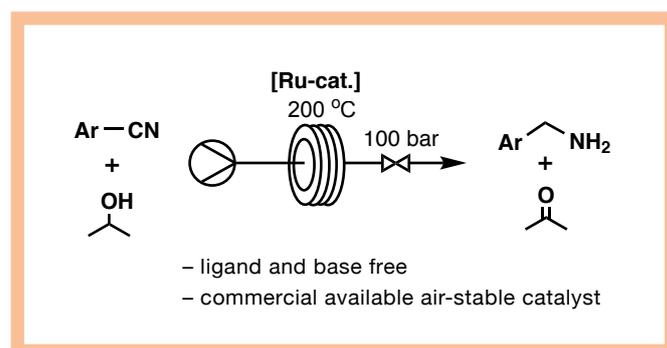




PHOENIX

# Fast and Continuous Transfer Hydrogenation of Aromatic Nitriles to Amines



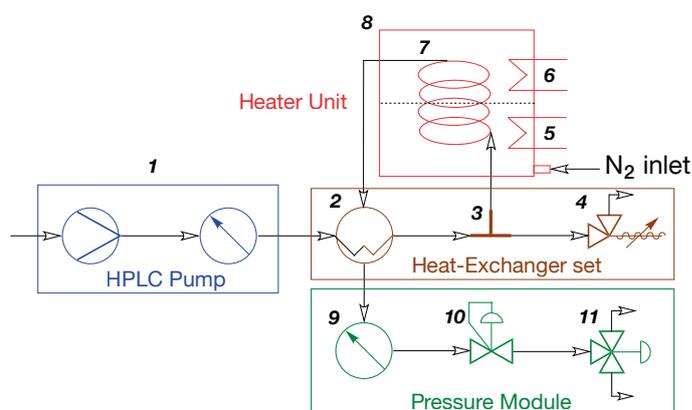
## Introduction

The reduction of nitriles is one of the most common route to synthesize primary amines, which are key intermediates in fine-chemical, pharmaceutical, and agricultural industries. Both direct (employing H<sub>2</sub> gas) and transfer hydrogenation (TH) can be used for this purpose. The latter is a rapidly growing field taking into account green chemistry and economic considerations, avoiding the handle of hazardous hydrogen gas.<sup>1</sup> By considering the last restriction, smart systems with *in situ* H<sub>2</sub> gas production could be also an alternative solution.<sup>2</sup>

Recently, Lindhardt et al. reported the successful TH of various substrates in flow on 10% Pd/C, however under these conditions the nitrile substrate remained unreacted.<sup>3</sup> TH reactions in continuous flow have been thoroughly investigated in the past years, but no nitrile reduction has been reported so far. Recently, researchers from Eli Lilly together with the University of Cambridge have developed a rapid, continuous, base-free method using the Phoenix Flow Reactor™. The method employs commercial dichloro(*p*-cymene)ruthenium(II) dimer as catalyst, *iso*-propanol (IPA) as solvent and hydrogen donor, and requires no additives.<sup>4</sup> Interestingly, Beller's group have reported, that no conversion was observed under similar condition in batch, using potassium *tert*-butylate as base.<sup>5</sup>

## Instrumentation

The pump (1) delivers the liquid through the heat exchanger (2) to the heated zone. The relief valve (4) is responsible for avoiding over pressurization. Then the liquid



**Figure 1.** Schematic representation of the Phoenix Flow Reactor™

1. HPLC pump (with readable inlet pressure) 2. Heat exchanger; 3. Tee connector; 4. Relief valve; 5. and 6. Independent heater wires; 7. Stainless steel loop; 8. Heated blocks; 9. Back pressure sensor; 10. Back pressure regulator; 11. Switching valve

re-enters into the heat exchanger, followed by the pressure module. The product and waste can be separately collected by using the switching valve (11) at the end of the flow. See the details in Figure 1.

The system operates at up to 450 °C and 200 bar. The N<sub>2</sub> gas ensures quick cooling.

Gas introduction into the reaction line is also available, using ThalesNano's mass flow controller unit, the Gas Module™ or the H-Cube Pro™, if H<sub>2</sub> gas is involved.<sup>6</sup>

## Experimental

### PRECONDITIONING:

The Phoenix Flow Reactor™ was set to the required temperature (200 °C) and pressure (100 bar), and pure solvent was flown (4 mL/min) through the reactor lines until the system have reached thermal equilibrium and the pressure became stable.

### THE SYNTHESIS OF 4-METHOXYBENZYLAMINE:<sup>4</sup>

The solution of 4-methoxybenzonitrile (665 mg, 5 mmol) and [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> catalyst (30 mg, 0.05 mmol, 1 mol% catalyst loading) in IPA (50 mL) was pumped through the pre-equilibrated (200 °C, 100 bar) 35 mL stainless steel loop (SS 316L, 1/16" OD, 1 mm ID) with a flow rate of 4 mL/min. Before the introduction of the reaction mixture, it was sonicated to fully dissolve the catalyst. Work-up procedure: 1 M HCl in dioxane (4 mL), then hexane (4 mL) was added to the collected fraction to form hydrochloride salt, which was filtered and washed with hexane (30 mL) and diethyl-ether (30 mL), respectively. The residual solvent was removed in vacuo. The product was isolated as white solid. <sup>1</sup>H NMR (600 MHz, MeOD): δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 4.14 (s, 2H), 3.82 (s, 3H). <sup>13</sup>C NMR (151 MHz, MeOD): δ 160.75, 131.13, 122.75, 114.15, 54.40, 49.94.

### RISK ASSESSMENT AND HAZARDS

Mind hot surfaces, do not touch possibly hot parts of the system. Above 250 °C it is mandatory to connect the heat exchanger and the safety valve to the system. Hot material may cause damage to the back pressure sensor or personal injury if the liquid remains above boiling point. Connect a tube to the outlet of the relief valve and place it in a flask to collect the released liquid/gas in case of over pressurization. Never open the system at high temperature/high pressure, the uncontrolled release of high pressure liquid can potentially come into contact with the operator.

Depending on the substrate, the temperature and the concentration of the Ru-catalyst, Ru(0) nanoparticles might form and cause blockage in the liquid flow.<sup>7</sup> In these experiments this issue was not observed.

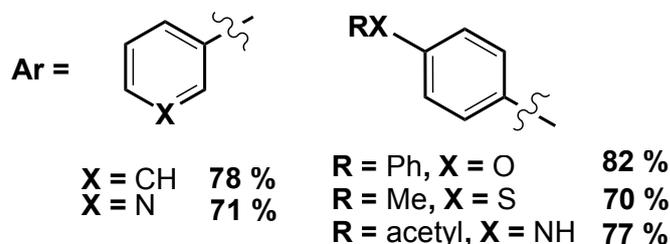
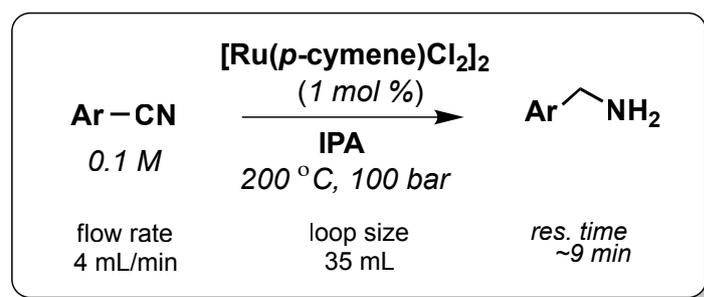
## Results and discussion

After the initial optimization, using benzonitrile as a substrate, Mateos, Ley et al. have performed successful TH on various aryl-nitrile derivatives with good yields. The amount of unreacted imine was increased by reducing the residence time, while at longer residence time the *N*-alkylated by-product was observed. Substrates bearing ether, thioether and amide functionalities were all successfully reduced with good yields. A pyridine derivative was also converted into the desired primary amine with good yield (Scheme 1). Substrates with more reactive carbonyl groups (aldehydes, ketones) led to a mixture of

products. To demonstrate the scale-up opportunity, the production of 4 g benzylamine was achieved in 2 hours of continuous operation.

## Conclusion

The teams at Eli Lilly and the University of Cambridge developed a rapid and continuous process for TH of aryl-nitriles to the corresponding primary amines in good



*Isolated yields as hydrochloride salts*

### Scheme 1. Selected examples for the TH of aromatic nitriles

yields. The system was successfully applied to reduce 17 different nitriles at a residence time of ca. 9 minutes. To further evaluate the robustness of the methodology, the system was capable of producing 4 g of benzylamine in 2 hours.

## Acknowledgement

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## REFERENCES

- 1) D. Wang, D. Astruc *Chem. Rev.* **2015**, *115*, 6621-6686; 2) L. Üрге, J. Alcazar, L. Huck, G. Dormán, *Ann. Rep. Med. Chem.*, **2017**, *50*, 87-147; 3) R. K. Jensen, N. Thykier, M. V. Enevoldsen, and A. T. Lindhardt *Org. Process Res. Dev.* **2017**, *21*, 370-376; 4) R. Labes, D. González-Calderón, C. Battilocchio, C. Mateos, G. R. Cumming, O. de Frutos, J. A. Rincón and S. V. Ley *Synlett* **2017**, *28*, 2855-2858; 5) S. Werkmester, C. Bornschein, K. Junge, M. Beller *Chem. Eur. J.* **2013**, *19*, 4437-4440; 6) <http://thalesnano.com/products/>; 7) R. Labes, C. Battilocchio, C. Mateos, G. Cumming, O. de Frutos, J. A. Rincon, K. Binder, S. V. Ley *Org. Process Res. Dev.* **2017**, *21*, 1419-1422.