a heating rate of 3 °C min^{-1} in a flow 10 mL min^{-1} of 10 vol% O_2 in He.

2.3. Hydrogenation experiments

Figure 2 shows the continuous-flow system used in the experiments. Two solutions were supplied with two HPLC pumps (Knauer P4.1S): (i) an imine solution with a tetradecane internal standard, and (ii) the solvent with dodecane. The internal standards improved reproducibility of the analysis and confirmed the flow rate ratio of the pumps. The hydrogen (99.9%) flow was added with a mass flow controller (Bronkhorst). The mixture passed through a catalyst-coated tube reactor in a convection oven followed by a back-pressure regulator (Equilibar) and a fraction collector. During the experiments, the oven temperature and the liquid flow rates varied in a range of 70-170 °C and 200-6000 μL min^{-1}, respectively. The hydrogen to imine molar ratio was maintained at 1.1 in all experiments. At a high substrate conversion, virtually all the hydrogen had been consumed and gas bubbles disappeared from the reaction mixture. Absorption of hydrogen indicates that transfer hydrogenation (reduction of imine with hydrogen originating from the solvent) was minor and the main hydrogenation was taking place with gaseous hydrogen. Similarly, the experiments performed under the same conditions in THF and IPA solvents but without hydrogen gas added demonstrated a low conversion (<1%) confirming a negligible role of transfer hydrogenation.

The reactor was operated autonomously executing a pre-defined reaction program and injecting liquid samples into vials equipped with septa to minimize sample evaporation.[40] The samples were taken after the time required for the liquid to displace at least 3 times the reactor volume before collecting 3–4 samples for every set of reaction conditions.
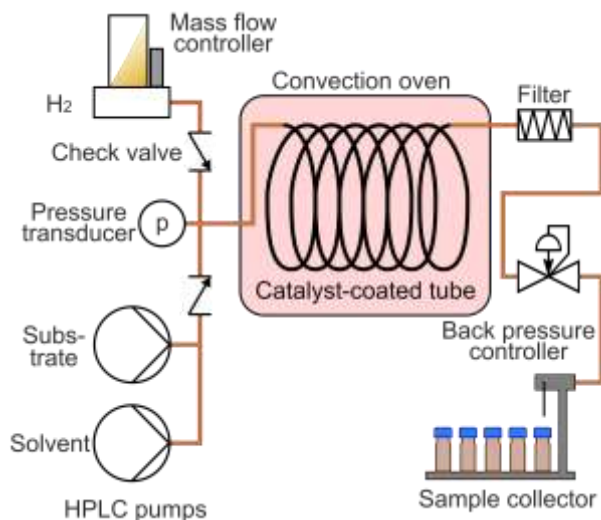

Figure 2. S*cheme of the continuous-flow hydrogenation system.*

The liquid samples collected were analyzed by the GC with the response factors related to tetradecane and calibrated using a series of reference solutions for every compound. The imine conversion (*X*) was calculated with Equation (1):

$$X = \left(1 - \frac{c_{CPI}}{c_{CPIin}}\right),$$

(1)

where C_{CPI} and C_{CPIin} are the imine concentration at the outlet and the initial concentration, respectively. The carbon balance, except where specified, was 100 ± 2%. The selectivity (S) was calculated with Equation (2):

$$S_{product} = \frac{C_{product}}{C_{CPIin} - C_{CPI}},$$ (2)

where $C_{product}$ is the product concentration.

During the cascade reaction, the solutions of (i) benzaldehyde with tetradecane, and (ii) cyclohexylamine with dodecane were fed with two HPLC pumps. The conversion (X_{CHA}) was calculated with Equation (3):

$$X_{CHA} = \left(1 - \frac{C_{CHA}}{C_{CHAin}} \cdot \frac{Q_{CHA} + Q_{BA}}{Q_{CHA}}\right),$$ (3)

where C_{CHA} and C_{CHAin} are the cyclohexylamine concentrations in the product and in the initial solution, respectively. Q_{CHA} and Q_{BA} are the flow rates of cyclohexylamine and benzaldehyde solutions to account for dilution on combining the two liquid flows. The product yield was calculated with Equation (4):

$$Y_{product} = \frac{C_{product}}{C_{CHAin}\frac{Q_{CHA}}{Q_{CHA} + Q_{BA}} - C_{CHA}}.$$ (4)

The average liquid residence time, τ_{res}, in the reactor was calculated with Equation (5):

$$\tau_{res} = \frac{V_r}{Q_L + Q_G \cdot P_{NTP}/P_G},$$ (5)

where V_r is the reactor volume, Q_L is the liquid flow rate, Q_G is the gas flow rate (at normal temperature and pressure), P_{NTP} is the outlet pressure (atmospheric) and P_G is the inlet pressure (varied in the range 25-40 bar), respectively. Equation (5) assumes Taylor flow regime, which was observed under all conditions studied.[11,41,42]

3. Results and Discussion

3.1. Parameter optimization in the hydrogenation of imine

The solvent effect was studied on the imine hydrogenation. This is an important optimization step because solvents are known to dramatically change the reaction rates. For example, hydrogenation of cinnamaldehyde proceeds at a rate at least 1000 times slower in a toluene solution compared to isopropanol.[43,44]

Table 1 overviews the literature data on solvent effects on hydrogenation of various imines. Tert-butyl-2-(2H-pyran-3(4H,5H,6H)-ylidene)hydrazine-carboxilate hydrogenation showed 20 times higher conversion in THF compared to toluene.[45] Similarly, N-benzylideneaniline hydrogenation favors alcohols over THF or toluene.[32] In another work, methanol and 2,2,2-trifluoroethanol showed dramatically higher imine hydrogenation rates compared to dichloromethane, toluene, THF or 1,4-dioxane.[46] On the other hand, Li et al. found that phenyl-(1-phenylethylidene)imine hydrogenation proceeds about twice faster in toluene, fluorobenzene, or dichloromethane compared to hexane as solvent.[47] Thus, the solvents significantly affect the imine hydrogenation rates, but the optimum solvent cannot be predicted in advance.

Table 1. Literature summary on the favorable solvent in imine hydrogenation reactions.

Hydrogenation reaction	Favorable Solvent
	Toluene[43,44]
	THF[45]
	Alcohols[32]
	Methanol and 2,2,2-trifluoroethanol[46]
	Dichloromethane, toluene and fluorobenzene[47]

In this study, a polar protic solvent (IPA), a polar aprotic (THF) and a non-polar solvent (toluene) were used. The results obtained (Figure 3) show that the imine conversion was substantially lower in toluene and IPA compared to THF. The apparent reaction rate in THF was more than five times higher compared to the other solvents studied.
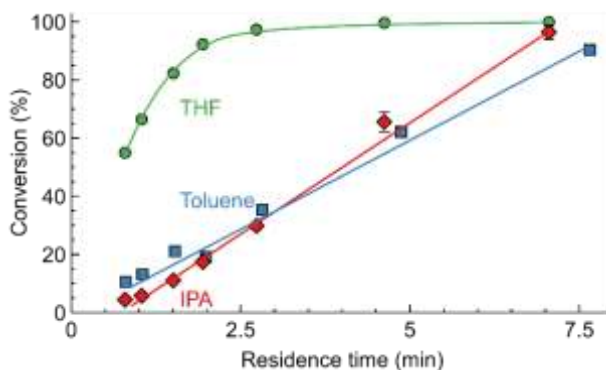

Figure 3. Effect of solvent and residence time on N-Cyclohexyl(benzylidene)imine (100 mM) hydrogenation in a 5 m Pd/SiO$_2$-coated tube reactor at 40 bar and 70 ºC.

The likely reason for the decreased reaction rates in toluene and IPA is a stronger adsorption of products on the catalyst surface resulting in the blockage of catalyst active sites. The adsorption was shown to be associated with the solubility in case of cinchona alkaloid on the Pd and Pt catalyst surface.[48,49] Drexler studied solvent effects in flavanone synthesis over MgO and found that

competitive adsorption of reactants, products, and solvents can limit the number of reactive surface sites.[50]

In the experiments carried out in toluene and IPA, some precipitation was observed in the product vials, while no precipitate was observed from the THF solution. Likely, precipitation occurred on cooling down the reaction solution to room temperature. The possibility of the reactor blockage exists in case of a severely limited product solubility with the blockage expected not in the reactor but filter. The filter placed at the reactor outlet (Fig 1) combines the smallest diameter of the openings with a substantial heat exchange area to decrease the feed stream temperature. If precipitation is likely, it is advisable to decrease the substrate concentration or find a more suitable process solvent. An unsuitable solvent creates problems not only in flow reactors, but may decrease the overall reaction rates rendering the catalytic process inefficient in any reactor. Therefore, THF was selected for further experiments because it showed a high imine solubility and faster reaction rates.

Figure 4 shows the comparison of the Pd/SiO_2 and Pd/C catalyst-coated tube reactors at different imine concentrations and flow rates. In these experiments, the only by-product observed was benzyl alcohol with the selectivity below 0.15%. The carbon balance was 100±3% confirming high reaction selectivity for the secondary amine.
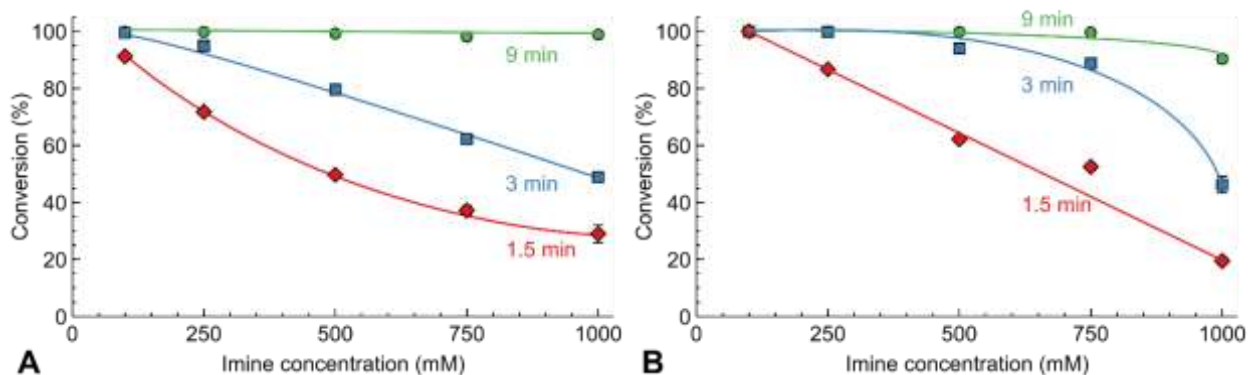

Figure 4. Effect of substrate concentration and residence time on N-Cyclohexyl(benzylidene)imine hydrogenation in a 5 m tube reactor wall-coated with (A) Pd/SiO_2, or (B) Pd/C catalysts at 40 bar and 70 ºC.

At a residence time of 9 min, the imine conversion was complete up to the imine initial concentration of 1000 mM for both the catalyst-coated tubes studied. However, at the highest concentration, the Pd/C tube showed a slightly lower conversion, which is in line with a lower Pd loading in the tube. At a residence time of 3 min, the conversion in the Pd/SiO_2 tube linearly decreased with the increase of the initial imine concentration, in agreement with the generally observed independence of the hydrogenation rate from concentration for many substrates.[17,51–54] The Pd/C tube showed a consistently higher conversion (compared to Pd/SiO_2) in the range of imine initial concentration from 250 to 750 mM. At the residence time of 1.5 min, the behavior of both tubes was similar, but the Pd/C tube showed a slightly higher conversion.

Deviations from the linear dependence of the imine conversion from the initial imine concentration observed at 1000 mM (Figure 4B) might be caused by the onset of product precipitation indicated by a minor increase (by about 15-25% compared to lower concentrations) in the pressure drop observed for these experiments. Therefore, imine at the concentration of 750 mM was selected for further experiments.

At the next step, the effect of the reaction temperature was studied on imine hydrogenation, shown in Figure 5. At a fixed residence time, the conversion increased with the reaction temperature for both catalysts. The full conversion was obtained at reaction temperatures of 90 °C or above with the residence time slightly over 6.5 minutes. At a temperature of 110°C, the imine was fully hydrogenated at all residence times above 1.5 min. Overall, both catalysts showed a comparable performance.
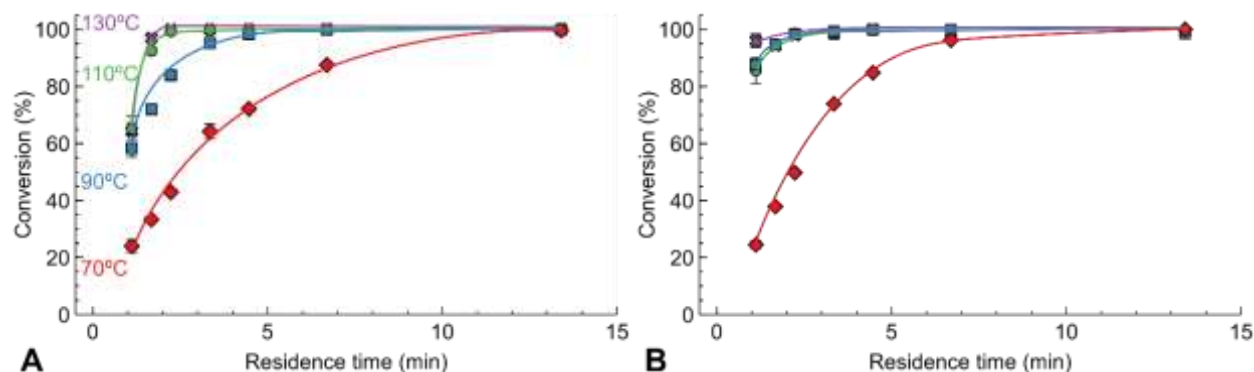

Figure 5. Effect of the reaction temperature and residence time on N-Cyclohexyl(benzylidene)imine (750 mM) hydrogenation in a 5 m tube reactor wall-coated with (A) Pd/SiO$_2$, and (B) Pd/C catalysts at 40 bar and 70 °C.

3.2. Catalyst deactivation

Long-term stability is an essential practical consideration for using heterogeneous catalysis in continuous-flow hydrogenation. Frequent catalyst replacement may increase the operational expenditure and make the batch hydrogenation more cost-efficient compared to the continuous-flow. Figure 6 shows the long-term stability study of both catalysts. The reaction conditions were selected to provide the initial conversion about 80% over both catalysts. The activity of catalysts decreased with time. After 5 h, the Pd/C catalyst showed a faster deactivation compared to Pd/SiO$_2$. As a result, the conversion showed twofold decrease over the Pd/SiO$_2$ catalyst, while more than four-fold decreased over the Pd/C catalyst after 20 h.
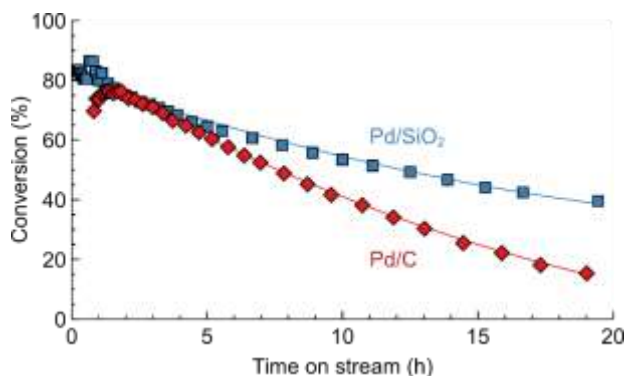

Figure 6. Deactivation of Pd/SiO$_2$ and Pd/C catalyst-coated tubes in N-Cyclohexyl(benzylidene)imine (0.3 mL min^{-1}, 750 mM) hydrogenation at 40 bar, 70 °C.

Considering a rather quick deactivation observed, we decided to study several catalyst regeneration protocols (Supporting Information, S1). In these experiments, a 2.5 m catalyst-coated tube (either Pd/SiO$_2$ or Pd/C) was deactivated for 6 h and then it was cut into shorter sections of 15 cm.

The sections of the tubes were subjected to various regeneration treatments. Before and after each treatment, a reference imine hydrogenation experiment was performed under the same conditions to calculate the regeneration degree (θ) with Equation (6):

$$\theta = \frac{X_{after\ reg} - X_{before\ reg}}{X_{before\ reg}}, \tag{6}$$

where $X_{before\ reg}$ and $X_{after\ reg}$ are the imine conversion observed before and after the regeneration treatment, respectively.

Table 2 shows the comparison of the regeneration treatments. Because the mechanism of catalyst deactivation is not known, we compared several options including solvent washing (to desorb compounds that block the catalyst surface) and oxidative treatments (to remove compounds that might be too strongly bound to the catalyst surface for solvent removal). The selected solvents varied in polarity ranging from an acetic acid solution widely used in hydrogenation of basic nitrogen compounds[55,56] to water and THF.

Table 2. Regeneration degree (θ, Equation (6)) of partially-deactivated Pd/C and Pd/SiO$_2$ catalyst-coated tubes in the imine hydrogenation reaction.

Regeneration method	Relative Polarity[a]	$\theta_{Pd/SiO2}$ (%)	$\theta_{Pd/C}$ (%)
10 wt% HAc in H_2O [b]	0.648	63	41
IPA [b]	0.546	141	201
THF [b]	0.210	26	-
H_2O [b]	1.000	-52	-
Calcination [c]	-	-19	-
0.05 wt% $(NH_4)_2S_2O_8$ [b]	-	2	-
1 wt% $(NH_4)_2S_2O_8$ [b]	-	-100	-
H_2O_2 [b]	-	-53	-

[a] Data adapted from reference. [57]
[b] 500 µL min^{-1} for 30 min at 70 ºC.
[c] 450 ºC for 8 hours at a heating rate of 10 ºC min^{-1}.

When regenerating the Pd/SiO$_2$ tubes, acid treatment increased activity substantially, while IPA washing was found to be the most efficient. THF also showed a slight regeneration, but water showed only catalyst deactivation. Therefore, there was no obvious correlation between the solvent properties and the degree of catalyst regeneration. Oxidative, on the other hand, showed strong catalyst deactivation. For example, the treatment with a 0.05 wt% $(NH_4)_2S_2O_8$ solution showed little effect, but a 1 wt% $(NH_4)_2S_2O_8$ solution resulted in a complete loss of the catalyst activity. Calcination also led to dramatic deactivation of the catalysts. Therefore, the data show that both Pd/SiO$_2$ and Pd/C deactivated catalysts can be regenerated by washing with IPA.

A temperature-programmed oxidation study for one of the deactivated Pd/SiO$_2$ tube sections is shown in Supporting Information, Figure S1. There are strong peaks for H_2O and CO_2 about 70 ºC likely caused by desorption of organic species from the catalyst surface. The other CO_2 peak about 420 ºC is likely associated with the oxidation of carbonaceous species deposited on the catalyst surface – species known to deactivate the catalyst.[58] Likely the same carbonaceous species were formed on the Pd/C catalyst and resulted in its reversible deactivation. Unfortunately, TPO cannot be used to study the carbon-supported catalyst due to oxidation of the catalyst support.

The EDS analysis showed a decrease in the Pd loading after regeneration of the Pd/SiO$_2$ tubes indicating some irrecoverable loss of catalyst activity. The interaction on the basic imine and amine

molecules might disperse or even dissolve the silica coating releasing Pd nanoparticles. On the contrary, the Pd/C tube showed no Pd loss after regeneration highlighting the importance of the catalyst support to avoid leaching of the catalyst in this case. The combination of TPO and EDS studies allowed us to infer that the likely catalyst deactivation mechanism of Pd/C is the catalyst surface blockage with heavy carbonaceous species.

The long-term effect of regeneration treatment on the catalyst stability was also studied performing several IPA washing steps (Figure 7). The imine conversion over the Pd/C catalyst steadily decreased over time, and the IPA washing step increased the conversion. After the first regeneration step, the conversion increased beyond the value observed over the fresh catalyst 80%. After the second and subsequent IPA washing steps, the maximum conversion decreased, but the difference was below 1% as compared to that in the previous regeneration cycle. Therefore, the Pd/C catalyst-coated tube can be regenerated many times by IPA washing, but suffers from a minor irrecoverable deactivation.
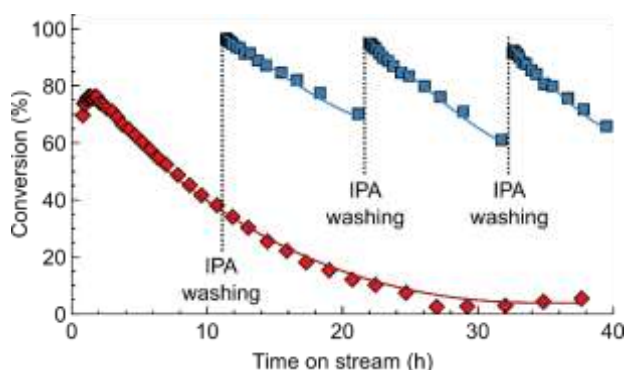

Figure 7. Deactivation of the 1.5 m Pd/C catalyst-coated tube in N-Cyclohexyl(benzylidene)imine (0.3 mL min^{-1}, 750 mM) hydrogenation at 40 bar, 70 ºC and the effect of isopropanol washing (0.5 mL min^{-1} for 30 min).

3.3. Process intensification

The complexity of the imine molecules with several functional groups makes them liable to thermal degradation. Therefore, the hydrogenation reaction is typically carried out under moderate temperatures. In a flow reactor, however, high temperature can be used to increase the reaction rates with thermal decomposition minimized by short residence time.[59–62]

Figure 8A shows the effect of increasing temperature on the rate of imine hydrogenation in the Pd/C catalyst-coated tube. The apparent hydrogenation reaction rate[63] (calculated in the Supporting Information, S2) increased with temperature rise in the range up to 130 ºC which was followed by a sharp drop when the temperature was further increased. This volcano curve likely originates from deactivation caused by Pd site blockage with by-products strongly adsorbed on the catalyst surface. These products, however, were formed in minor quantities as the carbon balance was constant in the whole temperature range studied (70-170 ºC) and no significant imine decomposition was observed. Therefore, an increase of temperature from 70 to 130 ºC has increased the imine hydrogenation rate. The presence of catalyst deactivation, however, made a detailed analysis of reaction kinetics and activation energies impossible.
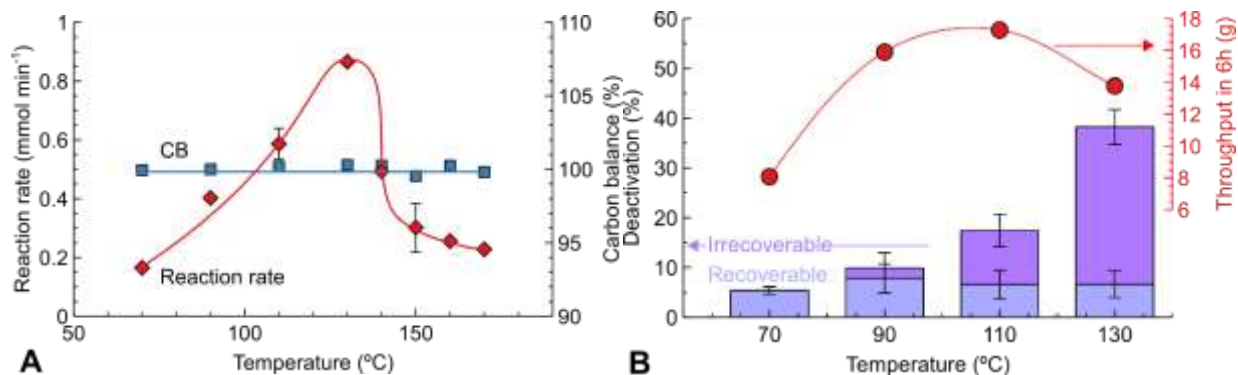
Figure 8. (A) Effect of the reaction temperature on apparent reaction rates and carbon balance on N-Cyclohexyl(benzylidene)imine (750 mM) hydrogenation in a 1.5 m Pd/C catalyst-coated tube at 25 bar; (B) Effect of the reaction temperature on catalyst deactivation (Equations (7) and (8)) and total amine generation in 6 hours on stream.

We studied whether the exposure to higher temperatures affects the degree of catalyst recovery after the IPA washing step. Figure 8B shows the effect of the reaction temperature on catalyst deactivation (ϵ) – both recoverable with IPA washing and irrecoverable – as calculated with Equations (7), (8). The data were obtained by carrying out the imine hydrogenation at 90, 110 or 130 °C for 30 min followed by hydrogenation at 70 ºC and calculation clarified in (Supporting Information, S3 and Figure S2).

$$\varepsilon_{irrecoverable} = X_{prior\,to\,test} - X_{after\,the\,test\,and\,IPA\,wash}, \tag{7}$$

$$\varepsilon_{recoverable} = X_{after\,the\,test\,and\,IPA\,wash} - X_{after\,the\,test\,prior\,to\,IPA\,wash}, \tag{8}$$

The level of recoverable deactivation remains rather constant at all temperatures, while the degree of irrecoverable deactivation increases with reaction temperature. The latter explains a sharp decline in the imine hydrogenation rate observed above 130 ºC in Figure 8A. The increasing reaction and deactivation rates work in the opposing directions: high reaction rate increases the reactor throughput, while high deactivation rate decreases it. There exists an optimum temperature of 110 ºC where the production rate of the secondary amine reaches a maximum value.

The turn-over number (TON) is one of the key economic factors indicating the frequency of the catalyst replacement. This is the ratio of amount substrate converted to the amount of Pd in the reactor. Several groups reported TONs in the range from 120 to 15,000 in the C=N bond hydrogenation over heterogeneous supported Pd catalysts in batch and flow reactors.[22,25–30,64,65] In this study, a TON of 150,000 was obtained in an experiment carried out at optimized reaction conditions (110 ºC, 40 bar) with the IPA washing step every 6 hours on stream (Figure 9). The TON value obtained is by more than 10 times higher than previously reported data. Implementation of the online process control and low-cost sensors to measure hydrogen absorption may increase the TON further and provide constantly high conversion regardless of catalyst deactivation as demonstrated in reference.[66] Therefore, catalyst-coated tube reactors provide excellent utilization of noble metals facilitated by catalyst immobilization and simple regeneration via solvent washing.
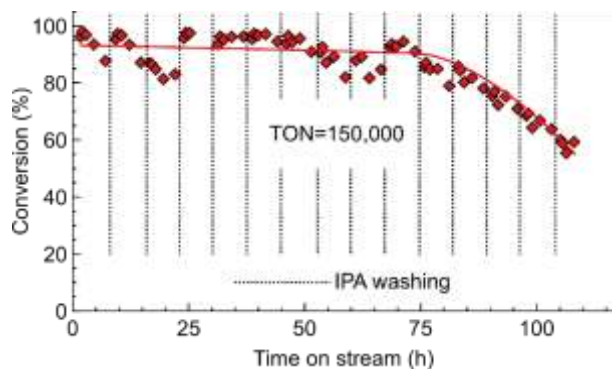
Figure 9. Long-term stability study and isopropanol washing cycles (0.5 mL min^{-1} for 30 min) of the 2.5 m Pd/C catalyst-coated tube in N-Cyclohexyl(benzylidene)imine (0.2 mL min^{-1}, 750 mM) hydrogenation at 40 bar, 110 ºC.

3.4. Cascade reaction

So far in this study, the imine solution was prepared prior to the hydrogenation reaction and water released during the condensation was absorbed to eliminate the possibility for the reverse reaction. To simplify the overall secondary amine synthesis procedure, we studied a combination widely used in batch – a cascade reaction of the imine synthesis (Figure 1) with its hydrogenation (commonly referenced as reductive amination).[67,68] In the cascade reaction, however, there is a possibility for competition between benzaldehyde and imine hydrogenation. This competition can decrease the yield of desired secondary amine in case of equimolar reactant combination by consuming a part of benzaldehyde introduced. Therefore, the cascade reaction was studied at various levels of benzaldehyde excess.

Figure 10A shows the effect of reaction parameters on cyclohexylamine conversion, which was close to 100% under all conditions studied. The yield of the secondary amine, however, was lower (Figure 10B), between 5 and 90% and increased with temperature. The effect of temperature was caused by the increase of the imine hydrogenation rate studied previously (Figure 8A). A low benzyl alcohol selectivity below 3% (Figure 10C) indicates that benzaldehyde hydrogenation was slow.
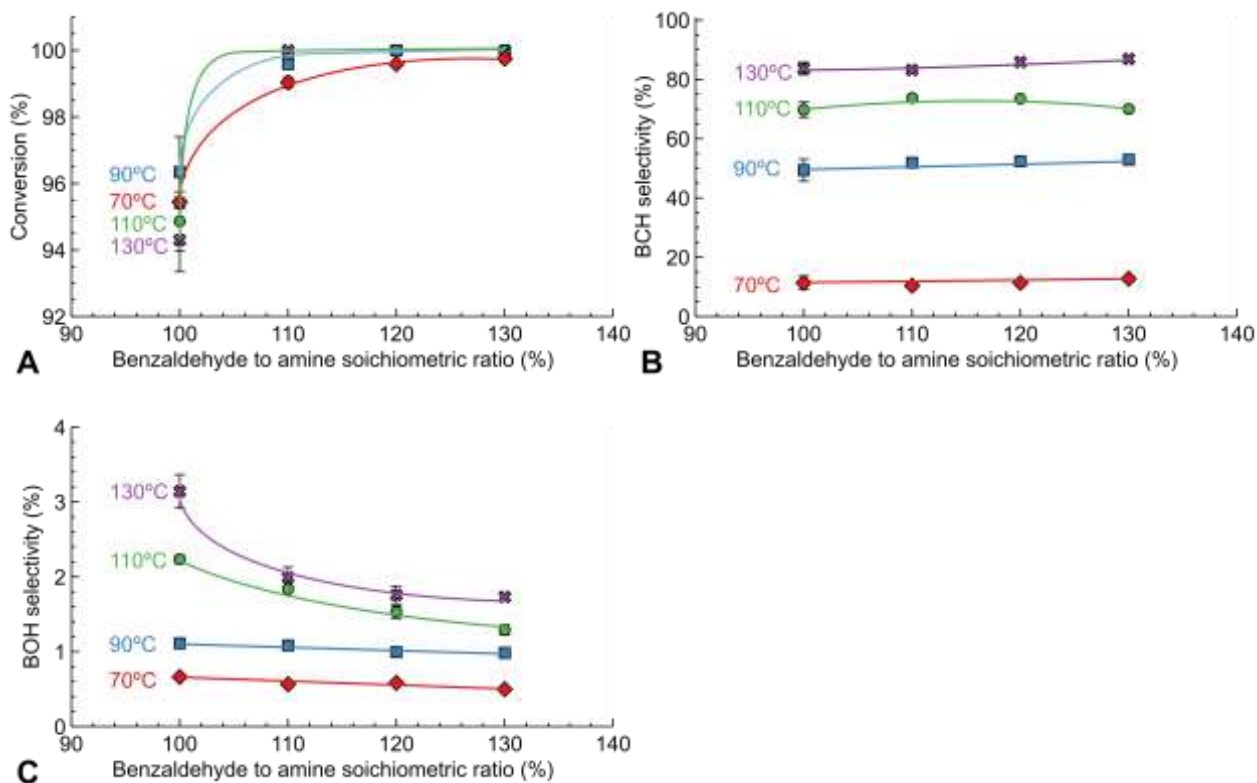
Figure 10. Influence of the excess of benzaldehyde and temperature in a cascade reaction. (A) conversion of benzaldehyde, (B) yield of N-Benzylcyclohexylamine, and (C) yield of benzaldehyde. Pd/C; P=40 bar; Residence time= 1.1 min; [Bezaldehyde]= 750 mM; [Cyclohexylamine]= 750 mM

The yield of N-Benzylciclohexylamine under the same conditions was 40-45% lower compared with the cascade reaction with the direct imine hydrogenation (Figure 5B). The difference may be explained by the effect of other species (such as water, unreacted aldehyde and amine) on the hydrogenation reaction performance. However, the N-Benzylcyclohexylamine production via the cascade reaction in a single 5 m long catalyst-coated tube is still significant. Extrapolating the results obtained in the cascade experiments to 24 hours (including IPA washing cycles), it was calculated a throughput of 754 g day^{-1} for multi-kilogram manufacture in longer tubes or tubes put in parallel.

4. Conclusions

We optimized the solvent, residence time, substrate concentration, and the reaction temperature in the N-Cyclohexyl(benzylidene)imine hydrogenation reaction in catalyst-coated tube reactors. The use of tetrahydrofuran as a solvent was found to provide high reaction rates and slow catalyst deactivation. Isopropanol, however, was the optimal solvent for catalyst regeneration by washing for many cycles. The reaction rates increased with the reaction temperature as well as deactivation irrecoverable by IPA washing resulting in an optimal hydrogenation temperature of 110 °C.

Secondary amines can be obtained with a cascade reaction – condensation of an aldehyde and a primary amine simultaneously performed with the imine hydrogenation. The imine selectivity was above 97% under all the conditions studied.

The Pd/C catalyst-coated tube reactors showed an excellent noble metal utilization providing, during a long-term experiment, the turn-over number of 150,000. The value is a factor of 10-1,000 higher than the reported batch synthesis procedures. A single 5 m tube was shown to provide the secondary amine hydrogenation throughput of 0.75 kg per day.

Supporting Information

Regeneration protocols, reaction rate calculation and calculation of the deactivation. This information is available free of charge via the Internet at http://pubs.acs.org/.

Acknowledgements

Conflict of Interest

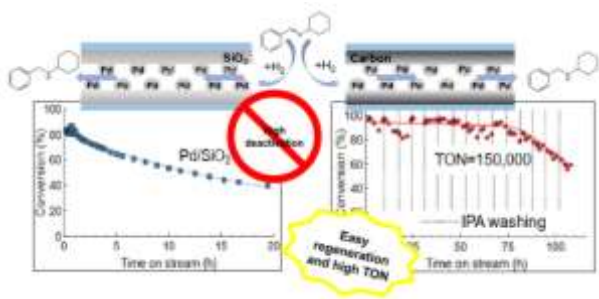NC and EVR are founders, directors and shareholders of Stoli Catalysts Ltd.

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