



# Continuous Hydrogenation | Very Important Paper |

### VIP

Continuous Platinum-Mediated Hydrogenation of *Refametinib* lodo-nitroaniline Key Intermediate DIM-NA: The Combined Challenges of Selectivity and Catalyst Deactivation

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**Abstract:** The chemoselective, continuous, multistep reduction of iodo-nitroaromatics in a fixed-bed hydrogenation reactor has been investigated. This transformation poses challenges upon both the catalyst and process conditions if high yields are to be achieved. First, the stability and selectivity of four flow-compatible Pt catalysts, Pt(X)/C (X = Fe, V), were investigated by using 1-iodo-4-nitrobenzene as the model substrate. Granular Pt(Fe) on carbon was identified as the most promising candi-

# ceutical ingredient) intermediate DIM-NA [(2,3-difluoro-5-methoxy-6-nitrophenyl)(2-fluoro-4-iodophenyl)amine] could be converted into the corresponding aniline with high selectivity on a preparative scale. UV/Vis spectroscopy was successfully applied for online conversion control, proving to be highly useful for detecting the effects of catalyst deactivation.

date. With this catalyst, iodo-nitroaromatic API (active pharma-

### Introduction

Continuous processing is a long-known technology that has been successfully applied in the manufacture of large-scale bulk chemicals.<sup>[1]</sup> Recently, an intense debate has arisen on the advantages of this type of processing in the pharmaceutical industry.<sup>[2]</sup> Today, the production scales of active pharmaceutical ingredients (APIs) often do not reach multi-ton levels, but the syntheses typically involve multistep transformations of complex and highly functionalized (i.e., precious) substrates in the liquid phase, which renders selectivity a major challenge. The advantages of the continuous-processing of fine organic reactions in tubular micro- or meso-reactors, compared with standard batch reactors, have been extensively reviewed.<sup>[3]</sup> These include considerable process intensification in terms of spacetime yield, possible because of extended process windows, and a higher quality output resulting from a better control of key process parameters such as reaction (residence) time, temperature, and, if applicable, pressure. The easier and safer utilization of highly reactive or toxic reactants and/or intermediates may, furthermore, facilitate alternative and more efficient synthetic routes. Thus, a "batch-to-conti" (batch-to-continuous) transfer often leads to higher productivities or product yields,<sup>[4]</sup> but it

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should be emphasized that in many cases the use of multipurpose batch reactors may represent the best solution. Still, for a number of specific organic transformations, the advantages of scaling a synthesis by means of continuous processing time rather than batch reactor volume or number of batch syntheses are intriguing.<sup>[3b]</sup>

Heterogeneously catalyzed hydrogenation is certainly a reaction class for which continuous processing should be considered. When performed in a fixed-bed reactor, continuous-flow hydrogenation, as compared with batch hydrogenation, benefits from improved gas/liquid mixing,<sup>[5]</sup> heat management, and a simple and safe utilization of hydrogen at high reaction pressures and temperatures.<sup>[6]</sup> This is especially valid for the strongly exothermic hydrogenation of organic nitro compounds  $(\Delta H^{\rm r} = 500-550 \text{ kJ/mol})$ ,<sup>[7]</sup> which represents a key fine organic chemical transformation that is widely employed in industry to synthesize functionalized primary amines. The reaction proceeds by a complex, multistep, six-electron reduction pathway comprising the formation of reactive nitroso and hydroxylamine intermediates, which are prone to a variety of side-reactions.<sup>[7]</sup> If halogens are involved, a further selectivity challenge arises, because the action of H<sub>2</sub> in the presence of a hydrogenation catalyst can induce hydrodehalogenation (Figure 1, bottom). Here, the narrower temperature profile resulting from a continuous process may allow for better control of these side-reactions effecting higher selectivities and a uniform guality of the reactor output. Thus, selectivity represents a major chemical challenge during nitro-to-amine hydrogenation, and considerable efforts have been devoted to the development of highperforming catalysts.<sup>[8]</sup>

In the present contribution, we report on our studies on the selective continuous hydrogenation of (2,3-difluoro-5-methoxy-

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Figure 1. Top: Hydrogenation of iodo-nitroaromatic derivative 1 to iodoaniline 2 as part of a possible synthetic route to the anticancer agent *Refametinib*. Bottom: Hydrogenation of 1-iodo-4-nitrobenzene (4) to 4-iodoaniline (5). Hydrodehalogenation leads to the formation of the deiodinated products 3 and 6, lowering selectivity.

6-nitrophenyl)(2-fluoro-4-iodophenyl)amine (DIM-NA, **1**) to the corresponding primary amine 3,4-difluoro- $N^2$ -(2-fluoro-4-iodophenyl)-6-methoxybenzene-1,2-diamine (DIM-DAB, **2**; Figure 1, top) on a preparative scale. Compounds **1** and **2** are key intermediates in the multistep synthesis of the antitumor agent *Refametinib*, a highly potent and selective MEK1/2 inhibitor, which is currently undergoing phase II clinical trials for late-stage cancer treatment.<sup>[9]</sup>

Regarding hydrodehalogenation, the highest lability has been reported for the iodine in the amine product.<sup>[7]</sup> This means that the dehalogenation side-product primarily forms in a follow-up reaction of the targeted product (Figure 1, bottom), so iodo-nitroaromatics can be considered the most challenging substrates for selective hydrogenation up to full conversion of the starting nitro compound. A selective catalyst must, therefore, be active enough to suppress the accumulation of reactive intermediates from nitro group reduction, but, at the same time, it should not show a pronounced activity towards deiodination upon reaching full conversion.

To date, only a few heterogeneous catalysts have been applied in the continuous hydrogenation of halo-nitroaromatics. Loos et al. reported that Raney cobalt could be a selective catalyst for this transformation. They found that conti-hydrogenation of the highly labile 4 (Figure 1) in a 5 mL fixed-bed reactor at 80 °C and 85 bar gave only 1.5-2 % of the deiodinated sideproduct aniline at full conversion.<sup>[10]</sup> Encouraged by those promising results, we recently scaled the conti-hydrogenation process over a fixed bed of Raney Co catalyst to 50 mL reactor volume. Using a 9 mm (inner diameter, ID) reactor tube, we successfully converted 1 kg of Refametinib intermediate DIM-NA (1) into DIM-DAB (2) at 60 °C within 8 h (Figure 1).<sup>[11]</sup> The selectivities obtained were remarkable: At >99.5 % conversion, only negligible amounts of deiodinated 3 (≤0.5 %) or other side-products were formed throughout the process, and the industrial specifications for this step were clearly matched. However, high pressure drops (up to 80 bar) resulted from the small particle size (40 µm) of the Raney Co catalyst and the throughput employed.

Building on recent reports by Beller and co-workers on a novel cobalt catalyst for the selective hydrogenation of (halo-)nitroaromatics,<sup>[8b]</sup> we used carbon nanotube (CNT) agglomerates with particle sizes of 200–800 µm [d(50) = 564 µm] as the support material for a related cobalt catalyst, CoNGr@CNT, with a morphology more suitable for applications in flow chemistry.<sup>[12]</sup> This catalyst proved to be highly selective, and under optimized conditions (80 °C, 60 bar) 1-iodo-4-nitrobenzene was hydrogenated without any notable deiodination. However, the productivity of the catalyst [3.0 mmol(**5**)/ {g(cat.) h]] was rather unsatisfactory due to a comparatively low catalyst activity and the low bulk density (0.27 g/mL) of the material.<sup>[12]</sup>

Doped Pt catalysts, 1 % Pt(X)/C (X = V, Fe), can also be used for the selective hydrogenation of (halo)nitroaromatics.<sup>[10]</sup> Their commercial, standardized availability is an advantage, at least for industrial applications, especially under the constraints of GMP (good manufacturing practice) manufacture. A 1 % Pt(V)/ C catalyst has been shown to perform reasonably well in the conti-hydrogenation of **4**.<sup>[10]</sup> However, mechanical fragility and severe deactivation have prohibited the repeated use of this catalyst, even in small-scale processes.<sup>[10,12]</sup> We, therefore, decided to evaluate in more detail the potential of this family of catalysts for the conti-hydrogenation of DIM-NA, not only regarding the selectivity but also the scalability of the process up to preparative amounts useful for early preclinical pharmacological studies.

### **Results and Discussion**

When switching from batch hydrogenation in an autoclave to a continuous-flow process in which the catalyst is employed in a packed bed, special attention has to be given to the morphology of the catalyst. For proper flow dynamics, the particle size should match the dimensions of the reactor tube to avoid nonuniform process conditions throughout the reactor due to pressure drops or channeling. Accordingly, suitable ratios between



the diameter of the reactor tube (*D*) and the catalyst particle size ( $d_p$ ) have been reported to be  $D/d_p > 10$ .<sup>[13]</sup>

Vanadium- and iron-doped carbon-supported platinum catalysts as well as undoped Pt/C with a morphology suitable for application in our flow reactor were obtained from two commercial catalyst providers as 0.8 mm catalyst extrudates and 0.4–0.8 mm granules, respectively (Table 1 and Figure S1 in the Supporting Information). To determine the best candidate for the envisioned preparative reactions in a 50 mL reactor employing **1** as the starting material, the stability and selectivity of the five catalysts were evaluated using 1-iodo-4-nitrobenzene (**4**) as a model substrate (Figure 1).

Table 1. Catalysts investigated for their stability and selectivity in the continuous hydrogenation of **4** at 0.43 mmol(**4**)/{g(cat.) min}.  $c(\mathbf{4}) = 0.1 \text{ M}$  in THF/ H<sub>2</sub>O (95:5, v/v), T = 80 °C, p = 40 bar, 6 equiv. H<sub>2</sub>.

Catalyst <sup>[a]</sup>	Amount <sup>[b]</sup> [g]	Flow rate [mL/min]	Deactivation <sup>[c]</sup> [%]	Aniline [%] <sup>[d]</sup>
1 % Pt(V)/C <sup>gran</sup>	0.79	3.4	16.5	1.2
1 % Pt(V)/C <sup>extr</sup>	0.93	4.0	19.8	1.9
1 % Pt(Fe)/C <sup>gran</sup>	0.84	3.6	10.6	1.4 <sup>[e]</sup>
1 % Pt(Fe)/C <sup>extr</sup>	1.17	5.0	24.5	4.6
1 % Pt/C <sup>extr</sup>	0.79	3.4	24.6	9.0

[a] The catalyst morphology was either granules (gran) or extrudates (extr). [b] Amount of catalyst required for a 2.75 mL catalyst bed, the remaining volume of the catalyst cartridge was filled with inert material (see the Supporting Information). [c] After 12 h time on stream with respect to the initial activity, as calculated from the GC area%. [d] Compared at around 78–81 % conversion; see Table S1 in the Supporting Information. [e] Reported at 87 % conversion as lower conversions were not reached within the experimental time.

A 0.1  $\,$ m solution of **4** was hydrogenated at 80–99 % conversion in a commercial cartridge reactor (10 mm ID, see the Supporting Information for details) loaded with 2.75 mL of the respective catalyst (Table 1). For proper evaluation and comparison of the different materials, the flow rate was adjusted to achieve a uniform workload [mmol(**4**)/{g(cat.) min}]. The hydrogenation experiments were conducted over a total period of 12 h with an interruption after 5 h, during which the catalyst bed was stored in THF/H<sub>2</sub>O (95:5, v/v) overnight. The product mixtures were analyzed at regular intervals by gas chromatography (GC) for conversion of the starting material and the content of the deiodinated product aniline.

For all catalysts, a steady deactivation profile was found in the investigated timespan (Figure 2), which may be due to metal leaching or inhibition of the Pt catalyst by the product amine.<sup>[14]</sup> After 12 h time on stream (TOS), the extent of deactivation was in the range of 11–25 % (Table 1), and there were no indications that the catalyst activity would converge towards a stable value. Pt(Fe)/C<sup>gran</sup> turned out to be the best-performing catalyst, showing the highest stability as well as the highest activity and selectivity (Figure 2, Table 1). As expected, the selectivity of the undoped catalyst Pt/C<sup>extr</sup> was rather poor with a 4.7-fold higher amount of aniline in the product mixture (at 80 % conversion) as compared, for example, with the 1 % Pt(V)/ C<sup>extr</sup> catalyst (see Figure S3 and Table S1).

The combination of catalyst deactivation and a follow-up dehalogenation side-reaction poses considerable challenges to the task of selective continuous hydrogenation at full conver-





Figure 2. Deactivation profiles of the five carbon-supported Pt catalysts employed in this study during the selective continuous hydrogenation of 4-iodonitrobenzene (**4**; see Figure S3 and Table S1 in the Supporting Information for the dehalogenation profiles).

sion. For a conti-process based on a fixed-bed reactor, three cases can be considered that may influence the processing options and selectivity of the reaction (Figure 3).



Figure 3. Different scenarios for the selective continuous hydrogenation of halo-nitroarenes in a fixed-bed reactor. Case I (left): stable and highly selective catalyst. Case II (middle): combination of a deactivating but selective catalyst. Case III (right): deactivating catalyst with modest to low selectivity regarding the follow-up dehalogenation reaction.

Case I (Figure 3, left) represents the favorable situation in which a non-deactivating and highly selective catalyst is available. Under these conditions, neither catalyst deactivation affects the targeted conversion over time nor will selectivity deteriorate by the presence of the excess catalyst bed fostering the follow-up dehalogenation reaction. This constellation allows for variation of the reactor throughput within a given range, and the process-optimization efforts are comparatively low. In case II (Figure 3, middle), a deactivating but still highly selective catalyst is present. Here, the implementation of an excess catalyst bed (as realized by a proper flow rate) is a possible measure to compensate for catalyst deactivation because the presence of excess catalyst will not affect the selectivity of the process. Case III (Figure 3, right) represents the most challenging situation. It illustrates the combination of a deactivating catalyst and a reaction system characterized by the existence of a follow-up reaction of the targeted product(s) catalyzed by the same material (hydrodehalogenation in the present case). Here, excess catalyst bed will (further) increase the concentration of such





byproducts, and to minimize their formation (1) the catalyst must have a minimum selectivity to inhibit the follow-up reaction at lower conversions of the reactant and (2) the process conditions have to be adjusted to exactly reach full conversion just at the outlet of the reactor. In such a scenario, if the catalyst employed suffers from deactivation, the conversion will quickly drop below the tolerable limit and immediate measures will be required to avoid product contamination by too much unreacted starting material. The latter can be simply accomplished by reducing the reactant's flow rate, that is, by increasing the residence time, but this requires a fast-responding tool for online conversion determination and is at the cost of the throughput of the process.

In view of the above discussion, if there is no extraordinarily selective catalyst available, the conti-hydrogenation of iodonitroarenes is to be classified in category three.

#### **Continuous DIM-NA Hydrogenation**

Due to its superior activity and selectivity among the catalysts evaluated, we chose Pt(Fe)/C<sup>gran</sup> for further studies of DIM-NA

(1) hydrogenation on a preparative scale using the reactor setup schematically shown in Figure 4 (see ref.<sup>[11]</sup> and the Supporting Information for a detailed description of the experimental setup). In a typical experiment, the liquid reactant solution and gaseous hydrogen are combined in a microstructured gas/ liquid mixer. The resulting reaction mixture is then passed over a heated catalyst bed packed into a 50 mL reactor tube with 10.2 mm ID. The reaction pressure is established by a back-pressure retention valve installed following the reactor outlet. On exiting the pressurized part of the setup, the product stream is collected in either a nitrogen-purged product or waste container. Two valves (V16 and V17 in Figure 4) installed after the back-pressure regulator allow for incorporation of an online monitoring module prior to product collection.

Table 2 summarizes the results obtained for the continuous-flow hydrogenation of DIM-NA over Pt(Fe)/C<sup>gran</sup>.

The experiments were performed with 10.7 g of the irondoped Pt catalyst loaded into the heated part of the reactor tube giving a catalyst bed volume of 30 mL. Entries 1–3 (Table 2) show the results of a 100 min experimental run during which the process temperature and flow rate were varied. The



Figure 4. Reactor setup for continuous hydrogenation (see the Supporting Information, Figure S4 for a representation including a picture).





Table 2 Summ	arv of the re	sults obtained	for the continuous	hydrogenation of DIM-	NA over the 1.9	6 Pt(Fe)/C <sup>gran</sup> ca	talvst [a]
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Entry	Flow rate [mL/min]	Catalyst workload [mmol( <b>1</b> )/{g(cat.) min}]	p [bar]	Т [°С]	X( <b>1</b> ) <sup>[b]</sup> [%]	S( <b>2</b> ) <sup>[b]</sup> [%]	S( <b>3</b> ) <sup>[b]</sup> [%]	S(other) <sup>[b]</sup> [%]	P( <b>2</b> ) <sup>[c]</sup> [g( <b>2</b> )/h]
1	10 <sup>[d]</sup>	0.094	40	40-43 <sup>[e]</sup>	99.1	99.0	0.6	0.4	23.2
2	10 <sup>[d]</sup>	0.094	40	60	>99.9	98.7	0.9	0.5	23.3
3	12 <sup>[d]</sup>	0.112	40	60	99.6	98.8	0.8	0.4	27.9
4	10 <sup>[f]</sup>	0.187	60	60	99.7	99.4	0.5	0.0	46.9
5	10 <sup>[f]</sup>	0.187	60	80	99.6	98.9	1.1	0.0	46.6

[a] 10.7 g of 1 % Pt(Fe)/ $C^{gran}$  granules loaded into the reactor tube gave a catalyst bed volume of 30 mL. [b] Conversion (*X*) and selectivity (*S*) were derived from the HPLC area% (see the Supporting Information). [c] Productivity (*P*). [d] A 0.1 m solution of **1** in THF/H<sub>2</sub>O (95:5, v/v) was processed, 6.0 equiv. H<sub>2</sub> were applied. [e] The temperature of the heating fluid increased slightly during the experiment. [f] A 0.2 m solution of **1** was processed, 3.4 equiv. H<sub>2</sub> were applied.

compositions of the product mixtures were determined by HPLC analysis of samples taken at regular time intervals after reaching stationary reactor output for a given set of process parameters (ensured by unchanged compositions of sequential product samples, see the Exp. Sect.). Passing a 0.1 M DIM-NA solution in THF/H<sub>2</sub>O (95:5, v:v) at 40 °C and 40 bar at 10 mL/ min over the catalyst bed in the presence of excess H<sub>2</sub> gas (Table 2, Entry 1) led to 99.1 % conversion. No pressure drops were observed at the applied liquid and gas flow rates on comparing the reactor inlet pressure with the applied back pressure. The selectivity of the reaction was excellent, with only 0.6 % deiodinated side-product 3 and negligible amounts (0.4 %) of other byproducts in the product solution (see Figure S5 in the Supporting Information). Deiodination was, therefore, considerably lower than in the case of the hydrogenation of 4 (5.3 % aniline at 97.8 % conversion; Figure 2), but that reaction was performed at a higher temperature and throughput. The productivity of DIM-DAB was P = 23.2 g(2)/h under these conditions (Table 2, Entry 1), as calculated from the concentration, flow rate, conversion, and selectivity. Accordingly, running a DIM-NA hydrogenation process according to Entry 1 (Table 2) allows for the simple synthesis of several hundred grams of raw DIM-DAB in an ordinary laboratory hood within a couple of hours. The low residual amounts of starting material and sideproducts enable an easy purification by crystallization.<sup>[11]</sup> We isolated 4.9 g of raw material by solvent evaporation after a collection period of about 15 min, and HPLC analysis gave the same composition as for the reactor sample [i.e., X = 99.3 %, S(2) = 99.5 %, S(3) = 0.5 %], thereby confirming a stable and stationary reactor output during this period (see Figure S6). Increasing the process temperature to 60 °C led to full DIM-NA conversion without any detectable amounts of 1 in the product solution (Table 2, Entry 2; see Figure S7). Deiodination was slightly higher (0.9 %) under these conditions, which is a consequence of both the higher temperature and some excess catalyst bed, which according to the discussion above, in the presence of excess H<sub>2</sub> triggers the dehalogenation follow-up reaction. At higher throughput, that is, upon increasing the flow rate to 12 mL/min but maintaining constant the reactor pressure and temperature (Table 2, Entry 3), conversion and deiodination dropped to 99.6 % and  $S(\mathbf{3}) = 0.8$  %, respectively, which is in accord with expectations. Under these conditions, P(2) increased to 27.9 g/h. To further increase the productivity of the process, a higher-concentrated reactant solution was employed. At 10 mL/min, 60 bar, and 60 °C, a 0.2 м DIM-NA reactant solution was hydrogenated with 99.7 % conversion and

only S(3) = 0.5 % dehalogenated side-product (Table 2, Entry 4). No further side-products were detected by HPLC (see Figure S8). This reactor output corresponds to a productivity P(2) =46.9 g/h, which was confirmed by analysis of the crude product (approx. 10 g) isolated after a collection period of about 15 min (see Figure S9). The solid material was found to contain minor amounts of Pt (6 ppm; ICP-OES), which indicates some Pt leaching, but overall it can be considered a rather small amount for an isolated crude solid material.<sup>[15]</sup> Surprisingly, increasing the process temperature to 80 °C did not lead to full conversion of 1 (Table 2, Entry 5). Instead, DIM-NA conversion remained unchanged (99.6 %), and there was a notably higher degree of deiodination [S(3) = 1.1 %]. Greater dehalogenation can be expected from higher reaction temperatures at a given conversion. The lack of increase of DIM-NA conversion at higher temperature may be an effect of catalyst deactivation hitherto unnoted due to comparatively short experimental runs and collection times. However, it matches observations made during catalyst screening experiments with 1-iodo-4-nitrobenzene (Figure 2).

#### **Online Monitoring**

Although the Pt(Fe)/C<sup>gran</sup> catalyst exhibits very good selectivity for DIM-NA hydrogenation at high conversions, it suffers from deactivation. As discussed above, processing a reaction that is characterized by the combination of a selectivity challenge due to a follow-up reaction, and a deactivating catalyst requires a quick-responding, efficient, online-monitoring tool to recognize conversions dropping below a predetermined limit. In such cases, the residence time can be adapted to reconstitute the targeted conversion without interrupting the entire conti-process. In the present case, up to 2 % of starting material can be tolerated in the raw product to minimize the formation of impurity 3. At the same time, online monitoring has to ensure that the conversion remains just at (or closely below) 100 % to limit the occurrence of undesired overhydrogenation. The pronounced color difference between the starting nitro compound 1 (yellow) and the amino product 2 (colorless; see Figure S10 in the Supporting Information) makes UV/Vis spectroscopy a suitable tool for online-monitoring of the conversion of the reaction. A UV/Vis detection module can be easily integrated into a continuous product stream, allowing for fast analysis at specific wavelengths. Accordingly, the experimental setup was extended by incorporating a UV/Vis flow cell and



detector into the depressurized part prior to product collection (Figure 4 and Figure S4). Because the presence of hydrogen gas affects UV detection, the product stream was passed through an inline gas/liquid phase separator before entering the flow cell (see Figure S4).<sup>[11]</sup> On comparing the full-range UV/Vis spectra of diluted and more concentrated (0.1, 0.2 M) solutions of starting material 1 and product 2, we selected 425 nm as a suitable wavelength to monitor the concentration of (residual) DIM-NA in the product stream (see Figure S11). The UV/Vis absorption was calibrated externally with model mixtures of 1 and **2** in THF/H<sub>2</sub>O, mimicking conversions in the range of 95-100 %at the concentration level of interest (see Figure S12), to allow for immediate determination of the actual conversion from the absorption recorded online. The functionality of the new online-monitoring module was checked within a conti-hydrogenation experiment conducted in the 50 mL reactor by pumping a 0.1 M DIM-NA (1) solution at various flow rates through the catalyst bed (Table 3).

Table 3. Process conditions applied in the continuous hydrogenation of DIM-NA (1) with online conversion control. c(1) = 0.1 M in THF/H<sub>2</sub>O (95:5, v/v), T = 40 °C, p = 40 bar, 3.4 equiv. H<sub>2</sub> (6.1, 7.6, 9.1 L/h).

TOS <sup>[a]</sup> [min]	Flow rate <sup>[b]</sup> [mL/min]	Catalyst workload [mmol( <b>1</b> )/{g(cat.) min}]
1–67	12	0.087
67-121	15	0.108
121–165	18	0.130

[a] Time on stream. [b] Liquid flow rate (DIM-NA solution).

The reactor setup was first purged with pure solvent, and the experiment was subsequently initiated (t = 0 in Figure 5) by applying a liquid flow rate of 12 mL/min. After an equilibration period of approximately 12 min, full DIM-NA conversion (Figure 5) was achieved (as indicated by the online UV/Vis absorption values; see Figure S13 in the Supporting Information). However, within the following 55 min, the conversion steadily dropped to 99.5 % (revealed by a continuously increasing UV/ Vis absorption). This result points to a slow but ongoing catalyst deactivation, which, as in the case of the hydrogenation of 4 (Figure 2), may result from the combined effects of Pt leaching (see above) and product inhibition due to adsorption of the product amine at the metal surface.<sup>[14,16]</sup> The flow rate was then raised to 15 mL/min, and, as expected, the DIM-NA conversion decreased as a consequence of the reduced residence time of the reactants over the catalyst bed. As can be seen in Figure 5 (and Figure S13), the reactor output quickly adapted to the flow-rate change, that is, the drop in conversion from  $X^{UV}$  = 99.5 % (t = 69 min) to  $X^{UV} = 98.4$  % (t = 73 min) occurred within only 4 min. Ongoing catalyst deactivation is reflected by the UV/Vis absorption profile recorded over the entire 54 min during which the process was run at 15 mL/min; the conversion ultimately dropped to  $X^{UV} = 97.7$  % (at t = 121 min). Eventually, the liquid flow rate was increased to 18 mL/min, and again, the resulting change in conversion as well as the ongoing catalyst deactivation are nicely reflected by the online UV/Vis absorption profile (Figures 5 and S13).

The accuracy of the online UV/Vis conversion determination was verified by HPLC analysis of product samples taken at dif-





Figure 5. Online conversion control of the DIM-NA hydrogenation by UV/Vis spectroscopy. HPLC analytical results obtained from individual samples taken during the process are superimposed on the respective TOS (blue marks; Table 4).

ferent times during the experiment. Although the results from online analysis and offline HPLC were generally in good agreement (Table 4), the conversions determined by HPLC analysis were found to be systematically lower than those derived from online UV absorption (Figure 5, Table 4), with slightly higher discrepancies (≤1.0 %) at around 95 % conversion than at 99 % conversion (≤0.3 %). To further improve the agreement between the two techniques, calibration of the UV/Vis online absorption system should be performed with the corresponding offline HPLC analyses rather than by using model sample mixtures. Catalyst deactivation reached 1.8 % over the entire experimental runtime (165 min) at an average catalyst workload of 0.11 mmol(1)/{g(cat.) min}. This compares well with the observations made for the Pt(Fe)/C<sup>gran</sup> catalyst in the catalyst screening pre-study performed on 1-iodo-4-nitrobenzene (Table 1, Figure 2). In that case, 2.2 % deactivation occurred at 0.43 mmol(4)/{g(cat.) min} within 180 min.

Table 4. Comparison of DIM-NA conversions determined by online UV/Vis monitoring and offline HPLC analysis.

TOS [min]	Flow rate [mL/min]	UV <sup>425</sup> [a.u.] <sup>[a]</sup>	X(UV <sup>425</sup> ) [%]	X(HPLC) [%]
45	12	0.058	99.7	99.4
57	12	0.068	99.5	99.3
67	12	0.074	99.5	99.2
103	15	0.199	97.9	97.3
112	15	0.211	97.7	97.2
121	15	0.216	97.7	97.1
151	18	0.381	95.6	94.6
159	18	0.394	95.4	94.5
165	18	0.397	95.4	94.4

[a] Absorption at 425 nm, see Figure S13 in the Supporting Information.

The online-monitoring experiment clearly shows that variations in the DIM-NA conversion (as induced by changes in flow rate and catalyst deactivation in the present case) can be easily and quickly detected in situ by UV/Vis spectroscopy. Thus, if as a consequence of catalyst deactivation the conversion drops below a specific limit, the targeted range can be easily readjusted by adapting the flow rate to the required UV/Vis absorption.



## Conclusions

We have shown that hydrogenation of the iodo-nitroaromatic API precursor DIM-NA (1) to the corresponding aniline DIM-DAB (2) can be successfully achieved in the presence of 1 % Pt(Fe)/C in a continuous process on a preparative scale. The pronounced selectivity challenge of this reaction, arising both from the stepwise, six-electron reduction of the nitro functional group and a follow-up deiodination reaction of the product, poses high demands on the catalyst and process conditions if high product yields are to be achieved. Five Pt catalysts with different dopants and morphologies of the carbon support (granules or extrudates) were evaluated by employing a fixed-bed reactor. We first assessed their performance in the conti-hydrogenation of iodo-nitroaromatics by using 1-iodo-4-nitrobenzene (4) as the substrate. In a 5 mL flow reactor, 1 % Pt(Fe)/Cgran was identified as the best catalyst both in terms of selectivity and stability. Subsequently, we used this material for the successful contihydrogenation of DIM-NA on a 50 mL reactor scale. Excellent selectivities at >99 % conversion and productivities of up to 47 g(DIM-DAB)/h were achieved by employing 0.1 or 0.2 м reactant solutions in THF/H<sub>2</sub>O. Online UV/Vis spectroscopy proved to be a useful tool for conversion control, allowing for in situ compensation of the effects of catalyst deactivation by flowrate adaptation.

The combined challenges of catalyst deactivation and selectivity resulting from the presence of a side-reaction following product formation during continuous processing were evaluated in depth and the consequences analyzed for three different scenarios.

## **Experimental Section**

**General:** DIM-NA (1), DIM-DAB (2), and deiodo-DIM-DAB (3) were provided by Bayer AG and used as received. 1-lodo-4-nitrobenzene (4; Sigma–Aldrich, Lot STBD1156V), 4-iodoaniline (5; TCI, Lot KCWYG-RR), and aniline (6; Sigma–Aldrich, Lot 10420MD) were purchased from commercial suppliers. Pt(Fe)/C<sup>gran</sup> and Pt(V)/C<sup>gran</sup> were obtained from Heraeus. Pt(Fe)/C<sup>extr</sup>, Pt(V)/C<sup>extr</sup>, and Pt/C<sup>extr</sup> were provided by Chimet. The solvents (THF: Acros, 99.6 %, stabilized with butylated hydroxytoluene, BHT; acetonitrile: LC-MS Chromasolv) were purchased from commercial sources. H<sub>2</sub> (99.999 %) was purchased from Air Liquide. All materials were used without further purification. H<sub>3</sub>PO<sub>4</sub> and KH<sub>2</sub>PO<sub>4</sub> were used for buffer preparation. Deionized water, used for the preparation of the reactant solution and the HPLC buffer solution, was purified by employing a Millipore Milli-Q<sup>®</sup> system.

**Procedure for Catalyst Stability Tests:** The catalyst cartridge of a commercial Ehrfeld cartridge reactor 240 was loaded as follows (see Figure S2 in the Supporting Information): glass wool (0.150 g), the corresponding catalyst [Pt(Fe)/C<sup>gran</sup>, Pt(V)/C<sup>gran</sup>, Pt(Fe)/C<sup>extr</sup>, Pt(V)/C<sup>extr</sup>, Pt/C<sup>extr</sup>], as indicated in Table 1, glass wool (0.150 g), glass beads 0.75–1.0 mm (ca. 2.4 g), glass wool (0.150 g), giving a catalyst bed volume of 2.75 mL (3.5 × 1.0 cm). The desired reaction conditions (*T*, *p*, liquid flow rate, H<sub>2</sub> flow rate) were established by using THF/H<sub>2</sub>O (95:5, v/v) as the solvent. After catalyst activation for 30 min under these conditions, a 0.1 m solution of 1-iodo-4-nitrobenzene (4) in THF/H<sub>2</sub>O was passed over the catalyst bed at the desired flow rate for a total of 12 h with an interruption after 5 h, during which the catalyst was stored in THF/H<sub>2</sub>O overnight.



Hydrogenation was performed at 40 bar, 80 °C, and flow rates individually adapted to the amount of the respective catalyst for a consistent catalyst workload of 0.43 mmol(**4**)/{g(cat.) min} (Table 1). At the end of the experiment, the system pressure was released, heating switched off, and the reactor purged with THF/H<sub>2</sub>O (at 2 mL/min) while cooling to room temperature for 1 h.

Procedure for the Continuous Hydrogenation of DIM-NA: The continuous hydrogenation of DIM-NA was performed in a 50 mL reactor tube (L = 60.9 cm, ID = 1.02 cm) installed in the experimental setup shown in Figure 4 and described in the Supporting Information (Figure S4). The heated part of the reactor tube was loaded with 10.7 g of fresh 1 % Pt(Fe)/C<sup>gran</sup> resulting in a catalyst bed with a volume of 29.9 mL (L = 36.6 cm). The reactor volume not covered by the heating medium was filled with glass beads. Before starting the hydrogenation, the reactor was purged for 10 min with a mixture of THF/H<sub>2</sub>O (10 mL/min) and N<sub>2</sub> (25 L/h) keeping the backpressure valve at atmospheric pressure while heating to the corresponding reaction temperature (Table 2; the reaction temperature was typically adjusted at thermocouple T08, see Figure 4 and Figure S4). After reaching the desired temperature, the nitrogen flow was replaced by  $H_2$  (10 L/h), and the back pressure was gradually increased to the desired value (Table 2) maintaining the liquid flow rate (10 mL/min) for additional 10 min. After catalyst activation under the reaction conditions, the liquid feed was switched to the reactant solution (0.1 or 0.2 M DIM-NA in THF/H<sub>2</sub>O, 95:5, v/v), and the H<sub>2</sub> flow was adjusted accordingly (Table 2). The composition of the reaction mixture was analyzed by HPLC (see the Supporting Information for details) in regular intervals to verify the steady state of the reactor output. The same procedure was repeated for each set of reaction parameters. The product solution was collected in a nitrogen-purged phase segregator from which the sample solution was removed for further isolation if desired (see below). At the end of the experiment, the reactor was purged with THF/H<sub>2</sub>O (10 mL/ min)/N<sub>2</sub> (25 L/h) and the back pressure was gradually released to atmospheric pressure while cooling to room temperature. The product solutions obtained from process conditions E1 and E4 (Table 2) were collected during approximately 15 min. Solvent removal under reduced pressure yielded 4.9 (81 %) and 10.2 g (86 %) of a grayish crude product, respectively (see Figures S6 and S9 in the Supporting Information). Yield losses were due to sampling from the product stream during the collection period. Analytical data for DIM-DAB (2):  $^{[9e]}$  <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.37 (dd, J = 10.6, 1.9 Hz), 7.22 (dt, J = 8.5, 1.3 Hz, 1 H), 6.61 (dd, J = 11.6, 7.0 Hz, 1 H), 6.23 (dt, J = 9.1, 0.8 Hz, 1 H), 5.34 (s, 1 H), 3.85 (s, 3 H) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 151.69 (d, J = 245.8 Hz), 142.46 (d, J = 12.0 Hz), 142.44 (dd, J = 237.7, 13.0 Hz), 141.23 (d, J = 228.9, 13.4 Hz), 133.46 (d, J = 3.4 Hz), 133.01 (d, J = 10.9 Hz), 130.49 (s), 123.87 (d, J = 20.8 Hz), 116.36 (d, J = 2.9 Hz), 114.38 (d, J = 14.6 Hz), 98.17 (d, J = 22.4 Hz), 78.75 (d, J = 7.7 Hz), 56.09 (s) ppm. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -132.15 (s, 1 F), -150.46 (d, J = 22.9 Hz, 1 F), -157.13 (d, J = 23.9 Hz, 1 F) ppm. HRMS (ESI): calcd. for C<sub>13</sub>H<sub>11</sub>F<sub>3</sub>IN<sub>2</sub>O 394.9868 [M + H]+; found 394.9882.

**Procedure for the Continuous Hydrogenation of DIM-NA with Online Monitoring:** DIM-NA hydrogenation was carried out by using the experimental setup shown in Figure 4, extended to UV/Vis online monitoring (see Figure S4 in the Supporting Information). A 50 mL reactor tube (L = 79.0 cm, ID = 0.9 cm) was loaded with 13.8 g of fresh catalyst giving a catalyst bed volume of 44.3 mL (L = 69.7). A 0.1 m DIM-NA solution in THF/H<sub>2</sub>O (95:5, v:v) was hydrogenated under the conditions given in Table 3. The conversion of the staring material was monitored online based on the UV absorption recorded at 425 nm as well as offline by HPLC (see the Supporting Information for details).



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**Keywords:** Flow chemistry · Hydrogenation · Heterogeneous catalysis · Nitroarenes · Online monitoring · UV/Vis spectroscopy

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