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Selective Hydrogenation of Halogenated Nitroaromatics to Haloanilines in Batch and Flow

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Supporting Information

ABSTRACT: The selective hydrogenation of functionalized nitroaromatics poses a major challenge from both academic as well as industrial viewpoints. As part of the CHEM21 initiative (www.chem21.eu), we are interested in highly selective, catalytic hydrogenations of halogenated nitroaromatics. Initially, the catalytic reduction of 1-iodo-4-nitrobenzene to 4-iodoaniline served as a model system to investigate commercial heterogeneous catalysts. After determining optimal hydrogenation conditions and profiling performances of the best catalysts, hydrogenations were transferred from batch to continuous flow. Finally, the optimized flow conditions were applied to transformations which represent important steps in the syntheses of the active pharmaceutical ingredients clofazimine and vismodegib.

INTRODUCTION

Nitration is one of the most versatile ways of introducing nitrogen into aromatic compounds. The resulting nitroaromatics can easily undergo further functionalization, e.g. by nucleophilic aromatic substitution or hydrogenation. This is one reason for their widespread use en-route to highly functionalized molecules. For example, 2-chloroaniline, 4-chloroaniline, and 2,4-dichloroaniline can be converted into a variety of functional molecules like active pharmaceutical ingredients, agrochemicals, or pigments.[1e] These anilines are produced by nitration of chlorobenzene and dichlorobenzene followed by selective reduction of the nitro group.[2] However, it can be challenging to hydrogenate the nitro group in densely functionalized aromatics selectively. Many catalysts will also reduce functionalities such as multiple bonds, cyano groups, heterocycles, benzyl protecting groups, or halogens in addition to the nitro group. Therefore, the selective reduction of nitroaromatics to anilines has been subject of substantial research efforts over the last decades.[1,3]

While well-defined homogeneous catalysts allow fine-tuning of the catalytic activity,[4] we decided to focus this study on heterogeneous catalysts to facilitate product separation. Apart from the abundantly used heterogeneous Pt- and Pd-catalysts, other metals like Ru, Rh, Ag, Ir, and Au, have also been used for hydrogenations, with Au-based catalysts showing exceptionally high chemoselectivity.[5,6] Considering the limited supply of conventional resources, catalysts based on the nonprecious transition metals iron,[7] cobalt,[8] or nickel[8b,d,9] should be preferred over platinum group metals.[10] However, catalyst activity, space-time yield, catalyst recycling (or long-term performance for continuous reactions), and ease of metal recycling are also important factors for the evaluation of the sustainability of a process. A variety of supports have been used to immobilize catalytically active metals. Activity and selectivity of the resulting catalysts can be influenced by both the metal and the respective support.[11] Nevertheless, activated carbon is by far the most widespread support for hydrogenation catalysts, very likely due to its competitive price.

High yield and selectivity are of major importance in order to develop efficient processes, but aspects of sustainability have to be considered to promote the continuing improvement in this field. Hence, low-cost, abundant metals, and solvents, which can be produced in a sustainable fashion, should be taken into account.

With these considerations in mind we set out to investigate selective reductions of nitro aromatics, initially focusing on retaining halogens in the substrate. In order to facilitate separation, we confined this study to heterogeneous catalysts and the most atom-efficient reducing agent hydrogen.

Continuous processes in microstructured reactors can offer excellent control over residence time, reaction temperature, and mixing efficiency.[12,13] They can also be advantageous for highly exothermic reactions and for the synthesis of unstable or explosive compounds.[14] Providing large interfaces can be especially important for multiphasic hydrogenation reactions involving a gas phase, a liquid phase and a solid catalyst bed.[15] Until today, the continuous hydrogenation of nitroaromatics in liquid phase has been investigated only to a limited extent.[16,17] Therefore, we compared promising catalysts for different halogen-substituted nitroaromatics, so as to provide an informed and balanced comparison of batch and flow processes.

Initially, the selective hydrogenation of 1-iodo-4-nitrobenzene **1a** to 4-iodoaniline **4a** served as a model system (Figure 1), which is already well-known in the literature.[1d,11b,d,17a] Mechanistically, reduction of 1-iodo-4-nitrobenzene **1a** can proceed via nitroso compound **2** and

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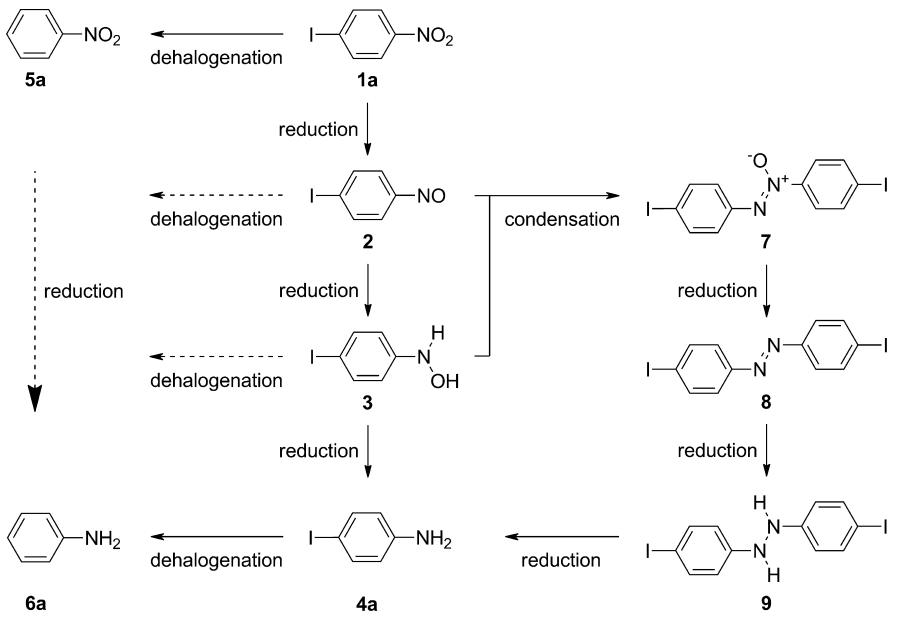

Figure 1. Mechanistic pathways for the reduction of 1-iodo-4-nitrobenzene.[1e]

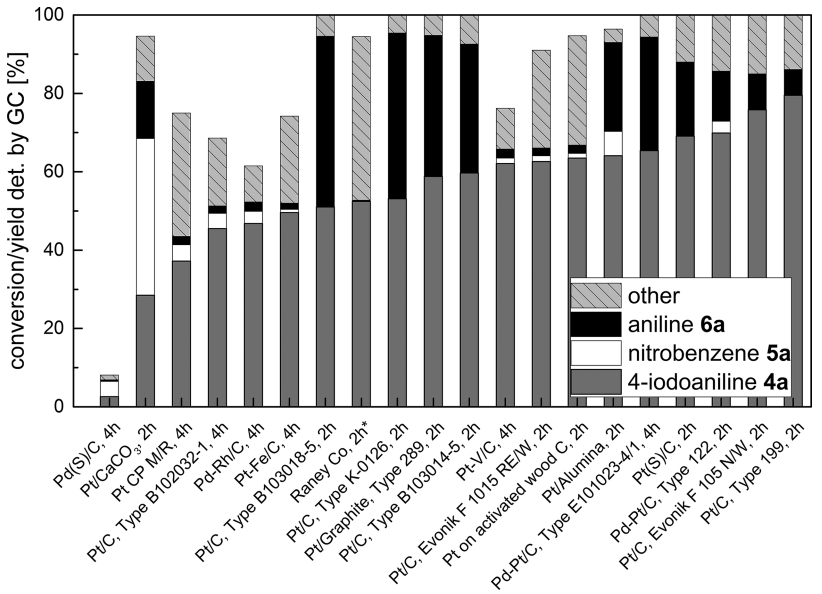

Figure 2. Product composition in the batch hydrogenation of 1-iodo-4-nitrobenzene **1a** for different catalysts after 2/4 h reaction time (data point with higher amount of 4-iodoaniline **4a** shown). Dark gray: 4-iodoaniline **4a**, white: nitrobenzene **5a**, black: aniline **6a**, light gray-striped: unmonitored/adsorbed compounds based on detected starting material. The absolute height of the bars reflects conversion of the starting material; Reaction conditions: 2 mmol 1-iodo-4-nitrobenzene **1a** in 10 mL of THF/H_2O (95:5), 1 mol % catalyst (*Raney Co: 15 mol %, 110 °C, 20 bar H_2), 5 bar H_2, 80 °C, 2 or 4 h. Internal analytical GC standard: diethylene glycol dibutyl ether.

hydroxylamine **3** to iodoaniline **4a**. In this sequence, reduction of hydroxylamine **3** is usually the rate limiting step.[1e] Dehalogenation of the nitro starting material (**1a** → **5a**) is possible, but the dehalogenation of the more electron-rich aniline product **4a** is usually faster (**4a** → **6a**).[1e] Another possible pathway can accrue from condensation of these intermediates. For example, nitroso (**2**) and hydroxylamine (**3**) intermediate can condense to give azoxy compound **7**. Similarly, nitroso intermediate **2** can react with aniline **4a** to form diazo compound **8**. These compounds can be reduced to iodoaniline **4a** via a hydrazo intermediate **9**. Additionally, the formation of water during in the hydrogenation and HI in case of hydrodehalogenation can affect solubility of the products and the pH of the reaction mixture.

The seemingly simple hydrogenation proceeds through a reaction network with many intermediates, which can be influenced by multiple parameters. At the same time, iodoaniline **4a** is highly prone for hydrodehalogenation. Trapping of this intermediate is therefore a challenging task.

BATCH REACTION OPTIMIZATION

Catalyst Screening. Using the 1-iodo-4-nitrobenzene model system, suitable catalysts were identified by a broad screening of commercially available catalysts (Figure 2). In

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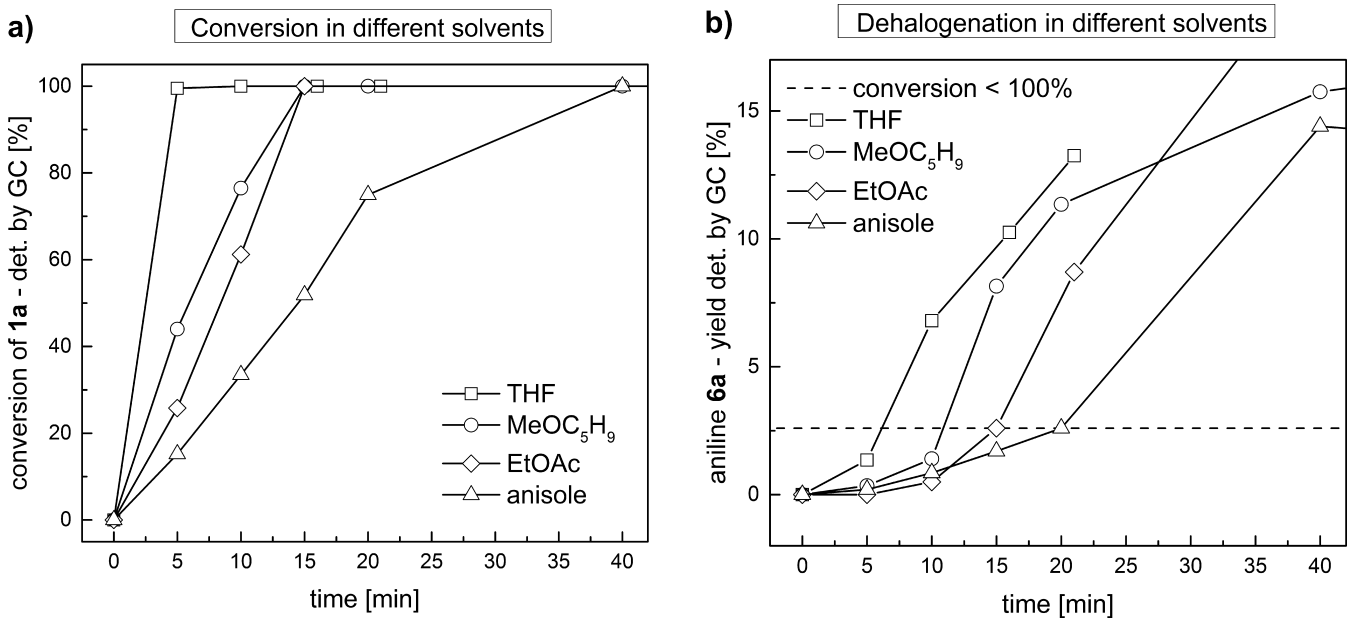

Figure 3. (a–b) Hydrogenation of 1-iodo-4-nitrobenzene **1a** in different solvents; conversions/yields represent mean values of two experiments; reaction conditions: 1 mol % Pt–V/C, 25 bar H_2, 95 °C, 0.05 M 1-iodo-4-nitrobenzene, 10 mL of the corresponding solvent, analytical standard: diethylene glycol dibutyl ether; (a) conversion of 1-iodo-4-nitrobenzene **1a** in squares: THF; circles: $MeOC_5H_9$; diamonds: EtOAc; triangles: anisole; (b) yield of aniline **6a** (det. by GC): squares: THF; circles: $MeOC_5H_9$; diamonds: EtOAc; triangles: anisole; all data points below the dotted line were measured at <100% conversion of **1a**.

these batch experiments, samples were taken after 2 and 4 h in order to accommodate for varying hydrogenation rates.

Relative and absolute amounts of compounds **1a**, **4a**, **5a**, and **6a** in the reaction mixture (i.e., the supernatant) were determined by GC against diethylene glycol dibutyl ether as nonreactive internal analytical standard. Each bar in Figure 2 shows the composition of the reaction mixtures at the specified reaction time. The absolute height of the bar represents the conversion of the starting material. Therefore, the deviation between conversion and the sum of the monitored products can be attributed to unmonitored compounds (i.e., compounds of the diazo pathway) or compounds, which remain adsorbed to the catalyst surface. Further optimization might suppress the formation of the unknown intermediates in favor of 4-iodoaniline **4a**.

In line with earlier findings,[18] low conversion was observed for Pd(S)/C, which shows less than 10% conversion of 1-iodo-4-nitrobenzene **1a** after 4 h (a control reaction without catalyst did not give any conversion after 4 h, not shown). For many other catalysts hydrogenation of the nitro group was accompanied by significant hydrodehalogenation. It has to be taken into account that the product 4-iodoaniline **4a** is significantly more prone to dehalogenation than the starting material 1-iodo-4-nitrobenzene **1a**.[1e] At the same time, nitro reduction is usually faster than hydrodehalogenation. Therefore, examples where 1-iodo-4-nitrobenzene **1a** is fully converted show comparatively large amounts of aniline **6a**. In order to achieve precise control over the reaction time on technical scale, the use of a flow reactor might prove advantageous.

Particularly Pt–Fe and Pt–V based catalysts on activated carbon gave promising results. The most selective catalyst in this screening was Raney Co with less than 1% overall dehalogenation, albeit 15 mol % had to be used at elevated H_2 pressure and temperature to adjust for its lower activity. Using 15 mol % Raney Co at 5 bar H_2, 80 °C resulted in only 2% conversion after 4 h. Pt–V/C and Raney Co were chosen as representative precious and base metals for further studies. The first step was a solvent and additive screening using Pt–V/C as catalyst.

Solvent and Additive Screening. Solvents can represent a substantial fraction of the material used for the production of chemicals.[19] The development of more sustainable processes should therefore include the screening of solvents which can be produced in a sustainable fashion.[20]

Toward this end we screened the solvents 2-methyl-THF, methoxycyclopentane ($MeOC_5H_9$), ethyl acetate, and anisole to compare reaction rates, selectivities as well as solubility of substrate **1a** in these solvents in analogy to THF. The more polar solvents DMF and *N*-methyl-2-pyrrolidone have been omitted from this study due to their high toxicity. Alcohols have not been investigated due to very low solubility of the substrates in these solvents (see below).

Solubility is especially important for continuous reactions in order to prevent potential precipitation issues and subsequent clogging in the reactor. At ambient temperature, the model substrate 1-iodo-4-nitrobenzene **1a** was soluble in THF in concentrations of approximately 0.6 M (149 g/L; in the presence of the analytical standard diethylene glycol dibutyl ether solubility decreased drastically). In EtOAc the solubility was between 0.2 and 0.25 M, while in EtOH solubility it was less than 0.05 M.

In the next step, we compared the conversion of **1a** in the chosen solvents. To prevent compromising solubility issues, a substrate concentration of 0.05 M was used. Figure 3a shows that almost full conversion (99.5%) was observed in THF after 5 min. In $MeOC_5H_9$, which was comparable to 2-methyl-THF (Supporting Information Figure S1), full conversion was observed after 15 min. EtOAc also showed complete

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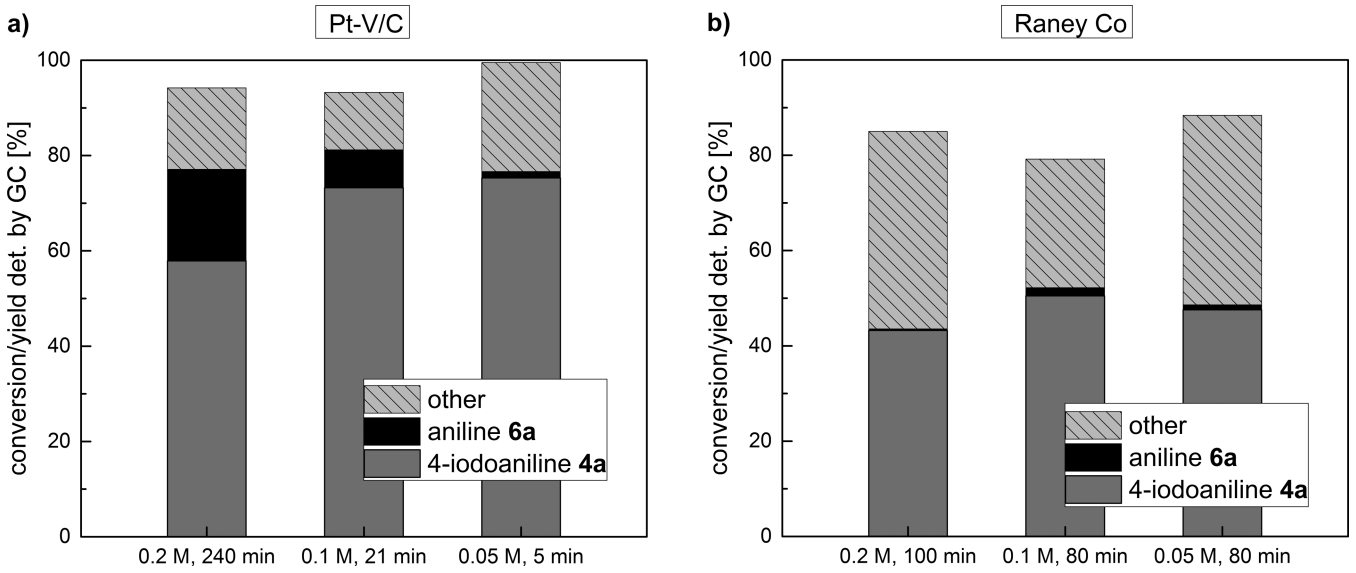

Figure 4. (a) Product composition in the batch hydrogenation of 1-iodo-4-nitrobenzene **1a** with Pt−V/C for different concentrations; conversions/yields represent mean values of two experiments; reaction conditions: 1 mol % Pt−V/C, 25 bar H_2, 95 °C, 10 mL of THF, analytical standard: diethylene glycol dibutyl ether; (b) product composition in the batch hydrogenation of 1-iodo-4-nitrobenzene **1a** with Raney Co for different concentrations; conversions/yields represent mean values of two experiments; reaction conditions: 15 mol % Raney Co, 20 bar H_2, 110 °C, 10 mL THF, analytical standard: diethylene glycol dibutyl ether; dark gray: 4-iodoaniline **4a**, black: aniline **6a**, light gray-striped: unmonitored/adsorbed compounds based on detected starting material. The absolute height of the bars reflects conversion of the starting material.

consumption of the starting material after 15 min, while in anisole full conversion was observed after 40 min.

Below 100% conversion, similar levels of dehalogenation were observed for these solvents (Figure 3b, values below the dotted line). Maximal 2.6% dehalogenation were observed (EtOAc, anisole) when substrate **1a** was still present in the reaction mixture. Upon full conversion, the dehalogenation rate increased significantly in all investigated solvents.

In summary, using alkyl ethers like THF or 2-methyl-THF (15 min: full conversion, 2.5% aniline **6a**, Figure S1) resulted in high reaction rates together with good substrate solubility. In anisole (and toluene), much lower reaction rates were observed. EtOAc showed a high reaction rate, but lower substrate solubility compared to THF. For further optimization, THF was chosen to allow for maximum concentration, fast turnover, and maintaining high selectivity.

As shown above, Pt-based catalysts usually offer high catalytic activity but often suffer from decreasing selectivity at conversions close to 100%. Hence, numerous modifiers for Pt-based catalysts have been reported.[21] Using modifiers can not only increase selectivity but can also suppress the formation of hydroxylamine intermediates, whose accumulation can lead to run-away reactions. Vanadium seems to be useful in this regard for Pt-[22] as well as for Ni-based catalysts.[23] Thiol modifiers have been added in order to retain vinyl groups.[21] The presence of heteroaryl halides was tolerated well when a Pt(S)/C catalyst was used.[24] Remarkably, unmodified Pd/C and Pt/C catalysts have been used for the selective hydrogenation of 1-iodo-2-methyl-4-nitrobenzene by simply adding 0.4% zinc iodide to the reaction mixture.[25] It was therefore applied to the hydrogenation of our model substrate 1-iodo-4-nitrobenzene **1a** with Pt−V/C (Supporting Information, Figure S2). Interestingly, the use of ZnI_2 slowed down hydrogenation of starting material **1a** as well as dehalogenation of 4-iodoaniline **4a**. It has been suggested that ZnI_2 might block highly active catalytic centers and thus suppress dehalogenation.[25] Slower nitro hydrogenation might be a side effect of this phenomenon. However, in contrast to the results reported for Pt/C,[25] using ZnI_2 in combination with Pt−V/C did not lead to significantly lower dehalogenation at high conversion.

Concentration Screening. Initially, the concentration screening for the hydrogenation was performed in batch with Pt−V/C as a catalyst. It was observed that substrate concentration plays a significant role for the hydrogenation rate and selectivity of the reaction (Figure 4a). At 0.2 M concentration in THF, 94% of the substrate 1-iodo-4-nitrobenzene **1a** were converted after 240 min. With a 0.1 M solution 93% conversion was observed after 21 min. At 0.05 M 99.5% were consumed after 5 min. At the same time, dehalogenation decreased with lower substrate concentration from 27% over 8% to 1%.

On the other hand, in order to achieve high conversions together with high selectivity, precise control over the reaction time was found to be crucial. For example, at 0.05 M concentration 1.4% dehalogenation were observed after 5 min (at 99.5% conversion). After 10 min, full conversion and 6.8% aniline were observed (Figure 3). Residence time can be controlled very precisely in continuous flow reactors, which might prove advantageous in order to achieve conversions close to 100%, while separating the dehalogenation prone product from the catalyst as quickly as possible.

The same concentrations were employed for hydrogenations with Raney Co as catalyst (Figure 4b). In contrast to reactions with Pt−V/C, conversions between 77 and 82% were observed after very similar reaction times of 80−100 min for the different concentrations. For Raney Co, dehalogenation did not vary significantly for different concentrations, less than 2% aniline were detected. Hence, hydrogenations using Raney Co could allow to maximize substrate concentration and reduce solvent consumption without significant decrease in product selectivity. Even at full conversion, dehalogenation increased only

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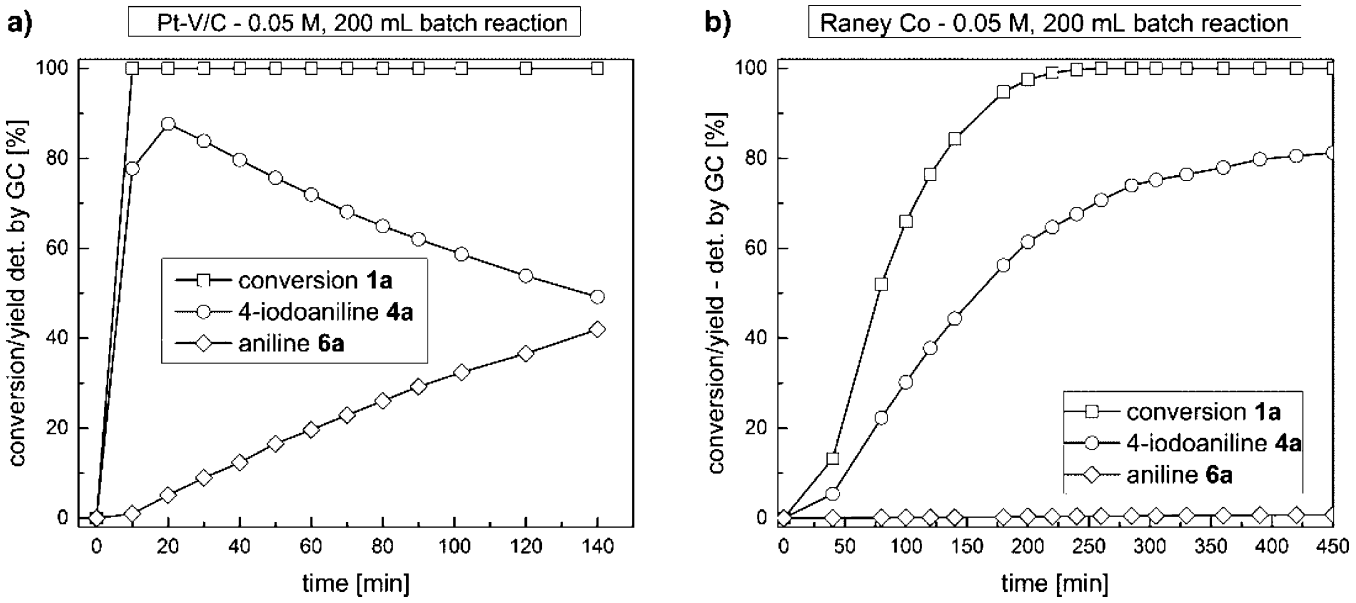

Figure 5. Product composition over time in 200 mL batch hydrogenations of 1-iodo-4-nitrobenzene **1a** with Pt−V/C and Raney Co; conversions/yields represent mean values of two experiments; (a) reaction conditions: 1 mol % Pt−V/C, 25 bar H_2, 95 °C, 200 mL of THF, analytical standard: diethylene glycol dibutyl ether; (b) reaction conditions: 15 mol % Raney Co, 20 bar H_2, 110 °C, 10 mL THF, analytical standard: diethylene glycol dibutyl ether; squares: conversion of 1-iodo-4-nitrobenzene **1a**; circles: 4-iodoaniline **4a**; diamonds: aniline **6a**.

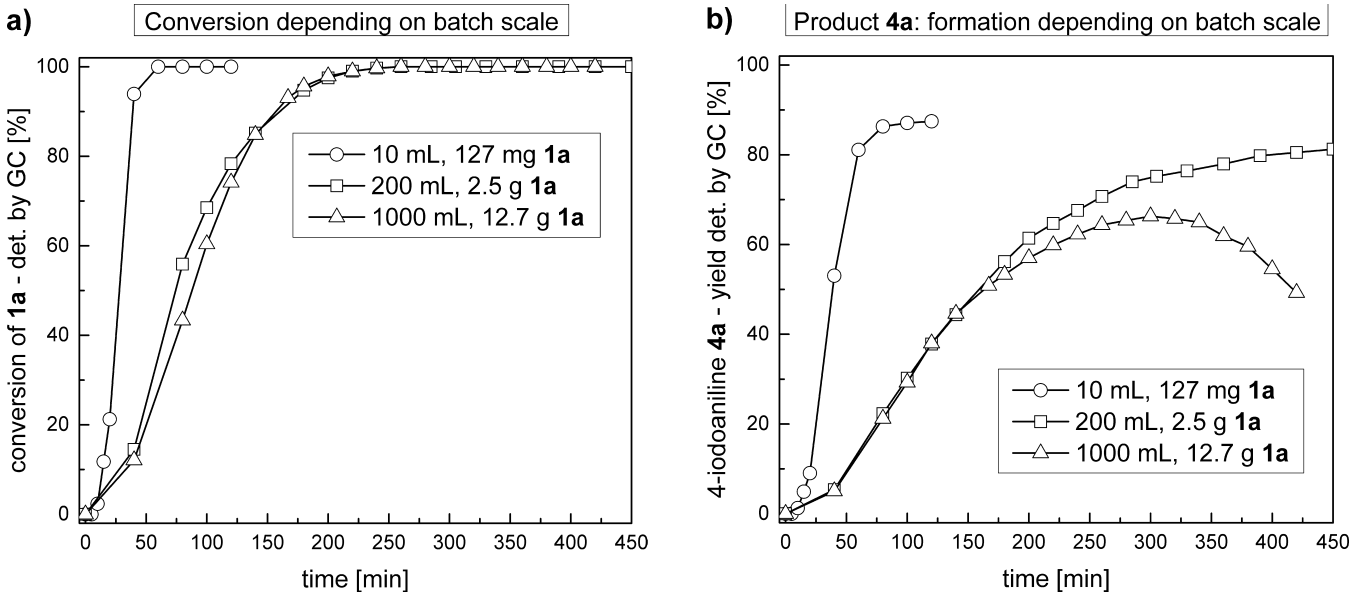

Figure 6. Hydrogenation with Raney Co on different scales; conversions/yields represent mean values of two experiments; reaction conditions: 15 mol % Raney Co, 20 bar H_2, 110 °C, 0.05 M 1-iodo-4-nitrobenzene **1a**, THF:H_2O = 95:5, analytical standard: diethylene glycol dibutyl ether; (a) conversion of 1-iodo-4-nitrobenzene **1a**; (b) formation of 4-iodoaniline **4a**; circles: 10 mL of solvent, 127 mg of 1-iodo-4-nitrobenzene **1a**; squares: 200 mL of solvent, 2.5 g of 1-iodo-4-nitrobenzene **1a**; triangles: 1000 mL of solvent, 12.7 g of 1-iodo-4-nitrobenzene **1a**.

moderately when Raney Co was used (1.3% in 50 min, Figure S3).

Not unexpectedly, Raney Co showed significantly slower reaction rates compared to Pt−V/C, necessitating higher metal loadings (15 mol % vs 1 mol %) and longer reaction times. However, it has to be taken into account, that in the case of Pt−V/C, the metal is finely dispersed on the carbon support. In contrast, a comparably large number of cobalt atoms are buried deeply in the sponge-like Raney Co and thus not available for catalysis. Heterogeneous catalysts featuring cobalt which is immobilized on carrier materials might improve the reaction rates.

Raney Ni, which is highly pyrophoric when freshly prepared,[26] has also been used for hydrogenations in order to compare its performance to Raney Co. Raney Ni showed lower catalytic performance compared to cobalt and slightly higher dehalogenation. We observed that Raney Ni lost its catalytic activity in hydrogenation reactions successively, when it was stored for several months in water at ambient atmosphere. In contrast, Raney Co showed stable catalytic activity after up to 1.5 years of storage time under the same conditions. The Raney Co used in this study contained up to 2.5% nickel as specified by the manufacturer; varying amounts of nickel in Raney Co might lead to differences in catalytic performance. In our hands

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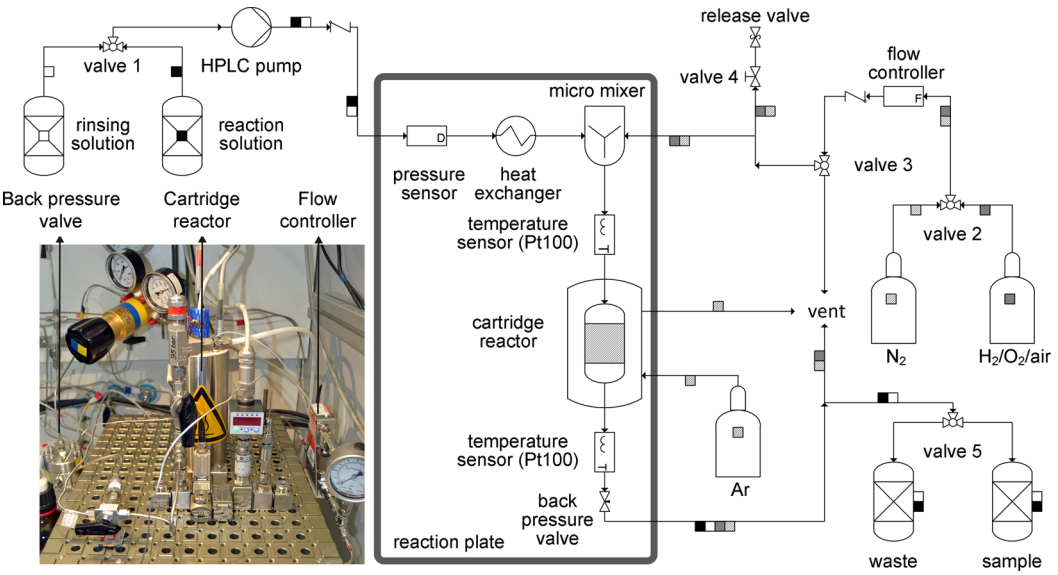

Figure 7. Flow scheme of the reaction setup for continuous flow reactions with a solid catalyst bed in microfluidic devices.

Raney Co was less pyrophoric than freshly prepared Raney Ni. However, when water was removed by washing of the Raney cobalt catalyst with EtOH and drying of the catalyst was attempted under a constant stream of air, the material eventually ignited. In general, using a pyrophoric material will hamper the scale-up of a reaction.

To summarize, Pt−V/C is by far more active than Raney Co, but less selective, especially at higher concentrations, while Co is selective over a broad range of concentrations. After these screening experiments with reaction volumes of 10 mL, we wished to evaluate hydrogenations with Raney Co on larger scale using the previously optimized conditions.

Scale-Up Experiments. The scale-up experiments were performed with low substrate concentration (0.05 M) in order to minimize effects of increasing dehalogenation with a higher substrate concentration (Figure 4). First, the 10 mL reaction volume used in the screening experiments was increased to 200 mL in a 300 mL autoclave, all other parameters staying constant (Figure 5).

With Pt−V/C as well as with Raney Co, it was observed that after full conversion, additional reaction time was necessary before maximal yields of 4-iodoaniline **4a** were obtained, an observation which can be attributed to the reduction of hydroxylamine **3** and diazo compounds **7**−**9**. Reactions with Pt−V/C showed a strong increase of the dehalogenation rate immediately after reaching full conversion (Figure 5a) as opposed to reactions with Raney Co (Figure 5b) where dehalogenation increased from 0.5% (260 min) to 0.8% (450 min). 4-Iodoaniline **4a** was formed in 81% yield.

After the promising results with 200 mL reaction volume, we focused on scale-up experiments with Raney Co (Figure 6). Upon scaling up from 10 to 200 mL reaction volume, longer reaction times were required for full conversion (Figure 6a) and maximum product formation (Figure 6b). Heating was slower for larger reaction volumes. However, this can only partially account for the longer reaction time (at 10 mL scale, autoclaves were heated with a preheated block, heating the reaction solution to 110 °C was completed after 1−2 min; on 200 mL scale heating required 40 min). For this reason it can be assumed that the decreased performance might be due to a hydrogen mass transfer limitation. Scaling up from 200 to 1000 mL necessitated using a multipurpose 1.8 L stainless steel autoclave. This autoclave had been used with a variety of rhodium-, palladium-, and platinum-based catalysts before. After dismantling, manual scrubbing, and using clean-in-place cleaners,[27] hydrogenation experiments with 1-iodo-4-nitrobenzene **1a**, but without Raney Co were performed in order to determine the influence of residual catalysts. After 6 h at 110 °C and 20 bar H_2, 10% of substrate **1a** were converted to a mixture of nitrobenzene, 4-iodoaniline, and aniline. Further suppression of the background reactivity could not be achieved by cleaning. Accordingly, the yields for **4a** which had been observed on a 10 and 200 mL scale could not be attained on a 1000 mL scale. After full conversion of **1a** (Figure 6a), comparatively stronger dehalogenation of 4-iodoaniline **4a** to aniline **6a** was observed (not shown). Concomitantly, the yield of 4-iodoaniline **1a** decreased (Figure 6b).

Therefore, using highly selective Raney Co on sensitive substrates in batch processes might necessitate the use of designated equipment. At this point, we investigated the use of Pt−V/C and Raney Co in continuous flow hydrogenations.

Flow Experimental Setup. Continuous reactions were performed using a customized microreactor, based on a modular microreaction system from Ehrfeld Mikrotechnik BTS (Figure 7).[28]

A Knauer K-501 HPLC pump (0.001−9.999 mL/min)[29] was used to pump the reaction solution through the microreactor. Valve 1 allowed switching between a rinsing solution used for conditioning and washing of the catalyst and the reaction solution. A check valve behind the pump ensured that no gas could pass from the reaction system to the HPLC pump. After passing a pressure sensor and a heat exchanger, which allowed to preheat the reaction solution, liquid and gaseous phase were combined in a micro mixer. The gaseous phase was introduced into the system with a mass flow controller.[30] Valve 2 allowed switching between nitrogen and hydrogen. In order to prevent uncontrolled pressure build-up in case of clogging, a pressure release valve (95 bar) was included into the system. After passing a temperature sensor, the gas−liquid mixture was introduced into an Ehrfeld cartridge reactor 240. For safety reasons, the housing of this cartridge reactor was continuously flushed with argon during the hydrogenations. The total

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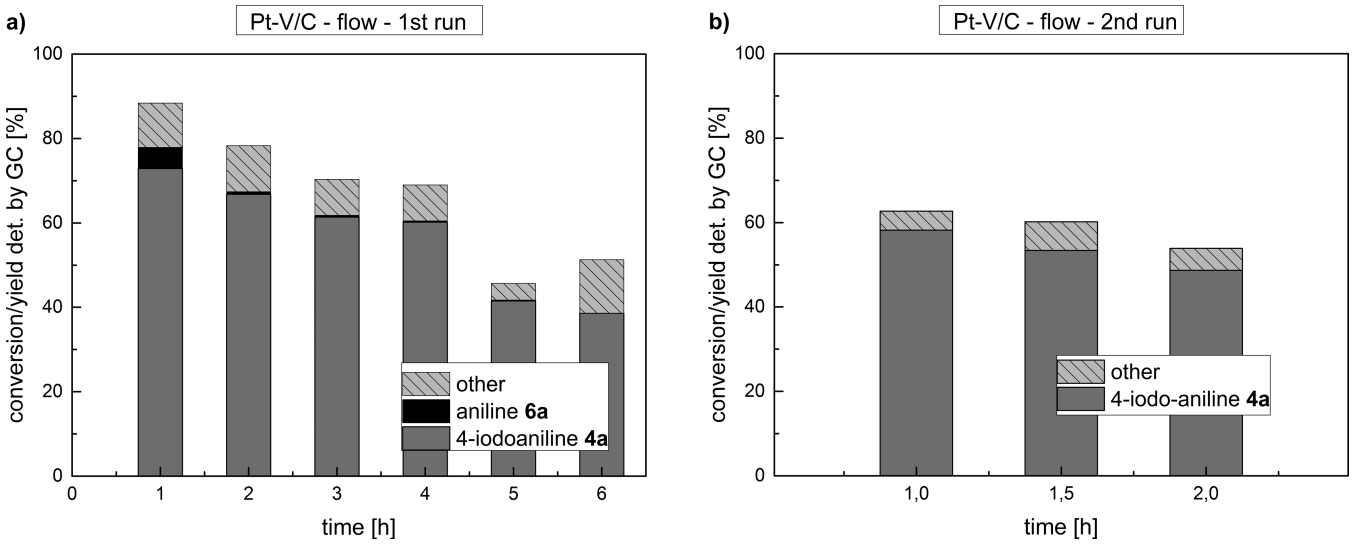

Figure 8. Product composition in the continuous hydrogenation of 1-iodo-4-nitrobenzene **1a** with Pt−V/C; (a) first run, and (b) second run after cartridge recycling; reaction conditions: 547 mg of Pt−V/C (11 μmol Pt), 20 bar of H_2, 95 °C, 0.125 M in THF, 1.25 mL/min, cartridge recycling after 6 h: washing with THF (1 mL/min, 30 min), then second run of hydrogenation under otherwise identical conditions, analytical standard: diethylene glycol dibutyl ether; dark gray: 4-iodoaniline **4a**, black: aniline **6a**, light gray-striped: unmonitored compounds based on detected starting material. The absolute height of the bars reflects conversion of the starting material **1a**.

volume of the reactor was 5 mL; the catalyst bed in the cartridge had a constant volume of 2.5 mL. After leaving the reactor, the mixture passed a second temperature sensor and an Equilibar back pressure valve,[31] which assured precise back-pressure control. Valve 5 allowed to switch between discarding and collecting of the reaction mixture. The Ehrfeld cartridge reactor 240 has a pressure limit of 100 bar at 25 °C and 90 bar at 150 °C. In this study we limited the pressure to 85 bar and the temperature to 150 °C.

Flow Experiments with Pt−V/C. When this system was used with Pt−V/C, the conversion of 1-iodo-4-nitrobenzene **1a** usually decreased rapidly over time. Figure 8a shows a typical experiment, with conversion dropping from 88 to 51% over 5 h. Flushing reactor and catalyst with THF could only partially restore the catalytic activity (Figure 8b).

This effect was more pronounced at temperatures below 100 °C, but even at temperatures as high as 150 °C, conversion dropped from 100 to 80% over 6 h. Decreasing the concentration to 0.05 M or reducing the flow rate to 0.5 mL/min did not alter this effect. Pt−V/C did not meet our expectation to show stable performance over time, which is perceived to be an important prerequisite for continuous flow reactions. For this reason, comparison to the reactions in batch was not possible and the continuous hydrogenation of other nitroaromatics was not further investigated with Pt−V/C as catalyst. Continuous hydrogenation with Raney Co was investigated next.

Continuous Hydrogenation with Raney Co. Under continuous flow conditions, Raney Co showed higher long-term stability in comparison to Pt−V/C. Compared to hydrogenations in batch (Figure 5b) at 20 bar and 110 °C, it was found that increasing the pressure to 85 bar and lowering the temperature to 80 °C, increased the yield of 4-iodoaniline **4a** from 80 to 90% together with slightly higher overall dehalogenation to aniline **6a** between 1.5 and 2% at full conversion (Figure 9). 1−2 h of equilibration were required to reach stable catalytic performance. Three equiv of hydrogen were used for these experiments. Increasing the hydrogen flow

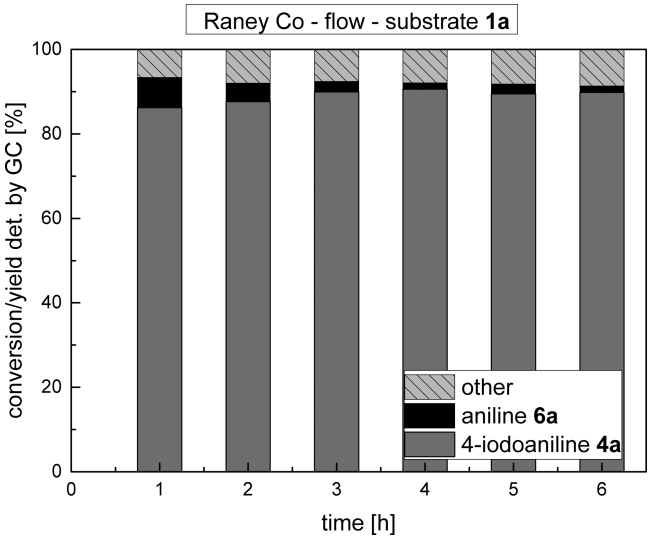

Figure 9. Continuous hydrogenation of 1-iodo-4-nitrobenzene **1a** with Raney Co; reaction conditions: 1.32 g of Raney Co (16.9 mmol Co), 85 bar H_2, 1.8 mL of H_2/min, 80 °C, 0.05 M in THF/H_2O (95:5), 0.5 mL/min; dark gray: 4-iodoaniline **4a**, black: aniline **6a**, light gray, striped: unmonitored compounds based on detected starting material.

to 9 equiv with respect to the substrate did not change the catalytic performance significantly. After 7 h, the system was flushed with THF and could be reused for several different substrates before a drop in performance became apparent.

Application to Pharmaceutically Relevant Substrates. While 1-iodo-4-nitrobenzene **1a** represents a suitable model compound for the profiling of different catalysts and the optimization of general reaction conditions, we also investigated transformations, which are relevant examples for the synthesis of active pharmaceutical ingredients.

The reduction of *N*-(4-chlorophenyl)-2-nitroaniline **1b**, an intermediate in the synthesis of clofazimine, which is used for the treatment of leprosy,[32] has been reported using stoichiometric amounts of zinc,[33a] iron powder,[33b] or

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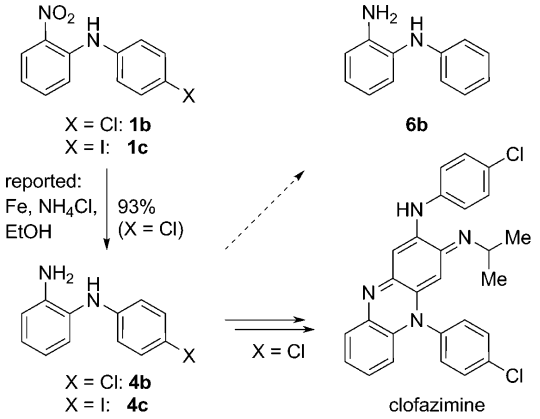
$SnCl_2$[33c] (Scheme 1). Interestingly, unlike 1-iodo-4-nitrobenzene **1a**, nitro compound **1b** features a chlorine atom

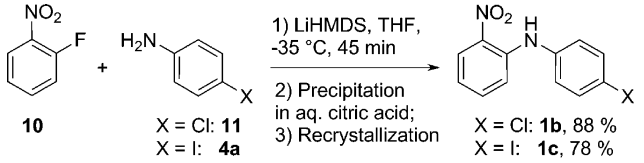
Scheme 1. Reduction of *N*-(4-Chlorophenyl)-2-nitroaniline 1b in the Synthesis of Clofazimine,[33b] Reduction of Iodinated Analogue 1c, and Reduction to Dehalogenated Aniline 6b



which is attached to an electron-rich aniline. Therefore, we also investigated iodinated model compound **1c** to benchmark our reaction setup, assuming that this substrate would be even more prone to dehalogenation to aniline **6b** than electron-poor nitroaromatic **1a**.

The synthesis of *N*-(4-chlorophenyl)-2-nitroaniline **1b** from 1-fluoro-2-nitrobenzene **10** and 4-chloro-aniline **11** (Scheme 2)

Scheme 2. Synthesis of Halogenated Nitro Compounds 1b and 1c; LiHMDS: Lithium Bis(Trimethylsilyl)amide

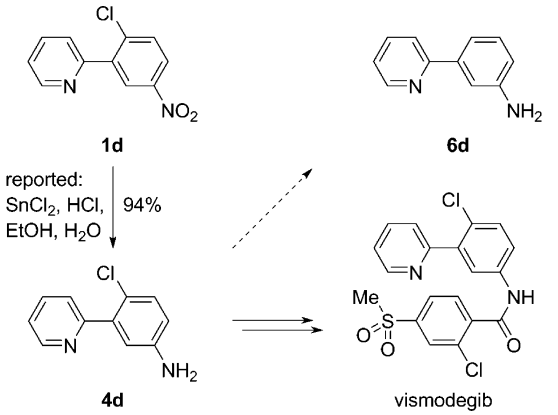


has been described using KF at 180 °C for 48 h.[34] However, strong decomposition was observed when these conditions were used for the synthesis of iodoaniline **1c**. Using the stronger base LiHMDS at −35 °C, complete and clean conversion was achieved after 45 min. After inverse quench into 10% citric acid, washing of the precipitate and recrystallization, chloroaniline **1b** and iodoaniline **1c** were obtained in 88 and 78% yield, respectively (Scheme 2). This procedure was easily scalable to produce 40−50 g batches of diphenylamines **1b** and **1c**.

The selective transformation of chlorinated nitro compound **1d** to aniline **4d** en-route to the Hedgehog signaling pathway inhibitor vismodegib (Scheme 3) has been described to be challenging and is only reported to be successful by using overstoichiometric amounts of iron or $SnCl_2$.[35] Nitroaromatic **1d** also features a pyridyl substituent, which is potentially prone to reduction. Hence, we felt it would be worthwhile to investigate the catalytic hydrogenation of **1d**. This substrate was synthesized according to previously described procedures.[35]

Figure 9, Figure 10a, and Figure 10b show a three-day hydrogenation experiment using the same Raney Co cartridge for nitro compounds **1a**−**1c**. After hydrogenation of 1-iodo-4-nitrobenzene **1a** on day 1 (Figure 9), the cartridge was reused

Scheme 3. Reduction of 4-Chloro-3-(pyridine-2-yl)nitrobenzene 1d in the Synthesis of Vismodegib[35] and Reduction to Dehalogenated Aniline 6d



at slightly higher temperature (80 → 100 °C) for hydrogenation of nitro compounds **1b**−**1c** on days 2 and 3.

Clofazimine precursor **1b** was hydrogenated on day 2, yielding the corresponding chloroaniline **4b** almost quantitatively (Figure 10a). Dehalogenation occurred below the detection limit of the HPLC analysis (ca. 0.5%). On day 3, iodinated analog **1c** showed 2.5−3.5% dehalogenation at conversions of 98−100% (Figure 10b).

Subjecting the same catalyst cartridge to vismodegib precursor **1d** on day 4, almost quantitative conversion and 1−2% dehalogenation were observed by HPLC. However, upon HPLC monitoring of this hydrogenation, an additional side product was observed, eluting together with chloroaniline **4d**. The two peaks could not be separated completely by HPLC, but after evaporation of the solvent mixture this compound was converted into the azoxy compound[36] (approximately 10% in the crude product), suggesting that the unidentified side product could have been the hydroxylamine intermediate 4-chloro-*N*-hydroxy-3-(pyridine-2-yl)-aniline.

The experiment with vismodegib precursor **1d** of day 4 was repeated with fresh catalyst (Figure 10c). No formation of hydroxylamine or azoxy compound was observed in this experiment, which suggests beginning deactivation of the catalyst in the previous experiment. Higher dehalogenation tendency compared to the aromatic chloride **1b** (<0.5% vs 2%) might be explained by the adjacent coordination site provided by the pyridine nitrogen.

After equilibration times of 1−2 h, the reaction mixtures of **4b**−**4d** were collected for the purpose of product isolation (Table 1). Entry 1 shows conversion and product composition of crude model compound **4a** for comparison. After collecting for 5−6 h (total hydrogenation time: 7 h) acid−base extraction was used in order to separate the crude products **4b** − **4d** from the internal analytical standards. Dispersion in acidic aqueous solution as aqueous ammonium salt was followed by washing with organic solvents. For clofazimine related anilines **4b** and **4c**, this procedure also allowed to remove traces of unreacted starting materials (Table 1, entries 2−5). Aniline **4b** was isolated by this procedure with a yield of 98% (entry 3). Iodinated analog **4c** was isolated with a yield of 90% after washing, but contained 2% of the dehalogenated derivative **6c** (entry 5). This impurity could be further depleted by crystallization to furnish iodinated aniline in an overall yield

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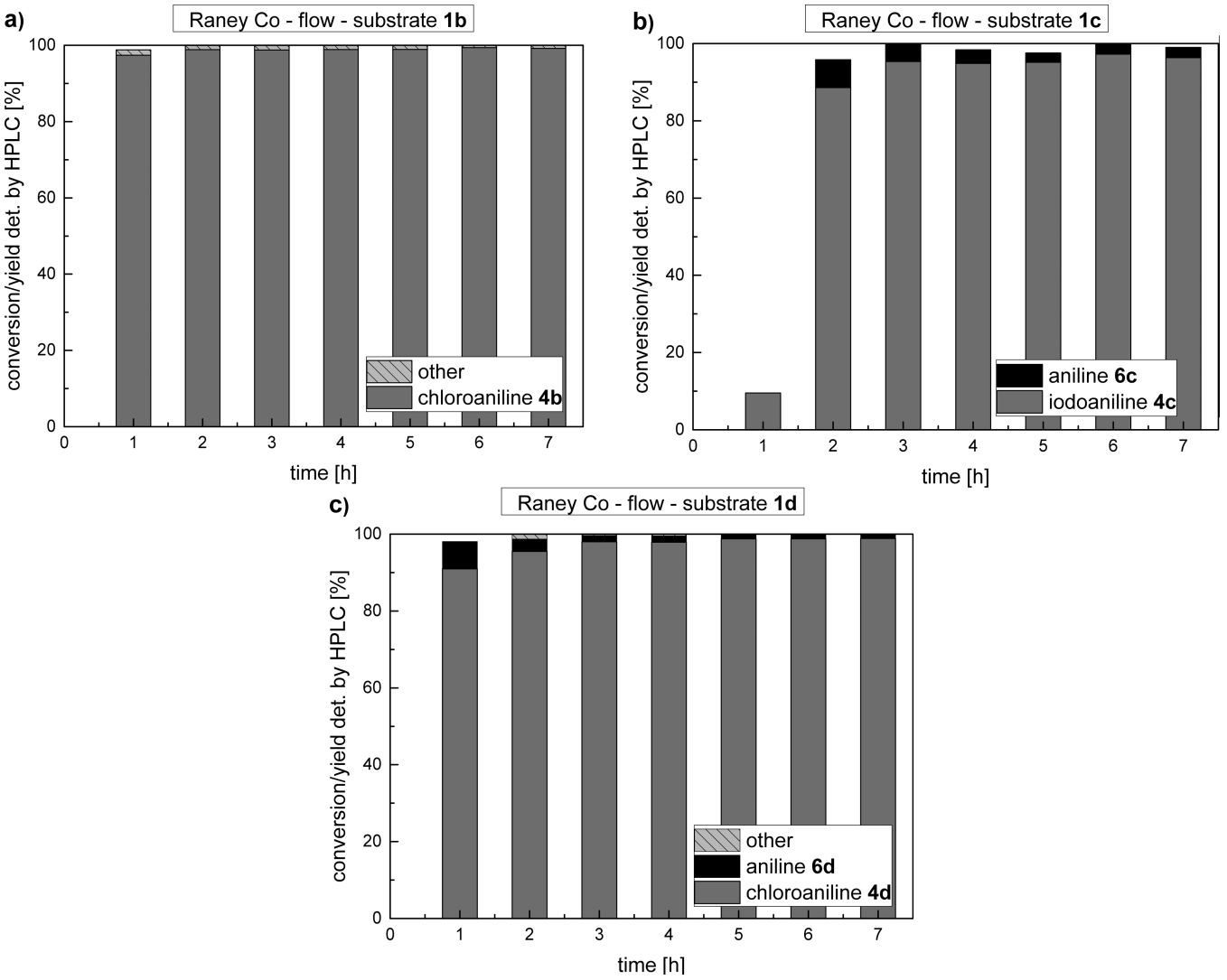

Figure 10. Continuous hydrogenation of other substrates with Raney Co; (a) nitro compound **1b** (day 2); conditions and cartridge from day 1 (Figure 9) but at 100 °C; dark gray: chloroaniline **4b**, light gray, striped: unmonitored compounds based on detected starting material; (b) nitro compound **1c** (day 3); conditions and cartridge from day 2; dark gray: iodoaniline **4c**, black: aniline **6c**; (c) nitro compound **1d**; reaction conditions as for day 3 but in THF/H_2O (9:1), fresh catalyst used; dark gray: chloroaniline **4d**, black: aniline **6d**, light gray, striped: unmonitored compounds based on detected starting material. The absolute height of the bars reflects conversion of the starting material.

of 78% (entry 6). In case of the vismodegib intermediate, the previously described washing procedure delivered the chlorinated aniline **4d** together with 2% of dehalogenated aniline **6d** (entries 7−8). Again, removal of the dehalogenated aniline **6d** was possible by crystallization (entry 9), giving chlorinated aniline **4d** with an overall yield of 88%.

CONCLUSION

The catalysts Pt−V/C and Raney Co were found to be high performance catalysts in the selective hydrogenation of halogenated nitroaromatics. Dialkylethers like THF, 2-methyl-THF, or $MeOC_5H_9$ are suitable solvents for this transformation, because they show both, high substrate solubilities and high hydrogenation rates. Alternatively, anisole and toluene are also suitable as solvents but showed lower substrate solubilities and hydrogenation rates in our investigation. In the hydrogenation of 1-iodo-4-nitrobenzene **1a** using Pt−V/C and THF in batch, selective reaction to 4-iodo-aniline **4a** was highly dependent on the substrate concentration. In contrast, using Raney Co with different substrate concentrations did not significantly affect the selectivity. Upon scale-up of batch hydrogenations, it was found that undesired background reactions can play a role when using multipurpose equipment.

Moving to continuous flow conditions using Pt−V/C led to a fall in catalyst performance under various conditions, which is in agreement with previous work.[17f] This prevented use of Pt−V/C for long-term continuous hydrogenation at high conversion. On the other hand, Raney Co showed stable catalytic performances in continuous flow for up to 20 h reaction time. Chlorinated intermediates of the active pharmaceutical ingredients clofazimine and vismodegib as well as iodinated model compounds were hydrogenated with Raney Co in continuous flow and less than 2% dehalogenation at nearly quantitative conversions. Depending on the substrate, aqueous extraction or crystallization afforded the pure anilines in overall yields of 78−98%.

It has to be kept in mind that cobalt gives space−time yields which are almost 1 order of magnitude lower than space−time yields for Pt−V/C. However, at the same time the price per mol cobalt is more than 1 order of magnitude lower than the

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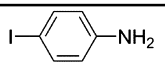
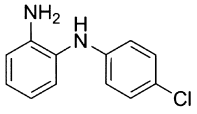
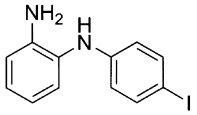
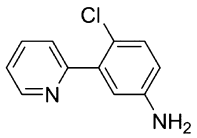
Table 1. Data on Hydrogenation of 4-Iodoaniline 4a and Isolation of Halogenated Anilines 4b−4d by Extraction and Crystallization

Entry	Product 4b – 4d	Reaction step	Conversion 1b – 1d [%]	Yield [%]	Product Composition	
					Halo-amino 4b – 4d [%]	Dehal. aniline 6b – 6d [%]
1	 4a	crude[a]	100		90	2
2	 4b	crude[a]	100		>99	<0.5
3		after extraction[b]		98	>99	<0.5
4	 4c	crude[a]	97		95	2
5		after extraction[b]		90	98	2
6		after crystallization[b]		78	>99	<0.5
7	 4d	crude[a]	100		98	2
8		after extraction[b]		100	98	2
9		after crystallization[b]		88	>99	<0.5

[a]Product compositions were determined by HPLC with internal analytical standard. [b]Product compositions were determined by comparing peak areas of HPLC separations at 230 nm.

price per mol platinum. Nevertheless, considering scale-up and process intensification, optimization toward higher substrate concentration and flow rate will be crucial for further development.

OUTLOOK

A rational choice between batch and flow might be alleviated by the following approach. In a first step, a catalyst system suitable for the given transformation should be identified. A quick evaluation of a suitable parameter window in batch will allow to judge whether development of a flow process might be useful. This can be the case for very fast and exothermic reactions or if the reaction has to be stopped within a short time frame, e.g., to isolate an intermediate. It might also be useful if very high pressures or temperatures are necessary or if mass transport limitations play an important role in the process. Telescoping into a second reaction or continuous workup can streamline a process, but it can also be inevitable if the intermediate is unstable or highly toxic.[14]

At the moment, we are also investigating catalysts with higher hydrogenation rates like Pt and Pd. For these catalysts, advantages like precise control over residence time and increased availability of hydrogen on the catalyst surface might favor selectivity in continuous processing. However, a sustainable process should involve recycle/reuse of the precious metals from used catalysts.

For cobalt-based systems, tolerance of other functional groups and the reduction of solvent amounts and catalyst loadings will be vital in order to exploit the surpassing chemoselectivity for technical applications.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Substrates 1b and 1c. The corresponding haloaniline **11** or **4a** (178.9 mmol) was dissolved in THF (90 mL) and cooled to −50 °C. After addition of 1-fluoro-2-nitrobenzene **10** (25 g, 177.2 mmol) and rinsing with THF (35 mL), LiHMDS (1 M solution in THF, 354 mL, 354 mmol) was added dropwise over 30 min. The purple reaction mixture was stirred at −40 to −30 °C until the 1-fluoro-2-nitrobenzene was completely converted (30−45 min, monitored by GCMS). The reaction mixture was added over approximately 20 min to 10% aqueous citric acid (2000 mL) at 0 °C. The dark red precipitate was washed with water (1000 mL) and dried in vacuo. The crude product was recrystallized as indicated to give bright red needles of the corresponding *N*-(4-halophenyl)-2-nitroaniline.

N-(4-Chlorophenyl)-2-nitroaniline ***1b***.[34] Recrystallized from EtOH (2200 mL) and water (900 mL). Yield: 39.1 g (88%) *N*-(4-chlorophenyl)-2-nitroaniline; purity: 98%, determined by quantitative NMR using dimethyl sulfone (Sigma-Aldrich standard for quantitative NMR, catalog no. 41867) as internal analytical standard; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.30 (s, 1H), 8.11 (dd, J = 8.5, 1.6 Hz, 1H), 7.52 (ddd, J = 8.6, 7.0, 1.6 Hz, 1H), 7.47−7.39 (m, 2H), 7.37−7.29 (m, 2H), 7.21 (dd, J = 8.6, 1.2 Hz, 1H), 6.92 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 141.2, 138.7, 135.9, 134.3, 129.3, 128.2, 126.2, 124.8, 118.7, 117.3; HRMS (ESI): for $C_{12}H_9ClN_2NaO_2$ ($[M + Na]^+$) calc.: 271.02448, found: 271.0245.

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N-(4-Iodophenyl)-2-nitroaniline ***1c.*** Recrystallized twice from EtOAc (600 mL), EtOH (2275 mL), and water (420 mL). Yield: 48.3 g (79%) *N*-(4-iodophenyl)-2-nitroaniline. Purity: 98%, determined by quantitative NMR using dimethyl sulfone (Sigma-Aldrich standard for quantitative NMR, catalog no. 41867) as internal analytical standard; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.26 (s, 1H), 8.10 (dd, J = 8.5, 1.6 Hz, 1H), 7.76−7.65 (m, 2H), 7.52 (ddd, J = 8.6, 7.0, 1.6 Hz, 1H), 7.25 (dd, J = 8.6, 1.2 Hz, 1H), 7.19−7.07 (m, 2H), 6.93 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 140.8, 139.7, 138.1, 135.9, 134.6, 126.2, 125.0, 118.9, 117.5, 88.1; HRMS (ESI): for $C_{12}H_8IN_2O_2$ ([M − H]$^-$) calc.: 338.96359, found: 338.9641.

Three-Day Hydrogenation Experiment in the Ehrfeld Microreaction System with Halogenated Nitro Compounds 1a−c. *Reactor Cartridge Preparation.* Raney Co (1.322 g, ca. 16.8 mmol) was mixed with glass beads (20−200 μm) to give a total volume of 2.5 mL. The cartridge (Ehrfeld cartridge reactor 240) was consecutively filled with layers of glass wool (150 mg), Celite (150 mg), glass wool (150 mg), the mixture of catalyst with glass beads, glass wool (150 mg), Celite (150 mg), and glass wool (150 mg).

Day 1: Hydrogenation of 1-Iodo-4-nitrobenzene ***1a.*** 1-Iodo-4-nitrobenzene (6.358 g, 12.5 mmol) and diethylene glycol dibutyl ether (2.781 g, 6.3 mmol, analytical standard) were dissolved in 500 mL of stabilized THF and water (95:5). The Ehrfeld system was equilibrated with THF (0.5 mL/min) and H_2 (3 equiv corresponding to the substrate) at 80 °C and 85 bar for 30 min before switching to the substrate solution. Samples were collected hourly, diluted with stabilized THF (1:5) and analyzed by GC. After 6 h the system was rinsed with pure THF for 45 min to be reused on day 2.

Day 2: Hydrogenation of N-(4-Chlorophenyl)-2-nitroaniline ***1b.*** *N*-(4-chlorophenyl)-2-nitroaniline **1b** (3.177 g, 12.5 mmol) and 2-methoxynaphtalene (333 mg, 2.1 mmol, analytical standard) were dissolved in 250 mL of stabilized THF and water (95:5). The Ehrfeld system was primed with THF (0.5 mL/min) and H_2 (3 equiv corresponding to the substrate) at 100 °C and 85 bar for 10 min before switching to the substrate solution. Samples were collected every 30 min, diluted with MeOH (20 volumes), and analyzed by HPLC. The reaction solution was collected in 30 min fractions. After 7 h the system was rinsed with THF for 45 min and reused on day 3. The fractions collected between 60 and 420 min were combined and concentrated in vacuo. The crude product was dissolved in EtOH (45 mL) and aq. HCl (0.45 M, 150 mL) was added. The mixture was extracted with petroleum ether (3 × 30 mL). pH 10 carbonate buffer (79 mL, cf. Supporting Information) was added to the aqueous solution, and the precipitate was filtered and washed with water until the filtrate reached pH 7. The precipitate was dried in vacuo to give *N*-(4-chlorophenyl)-benzene-1,2-diamine **4b**[33] (1.936 g, 98%) as beige-colored solid (>99% area by HPLC, 230 nm). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19−7.12 (m, 2H), 7.12−7.00 (m, 2H), 6.84−6.73 (m, 2H), 6.69−6.60 (m, 2H), 5.19 (bs, 1H), 3.39 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.2, 142.1, 129.3, 128.1, 126.3, 125.2, 124.0, 119.4, 116.38, 116.37; HRMS (ESI): for $C_{12}H_{12}ClN_2$ ([M + H]$^+$) calc.: 219.06835, found: 219.0686.

Day 3: Hydrogenation of N-(4-Iodophenyl)-2-nitroaniline ***1c.*** *N*-(4-Iodophenyl)-2-nitroaniline **1c** (4.386 g, 12.5 mmol) and 4-methylanisole (1.541 g, 2.0 mmol, analytical standard) were dissolved in 250 mL of stabilized THF and water (95:5). The Ehrfeld system was equilibrated with THF (0.5 mL/min) and H_2 (3 equiv corresponding to the substrate) at 100 °C and 85 bar for 10 min before switching to the substrate solution. Samples were collected every 30 min, diluted with MeOH (20 volumes), and analyzed by HPLC. The reaction solution was collected in 30 min fractions. The fractions collected between 120 and 420 min were combined and concentrated in vacuo. The crude product was dissolved in a mixture of EtOH (60 mL) and THF (52 mL); then aq. HCl (0.45 M, 145 mL) was added. The mixture was extracted with petroleum ether (2 × 40 mL). The aqueous phase was filtered, and the filter was washed with a mixture of EtOH (20 mL), THF (17 mL), and aq. HCl (48 mL). After adding pH 10 carbonate buffer (105 mL) to the combined aqueous phases, the mixture was extracted with EtOAc (3 × 150 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo to give *N*-(4-iodophenyl)benzene-1,2-diamine **4c** as a purple solid (2.100 g, 90%), which contained around 2.5% *N*-phenylbenzene-1,2-diamine **6b** (det. by comparing HPLC peak areas at 230 nm). The crude product was recrystallized from a mixture of EtOAc (34 mL) and *n*-heptane (165 mL, 80 °C to −30 °C). The mother liquor was concentrated in vacuo and recrystallized from a mixture of EtOAc (4 mL) and *n*-heptane (10 mL, 80 °C to −30 °C). The beige-colored crystals were washed with cold *n*-pentane (0 °C, 3 × 5 mL) and dried in vacuo to give *N*-(4-iodophenyl)benzene-1,2-diamine **4c** in a combined yield of 78% (containing approximately 0.4% *N*-phenylbenzene-1,2-diamine **6b** and 0.3% of the diiodinated azoxycompound *N*-(4-iodophenyl)-2-[{2-[(4-iodophenyl)amino]phenyl}-*NNO*-azoxy]aniline, det. by HPLC comparing peak areas at 230 nm). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.42−7.35 (m, 2H), 7.33 (s, 1H), 6.97 (dd, J = 7.8, 1.5 Hz, 1H), 6.88 (ddd, J = 7.9, 7.3, 1.5 Hz, 1H), 6.74 (dd, J = 8.0, 1.5 Hz, 1H), 6.58−6.47 (m, 3H), 4.75 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 146.1, 143.0, 137.1, 126.4, 125.0, 124.3, 116.6, 116.4, 115.3, 78.1; HRMS (ESI): for $C_{12}H_{12}IN_2$ ([M + H]$^+$) calc.: 311.00397, found: 311.0041.

Hydrogenation of 2-(2-Chloro-5-nitrophenyl)pyridine 1d with Fresh Catalyst. The reactor cartridge was filled with fresh Raney Co as described before. 2-(2-Chloro-5-nitrophenyl)pyridine **1d** (3.087 g, 12.5 mmol) and 2-methoxynaphtalene (332 mg, 2.1 mmol) were dissolved in 250 mL of stabilized THF and water (9:1). The Ehrfeld system was primed with THF (0.5 mL/min) and H_2 (3 equiv corresponding to the substrate) at 100 °C and 85 bar for 45 min before switching to the substrate solution. Samples were collected every 30 min, diluted with MeOH (20 volumes) and analyzed by HPLC. The reaction solution was collected in 30 min fractions. The fractions collected between 90 and 420 min were combined and concentrated in vacuo. The crude product was suspended in EtOH (35 mL), and aq. HCl (0.45 M, 120 mL) was added. The mixture was extracted with petroleum ether (3 × 25 mL) and EtOAc (1 × 15 mL). pH 10 carbonate buffer (65 mL) was added, and the aqueous phase was extracted with EtOAc (4 × 50 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo to give 4-chloro-3-(pyridin-2-yl)aniline **4d** as a yellow solid (1.622 g, 96%, containing 2% 3-(pyridin-2-yl)aniline **6d**, det. by HPLC comparing peak areas at 230 nm). The crude product was recrystallized from toluene (27 mL, 80 °C to −30 °C) and *n*-pentane (8 mL). The yellow-colored crystals were washed with *n*-pentane (3 × 1 mL) and dried in vacuo to give 4-chloro-3-(pyridin-2-yl)aniline **4d**[35] (1.485 g, 88% yield, >99% purity, det. by HPLC, 230 nm). ^{1}H NMR (400 MHz, benzene-d_6): δ =

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8.57 (ddd, J = 4.8, 1.9, 1.0 Hz, 1H), 7.53−7.50 (m, 1H), 7.17−7.15 (m, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.70 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 6.09 (dd, J = 8.5, 2.9 Hz, 1H), 2.88 (bs, 2H); ^{13}C NMR (100 MHz, benzene-d_6): δ = 157.8, 149.8, 146.1, 140.4, 135.3, 130.9, 125.0, 122.1, 121.0, 118.5, 116.2; HRMS (ESI): for $C_{11}H_{10}ClN_2$ ([M + H]$^+$) calc.: 205.05270, found: 205.0528.

■ ASSOCIATED CONTENT

Supporting Information

Additional experiments and data on catalysts and analytical methods. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00170.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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