Adaptive and automated system-optimization for heterogeneous flow-hydrogenation reactions

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The hydrogenation of carbonyl compounds over a solid Pd/C catalyst to the corresponding alcohols and of N-heterocycles over a solid Ir@CNT catalyst to the corresponding amines with gaseous hydrogen from water electrolysis without human interaction is presented. This is achieved in three-dimensional parameter space (flow rate, temperature and hydrogen pressure) through an integration of on-line FTIR-analysis, a simplex control algorithm and an H-Cube microreactor setup. The simplex method can cope with an initial transient behaviour which is characteristic for heterogeneous catalysis.

A growing number of new, catalytic, continuous-flow reactions in microreactors not only demonstrates the increased interest in micro-reaction processes but also that access and ease of installation have improved.^{1–8} In particular, heterogeneously catalyzed, continuous processes in microreactors have received significant attention as costs arising from energy, solvent and substrate usage can be reduced while simultaneously the quality and controllability of both the production process and resulting product can be improved. In this context, heterogeneously catalyzed, continuous-flow hydrogenations represent one of the most frequently performed reactions in research laboratories and in chemical and pharmaceutical industries. Hydrogenations conducted in batch reactors are considered a safety risk due to comparatively large quantities of hydrogen employed and are often only performed in specialized high-pressure reactors or in autoclaves with increased safety controls. In contrast, conducting continuous-flow hydrogenation in microreactors negates these safety issues, hence rendering the process highly advantageous.⁹ Further benefits include the regulation of the reaction parameters, improved mixing of the hydrogen gas/solvent/catalyst 3-phase system, improved operational

Catalyst Behaviour during Process Optimization

IDEAL CASE

REAL CASE

Scheme 1 Conventional synthesis of heterogeneous catalysts and their behaviour in ideal and realistic scenarios.

safety, long-term use of the catalyst and continual product formation.

Although approximately over 90% of all chemical production processes involve catalytic reactions and most of them are heterogeneously catalyzed by mainly precious metals,¹⁰ understanding of heterogeneous catalysis is rather low compared to homogeneous catalysts with a well-defined structure and reaction mechanism.^{11–12} This is caused by the fact that the actual reaction takes place at the surface or in pore systems of a catalyst that is rather difficult to analyse or monitor by e.g. spectroscopic methods. Thus, identification of

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the actual active site is mostly not possible and rather based on speculations going along with dependences on material support, additives, promoters, particle sizes or types of surface defects. As illustrated in Scheme 1, the catalyst history is an important aspect for chemists in order to guarantee reproducibility. Catalysts of heterogeneous nature often undergo changes regarding shape and size due to high temperatures, catalyst leaching, or poisoning over the time being used in a reactor.

So there can be no wondering why chemists and engineers mainly rely on trial-and-error methods in order to identify appropriate catalysts and reaction conditions since these effects are very difficult to analyze and characterize. This optimization strategy therefore goes along with time-consuming and cost-intensive screenings.¹³⁻¹⁷

Other aspects that are also concerning heterogeneous-catalyzed reaction systems involve the reactor system itself. Having mentioned a gas/solvent/catalyst 3-phase system that is typical for hydrogenation reactions, multiphase reactions represent one of the more complicated systems to be analyzed and understood for chemical engineers. Lately, first attempts were undertaken from a theoretical point of view since computer capacities and their power have been continuously increased. Nevertheless, only rudimental knowledge could be gained that indeed can help to optimize reactor systems and model specific reactions within usual reactor types, but that is still away from being used as *a priori* analysis method.¹⁸⁻²³

Further issues are concerned with the reactor hardware. Fluctuations of feed pumps, heating devices or mixing chambers often result in slight changes of conversion, yield or product purity and thus have a major impact on the whole

reaction system and its related processes. Usually, only by manual reactor adjustments that are mostly based on human experience can the reactor be brought back to its stable residence state. Again, this procedure is time-consuming and compared to automated systems not very effective.²⁴

To address these issues, we herein report the first self-optimizing flow reactor system for a heterogeneously catalyzed reaction, consisting of a computer-controlled hydrogenation apparatus with an integrated in-line ATR-IR flow cell²⁵⁻³⁶ for reaction analysis and the application of a Simplex search algorithm for the autonomous self-optimization (Scheme 2). The spectroscopic method permits real-time optimization without delays. The objective of this study is to lead a reaction from its first few experiments with low performance to a target performance in an autonomous manner. Here, the target is a conversion > 90%.

Progress in the field of automated reactors and self-optimizing reactor systems were recently summarized underlining the growing interest on such handling and optimization strategies without human interaction.³⁷⁻⁴⁴ A frequently used alternative to conventional hydrogenation reactors that require pressurized hydrogen supply is the use of an apparatus which allows the direct formation of hydrogen by electrolysis (for further information see SI).⁴⁵⁻⁴⁹ To test the feasibility of the hydrogenation reactor system and to obtain proof of concept we chose to optimize the heterogeneous catalyzed continuous flow hydrogenation of benzaldehyde **1** to benzyl alcohol **2**, as an initial example (Figure 1).

From the optimization pathway, various trends could be seen. Increasing the temperature at constant flow rate and pressure improved the results. There is also a strong correlation between the flow rate and H₂ pressure. In order to maintain the same conversion for various flow rates, the H₂ pressure has

Scheme 2 Autonomous self-optimizing reactor system for the automated heterogeneous catalyzed hydrogenation using ATR-FTIR analysis and an integrated feedback-software. P: pump; E: electrolysis cell; M: mixer; H: heating block; CAT: heterogeneous catalyst; B: backpressure valve; FTIR: inline-ATR-IR flow cell; V: valve; A: autosampler.

Figure 1 Optimization pathway of the automated Pd/C-catalyzed hydrogenation of benzaldehyde (conversion is colour-coded); Pd/C-catalyzed hydrogenation of benzaldehyde **1**. The aldehyde in acetonitrile was pumped from a reservoir into the hydrogenation apparatus which was fitted with a 5%-Pd/C cartridge. The catalyst cartridges (1 mL reactor volume) were manually packed and loaded with 0.307 g 5 wt.-% Pd/C (E101 O/W) from Evonik Degussa (for further description see SI).

been adjusted. Thus, an increase in flow rate requires an increase in pressure. The optimization curve initially shows 10 to 20% conversion followed by a target phase of 90 to 95% (see SI, Table S1). The feedback loop was automatically stopped after multiple parameter sets gave rise to conversions, and hence yields, in excess of 90%.

With regard to practicability the best parameter set for conducting the heterogeneous continuous hydrogenation was 30 bar pressure, a temperature of 100 °C, and a flow rate of 0.9 mL min⁻¹. Alternatively, using the same pressure and reducing the flow rate to 0.8 mL min⁻¹, the temperature could be reduced by 15 °C (see SI, Table S1).

This result demonstrates rather impressively that the new self-optimizing reactor system can, for the first time, fully autonomously, i.e. without any manual interaction, optimize reaction conditions for a heterogeneously catalyzed continuous hydrogenation. This provides enormous time and cost saving benefits.

In order to validate the accuracy of the in-line FTIR spectroscopy the correlation between IR peak height and NMR yield was examined. A plot of both parameters (see SI Figure S1) showed a linear relationship ($R^2 = 0.996$). For additional control we also determined the conversion by gas chromatography which also correlates with the peak height. Thus, by using FTIR analysis the conversion can be accurately determined.

To further demonstrate the applicability of the system described, α -ketoester **3** was used as a second substrate. In order to ensure a sufficiently complex system, acetonitrile was chosen as solvent and selective reduction of the keto functional group (carbonyl band at 1688 cm⁻¹) to the corresponding α -hydroxy ester was observed. The automated optimization curve yielded conversion values between 20 and up to 64% in the starting tetragon, followed by two similar values. Subsequently, higher conversions are observed at 80 - 90% (Figure 2).

Figure 2 Optimization pathway of the Pd/C-catalyzed hydrogenation of ethylphenyl glyoxylate **3** (conversion is colour-coded).

Finally, there is a region in which, under high pressure and at high temperature, excellent conversions of up to 99% are achieved (see SI, Table S2, “opt”). The best parameter set for the heterogeneous continuous reduction of ethyl phenyl glyoxylate **3** was found to be a pressure of 70 bar, a temperature of 75 °C and a flow rate of 0.8 mL min⁻¹. When the values for the temperature and hydrogen pressure were maintained, the flow rate could even be increased to 1 mL min⁻¹ without significant loss in conversion.

In comparison to the reduction of the aldehyde the system finds the optimal reaction conditions for the hydrogenation of the ketoester in a completely different parameter space. From a chemical perspective this is not surprising. However, it impressively demonstrates that the system is flexible, adjusting to the given task to rapidly identify the best parameters.

We then went on to N-heterocyclic, aromatic substrates that could be efficiently hydrogenated using our previously⁵⁰ described Ir@CNT heterogeneous catalyst. Quinaldine **5** (0.1 M in ethyl acetate) was chosen as first substrate that could be reduced applying a 10 wt.% iridium nanoparticles on carbonanotubes catalyst.

Also for this substrate the accuracy of the in-line FTIR spectroscopy by correlation between IR peak height and GC conversion was examined which showed a linear relationship ($R^2 = 0.992$, see SI Table S3,). Similar to previous described carbonyl reductions, a characteristic IR band for the substrate at 825 cm⁻¹ was observed during the optimization process. Starting with rather mild hydrogenation conditions (0.7 mL min⁻¹, 40 °C, 10 bar) and a stock solution concentration of 0.1 M, already 39% conversion could be achieved (Figure 3). Within this first orientation phase of the first four points, 94% conversion represents the highest yield whose parameter points built the foundation for later optimal reaction conditions. After 12 points, a broad parameter space could be identified that delivers the desired [4H]-quinaldine with conversions of >98%.

Figure 3 Ir@CNT-catalyzed (10 wt.%) hydrogenation of quinaldine **5**.

Using this optimization method the user will not only get one ideal parameter set but is even more capable of choosing from many suggestions that suit best for a specific purpose. So, one can choose e.g. between harsher conditions (1.3 mL min^{-1} , 85°C , 50 bar) with high hydrogen pressures and temperatures that in exchange deliver more product due to high flow rates. On the other hand, also mild reaction conditions (1.1 mL min^{-1} , 55°C , 40 bar) can be chosen but therefore at the expense of space-time yields.

Having seen the envisioned hydrogenation system working well also for quinaldine **5**, control experiments were conducted regarding the optimization process and stability of the system (see SI, Figure S4+S5). The same hydrogenation of quinaldine was run again, also starting from the exact same parameter point (see SI, Table S4, Figure S7+S8). Observing that the same optimization route was followed, reproducibility of the described system-optimization can be verified. Once conversions $>96\%$ are reached resulting in complete minimized IR peak (after point 8), different parameter sets are conducted as slightest differences in peak heights results in different calculated parameter points. Nevertheless, high conversions of $>95\%$ were achieved after 11 points giving the user again the possibility to choose between several optimal reaction conditions. In order to validate the quality of catalyst and its comparability to the previously described hydrogenation system of quinolines, already optimal reaction conditions were chosen as starting parameter (1.5 mL min^{-1} , 20°C , 50 bar). As a reason of that, the first parameter set could also give the desired product with 90% conversion (see SI, Table S5, Figure S9+S10). Again within the first four points, conversions of 96% could be obtained. After a total of 12 analyzed, points a variety of different conditions were identified giving conversions of 99% for the hydrogenated quinaldine.

To further extend the described reactor system and demonstrate the acceptance of the system-optimization, quinoxaline **7** (0.1 M in ethyl acetate, 2.5 wt.% Ir@CNT catalyst) was applied to the hydrogenation process. Also for this substrate, conversions of $>95\%$ could be found after only four parameter sets followed by identification of several optimal reaction conditions (Figure 4, Table S6, Figure S14).

As outlined in the introduction, also the adaptivity of the system-optimization should be further investigated in order to compensate possible disadvantages of heterogeneous catalysis. Therefore, concentration increase was chosen as condition variation as it was both easy to conduct, measurably detectable and representative for common fluctuations in industrial plants. Allowing the system to optimize in the same manner as before (conversions of $>95\%$ were achieved after point 5, Figure 5), addition of neat quinaldine to the stock solution after point 6 was executed (Figure 5, 0.2 M). Observing only the slightest decrease in conversions ($90\% \pm 5$), the control algorithm was anyhow able to find back to reaction conditions above 98%. Within the same run, the stock solution concentration was further increased from initial 0.1 M to 0.3 M after point 12 resulting in a major distortion of the reaction system. First tendency showed a decrease in conversions that yields in inflexion point 19 with 55% conversion from which again a positive growth can be observed. From point 24 on stagnant conversions $>95\%$ are once again obtained.

This illustrates that the implemented control algorithm is not only capable of automatically finding optima, but also can be used as backup routine to adaptively regulate fluctuations of any kind, in this case demonstrated on an abrupt boost of stock concentration. This procedure was also repeated with a 10 wt.% Ir@CNT catalyst and a concentration increase from 0.1 to 0.3 M (see SI for further information).

Figure 4 Ir@CNT-catalyzed (2.5 wt.%) hydrogenation of quinoxaline **7**.

Figure 5 Adaptive optimization of Ir@CNT-catalyzed hydrogenation of quinaldine **5** (red line indicates increase of concentration).

In order to analyse the same principle on a more serious reaction system, a 2.5wt.% Ir@CNT catalyst was used (Table S9, Figure S18+S19, Supporting Information). Again, after full conversion after the sixth point, doubling of concentration was conducted. As expected, the optimization back to full-conversion conditions was more difficult to achieve than before. Decrease of conversion down to 41% occurred within the first eight parameter points followed by a stepwise, rising reorientation phase up to $\pm 80\%$ conversion. Finally, conversions $>90\%$ could once again be obtained after in total 31 measured points.

Conclusions

In summary, for the first time, we were able to develop a self-optimizing reactor system for continuous, heterogeneous catalytic hydrogenations in which the reaction conditions for different substrates could be autonomously optimized without any need for manual intervention. To achieve our goal, in-line ATR-FTIR spectroscopy for real-time analysis was integrated within the system as in contrast to other analytical techniques it is faster, a more convenient apparatus, and is applicable to multi-phase systems. The self-optimization of continuous reductions with molecular hydrogen is particularly interesting as hydrogenations are used in many scientific institutes as well as in industrial laboratories. Therefore, the first self-optimizing heterogeneous catalysis represents a further step towards achieving efficient, sustainable processes which are ecologically and economically advantageous compared to conventional methods and technologies for reaction optimization.

Conflicts of interest

There are no conflicts to declare.

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Keywords: H-Cube • online-IR • Palladium • monitoring • catalysis

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