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Recent Developments in the Use of Flow Hydrogenation in the Field of Medicinal Chemistry

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Abstract

This chapter focuses on recent applications of flow hydrogenation in medicinal chemistry. Flow reactors can enhance laboratory safety, reducing the risks associated with pyrophoric catalysts, due to their containment in catalyst cartridges or omnifit columns. Flow hydrogenation reduces the risks arising from hydrogen gas, with either hydrogen generated in situ from water, or precise management of the gas flow rate through tube-in-tube reactors. There is an increasing body of evidence that flow hydrogenation enhances reduction outcomes across nitro, imine, nitrile, amide, azide, and azo reductions, together with de-aromatisation and hydrodehalogenation. In addition, olefin, alkyne, carbonyl, and benzyl reductions have been widely examined. Further, protocols involving multistage flow reactions involving hydrogenation are highlighted.

Keywords: hydrogenations, flow technologies, flow synthesis, reduction, multistage, flow hydrogenation, chemoselective, catalyst

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1. Introduction

In 2013, 25% of marketed drugs required at least one hydrogenation step in their production [1, 2]. Hydrogenation mediated manipulation of nitro, imine, nitrile, amide, azide, and azo moieties, as well as de-aromatisation, hydrodehalogenation, olefin, alkyne, carbonyl, and benzyl reductions are fundamental to drug discovery and development programmes [1, 3].

Flow hydrogenation offers the benefits of improved safety, yield, selectivity and reduced purification over traditional hydrogenation approaches. Flow hydrogenation through the use

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of contained pyrophoric catalysts, replacement of hydrogen reservoirs with in situ hydrogen generation, improved temperature control, and smaller solvent volumes all contribute to an increase in hydrogenation safety [4]. Flow technologies have improved hydrogenation outcomes by increasing substrate-gas-catalyst interactions and permitting stringent control of reaction parameters (temperature, flow rate, and pressure) with a commensurate reduction in undesirable side product and improved selectivity. Combined with optimised reaction conditions, this generally means very little or no further purification is required after the reaction [1].

This chapter details key recent development in functional group transformation, multistep synthesis utilising flow hydrogenation and technology advances [1, 3].

2. Instrumentation

Unlike batch reactions where gas-solvent contact is limited by diffusion of gas into the bulk solvent, flow hydrogenation rapidly saturates the solvent with hydrogen using two different approaches [5]. The first, used by the ThalesNano H-cube®, employs in-line mixing of hydrogen with the solvent under pressure, which prevents outgassing and rapid solvent stream saturation (**Figure 1A**) [6]. The second approach, used by the Vapourtec Gas/Liquid reactor (**Figure 1B**) and Gastropod Gas Liquid Module, employs gas permeable membranes in a tube-in-tube reactor. These systems enable solvent stream saturation by passing hydrogen gas under pressure through a gas porous polymer and into the solvent [7–10].

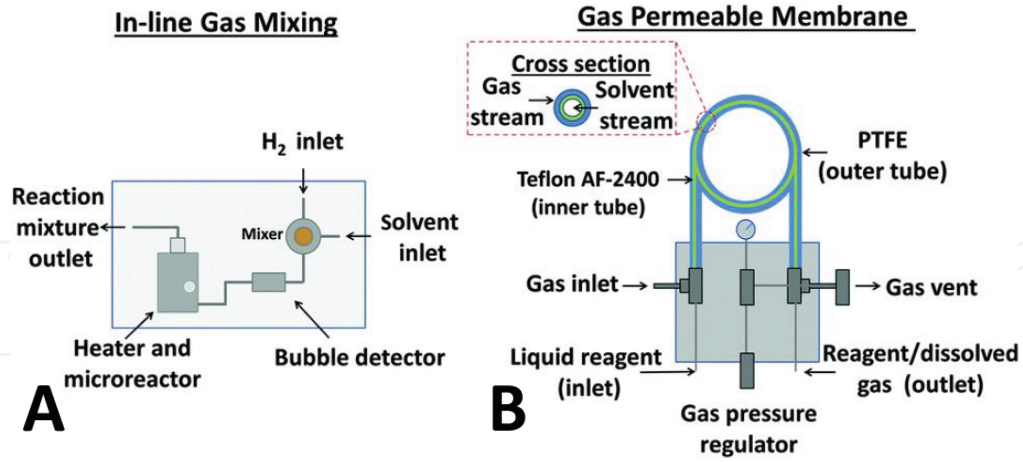

Figure 1. Schematic of the mechanical mixing setup in (**A**) the ThalesNano H-Cube® and (**B**) schematic of the gas permeable membrane (tube-in-tube) technology [1].

The Thalesnano H-cube® was the first commercial flow hydrogenator. Together with the use of in-line gas mixing, the H-cube uses exchangeable 30 or 70 mm heterogeneous catalyst cartridges and a HPLC pump. Hydrogen gas is generated in situ through water electrolysis. The system is capable of heating to 100°C and 150 bar, with a flow rate range from 0.5 to 5.0

mL min^{-1} [11]. Tube-in-tube reactors require specialised materials displaying high gas permeability while being impermeable to (nonfluorinated) liquids and corrosive chemicals, e.g., Teflon AF-2400 [12]. The Vapourtec Gas/Liquid system uses 'plug-in reactors' and the Gastropod Gas Liquid Module can be equipped with a small gas cylinder or attached to any custom flow systems [9, 10].

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3. Functional group transformations

3.1. Nitro reductions

Flow nitro reductions, using palladium, platinum, and Raney Ni catalysts, under optimised conditions have been shown to provide both increased yield and simplified work up [1, 3]. Abdel-Hamid et al's recent synthesis of 1,8-naphthalimide derivatives illustrates this with an increase in yield (86–98%) and purification simplification (chromatographic to extractive) (**Figure 2**) [13].

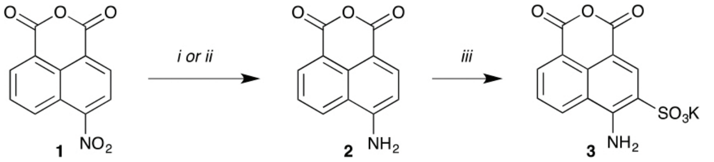

Figure 2. Synthesis of 1,8-naphthalimide derivatives. Reagents and conditions: (i) ThalesNano H-Cube®, 10% Pd/C, THF, 40°C, 10 bar, 1 mL min^{-1}, 2 cycles; (ii) $SnCl_2$, HCl, ethanol, reflux 2 h; (iii) (a) fuming sulfuric acid, 50°C, 3 h; (b) saturated aq. KCl, room temperature.

The utility of the flow nitro reduction extends across pyrrolidine, carboxylate ester, phenyl propanoate, benzothiopene, benzofurans, and indole-carboxylate scaffolds. These reactions employed either Raney Ni or 10% Pd/C catalysts from 25 to 65°C and atmospheric (atm)—20 bar, respectively, providing excellent reaction outcomes (**Table 1**).

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3.2. Alkene reductions

Flow hydrogenation is particularly useful in the reduction in alkene and alkyne bonds as is evident from the examples shown in **Table 2**. Gericke et al. developed ruthenium-nitrogen-doped carbon nanotubes (NCNT) and ruthenium-hyperbranched polystyrene-supported (HPS) catalysts, providing a more sustainable process [24]. Gericke et al. suggested that HPS- and NCNT-supported catalysts are a suitable alternative to Raney Ni and have an increased production rate per mole of catalyst compared to Raney Ni. Multiple similar alkene and alkyne reductions have been reported (**Table 2**). These hydrogenation catalysts were found not to be limited to the hydrogenation of alkenes and alkynes and have been applied in the reduction in glucose **4** to sorbitol **5**, which traditionally has relied on expensive catalysts such as Raney Ni (**Figure 3**).

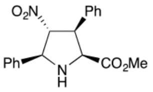
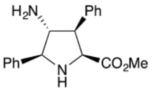
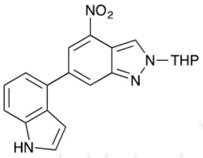
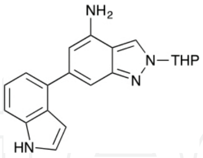
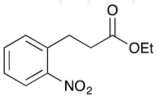
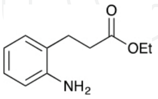
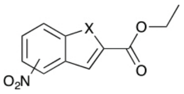
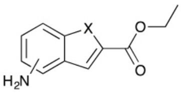
Starting material	Product	Yield	Catalyst	Conditions	References
		90%	Ra-Ni	65°C, 20 bar, 1.0 mL min^{-1}	[14]
		100%	10% Pd/C	25°C, 1–30 bar	[15]
		100%	10% Pd/C	50°C, 1 bar, 1.0 mL min^{-1}	[16]
 X = O, S, NH	 X = O, S, NH	88–98%	10% Pd/C	40–60°C, 1 bar, 0.5–1.0 mL min^{-1}	[17]

Table 1. Flow nitro reduction of selected analogues.

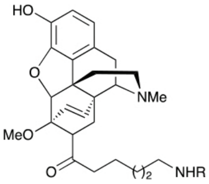
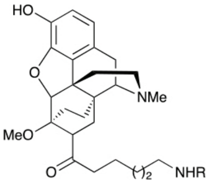
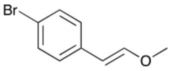
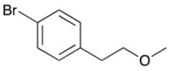
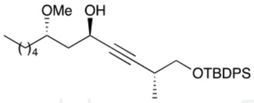
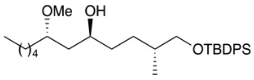
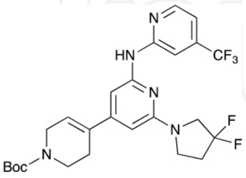
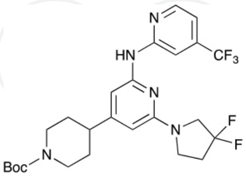
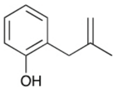
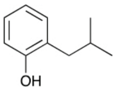
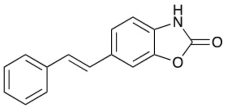
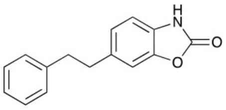
Starting material	Product	Yield	Catalyst	Conditions	References
		86%	10% Pd/C	25°C, 10 bar, recirculate 2 h	[18]
		21%	5% Rh/C	70°C, 1 bar, 1.5 mL min^{-1}, 3 cycles	[19]
		98%	10% Pd/C	40°C, 1 mL min^{-1}	[20]
		84%	10% Pd/C	30°C, 40 bar, 1 mL min^{-1}, 2 cycles	[21]
		99%	RaNi	60°C, 60 bar, 1 mL min^{-1}, 24 h	[22]
		Quant.	10% Pd/C	50°C, 1 bar	[23]

Table 2. Flow reduction of selected alkenes and alkynes.

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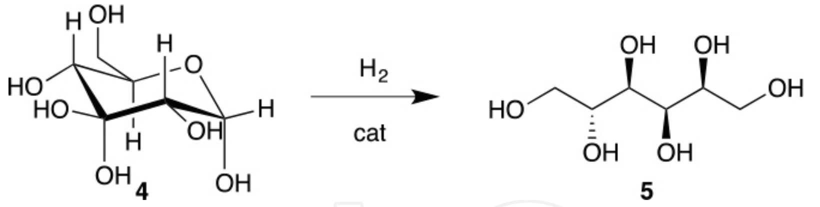


Figure 3. Reaction scheme for the hydrogenation of D-glucose (**4**).

Initial attempts by Yadav et al. under batch reaction conditions to access alcohol **6** afforded an 8:2 mixture of **6** and ketone **7** [20]. The use of the H-cube® and relatively mild reducing conditions (10% Pd/C, 40°C, and 6 bar) gave exclusively **6** in a near-quantitative yield (**Figure 4**).

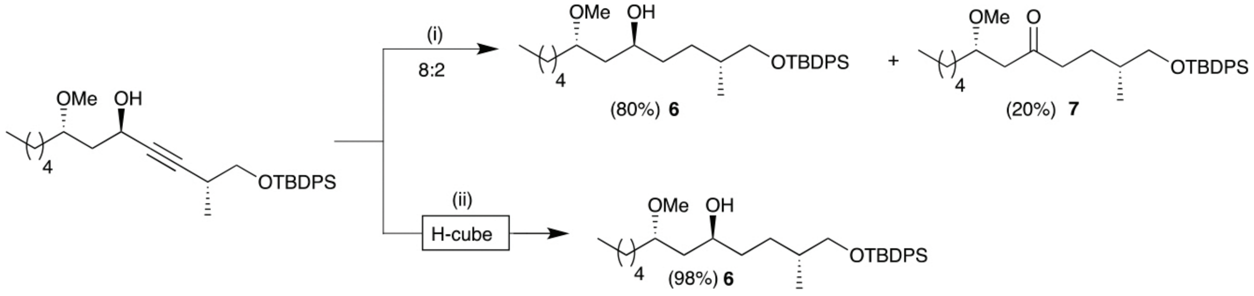


Figure 4. Synthesis of the marine macrolide sanctolide **6** via batch and flow hydrogenation. Reagents and conditions: (i) H_2, Pd/C (10%), EtOAc, rt, 8 h; (ii) H-cube®, Pd/C (10%), MeOH, 40°C, 6 bar.

Trobe and Breinbauer highlighted the use of flow methodologies to improve reaction yields (**Figure 5**) [22]. The trifluoroether **11** was accessed through a conventional traditional Witting/hydrogenation approach in a 32% yield. A modified access via a Claisen rearrangement and flow hydrogenation was developed leading to **11** in a 71% yield.

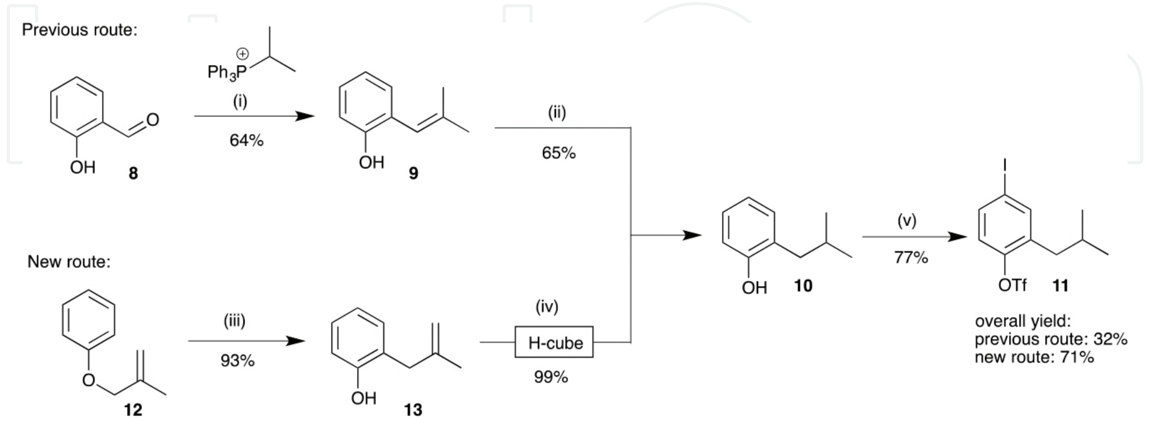


Figure 5. Improving the yield of a synthetic route from 32% to 71% with the aid of flow hydrogenation. Reagents and conditions: (i) salicylaldehyde, toluene, 80°C, 8 h; (ii) H_2, Pd/C, MeOH, 22°C, 3 h; (iii) DMAc, 190°C, 5 d; (iv) H-cube®, Ra-Ni, 60°C, 60 bar; (v) (i) ICl, AcOH, 22°C, 24 h; (ii) Tf_2O, pyridine, 0°C, 2 h.

3.3. Reductive amination

Traditionally, borohydride reagents such as $NaCNBH_3$, $NaBH(OAc)_3$, or pyridine-BH_3 have been used for reductive amination [25]. However, flow hydrogenation offers considerable advantages over transfer hydrogenation, such as improved atom economy, reduced environmental impact, simple reaction workups, and reduced exposure to toxic or reactive starting materials [26].

Flow reductive aminations are generally conducted using 10% Pd/C or 20% $Pd(OH)_2$/C, with the temperatures and pressures used substrate-dependent [1]. However, the use of an Au/Al_2O_3 catalyst has facilitated a cascade nitro reduction and direct reductive amination to afford secondary amine **16** (**Figure 6**). Unlike many conventional Pd- and Ni-based catalysts, the Au/Al_2O_3 catalyst showed selective reduction in the nitrobenzene **14** over benzaldehyde **15**, aiding imine formation and subsequent reductive amination. Under optimised conditions (1:1.5 nitrobenzene **14**: benzaldehyde **15**, 80°C and 50 bar), the desired *N*-benzylaniline **16** was generated in a 91% yield (**Figure 6**) [27].

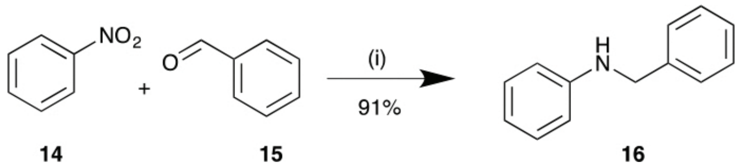


Figure 6. Flow reductive amination to afford *N*-benzylaniline **16**. Reagents and conditions: H-cube® Pro, 0.05 M **15** in EtOH, Au/Al_2O_3 (70 mm), 125°C, 10 bar, 0.3 mL min^{-1}.

Treatment of phenethylamine (**18**) and levulinic acid (**17**) in 2-methylfuran under the hydrogenation conditions of 85 bar H_2 pressure, 150°C and carbon-supported Fe/Ni yielded pyrrolidine **19** with a 91% conversion via a sequential reductive amination and cyclisation process (**Figure 7**) [28].

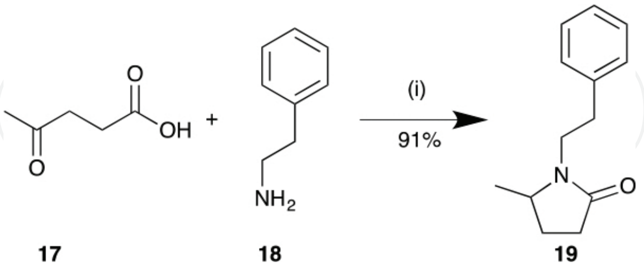


Figure 7. Flow reductive amination with carbon-supported Fe/Ni (C-Fe/Ni) to form pyrrolidine **19**. Reagents and conditions: H-cube® Pro, 0.025 M **18** in 2-methylfuran, C-Fe/Ni alloy (70 mm), 150°C, 85 bar, 0.3 mL min^{-1}.

3.4. Protecting group manipulation

The synthesis of carbohydrate and nucleoside mimics has led to the development of C-nucleosides and C-glycosides as antibiotic, anticancer, and antiviral agents [29]. Using flow chemistry, Redpath et al. were able to access the deprotected 2-deoxy-C-galac-topyranosyl-benzoic acid **26** (**Figure 8**) [29]. The final stage of the multistep reaction, including the hydrogenation, provided **26** in a 39% yield over five steps. This route was found to provide access to galactoside and mannoside type C-nucleosides incorporating functionality analogous to the biologically important benzamide riboside through the use of an oxazoline protecting group, which had been previously inaccessible using a transmetallation/inter molecular Sakura condensation approach.

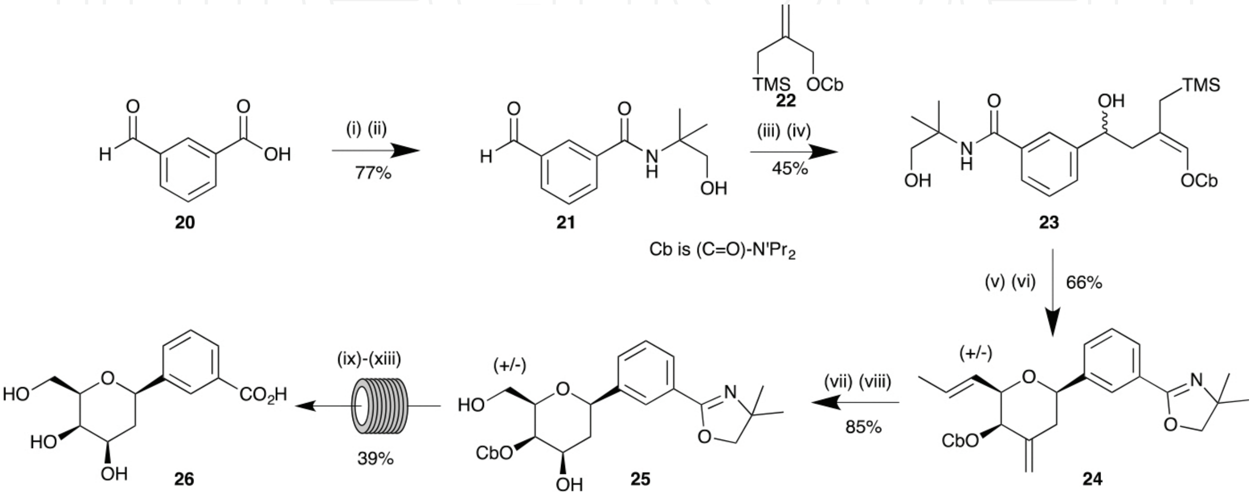


Figure 8. Synthesis of (D/L)-deoxy-β-galactopyranosyl-benzoic acid (**26**). Reagents and conditions: (i) $SOCl_2$, toluene; (ii) $H_2NC(CH_3)_2CH_2OH$, CH_2Cl_2; (iii) *sec*-BuLi, TMEDA, Et_2O; (iv) $Ti(O^iPr)_4$; (v) crotonaldehyde, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (vi) MsCl, Net_3, CH_2Cl_2; (vii) O_3, CH_2Cl_2/MeOH then Me_2S; (viii) $NaBH_4$; (ix) $LiAlH_4$, THF; (x) BnBr, TBAI, NaH, 15-crown-5, THF; (xi) MeI, $MeNO_2$; (xii) 20% KOH, MeOH; (xiii) H_2, 10% Pd/C, MeOH.

Pd-catalysts and mild (RT, 1 bar) to moderate (45°C, 10 bar) conditions have been employed for the removal of benzyloxy carbamate (CBz) and benzyl (Bn) protecting groups (**Table 3**).

3.5. Multistep synthesis

A number of integrated multistep flow syntheses, with hydrogenation a key step, have been reported and are typically characterised by the reduced need for purification between synthetic steps.

Previous batch syntheses of the kinase inhibitors CTx-0152960 and CTx-029488 required the use of Boc-piperidine in the key S_NAr coupling with 1-fluoro-4-nitrobenzene to prevent formation of unwanted side products. Flow approaches removed this requirement facilitating rapid access to the Boc-free analogues in high yields (**Figure 9**) [33]. Of note, the flow hydrogenation of both the S_NAr adducts of piperidine and morpholine (**27**) required no purification. Microwave coupling of 4-morphilinoaniline and 4-(piperazine-1-yl)aniline with 2-(2,5-dichloropyrimidine-4-ylamino)-*N*-methylbenzamide afforded access to the desired **31a** and **31b**. This hybrid approach reduced the number of synthetic steps, enhanced product yield, and increased atom economy through step reduction and minimal requirement for chromatographic purification, relative to the original batch approach [33].

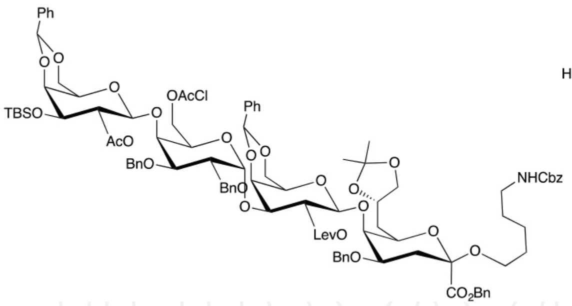
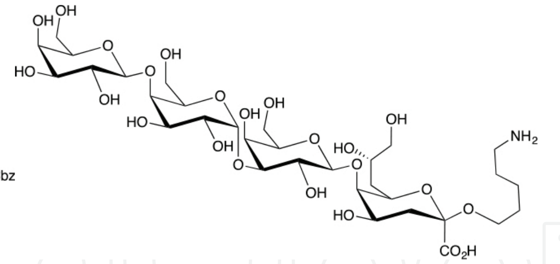
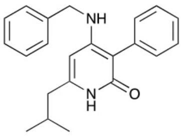
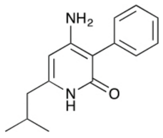
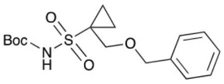
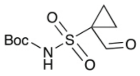
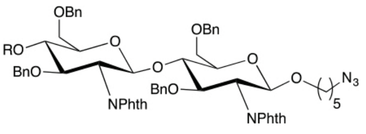
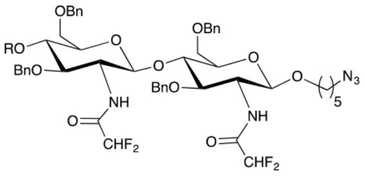
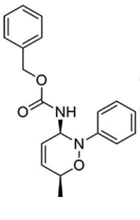
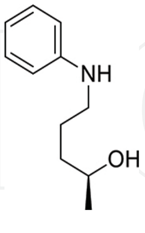
Starting material	Product	References
		[30]
CBz protecting group	20% Pd(OH)$_2$/C; 45°C, 10 bar, 1.0 mL min^{-1}, 1 cycle; 67%	
		[31]
Benzyl protecting group	10% Pd/C; 65°C, full H$_2$ mode, 1.0 mL min^{-1}, 1 cycle; 60%	
		[32]
Benzoyl protecting group		
		[56]
Phthalimide protecting group	10% Pd/C; 50°C, 1 bar, 50°C, 0.5 mL min^{-1}; 56–81%	
		[57]
Cbz protecting group	10% Pd/C; RT, 1 bar, 50°C, 1.0 mL min^{-1}; 99%; 97% ee	

Table 3. Flow reduction and removal of protecting groups.

The modular nature of flow chemistry instrumentation has allowed Ghislieri et al. by simple manipulation of the module order and selection of staring material to produce five active pharmaceutical ingredients (APIs) across three structural classes (γ-amino acids, γ-lactams, β-amino acids). From benzyl alcohol eight compounds of interest including the drugs Lyrica and Gabapentin were synthesised in good overall yields (49–75%) (**Figure 10**) [34].

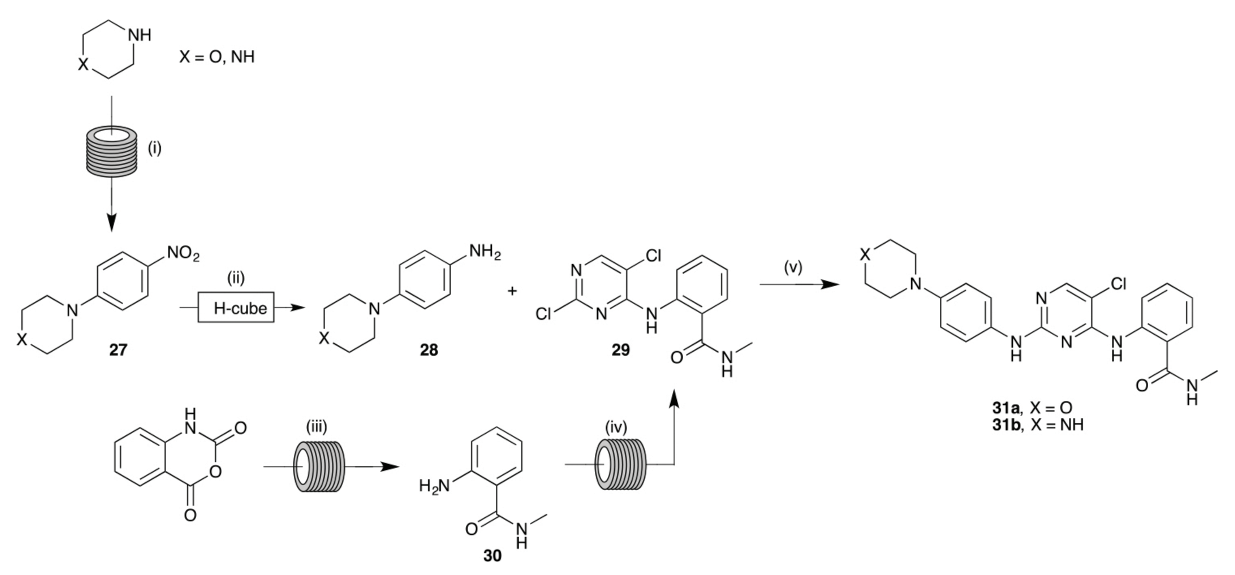


Figure 9. Synthesis of broad kinase inhibitors **31a** and **31b** by multistep flow synthesis. Reagents and conditions: (i) Vapourtec R2+, 4M piperidine or morpholine in DMF, 2 M 1-fluoro-2-nitrobenzene in DMF, 8 bar, 5 mL min^{-1}; (ii) H-CubePro, 0.05M in MeOH, 10% Pd/C CatCart® (70 mm), 50 bar, 50°C, 1.0 mL min^{-1}; (iii) Syrris FRX-100, 40% w/w aq. $MeNH_2$, 0.5 mL min^{-1}, 0–19°C, 19 h; (iv) Vapourtec R2+, 2,3,5-tri-chloropyrimidine, ^{i}PrNEt, ^{i}PrOH, 4 bar 100°C; (v) *n*-BuOH, 4 M HCl in dioxane (cat), 150°C, μW, 20 min.

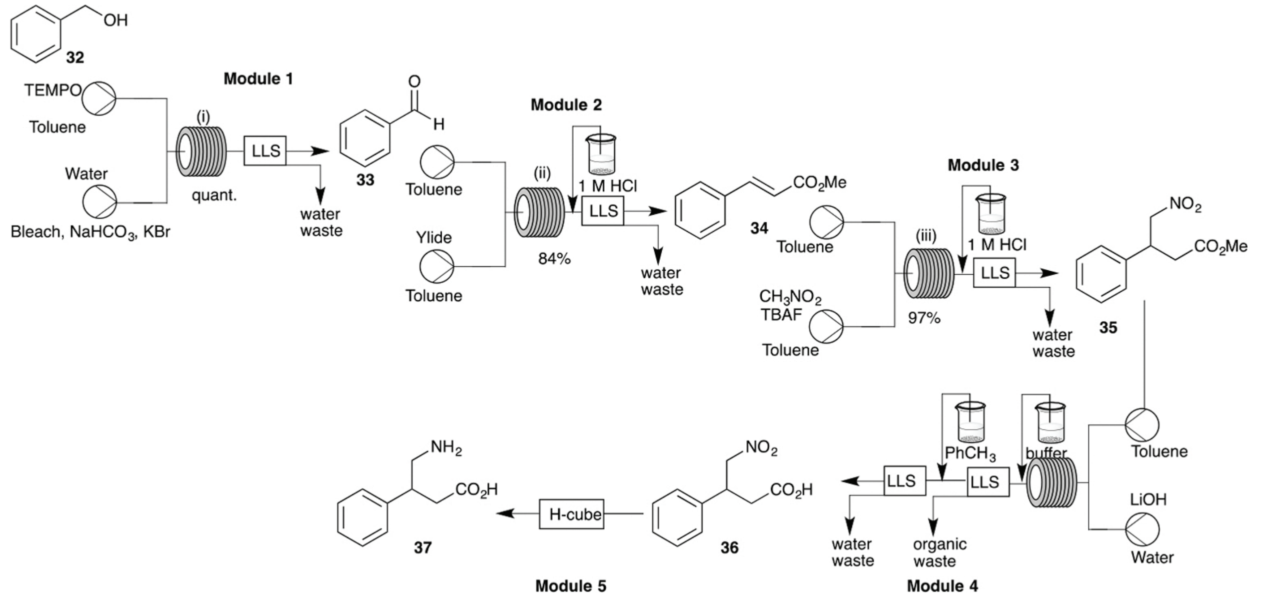


Figure 10. Divergent multistep flow synthesis of γ-amino acid derivatives. Reagents and conditions: (i) bleach (2.5 eq.), TEMPO (0.05 eq.), $NaHCO_3$ (0.3 eq.), KBr (0.2 eq.), 0°C; (ii) triethylphosphonoacetate (1.1 eq.), *t*BuOK (1.1 eq.), 50°C; (iii) CH_3NO_2 (11 eq.), TBAF (1.3 eq.), 50°C; (iv) H-cube®, Pd/C (10%), 60°C, 60 bar; (v) LiOH (3 eq.), 50°C. LLS = liquid-liquid separator. Yields for individual modules determined upon isolation.

The flow chemistry modules above have also been used for the efficient synthesis of a number of known APIs (**Figure 11**). Within this multistage process, module five employed the use of the H-cube for the preparation of β-amino acids from unsaturated α-nitrile ester (90 bar, 100°C, Raney Ni). For nitro reductions, Pd/C and Raney Ni catalysts were favoured and afforded the desired compounds in good-to-excellent yields.

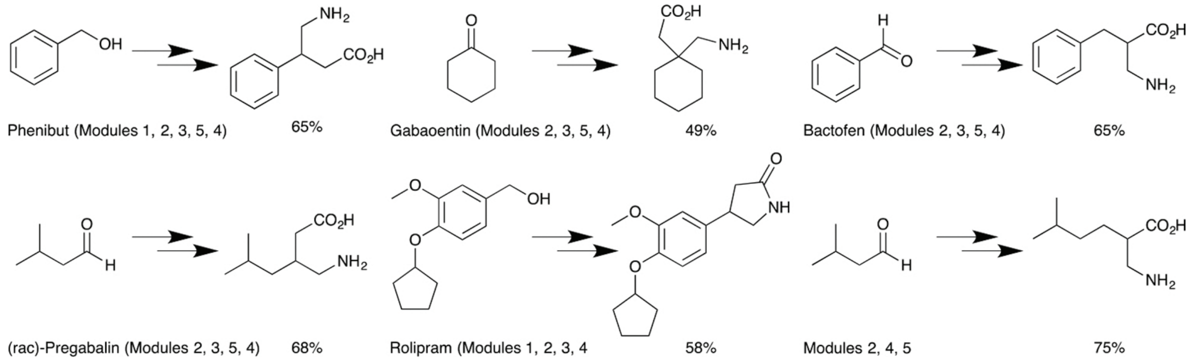


Figure 11. APIs prepared via the convergent multistep synthesis exemplified in **Figure 10**. Yields are reported for full processes without immediate purification over the 3–5 steps.

Both (*R*)- and (*S*)-rolipram were generated by using flow approaches and required no isolation of intermediates or purification, a significant step towards the automated manufacture of APIs [35]. The overall process used is outlined in **Figure 12**. While commercially available Ni and Pd catalysts failed in the case of aliphatic nitro compounds, however, a newly developed dimethylpolysilane-supported palladium/carbon (Pd/DMPSi-C) catalyst afforded the desired δ-lactam in a 74% yield (94% ee).

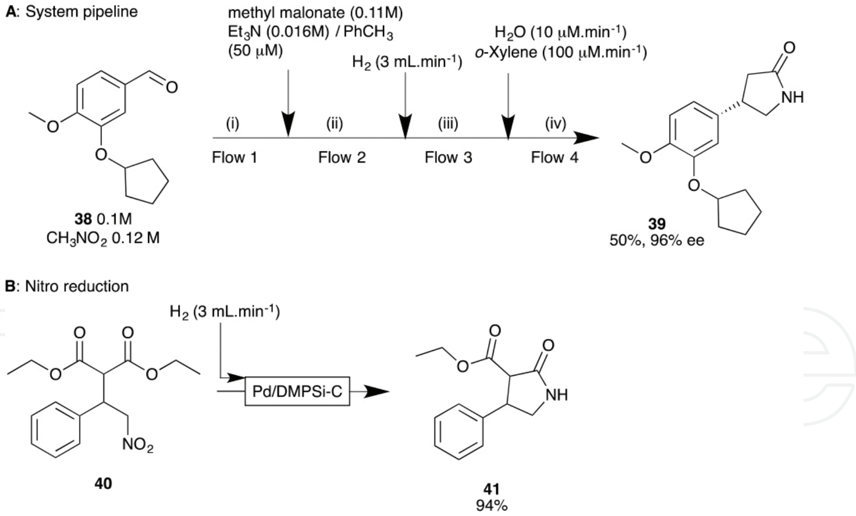


Figure 12. (**A**) Multistep flow synthesis of (*S*)-rolipram. Reagents and conditions: (i) Si-NH_2/$CaCl_2$, toluene, 75°C, 50 μL min^{-1}; (ii) PS-(*S*)-Pybox, $CaCl_2{\cdot}2H_2O$, 0°C, 100 μL min^{-1} (total); (iii) Pd/(DMPSi-C) (1.6 mmol), 100°C, 100 μL min^{-1} (total); (iv) HOOC-silica gel, 120°C, 210 μL min^{-1} (total). The flow reaction was continued for a week and the yield and the enantioselectivity maintained. (**B**) Further details of the flow hydrogenation step.

The success of multistage flow synthesis in API production, especially the use of flow hydrogenation suggests that these approaches will continue to rapidly develop and potentially become a standard method of synthesis.

http://dx.doi.org/10.5772/65518

3.6. Scaffold formation

Flow hydrogenation has provided access to scaffolds that were inaccessible via batch hydrogenation pathways such as the 1,4-benzodiazepin-5-ones (**Figure 13**). This scaffold has been targeted in treatments for tuberculosis [36] and control of the melanocortin receptors implicated in appetite control [37] and was readily accessed under flow conditions (THF, 0.3 mL min^{-1}, 50 bar and 80°C). Isolated yields of up to 94% (**45**) requiring no purifications were noted [38].

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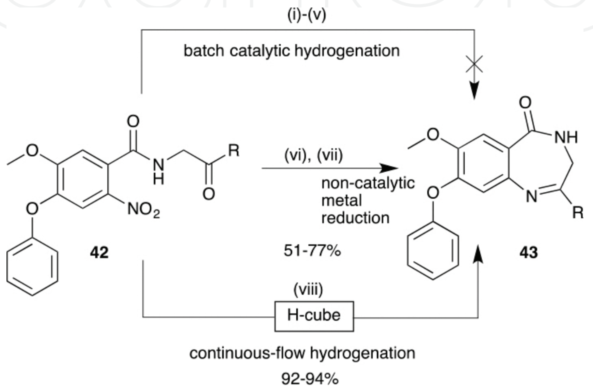


Figure 13. Synthesis of the desired 1,4-benzodiazepin-5-ones **43** via batch and flow hydrogenation. Reagents and conditions: (i) H_2, Pd/C (10%, 0.1 eq.), EtOAc:EtOH, 2:1 (0.03 M), 20°C, 1 atm; (ii) 1,4-cyclohexadiene (6 eq.), microwave mode, Pd/C (10%, 0.05 eq.), MeOH (0.1 M), 120°C; (iii) H_2, Ru/C (5%, 0.02 eq.), THF (0.03 M), 20°C, 1 atm; (iv) H_2, Ru/C (5%, 0.02 eq.), THF (0.03 M), reflux, 1 atm; (v)) H_2, Ru/C (5%, 0.04 eq.), THF (0.03 M), 20°C, 1 atm; (vi) $FeSO_4{\cdot}7H_2O$ (10 eq.), NH_4OH, EtOH, reflux; (vii) Fe (20 eq.), AcOH (0.1 M), 70°C; (viii) H-cube Pro®, Ru/C (5%), THF, 80°C, 50 bar, 0.3 mL min^{-1}.

The chiral ester (**45**) is a key intermediate in the synthesis of the angiotensin II receptor blocker sacubitril. Enantioselective flow hydrogenation using a tube-in-tube system, through two loops, provided access to the required diastereomer at 0.45 g h^{-1}. The introduction of the second loop was critical increasing the yield from 78 to 99% (**Figure 14**) [39].

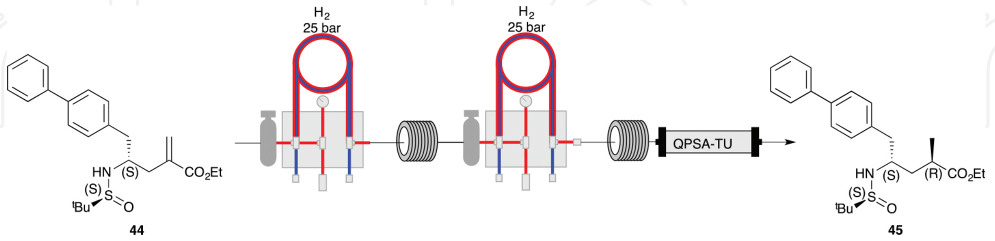
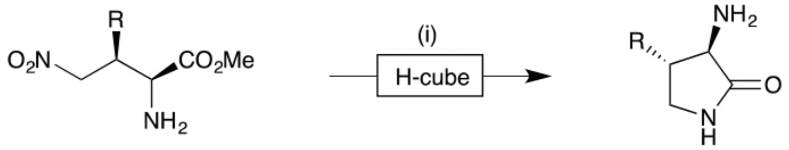


Figure 14. Enantioselective hydrogenation flow preparation of chiral ester **45**. Reagents and conditions: H_2, cat. DIPEA in EtOH (1 mol%), 20°C, 25 bar, 0.2 mL min^{-1}.

In a similar manner, H-cube mediated nitro reduction and lactam cyclisation of γ-nitro-α-amino esters with in situ cyclisation afforded, quantitatively, the corresponding γ-lactams (**47**) (**Figure 15**). Raney Ni hydrogenation (10 bar, 65°C) of the *syn*- diastereomer affords exclusively the *trans*- configuration with the *anti*-γ-nitro-α-amino esters gave the *cis* diastereomer [40].



syn **46**
R = Ph, 4-F-C_6H_4, 4-MeO-C_6H_4

trans **47**
quant.

Figure 15. Formation of γ-lactams via flow hydrogenation. Reagents and conditions: (i) H-cube®, Raney Ni, MeOH (0.01 M), 65°C, 10 bar, 1.0 mL min^{-1}.

3.7. Other reactions

A variety of other reductions that are pertinent to medicinal chemistry can also be performed via flow hydrogenation as shown in **Table 4**.

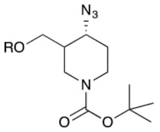
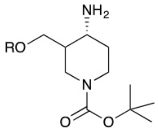
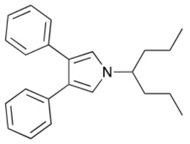
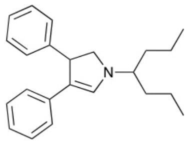
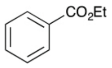
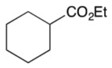
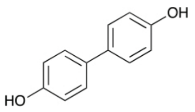
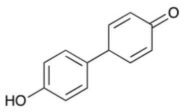
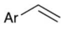
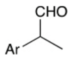
Type of reaction	Starting material	Product	Conditions	References
Azide reduction			10% Pd/C, RT, 1 bar, 1.0 mL min^{-1}, 94%	[41]
Olefin reduction			10% Pd/C, 80°C, 60 bar, 2.0 mL min^{-1}, 90%	[42]
De-aromatisation			10% Ru/C or 10% Rh/C, 75–100°C, 50 bar, 1.0 mL min^{-1}, 100%	[43]
Selective reduction			20% Pd/C, 100°C, 5 bar, 1.0 mL min^{-1}, 58%	[44]
Hydroformylation		 11 examples	Rh$(CO)_2$(acac), 65°C, 25 bar, 0.6 mL min^{-1}, 69–94%	[45]

Table 4. Selected other common flow reduction reactions.

In the synthesis of the antimalarial drug, OZ439 **49**, Lau et al. optimised the hydrogenation step successfully reducing only one of the aromatic rings using 20% Pd/C (**Figure 16**) [44]. The concentration of the undesired minor by-products **50** and **51** was minimised by control of the temperature and the amount of hydrogen entering the system. This flow approach to **49** also avoided the use of genotoxic 4-(2-chloroethyl)morpholine.

3.8. Deuteration

The incorporation of a deuterium label has been used widely to probe reaction mechanisms, to probe a compound's pharmacokinetic properties, and as an internal standard in NMR and mass spectrometry [46]. The increase in bond strength (C-H versus C-D) can modify a drug's pharmacokinetic profile, and this has led to the development of deuterium containing drugs. Deutetrabenazine (SD-809) is expected to be the first deuterated drug approved by the FDA.

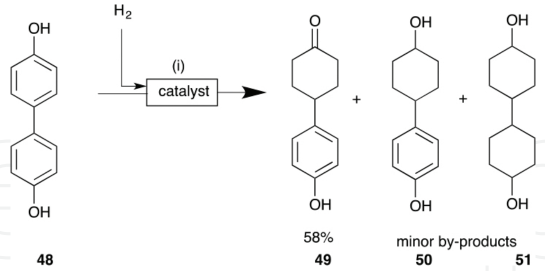


Figure 16. Selective continuous flow hydrogenation of 4-4′-biphenol **48**. Reagents and conditions: (i) H_2 (0.1 L min^{-1}), Pd/C (20%), EtOH/H_2O (1:1 v/v, 0.05 M), 100°C, 5 bar, 1.0 mL min^{-1}.

The synthesis of SD-809 is not flow mediated, but its success does suggest that the incorporation of deuterium will become a more common feature in future drugs [47]. Deuterium incorporation can be accomplished from D_2 gas and catalytic H-D exchange reactions between H_2 and D_2O. There are disadvantages to using deuterium gas on a laboratory scale, such as the handling of the gas itself, and the catalytic approaches are time consuming and do not always produce high purity D_2. However, electrolysis of D_2O by the Thales Nano H-cube® offers direct and rapid access to high purity D_2 gas and is applicable across the suite of reduction chemistries discussed above affording highly flexible incorporation of deuterium. Hsieh et al. have demonstrated this in the deuteration of a series of *trans*-chalcones (**52**) of interest for their antidiabetic activity (**Figure 17**) [48].

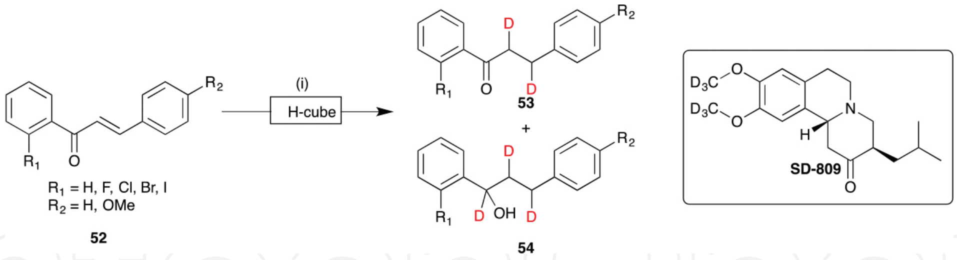


Figure 17. Deuteration of *trans*-chalcone and various derivatives. Reagents and conditions: (i) H-cube®, D_2O, 5% Pt/Al_2O_3, 100°C, 100 bar, 1 mL min^{-1}. Insert: chemical structure of SD-809.

Access to the required D_2-gas uses two separate inlet streams where the sample is introduced in an aprotic solvent and with D_2O electrolysis providing the required gas at which point the streams were combined and passaged over the deuteration catalyst (**Figure 18**).

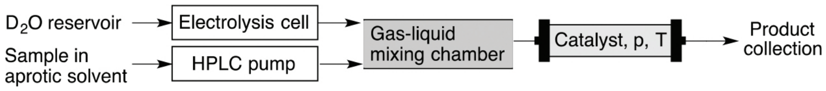


Figure 18. Schematic outline of the continuous flow reactor used to prepare deuterated compounds by Hsieh et al [48].

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The C2-halogen played a significant role in determining the ratio of di- to tri-deuterated species. With all analogues except the 2-F, conversions of ≥90% and exclusive formation of the di-deuterated species (**53**) were observed with 5% Pt/Al_2O_3. However with (*E*)-1-(2-fluorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one this catalyst afforded a 5:95 ratio of **53**:**54** with 97% conversion. Switching to the less active Pd/$BaSO_4$ catalyst afforded 100% conversion of the 2-F analogue, with a best ratio of 89:11 (**53**:**54**). The presence of the fluorine had a significant effect on the deuteration of this family of chalcones.

3.9. New catalysts

As further catalysts are developed for flow hydrogenation, the specificity and robustness of the chemical transformations achievable increase. Flow hydrogenation does require the use of a rare metal catalyst, which can be both expensive and potentially environmentally unsustainable. This negates the toxicity and disposal problems related to classical reducing agents and suggests that flow hydrogenation approaches may be expensive and not environmentally benign. This has led to the development of alternative hydrogenation catalysts such as carbon-supported iron-phenanthroline complexes, nickel nanoparticles, and FeNi alloys. These new catalysts show broad spectrum reductive capabilities (**Table 5**).

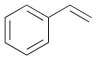
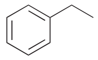
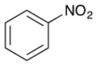
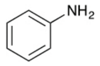
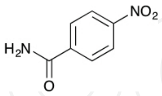
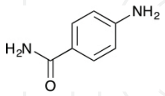
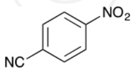
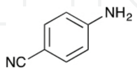
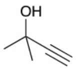
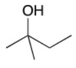
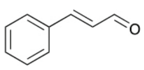
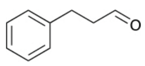
Catalyst	Starting material	Product	Conditions	References
1.9% Au/Al_2O_3	Substituted nitrobenzenes (6 examples)	Substituted anilines (6 examples)	60–110°C, 10–20 bar, 0.5 mL min^{-1}, 98–100%	[49]
Pd/C (3%) Bimodal and trimodal	Alkyne, aldehyde, and halogenated species	Various	60–110°C, 1 bar, 0.5 mL min^{-1}, 24–43 Selectivity 51–100%	[50]
ARP-Pt	Olefins (24 examples) and nitrobenzenes (9 examples)		Olefin yield not reported; nitro reduction up to 99%	[51]
			25°C, 5 bar, 2.0 mL min^{-1}, >99%	
			25°C, 15 bar, 1.5 mL min^{-1}, >99%	
Pd-Maghemite	Substituted nitrobenzenes (13 examples)	Substituted anilines	30°C, 1 bar, 0.5 mL min^{-1}, 86–98%	[52]
			30°C, 1 bar, 94%	
			30°C, 1 bar, 0.5 mL min^{-1}, 88%	
Designed porous structure reactor (DPSR) Al_2O_3-ZnO			60–80°C, 6 bar, 37 kg h^{-1}, >99%	[53]
Pd^0-AmP-MCF (heterogeneous Pd nanocatalyst supported on aminofunctionalized mesocellular foam)	Michael acceptors (14 examples)	Aldehydes and alcohols		[54]
			20°C, 1 bar, 1.5 mL min^{-1}, 94%	

Table 5. Use of novel catalysts in flow reduction reactions.

Dehydrohalogenation is a significant and ongoing concern in flow (and batch) reduction [55], and thus the development of new catalysts that specifically avoid this outcome is a valuable research tool. Osako et al. used platinum nanoparticles dispersed on an amphiphilic polystyrene-poly(ethylene glycol) (ART-Pt) resin as a catalyst was specifically developed to avoid reduction of –Cl, −C=O, and –CN moieties, e.g., **55a-56c** (**Figure 19**) [51].

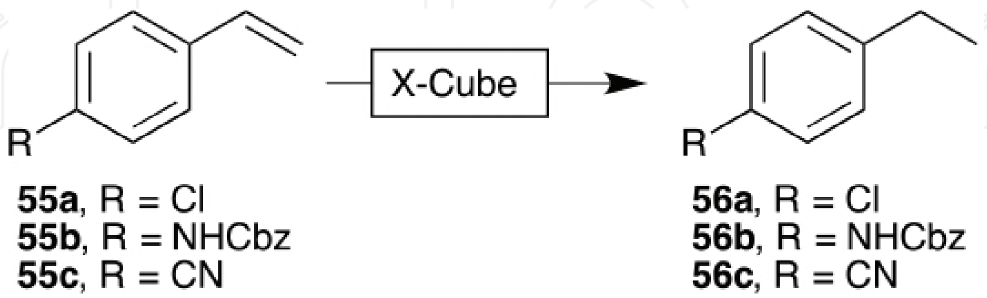


Figure 19. Alkene reductions via flow hydrogenation using the ARP-Pt catalyst. Reagents and conditions: X-cube®, H_2 (5 vol%), ARP-Pt (0.073 mmol Pt), EtOH (50 mM), 5 bar, 2mL min^{-1}.

Specialist catalyst development has often been targeted towards chemoselectivity. Fan et al. have shown that the Pd/triC catalyst was selectively reduced alkyne groups over nitro, bromo, and aldehyde groups [50]. While Rathi's palladium nanoparticles supported on maghemite were effective in reducing nitroarenes, azides, and alkenes in good to excellent yields [52].

Nagendiran et al. detail the use of aminofunctionalised mesocellular foam-supported nanopalladium in the conjugate reduction in a series of Michael acceptors [54]. Both the Vapourtec (1.0 mL min^{-1}, 0.1 M, 1 bar H_2, 20°C) and the H-cube (1.0 mL min^{-1}, 0.1 M, 40 psi H_2, 50°C) with this catalyst afforded chemoselective reduction in the olefin moiety. This approach was scalable enabling the selective reduction of cinnamaldehyde to 3-phenylpropanal on an approximately 20 g scale with no observed loss of catalysts' activity or selectivity.

4. Conclusions

The body of evidence continues to grow illustrating that flow methodologies, in particular flow hydrogenation, offer significant advantages over batch technologies in medicinal chemistry. Flow chemistry has been demonstrated to enhance yields, simplify reaction work up, improve safety, and allow in-line analysis. The coupling of modular flow systems has allowed automated and semiautomated high yield, low purification requirement synthesis of active pharmaceutical ingredients over multiple cascading steps.

Flow-based reductions continue to provide greater access to new chemical scaffolds for use in drug design and development as well as to provide efficient methods for the production of current pharmaceuticals.

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