

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



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

Cecilia C. Russell, Jennifer R. Baker,
Peter J. Cossar and Adam McCluskey

Additional information is available at the end of the chapter

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

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

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

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].

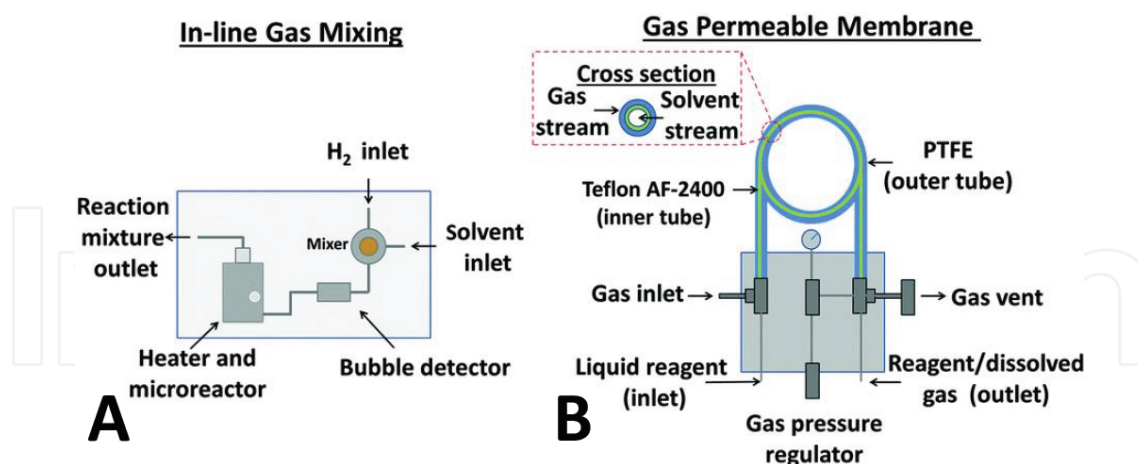


Figure 1. Schematic of the mechanical mixing setup in (A) the ThalesNano H-Cube[®] and (B) schematic of the gas permeable membrane (tube-in-tube) technology [1].

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 Gastro-pod Gas Liquid Module can be equipped with a small gas cylinder or attached to any custom flow systems [9, 10].

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].

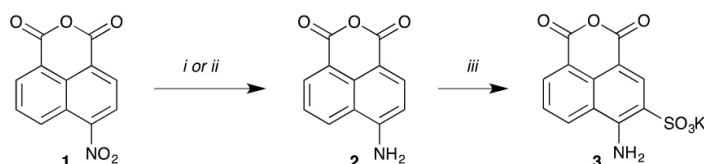


Figure 2. Synthesis of 1,8-naphthalimide derivatives. Reagents and conditions: (i) ThalesNano H-Cube®, 10% Pd/C, THF, 40°C, 10 bar, 1 mL min⁻¹, 2 cycles; (ii) SnCl₂, HCl, ethanol, reflux 2 h; (iii) (a) fuming sulfuric acid, 50°C, 3 h; (b) saturated aq. KCl, room temperature.

The utility of the flow nitro reduction extends across pyrrolidine, carboxylate ester, phenyl propanoate, benzothiophene, 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).

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).

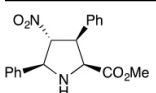
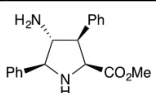
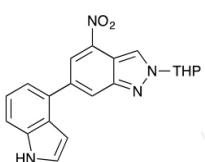
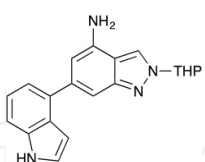
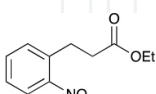
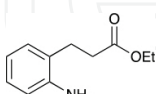
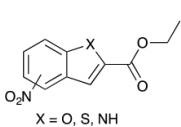
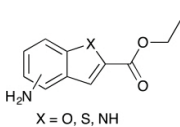
Starting material	Product	Yield	Catalyst	Conditions	References
		90%	Ra-Ni	65°C, 20 bar, 1.0 mL min ⁻¹	[14]
		100%	10% Pd/C	25°C, 1–30 bar	[15]
		100%	10% Pd/C	50°C, 1 bar, 1.0 mL min ⁻¹	[16]
		88–98%	10% Pd/C	40–60°C, 1 bar, 0.5–1.0 mL min ⁻¹	[17]

Table 1. Flow nitro reduction of selected analogues.

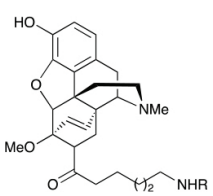
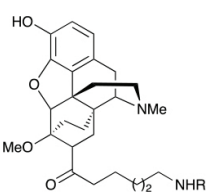
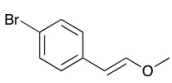
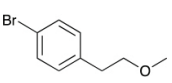
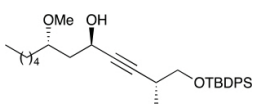
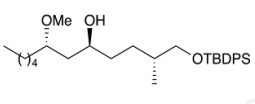
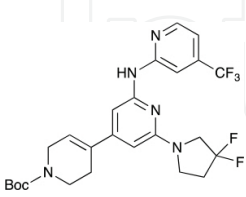
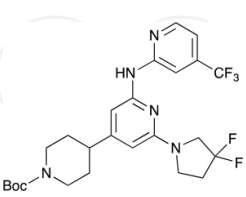
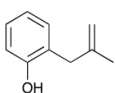
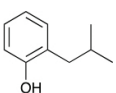
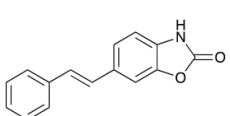
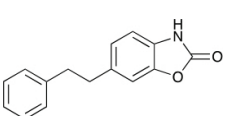
Starting material	Product	Yield	Catalyst	Conditions	References
		86%	10% Pd/C	25°C, 10 bar, recirculate 2 h	[18]
		21%	5% Rh/C	70°C, 1 bar, 1.5 mL min ⁻¹ , 3 cycles	[19]
		98%	10% Pd/C	40°C, 1 mL min ⁻¹	[20]
		84%	10% Pd/C	30°C, 40 bar, 1 mL min ⁻¹ , 2 cycles	[21]
		99%	RaNi	60°C, 60 bar, 1 mL min ⁻¹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

Table 2. Flow reduction of selected alkenes and alkynes.

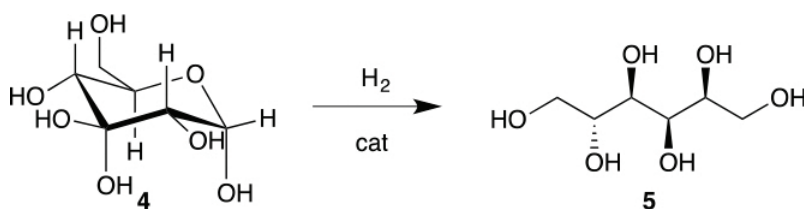


Figure 3. Reaction scheme for the hydrogenation of D-glucose (4).

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**).

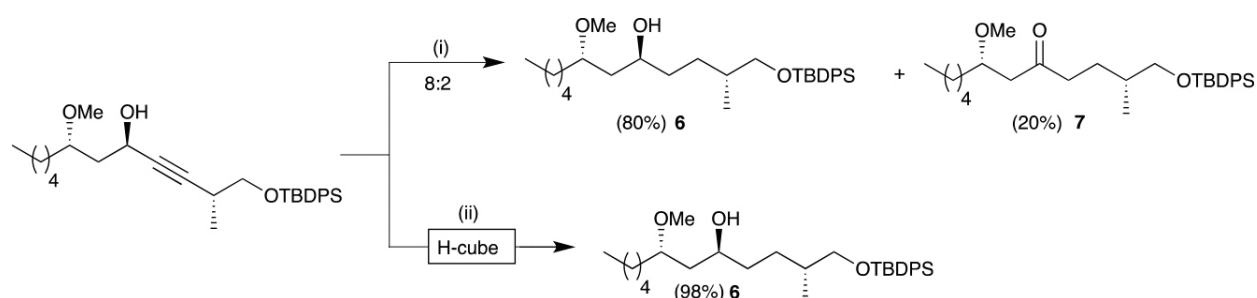


Figure 4. Synthesis of the marine macrolide sanctolide **6** via batch and flow hydrogenation. Reagents and conditions: (i) H₂, Pd/C (10%), EtOAc, rt, 8 h; (ii) H-cube[®], Pd/C (10%), MeOH, 40°C, 6 bar.

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 Wittig/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.

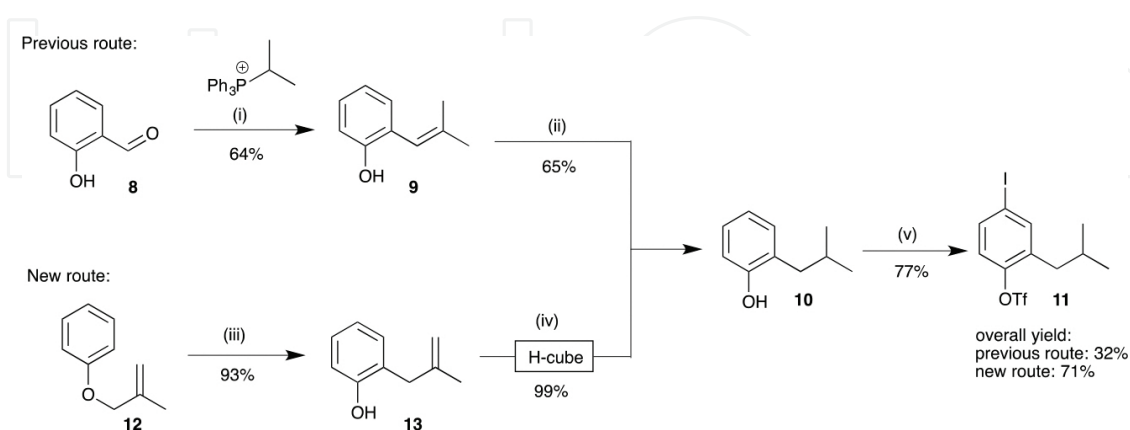


Figure 5. Improving the yield of a synthetic route from 32% to 71% with the aid of flow hydrogenation. Reagents and conditions: (i) salicylaldehyde, toluene, 80°C, 8 h; (ii) H₂, Pd/C, MeOH, 22°C, 3 h; (iii) DMAc, 190°C, 5 d; (iv) H-cube[®], Ra-Ni, 60°C, 60 bar; (v) (i) ICl, AcOH, 22°C, 24 h; (ii) Tf₂O, pyridine, 0°C, 2 h.

3.3. Reductive amination

Traditionally, borohydride reagents such as NaCNBH_3 , $\text{NaBH}(\text{OAc})_3$, 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% $\text{Pd}(\text{OH})_2/\text{C}$, with the temperatures and pressures used substrate-dependent [1]. However, the use of an $\text{Au}/\text{Al}_2\text{O}_3$ 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 $\text{Au}/\text{Al}_2\text{O}_3$ 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].

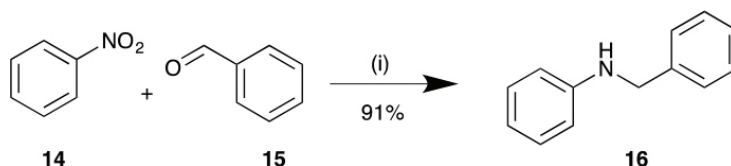


Figure 6. Flow reductive amination to afford *N*-benzylaniline **16**. Reagents and conditions: H-cube[®] Pro, 0.05 M **15** in EtOH, $\text{Au}/\text{Al}_2\text{O}_3$ (70 mm), 125°C , 10 bar, 0.3 mL min^{-1} .

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].

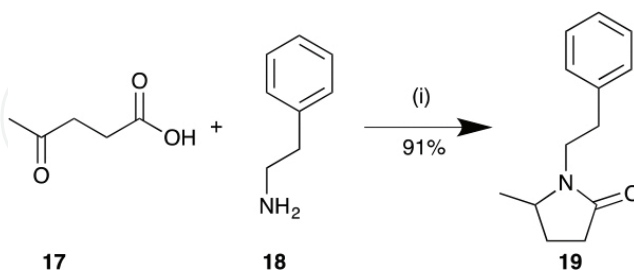


Figure 7. Flow reductive amination with carbon-supported Fe/Ni (C-Fe/Ni) to form pyrrolidine **19**. Reagents and conditions: H-cube[®] Pro, 0.025 M **18** in 2-methylfuran, C-Fe/Ni alloy (70 mm), 150°C , 85 bar, 0.3 mL min^{-1} .

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.

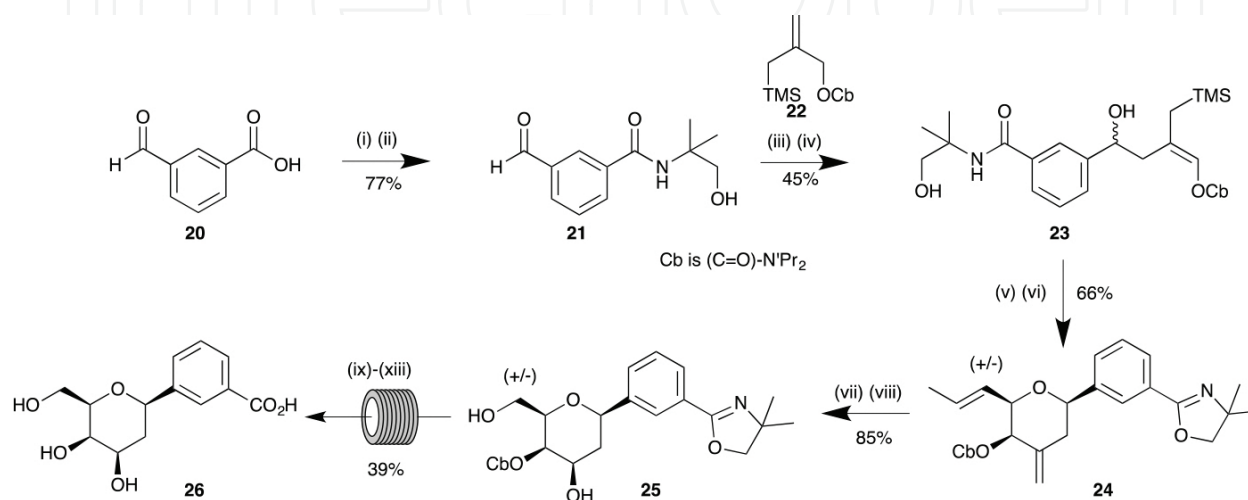


Figure 8. Synthesis of (D/L)-deoxy-β-galactopyranosyl-benzoic acid (**26**). Reagents and conditions: (i) SOCl_2 , toluene; (ii) $\text{H}_2\text{NC}(\text{CH}_3)_2\text{CH}_2\text{OH}$, CH_2Cl_2 ; (iii) *sec*-BuLi, TMEDA, Et_2O ; (iv) $\text{Ti}(\text{O}^i\text{Pr})_4$; (v) crotonaldehyde, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 ; (vi) MsCl, Net_3 , CH_2Cl_2 ; (vii) O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ then Me_2S ; (viii) NaBH_4 ; (ix)-(xiii) 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 $\text{S}_\text{N}\text{Ar}$ 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 $\text{S}_\text{N}\text{Ar}$ adducts of piperidine and morpholine (**27**) required no purification. Microwave coupling of 4-morpholinoaniline 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].

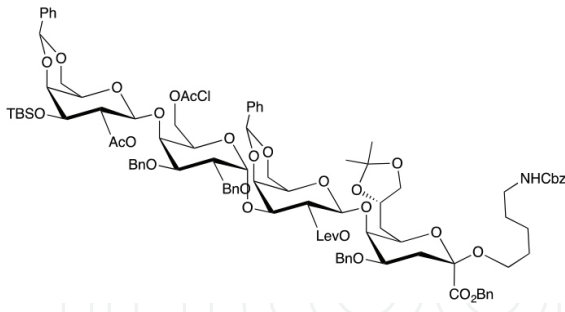
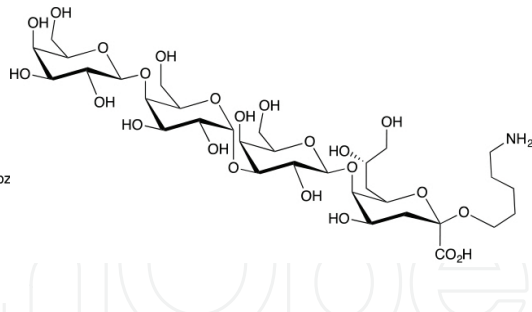
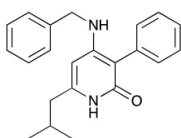
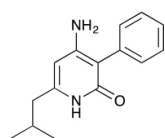
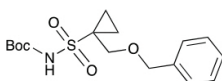
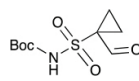
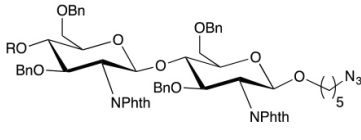
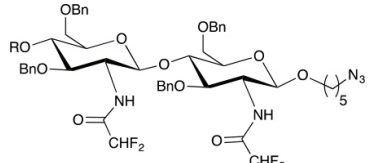
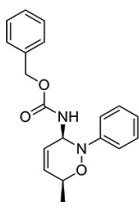
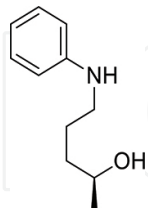
Starting material	Product	References
 <p>CBz protecting group</p>	 <p>20% Pd(OH)₂/C; 45°C, 10 bar, 1.0 mL min⁻¹, 1 cycle; 67%</p>	[30]
 <p>Benzyl protecting group</p>	 <p>10% Pd/C; 65°C, full H₂ mode, 1.0 mL min⁻¹, 1 cycle; 60%</p>	[31]
 <p>Benzoyl protecting group</p>		[32]
 <p>Phthalimide protecting group</p>	 <p>10% Pd/C; 50°C, 1 bar, 50°C, 0.5 mL min⁻¹; 56–81%</p>	[56]
 <p>Cbz protecting group</p>	 <p>10% Pd/C; RT, 1 bar, 50°C, 1.0 mL min⁻¹; 99%; 97% ee</p>	[57]

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 starting 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].

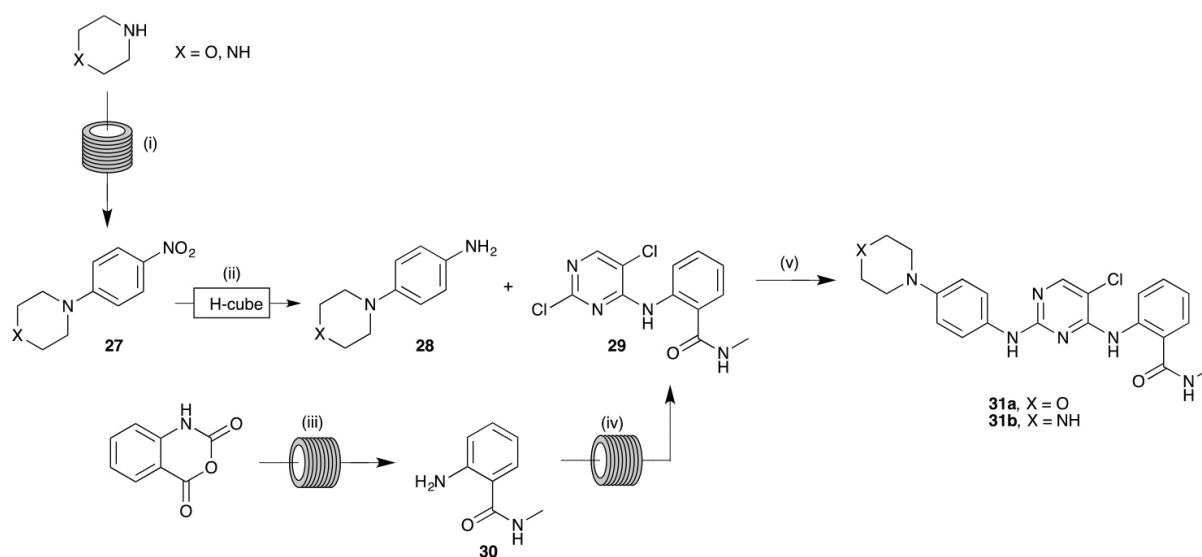


Figure 9. Synthesis of broad kinase inhibitors **31a** and **31b** by multistep flow synthesis. Reagents and conditions: (i) Vapourtec R2+, 4M piperidine or morpholine in DMF, 2 M 1-fluoro-2-nitrobenzene in DMF, 8 bar, 5 mL min⁻¹; (ii) H-CubePro, 0.05M in MeOH, 10% Pd/C CatCart® (70 mm), 50 bar, 50°C, 1.0 mL min⁻¹; (iii) Syrris FRX-100, 40% w/w aq. MeNH₂, 0.5 mL min⁻¹, 0–19°C, 19 h; (iv) Vapourtec R2+, 2,3,5-tri-chloropyrimidine, ⁱPrNEt, ⁱPrOH, 4 bar 100°C; (v) *n*-BuOH, 4 M HCl in dioxane (cat), 150°C, μ W, 20 min.

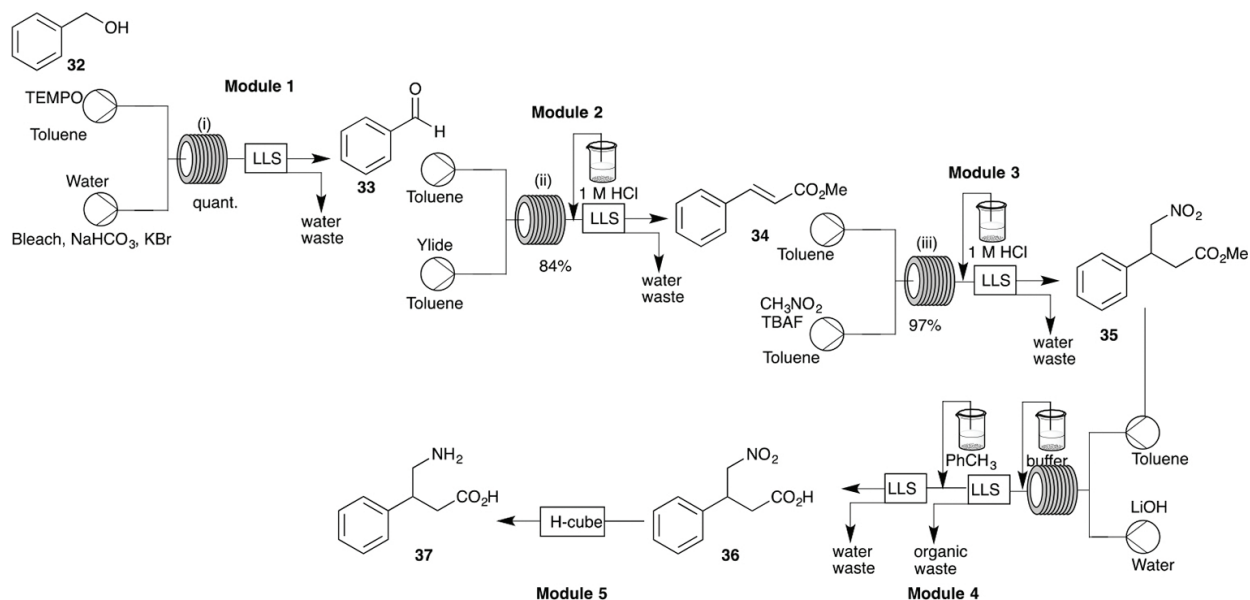


Figure 10. Divergent multistep flow synthesis of γ -amino acid derivatives. Reagents and conditions: (i) bleach (2.5 eq.), TEMPO (0.05 eq.), NaHCO₃ (0.3 eq.), KBr (0.2 eq.), 0°C; (ii) triethylphosphonoacetate (1.1 eq.), *t*BuOK (1.1 eq.), 50°C; (iii) CH₃NO₂ (11 eq.), TBAF (1.3 eq.), 50°C; (iv) H-cube®, 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.

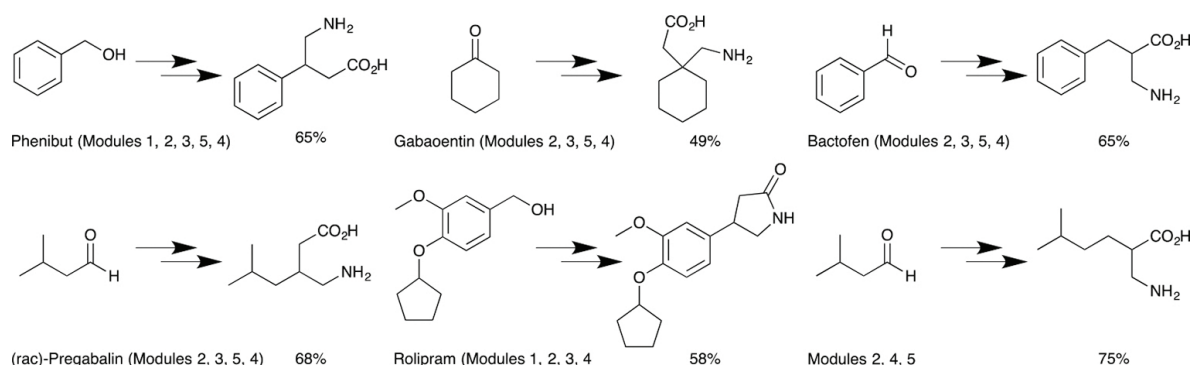


Figure 11. APIs prepared via the convergent multistep synthesis exemplified in **Figure 10**. Yields are reported for full processes without immediate purification over the 3–5 steps.

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).

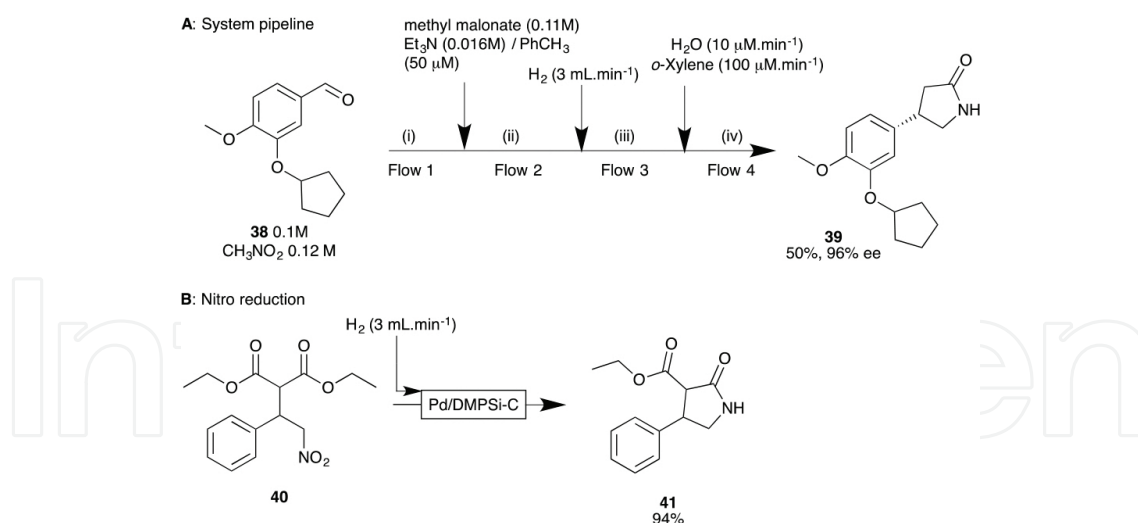


Figure 12. (A) Multistep flow synthesis of (*S*)-rolipram. Reagents and conditions: (i) Si-NH₂/CaCl₂, toluene, 75°C, 50 μ L min⁻¹; (ii) PS-(*S*)-Pybox, CaCl₂·2H₂O, 0°C, 100 μ L min⁻¹ (total); (iii) Pd/(DMPSi-C) (1.6 mmol), 100°C, 100 μ L min⁻¹ (total); (iv) HOOC-silica gel, 120°C, 210 μ L min⁻¹ (total). 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.

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].

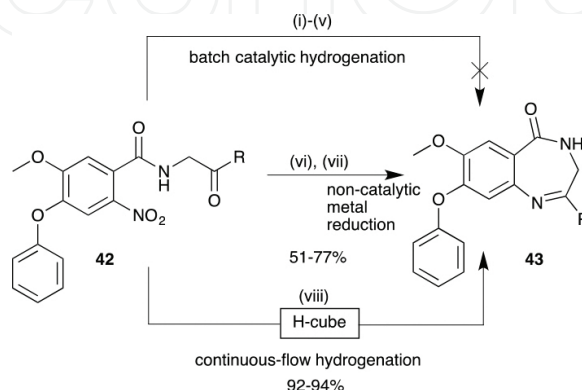


Figure 13. Synthesis of the desired 1,4-benzodiazepin-5-ones **43** via batch and flow hydrogenation. Reagents and conditions: (i) H₂, Pd/C (10%, 0.1 eq.), EtOAc:EtOH, 2:1 (0.03 M), 20°C, 1 atm; (ii) 1,4-cyclohexadiene (6 eq.), microwave mode, Pd/C (10%, 0.05 eq.), MeOH (0.1 M), 120°C; (iii) H₂, Ru/C (5%, 0.02 eq.), THF (0.03 M), 20°C, 1 atm; (iv) H₂, Ru/C (5%, 0.02 eq.), THF (0.03 M), reflux, 1 atm; (v) H₂, Ru/C (5%, 0.04 eq.), THF (0.03 M), 20°C, 1 atm; (vi) FeSO₄·7H₂O (10 eq.), NH₄OH, 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].

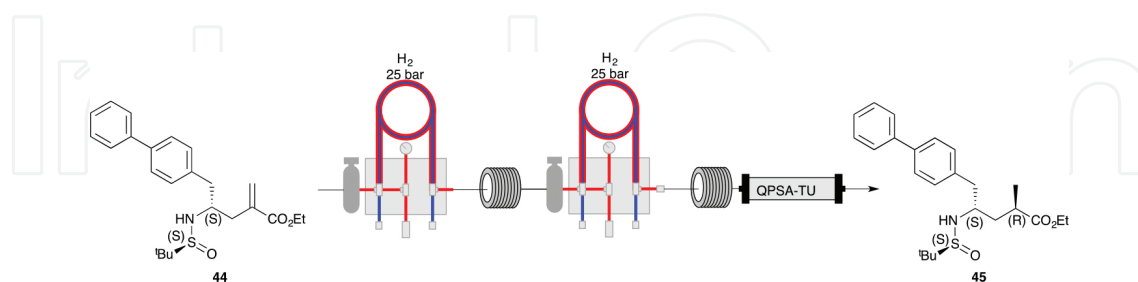


Figure 14. Enantioselective hydrogenation flow preparation of chiral ester **45**. Reagents and conditions: H₂, cat. DIPEA in EtOH (1 mol%), 20°C, 25 bar, 0.2 mL min⁻¹.

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].

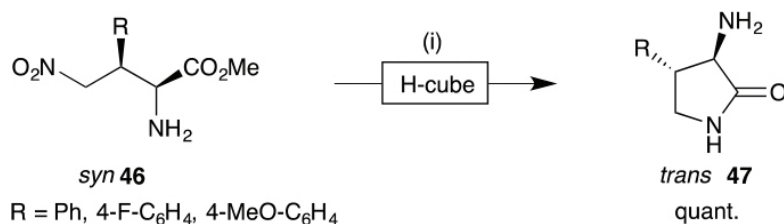


Figure 15. Formation of γ -lactams via flow hydrogenation. Reagents and conditions: (i) H-cube®, Raney Ni, MeOH (0.01 M), 65°C, 10 bar, 1.0 mL min⁻¹.

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			Rh(CO) ₂ (acac), 65°C, 25 bar, 0.6 mL min ⁻¹ , 69–94%	[45]
		11 examples		

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.

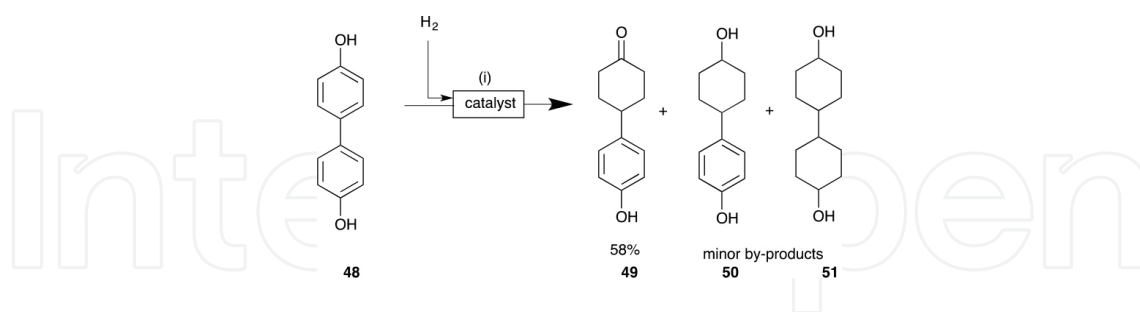


Figure 16. Selective continuous flow hydrogenation of 4,4'-biphenol **48**. Reagents and conditions: (i) H_2 (0.1 L min^{-1}), Pd/C (20%), EtOH/ H_2O (1:1 v/v, 0.05 M), 100°C , 5 bar, 1.0 mL min^{-1} .

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].

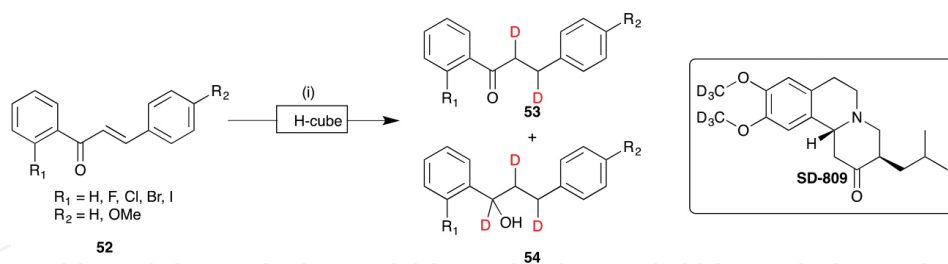


Figure 17. Deuteration of *trans*-chalcone and various derivatives. Reagents and conditions: (i) H-cube[®], D_2O , 5% Pt/ Al_2O_3 , 100°C , 100 bar, 1 mL min^{-1} . Insert: chemical structure of SD-809.

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**).

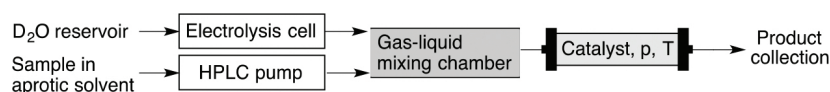


Figure 18. Schematic outline of the continuous flow reactor used to prepare deuterated compounds by Hsieh et al [48].

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 $\geq 90\%$ and exclusive formation of the di-deuterated species (**53**) were observed with 5% Pt/Al₂O₃. 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/BaSO₄ 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**).





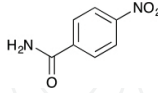
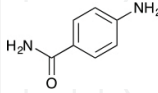
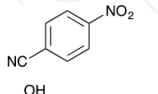
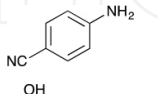


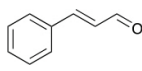
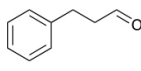
Catalyst	Starting material	Product	Conditions	References
1.9% Au/Al ₂ O ₃	Substituted nitrobenzenes (6 examples)	Substituted anilines (6 examples) ⁻¹	60–110°C, 10–20 bar, 0.5 mL min [49]	
Pd/C (3%)	Alkyne, aldehyde, and halogenated species	Various	60–110°C, 1 bar, 0.5 mL min ⁻¹ , 24–43 Selectivity	[50]
Bimodal and trimodal 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 ₂ O 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. Osaka 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].

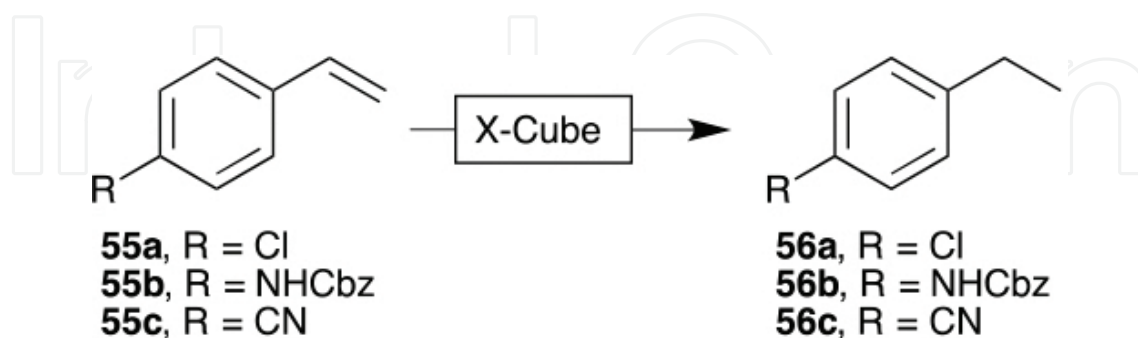


Figure 19. Alkene reductions via flow hydrogenation using the ARP-Pt catalyst. Reagents and conditions: X-cube®, H₂ (5 vol%), ARP-Pt (0.073 mmol Pt), EtOH (50 mM), 5 bar, 2 mL min⁻¹.

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 H₂, 20°C) and the H-cube (1.0 mL min⁻¹, 0.1 M, 40 psi H₂, 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.

Author details

Cecilia C. Russell, Jennifer R. Baker, Peter J. Cossar and Adam McCluskey*

*Address all correspondence to: Adam.McCluskey@newcastle.edu.au

Centre for Chemical Biology, Chemistry, School of Environmental Life Science, The University of Newcastle, Callaghan, New South Wales, Australia

References

- [1] Cossar PJ, Hizartzidis L, Simone MI, McCluskey A, Gordon CP. The expanding utility of continuous flow hydrogenation. *Organic and Biomolecular Chemistry* 2015;13:7119–7130.
- [2] Dormán G, Kocsis L, Jones R, Darvas F. A benchtop continuous flow reactor: a solution to the hazards posed by gas cylinder based hydrogenation. *Journal of Chemical Health and Safety* 2013;20:3–8.
- [3] Irfan M, Glasnov TN, Kappe CO. Heterogeneous catalytic hydrogenation reactions in continuous-flow reactors. *ChemSusChem* 2011;4:300–316.
- [4] Chandra BT, Zebrowski JP. Hazards associated with laboratory scale hydrogenations. *Journal of Chemical Health and Safety* 2015;23:1–10.
- [5] Hizartzidis L, Tarleton M, Gordon CP, McCluskey A. Chemoselective flow hydrogenation approaches to isoindole-7-carboxylic acids and 7-oxa-bicyclo[2.2.1]heptanes. *RSC Advances* 2014;4:9709–9722.
- [6] Jones RV, Godorhazy L, Varga N, Szalay D, Urge L, Darvas F. Continuous-flow high pressure hydrogenation reactor for optimization and high-throughput synthesis. *Journal of Combinatorial Chemistry* 2006;8:110–116.
- [7] Newton S, Ley SV, Arcé EC, Grainger DM. Asymmetric homogeneous hydrogenation in flow using a tube-in-tube reactor. *Advanced Synthesis and Catalysis* 2012;354:1805–1812.
- [8] Madarász J, Farkas G, Balogh S, Szöllősy A, Kovács J, Darvas F, Ürge L, Bakos J. A continuous-flow system for asymmetric hydrogenation using supported chiral catalysts. *Journal of Flow Chemistry* 2011;1:62–67.
- [9] www.cambridgereactordesign.com/Gastropod_online.html (accessed August 2016).
- [10] www.vapourtec.co.uk/products/eseriessystem/reactors (accessed August 2016).
- [11] www.thalesnano.com (accessed August 2016).

- [12] O'Brien M, Baxendale IR, Ley SV. Flow ozonolysis using a semipermeable Teflon AF-2400 membrane to effect gas - liquid contact. *Organic Letters* 2010;12:1596–1598.
- [13] Abdel-Hamid MK, Macgregor KA, Odell LR, Chau N, Matiana A, Whitting A, Robinson PJ, McCluskey A. 1,8-Naphthalimide derivatives: new leads against dynamin I GTPase activity. *Organic and Biomolecular Chemistry* 2015;13:8016–8028.
- [14] Ruiz-Olalla A, Retamosa MDG, Cossío FP. Densely substituted L-proline esters as catalysts for asymmetric Michael additions of ketones to nitroalkenes. *Journal of Organic Chemistry* 2015;80:5588–5599.
- [15] Down K, Amour A, Baldwin IR, Cooper AW, Deakin AM, Felton LM, Guntrip SB, Hardy C, Harrison ZA, Jones KL, Jones P, Keeling SE, Le J, Livia S, Lucas F, Lunniss CJ, Parr NJ, Robinson E, Rowland P, Smith S, Thomas DA, Vitulli G, Washio Y, Hamblin JN. Optimization of novel indazoles as highly potent and selective inhibitors of phosphoinositide 3-kinase δ for the treatment of respiratory disease. *Journal of Medicinal Chemistry* 2015;58:7381–7399.
- [16] Egle B, Munoz J, Alonso N, De Borggraeve W, de la Hoz A, Diaz-Ortiz A, Alcázar J. First example of alkyl–aryl Negishi cross-coupling in flow: mild, efficient and clean introduction of functionalized alkyl groups. *Journal of Flow Chemistry* 2014;4:22–25.
- [17] Lövei K, Greiner I, Éles J, Szigetvári A, Dékány M, Lévai S, Novák Z, Túrós GI. Multistep continuous-flow synthesis of condensed benzothiazoles. *Journal of Flow Chemistry* 2015;5:74–81.
- [18] Schembri LS, Stoddart LA, Briddon SJ, Kellam B, Canals M, Graham B, Scammells PJ. Synthesis, biological evaluation, and utility of fluorescent ligands targeting the μ -opioid receptor. *Journal of Medicinal Chemistry* 2015;58:9754–9767.
- [19] Bartolomé-Nebreda JM, Alonso de Diego SA, Artola M, Delgado F, Delgado Ó, Martin-Martin CM, Pena MA, Tong HM, Van Gool M, Alonso JM, Fontana A, Macdonald GJ, Megens A, Langlois X, Somers M, Vanhoof G, Conde-Ceide S. Identification of a novel orally bioavailable phosphodiesterase 10A (PDE10A) inhibitor with efficacy in animal models of schizophrenia. *Journal of Medicinal Chemistry* 2015;58:978–993.
- [20] Yadav JS, Suresh B, Srihari P. Stereoselective total synthesis of the marine macrolide sanctolide A. *European Journal of Organic Chemistry* 2015; 26: 5856–5863.
- [21] Patel S, Cohen F, Deans BJ, de la Torre K, Deshmukh G, Estrada AA, Sengupta AS, Gibbons P, Gustafson A, Huestis MP, Le Pichon CE, Lin H, Liu W, Liu X, Liu Y, Ly CQ, Lyssikatos JP, Ma C, Searce-Levie K, Shin YG, Solanoy H, Stark KL, Wang J, Wang B, Zhao X, Lewcock JW, Siu M. Discovery of dual leucine zipper kinase (DLK, MAP3K12) inhibitors with activity in neurodegeneration models. *Journal of Medicinal Chemistry* 2015;58:401–418.
- [22] Trobe M, Breinbauer R. Improved and scalable synthesis of building blocks for the modular synthesis of teraryl-based α -helix mimetics. *Chemical Monthly* 2016;147:509–521.

- [23] Bach A, Pizzirani D, Realini N, Vozella V, Russo D, Penna I, Melzig L, Scarpelli R, Piomelli D. Benzoxazolone carboxamides as potent acid ceramidase inhibitors: synthesis and structure-activity relationship (SAR) studies. *Journal of Medicinal Chemistry* 2015;58:9258–9272.
- [24] Gericke D, Ott D, Matveeva VG, Sulman E, Aho A, Murzin DY, Roggan S, Danilova L, Hessel V, Loeb P, Kralisch D. Green catalysis by nanoparticulate catalysts developed for flow processing? Case study of glucose hydrogenation. *RSC Advances* 2015;5:15898–15908.
- [25] Johnstone RAW, Wilby AH, Entwistle ID. Heterogeneous catalytic transfer hydrogenation and its relation to other methods for reduction of organic compounds. *Chemical Reviews* 1985;85:129–170.
- [26] Liu J, Fitzgerald A, Mani N. Reductive amination by continuous-flow hydrogenation: direct and scalable synthesis of a benzylpiperazine. *Synthesis* 2012;44:2469–2473.
- [27] Artiukha EA, Nuzhdin AL, Bukhiyarova GA, Zaytsev SY, Plyusnin PE, Shubin YV, Bukhtiyarov VI. One-pot reductive amination of aldehydes with nitroarenes over an Au/Al₂O₃ catalyst in a continuous flow reactor. *Catalysis Science and Technology* 2015;5:4741–4745.
- [28] Chieffi G, Braun M, Esposit, D. Continuous reductive amination of biomass-derived molecules over carbonized filter paper-supported FeNi alloy. *ChemSusChem* 2015;8:3590–3594.
- [29] Redpath P, Ness KA, Rousseau J, Macdonald SJF, Migaud ME. Facile access to new C-glycosides and C-glycoside scaffolds incorporating functionalised aromatic moieties. *Carbohydrate Research* 2015;402:25–34.
- [30] Laroussarie A, Barycza B, Andriaamboavonjy H, Kenfack MT, Blériot Y, Gauthier C. Synthesis of the tetrasaccharide repeating unit of the β-Kdo-containing exopolysaccharide from *Burkholderia pseudomallei* and *B. cepacia* complex. *Journal of Organic Chemistry* 2015;80:10386–10396.
- [31] Ng PS, Manjunatha UH, Rao SP, Camacho LR, Ma NL, Herve M, Noble CG, Goh A, Peukert S, Diagana TT, Smith PW, Kondreddi RR. Structure activity relationships of 4-hydroxy-2-pyridones: a novel class of antituberculosis agents. *European Journal of Medicinal Chemistry* 2015;106:144–156.
- [32] Alexandre F-R, Brandt G, Caillet C, Chaves D, Convard T, Derock M, Gloux D, Griffon Y, Lallois L, Liuzzi M, Loi AG, Moulat L, Musiu C, Parsy C, Rahali H, Roques V, Seifer M, Standing D, Surleraux D. Synthesis and antiviral evaluation of a novel series of homoserine-based inhibitors of the hepatitis C virus NS3/4A serine protease. *Bioorganic and Medicinal Chemistry Letters* 2015;25:3984–3991.
- [33] Russell CC, Lin AYS, Hains P, Simone MI, Robinson PJ, McCluskey A. An integrated flow and microwave approach to a broad spectrum protein kinase inhibitor. *RSC Advances* 2015;5:93433–93437.

- [34] Ghislieri D, Gilmore K, Seeberger PH. Chemical assembly systems: layered control for divergent, continuous, multistep syntheses of active pharmaceutical ingredients. *Angewandte Chemie, International Edition* 2015;54:678–682.
- [35] Tsubogo T, Oyamada H, Kobayashi S. Multistep continuous-flow synthesis of (R)- and (S)-rolipram using heterogeneous catalysts. *Nature* 2015;520:329–332.
- [36] Upadhyay K, Manvar A, Rawal K, Joshi S, Trivedi J, Chaniyara R, Shah A. Evaluation of structurally diverse benzoazepines clubbed with coumarins as *Mycobacterium tuberculosis* agents. *Chemical Biology and Drug Design* 2012;80:1003–1008.
- [37] Joseph CG, Wilson KR, Wood MS, Sorenson NB, Phan DV, Xiang Z, Witek RM, Haskell-Leuvano C. The 1,4-benzodiazepine-2,5-dione small molecule template results in melanocortin receptor agonists with nanomolar potencies. *Journal of Medicinal Chemistry* 2008;51:1423–1431.
- [38] Viviano M, Milite C, Rescigno D, Castellano S, Sbardella G. A continuous-flow synthesis of 1,4-benzodiazepin-5-ones, privileged scaffolds for drug discovery. *RSC Advances* 2015;5:1268–1273.
- [39] Lau SH, Bourne SL, Martin B, Schenkel B, Penn G, Ley SV. Synthesis of a precursor to Sacubitril using enabling technologies. *Organic Letters* 2015;17:5436–5439.
- [40] Conde E, Rivilla I, Larumbe A, Cossío FP. Enantiodivergent synthesis of bis-spiropyrolidines via sequential interrupted and completed (3 + 2) cycloadditions. *Journal of Organic Chemistry* 2015;80:11755–11767.
- [41] Bamborough P, Chung CW, Furze RC, Grandi P, Michon AM, Sheppard RJ, Barnett H, Diallo H, Dixon DP, Douault C, Jones EJ, Karamshi B, Mitchell DJ, Prinjha RK, Rau C, Watson RJ, Werner T, Demont EH. Structure-based optimization of naphthyridones into potent ATAD2 bromodomain inhibitors. *Journal of Medicinal Chemistry* 2015;58:6151–6178.
- [42] Yu X, Guttenberger N, Fuchs E, Peters M, Weber H, Breinbauer R. Diversity-oriented synthesis of a library of star-shaped 2*H*-imidazolines. *ACS Combinatorial Science* 2015;17:682–690.
- [43] Hattori T, Ida T, Tsubone A, Sawama Y, Monguchi Y, Sajiki H. Facile arene hydrogenation under flow conditions catalyzed by rhodium or ruthenium on carbon. *European Journal of Organic Chemistry* 2015;11:2492–2497.
- [44] Lau S-H, Galván A, Merchant RR, Battilocchio C, Souto JA, Berry MA, Ley SV. Machines vs malaria: a flow-based preparation of the drug candidate OZ439. *Organic Letters* 2015;17:3218–3221.
- [45] Brzozowski M, O'Brien M, Ley SV, Polyzos A. Flow chemistry: intelligent processing of gas-liquid transformations using a tube-in-tube reactor. *Accounts of Chemical Research* 2015;48:349–362.

- [46] Mullard A. Deuterated drugs draw heavier backing. *Nature Reviews Drug Discovery* 2016;15:219–221.
- [47] Katsnelson A. Heavy drugs draw heavy interest from pharma backers. *Nature Medicine* 2013;19:656.
- [48] Hsieh C, Ötvös S, Wu Y-C, Mándity IM, Chang F-R, Fulöp F. Highly selective continuous-flow synthesis of potentially bioactive deuterated chalcone derivatives. *ChemPlusChem* 2015;80:859–864.
- [49] Nuzhdin AL, Moroz BL, Bukhtiyarova GA, Reshenikov SI, Pyrjaev PA, Aleksandrov PV, Bukhtiyarov VI. Selective liquid-phase hydrogenation of a nitro group in substituted nitrobenzenes over Au/Al₂O₃ catalyst in a packed-bed flow reactor. *ChemPlusChem* 2015;80:1741–1749.
- [50] Fan X, Sans V, Sharma SK, Plucinski PK, Zaikovskii VA, Wilson K, Tennison SR, Kozynchenko A, Lapkin AA. Pd/C catalysts based on synthetic carbons with bi- and tri-modal pore-size distribution: applications in flow chemistry. *Catalysis Science and Technology* 2016;6:2387–2395.
- [51] Osako T, Torii K, Tazawa A, Uozumi Y. Continuous-flow hydrogenation of olefins and nitrobenzenes catalyzed by platinum nanoparticles dispersed in an amphiphilic polymer. *RSC Advances* 2015; 5: 45760–45766.
- [52] Rath AK, Gawande MB, Ranc V, Pechousek J, Petr M, Cepe K, Varma RS, Zboril R. Continuous flow hydrogenation of nitroarenes, azides and alkenes using maghemite-Pd nanocomposites. *Catalysis Science and Technology* 2016;6:152–160.
- [53] Elias Y, von Rohr PR, Bonrath W, Medlock J, Buss A. A porous structured reactor for hydrogenation reactions. *Chemical Engineering and Process Intensification* 2015;95:175–185.
- [54] Nagendiran A, Sörensen H, Johansson MJ, Tai C-W, Bäckvall J-E. Nanopalladium-catalyzed conjugate reduction of Michael acceptors – application in flow. *Green Chemistry* 2016;18:2632–2637.
- [55] Hizartzidis L, Cossar PJ, Robertson MJ, Simone MI, Young KA, McCluskey A, Gordon CP. Expanding the utility of flow hydrogenation – a robust protocol restricting hydrodehalogenation. *RSC Advances* 2014;4:56743–56748.
- [56] Calle LP, Echeverria B, Franconetti A, Serna S, Fernández-Alonso MC, Diercks T, Cañada FJ, Ardá A, Reichardt NC, Jiménez-Barbero J. Monitoring glycan-protein interactions by NMR spectroscopic analysis: a simple chemical tag that mimics natural CH- π interactions. *Chemistry – A European Journal* 2015;21:11408–11416.
- [57] Pous J, Courant T, Bernadat G, Iorga BI, Blanchard F, Masson G. Regio-, diastereo-, and enantioselective nitroso-Diels–Alder reaction of 1,3-diene-1-carbamates catalyzed by chiral phosphoric acids. *Journal of the American Chemical Society* 2015;137:11950–11953.