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Scalable Wolff−Kishner Reductions in Extreme Process Windows Using a Silicon Carbide Flow Reactor

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Supporting Information

ABSTRACT: A safe and scalable continuous flow strategy for Wolff−Kishner reductions that employs methanol as the solvent has been developed. The use of low-cost hydrazine as the reducing agent in combination with a caustic base provides an atom-efficient, environmentally friendly method for the deoxygenation of aldehydes and ketones to alkanes. Because of the required harsh and corrosive reaction conditions (200 °C, 50 bar), reactor materials such as stainless steel, glass, or any type of polymer have compatibility problems, rendering this process problematic on a production scale. The use of corrosion-resistant silicon carbide (SiC) as the reactor material opens up the possibility of performing Wolff−Kishner reductions on scale with a considerably improved safety profile. Methanol as the solvent significantly simplifies the workup procedure compared with the generally employed high-boiling solvents such as diethylene glycol. The continuous flow protocol was applied to a number of substrates and provided the desired products in good to high yields with space-time yields of up to 152 g L^{-1} h^{-1}. In addition, a pharmaceutically valuable active pharmaceutical ingredient precursor was synthesized by employing this high-temperature/pressure Wolff−Kishner protocol.

KEYWORDS: *reduction of carbonyls, hydrazine, process intensification, continuous flow, silicon carbide*

INTRODUCTION

Hydrazine has been used as a hydrogenation agent in synthetic organic chemistry for more than a century.[1] In particular, employing hydrazine in the presence of a strong base for the conversion of the carbonyl functionality in aldehydes and ketones into a methylene moiety has attracted considerable interest and is commonly known as the Wolff−Kishner reduction.[2−6] The original protocols require the preformation and isolation of the corresponding hydrazones, which are then added to a hot solution of the base.[2,3] Since then, several modifications have been developed, with the Huang−Minlon modification nowadays being the most frequently used procedure.[7] Compared with the original Wolff−Kishner protocol, the use of hydrazine hydrate—instead of highly explosive anhydrous hydrazine—in the presence of KOH or NaOH in a high-boiling solvent such as diethylene glycol renders the process much safer. In addition, the isolation of the (sometimes) unstable hydrazone intermediate prior to the actual reduction step can often be avoided. The Huang−Minlon procedure takes place over three steps (Scheme 1) and usually requires extended reaction times of several hours. First, the hydrazone is formed with a large excess of hydrazine hydrate under reflux conditions. To shift the equilibrium toward the hydrazone intermediate, the temperature is increased in order to remove the generated water and residual hydrazine hydrate. During the hydrazone formation process, azine byproduct formation via reaction of the hydrazone with the carbonyl compound is often an issue (Scheme 1).[4,5] The third stage involves an irreversible thermal reduction with KOH (>180 °C) that includes rapid nitrogen liberation.

Compared with other deoxygenation methods, such as the Clemmensen reduction, the use of metal hydrides with a Lewis acid, and metal-catalyzed hydrogenations, the Wolff−Kishner reduction is probably the most appealing because of the low cost and atom efficiency of hydrazine as a reducing reagent.[4] The only chemical waste products formed are environmentally benign water and nitrogen. However, from an industrial manufacturing point of view this protocol raises serious concerns regarding safety and reactor material compatibility. Hydrazine hydrate is a highly toxic, potentially carcinogenic, and corrosive liquid with a relatively low boiling point (120 °C) considering the required reaction temperature of around 180−200 °C. In particular, the accumulation of this volatile reaction component in the headspace of a batch reactor can result in violent explosions.[8] Employing continuous flow technology can overcome this limitation by eliminating gaseous headspace and reducing the exposure risk for the operator.[9,10] Other benefits in addition to increased safety are better process control and product quality along with a greater

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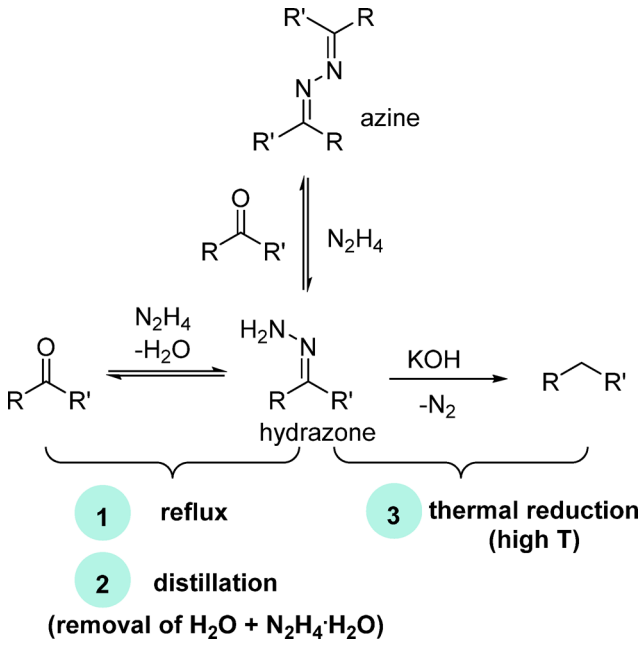
Scheme 1. Huang–Minlon Modification of the Wolff–Kishner Reduction



ability to seamlessly translate from lab scale to industrial scale, which significantly reduces the discovery-to-manufacturing time frame. These advantages are the main drivers for the pharmaceutical industry to implement continuous processes in active pharmaceutical ingredient (API) manufacturing.[11−16]

Furthermore, continuous reactors provide a wide temperature window and high pressure resistance, which together with their exceptional mass and heat transfer capacities make these reactors perfect tools for employing intensified conditions ("novel process windows") on scale.[17−20] Temperatures far beyond the atmospheric boiling point of a solvent can be safely attained, and consequently, the reaction rate can often be accelerated. High-temperature/high-pressure (high-T/p) processes require robust reactor materials and are usually conducted in stainless steel coils or other special alloys. However, as hydrazine is known to decompose in the presence of metals, stainless steel should be avoided as a reactor material, especially at high temperatures.[8] In the case of the Wolff–Kishner reaction, the use of glass is also not ideal, as the high concentration of base can cause etching of the glass at elevated temperature.[21]

In recent years, sintered silicon carbide (SiC) has been increasingly used in organic synthesis as an alternative to glass or stainless steel as the reactor material.[21−24] This chemically inert and corrosion-resistant advanced ceramic material can be utilized at extremely high temperatures because of its high thermal conductivity and very low thermal expansion coefficient (4.1×10^{-6} K^{-1}).[25] Microwave vials made of SiC allow the use of highly corrosive reagents under high-T/p conditions using microwave heating without degradation of the material.[21,22] Flow reactors made of SiC are already used in the pharmaceutical industry to handle, e.g., fluorine gas in a safe and scalable manner.[23] Notably, Jensen and co-workers developed a custom-made SiC microreactor (470 μL internal volume) for the implementation of Wolff–Kishner reductions under continuous flow conditions.[24] Significantly shortened reaction times and a decreased hydrazine loading could be achieved by employing an intensified continuous flow approach. Carbitol (diethylene glycol monoethyl ether) as a high-boiling solvent (bp = 245 °C) was employed in their study, thus requiring chromatography to obtain the pure reduced products. Because of the small internal volume of the reactor, throughputs of only 0.85–9.3 mmol/h could be achieved with this protocol.

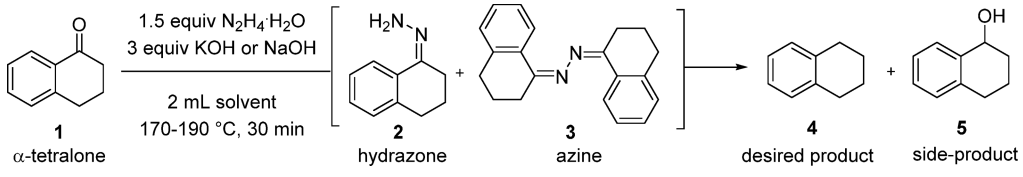
Herein we describe a safe and scalable Wolff–Kishner protocol under continuous flow conditions using a commercially available modular lab-scale SiC reactor, which provides seamless scale-up capabilities to a manufacturing process.[26] To our knowledge, large-scale Wolff–Kishner reductions have very little literature precedent to date,[27−29] presumably because of the hazards encountered in batch as described above. Therefore, a scalable and safe continuous flow process is of considerable interest to the pharmaceutical and related chemical industries. The high-pressure stability of sintered SiC enabled the use of MeOH as a low-boiling solvent in a high-T/p regime. This solvent switch allowed not only a higher-concentration substrate feed to be processed, and in turn a higher productivity, but also a simple extractive product isolation procedure because of the higher purity profile.

RESULTS AND DISCUSSION

Optimization in Batch. Before Wolff–Kishner reductions were performed in flow, a detailed optimization study was done in a single-mode batch microwave reactor using sealed 10 mL SiC reaction vials.[21] The optimized conditions could then be translated to a scalable high-T/p continuous flow process following the "microwave-to-flow paradigm".[30] In 2009, our group reported the use of SiC as a microwave reaction vessel material for the safe use of corrosive reagents in a high-T/p regime.[22] SiC is a strong microwave absorber and rapidly transfers the produced thermal energy to the reaction mixture via conduction, which allows uniform heating to rather high temperatures (up to 300 °C), thereby mimicking autoclave conditions.[31]

The reduction of α-tetralone (**1**) to 1,2,3,4-tetrahydronaphthalene (**4**) was chosen as the model transformation for a thorough study of the Wolff–Kishner reduction (Scheme 2). Fully homogeneous reaction mixtures, short reaction times (≤30 min), and high product purity were the major requirements for the microwave protocol to be translated into a continuous flow process. To visually inspect the

Scheme 2. Wolff–Kishner Reduction of α-Tetralone in a Batch Microwave Reactor



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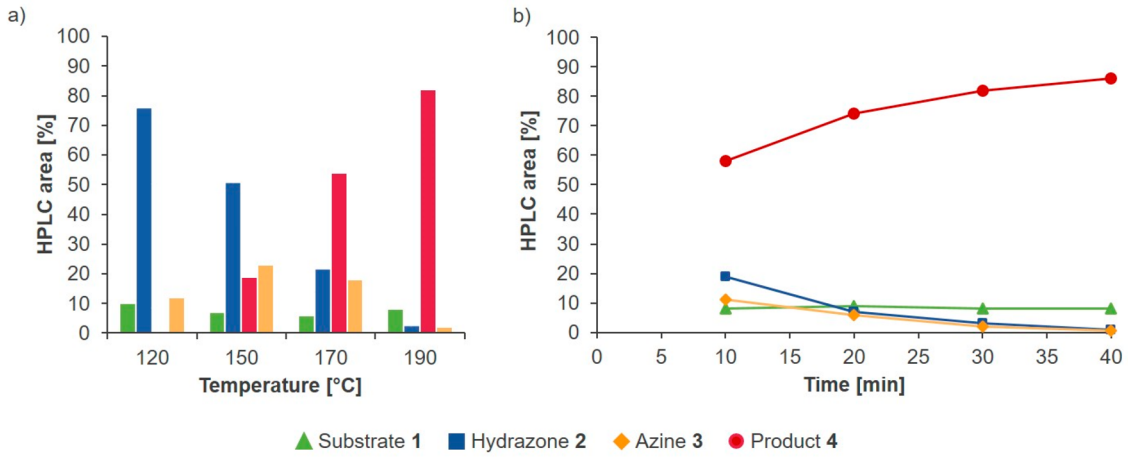

Figure 1. Process intensification for the reduction of α-tetralone (**1**) in the batch microwave reactor. Conditions: 1.6 mmol of **1**, 3 equiv of KOH, 1.5 equiv of $N_2H_4{\cdot}H_2O$, 2 mL of MeOH, 10 mL SiC vessel. (a) Temperature screening, keeping the reaction time constant at 30 min. (b) Reaction time screening, keeping the temperature constant at 190 °C.

Table 1. Batch Microwave Optimization of Substrate Concentration[a]

entry	conc [mol/L]	pressure [bar][b]	product **4** [%][c]	substrate **1** [%][c]	intermediates **2** and **3** [%][c]	alcohol **5** [%][c]
1	0.6	26.7	87	<1	10	3
2	1.0	24.6	97	<1	<1	3
3	1.4	31.6	95	<1	2	3

[a]Conditions: α-tetralone (**1**), 3.0 equiv of NaOH, 1.5 equiv of $N_2H_4{\cdot}H_2O$, 2 mL of MeOH, 30 min, 190 °C, FO temperature measurement, 10 mL SiC vessel. [b]Maximum pressure measured in the sealed microwave vessel. [c]Determined by HPLC peak area integration at 215 nm.

homogeneity of the reaction mixture, preliminary screening experiments were performed in sealed Pyrex microwave vials.

We initially performed a solvent screen in order to identify reaction conditions amenable to flow processing. Typically, a 0.6 M solution of α-tetralone in the respective solvent, 3 equiv of KOH, and 1.5 equiv of $N_2H_4{\cdot}H_2O$ were heated at 170 °C for 30 min in a single-mode microwave reactor employing a fiber optic (FO) sensor for internal temperature control.[31] Hydrazone intermediate **2**, azine intermediate **3**, product **4**, and alcohol **5** as a side product were detected via HPLC analysis (Scheme 2). This screening revealed that hydroxylic solvents showed the highest reactivity toward the reduction of model substrate **1** (Table S1 in the Supporting Information). These results were in good agreement with the mechanism proposed by Szmant, which indicates that the hydroxyl group of the solvent plays an important role in the reduction mechanism.[32] As expected, all typical Wolff–Kishner solvents such as ethylene glycol, diethylene glycol, and carbitol provided homogeneous reaction mixtures. Carbitol showed the highest conversion to the desired product **4** (67%), but the high boiling point of the solvent (245 °C) and low product purity (17% unidentified impurities) diminished its suitability for our purposes. Among the low-boiling solvents, MeOH proved to be the best; it provided homogeneous reaction mixtures, the highest conversion to **4** (53%), and an optimum purity profile (only 2% alcohol **5**). We therefore considered MeOH as the solvent of choice for the prospective flow process. Further optimizations were conducted using this solvent with respect to temperature, reaction time, type of base, reagent stoichiometry, and concentration for the reduction of α-tetralone (**1**). As expected, the high reaction temperature (170 °C) in conjunction with a strong base resulted in significant etching of the glass vessels after a single use.[21] For this reason, all further experiments where performed in SiC microwave vials.

Increasing the temperature to 190 °C resulted in significantly higher conversion, which reached 86% after 40 min (Figure 1). Because of the large amount of N_2 gas evolved during the reaction and the high vapor pressure of MeOH, the pressure limit of the microwave reactor (30 bar) was reached at this temperature. NaOH provided a slightly increased substrate conversion compared with KOH and NaOMe (Table S2). Further investigation of the reagent stoichiometry showed that 1.5 equiv of $N_2H_4{\cdot}H_2O$ and 3.0 equiv of NaOH presented the optimum with respect to conversion and reagent economy (Table S3).

A significant improvement in the conversion to the desired product **4** could be achieved by increasing the concentration (Table 1): 87% (0.6 M) versus 97% (1.0 M). The concentration could be raised to 1.4 M, but a further increase was again restricted by the operational pressure limit of the microwave reactor (Figure S1). The best results were achieved with microwave irradiation of 0.8–1.0 M solutions of substrate **1** in MeOH with 1.5 equiv of $N_2H_4{\cdot}H_2O$ and 3 equiv of NaOH for 30 min at 190 °C. Under these optimized conditions, the reduction of **1** proceeded to completion, and tetrahydronaphthalene **4** was isolated in 79% yield (containing 2% alcohol as a side product) after the addition of water and extraction with cyclohexane.

Observed Side Reactions. In an attempt to improve the purity profile of the reaction, we further investigated the formation of side products and insoluble intermediates. Hydrazone **2** is known to react with the substrate **1** to give azine **3**,[5] but this process is reversible at high temperatures in the presence of hydrazine (see Figure 1). Nevertheless, the formation of azine **3** was identified as problematic since it precipitates at room temperature and could potentially cause

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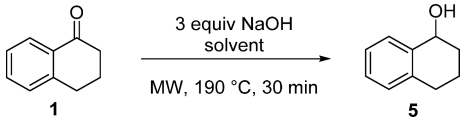
clogging in the flow system. Less problematic with respect to continuous flow processing is the base-mediated formation of secondary alcohol **5** as a side product. The reduction of the carbonyl to the corresponding alcohol seems to be competitive with the hydrazone formation. Although the possibility cannot be ruled out that the alcohol is generated in the presence of hydrazine (reduction in the presence of O_2 via diimide),[33] experiments have shown that its formation is mainly driven by the base. Considerable amounts of alcohol **5** were formed when substrate **1** was heated in the presence of 3 equiv of NaOH in different solvents without the addition of hydrazine hydrate (Table 2). Furthermore, the amount of alcohol **5** formed during the reaction was strongly dependent on the solvent. A clear trend with respect to the hydride-donating capacity of the alcoholic solvent could be observed: *i*PrOH > EtOH > MeOH (Table 2). A plausible mechanism for the formation of the secondary alcohol involves intramolecular hydride transfer similar to a Meerwein–Ponndorf–Verley-type mechanism.[34−36] It has to be noted that alcohol formation could be suppressed by preformation of the hydrazone and subsequent addition of the base. However, this was generally not necessary when MeOH was used since only 2% of alcohol **5** was formed in the one-pot Wolff–Kishner reduction.

Table 2. Influence of the Solvent on Alcohol Formation[a]



entry	solvent	substrate **1** [%][b]	alcohol **5** [%][b]	unidentified impurities [%][b]
1	MeOH	49	–	51
2	EtOH	–	44	56
3	*i*-PrOH	43	53	4
4	carbitol	26	20	54

[a]Conditions: **1** (1.2 M), 10 mL SiC vessel. [b]Determined by HPLC peak area integration at 215 nm.

Continuous Flow Reduction. Next, we turned our attention to the translation of the optimized batch microwave protocol toward a continuous flow process. In order to prove the necessity of SiC as the reactor material, a control experiment was performed using a stainless steel reactor coil (Uniqsis, FlowSyn).[37] As expected, immediate gas formation due to the decomposition of hydrazine to nitrogen and water or ammonia was observed at the reactor outlet when a solution of $N_2H_4{\cdot}H_2O$ in MeOH was pumped through the reactor at 150 °C.[8] Consequently, all further experiments were performed using a commercially available modular plate-based SiC flow reactor platform (Chemtrix, Protrix).[26]

To evaluate the performance of the continuous flow setup, initial experiments were conducted using carbitol as the solvent. This allowed the performance of our system to be directly compared to the microreactor procedure published by Jensen and co-workers,[24] and the high boiling point of carbitol (245 °C) allowed the use of a relatively low back pressure (15–20 bar), which for safety reasons was preferred for an initial validation of the system. The starting conditions were based on those reported by Jensen and co-workers.[24] The feed solution, containing α-tetralone (0.8 M), 3.0 equiv of KOH, 1.5 equiv of $N_2H_4{\cdot}H_2O$ and carbitol, was pumped into the reactor from a sample loop by a high-pressure syringe pump (HiTec Zang, Syrdos) at a flow rate of 0.5 mL/min to achieve a calculated residence time of 14 min (Figure 2). The mixture went through a 6.91 mL reaction zone consisting of two SiC plate modules at 200 °C.

Before the processed mixture left the system through an adjustable back-pressure regulator (BPR) (set to 15–20 bar), it was cooled to 40–50 °C in an additional SiC module (3.61 mL) that served as cooling zone. It should be noted that the actual residence time was lower than the calculated one because of the expulsion of N_2 gas during the reaction. Therefore, the residence time had to be experimentally determined.[38] Initial experiments were performed using a 1 mL sample loop (SL), and the system pressure was maintained by using an adjustable BPR (Swagelok, 0–70 bar). Surprisingly, the reaction outcome was comparable neither to the reported one[24] nor to the batch microwave experiment (Table 3, entry 1 vs 2). This could be attributed to dispersion issues caused by the small sample loop inserted in the feedline. By the simple change of the 1 mL SL to a 4 mL SL, the

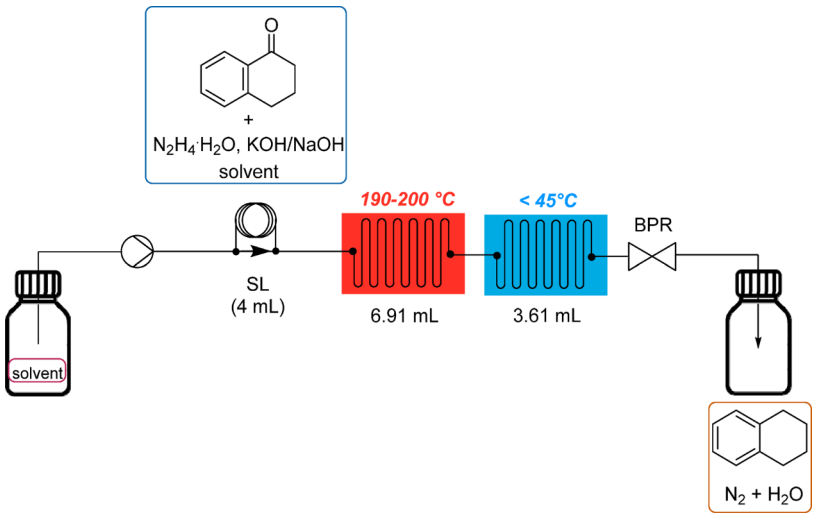


Figure 2. Schematic overview of the continuous flow setup for initial optimization studies of the Wolff–Kishner reduction using a modular SiC reactor. For further details, see Figures S2 and S3.

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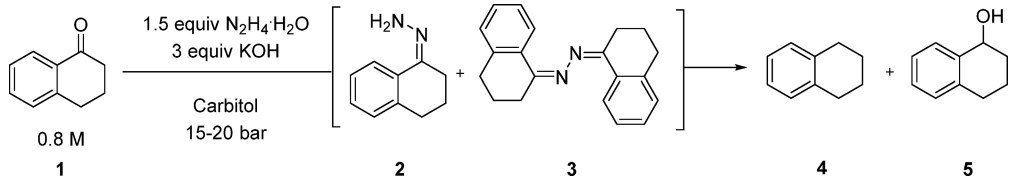
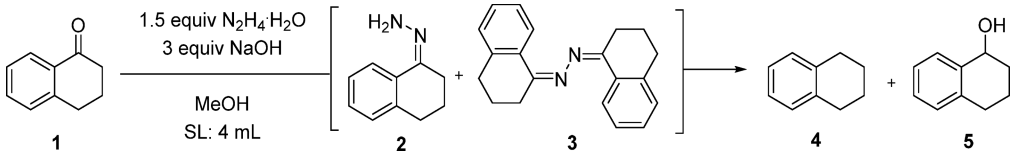
Table 3. Continuous Flow Optimization Study using Carbitol as the Solvent



entry	V_{SL} [mL]	t_{res} [min][a]	flow rate [mL/min]	T [°C]	product **4** [%][b]	**1** + **2** + **3** [%][b]	alcohol **5** [%][b]	other [%][b]
1	–	15	batch MW	200	86	–	10	4
2[c]	1	12	0.5	200	49	37	14	–
3[c,d]	4	9	0.5	200	74	17	9	–
4[c]	4	12	0.38	200	88	5	7	–
5[c]	4	18	0.25	200	87	5	8	–
6[e]	4	12	0.38	200	91	<1	9	–
7[d,e]	4	9	0.5	200	76	17	7	–
8[e]	4	8	0.5	210	91	<1	9	–
9[e,f]	–	11	0.38	200	91	<1	9	–

[a]Estimated by observing the total residence time in the reactor (visual inspection).[38] [b]Determined by HPLC peak area integration at 215 nm. [c]Swagelok BPR. [d]Conditions according to ref 24. [e]Chemtrix BPR. [f]Steady-state conditions: ~15 mL feed, direct injection through pump (Syrris, Asia), 15 bar.

Table 4. Fine-Tuning of the Conditions Using Methanol as the Solvent



entry	conc [mol/L]	t_{res} [min][a]	pressure [bar]	flow rate [mL/min]	T [°C]	product **4** [%][b]	**1** + **2** + **3** [%][b]	alcohol **5** [%][b]
1	1.0	25	30	batch MW	190	91	7	2
2	1.0	25	40	0.2	190	87	11	2
3	1.0	25	45	0.2	200	95	2	3
4	1.0	30	50	0.2	200	96	<1	4

[a]Estimated by observing the total residence time in the reactor (visual inspection).[38] [b]Determined by HPLC peak area integration at 215 nm.

reaction performance was significantly improved from 49% to 74% (Table 3, entries 2 and 3). However, neither the larger sample loop nor a longer residence time could drive the reaction to completion. We assumed that the large inner volume of the BPR (ca. 4 mL) in combination with the low flow rate might be the reason for the lower conversion and unstable product distribution (Table 3, entries 2–5; also see Figure S4). The reaction mixture accumulated inside the BPR, and because of the large amount of N_2 gas, it was pushed out uncontrollably, which in turn resulted in a pressure drop. Furthermore, the large inner volume led to diffusion inside the BPR. Indeed, when a different adjustable BPR (Chemtrix, 0–60 bar) with an inner volume of only 0.16 mL was employed, the holdup problem was overcome, and the reaction was driven to full conversion to give 91% of **4** and 9% of **5** (Table 3, entry 6). This result corresponds well to the 78% isolated yield reported by Jensen and co-workers.[24]

Having a reliable continuous flow setup, we aimed to increase the throughput of the reaction by increasing the flow rate to 0.5 mL/min. Again, the shorter residence time diminished the reaction performance, and only 76% conversion to the product could be achieved (Table 3, entry 7). Only an increase in the temperature to 210 °C at the same flow rate led to full conversion (Table 3, entry 8). However, since 200 °C is the recommended temperature limit for this specific configuration of the Protrix SiC reactor (see the Experimental Section), we decided to refrain from employing temperatures above 200 °C in all subsequent experiments. Increasing the productivity by enhancing the substrate concentration also remained unsuccessful because of the limited solubility of KOH in carbitol. A steady-state continuous flow experiment was conducted under conditions that provided the best results (Table 3, entry 9). The feed solution was directly pumped through the reactor system, and pure tetrahydronaphthalene **4** was isolated after column chromatography in 66% yield (806 mg), which corresponds to a throughput of 1.6 g/h.

Employing Methanol as the Solvent. Switching from carbitol (bp = 245 °C) to MeOH (bp = 65 °C) at reaction temperatures around 200 °C for a Wolff–Kishner reduction obviously requires a significantly higher back pressure because of the high vapor pressure of MeOH (38 bar at 200 °C). To ensure safe operation of the highly corrosive mixtures at these extreme temperatures and pressures, a customized high-T/p version of the Protrix SiC reactor was provided by the manufacturer (see the Experimental Section for details). After a careful validation of this reactor system under the intensified conditions, we were confident in operating it at up to 50 bar and 200 °C. Our initial conditions for the Wolff–Kishner reduction studies were based on the previously optimized batch protocol (see Table 1, entry 2). The same setup as described in Figure 2 was employed, and the feed solution containing **1**, 1.5 equiv of $N_2H_4{\cdot}H_2O$, and 3 equiv of NaOH in

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Table 5. Steady-State Experiments in Methanol[a]

entry	conc [mol/L]	t_{res} [min][b]	product **4** [%][c]	**1** + **2** + **3** [%][c]	alcohol **5** [%][c]	yield [%][d]	purity [%][c]	productivity [g/h]
1	1.0	25	96	<1	4	80	96	1.3
2	1.3	22	95	2	3	81	95	1.7
3	1.6	21	95	1	4	81	95	2.1

[a]Conditions: **1**, 1.5 equiv of $N_2H_4{\cdot}H_2O$, 3 equiv of NaOH, 12 mL of MeOH, 200 °C, 50 bar, 0.2 mL/min. [b]Estimated by observing the total residence time in the reactor (visual inspection).[38] [c]Determined by HPLC peak area integration at 215 nm. [d]Isolated yields.

MeOH was pumped into the reactor from a 4 mL sample loop by a high-pressure syringe pump (HiTec Zang, Syrdos) at a flow rate of 0.2 mL/min. We commenced our investigation by evaluating the minimum back pressure required to provide a controlled outlet stream. At 190 °C a back pressure of 40 bar (Table 4, entry 2) was sufficient to provide a stable flow. However, the resulting residence time of 25 min at 190 °C turned out to be too short to provide full conversion. A reaction temperature of 200 °C and a system pressure of 50 bar were required to achieve full conversion and a stable flow (Table 4, entry 4).

Since the productivity could not be further improved by increasing the flow rate, a higher substrate concentration was pursued. It was assumed that a larger amount of N_2 gas would be formed from the higher-concentration reaction mixtures and could potentially lead to unstable residence time distributions. Therefore, those reactions were performed under steady-state conditions by directly pumping the reaction mixture into the system, omitting the sample loop. By the use of the increased run time, a more stable system was achieved. As expected, the residence time decreased noticeably when the concentration of the feed was increased, while the high conversion was maintained up to a substrate concentration of 1.6 M (Table 5). Unfortunately, because of the large amount of N_2 gas generated, we did not achieve a controlled outlet stream for a 1.6 M solution at 50 bar. However, at a substrate concentration of 1.3 M, reliable and safe collection of the product at the outlet was still guaranteed (Figure 3), and

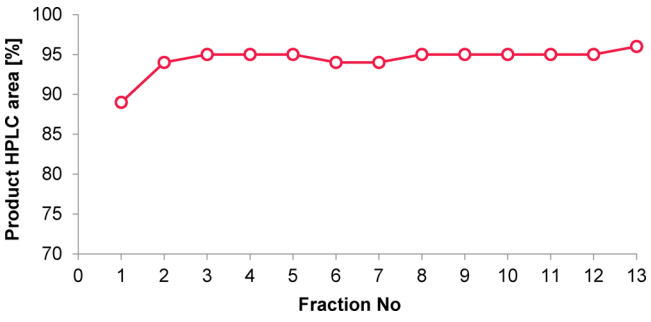
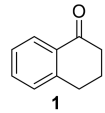
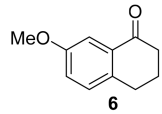
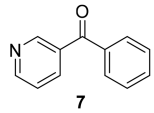
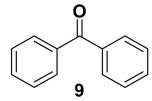
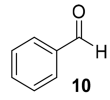
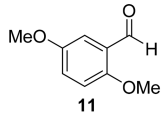


Figure 3. Product distribution of the steady-state experiment at a 1.3 M concentration of α-tetralone (**1**). Fractions were collected at 7 min intervals.

tetrahydronaphthalene **4** was isolated in 81% yield (Table 5, entry 2). Even though the reaction time was longer compared with that for carbitol as the solvent (22 vs 11 min), MeOH provided a slightly higher productivity (1.7 vs 1.6 g/h), a much better purity profile, and most importantly a significantly simplified workup procedure (extraction vs chromatography). Compared with the previously reported work,[24] the productivity could be increased by a factor of 10.

Substrate Scope. To investigate the applicability of the continuous Wolff–Kishner reduction in MeOH, a set of aldehydes and ketones were prescreened under batch microwave conditions with respect to homogeneity and substrate/product stability. Most of the selected ketones underwent full conversion to the corresponding alkanes under the conditions used for model substrate **1** in batch and could thus be easily translated to the optimized flow conditions (Table 6, entries 1–5). Aldehydes, on the other hand, reacted relatively fast at room temperature with hydrazine in the presence of base, which resulted in precipitation of the respective hydrazone. Therefore, the flow setup had to be modified to use a two-feed approach (Figure 4). Because of the modularity of the SiC reactor, the needs of various reaction conditions/types can be easily addressed by employing different mixing and residence time units (see the Experimental Section and the Supporting Information for more details). For reduction of the aldehydes,

Table 6. Substrate Scope for the Continuous Wolff–Kishner Reduction[a]

entry	substrate	product [%][b]	yield [%][c]	purity [%][b]
1	 **1**	96	80	96
2	 **6**	86	81	93
3	 **7**	92	90	91
4	 **8**	97	70	>99
5	 **9**	80	75	80
6	 **10**	>99	82	>99
7	 **11**	>99	87	>99

[a]Conditions: Entries 1–5: 1.0 M substrate, 1.5 equiv of $N_2H_4{\cdot}H_2O$, 3 equiv of NaOH, MeOH, 200 °C, 50 bar, 0.2 mL/min, 8 mL sample loop. Entries 6 and 7: feed 1: 2.0 M substrate, 1.5 equiv of $N_2H_4{\cdot}H_2O$, MeOH, 0.2 mL/min, 4 mL sample loop; feed 2: 6.0 M NaOH in MeOH, 0.2 mL/min; 200 °C, 50 bar. [b]Determined by HPLC peak area integration. [c]Isolated yields.

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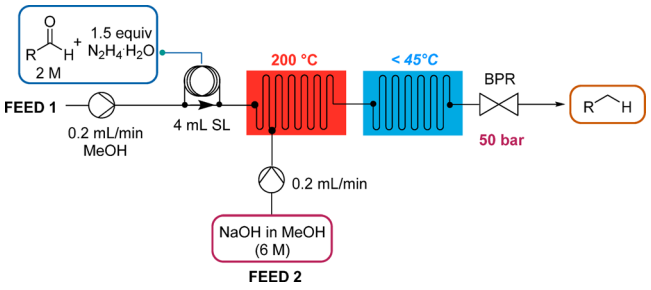


Figure 4. Continuous flow setup for the reduction of aldehydes employing a two-feed system.

the same SiC modules as for the single-feed system could be used, but an additional reaction channel was utilized. A 2 M solution of the substrate with 1.5 equiv of $N_2H_4·H_2O$ in MeOH was introduced via a 4 mL sample loop (feed 1), and in a 0.54 mL residence time unit the hydrazone intermediate was preformed (2.7 min residence time). Then the feed containing the 6 M NaOH (3 equiv) in MeOH was introduced into the reactor plate. The combined mixture then passed through the 6.91 mL reaction zone with a nominal total flow rate of 0.4 mL/min. Before the processed mixture left the system through the BPR, it was cooled to 40−50 °C in an additional cooling zone. In this way, aldehydes could also be reduced successfully under continuous conditions using MeOH as the solvent.

A small set of different ketones and aldehydes were successfully reduced and isolated by simple extraction in good yields with sufficient purities (Table 6). In the case of benzophenone (**9**), only 80% purity could be achieved because of the formation of 20% alcohol as a side product (Table 6, entry 5). Reduction of halogenated ketones was also attempted. However, dehalogenation and several other side reactions, resulting in insufficient purities, were experienced in the MW optimization studies (Table S4). It should be noted that the focus of the substrate scope was on simple, generic structures of ketones and aldehydes similar to AstraZeneca's API substructure (vide infra). Therefore, no further optimizations toward those substrates to improve the process or further extension of the substrate scope with respect to functional groups was pursued.

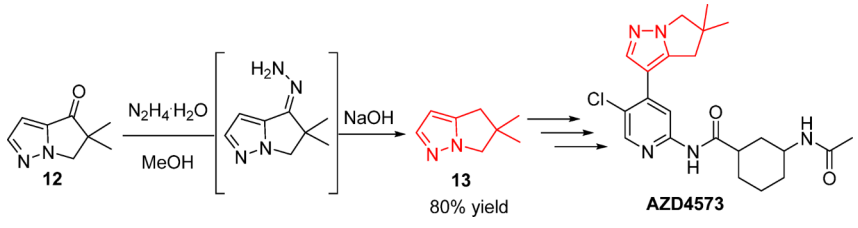
Synthesis of a Precursor of AZD4573. Pyrazole **13** is a key intermediate in the preparation of AZD4573, which has been demonstrated to be a potent CDK9 inhibitor. AZD4573, developed by AstraZeneca, is currently in Phase 1 clinical trials as an investigational treatment for hematological malignancies.[39] The disclosed batch procedure for the preparation of pyrazole **13** involves treatment of ketone **12** with 5 equiv of $N_2H_4·H_2O$ in diethylene glycol at 180 °C for 1 h followed by thermal reduction with 3.5 equiv of KOH at 150 °C for 2 h, which provides the product in 40% yield.[40] A one-pot approach was tested in preliminary batch microwave experiments, but a significant amount (22%) of the alcohol as a side product was detected by HPLC. Therefore, the two-feed approach developed for aldehydes (see Figure 4) was employed for the continuous synthesis (Scheme 3). We were able to significantly decrease the overall reaction time to less than 20 min and reduce the hydrazine loading to 1.5 equiv. The desired key intermediate **13** could be obtained in 80% yield with >99% purity after extraction with water and diethyl ether.

Long Run. The reduction of α-tetralone (**1**) was used as a model reaction to demonstrate the productivity of the reactor over an 8 h working day. First, investigations of the stability of the feed solution in MeOH were performed. Studies at different temperatures showed that reaction mixtures in MeOH stayed homogeneous over a period of 30 h at room temperature, but slow formation of hydrazone **2** and azine **3** was detected (Figure S8). Decreasing the storage temperature to 4 °C minimized the formation of **2** and prevented the generation of **3**. For the actual experiment, therefore, the feed solutions were freshly prepared every 1.5 h and stored at 0−10 °C to keep the hydrazone level below 5% in the feed.

For this proof-of-concept study, the reaction conditions of the optimization study (Table 5, entry 2) were applied. A solution containing 1.3 M α-tetralone in MeOH, 3 equiv of NaOH, and 1.5 equiv of $N_2H_4·H_2O$ was pumped through the reactor at a flow rate of 0.2 mL/min, which provided an estimated residence time of approximately 22 min. After steady state was reached, >95% product in the presence of less than 5% alcohol **5** was observed by HPLC in all nine analytical samples, which were taken every hour over the 8 h run time. In total, the reaction performed to an identical standard compared with the steady-state experiment (Table 5, entry 2). The amount of residual hydrazine in the product stream was determined by taking an aliquot and mixing it with benzaldehyde as a derivatization reagent. According to calibrated UPLC analysis, 0.43 equiv of residual N_2H_4 was detected in the product mixture, indicating that 1.07 equiv of N_2H_4 was consumed during the reaction and highlighting that no decomposition occurred when sintered SiC was used as the reactor material (for further details, see the Supporting Information). Since the outlet stream is cooled to ca. 45 °C, which is far below the boiling point (120 °C) and flash point (74 °C) of hydrazine hydrate, standard precautions were sufficient, and unconsumed hydrazine was depleted with hydrogen peroxide.[28,41] Alternatively, commercial bleach (5%) could also be employed to rapidly quench hydrazine.[28,41]

In total, 96 mL of reaction mixture was processed, resulting in 12.9 g (81% yield) of 1,2,3,4-tetrahydronaphthalene (**4**) after extraction. This corresponds to a productivity of 1.6 g/h (12.2 mmol/h) and a space-time yield of 152 g L^{-1} h^{-1}. A significant advantage of the Protrix reactor is that processes developed on the lab scale can be directly transferred to a

Scheme 3. Reduction To Obtain a Key Intermediate for AZD4573



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production-scale reactor (Plantrix), maintaining corrosion resistance and thermal control.[42] The performance of the reactor should remain unchanged by keeping the heat and mass transfer parameters constant ("smart dimensioning").[43] While not explored in this study, the use of such a large-scale reactor with an internal volume of 2.35 L would allow the production of 13.7 kg of material per day and thus fully exploit the potential of this atom-economical reduction process.

CONCLUSION

We have developed a safe and scalable methodology for the Wolff–Kishner reduction. Key to the success was the use of a continuous flow reactor made of SiC, which enabled the use of hydrazine hydrate and caustic bases at very high temperatures and pressures. Hydrazine hydrate is extremely dangerous to handle at high temperature on a production scale since it is volatile, toxic, and highly explosive as a gas. The laboratory-scale continuous flow process presented herein eliminates the risk of violent explosion in the headspace of a batch reactor and thus offers the promise to scale-up the process in a safe manner. Furthermore, elimination of headspace increases the concentration of the volatile hydrazine in the liquid phase, and in contrast to the batch process, a large excess of hydrazine can be avoided.[24] The use of MeOH as the solvent can be expected to be an additional factor in cost and time savings, in particular with respect to workup. Because of the higher purity profile and the straightforward removal of MeOH by simple evaporation, isolation of the alkanes could be simplified via an extractive workup procedure, which opens the possibility of a fully integrated Wolff–Kishner reduction utilizing in-line extraction strategies. A single-feed protocol, which can be applied for substrates that are not prone to fast hydrazone formation, was established. In addition, a two-feed process allowing preformation of the hydrazone before the addition of the base was developed. The methodology also proved to be suitable for the synthesis of an API intermediate from AstraZenca. Finally, a long run of the reduction of α-tetralone as a model substrate was performed. This strategy enabled the production of 13 g of material over 8 h, demonstrating a stable system over that time period. In order to manufacture sufficient quantities for industrial applications, scaling-up the reactor volume for implementing higher flow rates is a common method.[43]

EXPERIMENTAL SECTION

General Remarks. All chemicals, solvents, catalysts, and ligands were purchased from commercial suppliers and used without any further purification. If not stated otherwise, reagents were weighed and handled in air at room temperature. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in parts per million downfield from tetramethylsilane as an internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Analytical HPLC (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150 mm × 4.6 mm, particle size 5 μm) at 37 °C using mobile phases A (90:10 v/v water/acetonitrile + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL min^{-1}. The following gradient was applied: linear increase from 30% B to 100% B in 10 min. GC–MS spectra were recorded using a Thermo Focus gas chromatograph coupled with a Thermo DSQ II mass spectrometer (EI, 70 eV). An HP5-MS column (30 m × 0.250 mm × 0.025 μm) was used, and helium was the carrier gas (1 mL min^{-1} constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 4 min. UPLC-DAD (Shimadzu Nexera X2) analysis was carried out using a Phenomenex Luna Omega C18 column (50 mm × 2.1 mm, particle size 1.6 μm, pore size 100 Å) at 45 °C using mobile phases A (90:10 v/v water/acetonitrile + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 0.7 mL min^{-1}. The following gradient was applied: linear increase from 30% B to 100% B in 2.5 min. UPLC-DAD calibration curves were measured for benzaldehyde for quantitative determination of residual hydrazine. Microwave irradiation experiments were carried out in a Monowave 400 single-mode microwave reactor (Anton Paar) using 10–30 mL borosilicate Pyrex vials and 10 mL SiC vials. The reaction temperature was monitored either by an internal fiber optic sensor (SiC) or by an external infrared sensor (Pyrex) measuring the surface temperature of the reaction vial. Reaction times refer to hold times at the temperature indicated, not to total irradiation times. The stirring speed was set to 800 rpm. Column chromatography was carried out using an automated flash chromatography system (Biotage, Isolera) with cyclohexane/ethyl acetate mixtures as eluents.

Protrix SiC Reactor. Protrix is a silicon carbide flow reactor that is used for process development and small-scale production. The Protrix holder contains 3M SiC modules that can be flexibly configured (in terms of number and type) to deliver the required number of reagent inputs, reaction volume, and temperature zones (Figure S5). Each SiC module is fabricated from 3M grade C SiC and contains the process channel and an integrated heat exchange layer to give optimal thermal control. The SiC layers are diffusion-bonded to give a gas-tight metal-free flow path with high chemical compatibility (Figure S6). The flow path proceeds in series between the modules, and the heat exchange layers are arranged in parallel; the SiC modules are connected in the holder using FFKM O-rings. For the high-T/p experimentation described herein, the system was modified from the standard system and used a GF PEEK interconnector plate to create two temperature zones in the flow path. The standard FFKM O-rings were replaced with Chemraz type 605 O-rings. The Protrix flow reactor comprised two temperature zones (Figure S7), the first for the reaction and the second for safe cooling of the reaction mixture prior to collection at the outlet: T1 = MRPX + MRPA (volume = 6.9 mL) and T2 = MRPA (3.6 mL).

Reagent flow was controlled via high-pressure SyrDos (HiTec Zang) syringe pumps, and the feedlines were constructed from PFA and contained pressure relief assemblies (set to 5 bar above the BPR set point). An adjustable BPR was positioned at the outlet of the flow reactor to allow a range of pressures (0–60 bar) to be evaluated. For optimization experiments, a sample loop (4 to 8 mL) was employed. Wetted materials used in the flow path were PFA, ETFE, PCTFE, FFKM (Chemraz 605), PTFE, and 3M SiC.

Thermal control of the reaction step was achieved using a thermostat (CC304B, Huber) with a recirculating thermal fluid (P20.275.50), and the reaction mixture was cooled to 40 °C in the second thermal zone using recirculating deionized H_2O. Reaction products were collected in a vial prior to analysis and/or subsequent workup. As shown in Figure S3, the

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apparatus was operated within a fume hood and behind a safety blast shield at all times.

CAUTION: Hydrazine hydrate should be treated with extreme caution. It is potentially explosive in its pure and undiluted form. In addition, it is toxic by inhalation or contact with skin or eyes. Therefore, contact in any form should be avoided. Hydrazine is likely to be present under these high-*T* conditions, and particular care should be taken to avoid contact with any vapors or liquids. All reactions should be carried out in an efficient fume hood; the reactor should be placed in a spill tray, and a safety blast shield should be used. Laboratory personnel working with $N_2H_4{\cdot}H_2O$ must familiarize themselves with the potential hazards and prevention measures. Prior to performance of any high-T/p flow reaction, the apparatus must be checked with an inert solvent to ensure correct functionality of all valves and safety infrastructure.

Optimized Microwave Procedure for the Reduction of α-Tetralone (1). To a 10 mL SiC microwave process vial equipped with a magnetic stirring bar were added **1** (266 μL, 2.0 mmol), NaOH (240 mg, 6.0 mmol, 3 equiv), $N_2H_4{\cdot}H_2O$ (146 μL, 3.0 mmol, 1.5 equiv), and 2 mL of MeOH. The vial was sealed with a snap cap and heated for 30 min at 190 °C. A fiber optic sensor was used for internal temperature control. After the reaction time elapsed, the mixture was cooled to 55 °C, and an aliquot was taken for HPLC analysis.

General Flow Procedure for the Reduction of 1 in Carbitol. After KOH (538 mg, 9.6 mmol, 3.0 equiv) was dissolved in 3 mL of carbitol in an ultrasound bath, **1** (426 μL, 3.2 mmol) and $N_2H_4{\cdot}H_2O$ (234 μL, 4.8 mmol, 1.5 equiv) were added, and the total volume was brought to 4 mL by dropwise addition of carbitol. The flow reactor was equilibrated with carbitol at 200 °C, and the BPR was adjusted to 15 bar. The feed was introduced into the reactor via a sample loop (PFA, 0.8 mm i.d., 1.59 mm o.d., 4 mL internal volume) and pumped through at 0.38 mL/min using a Syrris Asia syringe pump. Fractions were collected from the reactor output, and an aliquot was taken for HPLC analysis.

Steady-State Reaction and Isolation Procedure for Carbitol (Table 3, Entry 9). After KOH (1.9 g, 36.0 mmol, 3.0 equiv) was dissolved in 10 mL of carbitol in an ultrasound bath, **1** (1.6 mL, 12.0 mmol) and $N_2H_4{\cdot}H_2O$ (874 μL, 18.0 mmol, 1.5 equiv) were added. The flow reactor was equilibrated with carbitol at 200 °C, and the BPR was adjusted to 15 bar. The feed was pumped through at 0.38 mL/min using a Syrris Asia syringe pump. Fractions were collected from the reactor output, and an aliquot was taken for HPLC analysis. Water (30 mL) was added to the combined fractions, and the mixture was extracted with cyclohexane (3 × 30 mL). Hydrogen peroxide was added to the aqueous phase in order to quench residual hydrazine. The combined organic phase was dried over Na_2SO_4. After evaporation of the solvent, the crude product was loaded onto a Biotage silica sample with cyclohexane and purified by flash chromatography using a 10 g SNAP cartridge and cyclohexane/ethyl acetate as the eluent. The desired fractions were combined, and the solvent was evaporated under reduced pressure to provide 806 mg (66% yield) of pure product **4** as a slightly yellow oil.

General Flow Procedure for the Reduction of 1 in MeOH. NaOH (480 mg, 12 mmol, 3 equiv) was dissolved in 3 mL of MeOH, and **1** (532 μL, 4 mmol) and $N_2H_4{\cdot}H_2O$ (292 μL, 6 mmol, 1.5 equiv) were added, after which the total volume was brought to 4 mL by dropwise addition of MeOH. The flow reactor was equilibrated with MeOH at 200 °C, and the BPR was adjusted to 50 bar. The feed was introduced into the reactor via a sample loop (PFA, 0.8 mm i.d., 1.59 mm o.d., 4 mL internal volume) and pumped through at 0.2 mL/min using a HiTec Zang SyrDos (90 bar) syringe pump. Fractions were collected from the reactor output, and an aliquot was taken for HPLC analysis.

Steady-State Reaction and Isolation Procedure for MeOH (Table 5, Entry 2). NaOH (1.9 g, 46.8 mmol, 3.0 equiv) was dissolved in 12 mL of MeOH, and **1** (2.1 mL, 15.6 mmol) and $N_2H_4{\cdot}H_2O$ (1.1 mL, 23.4 mmol, 1.5 equiv) were added. The flow reactor was equilibrated with MeOH at 200 °C, and the BPR was adjusted to 50 bar. The feed was pumped through at 0.2 mL/min using a HiTec Zang SyrDos (90 bar) syringe pump. Fractions were collected from the reactor output, and an aliquot was taken for HPLC analysis. Water (60 mL) was added to the combined fractions, and the mixture was extracted with cyclohexane (3 × 50 mL). Hydrogen peroxide was added to the aqueous phase in order to quench residual hydrazine. The combined organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to provide 1.7 g (81% yield) of pure product **4** as a slightly yellow oil.

General Flow Procedure for the Substrate Scope Study. *One-Feed Approach*. NaOH (840 mg, 21 mmol, 3 equiv) was dissolved in 7 mL of MeOH, and then the substrate (7 mmol) and $N_2H_4{\cdot}H_2O$ (511 μL, 10.5 mmol, 1.5 equiv) were added. The flow reactor was equilibrated with MeOH at 200 °C, and the BPR was adjusted to 50 bar. The feed was introduced into the reactor via a sample loop (PFA, 0.8 mm i.d., 1.59 mm o.d., 8 mL internal volume) and pumped through at 0.2 mL/min using a HiTec Zang SyrDos (90 bar) syringe pump. The effluent was collected from the reactor output, and an aliquot was taken for HPLC analysis. Water (30 mL) was added to the combined fractions, and the mixture was extracted with cyclohexane or diethyl ether (3 × 30 mL). Hydrogen peroxide was added to the aqueous phase in order to quench residual hydrazine. The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided the product.

Two-Feed Approach. The flow reactor was equilibrated with MeOH at 200 °C, and the BPR was adjusted to 50 bar. A solution of the substrate (8 mmol) and $N_2H_4{\cdot}H_2O$ (584 μL, 12 mmol, 1.5 equiv) in 4 mL of MeOH (2.0 M) was injected via a sample loop (PFA, 0.8 mm i.d., 1.59 mm o.d., 4 mL internal volume). After a 0.54 mL residence time unit, feed 1 was combined with the second liquid feed containing 6.0 M NaOH in MeOH (3 equiv). Both feed solutions were pumped at 0.2 mL/min each, using a HiTec Zang SyrDos (90 bar) syringe pump. The effluent was collected from the reactor output, and an aliquot was taken for HPLC analysis. Water (30 mL) was added to the combined fractions, and the mixture was extracted with cyclohexane or diethyl ether (3 × 30 mL). Hydrogen peroxide was added to the aqueous phase in order to quench residual hydrazine. The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided the product.

Long Run. The flow reactor was equilibrated with MeOH at 200 °C, and the BPR was adjusted to 50 bar. A solution containing 1.3 M α-tetralone in MeOH, 3 equiv of NaOH, and 1.5 equiv of $N_2H_4{\cdot}H_2O$ was pumped through at 0.2 mL/min using a HiTec Zang SyrDos (90 bar) syringe pump. The feed solutions were freshly prepared every ∼1.5 h and kept between 0−10 °C. After 44 min, a steady state was reached. Fractions

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were collected from the reactor output across an 8 h run time, and aliquots were taken for HPLC analysis. Water (350 mL) was added to the combined fractions, and the mixture was extracted with cyclohexane (3 × 250 mL). Hydrogen peroxide was added to the aqueous phase in order to quench residual hydrazine. The combined organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to provide 12.9 g (81% yield) of pure product **4** as a slightly yellow oil.

*Long-Run 1,2,3,4-Tetrahydronaphthalene (**4**).* Yield: 12.9 g, 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13−7.03 (m, 3H), 2.85−2.70 (m, 3H), 1.81 (dt, J = 6.6, 3.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 129.5, 125.8, 29.8, 23.6.

6-Methoxytetralin (Table 6, Entry 2). Yield: 924 mg, 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (t, J = 5.9 Hz, 1H), 6.73−6.59 (m, 2H), 3.78 (s, 3H), 2.71 (dd, J = 22.5, 15.5 Hz, 4H), 1.84−1.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 138.3, 130.1, 129.4, 113.8, 111.9, 55.4, 29.9, 28.7, 23.6, 23.3.

3-Benzylpyridine (Table 6, Entry 3). Yield: 1.06 g, 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, J = 15.0, 4.2 Hz, 1H), 7.42−7.03 (m, 4H), 3.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 147.7, 139.9, 136.5, 129.0, 128.8, 126.6, 123.5, 39.2.

2-Ethylpyrrole (Table 6, Entry 4). Yield: 461 mg, 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 6.69 (dd, J = 4.1, 2.6 Hz, 1H), 6.16 (dd, J = 5.8, 2.8 Hz, 1H), 5.95 (s, 1H), 2.66 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 116.2, 108.4, 104.3, 20.9, 13.7.

Diphenylmethane (Table 6, Entry 5). Yield: 878 mg, 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.13 (m, 10H), 4.04 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 129.1, 128.6, 126.2, 42.1.

Toluene (Table 6, Entry 6). Yield: 604 mg, 82% (extracted with diethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.17 (m, 5H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 129.2, 128.4, 125.4, 21.6.

2,5-Dimethoxytoluene (Table 6, Entry 7). Yield: 834 mg, 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87−6.65 (m, 3H), 3.78 (d, J = 8.2 Hz, 6H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 152.6, 128.4, 117.6, 111.4, 111.2, 56.4, 56.2, 17.0.

*5,5-Dimethyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (**13**).* Yield: 631 mg, 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 1.5 Hz, 1H), 5.93 (d, J = 0.6 Hz, 1H), 3.87 (s, 2H), 2.67 (s, 2H), 1.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 143.0, 99.3, 61.0, 43.4, 38.8, 28.3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00336.

Additional experimental information, supporting figures, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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