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The expanding utility of continuous flow hydrogenation

Peter J. Cossar, Lacey Hizartzidis, Michela I. Simone, Adam McCluskey and Christopher P. Gordon

There has been an increasing body of evidence that flow hydrogenation enhances reduction outcomes across a wide range of synthetic transformations. Moreover flow reactors enhance laboratory safety with pyrophoric catalysts contained in sealed cartridges and hydrogen generated in situ from water. This mini-review focuses on recent applications of flow chemistry to mediate nitro, imine, nitrile, amide, azide, and azo reductions. Methodologies to effect de-aromatisation, hydrodehalogenation, in addition to olefin, alkyne, carbonyl, and benzyl reductions are also examined. Further, protocols to effect chemoselective reductions and enantioselective reductions are highlighted. Together these applications demonstrate the numerous advantages of performing hydrogenation under flow conditions which include enhanced reaction rates, yields, simplified workup, and the potential applicability to multistep and cascade synthetic protocols.

Introduction

The recent application of flow chemistry methodologies to perform hydrogenations has afforded significant improvements in performance, safety, and environmental impact. Flow approaches provide superior gas-liquid contact compared with traditional hydrogenation approaches which are limited by the rate of hydrogen gas diffusion into the bulk solvent. Flow hydrogenation improves gas-liquid contact via the use of in-line gas mixing or gas permeable membranes (Figure 1). This rapidly saturates the solvent with hydrogen resulting in an increased gas-liquid-catalyst interaction, improving the rate of reaction. An example of an in-line gas-liquid mixing reactor is the Thalesnano H-cube®, however the use of gas permeable membranes in tube-in-tube systems is an emerging and increasingly popular technology (Figure 1). Here, the inner tube, which contains the liquid stream, is typically made of a gas permeable polytetrafluoroethylene (PTFE) membrane and the gas stream is flowed through the outer tube under pressure. Examples of this gas permeable membrane system are the Ley group tube-in-tube reactor and the Vapourtec Gas/Liquid reactor.

The stringent control of reaction parameters such as temperature, pressure and catalyst exposure offered by these flow systems enables rapid optimisation and reproducibility of reaction conditions. Moreover the application of flow chemistry also minimises many of the hazards associated with batch hydrogenation procedures. For instance the H-cube® removes the requirement of potentially hazardous hydrogen balloons or cylinders by in situ production of hydrogen through the electrolysis of water. The use of electrolysis does not require large gas reservoirs as high purity hydrogen is generated in-situ. Moreover, the use of catalyst cartridges also removes hazards related to contact with toxic or pyrophoric catalysts.

Figure 1. A) Schematic of the mechanical mixing setup in the ThalesNano H-Cube®; B) Schematic of the gas permeable membrane (tube-in-tube) technology.

As illustrated in Table 1, a number of commercially available flow systems capable of effecting hydrogenation-based reactions have been developed. The first of these was the Thalesnano H-cube® and more recently Uniqis and Vapourtec have also released “click in reactors” capable of performing both homogeneous and heterogeneous hydrogenations.
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Catalysts

Typical hydrogenation protocols require the use of heterogeneous or homogeneous organometallic catalysts. These catalysts activate hydrogen in three different ways, namely via oxidative addition, hydrolysis or heterolytic cleavage. Heterogeneous catalysts are catalysts which occupy an alternative phase to the reactants and in general refer to solid catalyst or catalysts which are immobilised on a solid support. Homogenous organometallic catalysts, such as RhE, RuE and IrE complexes, occupy the same phase as the reagents and in general refer to solid catalyst or catalysts which are immobilised on a solid support. Homogenous organometallic catalysts, such as Rh-, Ru- and Ir- complexes, occupy the same phase as the reagent offering greater catalyst reactant contact but often prove difficult to partition from a reaction mixture and difficult to recycle.12,13

A range of transition metal catalyst show excellent catalytic activity in hydrogenations reactions, e.g. Pt, Pd, Ru, Re, Rh and Ir, all of which show excellent activity as activated charcoal, zeolite, alumina and silica supported reagents.2,12 These solid supports function to improve surface area and serve to aid catalyst recovery. Supports such as barium sulfate and calcium carbonate are also used to improve chemoselectivity in the hydrogenation of acetylenic compounds.2,14 In addition to platinum group metals, Raney nickel, Raney cobalt, and Raney copper are also extensively used as unsupported catalysts for hydrogenation reactions.15

The scope of flow hydrogenation has been expanded to include use of immobilised asymmetric catalysts for enantioselective hydrogenations.16,17 These catalysts, typically tethered to inorganic oxides (such as silica and aluminium oxide), polymers, zeolites or mesoporous solids, offer advantages over their homogenous counterparts with efficient separation, reduced catalyst leaching and improved catalyst recycling.12,18. The solid support high surface area enable the bound metal complexes to effectively protrude from the surface, with minimal compromise to catalyst efficiency. These catalysts can be bound via covalent bonding, self-supporting methods, adsorption and electrostatic interactions approaches.18,19

Catalyst cartridges

Flow hydrogenation reactions typically employ cartridge packed catalysts, e.g. the ThalesNano Catcarts®. Catalyst cartridges offer benefits including reduced catalyst leaching, safer catalyst handling, a simple means of portioning the catalyst from the reaction mixture, and a straightforward process for catalyst re-use.2,3,20,21 The encapsulation of catalysts reduces potential contact with pyrophoric or toxic catalysts which is particularly advantageous for Raney nickel and palladium.3 In addition a number of groups have also demonstrated the ability to easily screen a wide selection of Catcarts to rapidly establish optimum reaction conditions.22–26 Further, while the initial costs of catalyst cartridges is perceived by some as high, the economic, environmental and safety advantages quickly outweigh the initial cost. Access to a wide range of Catcarts combined with flow chemistry approaches accelerates catalyst screening towards favourable reaction outcomes in a fraction of the time (and reagent use) associated with the corresponding batch hydrogenation screening approaches.2 The coupling of GC / LC (and mass spectroscopic) analysis with flow chemistry in general enables reaction optimisation of significantly smaller scales, as low as µg quantities. This aligns with the basic tenants of green chemistry of reducing reagent usage and chemical waste.25,27 Finally, with optimised reaction conditions facilitating near quantitative output of product, in combination with the partitioning of catalyst from reaction mixtures, the costs associated with lengthy purification procedures is significantly reduced.24,28

Hydrogenations reactions

Nitro reductions

Given the importance of nitro reductions in a vast number of drug discovery programs, it is unsurprising that there have been a number of reported flow chemistry protocols to effect aromatic nitro reductions using palladium, platinum or Raney nickel (Table 2).6,29–34 Whilst these methods are high yielding and robust (Table 2), the pressures and temperatures of reactions may vary greatly depending on the chemical scaffold.6,30,31,35 However, as previously reviewed by Irfan et al.,2 a variety of transition metal catalysts and flow reactors, along with relatively mild reaction conditions cleanly effect nitro reductions.

Table 1. Commercially available flow hydrogenation systems and their specifications.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Hydrogen source</th>
<th>Catalyst type</th>
<th>Pressure (bar)</th>
<th>Temperature range (°C)</th>
<th>Flow rate (mL.min⁻¹)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniqs flowsyn</td>
<td>H₂ Cylinder</td>
<td>Homogeneous or Heterogeneous</td>
<td>Max. 27</td>
<td>RT</td>
<td>0.1–10</td>
<td>9</td>
</tr>
<tr>
<td>Vapourtec™ (tube-in-tube reactor)</td>
<td>H₂ Cylinder</td>
<td>Homogeneous or Heterogeneous</td>
<td>20</td>
<td>RT–150</td>
<td>0.01–9.99</td>
<td>10</td>
</tr>
<tr>
<td>Gas/Liquid reactor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ThalesNano</td>
<td>Electrolysis</td>
<td>Heterogeneous</td>
<td>1–100</td>
<td>10–150</td>
<td>0.5–25</td>
<td>11</td>
</tr>
</tbody>
</table>

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Reports of aliphatic nitro group reduction are less common, presumably due to their lower reactivity in reduction reactions. The reduction of aliphatic nitro groups generally requires more forcing reducing conditions. For example the reduction of 1 required high pressures and temperatures to reduce both benzyl and nitro moieties affording the intermediate aminoamide, which was subsequently cyclised liberating 1-phenylethanol-1-amine to afford lactam 2 in an excellent yield over two steps.\textsuperscript{33} Raney nickel catalysis effects the aliphatic nitro reduction of 3 at relatively mild conditions affording amine 4 in near quantitative yields (Scheme 1).\textsuperscript{37}

Given the high yields of the aforementioned protocols they are ideally suited for incorporation into sequential cascade reaction sequences. As an example, utilising the H-cube, the reduction of 5 and subsequent cyclisation using flow hydrogenation was reported to afford indole 6 in near quantitative yield (Scheme 2).\textsuperscript{29} By contrast batch approaches to perform this transformation employing zinc and 5%Pd/C afforded the hydroxyindole as an undesired by-product. Similarly batch hydrogenation approaches to access imidazole 8 are highly dependent on reaction conditions, with temperatures below 10 °C or above 60 °C resulting in formation of various side products including N-oxide 9 under hydrogen starvation (<1.5 bar) conditions. By contrast an optimised flow protocol afforded 8 in a 95% yield (scheme 2B).\textsuperscript{7}

### Table 2. Commonly used heterogeneous catalysis used for the flow reduction of nitro moieties.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% Pd/C</td>
<td>30–100 bar, 25–90 °C, 1 mL min$^{-1}$</td>
<td>92–97%</td>
<td>6,30,31,35</td>
</tr>
<tr>
<td>Pd(OH)$_2$</td>
<td>60 bar, 25 °C, 1 mL min$^{-1}$</td>
<td>99%</td>
<td>34</td>
</tr>
<tr>
<td>10%</td>
<td>1 bar, 25 °C, 2 mL min$^{-1}$</td>
<td>99%</td>
<td>23</td>
</tr>
<tr>
<td>Pd/Al$_2$O$_3$</td>
<td>1 bar, 30 °C, 1 mL min$^{-1}$</td>
<td>99%</td>
<td>33</td>
</tr>
<tr>
<td>Raney nickel</td>
<td>1–100 bar, 55–100 °C, 0.5–1 mL min$^{-1}$</td>
<td>99%</td>
<td>6,7,23,32,36</td>
</tr>
</tbody>
</table>

### Direct Reductive Amination

Reductive amination is readily accomplished by flow using 10% Pd/C or 20% Pd(OH)$_2$/C with required reaction temperatures and pressures being substrate dependent.\textsuperscript{26,38–41} Flow reductive amination of N-alkylated iminosugar 12 using an H-cube\textsuperscript{*} overcame the limitations of batch approaches (Scheme 3). Specifically, the use of transfer hydrogenation for the upscale of 12 was limited by the water solubility of the product. Additionally, scale-up of batch catalytic hydrogenation was further limited by the size of pressure vessels. The use of flow hydrogenation circumvented these problems enabling optimum reaction conditions to be rapidly established. Utilisation of 20% Pd(OH)$_2$/C and a solvent mixture of 2:2:1 MeOH/THF/H$_2$O afforded the desired N-alkylated iminosugar 12 in an impressive 130 g yield.\textsuperscript{40} In another example the use of 20% Pd(OH)$_2$/C in conjunction with 13 and piperazine (4 equivalents) allowed essentially exclusive access to the mono-piperazinyl-adduct 15 in a 93% yield eliminating the issues observed with the batch protocol such as di-addition (14, Scheme 3) and aldehyde reduction (16, Scheme 3).\textsuperscript{33} This protocol demonstrates the improved atom economy and environmental impact achievable using flow hydrogenation, as the need for protecting group strategies and lengthy purification procedures is eliminated.
Nitrile reductions

An initial reported protocol to effect aromatic nitrile reduction to the corresponding benzylamine used 10% Pd/C and elevated reaction conditions of 100 bar and 100 °C. However the use of Raney nickel and milder reactions conditions provided clean access to a variety of benzylamines from aromatic nitriles. However, in some instances, particularly in the case of aliphatic nitriles, a single pass through the catalyst bed fails to elicit full conversion requiring substrate recirculation, as was the case with the Raney nickel mediated synthesis of 18 from 17 at 60 bar and 60 °C. Similarly, the reduction of olefin and nitrile moieties of 19 required the use of Raney Ni catalyst, 70 bar and 70 °C (Scheme 4). Notably ammonia was used to improve reaction rates, eliminating the need for lengthy residence times (t_r).

The relatively mild reducing conditions of azide moieties have been exploited for the chemoselective reduction of 27, eliminating over reduction of the ketone moiety (Scheme 7). By conducting a screen of reaction condition on a 2 mL (0.08 mmol) scale, utilising the H-cube and GC analysis, optimum reaction conditions were established with minimal consumption of reagents, solvents or catalyst. Ideal reaction conditions proved to be 10% Pt/C, THF, 30 °C, 1 mL.min⁻¹, providing minimal over reduction of the ketone moiety. Once established, these conditions were translated to preparative scale, with only minor changes to solvent and temperature. This optimisation screen demonstrates how the use of flow chemistry coupled with GC or LC analysis can be a powerful tool for rapidly establishing reaction conditions, with minimal environmental impact and high atom economy.
Traditionally the most robust and expedient method for the reduction of aliphatic azo moieties was the employment of a bacterial reductase. However recently a flow protocol utilising the H-cube® has been developed in which the hydrogenation of \(30\) with 10% Pd/C at 60 bar and 60 °C afforded bis-ammonium cation \(31\) (Scheme 8).\(^5\) Whilst only isolated in poor yield (36%), this approach highlights the potential applicability of flow hydrogenation in the typically problematic reduction of azo moieties.

Hydrogenolysis of alcohols and amines

Flow hydrogenation offers an efficient means of deprotection for both benzyl (Bn) and carbobenzyloxy (Cbz) moieties.\(^5\) Generally conditions for Bn group removal entail use of 10% Pd/C catalyst at > 40 bar and > 40 °C,\(^5\) with Cbz groups are amenable to removal at lower temperatures and pressures.\(^5\) These approaches have been used in the synthesis of compounds such as the lactone \(33\) which entailed concurrent de-benzylisation and aldehyde reduction \(32\) to afford \(33\) in a 90% yield based on recovered starting material (Scheme 9).\(^5\) A similar methodology gave pyrrolidine \(35\) via Bn-group hydrolysis and hydrogenation of the pyrrole moiety (Scheme 9).\(^5\)

Olefin Hydrogenations

The significant portion of currently reported olefin reduction flow protocols employ 10% Pd/C, with sterically hindered or highly substituted bonds requiring elevated temperature or pressures (Scheme 11).\(^4,44,61,63–66\) As previously mentioned flow reduction of olefins has been reviewed by Irfan \(et\) al\(^2\) and consequently discussion herein is limited to hydrogenation of olefin moieties using organometallic flow protocols, chemoselective and asymmetric olefin hydrogenations.
Ley et al. have pioneered the use of tube-in-tube reactors and/or the Vapourtec gas-liquid reactor combined with homogeneous catalysis for the reduction of olefin moieties \(^{3,5,67,68}\). Use of the Crabtree’s catalyst \(^{49}\) allowed quantitative hydrogenation of ethyl cinnamate \(^{48}\) at 17.2 bar (Scheme 12). \(^{4}\) The Vapourtec gas-liquid reactor has also been applied to the hydrogenation of a series of alkenes, e.g. 51 was quantitatively hydrogenated using Wilkinson’s catalysts \(^{52}\), 17.2 bar and 125 °C (Scheme 12). \(^{68}\)

**Chemoselective Olefin and alkyne hydrogenation**

The precise control of reaction parameters provided by flow reactors allows robust chemoselective olefin reduction protocols, previously not accessible under batch conditions, to be rapidly established. Approaches have been reported describing selective reduction of an olefin moiety in the presence of nitrile and indole moieties, for example in analogues such as 54, 10% Pd/C at 50 bar and 50 °C afforded a number of desired analogues, such as 55, in near quantitative yield (Scheme 13). \(^{63}\)

Precise control of temperature has been shown to significantly affect hydrogenation chemoselectivity, e.g. hydrogenation of 56 at 70 °C resulted in reduction of olefin and ketone moieties affording 57, and reduction at room temperature gave 58 in an excellent yield (Scheme 14). \(^{59}\)

Catalyst switching also effects chemoselectivity with hydrogenation of 19 using 10% Pd/C resulting in specific olefin reduction to afford 59. By contrast in the same system and a Raney Ni catalyst resulted in olefin and nitrile hydrogenation to 20 in a quantitative yield (Scheme 15). \(^{14}\)

Hydrogenation pressure can also impact on reaction outcomes, at low pressure hydrogenation of 60 results in selective reduction of the labile olefin moiety giving 61. Higher pressure results in the reduction of the olefin and the dihydro moieties to afford 62 (Scheme 16). \(^{64}\)

Selective control over olefin, furan and nitrile moiety hydrogenation has also been reported (Scheme 17). Reduction of 63 (10% Pd/C, 50 °C and 50 bar) specifically reduces furan and olefin moieties affording 64. Decreasing pressure, temperature and residence time enabled selective hydrogenation of the olefin to afford 65. Nitrile and olefin reduction required Raney nickel at
50 °C and 10 bar which furnished 66, whereas increasing pressure and temperature resulted in global hydrogenation to 67. Significantly, the optimisation reactions performed to establish these chemoselective conditions consumed just 200 mg of regent which further demonstrates the improved environmental impact of flow hydrogenation.24

Catalyst selection imparts variations in the chemoselectivity of alkyne reductions with Lindlar or Pd impregnated γ-Al₂O₃ catalysts facilitating partial hydrogenation of alkyne bonds. The Lindlar catalyst hydrogenation of 68 afforded olefin 69 in a 90% yield. Similarly, the synthesis of 71 employed a Pd impregnated γ-Al₂O₃ catalyst (Scheme 18).48,70 Complete alkyne hydrogenation was accomplished through the use of a more active catalyst such as 20% Pd(OH)₂/C affording 73 in a near quantitative yield (Scheme 18).71

Carbonyl reductions

The reduction of less reactive ketones in the presence of aldehyde moieties is a challenging transformation, typically requiring protecting group strategies. The reduction of 80 was accomplished by utilising a continuous flow protocol employing both protecting group installation and hydrogenation. Initially a solution of 80 in methanol was flowed through an omnifit column packed with Ti⁴⁺ montmorillonite (TiEmont) at 30 °C, followed by hydrogenation through a hydroxyapatite supported Ru nanoparticles (Ru₅₃/NanoHAP) column (Scheme 21). The hydrogenated product was deprotected using TiEmont at 80 °C and water to give alcohol 83 in a near quantitative yield.73

Restricting Hydrodehalogenation

Hydrodehalogenation has been reported with the use of Pd-, Ni- and Rh-based catalyst29,33,39,72 and whilst this provides expedient access to dehalogenated derivatives it is also particularly problematic if the halogen atom is required for subsequent synthetic manipulations. Kappe et al. have developed approaches for halogen retention in the synthesis of Boscalid® (Scheme 19). Use of 10 % Pd/C and Raney nickel catalysts resulted in nitro group reduction and hydrodechlorination. However, catalysts switching to 10% Pt/C with concurrent increase in flow rate to 3 mL min⁻¹ resulted in specific nitro moiety reduction and halogen retention affording 75 in a 93%.33

Scheme 19. Reagents and conditions (i) H-cube Pro®, MeOH, 10% Pd/C, 50 °C, 50 bar, 1 mL.min⁻¹ (t_r: 0.38 min); (ii) H-cube®, MeOH, 10% Pd/C, 25 °C, 0 bar, 10% H₂, 3 mL.min⁻¹ (t_r: 0.13 min); (iii) H-cube®, MeOH, Raney Ni, 60 °C, 60 bar, 1 mL.min⁻¹ (t_r: 0.38 min); (iv) H-cube®, MeOH, Raney Ni, 50 °C, 10 bar, 1 mL.min⁻¹ (t_r: 0.38 min).

Scheme 20. Reagents and conditions; (i) H-cube®, 0.05 M, 10% Pd/C, 40 °C, 50 bar H₂, MeOH, 1 mL.min⁻¹ (t_r: 0.38 min).

Scheme 21. Reagents and conditions; (i) H-Cube®, 0.1 M, 10% Pt/C, 40 °C, 50 bar H₂, MeOH, 1 mL.min⁻¹ (t_r: 0.38 min).

Scheme 22. Reagents and conditions: H-cube Pro®, 0.05 M, 5% Pt/C (sulfided), MeOH 30°C, 30 bar, 3 mL.min⁻¹ (t_r: 0.13 min).
Scheme 23. Reagents and conditions: (i) 0.2 M, Ti-mont (0.05 g), MeOH, Argon (1 bar), 30 °C, 0.2 mL.min⁻¹ (t: 5 min); H₂ (1 bar), Ru nano HAP (0.05 g), MeOH, 40 °C, 2 mL.min⁻¹ (t: 0.5 min); (iii) H₂O (4 mL), Ti-mont, Argon, 1 bar, 80 °C, 0.4 mL.min⁻¹ (t: 2.5 min).

Asymmetric hydrogenations

Transition metal catalysts alone allow rapid access to achiral products, however recently with the advancements in chiral catalysts the scope of flow hydrogenations has explained to include enantioselective hydrogenations. Both homogeneous and solid supported asymmetric catalysts have been reported for asymmetric flow hydrogenations. Asymmetric homogeneous catalysts offer the advantage of rapid catalyst screening to determine the optimum catalyst for high yield and high diastereomeric excess. As an example a series of eleven asymmetric catalysts were screened for the asymmetric hydrogenation of methyl acrylate. Catalyst (R,R)-85 was found to be optimal, affording (S)-86 in a 75% yield (77% de) (Scheme 24).

Scheme 24. Reagents and conditions: (i) Vapourtec R series, tube-in-tube reactor, 2.5 M, TEA (1 eq), 92 (1 mol %), 20 bar, 50 °C, 0.5 mL.min⁻¹.

Enantioselective Carbonyl reductions

Catalytic flow hydrogenation has been used to effect enantioselective reduction of carbonyl groups using Pt/Al₂O₃ and modifiers. Most reports have focused on activated ketones, such as methyl benzoylformate, pyruvic aldehyde dimethyl acetal and 2,2-diethoxyacetophenone. The yield and enantioselectivity of the reduction of 93 was dependent on the additive (Scheme 26). Additives cinchonidine and quinine afforded (R)E-94 (95%, (89% ee) or 94%, (54% ee), respectively). Whilst, cinchonine and quinidine furnished (S)E-94 (83% (63% ee) or 73% (23% ee), respectively).

Scheme 26. Reagents and conditions: (i) H-cube®, 11 mM of 93, Pt/Al₂O₃, 0.44 mM cinchonidine (or quinine), (9:1) toluene/ AcOH, 40 bar, rt, 1 mL.min⁻¹ (t: 0.4 min); (ii) H-cube®, 11 mM of 93, Pt/Al₂O₃, 0.44 mM cinchonine (or quinidine), (9:1) toluene/ AcOH, 40 bar, rt, 1 mL.min⁻¹ (t: 0.4 min).

Multi-step flow synthesis

As outlined throughout this perspective, at present the majority of recent literature on flow hydrogenation, and for that matter flow chemistry in general, has focused on a number of single-step organic transformations. In contrast, works published on complex multi-step total synthetic protocols, are few, primarily on account of the greater challenges they present. Nevertheless multi-step flow protocols are emerging. As an example Biaryl 98, a central building block in synthesis of HIV protease inhibitor atazanavir, has been accessed through a multi-step flow protocol comprising of a Suzuki-Miyaura cross coupling,
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Hydrazone formation and subsequent imine reduction in a 74% overall (Scheme 27). The batch Suzuki-Miyaura protocol gave excellent yields, but poor atom economy requiring a large excess of boronic acid 96 for the reaction to reach completion. However, reaction optimisation studies revealed 1.6 M K$_3$PO$_4$ and 1.2 eq. of boronic acid 96 was optimal with a 20 min residence time at 150 °C promoting a 95% conversion. Initial attempts to form hydrazone 97 using an acid catalyst were plagued with precipitation issues. Though a catalyst screen trimethylsilyl triflate (TMSOTf) was identified to promote the formation of the hydrazone 97 in a near quantitative yield, without the formation of precipitates. On translation of the optimised reaction conditions to the multi-step flow protocol a significant drop in reaction yields was observed, a consequence of the acidic hydrazone 97 requiring neutralisation preceding HEcube mediated imine reduction (10% Pd/C, 1 bar H$_2$, 40 ºC and 1 mL.min$^{-1}$). This neutralisation was achieved via a FLLEX liquid-liquid extraction step conducted in line with 0.5 M aqueous K$_2$CO$_3$.

While the ‘uncoupled’ flow process using two distinct steps proceeded with excellent yield, the multi-step flow afforded reduced yields as a consequence of X-cube Pd-catalyst leaching to the hydrogenation system. However this was circumvented with the use of an inline Quadrapure™ TU (QP-TU) resin cartridge which the prevented Pd-leachate from entering the hydrogenation flow reactor system, and 101 was isolated in a 77% yield.

This combination of aryl coupling and nitro reduction was applied to the synthesis of pyrazole 104 from 102 and 103 (Scheme 29). In this case the addition of 0.1 M AcOH and 1.05 eq. triethylamine resulted in improved yields, affording 104 in 91%, but as Raney Ni was incompatible with required solvent system, 10% Pd/Al$_2$O$_3$ was used as the reduction catalyst affording 104 in an 86% yield. A similar flow Suzuki-Miyaura cross coupling and nitro reduction was applied to the multi-step flow synthesis of biaryl 101, an important intermediate in the synthesis of the fungicide, Boscalid® (Scheme 28). The optimised flow protocol which used the ThalesNano X-cube to effect the Suzuki-Miyaura saw the use of Pd(PPh$_3$)$_4$, K'OBU at 160 ºC for 15 min. Chemoselective reduction and retention of the chlorine moiety was accomplished through the use of 10% Pt/C, (4:1) t-BuOH/H$_2$O, 1 bar, 30 ºC affording 101 in quantitative yield.

Total flow synthesis protocols to access natural products are also emerging. As an example (±)-oxomaritidine 113 was the first multi-step construction of a natural product, in which no intermediates were isolated. HEcube reduction of imine 109 was, one of many, key steps in this synthesis (Scheme 30).
The azide 106 was prepared from phenol 105 using a solid supported azide exchange resin at 70 °C and 50 μL·min⁻¹. A parallel reagent stream of aldehyde 108 was generated by perruthenate oxidation of 107.8 Subsequently a solution of azide 106 was reacted with an immobilised aza-Wittig intermediate at room temperature. Once bound to the column, the aldehyde 108 was then passed through the column at 55 °C, which afforded imine 109.8 Imine 109 was quantitatively reduced using 10% Pd/C, 20 bar, 25 °C, and 1 mL·min⁻¹ (t: 0.4 min); and a final amide cleavage afforded (±)-oxomaritidin 113. The seven-step flow total synthesis of (±)-oxomaritidin 113 gave a total yield of approximately 40%. Upon analysis of individual flow steps oxidation of 111 proved to be the limiting step, with the remaining steps affording qualitative or near qualitative yields.8

Ketone 117, which is a key intermediate in the synthesis of (-)-perhydrohistrionotoxin, represents another example of multi-step flow synthesis incorporating flow hydrogenation transformation (Scheme 31). The initial attempts to access 117 were hampered by the production of a lithium hydroxide precipitate. However, reaction optimisation, in particular altering the solvent and modification of the lithium base from n-BuLi to LDA in t-butyl methyl ether (TBME), resolved precipitation issues. In addition the use QuadraPure-IDADicarboxylic acid resin was successfully employed to quench unreacted lithium alkoxide. The resulting reaction mixture was the subjected to H-cube reduction (20% Pd(OH)₂) at 1 bar, and 40 °C. Notably diisopropylamine was added to prevent decomposition or over-reduction of the alkyne moiety in 114. Post hydrogenation, the crude reaction mixture was purified, affording 69 in a 49% isolated yield. Mesylation of 69 gave 117 in total yield of 49%.

**Scheme 30.** Reagents and Conditions: (i) Syrris AFRICA®, 20 eq. azide on Amberlite® IRA-400, (1:1) ACN/THF, 70 °C, 50 μL·min⁻¹; (ii) Syris, AFRICA®, 10 eq. tetra-N-alkylammonium per ruthenate (PSP), THF, rt, 50 μL·min⁻¹; (iii) Syris, AFRICA®, 20 eq. Di(N-butyl)phenylphosphine polystyrene Novabiochem® (α), rt (b) 55°C, flow rate not specified; (iv) H-cube®, 0.05 M, 10% Pd/C, 20 bar, 25 °C, 1 mL·min⁻¹ (t: 0.4 min); (v) Syris, AFRICA® microfluidic reactor chip, 5 eq. µL·min⁻¹ (t = 3.5 min); (vi) Syrris, AFRICA®, polymer-supported (ditrifluoroacetoxyiodo)benzene (PS-PIFA), DCM; (vii) Syrris, AFRICA®, Ambersep 900-OH ion-exchange resin, 35 °C, 40% yield. A parallel reagent stream of aldehyde 108 was prepared with 20% Pd(OH)₂, 1 bar, 450 μL·min⁻¹ (t: 1.8 min).

**Scheme 31.** Reagents and Conditions: (i) Vapourtec R2+, PTFE 5 mL flow coil, 0.4 M of 116 in t-butyl methyl ether (TBME), 0 °C, 200 μL·min⁻¹ (t: 25 min); (ii) Vapourtec R2+ PTFE 5 mL flow coil, 0.1 M of 117, TBME, 0 °C, 400 μL·min⁻¹ (t: 12.5 min); (iii) QuadraPure-IDA dicarboxylic acid resin; (iv) H-cube®, Pr₂Ne (0.9 mL), 20% Pd(OH)₂,TBME, 1 bar, 40 °C, 1 mL·min⁻¹ (t: 0.4 min); (v) Ismatec piston pump and glass microchip, 0.6 M of MsCl, 0.2 M of Pr₂Ne, DCM, rt, 450 μL·min⁻¹ (t: 1.8 min).

**Conclusion**

Despite remaining a relatively novel approach in the majority of research laboratories, substantial evidence is emerging that flow methodologies provide numerous advantages over traditional batch approaches including enhanced yields, simplified workup, in-line analysis, and the potential to develop multistep and cascade synthetic protocols. Flow hydrogenation protocols offer the ability to precisely control reaction conditions; such as pressure, temperature, and catalyst exposure. When coupled with self-contained heterogeneous catalyst and/or inline separation, combined with rapid reaction optimisation, the need for manual separation is significantly reduced. Further the stringent control of reaction conditions offered by flow hydrogenation also enables access to chemoselective or asymmetric products in high yields. This has led to the incorporation of flow hydrogenation into multi-step flow synthesis. Multi-step flow synthesis have many benefits over traditional syntheses; such as reduced need for purification, improved total yields, improved scale up and reduced synthesis times. Consequently the current expanding utility of flow based reductions indicates that these approaches are moving beyond a niche technology.
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Notes and References
