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The expanding utility of continuous flow hydrogenation

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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.[1] 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.[2] An example of an in-line gas-liquid mixing reactor is the Thalesnano H-cube®,[3] 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.[4,5]

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.[2,3] Moreover the application of flow chemistry also minimises many of the hazards associated with batch hydrogenation procedures.[6] 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.[3,6] The use of electrolysis does not require large gas reservoirs as high purity hydrogen is generated *in-situ*.[6] Moreover, the use of catalyst cartridges also removes hazards related to contact with toxic or pyrophoric catalysts.[3,6–8]

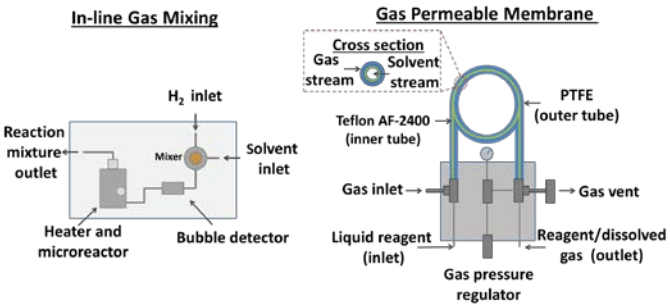


Figure 1. A) Schematic of the mechanical mixing setup in the ThalesNano H-Cube®; B) Schematic of the gas permeable membrane (tube-in-tube) technology.

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[3] H-cube® and more recently Uniqis and Vapourtec have also released "click in reactors" capable of performing both homogeneous and heterogeneous hydrogenations.[9,10]

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

Instrument	Hydrogen source	Catalyst type	Pressure (bar)	Temperature range (°C)	Flow rate ($mL.min^{-1}$)	Ref
Uniqis flowsyn (tube-in-tube reactor)	H_2 Cylinder	Homogeneous or Heterogeneous	Max. 27	RT	0.1–10	9
Vapourtec™ Gas/Liquid reactor	H_2 Cylinder	Homogeneous or Heterogeneous	20	RT–150	0.01–9.99	10
ThalesNano H-cube® / Pro™ / Midi	Electrolysis	Heterogeneous	1–100	10-150	0.5–25	11

Catalysts

Typical hydrogenation protocols require the use of heterogeneous or homogenous organometallic catalysts. These catalysts activate hydrogen in three different ways, namely *via* oxidative addition, hydrogenolysis 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 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.[3] 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

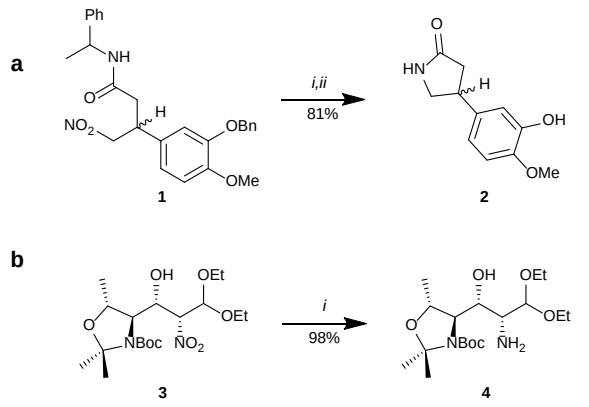
Nitro reductions

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 2. Commonly used heterogeneous catalysts used for the flow reduction of nitro moieties.

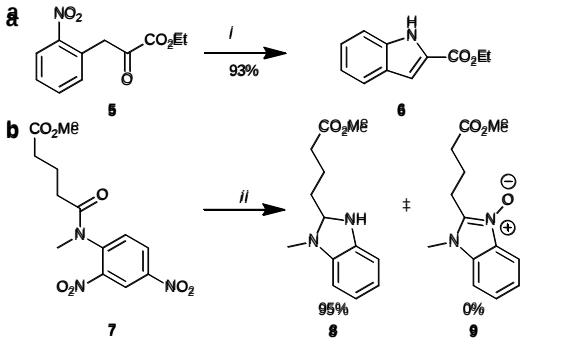
Catalyst	Conditions	Yield (%)	Ref
10% Pd/C	30–100 bar, 25–90 °C, 1 mL.min^{-1}	92–97%,	6,30,31,35
$Pd(OH)_2$	60 bar, 25 °C	99%	34
10% Pd/Al_2O_3	1 bar, 25 °C, 2 mL.min^{-1}	99%	23
10% Pt/C	1 bar, 30 °C, 1 mL.min^{-1}	99%	33
Raney nickel	1–100 bar, 55–100 °C, 0.5–1 mL.min^{-1}	99%	6,7,23,32,36

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-phenylethan-1-amine to afford lactam **2** in an excellent yield over two steps.[35] Raney nickel catalysis effects the aliphatic nitro reduction of **3** at relatively mild conditions affording amine **4** in near quantitative yields (Scheme 1).[37]



Scheme 1. Reagents and conditions: A. (i) H-cube®, 0.05 M, 10% Pd/C, (1:1) EtOH/EtOAc, 90 bar, 90 °C, 1 mL.min^{-1} (residence time (t_r): 0.38 min) ; (ii) p-xylene, 160 °C (sealed vessel), 36 h; B. (iii) H-cube®, 0.01 M, Raney Ni, MeOH, 1 bar RT, 0.7 mL.min^{-1} (t_r: 0.54 min).

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).[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).[7]

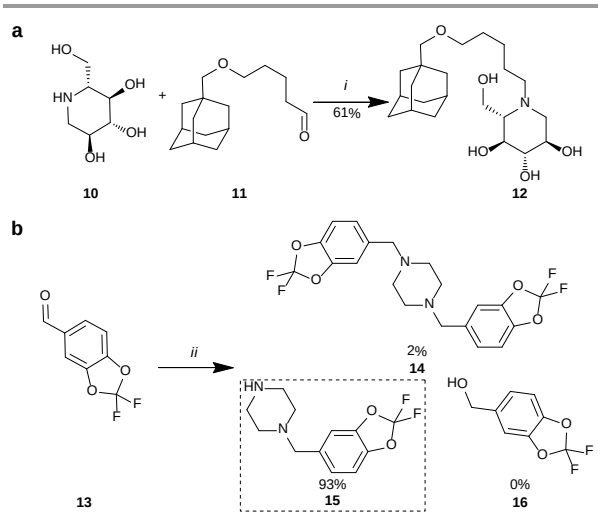


Scheme 2. Reagents and conditions: A. (i) H-cube®, 0.05 M, 10% Pd/C, (1:1) EtOH/EtOAc, 100 bar, 50 °C, 1 mL.min^{-1} (t_r: 0.88 min); B. (ii) H-cube Midi™, 0.05 M, 10% Raney Ni, MeOH, 1 bar, 70 °C, 5 mL.min^{-1} (t_r: 1.54 min).

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.[26,38–41]

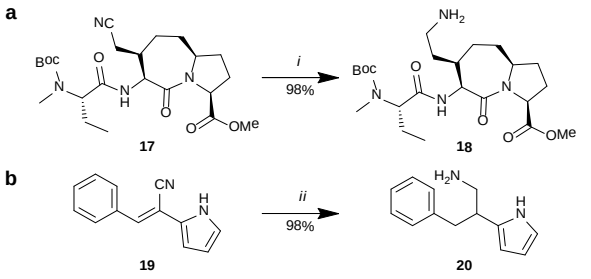
Flow reductive amination of *N*-alkylated iminosugar **12** using an H-cube overcame the limitations of batch approaches (Scheme 3). Specifically, the use of transfer hydrogenation for the upscale of **12** was limited by the water solubility of the product. Additionally, scale-up of batch catalytic 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_2O afforded the desired *N*-alkylated iminosugar **12** in an impressive 130 g yield.[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).[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.



Scheme 3. Reagents and conditions: A. (i) H-cube midi™, 0.5 M, 20% $Pd(OH)_2/C$, 2:2:1 THF/MeOH/H_2O, 100 bar, 150°C, 15 mL.min^{-1} (t_r: 0.51 min); B. (ii) H-cube midi™, 4 eq. piperazine, 0.5 M, 20% $Pd(OH)_2/C$, MeOH, 1 bar, 70°C, 6 mL.min^{-1} (t_r: 1.29 min).

Nitrile reductions

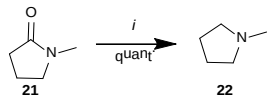
An initial reported protocol to effect aromatic nitrile reduction to the corresponding benzylamine used 10% Pd/C and elevated reaction conditions of 100 bar and 100 °C.[42] However the use of Raney nickel and milder reactions conditions provided clean access to a variety of benzylamines from aromatic nitriles.[35,43,44] 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.[43] 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).[44]



Scheme 4. Reagents and conditions: A. (i) H-cube®, 0.08 M, Raney Ni, EtOH, 60 bar, 60 °C, 0.5 mL.min^{-1} (t_r: 34 min); B. (ii) H-cube® 0.05M of **18** (1M NH_3 in MeOH), Raney Ni, 70 °C, 70 bar, 0.5 mL.min^{-1} (t_r: 0.75 min).

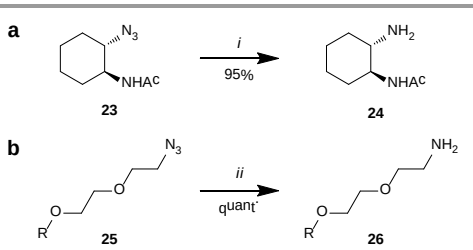
Amide, Azide and Azo reductions

The reduction of amide, azide, azo groups facilitates rapid access to primary amines, however at present there is a paucity of reported protocols to effect these transformations. In relation to amide reduction, flow chemistry offers an approach to avoiding the traditionally hazardous and poor atom economy associated with transfer hydrogenation.[45] As an example hydrogenation of **21** with 4%Pt–4%Re/TiO_2 catalyst at 20 bar and 120°C afforded the tertiary amine **22** from the corresponding amide **21** in quantitative yields (Scheme 5).[46]



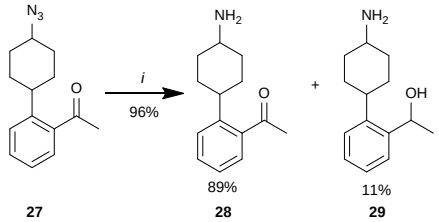
Scheme 5. Reagents and conditions: (i) Custom Flow hydrogenator (CFH), 0.67 M, 4% Pt¬4% Re/TiO_2, Hexane, 20 bar, 120 °C, 0.12 mL.min^{-1}.

In contrast azide reduction occurs under significantly milder conditions (c.f. amide reduction) with 10% Pd/C at low pressures and mild temperatures providing clean access to **24** and **26** from azido-**23** and **25** respectively in near quantitative yields (Scheme 6).[43,47,48]



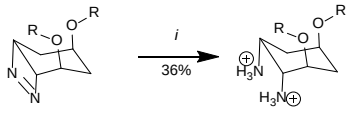
Scheme 6. Reagents and conditions: A. (i) H-cube®, 0.1 M, 10% Pd/C, MeOH, 1 bar, 20 °C, 1 mL.min^{-1} (t_r: 0.38 min); B. (ii) H-cube®, AcOH, 10% Pd/C, (1:9) H_2O/EtOH, 10 bar, 35°C, 0.5 mL.min^{-1} (t_r: 0.75 min).

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 power full tool for rapidly establishing reaction conditions, with minimal environmental impact and high atom economy.[49]



Scheme 7: Reagents and conditions: (i) H-cube®, 0.04, 10% Pt/C, MeOH, 1 bar, 50 °C, 1 mL.min^{-1} (t_r: 0.4 min).

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).[50] Whilst only isolated in poor yield (36%), this approach highlights the potential applicability of flow hydrogenation in the typically problematic reduction of azo moieties

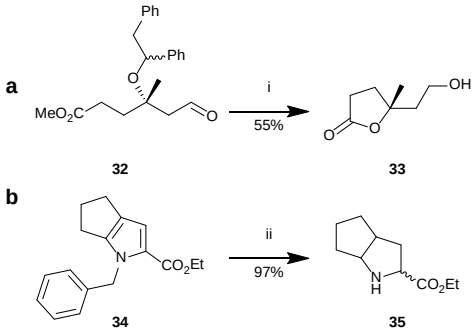


30 **31**

Scheme 8. Reagents and conditions: (i) H-cube®, 10% Pd/C, 60 bar, 60 °C, recirculated 0.5 h, (note: flow rate unknown).

Hydrogenolysis of alcohols and amines

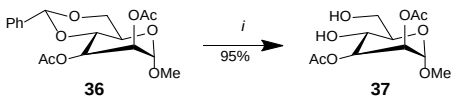
Flow hydrogenation offers an efficient means of deprotection for both benzyl (Bn) and carbobenzyloxy (Cbz) moieties.[51–55] Generally conditions for Bn group removal entail use of 10% Pd/C catalyst at > 40 bar and > 40 °C, [52–54,56–58] with Cbz groups are amenable to removal at lower temperatures and pressures.[59] These approaches have been used in the synthesis of compounds such as the lactone **33** which entailed concurrent de-benzylation and aldehyde reduction **32** to afford **33** in a 90% yield based on recovered starting material (Scheme 9).[52]. A similar methodology gave pyrrolidine **35** *via* Bn-group hydrogenolysis and hydrogenation of the pyrrole moiety (Scheme 9).[54]



32 **33** **34** **35**

Scheme 9. Reagents and conditions: A. (i) H-cube®, 10% Pd/C, MeOH, 80 bar, 45 °C, 0.3 mL.min^{-1} (t_r: 1.25 min); B. (ii) Custom Flow hydrogenator (CFH, 0.2 M, 10% Pd/C, EtOH/H_2SO_4 (50:1), 50 bar, 55 °C, 1.25 mL.min^{-1} (t_r: 8 min).

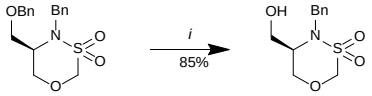
The chemoselective benzyl deprotection of the carbohydrate analogue **36** was achieved at 40 bar H_2 and 80 ºC to furnish **37** with no significant cleavage of acetate or methoxy groups observed (Scheme 22).[58]



36 **37**

Scheme 10. Reagents and conditions: (i) H-Cube®, 2.7 mM, 10% Pd/C, (1:1) EtOAc/MeOH, 40 bar, 80 °C, 1 mL.min^{-1} (t_r: 0.38 min).

Moreover, discrimination between *N*- and *O*-linked benzyl moieties is possible, with the *O*-benzyl moiety of **38** removed efficiently in the presence of the *N*-benzyl moiety (Scheme 23). Crucial to the reaction outcome was precise control of H_2 pressure with pressures > 50 bar resulting in global deprotections.[53]

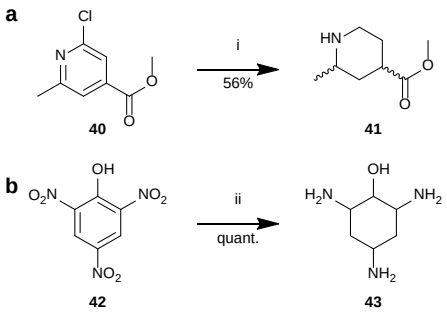


38 **39**

Scheme 11. Reagents and conditions: (i) H-cube, 0.1 M, 10% Pd/C, EtOH, 40 bar, 45 °C, 0.5 mL.min^{-1} (t_r: 1.51 min), 2 loops.

Saturation of aromatics

Generally complete saturation of aromatic rings has been previously regarded as problematic requiring the use of hazardous reagents.[60,61] However the development of flow hydrogenation has negated a number of safety issues. As an example the reduction of pyridine **40** to piperidine **41** was readily accomplished with a 10% Pt/C catalyst at 1 bar and 70 °C albeit in a moderate yield (56%; Scheme 10).[62] The less reactive picric acid **42** required the use of the more forcing conditions of 5% Rh/C at 100 bar and 100 °C but did allow the quantitative access to triamine **43**.[6]

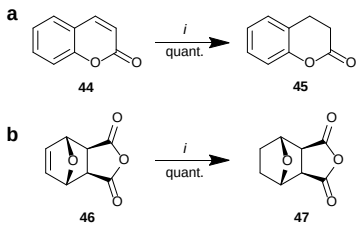


40 **41** **42** **43**

Scheme 12. Reagents and conditions: A. (i) H-cube®, 10% Pt/C, AcOH, 1 bar 70°C, flow rate unknown; B. (ii) H-cube®, 0.01 M, 5% Rh/C, 100 bar, 100 °C, 0.5 mL.min^{-1} (t_r: 0.75 min).

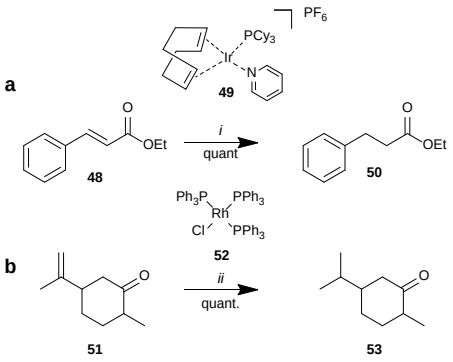
Olefin Hydrogenations

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.



Scheme 13. Reagents and conditions: (i) Flowsyn Tube-in-tube, 1.0 M, 10% Pd/C, EtOAc, 15 bar, rt, 5 mL.min^{-1}; (ii) H-cube®, 0.05 M, 10% Pd/C, Acetone, 50 bar, 50 °C, 1.0 mL.min^{-1} (t_r: 0.38 min).

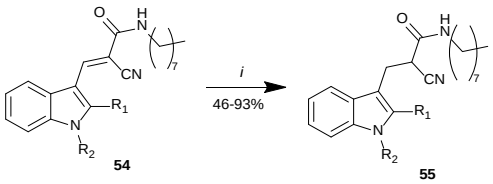
Ley *et al.* have pioneered the use of tube-in-tube reactors and/or the Vapourtec gas-liquid reactor combined with homogeneous catalysis for the reduction of olefin moieties.[4,5,67,68] Use of the Crabtree's catalyst **49** allowed quantitative hydrogenation of ethyl cinnamate **48** at 17.2 bar (Scheme 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]



Scheme 14. Reagents and conditions: (i) Flowsyn Tube-in-tube, 0.5 M, Crabtree's catalyst (**49**), DCM, 17.2 bar, rt, 2 mL.min^{-1};(ii) Vapourtec™ gas/liquid reactor, 5.0 M, Wilkinson's catalyst (**52**), DCM, 1 bar, 125 °C, 0.25 mL.min^{-1}.

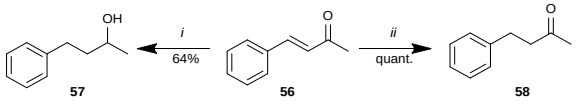
Chemoselective Olefin and alkyne hydrogenation

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 ºC afforded a number of desired analogues, such as **55,** in near quantitative yield (Scheme 13).[63]



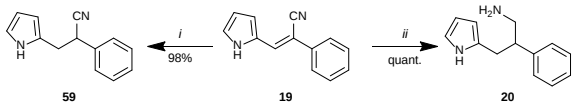
Scheme 15. Reagents and conditions: (i) H-cube®, 0.05 M, 10% Pd/C, EtOH 50 bar, 50 °C, 1.0 mL.min^{-1} (t_r: 0.38 min).

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).[69]



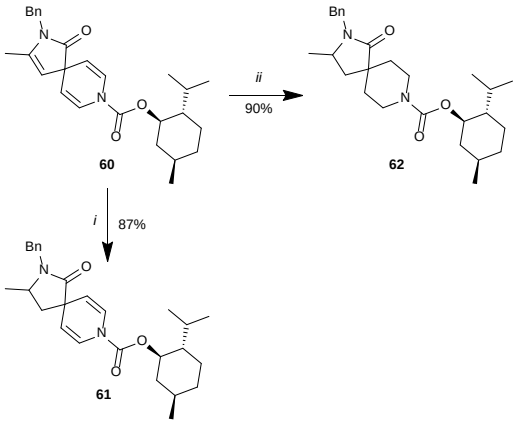
Scheme 16. Reagents and conditions: (i) H-cube®, 0.5 M, Raney Ni, EtOH, 1 bar, 70 °C, 1.5 mL.min^{-1} (t_r: 0.25 min) (ii) H-cube®, 0.5 M, Raney Ni, EtOH, 1 bar, rt, 1.5 mL.min^{-1} (t_r: 0.25 min).

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).[44]



Scheme 17. Reagents and conditions: (ii) H-cube®, 0.05 M, 10% Pd/C, Acetone 50 bar, 50 °C, 1.0 mL.min^{-1} (t_r: 0.4 min). (ii) H-cube®, 0.05 M, Raney Ni, Acetone 50 bar, 60 °C, 1.0 mL.min^{-1} (t_r: 0.4 min).

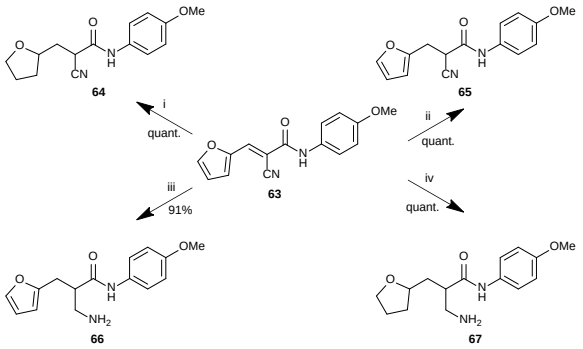
Hydrogenation pressure can also impact on reaction outcomes, at low pressure hydrogenation of **60** results in selective reduction of the labile olefin moiety giving **61**. Higher pressure results in the reduction of the olefin and the dihydro moieties to afford **62** (Scheme 16).[64]



Scheme 18. Reagents and conditions (i) H-cube®, 0.09 M, 10% Pd/C, (2:1) EtOH/EtOAc 40 bar, 30 °C, 1.0 mL.min^{-1} (t_r: 0.4 min). (ii) H-cube®, 0.09 M, 10% Pd/C, (2:1) EtOH/EtOAc 90 bar, 30 °C, 1.0 mL.min^{-1} (t_r: 0.4 min).

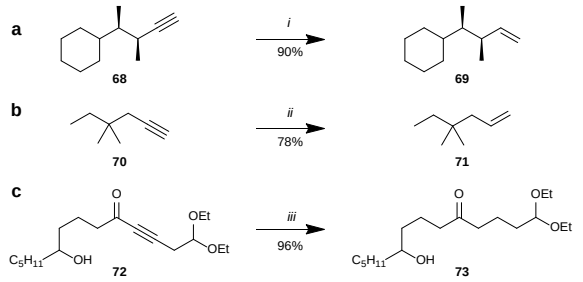
Selective control over olefin, furan and nitrile moiety hydrogenation has also been reported (Scheme 17). Reduction of **63** (10% Pd/C, 50 °C and 50 bar) specifically reduces furan and olefin moieties affording **64**. Decreasing pressure, temperature and residence time enabled selective hydrogenation 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 31optimisation reactions performed to establish these chemoselective conditions consumed just 200 mg of regent which further demonstrates the improved environmental impact of flow hydrogenation. [24]



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 % H_2, 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).

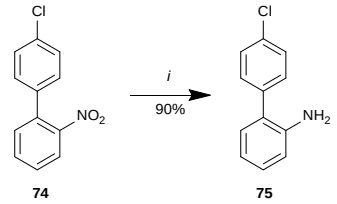
Catalyst selection imparts variations in the chemoselectivity of alkyne reductions with Lindlar or Pd impregnated γ-Al_2O_3 catalysts facilitating partial hydrogenation of alkyne bonds. The Lindlar catalyst hydrogenation of **68** afforded olefin **69** in a 90% yield. Similarly, the synthesis of **71** employed a Pd impregnated γ-Al_2O_3 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]



Scheme 20. Reagents and conditions; (i) H-cube®, 0.05 M, $Pd/BaSO_4/PbO$, DCM, 10 bar, 35 °C, 0.3 mL.min^{-1};(ii) segment-flow, 0.25 M, Pd/γ-Al_2O_3, EtOH, 1 bar, rt, r_t = 20s; (iii) H-cube®, 0.026 M, $Pd(OH)_2$, EtOAc/TEA (50:1), 1 bar, 40 °C, 1mL.min^{-1}.

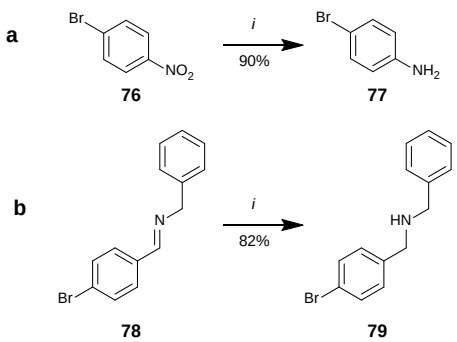
Restricting Hydrodehalogenation

Hydrodehalogenation has been reported with the use of Pd-, Ni- and Rh-based catalyst[29,33,39,72] 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 21. *Reagents and conditions*; (i) H-Cube®, 0.1 M, 10 % Pt/C, 40 ºC, 50 bar H_2, MeOH, 1 mL.min^{-1} (t_r: 0.38 min).

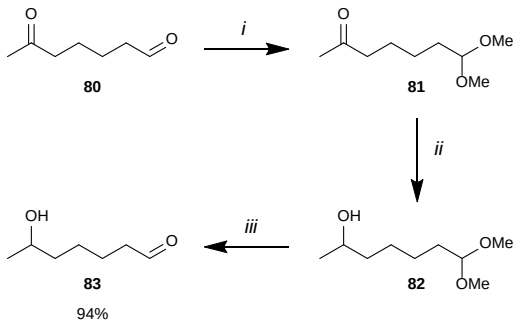
Gordon *et al*. have reported that use of poisoned catalysts, specifically 5% Pt/C (sulfided) serves as a robust approach to restrict dehalogenation. This catalyst cleanly effected both nitro and imine reductions in the presence of both chlorine and bromine atoms and displayed amenability with other label moieties such as furan (Scheme 20).[25]



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).

Carbonyl reductions

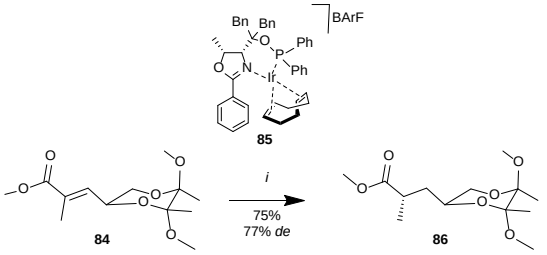
The reduction of less reactive ketones in the presence of aldehyde moieties is a challenging transformation, typically requiring protecting group strategies. The reduction of **80** was accomplished by utilising a continuous flow protocol employing both protecting group installation and hydrogenation. Initially a solution **80** in methanol was flowed through an omnifit column packed with Ti^{4+} montmorillonite (Ti-mont) at 30 °C, followed by hydrogenation through a hydroxyapatite supported Ru nanoparticles (Ru_{nano}HAP) column (Scheme 21). The hydrogenated product was deprotected using Ti-mont at 80 °C and water to give alcohol **83** in a near quantitative yield.[73]



Scheme 23. Reagents and conditions: (i) 0.2 M, Ti-mont (0.05g), MeOH, Argon (1 bar), 30 °C, 0.2 mL.min^{-1} (t_r: 5 min); H_2 (1 bar), $Ru_{nano}HAP$ (0.05g), MeOH, 40 °C, 2 mL.min^{-1} (t_r: 0.5 min); (iii) H_2O (4mL),Ti-mont, Argon, 1 bar, 80 °C, 0.4 mL.min^{-1} (t_r: 2.5 min).

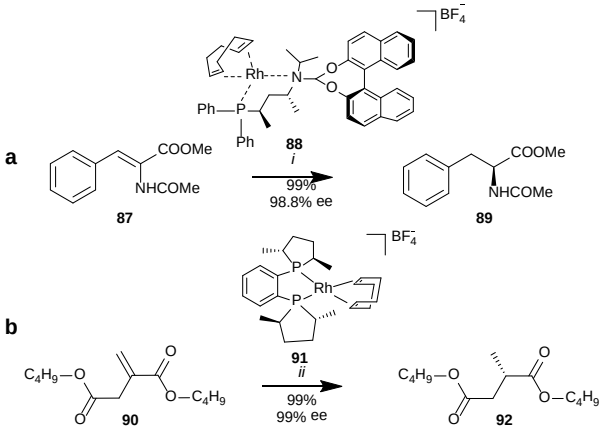
Asymmetric hydrogenations

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.[16,17,74] 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 **84**. Catalyst (*R*,*R*)-**85** was found to be optimal, affording (*S*)-**86** in a 75% yield (77% *de*) (Scheme 24).[74]



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}.

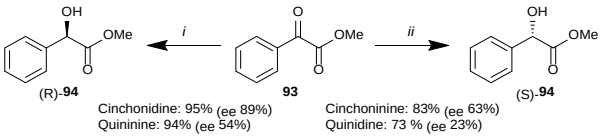
As alluded to previously a significant advantage of immobilised catalysts is the ease in which they can be partitioned from reaction mixtures.[16,17,75] Catalyst **90** was immobilised on mesoporous Al_2O_3 using phosphotungstic acid (PTA) and subsequent hydrogenation of **87** gave (*S*)-**89** (99%, 98.8% *ee*) (Scheme 25).[17] Moreover, the reduction of dibutyl itaconate **90** using immobilised **91** quantitatively afforded (*S*)-**92**.[75]



Scheme 25. Reagents and conditions: (i)H-cube®, 0.25 M, Al_2O_3/PTA/**88**, ethylene carbonate, 5 bar, 50 °C, 0.1 mL.min^{-1} (t_r: 3.77 min); (ii) CFH, neat, Al_2O_3/PTA/**91**, 5 bar, rt, 0.05 mL.min^{-1}.

Enantioselective Carbonyl reductions

Catalytic flow hydrogenation has been used to effect enantioselective reduction of carbonyl groups using Pt/Al_2O_3 and modifiers.[2,39] Most reports have focused on activated ketones, such as methyl benzoylformate, pyruvic aldehyde dimethyl acetal and 2,2-diethoxyacetophenone.[76,77] The yield and enantioselectivity of the reduction of **93** was dependent on the additive (Scheme 26). Additives cinchonidine and quinine afforded (*R*)-**94** (95%, (89% *ee*) or 94%, (54% *ee*), respectively). Whilst, cinchonine and quinidine furnished (*S*)-**94** (83% (63% *ee*) or 73% (23% *ee*), respectively).[77]



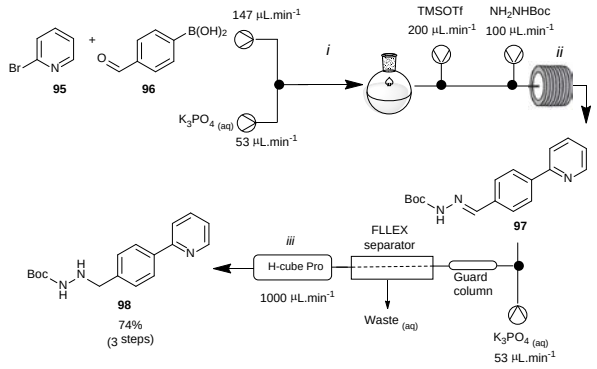
Scheme 26. Reagents and conditions: (i) H-cube®, 11 mM of **93**, Pt/Al_2O_3, 0.44 mM cinchonidine (or quinine), (9:1) toluene/AcOH, 40 bar, rt, 1 mL.min^{-1} (t_r: 0.4 min); (ii) H-cube®, 11 mM of **93**, Pt/Al_2O_3, 0.44 mM cinchonine (or quinidine), (9:1) toluene/AcOH, 40 bar, rt, 1 mL.min^{-1} (t_r: 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,

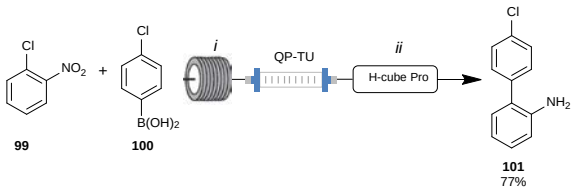
hydrazone formation and subsequent imine reduction in a 74% overall (Scheme 27).[78]

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.[78] However, reaction optimisation studies revealed 1.6 M K_3PO_4 and 1.2 eq. of boronic acid **96** was optimal with a 20 min residence time at 150 °C promoting a 95% conversion.[78] Initial attempts to form hydrozone **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 H-cube mediated imine reduction (10% Pd/C, 1 bar H_2, 40 °C 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_2CO_3.[78]



Scheme 27. Reagents and conditions: (i) 1 eq. **95**, 1.2 eq. **96**, 1.6 M K_3PO_4 (aq), (4:3) Toluene: Ethanol, 0.3 mol% $Pd(PPh_3)_4$, 150 °C, t_r: 20 min; (ii) 0.75 eq. TMSOTf, 1.2 eq. NH_2NHBoc, (4:3) Toluene: Ethanol, 50 °C, t_r: 8 min; (iii) H-cube Pro, 10% Pd/C, (4:3) Toluene: Ethanol, 1 bar, 40 °C, 1 mL.min^{-1} (t_r: 0.9 min).

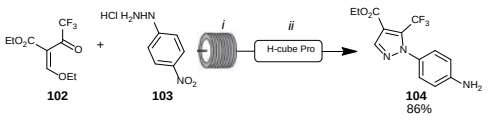
A similar flow Suzuki-Miyaura cross coupling and nitro reduction was applied to the multi-step flow synthesis of biaryl **101**, an important intermediate in the synthesis of the fungicide, Boscalid® (Scheme 28).[33] The optimised flow protocol which used the ThalesNano X-cube to effect the Suzuki-Miyaura saw the use of $Pd(PPh_3)_4$, K^{t}OBu at 160 °C 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_2O, 1 bar, 30 °C affording **101** in quantitative yield.[33]



Scheme 28. Reagents and conditions: (i) ThalesNano X-cube, 1 eq. **99**, 1.1 eq. **100**, 1.3 eq. K^{t}OBu, 0.25 mol% $Pd(PPh_3)_4$, (4:1) *t*-BuOH/H_2O, 1 mL.min^{-1} (t_r: 16 min) (ii) H-cube, 0.1M, 10% Pt/C, (4:1) *t*-BuOH/H_2O, 1 bar, 30 °C, 1 mL.min^{-1} (t_r: 0.4 min).

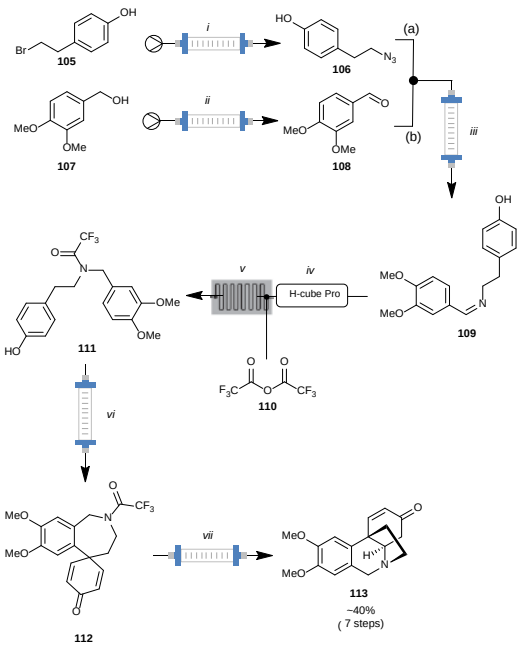
While the 'uncoupled' flow process using two distinct steps proceeded with excellent yield, the multi-step flow afforded reduced yields as a consequence of X-cube Pd-catalyst leaching to the hydrogenation system. However this was circumvented with the use of an inline Quadrapure™ TU (QP-TU) resin cartridge which the prevented Pd-leachate from entering the hydrogenation flow reactor system, and **101** was isolated in a 77% yield.[33]

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_2O_3 was used as the reduction catalyst affording **104** in an 86% yield.[23]



Scheme 29. Reagents and conditions: (i) X-cube 4 mL stainless steel coil reactor, 0.1 M, AcOH, 175 °C, 1.05 eq. TEA, 2.6 mL.min^{-1} (t_r: 1.5 min); (ii) H-cube, 0.03 M, 10% Pd/Al_2O_3, AcOH, 1 bar, 25 °C, 2 mL.min^{-1} (t_r: 0.2 min).

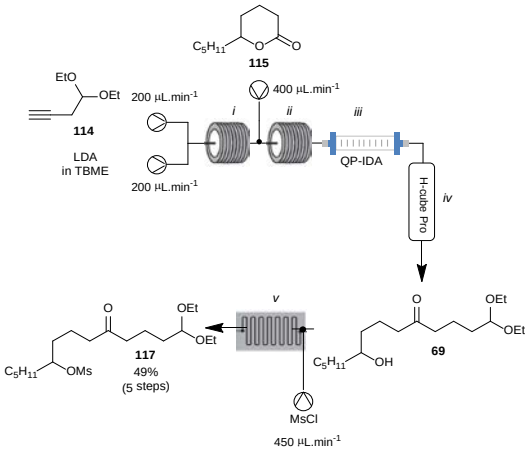
Total flow synthesis protocols to access natural products are also emerging. As an example (±)-oxomaritidine **113** was the first multi-step construction of a natural product, in which no intermediates were isolated. H-cube reduction of imine **109** was, one of many, key steps in this synthesis (Scheme 30).[38,41,79]



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) Syrris, AFRICA®, 10 eq. tetra- *N*-alkylammonium perruthenate (PSP), THF, rt, 50 µL.min^{-1}; (iii) Syrris AFRICA®, 20 eq. Di(N-butyl)phenylphosphine polystyrene Novabiochem® (a) 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_r: 0.4 min); (v) Syrris, AFRICA® microfluidic reactor chip, 5 eq. **110**, DCM, 80 °C, 34 µL.min^{-1} (t_r = 3.5 min); (vi) Syrris, AFRICA®, polymer-supported (ditrifluoroacetoxyiodo)benzene (PS-PIFA), DCM; (vii) Syrris, AFRICA®, Ambersep 900-OH ion-exchange resin, 35 °C,(4:1) MeOH/H_2O, 70 µL.min^{-1}.

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**.[38] 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**.[38] Imine **109** was quantitatively reduced using 10% Pd/C, 20 bar, 25 °C, and 1 mL.min^{-1}.[38,41] Amide coupling, phenol oxidation, and a final amide cleavage afforded (±)-oxomaritidine **113**. The seven-step flow total synthesis of (±)-oxomaritidine **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.[38]

Ketone **117**, which is a key intermediate in the synthesis of (-)-perhydrohistrioncotoxin, 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-IDA dicarboxylic 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%.[71]



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_r: 25 min); (ii) Vapourtec R2+ PTFE 5 mL flow coil, 0.1 M of **117**, TBME, 0 °C, 400 µL.min^{-1} (t_r: 12.5 min); (iii) QuadraPure-IDA dicarboxylic acid resin; (iv) H-cube®, *i*Pr_2NEt (0.9 mL), 20% $Pd(OH)_2$,TBME, 1 bar, 40 °C, 1 mL.min^{-1} (t_r: 0.4 min); (v) Ismatec piston pump and glass microchip, 0.6 M of MsCl, **,** 0.2 M of *i*Pr_2Net, DCM, rt, 450 µL.min^{-1} (t_r: 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

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