The use of a continuous flow-reactor employing a mixed hydrogen–liquid flow stream for the efficient reduction of imines to amines

Steen Saaby,[a] Kristian Rahbek Knudsen,[a] Mark Ladlow[b] and Steven V. Ley*[a]

Received (in Cambridge, UK) 7th April 2005, Accepted 21st April 2005
First published as an Advance Article on the web 17th May 2005
DOI: 10.1039/b504854k

Imines have been reduced to amines in high yield, and with excellent chemoselectivity, by catalytic hydrogenation in a continuous flow-reactor, utilising an electrochemically-generated hydrogen source to produce a mixed hydrogen–liquid flow stream.

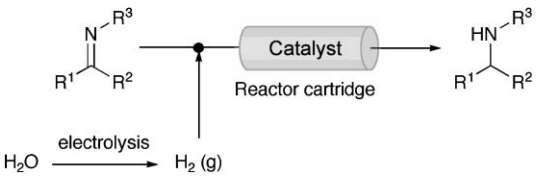
The ever-increasing number of potential therapeutic targets that are emerging from genomics and proteomics is driving the need to develop new synthetic technologies able to prepare small molecules as potential modulators.[1] In particular, flow processes, both on a microfluidic[2] and mesofluidic scale,[3] are receiving increased attention and offer a number of potential advantages over existing batch techniques. For example, reaction conditions (flow rate, stoichiometry, temperature and pressure) can be independently varied and precisely controlled. This leads to a high level of reproducibility, greatly facilitating the reaction optimisation process, whereby a range of different conditions can be rapidly investigated. In addition, the incorporation of real time, in-line monitoring, in combination with intelligent feedback loops, offers considerable scope for fully automated reaction optimisation. In a similar way, automated, rapid serial processing may be used to screen new transformations or generate compound libraries. The incorporation of in-line modules into flow devices presents opportunities to effect chromatographic separation, by-product scavenging, or the isolation of specific products by catch-and-release protocols. In addition, flow processes are readily scalable—either by running the flow-reactor for an extended time, or by employing multi-channel, parallel reactors. However, there is a considerable need to expand the repertoire of available reactions and processes available to these techniques, in particular to enable multi-step, flow-through compound synthesis.

Here we report on the application of a flow-through strategy to effect the catalytic hydrogenation of imines with high chemoselectivity (Scheme 1). Reductive amination is a key transformation in the synthesis of many drugs; however, problems often arise due to reversibility, compound/functional group incompatibility and over-reduction. In particular, the reduction of aryl imines often gives rise to secondary amines that are contaminated with the corresponding primary amine, derived from the desired product's over-reduction and debenzylation.

In connection with an ongoing synthesis program, we wished to establish a procedure for the continuous reduction of imine **1** into amine **2** that afforded a high purity product suitable for advancement to its next stage in the synthesis process. Initial attempts to perform this reduction as a flow process, using a reactor cartridge containing polymer-supported (PS) borohydrides (PS-BH_4 and PS-BH_3CN), proved unreliable and typically gave an impure product contaminated with both inorganic material and by-products derived from the hydrolysis of **1**.

We therefore decided to investigate a continuous, flow-through hydrogenation using a device that mixes hydrogen gas with a flowing sample stream in a T-piece mixer. This contained a titanium frit to ensure efficient gas dispersion (Fig. 1).[4] The hydrogen is generated internally on demand by the electrolysis of water and the gas–liquid mixture pumped through a suitable catalyst contained in an interchangeable metal cartridge.[5] An integral Peltier heater enables the cartridge to be heated up to 100 °C, and a responsive back-pressure regulator allows flow hydrogenation to be performed at pressures up to 100 bar (Fig. 2).[6]

An important prerequisite in flow chemistry is the choice of an effective solvent that avoids the precipitation of both starting materials and products, which may lead to a blockage of the flow stream. In this case, of the four solvents examined (DMF, THF, ethyl acetate, toluene), THF was found to be effective up to 0.5 M and gave the best results under representative reaction conditions (10% Pd–C, 20 bar, 25 °C, 0.05 M, flow rate 1.0 mL min^{-1}), affording **2** in quantitative yield and >95% purity according to ^1H NMR analysis.



Scheme 1 Continuous flow-through reduction of imines into amines.

Fig. 1 H-Cube® Flow Hydrogenator.

*svl1000@cam.ac.uk

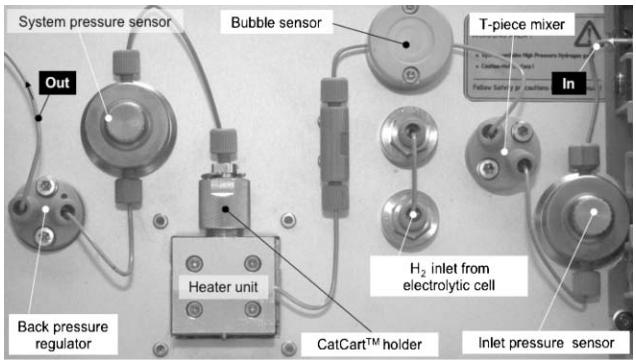


Fig. 2 H-Cube® Flow Hydrogenator front panel detail.

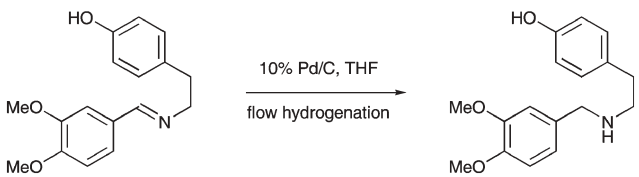
The optimisation of flow conditions for the conversion was systematically investigated by varying concentration, flow rate, pressure and temperature (Table 1). This process is greatly facilitated by continuous flow conditions and we were able to conduct a significant number of runs rapidly, in a sequential manner and without having to change or renew the catalyst cartridge (runs 1–11). Specifically, runs 1–4 show a clear correlation between the concentration of the injected sample and the conversion of **1** into **2**.

Increasing the flow rate (runs 5–8) results in a corresponding decrease in conversion, consistent with a reduction in residence time in the flow-reactor. Notably, optimal conditions at a flow rate of 1 mL min^{-1} were obtained with a substrate concentration of 0.05 M, whereas at 2 mL min^{-1}, a 0.025 M input afforded a quantitative conversion to **2**. Both of these conditions correspond to quantitative hydrogenation of **1** into **2** at a rate of 0.05 mmol min^{-1}, implying that the cartridge has a limiting ability to process material. This is further illustrated in runs 9–11, where a more concentrated solution of the imine **1** (0.5 M) was eluted at 1 mL min^{-1}, but at elevated temperature and/or pressure in an attempt to increase throughput further. In all of these cases, only a 33% conversion to the desired product **2** was obtained. Although this corresponds to a turnover of 0.16 mmol min^{-1}, the mixture of amine and imine starting material obtained was unsuitable for our purposes. Having established optimal conditions for the steady state production of pure **2**, we then demonstrated that the flow process can be readily scaled to provide a preparative quantity of material (run 12). A continuous flow hydrogenation was performed, eluting a 0.05 M THF solution of **1** at 25 °C and 20 bar at a flow rate of 1.0 mL min^{-1} for 70 min. This afforded 1.0 g of **2** in quantitative yield and excellent purity (>95%). Again, a single 10% Pd–C catalyst cartridge was used throughout.

In order to study the generality of flow-through hydrogenation for the selective reduction of imines, we prepared a variety of imines derived from aromatic and aliphatic aldehydes and ketones (Table 2).[7] The imines in entries 1–8 were introduced sequentially into the H-Cube® flow-reactor, followed by a short solvent wash step to purge the catalyst cartridge. The flow conditions employed were based upon the optimised conditions determined earlier (*i.e.* 20 bar, 25 °C, flow rate 1 mL min^{-1}). However, a lower concentration (0.025 M) was used in an attempt to compensate for the differing reactivities of the imine starting materials, thereby ensuring maximum conversion in all cases. Under these conditions, all of the desired amine products were obtained in good to excellent yields (>80%). Notably, other readily-reducible functionalities such as pyridines (entry 4) and nitriles (entry 5) were not affected, nor did the benzylic products of the reaction suffer further hydrogenolysis to any significant extent.

In this work we have described how imines can be selectively reduced to their corresponding amines in high yield and purity using in-line hydrogen gas generation as part of a continuous flow process. The amines obtained were of acceptable purity to advance to the next stage of a multi-step synthesis program.[8] Moreover, other applications can be envisaged using different gases or reactive species generated as part of the flow process, potentially in combination with reaction cartridges containing other catalysts or immobilised reagents. Efforts to implement multi-step syntheses by

Table 1 Flow hydrogenation optimisation results

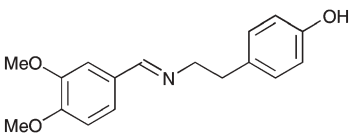
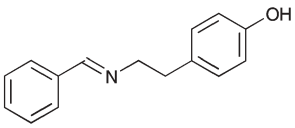
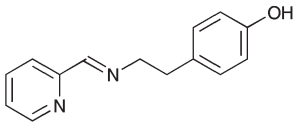
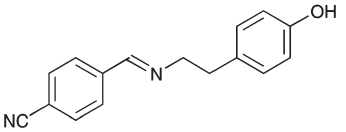
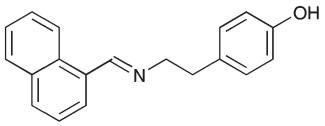
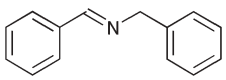
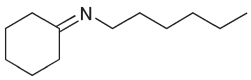
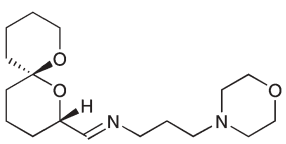


1 **2**

Run	Concentration/M	Flow rate/mL min^{-1}	Injection volume/mL	Pressure/bar	Temperature/°C	Conversion (%)[a]
1	0.5	1	5	20	25	17
2	0.1	1	5	20	25	85
3	0.05	1	5	20	25	100
4	0.025	1	5	20	25	100
5	0.5	2	5	20	25	4
6	0.1	2	5	20	25	70
7	0.05	2	5	20	25	85
8	0.025	2	5	20	25	100
9	0.5	1	5	20	60	33
10	0.5	1	5	40	25	33
11	0.5	1	5	40	60	33
12	0.05	1	70	20	25	95

[a] Estimated by ^{1}H NMR analysis.

Table 2 Study of flow hydrogenation scope

Entry	Imine	Yield (%)[a]	Purity (%)
1		quant.	>95
2		93	>95
3		quant.	95
4		quant.	84
5		96	85
6		92	>95
7		quant.	90
8		quant.	90

[a] quant. = quantitative.

linking flow reactors that perform specific synthetic transformations are currently under way in our laboratory.

We would also like to acknowledge the Carlsberg Foundation (to S. S. and K. R. K.) and the Novartis Research Fellowship (to S. V. L.) for their financial support. We also thank Dr. G. Zinzalla and L. Milroy for the preparation of imine **8**.

Steen Saaby,[a] Kristian Rahbek Knudsen,[a] Mark Ladlow[b] and Steven V. Ley*[a]
[a]*Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: svl1000@cam.ac.uk; Fax: 44 (0) 1223 336442; Tel: 44 (0) 1223 336398*
[b]*GlaxoSmithKline Cambridge Technology Centre, University of Cambridge, Cambridge, UK CB2 1EW*

Notes and references

1 S. V. Ley and I. R. Baxendale, *Nat. Rev. Drug Discovery*, 2002, **1**, 573.
2 (*a*) W. Ehrfeld, V. Hessel and H. Löwe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weinheim, 2000; (*b*) A. M. Hafez, A. E. Taggi, H. Wack, W. J. Drury, III and T. Lectka, *Org. Lett.*, 2000, **2**, 3963; (*c*) A. M. Hafez, A. E. Taggi, T. Dudding and T. Lectka, *J. Am. Chem. Soc.*, 2001, **123**, 10853; (*d*) N. G. Anderson, *Org. Process Res. Dev.*, 2001, **5**, 613; (*e*) M. Sands, S. J. Haswell, S. M. Kelly, V. Skelton, D. O. Morgan, P. Styring and B. Warrington, *Lab Chip*, 2001, **1**, 64; (*f*) S. J. Haswell, R. J. Middleton, B. O'Sullivan, V. Skelton, P. Watts and P. Styring, *Chem. Commun.*, 2001, **5**, 391; (*g*) P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong and X. Zhang, *Tetrahedron*, 2002, **58**, 4735; (*h*) A. M. Hafez, A. E. Taggi and T. Lectka, *Chem.–Eur. J.*, 2002, **8**, 4115; (*i*) G. Jas and A. Kirschning, *Chem.–Eur. J.*, 2003, **9**, 5708; (*j*) P. Watts and S. J. Haswell, *Curr. Opin. Chem. Biol.*, 2003, **7**, 380; (*k*) P. Watts and S. J. Haswell, *Drug Discovery Today*, 2003, **8**, 586; (*l*) A. Kirschning and G. Jas, *Top. Curr. Chem.*, 2004, 209; (*m*) D. Jönsson, B. H. Warrington and M. Ladlow, *J. Comb. Chem.*, 2004, **6**, 584; (*n*) H. R. Luckarift, L. J. Nadeau and J. C. Spain, *Chem. Commun.*, 2005, 383; (*o*) G. N. Doku, W. Verboom, D. N. Reinhoudt and A. van den Berg, *Tetrahedron*, 2005, **61**, 2733 and all the references cited therein (a)–(o).
3 (*a*) R. A. Kautz, W. K. Goetzinger and B. L. Karger, *J. Comb. Chem.*, 2005, **7**, 14; (*b*) D. M. Ratner, E. R. Murphy, M. Jhunjhunwala, D. A. Snyder, K. F. Jensen and P. H. Seeberger, *Chem. Commun.*, 2005, **5**, 578.
4 The Thales Nanotechnology H-Cube® flow hydrogenator is currently a prototype that is due to become available in the coming months. For further details, please refer to the product details on the company website: http://www.thalesnano.com. Address: Thales Nanotechnology, H-1031 Budapest, Záhony utca 7 (Graphisoft Park), Hungary. Fax: +36 16666 190. Tel: +36 1 6666 100.
5 Pre-packed cartridges (CatCart®) containing catalyst are available from Thales Nanotechnology. In this study 30 × 4 mm cartridges (CatCart®30) were used throughout.
6 For other applications of flow hydrogenation see: (*a*) A. J. Sandee, D. G. I. Petra, J. N. H. Reek, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Chem.–Eur. J.*, 2001, **7**, 1202; (*b*) N. Künzle, T. Mallat and A. Baiker, *Appl. Catal.*, 2003, **238**, 251; (*c*) J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori and S. Kobayashi, *Science*, 2004, **304**, 1305; (*d*) N. Yoswathananont, K. Nitta, Y. Nishiuchi and M. Sato, *Chem. Commun.*, 2005, **1**, 40.
7 All the imines used in this study were prepared by standard methods involving reaction of the appropriate carbonyl compound with amines in the presence of 3 Å molecular sieves.
8 S. V. Ley, M. H. Bolli, B. Hinzen, A.-G. Gervois and B. J. Hall, *J. Chem. Soc., Perkin Trans. 1*, 1998, 353.