

# Continuous and Selective Hydrogenation of Heterocyclic Nitroaromatics in a Micropacked Bed Reactor

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**ABSTRACT:** The hydrogenation of heterocyclic nitroaromatics is of great importance in the pharmaceutical industry for the synthesis of key intermediates. However, high selectivity is difficult to achieve in conventional batch reactors owing to severe back mixing and poor mass transfer performance, resulting in the high requirement for subsequent separation processes. In this work, a continuous flow system based on a micropacked bed reactor is developed for the selective hydrogenation of heterocyclic nitroaromatics and the reductions of 5-nitroisoquinoline to 5-aminoisoquinoline and 5-amino-1,2,3,4-tetrahydroisoquinoline are selected as the model reactions. With the optimal reaction conditions, maximal yields of 99.9% (5-aminoisoquinoline) and 99.3% (5-amino-1,2,3,4-tetrahydroisoquinoline) are obtained successfully. Moreover, this system exhibits remarkable performance for the selective hydrogenation of relevant heterocyclic nitroaromatics with all yields beyond the level of 97.5%. The continuous flow system enables efficient hydrogenation of heterocyclic nitroaromatics and remarkable selectivity of target products with shorter reaction time and safer operation compared with batch reactors.

**KEYWORDS:** continuous flow, hydrogenation, heterocyclic nitroaromatics

## INTRODUCTION

The reduction of heterocyclic nitroaromatics to the corresponding anilines is an important transformation in the pharmaceutical industry for the synthesis of key intermediates and active pharmaceutical ingredients.<sup>1–3</sup> For instance, the hydrogenation products of nitroisoquinoline, aminoisoquinoline, and tetrahydroaminoisoquinoline are significant skeletons of various biologically active natural products,<sup>4–7</sup> chemotherapeutic agents,<sup>8–10</sup> functional dyes,<sup>11–13</sup> pharmacodynamics agents,<sup>14–16</sup> ligands,<sup>17,18</sup> and many other fine chemicals.<sup>19</sup> Among all these synthesis methods, catalytic hydrogenation of heterocyclic nitroaromatics has been treated as one of the most atomic economic and feasible methods.<sup>19–21</sup>

Currently, catalytic hydrogenation of heterocyclic nitroaromatics is completed in batch reactors due to their simple structure and mature technology.<sup>22–24</sup> However, there are several drawbacks when batch reactors are adopted for the hydrogenation of heterocyclic nitroaromatics. First, the slow gas–liquid–solid mass transfer rate in batch reactors results in a long reaction time and relatively low efficiency.<sup>25</sup> For instance, Bao et al.<sup>26</sup> utilized palladium supported on a metal–organic framework as a catalyst for the hydrogenation of 5-nitroisoquinoline. The yield of 5-aminoisoquinoline (90%) was obtained with a reaction time of 3 h and more than 5% 5-nitroisoquinoline was detected in the product, indicating low reaction efficiency. Xue et al.<sup>19</sup> employed the Pt nanocatalyst for the hydrogenation of 5-nitroisoquinoline to synthesize 5-aminotetrahydroisoquinoline. A selectivity of 99% was obtained in the batch reactor within more than 2 h. Therefore, it is desired to develop a more efficient method for the hydrogenation of heterocyclic nitroaromatics.

Continuous flow technology is one of the most valuable advances in the chemical industry that offers several advantages including smaller reactor volume, lower operating cost, and improved mixing performance compared with batch reactors.<sup>27–31</sup> As a promising tool for heterogeneous reactions, the micropacked bed reactor has shown several advantages such as intensified mass transfer, uniform temperature distribution, and effective suppression of side reactions by the precise control of reaction conditions while maintaining the plug flow characteristics and fixed bed catalyst immobilization.<sup>31–38</sup> Su et al.<sup>39</sup> adopted continuous flow technology with prepassivated Raney Ni as the catalyst for the synthesis of a crizotinib intermediate in the micropacked bed reactor and different reaction parameters were screened to improve reaction performance. Compared with the batch reactor, the reaction yield increased from 95 to 99%, while the reaction time decreased significantly from 90 min to 6 s, validating the superiority of continuous flow technology over batch synthesis. Loos et al.<sup>40</sup> developed a continuous flow platform with the micropacked bed reactor for the selective hydrogenation of 1-iodo-4-nitrobenzene using the Raney-Co catalyst. Compared with batch reactors, selectivity was greatly improved, and less than 2% dehalogenation product was detected owing to the precise control of residence time. Hence, the continuous flow system based on the

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Scheme 1. Reaction Mechanism for the Hydrogenation of 5-NTIN

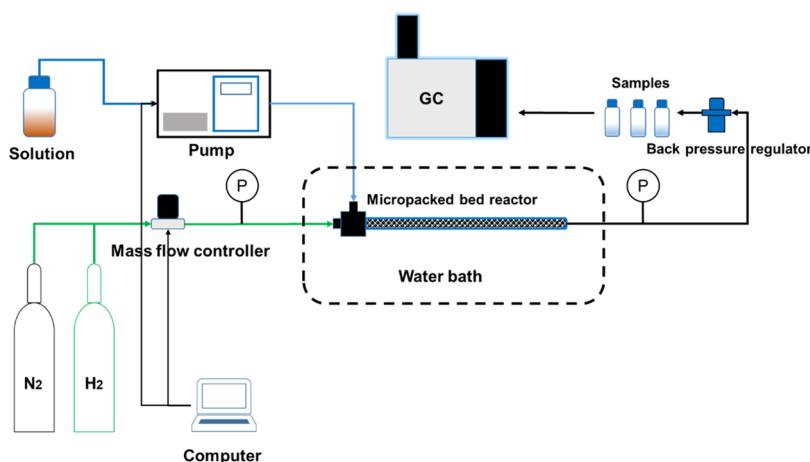
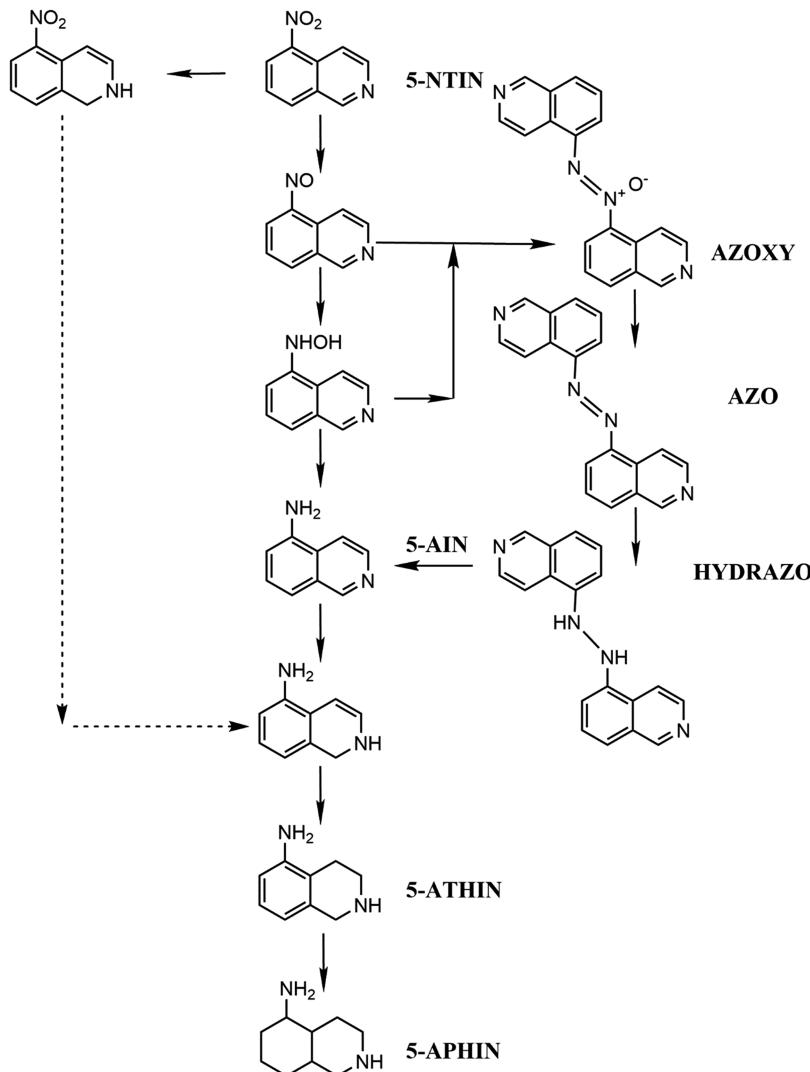


Figure 1. Schematic view of the continuous flow system based on the micropacked bed reactor for the hydrogenation of 5-NTIN.

micropacked bed reactor offers remarkable performance on the improvement of reaction selectivity and efficiency.

In this work, the hydrogenation of 5-nitroisoquinoline (5-NTIN) is selected as the model reaction and the continuous flow system based on the micropacked bed reactor is

developed for the synthesis of 5-aminoisoquinoline (5-AIN) and 5-amino-1,2,3,4-tetrahydroisoquinoline (5-ATHIN). The reaction mechanism is depicted in Scheme 1 to elucidate the complexity of this reaction. The hydrogenation of 5-NTIN potentially proceeds via several competitive ways, including

consecutive hydrogenation of the nitro group to nitroso and hydroxylamine compounds prior to undergoing the final reduction and the condensation of nitroso and hydroxylamine compounds into an azoxy compound, which would be further hydrogenated to 5-AIN, 5-ATHIN, and 5-APHIN. Different catalysts and reaction parameters (gas flow rate, hydrogen pressure, temperature, and liquid flow rate) were screened to improve the reaction performance, and some relevant heterocyclic nitroaromatics were also applied to demonstrate the efficiency and high selectivity of this continuous flow system.

## MATERIALS AND METHODS

**Chemicals.** 5-NTIN ( $C_9H_6N_2O_2$ , 98%) was acquired from Shanghai Bide Pharmaceutical Technology Co., Ltd. The solvent tetrahydrofuran ( $C_4H_8O$ , 99%) was purchased from Shanghai Titan Technology Co., Ltd. Hydrogen ( $H_2$ , 99.9%) and nitrogen ( $N_2$ , 99.9%) were supplied by Beijing Beiwen Gas Manufacturing Plant. The platinum/carbon particle catalyst (Pt/C, 1 wt %), nickel/silica particle catalyst ( $Ni/SiO_2$ , 20 wt %), and palladium/alumina ( $Pd/Al_2O_3$ , 5 wt %) with an average size of 400–500  $\mu\text{m}$  were all acquired from Dalian Institute of Chemical Physics.

**Experimental Setup.** A schematic of the continuous flow platform is shown in Figure 1, and the photograph is shown in Section 1 in the Supporting Information. The experimental setup was composed of a mass flow controller (Beijing Sevenstar Electronics Co., Ltd.), a plunger pump (Beijing Ou Shi Sheng Technology Co., Ltd.), a micropacked bed reactor (length: 20.00 cm, inner diameter: 4.35 mm), and a backpressure regulator (Beijing Xiongchuan Technology Co., Ltd.). The solution was premixed with hydrogen from the regulated cylinder prior to entering the reactor. A check valve was placed upstream of the reactor to prevent the backflow from damaging the mass flow controller. The reactor and two coils were immersed horizontally in the water bath to control the reaction temperature.<sup>41</sup> The system pressure was controlled by the backpressure regulator, and two pressure transducers were installed upstream and downstream of the micropacked bed reactor for the online monitoring of pressure drop. System parameters (liquid flow rate and gas flow rate) were both controlled using online control software on the computer. An H-cube reactor, as a continuous flow reactor, exhibits good applicability in gas–liquid–solid reactions.<sup>42,43</sup> However, the H-cube system is basically packed with powder catalysts, and a pseudo homogeneous liquid is transported through the reactor with a relatively large pressure drop.<sup>44</sup> To reduce the pressure drop, the micropacked bed reactor packed with the larger particle catalysts (the diameter around 500  $\mu\text{m}$ ) was adopted here.<sup>41</sup>

The reactant (5-NTIN) was dissolved in the solvent at a specific concentration and the reactor was fully packed with catalysts. The micropacked bed reactor was prewetted by the solution and  $H_2$  was transported into the reactor at the required flow rate. Then, the liquid flow rate was set to the required value and system pressure was gradually increased, while simultaneously increasing the system temperature. After waiting for at least three times the liquid residence time, the system reached a steady state and the catalysts approached adsorption equilibrium,<sup>45,46</sup> and a sample was collected while excess hydrogen was vented to the atmosphere. Before beginning each experiment, it was necessary to evaluate the activity of the catalyst, which may be varied during the reaction

process and further influence the reaction results. The samples using stale catalysts at the reaction conditions (temperature: 60 °C, hydrogen pressure: 2.0 MPa, liquid flow rate: 0.3 mL/min, and gas flow rate: 20 sccm) were analyzed and compared with the values obtained with fresh catalysts at the same conditions. If the yield of the main product decreased by more than 3%, the stale catalysts would be replaced by fresh catalysts. Besides, the stale catalysts were analyzed by inductively coupled plasma (ICP) to determine the reason for deactivation, and the results are shown in Section 2 in the Supporting Information, indicating obvious metal leaching.

When all of the experiments were completed, the water bath was closed first and system pressure was reduced to atmospheric pressure by releasing the backpressure regulator. Finally, a mixture of  $N_2$  and the solvent was transported into the system to fully remove the residual gas–liquid mixture, and the catalysts were stored in a nitrogen atmosphere.

**Analytical Method.** The samples were collected directly from the outlet of the continuous system. The samples were diluted with tetrahydrofuran (volume ratio of 1:5) and then measured by gas chromatography (Shimazhu, GC-2014) with a flame ionization detector (FID) detector and a Shimazhu RTX-5 column (length: 30 m, diameter: 0.32 mm, and film thickness: 0.25  $\mu\text{m}$ ) under the following conditions: the injection temperature: 280 °C; the column temperature: 50–110 °C, 20 °C/min; 110–150 °C, 10 °C/min; 150 °C, 4 min; 150–250 °C, 20 °C/min; and 250 °C, 3 min; and the detector temperature, 280 °C. The sample volume for all analyses was 1  $\mu\text{L}$ . Based on these analytical conditions, the retention times of the reactant and products were as follows: 5-APHIN: 11.8 min, 5-ATHIN: 12.1 min, 5-AIN: 12.6 min, 5-NTIN: 12.9 min, and AZO: 16.2 min. For the synthesis of 5-AIN, 5-APHIN, 5-ATHIN, 5-AIN, 5-NTIN, and AZO were detected in the samples; hence conversion  $X$  and selectivity of 5-AIN  $S_C$  could be calculated as follows

$$X = 1 - \frac{C_D}{C_{D0}} \quad (1)$$

$$S_C = \frac{C_C}{C_A + C_B + C_C + C_E} \quad (2)$$

However, for the synthesis of 5-ATHIN, no 5-NTIN was detected in the samples, indicating that the conversion could be treated as 100%. 5-APHIN, 5-ATHIN, 5-AIN, and AZO were detected in the samples; hence the selectivity of 5-ATHIN  $S_B$  could be calculated as follows

$$S_B = \frac{C_B}{C_A + C_B + C_C + C_E} \quad (3)$$

where  $C_A$ ,  $C_B$ ,  $C_C$ ,  $C_D$ ,  $C_E$  and  $C_{D0}$  are the concentrations of 5-APHIN, 5-ATHIN, 5-AIN, 5-NTIN, AZO, and initial concentration of 5-NTIN, respectively.

## RESULTS AND DISCUSSION

**Catalyst Performance Evaluation.** The selection of proper catalysts was particularly important for the hydrogenation of 5-NTIN.<sup>47</sup> For the synthesis of 5-AIN, it is essential to inhibit the excessive hydrogenation of the pyridine and benzene rings and the formation of azoxy compounds. Therefore, the catalysts with mild reaction activity and high selectivity are supposed to be employed. Ni as a commonly utilized metal exhibits proper activity for the hydrogenation of

heterocyclic nitroaromatics and lower price compared with noble metal catalysts.<sup>19,48,49</sup> Besides, Ni catalysts could effectively suppress the formation of the azoxy compound;<sup>39</sup> hence Ni/SiO<sub>2</sub> was chosen for the selective hydrogenation of 5-NTIN to synthesize 5-AIN. Meanwhile, for the synthesis of 5-ATHIN, higher catalytic activity is required for the hydrogenation of the pyridine ring. It has been reported that Pd and Pt catalysts were widely used for the synthesis of tetrahydroisoquinoline<sup>50–56</sup> owing to the remarkable performance over the hydrogenation of the pyridine ring. Therefore, Pd/Al<sub>2</sub>O<sub>3</sub> and Pt/C catalysts were employed for the synthesis of 5-ATHIN, and the summary of reaction results is given in Table 1.

**Table 1. Product Compositions for the Continuous Hydrogenation of 5-NTIN with Different Catalysts<sup>a</sup>**

temperature (°C)	catalyst	5-APHIN	5-ATHIN	5-AIN	5-NTIN	AZO
40	Ni/SiO <sub>2</sub>	0	0	97.1	2.9	0
	Pd/Al <sub>2</sub> O <sub>3</sub>	0.4	24.9	1.6	0	73.1
	Pt/C	0.2	13.4	86.4	0	0
50	Ni/SiO <sub>2</sub>	0	0	98.9	1.1	0
	Pd/Al <sub>2</sub> O <sub>3</sub>	0.6	25.4	1.2	0	72.8
	Pt/C	0.2	15.2	84.6	0	0
60	Ni/SiO <sub>2</sub>	0	0	99.1	0.8	0
	Pd/Al <sub>2</sub> O <sub>3</sub>	0.8	27.5	1.2	0	70.5
	Pt/C	0.4	16.9	82.7	0	0
70	Ni/SiO <sub>2</sub>	0	0	99.2	0.9	0
	Pd/Al <sub>2</sub> O <sub>3</sub>	0.8	29.3	0.8	0	69.1
	Pt/C	0.4	18.7	80.9	0	0
80	Ni/SiO <sub>2</sub>	0	0	98.8	1.2	0
	Pd/Al <sub>2</sub> O <sub>3</sub>	0.9	29.8	0.7	0	68.7
	Pt/C	0.5	21.2	78.3	0	0

<sup>a</sup>Reaction conditions: mole concentration: 0.18 mol/L, liquid flow rate: 0.3 mL/min, system pressure: 2.0 MPa, gas flow rate: 20 sccm, hydrogen/substrate molar ratio: 16.5, solvent: tetrahydrofuran, and catalyst loading: 1.48 g.

Table 1 shows that Ni/SiO<sub>2</sub> catalysts exhibit remarkable performance over the synthesis of 5-AIN. No byproducts are detected in the products and the conversion of 5-NTIN approaches 99.2% at 70 °C, revealing the extraordinary selectivity and excellent applicability for the synthesis of 5-AIN. Hence, the Ni/SiO<sub>2</sub> catalyst is chosen as the representative catalyst for the synthesis of 5-AIN in the following experiments.

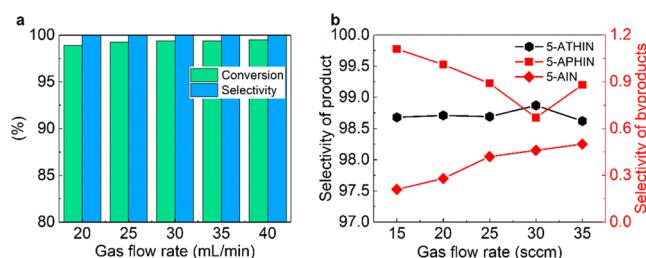
However, for the synthesis of 5-ATHIN, more than 65% azoxy compound is observed when adopting the Pd/Al<sub>2</sub>O<sub>3</sub> catalyst, and the maximal selectivity of 5-ATHIN is 29.6% at 80 °C. As the temperature increases, AZO gradually decreases to 68.7%. Other byproducts, 5-AIN and 5-APHIN, are in the range of 1–2%, indicating that AZO is dominated as the main byproduct and is difficult to be further reduced to the target product using the Pd/Al<sub>2</sub>O<sub>3</sub> catalyst. The formation of AZO is notably inhibited with the Pt/C catalyst. However, the catalytic activity of the Pt/C catalyst is insufficient to achieve the further hydrogenation of 5-AIN; hence more than 75% 5-AIN is detected in the products. To improve the reaction activity of the Pt/C catalyst and accelerate the reduction of 5-AIN into 5-ATHIN, an oil bath was used and the hydrogenation was conducted under temperatures ranging from 100 to 160 °C. The highest yield of 41.6% is obtained at 150 °C, and the

results are shown in Section 3 in the Supporting Information. Based on the results obtained from Pd/Al<sub>2</sub>O<sub>3</sub> and Pt/C catalysts, it can be concluded that the Pt/C catalyst is not suitable for the synthesis of 5-ATHIN due to low activity, while the inhibition for the formation of AZO using the Pd/Al<sub>2</sub>O<sub>3</sub> catalyst is highly required, although it exhibits excellent activity for the hydrogenation of 5-AIN. As shown in Scheme 1, the presence of the nitro group is the essential part for the formation of AZO, which indicates that the reduction of the nitro group using another catalyst prior to the hydrogenation of pyridine using the Pd/Al<sub>2</sub>O<sub>3</sub> catalyst may obtain satisfying results. Therefore, two-stage micropacked bed reactors were developed for the continuous synthesis of 5-ATHIN. Since high purity of 5-AIN without any AZO could be obtained using the Ni/SiO<sub>2</sub> catalyst, a micropacked bed filled with the Ni/SiO<sub>2</sub> catalyst (length: 18 cm, inner diameter: 4.57 mm) was placed upstream of the reactor packed with Pd/Al<sub>2</sub>O<sub>3</sub> for the synthesis of 5-ATHIN, which means two consecutive packed beds with different catalysts were adopted for the highly selective synthesis of 5-ATHIN.

For the optimization of the synthesis of 5-AIN and 5-ATHIN, the effect of reaction parameters on the reactor performance was investigated by comparing the conversion and selectivity of 5-AIN and 5-ATHIN in products under different reaction parameters. For the synthesis of 5-AIN, a one-stage reactor packed with the Ni/SiO<sub>2</sub> catalyst was employed, while utilizing two-stage micropacked bed reactors packed with Ni/SiO<sub>2</sub> and Pd/Al<sub>2</sub>O<sub>3</sub> catalysts for the synthesis of 5-ATHIN.

**Effect of the Gas Flow Rate.** In the continuous hydrogenation process, the hydrogen flow rate may reduce the residence time and intensify the gas–liquid mass transfer by increasing the turbulence, which significantly influences the conversion and selectivity of the reaction.<sup>57</sup> To determine the effect of the gas flow rate on the synthesis of 5-AIN and 5-ATHIN, the experiments under different gas flow rates were conducted, and the results are shown in Figure 2.

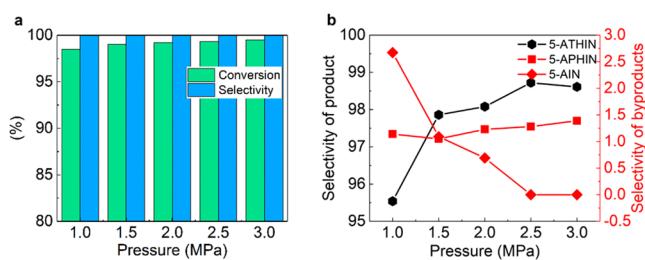
Figure 2a illustrates that the conversion of 5-NTIN constantly increases to beyond 99% as the gas flow rate increases beyond 30 sccm, and no byproduct is detected by GC. The results could be attributed to the intensified gas–liquid mass transfer at a higher gas flow rate, accelerating the hydrogenation of 5-NTIN. Therefore, a gas flow rate of 30



**Figure 2.** Product compositions for the synthesis of 5-AIN (a) and 5-ATHIN (b) at different gas flow rates. Reaction conditions: (a) system pressure: 2.0 MPa, mole concentration: 0.18 mol/L, temperature: 40 °C, liquid flow rate: 0.3 mL/min, hydrogen/substrate molar ratio: 16.5–33.0, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>) and (b) system pressure: 3.0 MPa, mole concentration: 0.18 mol/L, temperature: 80 °C, liquid flow rate: 0.3 mL/min, hydrogen/substrate molar ratio: 12.4–28.8, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>) and 2.3 g (Pd/Al<sub>2</sub>O<sub>3</sub>).

sccm was selected for the synthesis of 5-AIN. Figure 2b shows that the selectivity of 5-ATHIN remains basically constant under a gas flow rate range of 15–35 sccm, and the selectivity of 5-AIN continuously increases as the gas flow rate increases, while another byproduct APHIN exhibits an opposite trend. The reason may be that a higher gas flow rate results in a shorter residence time, which alleviates the reduction of 5-AIN and 5-APHIN. The maximal yield of 5-ATHIN is obtained with a gas flow rate of 30 sccm. However, a gas flow rate of 20 sccm was selected as the optimized condition for the following experiments since the gas flow rate shows a negligible effect on the reaction performance.

**Effect of Hydrogen Pressure.** Hydrogen pressure would influence the concentration of hydrogen in solution, which significantly affects the reaction rate and selectivity of products.<sup>46</sup> Here, the effect of hydrogen pressure on the synthesis of 5-AIN and 5-ATHIN was studied, and the results are shown in Figure 3a,b.

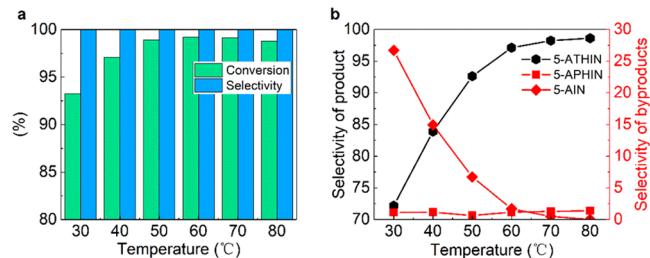


**Figure 3.** Product compositions for the synthesis of 5-AIN (a) and 5-ATHIN (b) at different hydrogen pressures. Reaction conditions: (a) mole concentration: 0.18 mol/L, temperature: 60 °C, liquid flow rate: 0.3 mL/min, gas flow rate: 30 sccm, hydrogen/substrate molar ratio: 24.8, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>); (b) mole concentration: 0.18 mol/L, temperature: 80 °C, liquid flow rate: 0.3 mL/min, gas flow rate: 20 sccm, hydrogen/substrate molar ratio: 16.5, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>) and 2.3 g (Pd/Al<sub>2</sub>O<sub>3</sub>).

Figure 3a shows that when the hydrogen pressure increases from 1.0 to 3.0 MPa, the conversion of 5-NTIN increases from 98.5% at 1.0 MPa to 99.5% at 3.0 MPa since higher pressure favors the reduction of 5-NTIN, and no byproduct is detected by GC. To reduce the energy cost, a pressure of 2.0 MPa was chosen for the synthesis of 5-AIN. In Figure 3b, the selectivity of 5-ATHIN gradually increases from 95.5 to 98.7% as the hydrogen pressure increases to 2.5 MPa. Besides, the amount of 5-APHIN is also increased from 1.1 to 1.4%, indicating higher pressure accelerates the hydrogenation of the benzene ring. However, there is a slight decrease of 5-ATHIN from 2.5 to 3.0 MPa, which may be attributed to the excessive hydrogenation of 5-ATHIN into 5-APHIN. Hence, the synthesis of 5-ATHIN is preferred to be conducted under hydrogen pressures ranging from 2.5 to 3.0 MPa.

**Effect of Temperature.** It is known that AZO is prone to be formed at higher temperatures, which causes an adverse effect on the catalyst activity and product purity.<sup>58</sup> Meanwhile, complete conversion of 5-NTIN and the hydrogenation of the pyridine ring to synthesize 5-ATHIN are difficult to accomplish at low temperatures. As a result, a proper reaction temperature is important to improve selectivity. To investigate the effect of temperature on the synthesis of 5-AIN and 5-ATHIN, experiments at different temperatures ranging from

30 to 80 °C were conducted to determine a suitable temperature, and the results are shown in Figure 4a,b.

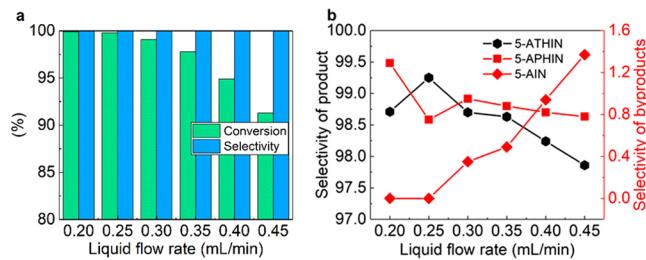


**Figure 4.** Product compositions for the synthesis of 5-AIN (a) and 5-ATHIN (b) at different temperatures. Reaction conditions: (a) system pressure: 2.0 MPa, mole concentration: 0.18 mol/L, liquid flow rate: 0.3 mL/min, gas flow rate: 30 sccm, hydrogen/substrate molar ratio: 24.8, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>) and (b) system pressure: 3.0 MPa, mole concentration: 0.18 mol/L, liquid flow rate: 0.3 mL/min, gas flow rate: 20 sccm, hydrogen/substrate molar ratio: 16.5, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>) and 2.3 g (Pd/Al<sub>2</sub>O<sub>3</sub>).

As shown in Figure 4a, the conversion of 5-NTIN beyond 99% is obtained when the temperature is higher than 60 °C, and a maximal yield of 99.2% is obtained at 60 °C. Hence, a temperature of 60 °C was selected for the synthesis of 5-AIN in the following experiments. Figure 4b illustrates that the selectivity of 5-ATHIN gradually increases to a high value of 98.6% at 80 °C, while the selectivity of 5-AIN continuously decreases to 0%, revealing that the high temperature accelerates the reduction of the pyridine ring with the Pd/Al<sub>2</sub>O<sub>3</sub> catalyst. Additionally, negligible variation of 5-APHIN is observed at different temperatures, indicating the difficulty for the reduction of the benzene ring even with the high-activity 5% Pd/Al<sub>2</sub>O<sub>3</sub> catalyst. AZO is not detected in the products, indicating the remarkable performance of Ni/SiO<sub>2</sub> on the suppression of azoxy compounds. For the consideration of the maximal yield of 5-ATHIN, a temperature of 80 °C was chosen for the following experiments.

**Effect of the Liquid Flow Rate.** The variation of the liquid flow rate would change the residence time, which significantly influences reaction performance and product composition. For hydrogenation under shorter residence times, the reactant 5-NTIN could not be transformed into 5-AIN or 5-ATHIN completely, as part of the reactant flows out of the reactor before coming in contact with hydrogen on the catalysts, while for hydrogenation under longer residence times, it is inevitable for 5-ATHIN to be further reduced to 5-APHIN. Hence, it is important to determine a proper liquid flow rate for the selective hydrogenation of 5-AIN and 5-ATHIN to improve the reaction performance and obtain maximal yields of 5-AIN and 5-ATHIN.

As shown in Figure 5a, the conversion of 5-NTIN is below 99% when the liquid flow rate is higher than 0.3 mL/min and continuously decreases to 91.3% with a liquid flow rate of 0.45 mL/min, which could be attributed to the insufficient residence time at a high liquid flow rate. Meanwhile, the selectivity of 5-AIN is approaching 100% for flow rates ranging from 0.2 to 0.45 mL/min. Hence, a liquid flow rate of 0.3 mL/min was selected for the following experiments. Figure 5b illustrates that the selectivity of 5-ATHIN decreases from 99.3 to 97.9% when the liquid flow rate increases from 0.25 to 0.45 mL/min, while the selectivity of 5-AIN exhibits an opposite



**Figure 5.** Product compositions for the synthesis of 5-AIN (a) and 5-ATHIN (b) at different liquid flow rates. Reaction conditions: (a) system pressure: 2.0 MPa, mole concentration: 0.18 mol/L, temperature: 60 °C, gas flow rate: 30 sccm, hydrogen/substrate molar ratio: 16.5–37.2, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>) and (b) system pressure: 3.0 MPa, mole concentration: 0.18 mol/L, temperature: 80 °C, gas flow rate: 20 sccm, hydrogen/substrate molar ratio: 11–24.8, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>) and 2.3 g (Pd/Al<sub>2</sub>O<sub>3</sub>).

trend increasing from 0 to 1.4%, which indicates that a longer residence time is demanded for the hydrogenation of the pyridine ring in 5-AIN. However, it is found that the selectivity of 5-ATHIN increases slightly from 98.7 to 99.3% when the liquid flow rate increases from 0.2 to 0.25 mL/min, indicating that the formation of 5-APHIN is accelerated for a liquid flow rate lower than 0.25 mL/min. The highest yield of 99.3% is achieved at a reaction temperature of 80 °C, a hydrogen pressure of 3.0 MPa, and a liquid flow rate of 0.25 mL/min.

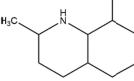
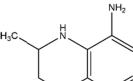
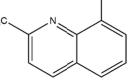
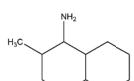
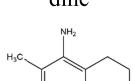
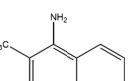
For the scaling up of the flow system, we have realized the scaling up of the micropacked bed system to the production capacity of 100–300 kg/day in PharmaBlock Company with the acceptable pressure drop and similar gas–liquid mass transfer. The principles of scaling up are based on the parallel numbering-up and scale-out by suitable dimension enlarging.<sup>59</sup> However, this work aims to realize high yields of 5-aminoisoquinoline and 5-amino-1,2,3,4-tetrahydroisoquinoline by screening the experimental conditions and catalysts in a

**Table 2. Selective Hydrogenation of the Nitro Group of Heterocyclic Nitroaromatics in the Continuous Flow System<sup>a</sup>**

Substrate	T/°C	Liquid flow rate/mL/min	Gas flow rate/sccm	Yield of main product/%
5-aminoquinolin e				
5-nitroquinoline	60	0.2	30	 99.2
6-aminoquinolin e				
6-nitroquinoline	60	0.2	20	 99.4
8-aminoquinolin e				
8-nitroquinoline	70	0.3	20	 99.4
8-aminoquinaldi ne				
8-nitroquinaldine	70	0.2	20	 99.7
6-aminoquinaldi ne				
6-nitroquinaldine	70	0.2	20	 99.9

<sup>a</sup>Reaction conditions: mole concentration: 0.18 mol/L, hydrogen pressure: 2.0 MPa, hydrogen/substrate molar ratio: 16.5–37.1, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>).

**Table 3. Selective Hydrogenation of the Nitro Group and the Pyridine Ring of Heterocyclic Nitroaromatics in the Continuous Flow System<sup>a</sup>**

Substrate	Yield of over hydrogenation products/%	Yield of main products/%	Yield of incomplete hydrogenation products/%
5-nitroquinoline <sup>a</sup>	5-aminoperhydroquinoline 	5-amino-1,2,3,4-tetrahydroquinoline 	5-aminoquinoline 
	1.1	98.6	0.3
6-nitroquinoline <sup>a</sup>	6-aminoperhydroquinoline 	6-amino-1,2,3,4-tetrahydroquinoline 	6-aminoquinoline 
	1.4	98.3	0.3
8-nitroquinoline <sup>b</sup>	8-aminoperhydroquinoline 	8-amino-1,2,3,4-tetrahydroquinoline 	8-aminoquinoline 
	1.3	98.0	0.7
8-nitroquinaldine <sup>b</sup>	8-aminoperhydroquinaldine 	8-amino-1,2,3,4-tetrahydroquinaldine 	8-aminoquinaldine 
	1.4	98.0	0.6
6-nitroquinaldine <sup>b</sup>	6-aminoperhydroquinaldine 	6-amino-1,2,3,4-tetrahydroquinaldine 	6-aminoquinaldine 
	0.6	97.8	1.6

<sup>a</sup>Reaction conditions: mole concentration: 0.18 mol/L, temperature: 90 °C, hydrogen pressure: 3.0 MPa, gas flow rate: 20 sccm, liquid flow rate: 0.2 mL/min<sup>a</sup>, 0.3 mL/min<sup>b</sup>, hydrogen/substrate molar ratio: 16.5–24.8, solvent: tetrahydrofuran, and catalyst loading: 1.48 g (Ni/SiO<sub>2</sub>) and 2.3 g (Pd/Al<sub>2</sub>O<sub>3</sub>).

continuous flow system and the scaling up of this continuous system is out of scope in this study.

**Applications in Relevant Substrates.** The synthesis of 5-AIN and 5-ATHIN in the continuous flow system exhibited remarkable performance, and optimized reaction parameters (gas flow rate, hydrogen pressure, temperature, and liquid flow rate) were obtained successfully. Besides, the continuous flow

platform was running at a capacity of 12.8 g/h and the system was operated in the range of 20–25 h before the catalytic activity loss was beyond 3%. Additionally, in our research, the gas superficial velocity was in the range of 16.8–44.8 mm/s, and the liquid superficial velocity was in the range of 0.23–0.51 mm/s; hence all of the experiments were conducted under a low interaction regime.<sup>37,38</sup> The yields of 5-AIN and 5-

ATHIN at different reaction conditions are summarized in Section 4 in the Supporting Information. The continuous system was also applied for the hydrogenation of relevant heterocyclic nitroaromatics, which are also important intermediates in the fine chemical industry.<sup>18,19,60</sup>

Table 2 presents the results for the selective hydrogenation of the nitro group of other heterocyclic nitroaromatics in the continuous flow system. Compared with the reduction of 5-NTIN, a higher gas flow rate was required for 5-nitroquinoline, and a shorter residence time favors the hydrogenation of 8-nitroquinoline. This difference may be attributed to the higher reaction activity of 5-nitroquinoline and 8-nitroquinoline, while for the hydrogenation of 6-nitroquinaldine and 8-nitroquinaldine, the reaction rate is slower owing to the presence of the methyl group; hence the reaction temperature was altered to 70 °C to achieve the complete conversion. The yields of the corresponding products are all beyond the level of 99%, validating the efficiency and applicability of the continuous flow system for the selective hydrogenation of nitro groups of heterocyclic nitroaromatics.

Table 3 illustrates the reaction results for the selective hydrogenation of the nitro group and the pyridine ring of other heterocyclic nitroaromatics in the continuous flow system. In comparison with the synthesis of 5-ATHIN, a higher temperature was employed to accelerate the reduction of the pyridine ring, which is the determining step for the reaction. The liquid flow rate was altered to 0.3 mL/min for the reduction of 6-nitroquinoline, 6-nitroquinaldine, and 8-nitroquinaldine to alleviate the excessive hydrogenation of the benzene ring. The yields of the corresponding products are all beyond the level of 97.5%, verifying the applicability of this continuous flow system for the selective hydrogenation of the nitro group and the pyridine ring of heterocyclic nitroaromatics.

## CONCLUSIONS

The continuous flow system based on a micropacked bed reactor has been successfully employed for the synthesis of 5-AIN and 5-ATHIN. The effects of the gas flow rate, hydrogen pressure, temperature, and liquid flow rate were determined for the optimization of reaction performance, and maximal yields of 5-AIN and 5-ATHIN were determined to be 99.9 and 99.3%, respectively. Additionally, the continuous flow system was also applied for the synthesis of other heterocyclic nitroaromatics to achieve the selective hydrogenation of the nitro group and the pyridine ring, and all of the yields were obtained at levels of 99 and 97.5%, respectively. The continuous flow system based on a micropacked reactor exhibits remarkable performance and efficiency for the hydrogenation of heterocyclic nitroaromatics, and side reactions are effectively suppressed by the precise control of residence time. Nevertheless, further optimization of catalysts and a relevant reaction kinetics model are required for the improvement of selectivity and process scaling up.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.oprd.1c00164>.

Photograph of the continuous flow platform; experimental data of catalyst deactivation; oil bath; and

summary of yields of 5-AIN and 5-ATHIN at different reaction parameters ([PDF](#))

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### Notes

The authors declare no competing financial interest.

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