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

3,900
Open access books available

116,000
International authors and editors

120M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the 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

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].

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
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].

![Image](image_url)

**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, 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).

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).
### Table 1. Flow nitro reduction of selected analogues.

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product</th>
<th>Yield</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>90%</td>
<td>Ra-Ni</td>
<td>65°C, 20 bar, 1.0 mL min⁻¹</td>
<td>[14]</td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>100%</td>
<td>10% Pd/C</td>
<td>25°C, 1–30 bar</td>
<td>[15]</td>
</tr>
<tr>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>100%</td>
<td>10% Pd/C</td>
<td>50°C, 1 bar, 1.0 mL min⁻¹</td>
<td>[16]</td>
</tr>
<tr>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>88–98%</td>
<td>10% Pd/C</td>
<td>40–60°C, 1 bar, 0.5–1.0 mL min⁻¹</td>
<td>[17]</td>
</tr>
</tbody>
</table>

### Table 2. Flow reduction of selected alkenes and alkynes.

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product</th>
<th>Yield</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td>86%</td>
<td>10% Pd/C</td>
<td>25°C, 10 bar, recirculate 2 h</td>
<td>[18]</td>
</tr>
<tr>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
<td>21%</td>
<td>5% Rh/C</td>
<td>70°C, 1 bar, 1.5 mL min⁻¹, 3 cycles</td>
<td>[19]</td>
</tr>
<tr>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td>98%</td>
<td>10% Pd/C</td>
<td>40°C, 1 mL min⁻¹</td>
<td>[20]</td>
</tr>
<tr>
<td><img src="image15" alt="Image" /></td>
<td><img src="image16" alt="Image" /></td>
<td>84%</td>
<td>10% Pd/C</td>
<td>30°C, 40 bar, 1 mL min⁻¹, 2 cycles</td>
<td>[21]</td>
</tr>
<tr>
<td><img src="image17" alt="Image" /></td>
<td><img src="image18" alt="Image" /></td>
<td>99%</td>
<td>Ra-Ni</td>
<td>60°C, 60 bar, 1 mL min⁻¹, 24 h</td>
<td>[22]</td>
</tr>
<tr>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
<td>Quant.</td>
<td>10% Pd/C</td>
<td>50°C, 1 bar</td>
<td>[23]</td>
</tr>
</tbody>
</table>
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).

Trope 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.
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$_2$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 Au/Al$_2$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](image-url) Flow reductive amination to afford N-benzylaniline 16. Reagents and conditions: H-cube$^{	ext{®}}$ Pro, 0.05 M 15 in EtOH, Au/Al$_2$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](image-url) Flow reductive amination with carbon-supported Fe/Ni (C-Fe/Ni) to form pyrrolidine 19. Reagents and conditions: H-cube$^{	ext{®}}$ 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/intermolecular Sakura condensation approach.

![Figure 8](http://dx.doi.org/10.5772/65518)

**Figure 8.** Synthesis of (D/L)-deoxy-β-galactopyranosyl-benzoic acid (26). Reagents and conditions: (i) SOCl₂, toluene; (ii) H₂N(CH₃)₂CH₂OH, CH₂Cl₂; (iii) sec-BuLi, TMEDA, Et₂O; (iv) Ti(O₂Bu)₄; (v) crotonaldehyde, BF₃·OEt₂, CH₂Cl₂; (vi) MsCl, Net₃, CH₂Cl₂; (vii) O₃, CH₂Cl₂/MeOH then Me₂S; (viii) NaBH₄; (ix) LiAlH₄, THF; (x) BnBr, TBAI, NaH, 15-crown-5, THF; (xi) MeI, MeNO₂; (xii) 20% KOH, MeOH; (xiii) H₂, 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 S₅Ar 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 S₅Ar 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].
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, iPrNEt, iPrOH, 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.), tBuOK (1.1 eq.), 50°C; (iii) CH$_3$NO$_2$ (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, 277).
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 μL min⁻¹; (ii) PS-(S)-Pybox, CaCl₂·2H₂O, 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.
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) 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%, 0.04 eq.), THF (0.03 M), reflux, 1 atm; (v) FeSO\(_4\), NH\(_4\)OH, EtOH, reflux; (vi) Fe (20 eq.), AcOH (0.1 M), 70°C; (vii) 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 \(\gamma\)-nitro-\(\alpha\)-amino esters with in situ cyclisation afforded, quantitatively, the corresponding \(\gamma\)-lactams (47) (Figure 15). Raney Ni hydrogenation (10 bar, 65°C) of the syn- diastereomer affords exclusively the trans- configuration with the anti-\(\gamma\)-nitro-\(\alpha\)-amino esters gave the cis diastereomer [40].
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.

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Starting material</th>
<th>Product</th>
<th>Conditions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azide reduction</td>
<td>10% Pd/C, RT, 1 bar, 1.0 mL min⁻¹</td>
<td>94% [41]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olefin reduction</td>
<td>10% Pd/C, 80°C, 60 bar, 2.0 mL min⁻¹</td>
<td>90% [42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De-aromatisation</td>
<td>10% Ru/C or 10% Rh/C, 75–100°C, 50 bar, 1.0 mL min⁻¹, 100%</td>
<td></td>
<td>[43]</td>
<td></td>
</tr>
<tr>
<td>Selective reduction</td>
<td>20% Pd/C, 100°C, 5 bar, 1.0 mL min⁻¹, 58%</td>
<td></td>
<td>[44]</td>
<td></td>
</tr>
<tr>
<td>Hydroformylation</td>
<td>Rh(CO)₂(acac), 65°C, 25 bar, 0.6 mL min⁻¹, 69–94%</td>
<td>11 examples</td>
<td>[45]</td>
<td></td>
</tr>
</tbody>
</table>

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) H₂ (0.1 L min⁻¹), Pd/C (20%), EtOH/H₂O (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 D₂ gas and catalytic H-D exchange reactions between H₂ and D₂O. 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 D₂. However, electrolysis of D₂O by the Thales Nano H-cube® offers direct and rapid access to high purity D₂ 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®, D₂O, 5% Pt/Al₂O₃, 100°C, 100 bar, 1 mL min⁻¹. Insert: chemical structure of SD-809.

Access to the required D₂-gas uses two separate inlet streams where the sample is introduced in an aprotic solvent and with D₂O 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 ≥90% and exclusive formation of the di-deuterated species (53) were observed with 5% Pt/Al₂O₃. However with (E)-1-(2-fluoro-phenyl)-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).

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Starting material</th>
<th>Product</th>
<th>Conditions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9% Au/Al₂O₃</td>
<td>Substituted nitrobenzenes (6 examples)</td>
<td>Substituted anilines (6 examples)</td>
<td>60–110°C, 10–20 bar, 0.5 mL min⁻¹</td>
<td>[49]</td>
</tr>
<tr>
<td>Pd/C (3%)</td>
<td>Alkyne, aldehyde, and halogenated species</td>
<td>Various</td>
<td>60–110°C, 1 bar, 0.5 mL min⁻¹, 24–43 Selectivity 51–100%</td>
<td>[50]</td>
</tr>
<tr>
<td>ARP-Pt</td>
<td>Olefins (24 examples) and nitrobenzenes (9 examples)</td>
<td>Olefin yield not reported; nitro reduction up to 99%</td>
<td>25°C, 5 bar, 2.0 mL min⁻¹, &gt;99%</td>
<td>[51]</td>
</tr>
<tr>
<td>ARP-Pt</td>
<td>Substituted nitrobenzenes (13 examples)</td>
<td>Substituted anilines</td>
<td>30°C, 1 bar, 0.5 mL min⁻¹, 86–98%</td>
<td>[52]</td>
</tr>
<tr>
<td>Designed porous structure reactor (DPSR)</td>
<td>Aldehydes and alcohols</td>
<td>60–80°C, 6 bar, 37 kg h⁻¹, &gt;99%</td>
<td></td>
<td>[53]</td>
</tr>
<tr>
<td>Pd²⁺-AmP-MCF (heterogeneous Pd nanocatalyst supported on aminofunctionalized mesocellular foam)</td>
<td>Michael acceptors (14 examples)</td>
<td>Aldehydes and alcohols</td>
<td>20°C, 1 bar, 1.5 mL min⁻¹, 94%</td>
<td>[54]</td>
</tr>
</tbody>
</table>

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](image_url)

**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, 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 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


