

# **Continuous Selective Hydrogenation of Refametinib** Iodo-nitroaniline Key Intermediate DIM-NA over Raney Cobalt Catalyst at kg/day Scale with Online UV–Visible Conversion Control

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**S** Supporting Information

ABSTRACT: The continuous selective hydrogenation of the iodo-nitroaromatic refametinib active pharmaceutical ingredient (API) intermediate (2,3-difluoro-5-methoxy-6-nitro-phenyl)-(2-fluoro-4-iodo-phenyl)-amine (DIM-NA) to the corresponding iodo-aniline 3,4-difluoro-N2-(2-fluoro-4-iodo-phenyl)-6-methoxy-benzene-1,2-diamine (DIM-DAB) was investigated using a conventional Raney cobalt catalyst in a cocurrent trickle-bed reactor. Suitable reaction conditions targeting full conversion and high selectivity, that is, low degrees of hydro-dehalogenation of the labile iodine substituent, were evaluated in investigations employing a short 4 mL screening reactor. The process was then transferred to a longer 40 mL reactor. Raney cobalt was found to be a highly selective catalyst, yielding only very small amounts of the desiodinated aniline desiodo-DIM-DAB or other side products. Productivities up to 144 g/h crude DIM-DAB were achieved operating the 40 mL reactor with a 0.2 M reactant solution in the presence of 3.4 equiv of  $H_2$  at 60 °C. Inlet pressure resulting from the flow rate increase was identified as a key parameter for successful throughput maximization. One kilogram of starting material was eventually converted to DIM-DAB in high yield and excellent quality within 8 h runtime. Online monitoring of the UV-vis absorption of the product stream allowed for conversion control and fast detection of process variations. Compared to the available DIM-NA batch reduction procedures, processing in continuous flow proves convincing by the safe implementation and reusability of the Raney type catalyst within a strongly intensified and highly selective process.

ontinuous processing represents a long-known industrial reaction engineering technology that has been widely employed for the large-scale production of bulk chemicals. Recently, increasing attention to this method of processing is arising also in the pharmaceutical industry where-depending on the respective phase of drug development-APIs (active pharmaceutical ingredients) and their intermediates are synthesized in quantities ranging from the gram scale in the preclinical stage to kg/year (early clinical phase) up to tons per year in the case of successful market entry.<sup>2</sup> Flow syntheses have been applied for selected transformations of multistep API synthesis sequences,<sup>3</sup> but also for the combination of several sequential reactions or process steps involving inline phase separation or solvent exchange.<sup>4</sup> The latter has been further elaborated to integrated drug substance and product manufacturing within a single continuous process including formulation procedures, thereby reducing the overall number of unit operations and thus the manufacturing time.<sup>5</sup> Accordingly, there is a pronounced current impetus both in academia and industry to further explore the possible advantages of converting API syntheses from (sequential) batch processes into continuous flow.<sup>4a</sup>

At the industrial scale, standard liquid phase organic transformations are usually performed in batch, the use of standard multipurpose plant equipment still representing the dominant approach for the synthesis of pharmaceutical compounds. However, for specific chemical transformations or reaction sequences, the advantages associated with continuous processing in micro- or mesoreactors appear evident. For example, reactions requiring or benefiting from elevated pressures can be accomplished as more cost-effective in a (tubular) flow reactor than a pressurized batch reactor, especially at a larger scale.<sup>6</sup> The pressure in a pilot or production scale vessel may be either as low as 2-3 bar (inducing prolonged reaction times) or will require cost intensive specialized equipment (autoclave) to meet technical and safety requirements. Compared to batch processing, strongly exothermic reactions will further benefit from the more efficient heat transfer of a flow reactor due to the much higher surface to volume ratio.<sup>2a,7</sup> Narrow temperature profiles resulting in consistent quality and yield of the isolated product often follow. Improved mixing and enhanced mass transfer represent additional advantages typically attributed to continuous processing.<sup>8,9</sup>

Hydrogenation reactions belong to the reaction classes particularly exploiting the advantages associated with continuous processing, as they are often strongly exothermic in nature and benefit from high reaction pressures.3b,6,9d If no enantioselectivity has to be considered, hydrogenations are

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<sup>a</sup>These two compounds are intermediates within the synthesis of refametinib. The side product desiodo-DIM-DAB (3) results from desiodination.

routinely conducted in the presence of a heterogeneous catalyst. In spite of the considerable safety risk associated with their handling, low-cost sponge metal type catalysts as Raney nickel (Ra–Ni) or cobalt (Ra–Co) are often a suitable choice for the hydrogenation of a wide range of organic compounds both at laboratory and industrial scales.<sup>10</sup> In addition, in terms of abundance and sustainability, these transition metals might also be regarded as attractive compared to precious metal catalysts.<sup>11</sup> Currently, supported precious metal catalysts M/S (e.g., M = Pt, Pd, Ru; S = C, Al<sub>2</sub>O<sub>3</sub>, SiO<sub>2</sub>) are employed in many cases, as they allow for mild reaction conditions and fast transformation.<sup>12</sup>

In a previous study, we showed Raney cobalt to be a promising catalyst for the selective hydrogenation of the aromatic nitro functional group to the primary amine. 1-Iodo-4nitrobenzene was used as a model substrate for APIs containing iodine substituents, which are very labile with regard to hydro-dehalogenation.<sup>13,14</sup> Due to its extraordinarily high exothermicity, the reduction of (halo)nitroarenes ( $\Delta H \sim 544$  kJ/mol in the liquid phase) is especially challenging in terms of (chemo)selectivity, as higher reaction temperatures usually favor dehalogenation.<sup>15</sup> Hence, the above-mentioned heat exchange qualities of a continuous flow reactor strongly encourage its use for such a transformation. It should be noted, however, that side products may not only result from hydro-dehalogenation, but also from the stepwise and complex mechanism of the six-electron nitroarene reduction.

Herein, we present investigations on the application of Ra– Co for selective continuous hydrogenation of the industrial API intermediate (2,3-difluoro-5-methoxy-6-nitro-phenyl)-(2-fluoro-4-iodo-phenyl)-amine (DIM-NA, 1, Scheme 1).

DIM-NA (1) represents a key intermediate in the multistep synthesis of the antitumor agent *refametinib* (BAY 86-9766, also known as RDEA119, Scheme 1).<sup>16</sup> Refametinib is a highly potent and selective MEK1/2 inhibitor<sup>17</sup> currently undergoing phase II clinical trials for late stage cancer treatment.<sup>18</sup>

DIM-NA (1) comprises two aromatic rings linked via an amine bridge (Scheme 1). In addition to the nitro group targeted for reduction, the presence of an iodine substituent introduces a selectivity challenge for catalytic hydrogenation, as this substituent is highly labile with regard to hydrodehalogenation. An even more sensitive function in the reaction system, however, is the iodine substituent in the hydrogenation product 3,4-difluoro-N2-(2-fluoro-4-iodo-phenyl)-6-methoxy-benzene-1,2-diamine (DIM-DAB, 2), as this more electron-rich aniline is more prone to dehalogenation than its halonitroaromatic precursor.

Consequently, the nitro reduction step within the synthesis of refametinib (Scheme 1) was originally performed with a large stoichiometric excess of reducing agents such as iron<sup>19</sup> or

zinc.<sup>20</sup> Albeit facilitating selective reduction, the use of these reagents entails not only significant amounts of metal waste byproduct but also the need for aqueous workup.

When DIM-DAB (2) is synthesized by hydrogenation, the desiodinated side product desiodo-DIM-DAB (3) can form via hydro-desiodination in a follow-up side reaction upon DIM-DAB (2) formation. The latter, therefore, is most pronounced at high conversion and strongly depends on the catalyst employed as it was previously demonstrated on the model substrate 1-iodo-4-nitrobenzene.<sup>13</sup> The required product specifications limit the tolerable concentrations of the desiodinated side product in (subsequently crystallized) DIM-DAB (2) to amounts  $\leq 0.13$  wt %. Due to a higher purge factor of the starting material DIM-NA (1) in the crystallization step ( $\sim$ 2% tolerated) as compared to the overreacted side product desiodo derivative (3), it was not required to achieve full conversion (X > 99.9%). Accordingly,  $X \ge 98\%$  was chosen as conversion target to limit desiodo-DIM-DAB (3) formation. Ra-Co was employed as a fixed bed catalyst in an experimental setup offering both a small scale, 4 mL reactor for economic screening studies with respect to the consumption of starting material and a larger, 40 mL reactor with the same diameter for preparative runs.<sup>21</sup> After orienting experiments in the 4 mL reactor, the process was transferred to the 40 mL reactor for throughput maximization and to study robustness toward further scale-up. Finally, 1 kg of DIM-NA (1) was converted into DIM-DAB (2) within a long-term experiment of 8 h duration including online conversion control by UV-vis spectroscopy. Our investigation therefore also serves as a case study for the successful development of a flow process for continuous hydrogenation over a heterogeneous catalyst at a kilogram per day scale.

# RESULTS AND DISCUSSION

In a continuous liquid-phase hydrogenation process, a heterogeneous catalyst is conveniently incorporated as a fixed bed, which can provide good mass transfer between the three phases involved and furthermore implements an intrinsic catalyst separation step.<sup>22</sup> On the other side, pumping a gas/ liquid mixture through the catalyst bed can result in reactor inlet pressures higher than the pressure defined by the back pressure regulator. Such phenomenon will result in a pressure gradient over the catalyst bed (and therefore nonuniform process conditions) and may set a physical upper limit to the throughput achievable in the process. To avoid the incidence of inlet pressure buildup, careful adaption of the catalyst's particle size to the dimensions of the reactor and the targeted process conditions is therefore required.<sup>23</sup> These circumstances render the application of pristine Raney type catalysts in continuous hydrogenation processes based on a fixed bed reactor



Figure 1. Reactor setup for continuous hydrogenation used in this study.

challenging as these catalysts can be regarded as fine powders (average particle size, e.g.,  $d(50) = 40 \ \mu m$  for Ra–Co)<sup>24</sup> and cannot readily be converted into a morphology with larger particles. In continuous processes Ra-type catalysts, therefore, have been usually employed as slurry in a continuously stirred tank reactor (CSTR).<sup>25</sup> In this context, the development of a flow compatible encapsulated Co catalyst on agglomerated carbon nanotubes ( $d(50) = 564 \mu m$ ), CoNGr@CNT, has been investigated within our group.<sup>26a</sup> In a related study, the continuous hydrogenation of a nitro stilbene derivative has been achieved employing nitrogen-doped carbon nanotubes (NCNT) containing cobalt residues as catalyst.<sup>26b</sup> As wellknown alternative, Ra-Ni catalysts suitable for a fixed-bed application have been prepared by immobilization within porous polymers.<sup>27</sup> More recently, a novel type of monoliths containing Ra-Ni deposited on metal foils have been developed, and their high potential in continuous hydrogenation has been demonstrated.<sup>28</sup>

**Reactor Setup.** A diagram of the reactor setup used is depicted in Figure 1. It contains two reactor tubes switchable installed in parallel providing approximately 4 and 40 mL catalyst bed volumes, respectively, which allows for optional investigations at small or larger reaction scales (see SI for a more detailed description of the experimental setup including photos, Figure S2). On exiting the pressurized part of the reactor, a bypass in the product stream allows for the integration of an online monitoring module (V16, V17). The monitoring and control of selected process parameters is accomplished by a HiTec Zang process control box (LabManager)<sup>29</sup> also providing a variety of electronic safety measures (e.g., alarming or automatic process shutdown).

Pretesting Continuous DIM-NA (1) Hydrogenation at 4 mL Reactor Scale. In a first step, handling of the pyrophoric Ra–Co catalyst as well as suitable reaction conditions for the selective hydrogenation of DIM-NA (1) to DIM-DAB (2) (Scheme 1) were explored using the 4 mL reactor of the experimental setup described in the previous section (Figure 1), targeting nearly full conversion ( $\geq$ 98% consumption of starting material). For this purpose the heated part of reactor was loaded with 12.1 g of Ra–Co slurry (Actimet-Co), which according to the technical datasheet should correspond to about 6.1 g of net catalyst mass,<sup>24</sup> giving a catalyst bed of 4.2 mL (SI, Table S1).

A comparatively moderate back pressure of 40 bar was chosen for the continuous hydrogenation of a 0.1 M DIM-NA (1) solution in THF/water (95:5 v/v).<sup>13</sup> Maintaining a constant flow rate (i.e., catalyst workload [mmol(1)/(g(cat)·min)]), the influence of reaction temperature on product composition was investigated (Table 1, exp. I–III). No significant inlet pressure buildup was observed under the applied conditions (see SI Figure S3 for pressure buildup characteristics of the 4 mL reactor). Product samples were taken after a stationary state was reached and analyzed offline by HPLC. The reaction temperature was found to have a

Table 1. Continuous Hydrogenation of DIM-NA (1) over Ra–Co Catalyst in 4 mL Reactor<sup>a</sup>

exp. <sup>b</sup>	T (°C)	conversion, X (%)	desiodo-DIM- DAB (3) (wt %) <sup>c</sup>	other $[\Sigma(ar\%)]^c$	inlet pressure (bar)
Ι	40	92	1.2	5.5	40
II	60	93	1.6	1.7	40
III	80	>99	1.8	1.8	40

<sup>*a*</sup>c(DIM-NA) = 0.1 mol/L in THF/H<sub>2</sub>O 95:5 (v/v), 40 bar back pressure. <sup>*b*</sup>12.1 g of Raney-Co catalyst (≈6.1 g net), cat. bed length: 6.6 cm, cat. bed volume: 4.2 mL, 2.1 mL/min liquid flow rate, superficial flow velocity  $u_{s,l}$  = 3.3 cm/min, catalyst workload ≈ 0.034 mmol(1)/(g(cat)·min), 1.9 nL/h H<sub>2</sub> (6 equiv),  $u_{s,g}$  = 49.8 cm/min; all experiments were performed with the same catalyst load. <sup>*c*</sup>See the SI.

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pronounced influence on the reaction course. While 92% conversion of 1 was already achieved at 40 °C, the selectivity of the reaction was rather poor with 1.2 wt % desiodo-DIM-DAB (3) and 5.5 area % (HPLC) summarizing additional side products. Surprisingly, increasing the temperature by 20 °C did not have a major influence on DIM-NA (1) conversion but rather on the selectivity of the reaction. The amount of desiodinated side product 3 slightly increased from 1.2 to 1.6 wt %, while the amount of the further side products strongly decreased to 1.7 area % (HPLC). This observation may indicate that side reactions resulting from intermediate accumulation of nitroso- or hydroxylamine intermediates in the course of the reaction<sup>15</sup> are suppressed at the higher temperatures due to increased reaction rates. Eventually, full DIM-NA (1) conversion was reached at 80 °C. The amount of 3 further increased (1.8 wt %), while the formation of other side products remained approximately constant. From the results obtained, it was deduced that temperatures  $\geq 60$  °C are required to suppress side product formation other than desiodination. We therefore decided to apply 60  $^\circ C$  and 40 bar in the following hydrogenation experiment at 40 mL reactor scale.

Continuous DIM-NA (1) Hydrogenation at 40 mL Reactor Scale. A sample of 70 g of Ra–Co slurry (50% in water,  $\approx$ 35 g net catalyst) was loaded into the 40 mL reactor tube resulting in a catalyst bed of 68 cm length and 43 mL volume (see SI for complete information on reactor tubes),<sup>21</sup> consistent with its original bulk density (0.820 kg/L).<sup>24</sup> In a first step the pressure characteristics of the packed reactor were studied, as some degree of inlet pressure buildup was expected upon the significantly increased reactor length. For this purpose, pure solvent (THF/H<sub>2</sub>O, 95:5 v/v) followed by a solvent/gas mixture was pumped at escalated flow rates through the catalyst bed. As shown in Figure 2, a pronounced inlet



Figure 2. Inlet pressure (against atmosphere) measured on pumping pure solvent or solvent–gas (25 L/h  $N_2$ ) mixtures through a 40 mL reactor tube packed with 70 g of Ra–Co slurry, as recorded for the freshly loaded reactor and after its first use in continuous-flow hydrogenation (exp. 1, Table 2).

pressure buildup resulted from the presence of the fine Ra–Co catalyst bed particles at this reactor scale, e.g., 24 mL/min pure solvent induced 30 bar inlet pressure. In the presence of additional 25 l/h  $N_2$  gas an inlet pressure of already 20 bar was recorded at only 2 mL/min liquid flow rate. On increasing the liquid flow rate (14 mL/min), the inlet pressure quickly reached 41 bar. It was anticipated, however, that such inlet pressure buildup would be less pronounced with (i) a back

pressure applied (SI, Figure S3) and (ii) in the presence of a reactive gas mostly consumed within the reactor tube.

We started investigations on Ra–Co catalyzed continuous DIM-NA (1) hydrogenation at 40 mL reactor scale, pumping a 0.1 M solution in THF/water (95:5 v/v) with a flow rate of 22 mL/min through the catalyst bed at 60 °C and 40 bar backpressure. The liquid flow rate corresponds to a catalyst workload of 0.063 mmol(1)/(g(cat)·min), which is higher than in the related experiments in the 4 mL reactor tube (Table 1, exp. I–III). In order to minimize the expected inlet pressure buildup, the amount of H<sub>2</sub> applied in the process was reduced to 3.4 equiv, close to the stoichiometric ratio (3 equiv theoretically required per nitro to amine reduction). Reaction samples were taken in regular intervals and analyzed offline by HPLC.

The inlet pressure recorded at the beginning of the experiment was 59 bar indicating  $\approx 20$  bar pressure buildup under the applied process conditions. Sample analysis (Table 2) showed that complete DIM-NA (1) conversion had resulted from the applied process conditions, i.e., not even traces of 1 were detected by HPLC. The decreasing extent of desiodination observed for samples 1.1 [8.0 wt % (3)], 1.2 [3.8 wt % (3)], and 1.3 [1.8 wt % (3)] collected within the first 50 min of the process indicates a run-up phase for the Ra–Co catalyst.

Surprisingly, after this initial period, the degree of desiodination increased again [exp. 1.4: 2.2 wt % (3), exp. 1.5: 2.7 wt % (3); Figure 3]. The reason for this behavior is most probably a more pronounced overhydrogenation of DIM-DAB (2) going along with the simultaneous inlet pressure increase from 67 bar at 50 min time on stream (TOS) to 80 bar at 75 min TOS (Figure 3, see further discussion below). The degree of dehalogenation was comparatively high (at low levels of further side products) but comprehensible by the presence of an excess catalyst bed under these forced conditions.

The inlet pressure resulting from the applied process conditions is an intrinsic reaction parameter to be regarded critical in the present context, i.e., the evaluation of the usability of Ra–Co as catalyst for continuous hydrogenation at 40 mL reactor scale. Consequently, the reactor behavior over time was observed in close detail. Figure 3 (right) shows the inlet pressure profile that was recorded during the first hydrogenation experiment at this scale. As mentioned above, at the beginning of the experiment the inlet pressure was 59 bar. It remained stable during the first 30 min of the experiment but then steadily increased reaching 80 bar after 75 min runtime (TOS), at which point this experiment was terminated.

To evaluate if the catalyst bed had suffered from any constitutional changes causing this behavior, a pressure buildup test analogous to the one performed with the freshly loaded reactor was conducted. If applicable, notably different inlet pressure characteristics would be expected. As evident on inspection of Figure 2, there is only a minor difference between the two experiments, suggesting other effects than changes in the catalyst bed responsible for the strong inlet pressure increase observed.

Increasing inlet pressures naturally limit the applicability of the related process as not only changes in the composition of the product mixture can follow but also an intolerably high pressure may be reached. Therefore, for the following experiments it was decided: (i) to increase the concentration of the reactant solution allowing for a reduction of the liquid flow rate and (ii) to reduce the back pressure in order to lower the pressure baseline for the (additional) inlet pressure arising

exp. <sup>b</sup>	T (°C)	conversion $X$ (%)	desiodo-DIM-DAB (3) (wt %) <sup><math>c</math></sup>	other $[\Sigma(ar\%)]^c$	inlet pressure (bar)
1.1 (10 min)	60	>99.9	8.0	0.6	59
1.2 (20 min)	60	>99.9	3.8	0.7	60
1.3 (50 min)	60	>99.9	1.8	0.9	67
1.4 (60 min)	60	>99.9	2.2	0.9	74
1.5 (75 min)	60	>99.9	2.7	0.7	80

Table 2. Continuous Hydrogenation of DIM-NA (1) over Ra-Co Catalyst in 40 mL Reactor<sup>a</sup>

 ${}^{a}c(\text{DIM-NA}) = 0.1 \text{ mol/L in THF/H}_{2}O 95:5 (v/v)$ , 40 bar back pressure.  ${}^{b}70 \text{ g of Raney-Co slurry}$  ( $\approx 35 \text{ g net}$ ), catalyst bed length: 68 cm, catalyst bed volume: 43 mL, 22 mL/min liquid flow rate, superficial flow velocity  $u_{s,l} = 34.6 \text{ cm/min}$ , catalyst workload  $\approx 0.063 \text{ mmol}(1)/(\text{g(cat)}\cdot\text{min})$ , 11.2 nL/h H<sub>2</sub> (3.4 equiv);  $u_{s,g} = 293.4 \text{ cm/min}$ .  ${}^{c}\text{See}$  the SI.



Figure 3. Concentration (left) and inlet pressure (right) profiles for the hydrogenation experiment exp. 1 performed with the freshly loaded 40 mL reactor tube (left). The increase of desiodination over samples 1.3–1.5 parallels the inlet pressure increase from 67 to 80 bar.

during operation. Accordingly, the next experiment (exp. 2, Table 3) was performed with a 0.2 M DIM-NA (1) solution and a back pressure lowered to 20 bar. The overall throughput (11 mL/min, 11 nL/h  $H_2$ ) was kept constant by 50% reduction of the liquid flow rate.

The effect of these measures on the pressure characteristics of the system was as desired (exp. 2, Figure 4): Comparing with



**Figure 4.** Inlet pressure profiles for continuous DIM-NA (1) hydrogenation in the 40 mL reactor at increasing liquid flow rates using a 0.2 M reactant solution in THF/H<sub>2</sub>O (95:5 v/v) and 3.4 equiv of H<sub>2</sub> at 20 bar back pressure. In case of exp. 7 the concentration was 0.4 M (Table 3). The initial higher inlet pressure observed in exp. 5 was an effect of the process start-up.

exp. 1 (Figure 3) a notable inlet pressure reduction (-20 bar) resulted from the combined effects of lower liquid flow rate and back pressure, the pressure remaining stable over 24 min process runtime. As expected, process conditions so closely related to the ones of exp. 1 gave very similar hydrogenation results: there was still full DIM-NA (1) conversion but with a slightly lower degree of dehalogenation (1.6 wt % desiodo-DIM-DAB (3), Table 3), probably following from the lower

inlet and back pressures and the associated reduced amount of overhydrogenation.

As mentioned above, the comparatively high degrees of desiodination observed in exp. 1 and exp. 2 (Table 3) should mostly result from residence times too long for the reaction conditions applied. Once full conversion has been reached along the reactor tube, passing the product solution [consisting mainly of DIM-DAB (2)] through the excess catalyst bed results in subsequent dehalogenation and increased amounts of desiodo-DIM-DAB (3).

To suppress this follow-up reaction, the liquid flow rate was increased by 45% (16 mL/min, exp. 3, Table 3) targeting conversion in the range  $98\% \le X < 100\%$  to allow for a more accurate evaluation of the quality of the Ra-Co catalyst in terms of desiodination selectivity. As expected, a (moderately) higher inlet pressure resulted under these conditions (slightly increasing from 42 to 46 bar over process runtime, Figure 4). Sample analysis by HPLC revealed that still not even traces of DIM-NA (1) could be detected in the product mixture, while desiodination was notably lower than in the experiments before that barely reached the acceptable limit for downstream processing (<1.0 wt % 3). In exp. 3, the residence time was closer to the one required for reaching exactly full conversion, and therefore, the degree of overhydrogenation was lower. It should be noted that the productivity of the process under these conditions was already quite high and corresponds to the formation of 74 g/h DIM-DAB (2).

In the following experiments the flow rates were subsequently increased to 22 mL/min (exp. 4) and 26 mL/min (exp. 5) to further lower the residence time and to explore the effect on selectivity. DIM-NA (1) in a detectable concentration corresponding to 99.9% conversion was first observed in exp. 4. The inlet pressure was in the range of 50–55 bar; the degree of desiodination further dropped to 0.9 wt % desiodo-DIM-DAB (3). Surprisingly, with the even higher flow

exp.	liquid flow (mL/min)	${}^{\rm H_2}_{\rm (nL/h)}$	catalyst workload $[mmol(1)/g(cat) \cdot min]$	IP (bar) <sup>b</sup>	$X (\%)^c$	desiodo-DIM-DAB (3) $(\text{wt \%})^d$	other, $[\Sigma(ar\%)]^d$	DIM-DAB (2) $(g/h)^e$
ŀ	22	11.2	0.063	60-80 <sup>g</sup>	>99.9	1.8-2.7	0.9-0.7	51
2	11	11.2	0.063	40	>99.9	1.6	1.6 <sup>h</sup>	50
3	16	16.2	0.091	42-46 <sup>g</sup>	>99.9	1.0	0.7	74
4	22	22.3	0.126	50-55	99.9	0.9	0.8	100
5	26	26.3	0.149	73	99.7	0.8	0.6	120
6	30	30.3	0.171	74—79 <sup>g</sup>	99.8	0.7	0.7	144
7 <sup>i</sup>	15	30.3	0.171	60	99.9	1.2	1.4	144

Table 3. Summary of Continuous DIM-NA (1) Hydrogenation Experiments Performed at 40 mL Reactor Scale (See SI for Full Experimental Details)<sup>a</sup>

<sup>*a*</sup>Conditions: 70 g of Raney-Co slurry ( $\approx$  35 g net), c(DIM-NA) = 0.2 mol/L in THF/water (95:5 v/v), T = 60 °C, backpressure = 20 bar, 3.4 equiv of H<sub>2</sub>. HPLC samples were taken on reaching stationary reactor output (see SI). All experiments were performed using the same catalyst load. <sup>*b*</sup>Inlet pressure, see also Figures 3 and 4. <sup>*c*</sup>DIM-NA (1) conversion. <sup>*d*</sup>See the SI. <sup>*c*</sup>DIM-DAB (2) reactor output. <sup>*f*</sup>A 0.1 M DIM-NA solution was employed at 40 bar backpressure (Table 1). <sup>*g*</sup>An inlet pressure increase was observed during operation. <sup>*h*</sup>HPLC samples of exp. 2 had a double concentration as usually; therefore, the amount of further side products appears to be more prominent in this experiment. <sup>*i*</sup>A 0.4 M DIM-NA solution was employed.

rate of exp. 5, the conversion only negligibly dropped to 99.7% at 0.8 wt % desiodo-DIM-DAB. The inlet pressure increased to  $\approx$ 73 bar remaining constant during the period of sampling. At a first glance, these findings appeared puzzling, that is, how an 18% increase in flow rate would only result in 0.2% lower conversion when comparing exp. 4 and exp. 5. A probable explanation for this observation and also for the rather dramatic increase in flow rate (11-26 mL/min) required to adjust conversion to just below 100% (considering experiments 2-5) can be found in the concomitantly increased pressure recorded at the reactor inlet, that is, the area where the reaction mixture reaches the catalyst bed and highest hydrogenation rate is to be expected. The pressure then gradually decreases over the catalyst bed until finally reaching the value defined by the back pressure regulator at the reactor exit. Accordingly, the reaction pressure is highest where the DIM-NA (1) concentration is maximal, determining the reaction rate and resulting in higher overall conversions as expected from exclusively considering the flow rate.

To challenge the maximum throughput for this reaction system, the flow rate was further increased to 30 mL/min (Table 3, exp. 6). Under these conditions the inlet pressure reached 79 bar after 30 min time on stream resulting, again, in close to full DIM-NA (1) conversion (99.8%). Under these conditions, the best selectivities regarding both desiodination (0.7 wt % desiodo-DIM-DAB (3)) and formation of further side products (0.7 Ar%) were achieved, while the DIM-DAB (2) productivity reached 144 g/h.

The DIM-DAB (2) productivities and selectivities achieved in exp. 5 and exp. 6 (Table 3) are remarkable, allowing for the preparation of DIM-DAB amounts  $\geq 1$  kg within 8 h, provided stable long-term reactor operation. It should be noted, however, that the increasing inlet pressure encountered in exp. 6 may represent a critical aspect for prolonged operation. We therefore investigated for a more stable pressure situation maintaining the reactor throughput. This was accomplished in exp. 7 (Table 3) by doubling the concentration of the DIM-NA (1) reactant solution to 0.4 M at 50% liquid flow rate (15 mL/ min). The resulting inlet pressure (60 bar) was indeed about 14 bar lower than at the beginning of exp. 6. Moreover, it remained constant for a period of 60 min, now indicating stable operation. Inspection of the analytical results, however, showed that the selectivity of the reaction suffered under these conditions. At 99.9% DIM-NA (1) conversion, 1.2 wt % desiodo-DIM-DAB (3) were present in the product mixture, which is higher than in exp. 4 with 0.9 wt % at the same

conversion. Selectivity might be, however, improved upon further optimization of the process conditions for a 0.4 M reaction mixture.

The extent of Co leaching was assessed in an independent experiment analogous to exp. 5: 28 ppm of Co were detected in the product solution (ICP-OES), 14 g of solid crude product obtained after completely evaporating the solvent from an approximately 7 min collection period contained 470 ppm of Co. In the crystallized product, the amount of Co is significantly lower (see below).

**Implementation of Online Monitoring.** Based on the present findings, we decided to run a longer term experiment targeting conversion of 1 kg DIM-NA (1) within one working day. For this purpose online monitoring the composition of the product mixture deemed us to be not only a reasonable process extension but rather indispensable to ensure high product quality over the whole runtime by real-time identification of, e.g., process instabilities or catalyst deactivation.

Accordingly, suitable analytical methods were evaluated, and the experimental setup eventually extended with an online UV–vis analysis module (Figure 1).

Main target of online analytics was conversion control under process conditions that had been optimized for selectivity (Table 3). In the course of a long-term production run, gradual catalyst deactivation would eventually lead to DIM-NA (1) concentrations above the threshold level defined by the product specifications ( $X(\text{DIM-NA}) \ge 98\%$ ). If noted in time, however, catalyst deactivation can be readily accounted for by adjustment of process parameters as, e.g., flow rate. Similarly, process variations due to temporary malfunction of the gas or liquid feed dosage or inhomogeneity of the catalyst bed with potential (negative) impact on conversion become observable. It should be mentioned that the applied technique does not allow for online selectivity determination of the reaction (i.e., detection of hydrogenation intermediates or deshalogenated side product 3).

As a very sensitive method was needed, online UV-vis spectroscopy was chosen to monitor the concentration of DIM-NA (1) in the product mixture, exploiting the pronounced visible color difference of the reactant (yellow) and product (colorless; SI, Figure S4) as well as its low equipment cost, simplicity, and robustness of the associated setup. An UV-vis flow cell with fiber optics connection to a two-channel UV-vis detector was installed in the experimental setup via bypass prior to product collection. Absorption data were collected by a digital chart recorder. The detection of UV-vis absorption was

initially impaired by  $H_2$  gas bubbles in the product stream stemming from excess hydrogen but finally enabled by installing an inline gas-liquid phase separator in the product stream prior to the flow cell (SI, Figures S1 and S2).

In a first step, full range spectra recorded from pure diluted DIM-NA (1) and DIM-DAB (2) solutions confirmed UV-vis spectroscopy to be a suitable analytical technique: DIM-NA exhibits a strong absorption band at 346 nm without overlap to any DIM-DAB absorption (SI, Figure S5). However, the envisioned product mixture stream of a 0.2 M reactant solution contains DIM-DAB in rather high concentrations and high excess relative to DIM-NA. Under these circumstances, DIM-DAB absorption nicely separated at high dilution may significantly tail into the region of the DIM-NA band initially targeted for detection. Therefore, the UV-vis spectrum of a 0.2 M model product mixture containing 98 mol % DIM-DAB (2) and 2 mol % DIM-NA (1) was recorded and compared with the spectrum of a pure 0.2 M DIM-DAB solution. As can be seen in Figure S6 in the Supporting Information, the DIM-DAB absorption is notably >0 AU at wavelengths >340 nm under these conditions. Nevertheless, the presence of 2 mol % DIM-NA can be still clearly detected at 400-460 nm. Next, we switched to a flow-compatible setup designated for online detection. Due to the rather high concentrations under consideration [in a 0.2 M reaction mixture with 99% conversion 1 mol % DIM-NA (1) still corresponds to a concentration of 0.002 mol/L a flow cell with shorter optical path length (2) mm) was chosen. 1/8'' connections ensured that no flow cell inlet pressure was formed in the targeted range of flow rates (SI, Figure S7). To determine the optimal wavelength for online conversion control, the absorption of a model product mixture composed of 98 mol % DIM-DAB (2) and 2 mol % DIM-NA (1) at overall 0.2 M [corresponding to 98% DIM-NA (1) conversion] was recorded between 400 and 500 nm in 25 nm increments and compared to the corresponding UV-vis absorptions of a pure 0.2 M DIM-DAB (2) solution (Figure 5).



**Figure 5.** Left: UV–vis absorptions of a model DIM-DAB (2)/DIM-NA (1) product mixture containing 0.004 M DIM-NA (2 mol %) and 0.196 M DIM-DAB (98 mol %) at 0.2 M overall concentration. Right: External calibration established from model DIM-DAB/DIM-NA mixtures in concentrations corresponding to 95–100% conversion of a 0.2 M DIM-NA solution. At 425 nm the slope of the calibration curve corresponds to a sensitivity of 0.16 AU/% (DIM-NA conversion).

Residual amounts of DIM-NA (1) can easily be observed at 400 or 425 nm. An external calibration was established at 400 and 425 nm based on a series of model product mixtures corresponding to DIM-NA (1) conversions in the range of 95–100% (Figure 5; SI, Figure S8).

The extended experimental setup was then tested with respect to functionality and accuracy of online UV-vis detection. Figure 6 shows the UV-vis absorption profile



**Figure 6.** UV–vis profile of a conti-DIM-NA (1) hydrogenation experiment performed at conversions X < 100% (0.1 M reaction solution, 4 mL reactor, Ra–Co, 80 °C, 40 bar, 6 equiv of H<sub>2</sub>; see SI Table S2 for further experimental details). Changes in DIM-NA conversion following variations of the reactor throughput (flow rate) are reflected by changes in UV–vis absorption.

recorded at 425 nm during a hydrogenation experiment with varying flow rates. Changes in the conversion resulting from different flow rates are nicely reflected by the UV-vis absorption. At the beginning of the experiment, it takes about 18 min until the reactor output reaches a steady state at 98.0% conversion as subsequently confirmed by off-line analysis of HPLC samples. The reduction of the flow rate to 6 and 4 mL/ min, respectively, leads to an increase of the conversion to 98.8% and 99.3% (HPLC). Accordingly, UV-vis absorption drops, as lower amounts of residual yellow DIM-NA (1) are present in the product mixture. The conversion determined online via UV-vis spectroscopy for the individual flow rates (97.2%, 98.2%, 99.1% at 8, 6, and 4 mL/min, respectively; SI, Table S2) compares reasonably well with the results from offline HPLC analysis, ensuring the main goal of online monitoring, i.e., conversion control within the specification limits.

Kilogram Scale Continuous Flow DIM-NA (1) Hydrogenation. For demonstration purposes, 1 kg of DIM-NA (1) was processed in a longer term hydrogenation experiment using a fresh Ra-Co catalyst load in the 40 mL reactor (SI, Table S3). To achieve the targeted throughput within one working day (8 h) a 0.2 M DIM-NA reactant solution was pumped at 26 mL/min liquid flow rate through the catalyst bed, which corresponds to a mass flow of 2.1 g/min. Compared with the experiments summarized in Table 3, the applied back pressure was reduced to 10 bar to lower the baseline for the expected inlet pressure, while temperature (60  $^{\circ}$ C) and H<sub>2</sub> excess (3.4 equiv) were maintained (see SI, Table S3 for full experimental details). Conversion control was performed by the online UVvis analytical module as described above. According to Figure 5, 0.349 AU<sup>425</sup> was chosen as the threshold absorption value (at 425 nm) for the conversion specification  $[X(DIM-NA) \ge$ 98%]. The product was collected batchwise over time and further processed as described below. Additionally, HPLC samples were taken from the product stream just before releasing such a product batch and analyzed off-line.

Figure 7 shows UV-vis absorption and inlet pressure profiles reflecting the longer term hydrogenation run. Recording was started after the reactor start-up phase on switching from solvent to reactant solution. According to online analysis, steady state reactor output was reached after  $\approx 8$  min. UV-vis absorption (0.10 AU<sup>425</sup>) indicated nearly full DIM-NA (1) conversion ( $X^{UV} = 99.6\%$ ). Spikes in the UV-vis absorption

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**Figure 7.** UV–vis absorption (425 nm) and inlet pressure profiles for long-term conti-DIM-NA (1) hydrogenation at the kilogram scale over Ra–Co (see text and SI Table S3 for experimental details).

profile are due to the presence of occasional gas bubbles (<1 spike/min; see SI, Figure S9) in the product stream.

The process started with an inlet pressure (80 bar) higher than expectable from the previous experiments under similar conditions (Table 3, exp. 5), which was attributed to an unforeseen consequence of the back pressure reduction from 20 to 10 bar. In initial pressure buildup tests conducted at the beginning of this study it was observed that, in the presence of gas, inlet pressures formed are lower at an applied back pressure (SI, Figure S3). This is probably due to higher solubility of hydrogen in the reaction solution and the lower superficial flow velocity of the gas at higher pressure. In the present case, the inlet pressure increase due to lower gas dissolution, thus more turbulent flow, overcompensated the effect of lowering the baseline for the inlet pressure buildup. The inlet pressure steadily increased to 88 bar within the first hour of process runtime reaching 90 bar after 90 min. It remained constant up to 160 min time on stream (TOS) and then, surprisingly, continuously dropped to 67 bar within 40 min, a behavior contrasting our initial observation of inlet pressure dependence from gas dissolution. As none of the process parameters had intentionally been changed, the reason for this phenomenon remains unclear. Importantly, the conversion of the reaction was unaffected by this behavior remaining constantly >99%. The inlet pressure ranged between 67 and 69 bar until  $\approx$ 300 min TOS and then sharply dropped to 57 bar (312 min), which was followed by an abrupt raise to 79 bar (316 min). Full scale deflection of the online UV<sup>425</sup>-absorption at 312 min TOS indicated the breakthrough of high concentrations of DIM-NA (1) through the reactor. In this critical instant of the experiment, process monitoring was continued and prompted us to continue the process instead of executing an immediate shutdown. To our delight, the UV absorption approximately returned to its original values indicating >99% conversion from  $\approx$ 322 min TOS, at which point collection of a new product batch was started. From this point, the UV signal remained constant until the end of regular processing after 445 min, while the inlet pressure showed a profile very similar to the beginning of the experiment: An increase up to 86 bar was followed by a steady inlet pressure drop to 63 bar. Offline HPLC analysis of the contaminated product fraction (550 g reaction solution) performed during the remaining process runtime indicated the presence of  $\approx 3$  area% starting material DIM-NA (1). To further demonstrate the utility of the flow process, this fraction was reworked at the end of the regular process, i.e., after all

amounts of the original starting solution had been processed (Figure 7, t = 445). For this purpose, the hydrogen flow was strongly reduced, as only minor amounts of residual DIM-NA (1) had to be converted, while the liquid flow rate was lowered to keep the inlet pressure at a tolerable level. Online UV absorption ranged between 0.133 AU (X = 99.4%) and 0.110 AU (X = 99.6%) during this period and indicated that the targeted composition was matched. After additional 35 min, all of the reactant solution had been converted with the targeted product specification regarding conversion. The reactor was then shut down by switching to pure solvent and N<sub>2</sub>.

Online analysis has proven highly useful during this longterm hydrogenation experiment, not only by rapidly indicating an unexpected process instability, immediately allowing for the necessary measures to be taken. It furthermore shows that otherwise the overall process was very stable in terms of conversion (>99%). As has been mentioned before, HPLC samples were taken in regular intervals when a new product batch was released from the collection vessel and subsequently analyzed offline (Figure 8; SI, Figure S10, Table S4). The



**Figure 8.** Composition of product samples 1–14 taken directly from the product stream at the end of each collection period as determined by HPLC. DIM-NA (1) conversion was >99.8% in all cases.

composition of the individual product fractions collected ( $3x \approx$ 350 g,  $11x \approx 750$  g;  $1x \approx 550$  g rework batch) was additionally analyzed by HPLC (SI, Table S5). Both the samples taken at individual process times and the averaged collected product batches indicated an excellent reactor performance with respect to quality. With the expected exception of the first two HPLC samples taken at the beginning of process, the level of desiodo-DIM-DAB (3) was impressively low throughout the 8 h runtime (0.4–0.6 wt % 3 for samples 3–14, Figure 8; SI, Table S4). Compared with the results obtained during process optimization (0.7–0.9 wt % 3 at X = 99.7-99.9%, Table 3), an even better selectivity was achieved at consistently high DIM-NA (1) conversion >99.8%. The relatively high amount of desiodo-DIM-DAB (3) in the first two product samples (2.3, 1.0 wt %) was attributed to a catalyst initiation effect as previously observed for all fresh catalyst loadings. Desiodination then steadily decreased in the further course of the process reaching values <0.5 wt %, which is remarkable for a crude product solution at this high conversion. As desiodination mainly takes place as follow-up reaction after full conversion, reaching this target by just-in-time termination of a similar batch hydrogenation process has to be considered very challenging. The level of combined observable side products was also very low (typical range 0.6-0.8 area%, see SI, Figure S11 for a sample HPLC chromatogram). After an additional

Table 4. Comparison of Labscale Batch DIM-NA (1) Hydrogenation Employing Fe,<sup>19</sup> Zn,<sup>20</sup> and Ra-Co Catalysts and the Continuous Hydrogenation Process over Ra-Co

	batch, Fe reduction <sup>19</sup>	batch, Zn reduction <sup>20</sup>	batch, Ra–Co	continuous process, Ra–Co
reactor dimensions (mL)	50 <sup>a</sup>	250 <sup>a</sup>	45	50
reaction type	reagent excess Fe (16 equiv), NH <sub>4</sub> Cl	reagent excess Zn (6 equiv), conc. HCl	catalytic Ra–Co (Actimet-Co)	catalytic Ra–Co (Actimet- Co)
amount of reductant or catalyst (g)	1.15	6.8	0.036 (slurry) <sup>b</sup>	62 (trickle bed) <sup>b</sup>
DIM-NA (1) concentration (g/L)	28	44	86	86
solvent	EtOH	THF/H <sub>2</sub> O 80:10	THF/H <sub>2</sub> O 95:5	THF/H <sub>2</sub> O 95:5
reaction time (h)	16	1	2	8
pressure (bar)	1	1	20	67-90
temperature (°C)	78	r.t.	110	60
isolated product (g)	0.47	6.3	0.74 <sup>c</sup>	831
catalyst or reductant (g)/isolated product (g)	2.5	1.2	0.02 <sup>b</sup>	0.04 <sup>b</sup>
space-time-yield [kg/L h]	0.0006	0.025	0.01	2.1
catalyst productivity [kg/(kg <sup>cat</sup> h)			20.6	3.3 <sup>d</sup>
process mass intensity	40 <sup><i>e</i>,<i>f</i></sup>	29 <sup><i>e</i>,<i>f</i></sup>	13 <sup><i>e</i>,<i>f</i></sup>	13 <sup>e</sup> (22)

<sup>*a*</sup>Volume required for workup not considered. <sup>*b*</sup>Corresponding to  $\approx$ 50% dry catalyst according to technical datasheet. <sup>*c*</sup>HPLC yield at full conversion, product not isolated. <sup>*d*</sup>Per run, the possibility to use a packed bed catalyst multiple times will significantly increase the final catalyst productivity. <sup>*e*</sup>Excluding workup. <sup>*f*</sup>See the SI for process details.

pass through the reactor also the rework fraction matched target quality and was included in subsequent collective workup performed to determine the overall isolated yield (SI, Table S5, Figure S12).

Workup of the product solutions (not optimized) was performed by a downstream procedure including concentration of the product solutions and precipitation by water addition (see SI for experimental details). The off-white precipitate was isolated and dried to yield 831g (89%) DIM-DAB (2), which contained only 0.09 wt % of the desiodo side product (3) (SI, Figure S13) and clearly fulfilled the product specification criteria–also with regard to residual trace metal amount (9 ppm of Co) and the presence of further impurities ( $\Sigma(ar\%) = 0.3$ ).

Table 4 shows a comparison of process and performance parameters for DIM-NA (1) hydrogenation in batch employing excess amounts of reducing reagents and the present continuous flow process. For the sake of completeness, data obtained from a related batch DIM-NA (1) hydrogenation with Ra-Co catalyst are included, too (see SI for experimental details). A comparison of the space time yields (STY) and total mass intensities of the different processes illustrates the high degree of process intensification resulting from continuous processing: 3500, 84, and 210 fold higher STY were achieved for the continuous process over Ra-Co as compared to the batch labscale processes, while the process mass intensity was significantly lower for the conti-hydrogenation process as compared to chemical reduction with Fe and Zn. The 2-3 fold higher substrate concentration applied in the flow process furthermore reflects lower solvent consumption, and it should be recalled that continuous DIM-NA (1) hydrogenation has already been successfully performed even at a 0.4 M concentration (Table 3).

# CONCLUSION

An experimental setup with 4 and 40 mL reactor tubes installed in an ordinary laboratory fume hood was employed for process development and scale up. After evaluating suitable process conditions in the material economic 4 mL reactor the hydrogenation process was transferred to 40 mL reactor scale. Although notable inlet pressures up to 90 bar resulted from implementation of the powderous Ra–Co as a packed bed catalyst, the reactor could still be operated at throughputs up to 144 g/h. One kilogram of DIM-NA (1) was eventually processed into DIM-DAB (2) within a longer term experiment of 8 h duration following conversion by online monitoring by UV-vis spectroscopy. This method proved to be highly reliable, allowing to rapidly respond to process variations leading to an increase of DIM-NA (1) concentration in the product stream above the tolerable levels. As compared to related batch processes at laboratory scale performing the hydrogenation in continuous flow convinces by a considerably higher space-time-yield, allowing for a safe and more compact and cost-efficient installation of the experimental setup compared to setting up a pilot scale batch autoclave environment for carrying out this reaction.

In summary, Ra–Co has been successfully employed as trickle bed flow reactor catalyst for the selective hydrogenation of the refametinib intermediate DIM-NA (1). Under optimized process conditions, reasonable amounts of the hydrogenation product DIM-DAB (2) were obtained as solid, fully matching generic industrial product quality expectations regarding the amount of residual substrate ( $\leq 2 \mod \%$ ) and desiodinated side product ( $\leq 0.13 \text{ wt \%}$ ).

# ASSOCIATED CONTENT

### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.7b00039.

Full description of experimental setup, procedures, and data. Description of HPLC analysis including sample chromatograms. Implementation of online monitoring (PDF)

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## Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) Dudukovic, M. P.; Larachi, F.; Mills, P. L. Chem. Eng. Sci. 1999, 54, 1975.

(2) (a) Gutmann, B.; Cantillo, D.; Kappe, C. O. Angew. Chem. 2015, 127, 6788; Angew. Chem., Int. Ed. 2015, 54, 6688. (b) Malet-Sanz, L.; Susanne, F. J. Med. Chem. 2012, 55, 4062. (c) Roberge, D. M.; Ducry, L.; Bieler, N.; Zimmermann, B. Chem. Eng. Technol. 2005, 28, 318.

(3) (a) Amara, Z.; Poliakoff, M.; Duque, R.; Geier, D.; Franciò, G.; Gordon, C. M.; Meadows, R. E.; Woodward, R.; Leitner, W. Org. Process Res. Dev. 2016, 20, 1321. (b) Zaborenko, N.; Linder, R. J.; Braden, T. M.; Campbell, B. M.; Hansen, M. M.; Johnson, M. D. Org. Process Res. Dev. 2015, 19, 1231. (c) Qian, Z.; Baxendale, I. R.; Ley, S. V. Synlett 2010, 2010, 505.

(4) (a) Porta, R.; Benaglia, M.; Puglisi, A. Org. Process Res. Dev. 2016, 20, 2. (b) Hawkins, J. M. Nature 2015, 520, 302. (c) Tsubogo, T.; Oyamada, H.; Kobayashi, S. Nature 2015, 520, 329. (d) Snead, D. R.; Jamison, T. F. Angew. Chem. 2015, 127, 997; Angew. Chem., Int. Ed. 2015, 54, 983.

(5) (a) Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J.-C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. Science **2016**, 352, 61. (b) Mascia, S.; Heider, P. L.; Zhang, H.; Lakerveld, R.; Benyahia, B.; Barton, P. I.; Braatz, R. D.; Cooney, C. L.; Evans, J. M. B.; Jamison, T. F.; Jensen, K. F.; Myerson, A. S.; Trout, B. L. Angew. Chem. **2013**, 125, 12585; Angew. Chem., Int. Ed. **2013**, 52, 12359.

(6) Mallia, C. J.; Baxendale, I. R. Org. Process Res. Dev. 2016, 20, 327.
(7) (a) Razzaq, T.; Kappe, C. O. Chem. - Asian J. 2010, 5, 1274.
(b) Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. Synlett 2008, 2008, 151. (c) Yoshida, J.; Nagaki, A.; Yamada, T. Chem. - Eur. J. 2008, 14, 7450.

(8) (a) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300. (b) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem.* **2004**, *116*, 410; *Angew. Chem. Int. Ed.* **2004**, *43*, 406. (c) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583. (d) Wiles, C.; Watts, P. *Chemistry Today* **2010**, *28*, 3.

(9) (a) Glasnov, T. Continuous flow chemistry in the research laboratory; Springer, 2016. (b) Pesti, J. Org. Process Res. Dev. 2012, 16, 843. (c) Anderson, N. G. Org. Process Res. Dev. 2012, 16, 852. (d) Hessel, V. Chem. Eng. Technol. 2009, 32, 1655.

(10) Yang, T.-K.; Lee, D.-S. Raney Nickel. In Handbook of Reagents for Organic Synthesis, Oxidizing and Reducing Agents; Burke, S. D., Danheiser, R. L., Eds.; John Wiley and Sons: Chichester, UK, 1999.
(b) Banwell, M. G.; Jones, M. T.; Reekie, T. A.; Schwartz, B. D.; Tan, S. H.; White, L. V. Org. Biomol. Chem. 2014, 12, 7433.

(11) Hunt, A. J.; Farmer, T. J.; Clark, J. H. Element Recovery and Sustainability; Hunt, A. J., Ed.; RSC: Cambridge, 2013; ch. 1, p 1.

(12) Nishimura, S. Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis; Wiley-Interscience: New York, 2001.

(13) Loos, P.; Alex, H.; Hassfeld, J.; Lovis, K.; Platzek, J.; Steinfeldt, N.; Hübner, S. Org. Process Res. Dev. 2016, 20, 452.

(14) Catalytic systems for selective hydrogenation of 1-iodo-4nitrobenzene in batch: Li, Y.; Wang, X. J. Mol. Catal. A: Chem. 2016, 420, 56–65. Corma, A.; Serna, P.; Concepción, P.; Calvino, J. J. J. Am. *Chem. Soc.* 2008, *130*, 8748–8753; Evonik Noblyst P8078, CAS 7440-06-4, http://www.strem.com/uploads/resources/documents/evonik\_heterocat\_kit.pdf.

(15) Pietrowski, M. Curr. Org. Synth. 2012, 9, 470-487.

(16) (a) Fey, P.; Mayer, A. C. Chiral synthesis of N-{3,4-diflouro-2-[(2-fluoro-4-iodophenyl)amino]-6-methoxyphenyl}-1-[2,3-dihydroxypropyl]cyclopropanesulfonamides. Patent WO 2012/163799 A1, December 6, 2012. (b) Xiao, D.; Zhu, L.; Wang, S.; Liang, Z.; Hu, W. Novel 6-Arylamino pyridine sulfonamides and 6-arylamino pyrazinone sulfonamides as MEK inhibitors. Patent WO 2010/ 145197 A1, December 23, 2010. (c) Maderna, A.; Vernier, J.-M. Preparation of (R)- and (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1sulfonamide and protected derivatives thereof WO 2011/009541 A1, January 27, 2011.

(17) Iverson, C.; Larson, G.; Lai, C.; Yeh, L.-T.; Dadson, C.; Weingarten, P.; Appleby, T.; Vo, T.; Maderna, A.; Vernier, J.-M.; Hamatake, R.; Miner, J. N.; Quart, B. *Cancer Res.* **2009**, *69*, 6839.

(18) https://clinicaltrials.gov/ct2/results?term=Refametinib&pg=1.

(19) (a) Yan, S.; Vernier, J.-M.; Hong, Z. N-Aryl-N'alkyl sulfamides as MEK inhibitors. US Patent application publication US 2007/ 0238710, October 11, 2007. (b) Maderna, A.; Vernier, J.-M.; Barawkar, D.; Chamakura, V.; El Abdellaoui, H.; Hong, Z. Derivatives of N-(arylamino) sulfonamides including polymorphs as inhibitors of MEK. US Patent application publication 2008/0058340, March 6, 2008. (c) Quart, B. D.; Rowlings, C. E. Compositions and methods for preparing and using same. Patent WO 2009/129246 A2, October 22, 2009. (d) Vernier, J.-M.; Rowlings, C. E.; Girardet, J.-L.; Dimoc, S.; Quart, B.; Miner, J. N. Derivatives of N-(arylamino) sulfonamides including polymorphs as inhibitors of MEK as well as compositions, methods of use and methods for preparing the same. U.S. Patent US 8,648,116 B2, February 11, 2014.

(20) Bock, M. G.; Chikkanna, D.; McCarthy, C.; Moebitz, H.; Pandit, C.; Poddutoori, R. Heterocyclic sulfonamide derivatives. Patent WO 2011/070030 A1, June 16, 2011.

(21) The reactor tubes have been named 4 and 40 mL reactor as an approximation of the heated total bed volume. Please refer to the Supporting Information for a detailed description of the reactors used. (22) Irfan, M.; Glasnov, T. N.; Kappe, C. O. *ChemSusChem* **2011**, *4*,

300. (23) Afandizadeh, S.; Foumeny, E. A. Appl. Therm. Eng. 2001, 21, 669.

(24) Actimet Co is a skeletal, nonpromoted cobalt catalyst supplied by BASF; metal content: Al 8%, Co 90%, Cr 2%, average particle size: 40  $\mu$ m, bulk density ca. 0.820 kg/L.

(25) (a) Rase, H. F. Handbook of commercial catalysis: heterogenous catalysis; Taylor & Francis Group: Boca Raton, 2000. (b) Foster, J. A.; Mueller, W. H.; Ryan, D. A. Process for preparing alkylanilines. US Patent 5,616,807, April 1, 1997.

(26) (a) Baramov, T.; Loos, P.; Hassfeld, J.; Alex, H.; Beller, M.; Stemmler, T.; Meier, G.; Gottfried, M.; Roggan, S. Adv. Synth. Catal. **2016**, 358, 2903–2911. (b) Rehm, T. H.; Reinhard, D.; Kost, H. J.; Hofmann, C.; Zapf, R.; Löb, P.; Laribi, Y.; Perrichon, P.; Berguerand, C.; Kiwi-Minsker, L.; Sulman, E.; Szirbik, G.; Richert, H.; Lang, J.; Gottfried, M.; Roggan, S. Chem. Eng. J. **2017**, 316, 1069–1077.

(27) (a) Cheng, W.-C.; Czarnecki, L. J.; Pereira, C. J. Ind. Eng. Chem. Res. 1989, 28, 1764–1767. (b) http://www.reaxa.com.

(28) Wolf, A.; Turek, T.; Mleczko, L. Chem. Eng. Technol. 2016, 39, 1933–1938.

(29) http://www.hitec-zang.de/en/laboratory-automation/ automation-systems.html.

(30) http://www.chem21.eu/.

(31) http://www.imi.europa.eu.