# Enabling the Scale-Up of a Key Asymmetric Hydrogenation Step in the Synthesis of an API using Continuous Flow Solid-Supported Catalysis

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## Abstract

The development of a continuous-flow process for asymmetric hydrogenation with a heterogenized molecular catalyst in a real industrial context is reported. The key asymmetric step in the synthesis of an API (active pharmaceutical ingredient) has been developed on a kilogram scale with constant high single-pass conversion (>95.0 %) and enantioselectivity (>98.6 % *ee*) through the asymmetric hydrogenation of the corresponding enamide. This performance was achieved using a commercially available chiral catalyst (Rh/(*S,S*)-EthylDuphos) immobilized on a solid support via electrostatic interaction. The factors affecting the long term catalyst stability and enantioselectivity were identified using small-scale continuous-flow set-ups. A dedicated automated software-controlled high-pressure pilot system with a small footprint was then built and the asymmetric hydrogenation on kilogram-scale was carried out with a space time yield (STY) of up to 400 $gL^{-1}h^{-1}$ at pre-defined conversion and enantiopurity levels. Most importantly, no catalyst leaching was detected in the virtually metal-free product stream, thereby eliminating costly and time-consuming downstream purification procedures. This straightforward approach permitted an easy and robust scale-up from gram to kilogram scale fully matching the pharmaceutical quality criteria for enantiopurity and low metal content, thus demonstrating the high versatility of fully integrated continuous flow molecular catalysis.

## Introduction

Continuous processing has long been recognized as a promising method for process intensification in the chemical industry. Although continuous manufacturing has long been common in large scale production, it only recently has begun attracting increased attention from the pharmaceutical industry.[1] It is now clear that continuous flow processing can contribute to minimizing costs and intensifying production,[2] especially in the production of complex molecules where constant quality standards are required and expensive catalyst and/or high pressure are needed. Small and flexible reactor systems can also allow the integration of multiple operations either consecutively or even simultaneously,[3] for example the incorporation of continuous workups and product extraction post-reaction.[4] Both upstream and downstream operations can be integrated into a single process unit rather than being separated in space or time, allowing a more efficient process. These technologies offer unique scale-up opportunities because of the improved control on mass and heat transfers and

the possibility to scale out with relatively small reactor footprints. Such reactor systems can also be automated with online analysis allowing for faster optimization and better control of the overall performance.[5]

The advantages of fully integrated continuous flow systems are best exemplified in the context of homogeneous catalysis where often additional purification steps are required to remove or potentially recycle an expensive organometallic catalyst.[3, 6] The use of solid supported homogeneous catalysts in continuous flow is therefore very attractive, because both the reaction and the purification/recycling steps can be combined into a single process.[7] The reagents are pumped through a tubular reactor containing high concentrations of catalyst, thereby allowing for shorter reaction times and substantial process intensification. Highly efficient, solid-supported continuous flow catalysis has yet to be adopted in real industrial situations and it is the purpose of this paper to demonstrate its viability in an actual application to the pharmaceutical industry.[8]

Non-covalent immobilization is a promising strategy in solid supported homogeneous catalysis as off-the-shelf catalysts can be easily dispersed within the stationary phase without need for extensive chemical modification.[9] This approach is, in principle, more attractive than the conventional covalent immobilization strategies. However, it is rather more challenging to implement because the catalyst has greater potential for leaching and contaminating the product. We show here that leaching can be reduced and even avoided completely, if electrostatic interactions are exploited to retain ionic catalysts within ionic matrices. Our groups have contributed largely to the implementation of such heterogenized systems in continuous flow apparatus to simplify and intensify asymmetric hydrogenation reactions. Recent examples have involved the use of ionic liquids (IL)[10] or supported ionic liquids (SILP) as stationary phase and supercritical $CO_2$ (*sc*$CO_2$) as the mobile phase.[11] An earlier example, developed at Nottingham, was based on the so-called "Augustine approach"[12] in a continuous *sc*$CO_2$ process.[13] The Augustine approach uses heteropolyacids which are dispersed on a metal oxide surface and serve as anchors for cationic organometallic complexes (Figure 1). The attachment is based on a strong electrostatic interaction between the charged metal center and an oxygen atom of the heteropolyacid anchor which itself interacts *via* hydrogen bonding with the hydroxyl groups of the metal oxide support.[14] This supramolecular assembly is further entrapped inside the pores of the support which, in most cases, enhances stability without altering selectivity. Such anchoring systems are now well established as being very robust and efficient in asymmetric hydrogenations.[15] Recently, Cole-Hamilton and co-workers used this anchoring method and obtained very good results in the continuous flow solvent-free hydrogenation of dibutyl itaconate at low pressure.[16] Several other elegant demonstrations in the area of non-covalent immobilization have been reported but all of them have used model substrates, e.g. dimethyl itaconate, and have been

limited to academic laboratory scales.[9, 17] Until now, however, adapting these modern technologies to more demanding substrates in a "real" industrial context has been an unmet challenge.[8]

This paper now reports how the Augustine immobilization technique can be applied to the synthesis of a key intermediate in the synthesis of an API (active pharmaceutical ingredient) and on a considerably larger scale than previously attempted. We show that a number of issues associated with catalyst stability can be simply solved by combining continuous flow technologies with an appropriate reactor system, thereby maximizing catalyst utilization in an optimized operation. Finally, we demonstrate an efficient scale-up from gram- to kilogram-scale production in a cost-effective manner compared to the original batch process. Moreover, the development of this process has been carried out in two different labs, by various operators and with different rig designs thereby demonstrating its inherent robustness for pharmaceutical and fine chemical production. The developments described in this paper have provided a set of parameters for successful operative conditions and have the potential to be adapted to other industrially relevant processes.

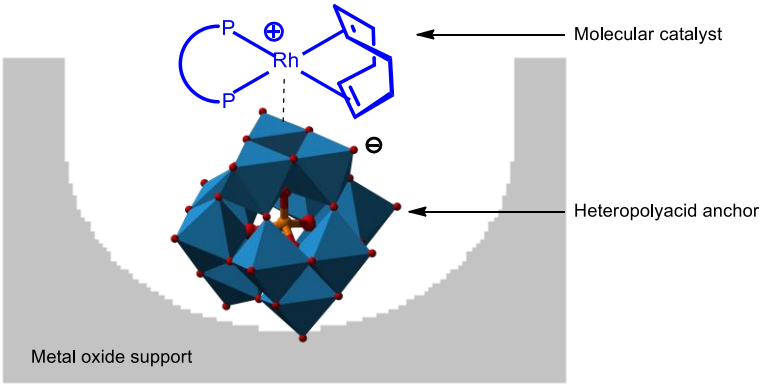
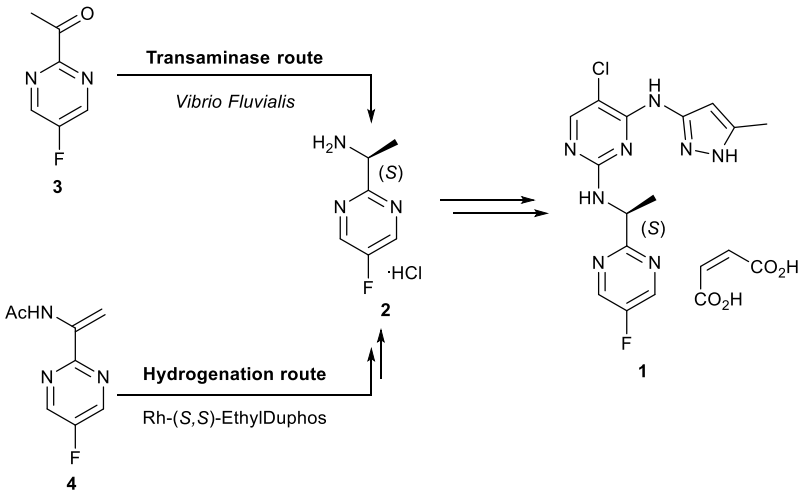


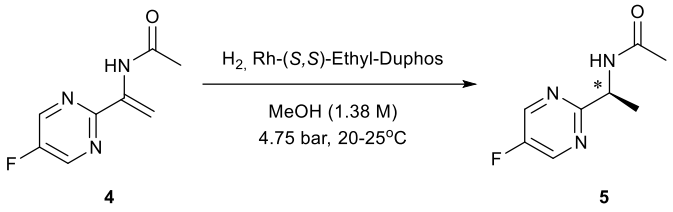

**Figure 1:** Depiction of the Augustine strategy showing anchoring of a molecular catalyst to a solid support via a heteropolyacid linker.

Our study has involved API, **1,** which is a JAK2 kinase inhibitor previously tested at the clinical level at AstraZeneca (Scheme 1).[18] A key step in the synthesis of **1** is the formation of the chiral amine intermediate **2**.[19] Two separate methodologies were developed for this step: a transamination reaction of the ketone **3** and the asymmetric hydrogenation of the enamide **4**.[20] The transaminase strategy was ultimately selected and successfully scaled up to a 2.5 kg two-phase process (100 L). However, although this method gave fairly high enantioselectivity (97.3 %), the final isolation of the amine **2** from the slight excess of amine donor was challenging and involved the derivatization of the amine by boc-protection to enable its extraction into an organic phase, due to its high aqueous-solubility.




**Scheme 1:** The two routes for the production by AstraZeneca of API **1**, the focus of this paper.

The hydrogenation route was originally developed as a batch process, and required relatively high loadings of the chiral catalyst Rh-(*S*,*S*)-EthylDuphos (Scheme 2), and still required the same boc-derivatization strategy for product extraction. Minimizing the costs and improving the environmental footprint of this process represents a real industrial challenge and converting the batch process to a heterogeneous continuous technology identified as the method of choice.




**Scheme 2:** The original Med Chem route[20] involves an asymmetric hydrogenation step which is transposed from batch to continuous flow in the present work.

## Results and Discussion

### Preliminary experiments, proof-of-concept and optimization

For our initial studies we selected a commercially available composite of PhosphoTungstic Acid (PTA) and aluminum oxide (Alox) as the support. PTA/Alox has been described as being the best performing material in previous examples available in the literature.[12a, 16] The Augustine method also provides a flexible way to immobilize cationic rhodium catalysts and several ligands can be screened efficiently. However, screening was not an important issue in this case because the original AstraZeneca batch process already performs with outstanding enantioselectivity using Rh-(*S*,*S*)-EthylDuphos as catalyst. We therefore kept the same catalyst and focused on identifying the best strategy for anchoring the

catalyst on the PTA/Alox support under continuous flow conditions; initial experiments were carried out in ethyl acetate solution (c = 0.009 g/mL) using custom-built high pressure medium scale reactors (Figure 2 and ESI).

Our first trials met with moderate success although the system was already outperforming the batch process providing a TON of ca. 235 with high selectivity (> 98 % *ee*) (ESI). Results were however difficult to reproduce, showing stable enantioselectivity but a relatively fast decrease in conversion, suggesting catalyst leaching or degradation (see e.g. Figure 3 in the supporting information). Due to the sensitivity of the catalyst system towards oxygen and moisture, we modified our reactor set-up by incorporating a high-vacuum pump and an argon purge to ensure oxygen and water free conditions in the reaction system prior to starting the experiment. Using this modified set-up, more stable catalyst activity was achieved with an improved total TON of 935 and high enantioselectivity (> 98 % *ee*) (see Figure 4 in the supporting information). Despite the diluted feed, the maximum TOF of 2.6 $min^{-1}$ (ESI) is comparable to the value of 4.4 $min^{-1}$ reported by Augustine for the batch hydrogenation of methyl 2-acetamidoacrylate with Rh/MeDuphos.[12a] In both of our experiments, ICP-MS measurements of the collected product mixtures revealed traces of rhodium between 5-15 ppm.

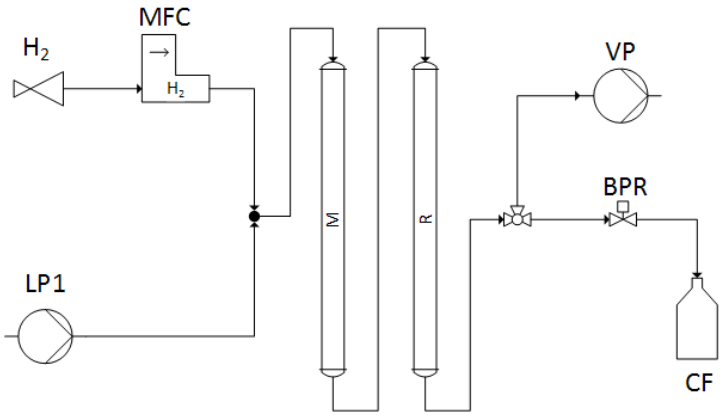



**Figure 2:** A schematic diagram of the reactor systems used for the development of immobilized rhodium catalyzed enantioselective hydrogenation in Nottingham and Aachen. BPR = back pressure regulator, CF = collecting flask, LP = liquid pump, M = mixer/moisture trap, MFC = mass flow controller, R = reactor, VP = vacuum pump.

A straightforward "on-line anchoring procedure" was then developed whereby the PTA/Alox support was first loaded into the tubular reactor and dehydroxylated at 200 °C under vacuum with regular argon flushes. Afterwards, a degassed ethanol solution of the air sensitive organometallic catalyst was pumped through the reactor containing the PTA/Alox support, where it is efficiently trapped in-situ by ion exchange (see Figure 2 in the supporting information). Following this online anchoring step, the hydrogenation of **4** to **5** was carried out in EtOH, a protic solvent already successfully used by Augustine (see Figure 6 in the supporting information). This procedure not only simplified operations but also

resulted in enhanced catalyst retention with a far lower levels of catalyst leaching than we had observed previously (rhodium content in the product mixture ≤ 0.77 ppm) at unchanged TON (ca. 1000). Visual inspection of the catalyst composite at the end of the reaction showed a non-uniform distribution of the catalyst; only the support material at the top of the reactor (entrance) was visibly colored. This observation suggests that any possible leaching was offset by a downstream capture of the rhodium by the vacant PTA sites.

Having demonstrated that the Augustine method is well-suited for the continuous-flow hydrogenation of **4**, efforts were devoted to enhancing the productivity. Intensification of flow processes are typically achieved by increasing flowrate, temperature and pressure. In asymmetric hydrogenations, the processing window is relatively narrow as increases in temperature and pressure can lead to lower enantioselectivity or detachment of the molecular catalyst. Thus, the use of reaction media other than EtOAc and EtOH was identified as a key parameter. Thus, the solubility of **4** in ethanol is relatively low (0.4 mol/L), thereby counteracting the productivity in terms of space-time-yield. Using ethanol (EtOH c = 0.011 g/mL), a maximum TOF value of 13.5 $min^{-1}$ was attained at full conversion, with an overall TON of 1000 similar to that achieved with EtOAc.

To enhance catalyst productivity, the reaction solvent was switched to tetrahydrofuran (THF), an excellent reaction medium for asymmetric hydrogenation.[21]. The solubility of **4** in THF is as high as 1.0 mol/L allowing a 10-fold increase in concentration (c = 0.11 g/mL) compared with EtOH. Initial experiments using a commercially available set-up with a small reactor ($V_{reactor}$ = 6.0; $V_{catalyst\ bed}$ = 2.7 mL) and substrate concentration of 0.2 M showed greatly improved catalyst stability with almost quantitative single-pass conversion at enantioselectivities ≥99% *ee* during the first 13 h on stream and a TON of ca. 5000 within 24 h. Overnight a drop in conversion occurred (see Table 2 and Figure 11 in the supporting information).

The productivity was further increased by increasing the substrate concentration to 0.6 M and using a reactor system constructed in Aachen[22] comprising a larger reactor ($V_{reactor}$ = 8.0 mL; $V_{catalyst\ bed}$ = 3.8 mL); this more productive system gave an overall TON of >5000 in < 7 h on stream with almost full conversion and enantioselectivity exceeding 98 % *ee*. This corresponds to an excellent STY of 520 g/L h for the entire experiment (Figure 3). Furthermore, the Rh content in the product stream was <1 ppm (ICP-MS).

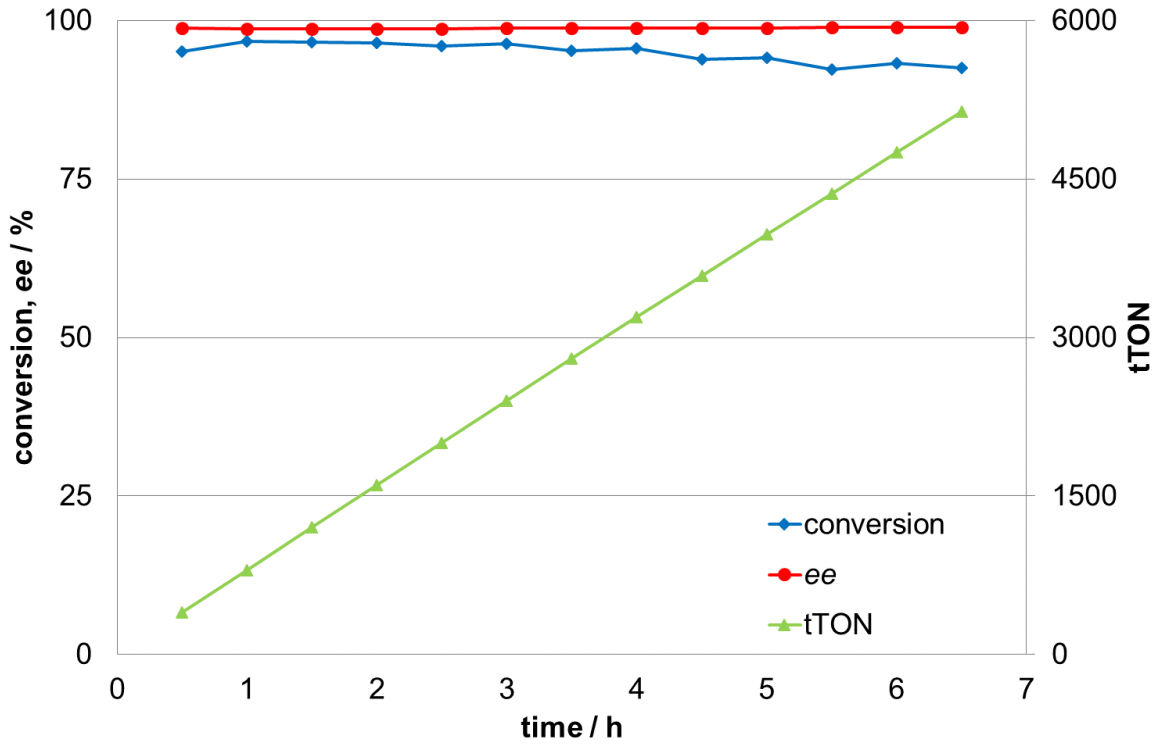



**Figure 3:** Continuous flow hydrogenation of **4** with [Rh{(*S,S*)-EthylDuphos}(cod)]$^{+}BF_4^{-}$/PTA/$Al_2O_3$ catalyst and THF as solvent. $\dot{V}(H_2)$ = 33 $mL_N$/min, $\dot{V}$(Substrate) = 0.3 mL/min, c(Substrate) = 0.6 M, $V_{catalyst\ bed}$ = 3.8 mL, *p* = 10 bar, *T* = 22 °C.

**Continuous-flow hydrogenation on a 1 kg/day scale**

Encouraged by successful and reproducible experiments at small scale even with different set-ups and different experimentalists in Aachen and Nottingham, it was decided to scale-up the continuous-flow hydrogenation of **4** to **5** in Aachen. A dedicated unit was constructed for its demonstration at 1 Kg/day scale, see Figure 4. Further details and operational procedures for this unit are described in ESI. The key feature is the exploitation of on-line analysis to discard any sub-standard product that might be formed as a result of a malfunction and which, if not removed, would contaminate and devalue the product. Briefly, the unit consists of dosing systems for liquids and gases ($H_2$), two vertical tubular reactors, 150 mL each, connected via a pneumatic valve, so that the reactors can be fed alternately. There is a gas/liquid separator downstream of the back-pressure regulator. . On exiting, the liquid product stream is directed to a continuous gas chromatograph (GC)-sampler and then on to 2 L collection vessels. The on-line GC allows the product quality to be monitored continuously, as defined by both conversion and *ee.* If the conversion should drop below the defined threshold of 90 % or the *ee* below 98 %, an automatic device will divert the product stream to another collecting vessel so as to avoid lowering the quality of the material already collected. If the conversion and/or *ee* values remain below the limits for three consecutive GC-measurements, one can either reduce all flows automatically or to switch to the second reactor containing fresh catalyst without interrupting the

continuous-flow experiment.[23] The entire set-up is controlled by software written using NATIONAL INSTRUMENTS' LabView, which permits the set-up and monitoring of all reaction parameters, viewing of the analytical data obtained by online chromatography, operation of the pneumatic valve for switching between the reactors and to execute a safe shut-down procedure.[24]

A minimum of 90 % conversion at 98 % enantioselectivity, and a maximum Rh contamination of 10 ppm were defined as target quality criteria. The asymmetric hydrogenation of 1 kg of **4** was performed at 25 °C and 10 bar. The substrate was dissolved in THF (c = 0.11 g/mL) and delivered at 9 mL/min. $H_2$ was dosed at 870 $mL_n$/min (molar ratio $H_2$ : substrate = 6.75) using a mass flow controller. The conversion and selectivity profile including the cumulated TON (tTON) are shown in Figure 5.

The continuous-flow reaction lasted ≈18 h, which was the time needed to flow the whole substrate solution (≈10 L) at the chosen flow rate (9 mL/min). The enantiomeric excess throughout the continuous reaction ranged between 98.9 % and 98.6 %, above the minimum acceptable limit of 98 %. An initial conversion of 99.6 % was detected. After 1 h, the dosage of the substrate was interrupted by a ruptured seal on the syringe pump. After replacing the pump with an HPLC-pump, the dosage of the substrate was restarted and a conversion >99 % was achieved. After 7 h on stream, there was a malfunction of the $H_2$ mass-flow controller (MFC), resulting in a sudden decrease in the $H_2$ flow from the initial 900 $mL_n$/min (molar ratio $H_2$ : substrate = 6.5) to only ≈250 $mL_n$/min (molar ratio $H_2$ : substrate = 1.8) causing a decrease in the conversion to 75 %. This drop in conversion, well below the set-point (90 %), triggered the automation to divert the next product fractions into a separate vessel. After the $H_2$ flow problem had been resolved (~30 min later), the conversion reverted to 99 % and remained at this level for 3 more hours before slowly decreasing to a minimum of 95 % in the final sample. The stable catalyst performance rendered any switch between the reactors unnecessary and the conversion of the 1 kg substrate was carried out only using the catalyst material contained in the first reactor.

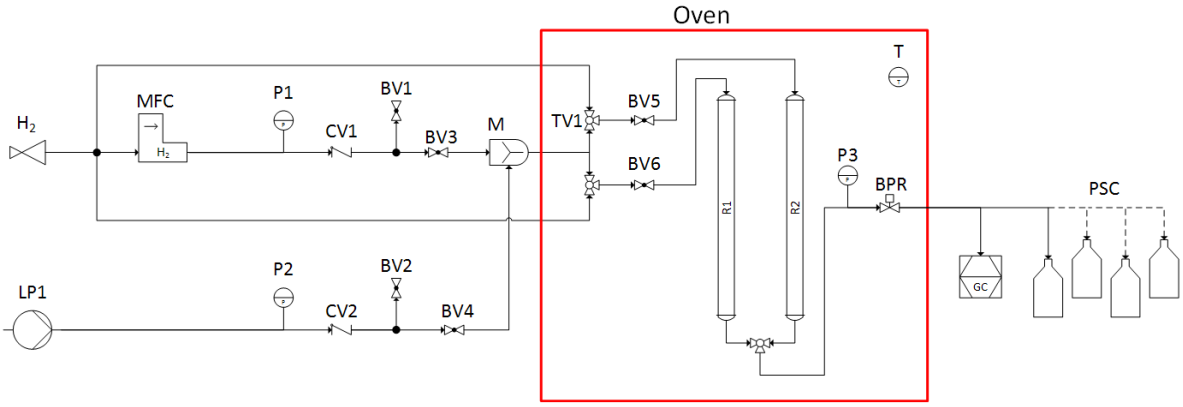



**Figure 4:** Scheme of the demonstrator unit. BPR = back pressure regulator; BV = ball valve; CV = check valve; GC = gas chromatograph; LP = high pressure syringe pumps; M = mixer; MFC = mass flow controller; P = pressure transducer; PCS = automated product collection system, PV = pneumatic three way valve; R = reactor; T = thermocouple. A more complete description is given in the ESI. The argon flush and vacuum pumps are not shown here.

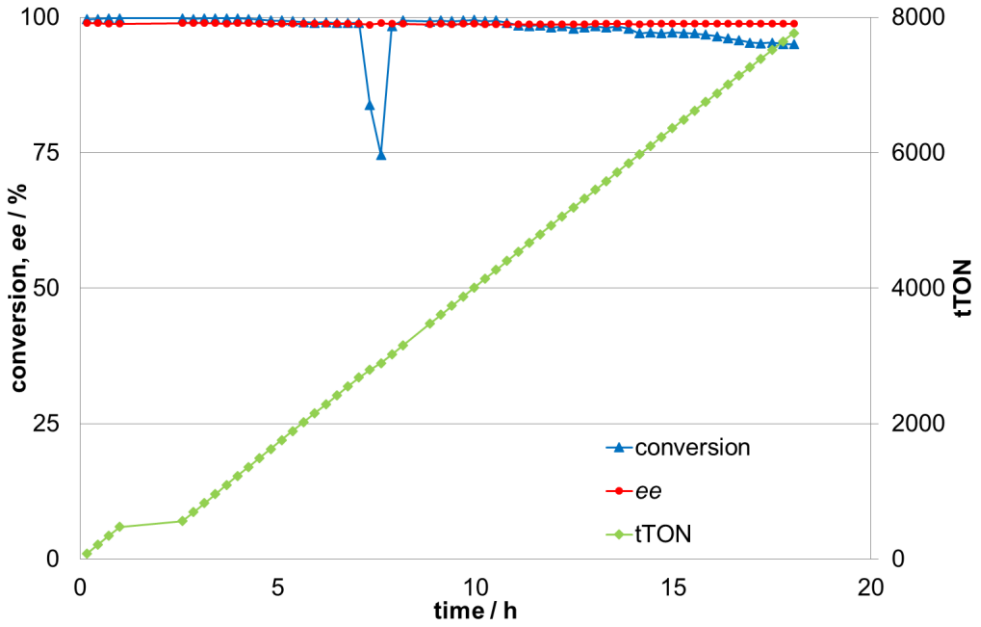



**Figure 5**: Reaction profile for the continuous-flow asymmetric hydrogenation of **4** on a kilogram scale.
Conditions: $\dot{V}(H_2)$ = 250 $mL_N$/min, $\dot{V}$(sub) = 9.0 mL/min, c(sub) = 0.6 M (THF), $V_{catalyst\ bed}$ = 147 mL, $p$ = 10 bar, $T$ = 22 °C.
1-2.5 h: dosage of the substrate interrupted because a pump defect → pump replaced;
At 7-8 h, there was a sudden drop in conversion due to a malfunction of the $H_2$ mass flowmeter; the system quickly detected the problem and diverted the sub-standard product until the problem was fixed and the system re-equilibrated.

Despite the problem with the pump and the malfunction of the $H_2$-MFC, the kilo-scale hydrogenation of **4** was realized in less than 18 h with an average conversion of all combined product samples of 97.6 % at an average selectivity of 98.8 % *ee* (see ESI). This corresponds to an STY of up to 400 g/L h was obtained with a tTON of ca. 7700 with the catalyst still retaining almost all of its initial activity and enantioselectivity even at the end of the campaign. The final work-up consisted of evaporation of the THF, to obtain the product as a yellowish solid material (purity ≥ 98%, *ee* ≥ 99%). Very gratifyingly, the ICP-MS analysis of the isolated product revealed a rhodium content below 1 ppm corresponding to less than 1%loss of the initial metal-loading of catalyst, very much in line with the stable performance

of the catalytic system on a smaller scale. By contrast, the product solution from the original industrial batch process contains 1.1 mol% of rhodium, which has to be carefully removed in the work-up procedure and requires additional solvents, use of a metal scavenger as well as further manufacturing time.

All the results from the 1kg scale continuous-flow hydrogenation were well above the predefined product specification limits (90 % conversion, 98 % *ee*, Rh-contamination <10 ppm) a striking demonstration of our methodology this-scale. In particular, AstraZeneca have identified the key drivers for implementing such an integrated continuous-flow process as the dramatic reduction in Rh-contamination of the product, and removing the need for additional solvent, metal scavenging, and labor-intensive work-up procedures . A comparison of the continuous flow and the original batch process is shown in Table 1 using a traffic light representation.

**Table 1:** Comparison of the current batch process and the results of the continuous flow experiments (green = better, yellow = similar, red = worse).

| | | **batch** | | **continuous flow** | |
|---|---|---|---|---|---|
| number of runs needed | | 6 | 🔴 | 1 | 🟢 |
| reactor unit | [mL] | 660 | 🔴 | 150 | 🟢 |
| amount of catalyst needed | [mmol] | 10.1 | 🔴 | 0.68 | 🟢 |
| *ee* | [%] | > 98.6 | 🟡 | > 98.6 | 🟡 |
| reaction time | [h] | 32[a] | 🔴 | 18 | 🟢 |
| process time | [h] | 64[a] (estim.) | 🔴 | 18 | 🟢 |
| $H_2$-pressure | [bar] | 4.75 | 🟢 | 10 | 🔴 |
| solvent | [L] | 4 (MeOH) | 🟢 | 10 (THF) | 🔴 |
| temperature | [°C] | 25 | 🟡 | 25 | 🟡 |
| estimated PMI[b] | | 4.2 | 🟡 | 10 | 🟡 |
| Rh contamination[c] | ppm | 260 | 🔴 | < 1 | 🟢 |
| space-time-yield | [g/L h] | 47 | 🔴 | 399 | 🟢 |

[a] Cumulative values for six batch reactions; [b] Reaction step only; [c] Rh-content in crude product solution

This comparison clearly favors the continuous-flow system over the batch process. The catalyst loading in the flow process is approximately 10 % of the quantity required by the batch methodology, resulting in a much more efficient utilization of the precious metal and expensive chiral ligand. The efficiency is also reflected by the 10-fold increase in STY in continuous flow. It is also important to note that the value for the PMI (process mass intensity) for the batch process refers only to the reaction step and

do not include the material–intensive work-up procedure needed in the batch process. The continuous process does not have such a work up stage. The higher efficiency and suppression of metal contaminants are key drivers for a larger scale implementation of this continuous process. Thus, according to ICH Q3D guidance on elemental impurities,[25] rhodium is a class 2B metal, meaning that manufacturers must quantify rhodium-content in the final API if rhodium is used intentionally at any stage of the manufacture. The PDE (permitted daily exposure) limit for rhodium via an oral route is 100 µg/day, and its permitted concentration in drug products, drug substances and excipients is 10 µg/g for doses up to 10 g/day. For parenteral and inhalation, the permitted concentrations are considerably lower (1 and 0.1 µg/g respectively). Therefore, controlling the levels of this metal in APIs and intermediates in their synthesis is of utmost concern in the pharmaceutical industry and access to a methodology, such as ours, that enables this metal to be used in chemical transformations without significant contamination of the resulting product or the need for metal scavenging is of great interest.

## Conclusions

The regulations of manufacturing of APIs are vitally important but it does inadvertently result in additional costs to pharmaceutical companies. Continuous technologies are now fully integrated platforms where quality is controlled by design and operations are automated, thereby offering the potential to significantly lower manufacturing costs. At the same time, safety concerns can be reduced by the use of smaller volume reactor units. We have shown that the conversion of a batch to a continuous-flow process can be achieved using the same commercially-available catalyst as in the batch process via a straightforward and effective immobilization method. Our continuous-flow process for the hydrogenation of **4** was optimized and scaled up in a tightly defined time-frame of only 8 months including the construction time for the production unit at Aachen). Excellent catalyst stability and retention in continuous-flow was demonstrated at 1 kg scale resulting in virtually metal-free product (Rh content < 1 ppm) with high optical purity (*ee* >98.6 %) within 18 h. The highly automated continuous-flow set-up with on-line analytics developed for this purpose, monitors the product specification, selects the appropriate collecting vessel, and even adjusts substrate flow or switches reactor cartridge, thus ensuring that the product meets all predefined quality criteria. As compared to the reference batch processes, our continuous flow approach exhibits a much simpler work-up, higher efficiency and greater sustainability, all likely to lead to lower manufacturing costs and to a robust and competitive process option for the (pharmaceutical) industry.

**Acknowledgement**

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***Catching phrase:*** *Pump up the pipe!*

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