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COMMUNICATION

# Simple reversible fixation of magnetic catalyst in continuous flow system: Ultrafast reduction of nitroarenes and subsequent reductive amination using ammonia borane

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**A continuous reductive amination of aldehydes with nitroarenes over a Pd-Pt-$Fe_3O_4$ catalyst was performed. We used $NH_3BH_3$ as not only a hydrogen source for nitro reduction but also a reductant for imine reduction. Secondary aromatic amines were obtained in the continuous flow reaction in good to excellent yields.**

Continuous flow reaction technology has become an ideal tool for organic transformations with distinctively advantageous characteristics such as the detection of transient reactive species,[1,2] safe usage of hazardous or explosive reagents,[3-8] multi-step capability of important compounds, and easy scale-up with no further process development.[9-15] As one successful example among many organic reactions, chemists have developed continuous hydrogenation to overcome the limited scale-up and slow $H_2$ diffusion rates in batch-type reactions.[16-23] In most cases, a direct connection to a high-pressure tank, special mixing setups such as H-Cube® or a gas-permeable membrane for the saturation of a solvent with $H_2$ is involved;[24-27] safety equipment for the prevention of potential explosion and an expensive in situ hydrogen generator are required. Towards avoiding the aforementioned drawbacks, in situ hydrogen generation from stable $H_2$ precursors, such as ammonium formate, hydrazine and metal hydrides, has been highly recommended as an ideal alternative.[28] In addition to them, $NH_3BH_3$ recently gathered great attention not only as a hydrogen storage but also a hydrogen precursor for easy laboratory manipulation due to its high solvolytic stability, quick $H_2$ evolution through contact with a transition metal, and its own intrinsic reduction power.[29-32]

Recently, we developed highly active and recyclable magnetic bimetallic nanoflakes for the conversion of $NH_3BH_3$ to $H_2$ gas (dehydrogenation) followed by the reduction of nitroarenes to amines (hydrogenation), which occurs within 5 min.[33] Furthermore, the magnetic catalyst was recycled over 300 times with easy retrieval through the use of an external magnet. To further improve this reaction for practical purposes, we began the pursuit of a versatile immobilisation strategy for this catalyst for application in a continuous process.

Neodymium magnets have been known to be the strongest type of commercially available permanent magnet. They have very diverse shapes and low prices and are made from alloys of neodymium, iron and boron.[34,35] Therefore, many attempts to utilise neodymium magnet are known in flow setups, such as continuous catalyst recirculation in microfluidic system,[36] catalyst agitation in a glass column,[37] and catalyst fixation in a micro device.[38] An induced magnet using a Helmholtz coil with an alternating current is also reported as an alternative to permanent magnet.[39] We have devised a new method for the simple fixation of the active magnetic nanoflakes in tubes using neodymium magnets as shown in Figure 1.[40] The tubes containing dispersed nanoflakes are placed in a strip of U-shaped staples with neodymium magnets, which is then covered with another strip and more magnets. The nanoflakes could be retrieved easily by removing the neodymium magnets (reversible fixation). With this robust method for nanoflake fixation, we began to devise a practical strategy to combine three reactions in flow.

**Figure 1.** Reversible fixation of magnetic nanoflakes to tubes with external magnets.

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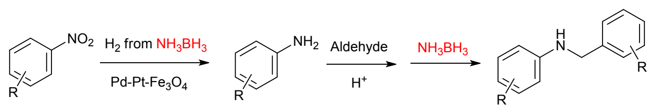
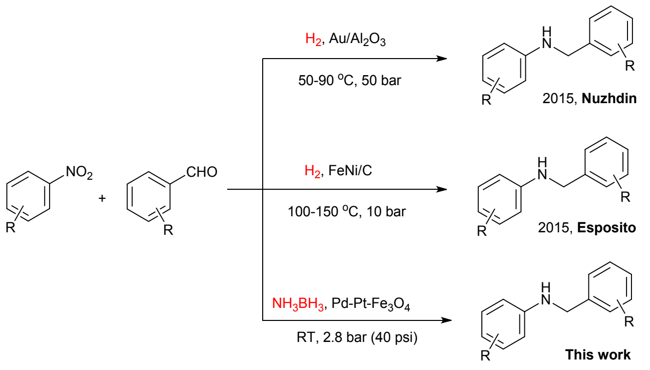


**Scheme 1.** Two roles of ammonia borane (hydrogen source and imine reductant)

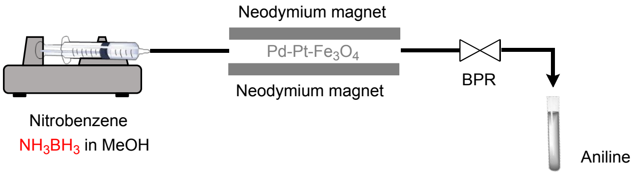
Following our previous successful nitro group reduction,[33] we targeted a continuous three-step process combining nitro group reduction, imine formation, and imine reduction (so called reductive amination) utilizing ammonia borane not only as a hydrogen precursor but also a reductant (Scheme 1). $NH_3BH_3$ has been known to be applicable to reductive amination in the presence of a Lewis acid.[41] Initially, this continuous approach may seem simple, but it is challenging because $NH_3BH_3$ can reduce both aldehydes and imines. Consequently, in batch-type reductive amination reactions, $NH_3BH_3$ should be added after the completion of imine formation. For successful execution of the three successive steps, fast induction of imine formation ahead of unwanted aldehyde reduction, taking advantage of the flow reaction technique, is essential; this cannot be realised in a batch-type reaction. In our strategy, a main stream of excess $NH_3BH_3$ and a nitroarene compound will be passed through a bed of a transition metal catalyst for nitro reduction, and then excess $NH_3BH_3$ will reduce the imine formed in situ from the reaction between already-reduced amine and a stream of aldehyde connected through a T-shaped tubing connector. The installation of various back pressure regulators (BPRs) (*i.e.,* for pressure control) could be the ideal option for reaction optimisation.



**Scheme 2.** Two roles of ammonia borane and continuous flow reductive aminations of aldehydes with nitroarenes.

Reductive amination of aldehydes with nitroarenes over a $Au/Al_2O_3$ catalyst in a continuous flow reactor has been reported; it was performed under a high pressure (50 bar) at 80–90 °C and afforded the desired products along with decent amounts of unreacted amine and imine (top, Scheme 2).[42] Continuous reductive aminations using $H_2$ catalysed by an Fe/Ni alloy are also known but require harsh conditions (100–150 °C, 10 bar) and give low yields (middle, Scheme 2).[43] Other seminal direct reductive aminations were reported as well using amine and carbonyl compounds.[44-46] Herein, we describe reductive amination between nitroarenes and aldehydes in a continuous manner at room temperature with a retention time of less than 1 min (bottom, Scheme 2).

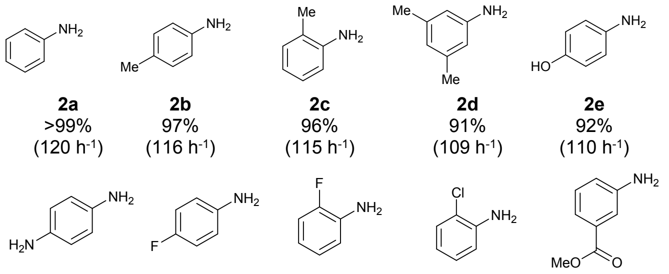
**Table 1**. Optimisation of nitro reduction conditions.[a]



| Entry | $NH_3BH_3$ (equiv) | Flow rate (mL/min) | Conversion[b] (%) | Yield[c] (%) |
|---|---|---|---|---|
| 1[d,e] | 3.0 | 0.2 | 86 | 70 |
| 2[d] | 3.0 | 0.2 | >99 | >99 |
| 3[d,f] | 3.0 | 0.2 | 99 | 89 |
| 4[d] | 3.0 | 0.4 | >99 | >99 |
| 5[d] | 3.0 | 0.8 | >99 | 97 |
| 6 | 3.0 | 0.4 | >99 | >99 |
| 7 | 2.5 | 0.4 | >99 | >99 |
| **8** | **2.0** | **0.4** | **>99** | **>99** |
| 9 | 1.5 | 0.4 | >99 | 97 |
| 10 | 1.0 | 0.4 | 94 | 84 |

[a] Tube was filled with 80 mg of $Pd-Pt-Fe_3O_4$ and reaction was carried out under the following conditions: room temperature, 40 psi, nitrobenzene (1.0 equiv, 0.2 M) and $NH_3BH_3$ (concentration varied to adjust its stoichiometry, for example 0.4 M for 2.0 equiv) in MeOH. [b] Gas chromatography (GC) conversion. [c] GC yield determined using 2-isopropylnaphthalene as an internal standard. [d] 0.1 M nitrobenzene. [e] 30 mg of $Pd-Pt-Fe_3O_4$ was used. [f] Without BPR.

We began the screening of the nitroarene reduction with $Pd-Pt-Fe_3O_4$ and 3 equiv of $NH_3BH_3$ with varying flow rates (Table 1). In the initial attempt, 30 mg of $Pd-Pt-Fe_3O_4$ was used, but this amount was not sufficient for the completion of the reaction (entry 1). However, product **2a** was obtained in 99% yield when the catalyst loading was increased to 80 mg (entry 2). Next, when the reaction was performed without using a BPR, a slight decrease in the yield (89%) was observed at the same flow rate (entry 3). Upon doubling the flow rate from 0.2 to 0.4 mL/min, the yield increased to 99% (entry 4). Increasing the flow rate to 0.8 mL/min led to a slight decrease in the yield (entry 5). When the reaction concentration was increased to 0.2 M, a 99% yield was achieved (entry 6). Then, we attempted to reduce the amount of $NH_3BH_3$. Reduction from 3 to 2 equiv did not affect the product yield (entries 6–8). However, decreasing the amount of $NH_3BH_3$ further resulted in 97% and 84% yields (entries 9 and 10, respectively).



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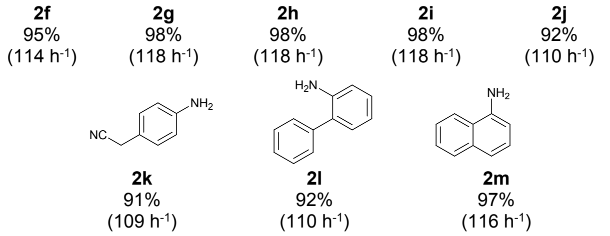
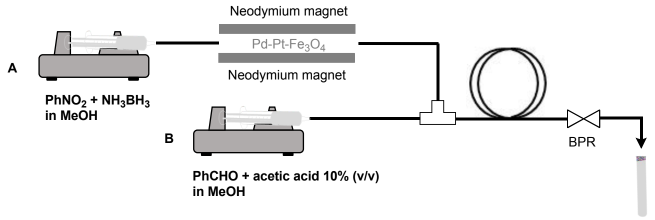


**Scheme 3**. Scope of nitro reduction reaction. Reaction conditions: room temperature, 40 psi, substrate (1.0 equiv, 0.2 M), Pd-Pt-$Fe_3O_4$ (80 mg, 0.04 mmol), ammonia borane (2.0 equiv, 0.4 M), MeOH, 0.4 mL/min flow rate. Isolated yields are shown and TOFs are in the parenthesis. The reaction mixture was collected for 12 min for the yield determination.

In order to investigate the generality of the reduction, we tested the reactivities of a variety of nitroarenes under the optimal conditions (entry 8, Table 1). As shown in Scheme 3, the reduction method turned out to be effective regardless of electronic and reduction-sensitive functionalities. From nitrobenzene substituted with a methyl group at either the ortho- or para-position, the corresponding anilines (**2b** and **2c**) were obtained in quantitative yield, while nitrobenzene substituted with two methyl groups at the meta-positions was also tolerated, albeit providing the corresponding aniline (**2d**) in a slightly lower yield (91%). Even nitrobenzene with a free hydroxyl group (**2e**) or amine (**2f**) showed excellent reactivity without any significant decrease in yield. Substrates with electron-withdrawing groups at the ortho-, para-, and meta-positions also gave the desired amines (**2g**–**2j**) in excellent yields (92–98%), indicating the mildness and selectiveness of the present catalyst system. Moreover, the reaction is not significantly impeded for nitroarenes with cyanomethyl substituent (**2k**) or multiple aryl rings (**2l** and **2m**).

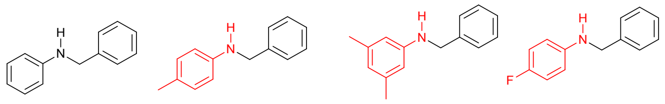
**Table 2**. Optimisation of reductive amination.[a]



| Entry | $NH_3BH_3$ (equiv) | PhCHO (equiv) | Flow rate[b] (mL/min) | Yield[c] (%) |
|---|---|---|---|---|
| 1[d] | 6.0 | 4.0 | 0.20 + 0.20 | 55 |
| 2 | 6.0 | 4.0 | 0.20 + 0.20 | 86 |
| 3 | 6.0 | 4.0 | 0.25 + 0.35 | >99 |
| 4 | 6.0 | 3.5 | 0.25 + 0.35 | >99 |
| 5 | 6.0 | 3.0 | 0.25 + 0.35 | 82 |
| **6** | **5.0** | **3.5** | **0.25 + 0.35** | **>99** |
| 7 | 4.5 | 3.5 | 0.25 + 0.35 | 89 |
| 8 | 5.0 | 3.5 | 0.35 + 0.45 | 91 |
| 9[e] | 5.0 | 3.5 | 0.35 + 0.45 | >99 |
| 10[f] | 5.0 | 3.5 | 0.25 + 0.35 | >99 |

[a] Reaction conditions: unless otherwise noted, all reactions were performed at room temperature and 40 psi using a 0.5 m residence element (6 s residence time). Syringe A: $PhNO_2$ (1.0 equiv, 0.2 M) and $NH_3BH_3$ (concentration varied to adjust stoichiometry, for example 1 M for 5.0 equiv) in MeOH with Pd-Pt-$Fe_3O_4$ (80 mg, 0.04 mmol). Syringe B: PhCHO (concentration varied to adjust stoichiometry, for example 0.7 M for 3.5 equiv) and acetic acid (10% of the total volume of solution B) in MeOH. [b] Flow rate of A + flow rate of B. [c] GC yield determined using 2-isopropylnaphthalene as an internal standard. [d] Amount of acetic acid was 5% of the total volume of solution B. [e] Length of residence element was 1 m (residence time of 8 s). [f] 0.1 M nitrobenzene.

Next, we attempted to combine the reductive amination with the nitroarene reduction for the synthesis of secondary amines (Table 2). A key idea for the reductive amination is the utilisation of leftover $NH_3BH_3$ for imine reduction. Specifically, excess $NH_3BH_3$ and a reduced amine injected by syringe A will meet a second stream containing benzaldehyde and acetic acid as an additive from syringe B at the junction of a T-shaped connector, where the desired imine formation followed by imine reduction should occur rather than aldehyde reduction. We varied the amounts of $NH_3BH_3$, aldehyde, and acetic acid and the flow rate of each to ensure complete reductive amination. The entire reaction was optimised at room temperature and 40 psi. We initiated our studies by screening the amount of acetic acid used in the one-pot reductive amination of benzaldehyde with nitrobenzene. When the amount was 5% of the total volume of solution B, a moderate yield of 55% of desired amine **3a** was obtained (entry 1). An improved yield of 86% was achieved upon increasing the amount to 10% of the total volume of solution B (entry 2). Increasing the flow rates from both syringes, with a slightly faster flow from syringe B, led to a quantitative yield of the reductive amination product (99%, entry 3); similar results were obtained using less benzaldehyde (3.5 equiv, entry 4). However, further reduction of the amount of aldehyde resulted in incomplete conversion. A complete imine formation should require an excess amount of aldehyde, which reveals the restriction of our substrate scope. Next, the effect of the ammonia borane amount was examined. Although complete conversion could still be achieved with 5 equiv of ammonia borane (entry 6), a slight decrease in yield was observed when 4.5 equiv was used (entry 7). Increasing the flow rate, which reduces the residence time, was not beneficial to the yield. Amine **3a** was obtained in only 91% yield (entry 8). This is presumably because a longer reaction time may be required for imine formation than for reduction. This assumption was confirmed by the detection of unreacted amine in the crude reaction mixture through GC analysis. Based on this observation, we doubled the length of the tube, or in other words, increased the retention time, and were able to obtain reduction product **3a** in 99% yield (entry 9). Finally, a 0.1 M solution of nitrobenzene was also found to be effective (entry 10). We chose the conditions in entry 6 as the optimal conditions to expand the scope further.



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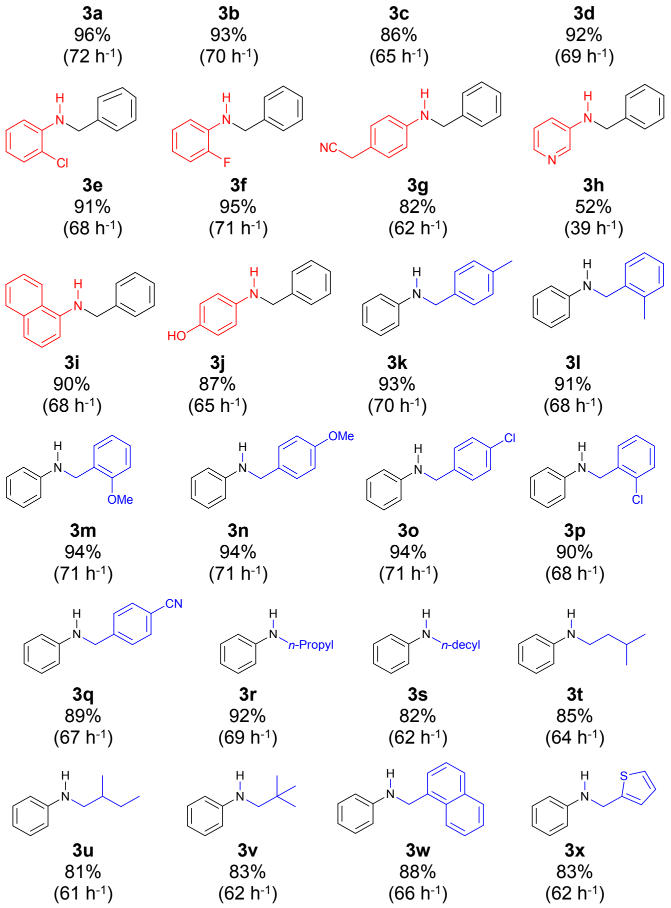

**Scheme 4**. Scope of reductive amination reaction. Reaction conditions: unless otherwise noted, all reactions were performed at room temperature and 40 psi using a 0.5 m residence element (6 s residence time). Syringe A: nitro substrate (1.0 equiv, 0.2 M) and $NH_3BH_3$ (5.0 equiv, 1.0 M) in MeOH with Pd-Pt-$Fe_3O_4$ (80 mg, 0.04 mmol), 0.25 mL/min flow rate. Syringe B: aldehyde substrate (3.5 equiv, 0.7 M) and acetic acid (10% of the total volume of solution B) in MeOH, 0.35 mL/min flow rate. Isolated yields are shown and TOFs are in the parenthesis. The reaction mixture was collected for 12 min for the yield determination. TOF of Pd-Pt was calculated based on the final yield.

Then, we ran the continuous three-step process with a broad range of nitroarenes and benzaldehydes with various substituents (Scheme 4). Nitrobenzene with one and two electron-donating methyl groups gave desired amines **3b** and **3c** in 93% and 86% yields, respectively. Nitrobenzene with halogen substituents, at either the para- or ortho-positions, also underwent the present reaction, yielding the corresponding products in comparable yields (up to 95%, **3d**–**f**). Similar to the arene reduction of **2k**, the one-pot reductive amination of 4-cyanomethylnitrobenzene proceeded smoothly without affecting the nitrile functionality, affording amine **3g** in 82% yield. The reaction with 3-nitropyridine gave product **3h** in a moderate yield (52%), while nitronaphthalene was transformed with good efficiency (**3i**, 90% yield). Adequate reactivity was also observed for 4-nitrophenol (**3j**, 87% yield). To further test the versatility of this reaction, we also examined the effect of substituents on the aryl aldehyde. Aryl aldehydes featuring electron-donating substituents (methyl or methoxy) at either the ortho- or para-positions readily afforded the respective amination products in comparable yields (**3k**–**n**, 91–94%). Substrates with chloro substituents were also effective in the present reaction and corresponding products **3o** and **3p** were isolated in excellent yields (up to 94%). Notably, the standard reaction conditions were compatible with cyano groups in aldehyde component; secondary amine **3q** was afforded in an impressive yield (89%). In addition, amines were prepared smoothly from aliphatic, polyaryl, and heteroaryl aldehydes with equal efficiency (**3r**–**3x**). It is noteworthy that the sterically bulky pivalaldehyde was readily reacted to provide **3v**. Lastly, we attempted the reductive amination of nitroalkanes with aliphatic aldehydes. Unfortunately, however, we observed only nitro and aldehyde reductions presumably because the imine formation must not be fast enough.

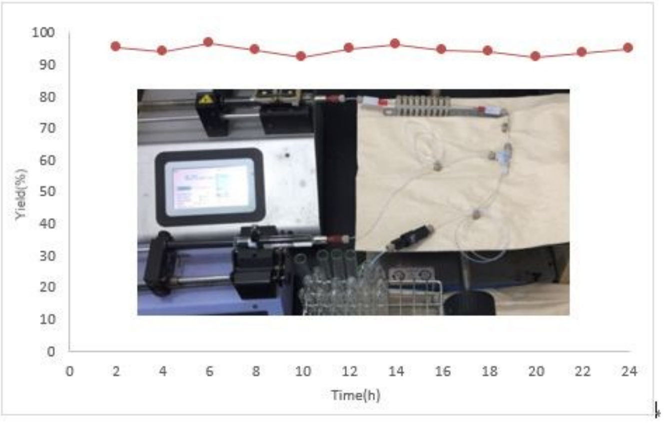

**Figure 2**. Results of long-term effectiveness experiment.

After successfully evaluating the generality of the scope with various nitroarenes and aldehydes, we became interested in verifying the effectiveness of the catalyst system in our T-shaped flow setup. Accordingly, we conducted the reductive amination for 24 hours under the optimal conditions (entry 6, Table 2) using nitrobenzene and benzaldehyde, and the hourly yields are presented in Figure 2. Notably, the catalytic activity in the present flow process was maintained even after 24 h with an average yield of 93%.[47] This gram-scale reaction provided 66.6 mmol (12.2 g, TON = 1.67 x $10^3$) of the secondary amine without much effort.

## Conclusions

In conclusion, we developed a rapid and continuous three-step process of nitro reduction, imine formation, and imine reduction, which enables direct and facile preparation of various secondary amines under relatively mild conditions. The reactions were carried out at ambient temperature with the use of ammonia borane as a hydrogen source. Because the previously reported reductive aminations have obstacles associated with them, this continuous flow technique is much more practical on the basis of the relative ease with which it delivers the desired amines, even on the gram scale.

## Conflicts of interest

There are no conflicts to declare

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## Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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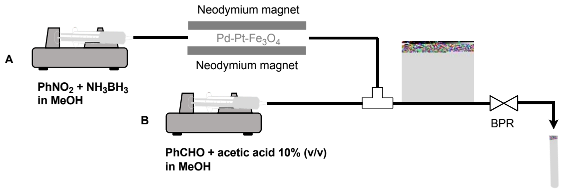

A continuous reductive amination was performed using $NH_3BH_3$ through reversible magnetic bimetallic fixation under room temperature.