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The Use of Gases in Flow Synthesis

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- 'Tube in Tube' reactors
- Falling Film microreactors
- Microchannel reactors
Abstract

This review will highlight the potential benefits that can be leveraged by using flow chemistry to allow a safer and more efficient way of using gases in research. An overview of the different approaches used to introduce gases into flow reactors is presented along with a synopsis of the different gaseous reactions classes already successfully translated into flow.

Keywords

Gases; Flow Chemistry; Tube in Tube reactors; Membrane reactors; Synthesis.
**Introduction**

The use of toxic and dangerous gases is highly restricted and controlled in modern synthetic laboratories. Increased safety considerations, including precautionary limitations on their use at scale, are often mandated for gas processing operations. Understandably, for something as ethereal as a gas, which cannot be easily contained, leakages are very difficult to prevent when conventional synthetic equipment is used. Consequently, dedicated high pressure facility rooms are normally built specifically to enable access to gas based transformations. Pressurised gas reactions are normally continually monitored for leakage using specialised gas and/or pressure detectors, with personnel using such facilities having to undergo specialised training. Furthermore, restrictions on the scales of high pressure reactions are also put in place to mitigate risks, making the scale up of these reactions challenging.

**Alternative approaches**

The use of gas surrogates has been developed to circumvent the direct use of certain gases, with the *in situ* liberation of the required gas being the most common method. Several carbon monoxide precursors exists such as those derived from aldehydes,\(^1\) formyl saccharine\(^2\) and various metal carbonyls, such as Ni(CO)\(_4\),\(^3\) W(CO)\(_6\)\(^4\) and Mo(CO)\(_6\).\(^5\) Similarly, the use of transfer hydrogenation is often applied as a substitute for gaseous hydrogen, which can be delivered through a donor such as formic acid via a metal complex (e.g. Ru),\(^6\) often in association with diamine or phosphine ligands. It is also possible to use metal free hydrogen gas substitutes such as Hantzsch esters often promoted by the addition of an auxiliary organocatalyst.\(^7\) Additional gas substitutes for less common species have also been developed such as Selectfluor® (which acts as a F donor)\(^8\) and DABSO as a gaseous sulfur dioxide substitute.\(^9\) Even though these gas substitutes are useful for small scale chemistry, they often tend to be either too toxic,\(^10\) atom inefficient or too expensive to be used at larger scales.
Application of gases
One of the main limiting factors when pursuing a transformation using a gaseous component is establishing the required stoichiometry by solubilising sufficient quantities of the gas into the reaction media. The low solubility of certain gases like carbon monoxide (Table 1), often deems that high pressures are required, with the concentration of the dissolved gas also showing a rapid decrease with an increase in temperature, especially when the boiling point of the solvent is approached. Thus, following Henry’s law, when the reaction temperature is elevated, an increase in pressure is required to maintain the same concentration of dissolved gas.

Table 1: Solubility of carbon monoxide in selected solvents at 25 °C.\textsuperscript{11}

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Molar Volume</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{n}-Heptane</td>
<td>146.46</td>
<td>11.71 \times 10^{-3}</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>108.75</td>
<td>9.12 \times 10^{-3}</td>
</tr>
<tr>
<td>Methylcyclohexane</td>
<td>128.35</td>
<td>9.68 \times 10^{-3}</td>
</tr>
<tr>
<td>Toluene</td>
<td>106.86</td>
<td>7.59 \times 10^{-3}</td>
</tr>
<tr>
<td>Perfluoroheptane</td>
<td>227.33</td>
<td>17.11 \times 10^{-3}</td>
</tr>
<tr>
<td>Perfluorobenzene</td>
<td>115.79</td>
<td>1.35 \times 10^{-3}</td>
</tr>
<tr>
<td>Chloroform</td>
<td>80.94</td>
<td>7.94 \times 10^{-3}</td>
</tr>
<tr>
<td>Acetone</td>
<td>74.01</td>
<td>10.44 \times 10^{-3}</td>
</tr>
<tr>
<td>Methanol</td>
<td>40.73</td>
<td>9.24 \times 10^{-3}</td>
</tr>
<tr>
<td>Ethanol</td>
<td>58.68</td>
<td>8.26 \times 10^{-3}</td>
</tr>
<tr>
<td>\textit{n}-Propanol\textsuperscript{b}</td>
<td>74.79</td>
<td>7.36 \times 10^{-3}</td>
</tr>
<tr>
<td>\textit{i}-Propanol\textsuperscript{b}</td>
<td>76.55</td>
<td>7.89 \times 10^{-3}</td>
</tr>
<tr>
<td>Isobutanol</td>
<td>92.88</td>
<td>7.03 \times 10^{-3}</td>
</tr>
<tr>
<td>Dimethylformamide\textsuperscript{b}</td>
<td>77.04</td>
<td>1.82 \times 10^{-3}</td>
</tr>
<tr>
<td>Water</td>
<td>18.07</td>
<td>0.95 \times 10^{-3}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Concentration in moles per litre at 1 atm. partial pressure of carbon monoxide.
\textsuperscript{b} Measurements taken at 20 °C.
Continuous flow technology can provide many advantages over traditional batch synthesis.\textsuperscript{12} Firstly, the high heat and mass transfer rates which are possible when using small channelled fluidic systems enable reactions to be performed under a wider range of conditions, many of which are not accessible within conventional batch reactors. In the case of gas-liquid reactions a high interfacial area ($a$) is essential for an efficient mass transfer rate. Batch reactions performed in a traditional round bottom flask have much lower interfacial areas and this decreases with an increase in the size of the flask, Figure 1. \textit{Note: when the reaction is stirred, the vortex formed increases the interfacial area which also depends on the speed of mixing.} Table 2 shows some published interfacial areas for different reactors, showing much larger values for certain reactor types especially microchannel reactors ($a = 3400$-$18000$ m\textsuperscript{2}m\textsuperscript{-3}), with a maximum interfacial value of 18000 m\textsuperscript{2}m\textsuperscript{-3} for a 300 $\mu$m x 100 $\mu$m microchannel.\textsuperscript{13}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Radius $r$ (m) & 0.014 & 0.021 & 0.025 & 0.033 & 0.043 \\
Interfacial area $a$ (m\textsuperscript{2}m\textsuperscript{-3}) & 107 & 71 & 60 & 46 & 35 \\
\hline
\end{tabular}
\caption{Qualitative measure of interfacial area ($a$) for typical round bottom flasks when the liquid is static.}
\end{table}
Table 2: Published interfacial area for different gas liquid contactors.\textsuperscript{13}

<table>
<thead>
<tr>
<th>Type of contactor</th>
<th>$a \text{ (m}^2\text{m}^{-3}\text{)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bubble columns</td>
<td>50-600</td>
</tr>
<tr>
<td>Couette-Taylor flow reactor</td>
<td>200-1200</td>
</tr>
<tr>
<td>Impinging jet absorbers</td>
<td>90-2050</td>
</tr>
<tr>
<td>Packed columns, concurrent</td>
<td>10-1700</td>
</tr>
<tr>
<td>Packed columns, counter current</td>
<td>10-350</td>
</tr>
<tr>
<td>Spray column</td>
<td>75-170</td>
</tr>
<tr>
<td>Static mixers</td>
<td>100-1000</td>
</tr>
<tr>
<td>Stirred tank</td>
<td>100-2000</td>
</tr>
<tr>
<td>Tube reactors, horizontal and coiled</td>
<td>50-700</td>
</tr>
<tr>
<td>Tube reactors, vertical</td>
<td>100-2000</td>
</tr>
<tr>
<td>Gas-liquid microchannel contactor</td>
<td>3400-18000</td>
</tr>
</tbody>
</table>

A significant increase in the interfacial contact area can permit reactions that are not normally feasible under conventional batch synthesis conditions to be promoted in flow. In general, gases are easier to use in flow as their delivery can be regulated by dosing controlled flow volumes and using the higher internal pressures within the flow system to aid dissolution. Since flow technology also allows for coupling multiple connected reactors, the storing of chemicals is reduced together with shipping costs as intermediates needed for the desired product can potentially be synthesised and used directly in the next step without the need of isolation. Also hazardous chemicals, such as pyrophoric or air sensitive chemicals are much easier to use without the need for complicated precautions. Scale-up to production levels is potentially easily achieved by replicating the same reactor used for pilot plant experiments via a numbering-up approach or through prolonged running of the same reactor in a continuous manufacture scenario without any redesign in the set-up. Both approaches drastically reduce the transition time moving to scale and are thus financially beneficial.
**Approaches used in micro and meso gas-liquid flow reactions**

Microchannel reactors have been extensively used employing a biphasic flow regime most commonly segmented flow, where bubbles of a gas are separated by slugs of a liquid (Figure 2). The toroidal currents formed in both the liquid and gas segments enhance the mixing and increase mass transfer. Another approach, which also involves a gas and a liquid stream concurrently flowing together, is created by the introduction of a fast flowing gas stream injected at high pressures into a slower liquid flow (Figure 2). The velocity of the gas creates an annular flow (pipe flow) with the liquid being pushed against the boundary walls of the microchannels. The thin liquid layer again allows for a high interfacial contact area, with a decrease in the diffusion length.

A further reactor design based upon this same principle is the falling film microreactor, in which the liquid phase flows through microchannels under gravity to form a thin liquid layer. The gas input then flows co-currently or counter-currently to the liquid (Figure 3).

![Segmented Flow and Annular Flow Diagram](image-url)

**Figure 2:** Gas-Liquid flow regimes: Segmented Flow and Annular Flow.
Mesh microreactors have also used for gas-liquid flow reactions. This design makes use of a fine metal or ceramic mesh separating the liquid flow in the microchannels. The gas component is passed into the reactor and flows through the mesh to enter the liquid stream. The fine openings in the mesh (average pore size of 76 µm) allows for an increase in the gas-liquid interfacial contact area and the small gap separating the mesh and the microchannel allows for a very short diffusion length.

A related approach involves the use of a gas-permeable membrane system which spatially separates the liquid and the gas flows by creating a mono-directional barrier. Several such systems have been constructed making use of this reactor format, employing gas porous interleaved sheets, wafers or tubing. As an example the conventional ‘tube in tube’ design reported by the Ley group makes use of an amorphous fluoropolymer Teflon AF-2400...
membrane which has high permeability for gases but not liquids.\textsuperscript{18} The design enables the formation of micro-bubbles around the outer walls of the membrane tubing which are quickly dissolved into the traversing liquid flow (Figure 4). As a consequence of the large surface area and small cross sectional diameter of the Teflon AF-2400 tubing, gas diffusion across the membrane and into the inertia flow stream is extremely rapid. The Jensen group studied the diffusion phenomenon of several different configurations of the ‘tube in tube’ design involving the ‘conventional’ and reengineered ‘reverse’ designs (Figure 4).\textsuperscript{19} The reverse ‘tube in tube’ design, also known as the ‘on-demand’ design, is capable of being additionally heated to warm the liquid flow whilst also supplying the gas, whereas the conventional ‘tube in tube’ design can only be used to saturate the liquid flow with a gas at ambient temperature. Despite this limitation the simple assembly of the conventional ‘tube in tube’ design still make the set-up attractive. It can be easily constructed from commercially available amorphous fluoropolymer Teflon AF-2400 membrane tubing simply inserted into a length of wider bore PTFE tube and connected by the appropriate Swagelock\textsuperscript{®} unions. The corresponding reverse ‘tube in tube’ design is now available as a ready-made unit from several leading flow equipment suppliers.
Figure 4: ‘Tube in tube’ reactors. Conventional design with liquid flowing through the inner tube (Top). Reverse design with gas flowing through the inner tube (Bottom).

Different gases used in flow
As a consequence of all the new techniques developed for the easier introduction of gases to flow systems the area of gas-liquid reactions has become an increasing popular research topic. Several groups have made substantial progress in overcoming problems normally encountered when gases are used in batch as we will illustrate in the next sections.

Carbon monoxide
Carbon monoxide is a toxic (poisoning symptoms occur above 50 ppm concentration in air) and highly flammable gas that due to its limited solubility in most organic solvents (Table 1),
reactions employing it are most commonly carried out at elevated pressure. This makes the use of carbon monoxide a risk, especially in standard laboratories or when large quantities are needed. However, because it is a synthetically versatile and low cost building block, chemists have continued using it despite its associated hazards.\textsuperscript{20} Indeed, carbon monoxide is perhaps one of the most used gases and as such it is used in several industrial process such as the Fischer-Tropsch process,\textsuperscript{21} and alcohol formation through hydroformylation.\textsuperscript{22} Carbon monoxide is also routinely used for the conversion of aryl halides and pseudo-halides to higher oxidation level groups such as amides, esters, aldehydes and carboxylic acids (Schemes 1-9, 16 and Tables 3-5).

The Long group reported one of the first flow-carbonylation in 2006 as a safe and scalable way to make simple amides from iodobenzene (1a), 4-iodoanisole (1b) and 2-bromopyridine (1c) with benzyl amine as the substrate. A microfluidic reactor was used to combine the reactants and a base and the carbon monoxide was delivered in an annular flow regime.\textsuperscript{23} The reactions were compared with existing batch protocols and although the yields from the micro-flow system were only moderate (12-58\% yields of amide formed), were an improvement on those obtained in batch (11-25\% yields, Table 3). Of note was the α-ketoamide by-product, formed through over-carbonylation, which was also observed in some of the flow reaction conditions.

**Table 3:** Amino-carbonylation in micro-flow with benzylamine as the nucleophile.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Residence time</th>
<th>Yield of amide (%)</th>
<th>Yield of α-ketoamide (%)</th>
<th>Total yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>3.75 min</td>
<td>31</td>
<td>18</td>
<td>49</td>
</tr>
<tr>
<td>1a</td>
<td>7.5 min</td>
<td>37</td>
<td>17</td>
<td>54</td>
</tr>
<tr>
<td>1a</td>
<td>15 min</td>
<td>46</td>
<td>9</td>
<td>55</td>
</tr>
<tr>
<td>Batch</td>
<td></td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>1b</td>
<td>3.75 min</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>1b</td>
<td>7.5 min</td>
<td>10</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>1b</td>
<td>15 min</td>
<td>12</td>
<td>28</td>
<td>40</td>
</tr>
<tr>
<td>Batch</td>
<td></td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>1c</td>
<td>3.75 min</td>
<td>46</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>1c</td>
<td>7.5 min</td>
<td>51</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>1c</td>
<td>15 min</td>
<td>58</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>Batch</td>
<td></td>
<td>18</td>
<td>0</td>
<td>18</td>
</tr>
</tbody>
</table>

Ryu et al. later published a flow carbonylation protocol for aryl iodides and phenylacetylene in ionic liquids such as [BMIm]PF₆ which can function as a recyclable reaction media and catalyst support. The results were again compared to the analogous batch reactions, and demonstrated higher yields when performed in flow (Scheme 1). Furthermore, the palladium-catalysed carbonylative Sonogashira coupling yielded only the acetylenic ketone when performed in micro-flow but also formed the Sonogashira coupled by-product when run under batch conditions. When diethylamine was used as the nucleophilic partner, the micro-flow procedure gave a mixture of the amide (14) and the α-ketoamide (15) the latter being the main product (95:6 – 87:13, 15:14). This was in drastic contrast to what was observed by the Long group who instead obtained the amide as the main product. This was probably due to the higher pressures used in the Ryu plug flow system (15-20 atm) which allows for a greater concentration of dissolved carbon monoxide in the solvent giving a higher proportion of the double addition α-ketoamide product.
Scheme 1: Palladium-catalysed carbonylative coupling of aryl iodides and phenylacetylene in flow.

The specific conditions leading to the formation of the \( \alpha \)-ketoamides was studied by the Buchwald group in an attempt to avoid its generation.\textsuperscript{25} As would be expected it was concluded that in a micro-flow reactor either elevating the temperature or decreasing the pressure increases the selectivity for the formation of the amide with carbon monoxide added as an annular flow.

The Long group additionally reported on the use of flow carbonylation for the synthesis of amides comprising radiolabelled \( ^{11}\text{CO}.\textsuperscript{26} In this reaction, a triphasic reaction system utilising a silica-supported palladium diphosphine catalyst was employed as a packed bed reactor, produced...
by loading the catalysts into a length of Teflon tubing. Very good yields were achieved for electron deficient bromo-arenes (99% yield, 3 examples) but much lower yields were obtained for the more challenging electron rich systems (23-26%, 2 examples). This would correlate well with the need for longer reaction times for electron rich systems which would be difficult to achieve in the low residence time reactor assembled for this study.

Miller et al. showed that the use of a chip based microfluidic system with an annular CO flow profile could be used to rapidly screen for ligand activity in amino-carbonylations. A simple coupling between iodobenzene \(1a\) and benzylamine \(2\) was used as a standard test reaction.\(^{27}\) A total of eight different catalysts were screened across a range of temperatures varying from 75 °C to 150 °C using very short residence times (2 min). Generally catalysts performed better as the temperature was increased, with \(\text{PdCl}_2(\text{dppf}), \text{PdCl}_2(\text{dppp}), \text{PdCl}_2(\text{Biphenphos}), \text{PdCl}_2(\text{DPEphos}), \text{PdCl}_2(\text{Synphos})\) and \(\text{Pd(PPh}_3)_4\) giving good GC yields (>75%) at 150 °C whereas \(\text{PdCl}_2(\text{BINAP})\) still only gave 45% GC yield even at the highest temperature of 150 °C. The best pre-catalyst was found to be \(\text{PdCl}_2(\text{Xanthphos})\) which gave 94% GC yield at the higher temperature range and was found to give even an 85% GC yield at 75 °C.

The Ryu group described their continuing studies of carbonylation chemistry expanding into radical carbonylation of aliphatic halides.\(^{28}\) They employed a microfluidic flow system with the carbon monoxide delivered through a simple T-piece connector (Table 4). It was shown that using the radical initiator V-65 [(2,2′-azobis(2,4-dimethylvaleronitrile), half-life time: 12 min at 80 °C] in the presence of 1-bromododecane (16), tributyltin hydride and carbon monoxide at 80 °C, full conversion of the 1-bromododecane was achieved in 12 minutes, with a 77% isolated yield of tridecanal (17). The same continuous micro-flow system was also used with silicon-
based hydride donors delivering various aldehydes, unsymmetrical ketones and a δ-lactam all in
good to excellent yields.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Substrate/Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate" /></td>
<td>0.02 M in toluene, Bu₃SnH (1.2 equiv.), V-65 (10 mol%), CO 83 atm 12 min</td>
<td><img src="image2" alt="Substrate" /> 17, 77%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate" /></td>
<td>0.02 M in toluene, Bu₃SnH (1.2 equiv.), V-65 (10 mol%), CO 85 atm 12 min</td>
<td><img src="image4" alt="Substrate" /> 19, 66%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate" /></td>
<td>0.02 M in toluene, Bu₃SnH (1.2 equiv.), V-65 (10 mol%), CO 85 atm 12 min</td>
<td><img src="image6" alt="Substrate" /> 21, 66%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate" /></td>
<td>0.05 M in toluene, Bu₃SnH (1.1 equiv.), V-65 (10 mol%), CO 79 atm 27 min</td>
<td><img src="image8" alt="Substrate" /> 23, 85% (E/Z = 9/100)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate" /></td>
<td>0.017 M in toluene, Bu₃SnH (1.5 equiv.), H₂C=CH-COCH₃ (4 equiv.), V-65 (10 mol%), CO 85 atm 29 min</td>
<td><img src="image10" alt="Substrate" /> 25, 78%</td>
</tr>
</tbody>
</table>
Table 4: Radical carbonylation in micro-flow system.

The de Mello group and collaborators reported a comparison between the use of annular flow and plug flow for amino-carbonylation reactions (Scheme 2).\textsuperscript{29} Even though the annular flow method was shown to be efficient, it was limited to short residence times (2-5 min). The plug flow method could enable longer residence times and had a reduced tendency to block the reactor due to formation of Pd black particulates during carbonylation. It was reported that the use of the Pd dimer [Pd\textsubscript{2}(\mu-I)\textsubscript{2}(P^\text{Bu}_3)\textsubscript{2}] served as an excellent pre-catalyst for aminocarbonylation being far superior to many other previously reported catalysts.
Scheme 2: Comparison between annular and segmented flow in amino-carbonylation system.

The amino-carbonylation of halogenated aryl carboxylic acids with various amines has also been reported by Csajági et al. using a commercial pressurised continuous flow reactor (Scheme 3). The substrates were passed through an phosphine immobilised version of \( \text{Pd}(\text{PPh}_3)_4 \) to generate moderate to good yields of a variety of amide products (27-39) which were prepared in very short residence times (~2 min).
Scheme 3: Amino-carbonylation of halogenated aryl carboxylic acids in flow using the X-cube™.

The use of a conventional ‘tube in tube’ configuration for carbonylation reactions was reported by the Ley group (Scheme 4). In this publication a selection of aryl iodides, bromides and vinyl iodides were tested, with most of the substrates giving good to excellent yields (62-93% yields, 14 examples). A solvent mixture of toluene, methanol and dimethylformamide was used. The methanol was utilised as the nucleophilic partner and the dimethylformamide was found to be beneficial for stabilising the palladium catalyst and thus preventing the formation of palladium
black. An in-line scavenger cartridge packed with polymer-bound thiourea resin was used to remove the palladium from the reaction mixture making the purification of the crude material easier. Furthermore a ReactIR detector was deployed in-line to monitor the carbon monoxide concentration in the flow stream. This was used to find the optimum pressure to give the highest carbon monoxide concentration in the liquid stream. The use of a second ‘tube in tube’ system under vacuum to remove the excess dissolved carbon monoxide as an in-line process was also described. The removal of residual carbon monoxide was also monitored using ReactIR. This is especially relevant for industrial processes that make use of carbonylation reactions facilitating detection and possible recycling of the excess gas.
Scheme 4: A) Methoxy carbonylation in flow using the ‘tube in tube’ reactor design. B) Use of in-line IR monitoring to determine concentration of dissolved carbon monoxide in solvent. C) Use of a second ‘tube in tube’ under vacuum to remove the dissolved carbon monoxide.

The use of a reverse ‘tube in tube’ configuration was exemplified by Leadbeater and co-workers for the carbonylation of several aryl iodides to give the alkoxy carbonylative products in...
excellent conversions (91-99%, 8 examples) (Scheme 5). The same group also published a carbonylative system where a plug flow system was used, and although it showed superior yields to the batch systems, it was still not as efficient as the reverse ‘tube in tube’ system.

Scheme 5: Alkoxy carbonylation of aryl iodides in flow using the reverse ‘tube in tube’ reactor.

The Ryu group devised an innovative use of the ‘tube in tube’ system (Scheme 6). Instead of directly dosing carbon monoxide to the inner gas-permeable tube, a mixture of concentrated sulfuric acid and formic acid was mixed to form carbon monoxide in situ (Morgan reaction), which was then shown to be available for Heck aminocarbonylation. Two flow streams were directed in a co-current flow configuration for the work described, however, no specific mention was made to acknowledge if the counter flow system was also trialled.

The same group published a similar protocol for the carbonylation of alcohols through the Koch-Haaf reaction. Again, concentrated sulfuric acid and formic acid were directly mixed with the substrate in a Hastelloy-made micromixer. The acid mixture forms carbon monoxide in situ through the Morgan reaction which in turn reacts with the carbocation formed after the elimination of the hydroxyl group. The authors showed that there were selectivity limitations and
the reaction in flow gave little improvement compared to batch protocols (Table 5). Additionally they also showed a multigram scale-up version for the synthesis of 1-adamantanecarboxylic acid 43 (Scheme 7).

**Scheme 6:** Aminocarbonylation of 40 in flow using the Morgan reaction in the reverse ‘tube in tube’ reactor.

**Table 5:** Comparison of Koch-Haaf reactions of adamantanol in microflow and batch.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reactor</th>
<th>Conditions</th>
<th>Product (yield)</th>
</tr>
</thead>
</table>
| 1     | ![Image](image1.png) | microflow | T: 20 °C  
        Flow rate (42/HCO₂H): 0.30 mL/min  
        Flow rate (H₂SO₄): 0.88 mL/min  
        Residence time: 2 min c  
        Residence time: 1.5 min d | ![Image](image2.png) | 43, 89% |
| 2     | ![Image](image3.png) | batch   | T: 15-20 °C  
        Addition time: 5 min  
        Reaction time: 2 min | ![Image](image4.png) | 43, 92% |
| 3     | ![Image](image5.png) | microflow | T: 20 °C  
        Flow rate (44/HCO₂H): 0.30 mL/min  
        Flow rate (H₂SO₄): 0.88 mL/min  
        Residence time: 2 min c | ![Image](image6.png) | 43, 82% (88:42) |
Scheme 7: Multigram scale flow synthesis of 1-adamantancarboxylic acid (43).

Recently, a conventional ‘tube in tube’ system was used to expand the scope of carbylilation reaction in flow such as aminocarbonylations (79-93%, 5 examples), alkoxyxcarbonylations (60-95%, 9 examples) and hydroxycarbonylations (58-100%, 5 examples) including some intra-molecular examples to form lactams and a lactone (95%, 3 examples).36 An interesting addition
was the use of a gaseous amine (dimethyl amine) in the hydrazine-promoted amino-
carbonylation process, achieved by coupling two conventional ‘tube in tube’ systems in series
(Scheme 8). In the initial screening, a higher concentration of substrates was investigated but this
gave low conversions, indicating that the reaction was limiting in at least one of the gases used.
An alternative set-up, where the substrates were directly passed through the ‘tube in tube’
reactors to saturate the streams was also tested but this showed low conversions. Eventually the
system set-up shown in Scheme 8 was used. This required the use of several back-pressure
regulators positioned at different locations within the set-up to stabilise the flow and to maintain
the required system pressure. Additionally, a small column packed with glass wool was
employed after the reactor to filter off any precipitate formed during the reaction, mainly
palladium black, which could lead to blocking of the final back pressure regulator.
Scheme 8: Aminocarbonylation in flow using two gases via conventional ‘tube in tube’ reactors.

A near stoichiometric (1.2 equiv.) amount of carbon monoxide was shown to be effective for the continuous flow Heck-carbonylation of 1-bromo-3,5-bis(trifluoromethyl)benzene (53). The reaction was promoted by PdCl$_2$(PPh$_3$)$_2$ as the catalyst with 1,4-bis(diphenylphosphino)butane (dppb) as the supporting ligand.$^{37}$ A kilogram-scale production of product 54 was successful when using a large tubular reactor ~900 mL (10.7 mm i.d. x 10 m) at 0.65 M concentration to produce a throughput of 1.86 kg/day while still maintaining the 99% yield originally obtained for the smaller scale reaction (Scheme 9). In addition, the flow deprotonation of allylsilane (55) to form a 1-silylallyllithium intermediate which was then carbonylated and quickly quenched with trimethylsilane chloride to furnish a dienol silyl ether 56 in excellent yield and $E/Z$ ratio: (93%, 97:3) was reported.$^{38}$ A comparison with the batch protocol indicated that the flow process was
more efficient and very straightforward to run (Scheme 10). The flow protocol was subsequently expanded to a wider selection of alkylsilanes and electrophiles all of which gave good to excellent yields and selectivities (77-88% yields, 91:9-97:3 (E/Z), 5 examples).

Scheme 9: Heck-carbonylation of bromide 45 in continuous flow.

Scheme 10: Formation, carbonylation and quenching of 1-silylallyllithium intermediate to give the dienol silyl ether in flow, also showing the comparison with the batch protocol.
A synthesis of a phenyl isocyanate starting from nitrobenzene (57) in flow was reported by Takebayashi and co-workers using carbon monoxide as a reductant (Scheme 11). The carbon monoxide was delivered at a 90° angle to the liquid flow through a T-piece connector, resulting in a segmented flow system, which was directed into a tubular reactor heated at 220 °C. The direct comparison of the corresponding batch protocol demonstrated that the flow procedure gave a higher yield, although the authors did not quantify the yield or how it was measured. It was shown that changing the inner diameter (i.d.) of the tubular reactor had a significant impact on the reaction efficiency. The use of a 1.0 mm i.d. tube reactor gave a lower yield than using a 0.5 mm i.d. tube reactor. This was explained as being due to a higher surface to volume ratio of the carbon monoxide with the liquid plug, thus a smaller inner diameter tube will give a higher concentration of dissolved carbon monoxide in the reaction mixture.

Scheme 11: Flow carboxylation of nitrobenzene to give phenylisocyanate 58.

**Hydrogen**

Hydrogen is another important synthesis gas. Hydrogenation reactions are frequently used in both research and at production scale, especially in the petrochemical industry to reduce alkenes and aromatic rings and in the food industry to reduce polyunsaturated fatty acids from vegetable oils to produce solid or semi-solid fats such as those found in margarine. Hydrogen also carries a
risk due to its high flammability and potential for extremely exothermic detonation. In addition, most hydrogenation reactions tend to be performed under high pressures; therefore the risk of using hydrogen is substantially increased. Hydrogenation reactions using heterogeneous and homogenous catalyst in continuous flow are well documented and have been extensively reviewed\textsuperscript{40} hence, this review will focus on a select set of publications which demonstrate some alternative approaches.

Thales Nano has developed several flow reactors, of which the H-Cube\textsuperscript{TM} series have been specifically tailored for the generation and direct use of heterogenous hydrogenation reactions in flow.\textsuperscript{41} The commercial units are now routinely used in various hydrogenation reactions. The system can also be automated to run in a high throughput manner, allowing multiple samples to be sequentially processed or various conditions to be screened.\textsuperscript{42} Alternatively, larger quantities can be produced through the use of longer production runs as well as using sequentially scaled reactors (H-Cube mini\textsuperscript{TM} $\rightarrow$ H-Cube\textsuperscript{TM} $\rightarrow$ H-Cube midi\textsuperscript{TM}).\textsuperscript{43}

Recently our group demonstrated the flow hydrogenation of various 2-nitroanilines using the H-Cube\textsuperscript{TM} to form reactive 1,2-diaminobenzene intermediates as part of the synthesis of riboflavine analogues (21-98\% yield, 8 examples), quinoxalinone analogues (4-98\% yields, 9 examples) and dibenzodiazepine derivatives (37-72\% yields, 11 examples) (Scheme 12).\textsuperscript{44} The regioselectivity of some of the products was not always optimal with a mixture of the two regioisomers being observed. However, importantly the short residence time (4-6 min) required for the hydrogenation step gave substantially less decomposition of the unstable diamine intermediates meaning this flow approach was beneficial.
Scheme 12: Synthesis of riboflavine, quinoxalinone and dibenzodiazepine analogues through a heterogeneous hydrogenation step.

A large scale hydrogenation has been conducted using the Corning® Advanced-Flow™ reactor. This multiple stacked chip reactor consists of a number of coupled units (15 glass
chips, total internal volume of 125 mL) with ‘heart cells’ to improve the flow of pumped slurries (Figure 5). The hydrogenation process was tested for the effect of temperature, residence time, hydrogen molar ratio, catalyst loading and concentration of reagents on conversion. The batch process gave excellent chemoselectivity (99%) but low conversion (<20%). Under the final optimised flow conditions an efficiency of 0.43 kg of product per hour could be processed which can be extrapolated to yield up to 200 tonnes per year with 98% conversion and 95% selectivity. Unfortunately, no details about the specific chemical transformation were given and thus the conversions, selectivity and productivity cannot be compared.

Figure 5: Glass fluidic modules used for the slurry hydrogenation.

A continuous flow homogenous hydrogenation of alkenes using a conventional ‘tube in tube’ reactor set-up was published in 2011 (Scheme 13) using hydrogen gas and [Ir(COD)(PCy3)]PF6 as the catalyst (Table 6). As a foresight to increasing the safety of the system when scaling up, several experiments were conducted to find a balance between a short residence time and sufficient hydrogen pressure to minimise the hydrogen excess and thus outgassing after the back pressure regulator. A total residence time of 93 seconds and a hydrogen pressure of 25 bar were deemed to be the optimised conditions. A degassing system was also
disclosed, which utilised a camera to evaluate bubble sizes for quantification of the amount of hydrogen gas remaining in the system. A standard digital photograph was taken and used to create a snapshot of the flow stream. This image was automatically pixelated and contrast controlled to enable counting of the void area (white in Figure 6) and solution filled area (Red in Figure 6). A calculation could then be performed to determine the proportion of gas bubbles and based upon the system pressure a good indication of the gas concentration could be derived.

**Figure 6**: Sudan red dye in DCM, lower image 1 is the photo and image 2 the pixelated rendering.
Scheme 13: Homogenous hydrogenation in flow using the ‘tube in tube’ reactor.

Table 6: Homogenous flow hydrogenation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conversion(^a)</th>
<th>Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[structure]</td>
<td>[structure]</td>
<td>100%</td>
<td>Quant.</td>
</tr>
<tr>
<td>2</td>
<td>[structure]</td>
<td>[structure]</td>
<td>100%</td>
<td>Quant.</td>
</tr>
<tr>
<td>3</td>
<td>[structure]</td>
<td>[structure]</td>
<td>100%</td>
<td>Quant.</td>
</tr>
<tr>
<td>4</td>
<td>[structure]</td>
<td>[structure]</td>
<td>100%</td>
<td>Quant.</td>
</tr>
<tr>
<td>5</td>
<td>[structure]</td>
<td>[structure]</td>
<td>100%</td>
<td>Quant.</td>
</tr>
<tr>
<td>6</td>
<td>[structure]</td>
<td>[structure]</td>
<td>100%</td>
<td>Quant.</td>
</tr>
<tr>
<td>7</td>
<td>[structure]</td>
<td>[structure]</td>
<td>100%</td>
<td>Quant.</td>
</tr>
<tr>
<td>8</td>
<td>[structure]</td>
<td>[structure]</td>
<td>100%</td>
<td>Quant.</td>
</tr>
</tbody>
</table>

\(^a\) Conversion to product based on \(^1\)H NMR spectroscopy  \(^b\) Isolated yield after removal of solvent

The Leadbeater group used \(\text{RhCl}(\text{PPh}_3)_3\) (Wilkinson’s catalyst) with a reverse ‘tube in tube’ reactor to perform a series of homogenous flow hydrogenation reactions (Scheme 14).\(^{47}\) Using
optimised conditions, substrates were screened to determine which functionalities were tolerated. Most of the alkenes gave good to excellent yields (77-99% yield, 11 examples) but certain functionalities were not tolerated such as an alcohol, which chelates with the metal complex, a diacetate functionality, which undergoes a Tsuji–Trost type reaction (elimination of one acetate moiety) followed by polymerisation and also an aldehyde moiety which underwent decarbonylation at the high temperatures used.\textsuperscript{48}

The reactor set-up for the transformations was very straightforward but required a diluent stream to prevent issues caused by precipitate blocking the back pressure regulator positioned at the exit of the reactor. Consequently, an additional stream of acetone was directed to mix with the reactor output stream via a T-piece, just after the second reactor and just before the back pressure regulator, this ensured any precipitate formed from the dimerisation of the catalysts or the formation of insoluble HRhCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} was solubilised. To evaluate the scalability of the reaction, 90.0 mmol of \textit{trans}-chalcone in 30 mL of DCM (3 M) was hydrogenated. This gave an excellent yield (99% yield) and corresponds to a throughput of 45 mmol h\textsuperscript{-1} under continuous operation.

![Scheme 14: The homogenous hydrogenation of alkenes using reverse configured ‘tube in tube’ reactors.](image)

The Ley group have demonstrated the asymmetric hydrogenation of tri-substituted olefins, having tested several homogeneous catalysts. UbaPhox (91) exhibited the highest reactivity and
selectivity. It was found that a set-up consisting of two ‘tube in tube’ reactors separated by a mixing chip, was optimal (Scheme 15). The second ‘tube in tube’ reactor replenishes the hydrogen needed to increase the diastereoselectivity of 92, with the mixing chip in between to ensure turbulent mixing of substrate and catalyst which was shown to improve conversion.

Scheme 15: Homogenous asymmetric hydrogenation of substrate 88 in continuous flow.

Syngas (carbon monoxide and hydrogen in a 1:1 mixture)
The mixture of carbon monoxide and hydrogen, normally in a 1:1 volumetric ratio, commonly known as syngas (synthesis gas), has been used in flow reactions by the Ley group. Initially, it was reported on simple styrene substrates to furnish mixtures of branched and linear aldehydes. Optimisation focused on the rhodium catalyst with [Rh(CO)₂(acac)] and triphenylphosphine giving the best conversion and selectivity. A solvent screen revealed that a 1:1 mixture of methanol/toluene was the most effective. In addition, temperature, flow rate, amount of ligand and pressure of the syngas used were systematically assessed. The reaction generally gave good yields (69-94%, 11 examples) and regioselectivities for the branched isomer (6:1 - 31:1).
Styrenes with electron-withdrawing substituents showed improved yields and regioselectivities compared to those possessing electron-donating groups, which was consistent with previous batch results (Scheme 16).

Scheme 16: Selective flow hydroformylation of styrenes.

**Carbon dioxide**
Carbon dioxide is normally used as a building block in synthesis by making use of its weak electrophilic characteristic. A flow procedure to trap carbon dioxide in the formation of carboxylate group has been developed. Grignard substrates were passed through a conventional ‘tube in tube’ reactor to deliver the carbon dioxide (Scheme 17). Optimum conditions were determined at 4 bar of carbon dioxide enabling near quantitative conversions even at moderate flow rates (0.4 mL/min, residence time = 42 s). A set of ten different carboxylic acids were prepared in good to excellent yields (75-100% yields), unfortunately, no examples using electron-withdrawing substituents were reported. An efficient ‘catch-and-release’ protocol was used to facilitate in-line purification of the carboxylic acid using a cartridge containing a polymer supported ammonium hydroxide species (A-900). Following trapping of the carboxylic acid, the cartridge was washed with THF to remove any unwanted organic impurities, then ‘released’ by treatment with a solution of formic acid in THF (1:9) to yield the pure carboxylic acid. Similarly,
the Rutjes group reported on the formation of benzoic acid through the hydroxycarbonylation of phenylmagnesium bromide in flow delivering a throughput of 0.52 g/h using a commercial (FlowStart Evo, Future Chemistry) pumping system.\textsuperscript{52}

\begin{center}
Scheme 17: Flow carboxylation of Grignard substrates using carbon dioxide.
\end{center}

The flow synthesis of Amitriptyline (94) using carbon dioxide in flow was reported by the Kirschning group.\textsuperscript{53} As part of the process development it was noted that excess carbon dioxide was possibly reacting with the \textit{n}-BuLi required for the second stage Parham cyclisation (Scheme 18). Ultimately, the excess carbon dioxide was removed by passing the liquid stream through a Teflon AF-2400 tube acting to degas the pressurised flow stream prior to adding the \textit{n}-BuLi and yielding the product in an isolated yield of 76\%. 
Scheme 18: The synthesis of Amitriptyline using carbon dioxide in flow.

A related transformation was performed by the Yoshida group, using \textit{in situ} generated organolithium species (Scheme 19).\textsuperscript{54} The organolithium intermediate formed by lithium halogen exchange was immediately trapped with carbon dioxide in an annular flow set-up. A stream of methanol quenched the excess \textit{n}-BuLi prior to collection of the product into a saturated sodium bicarbonate solution. Beneficially, the flow protocol did not yield any benzophenone or triphenyl methanol derivatives which are normally observed in the corresponding batch reactions. Using this set-up (Scheme 19), a selection of carboxylic acids were synthesised in good yields (59-89% yield, 13 examples) representing a range of different electronics which appear not to influence the carboxylic acid yield.
Scheme 19: Flow carboxylation of organolithiums using carbon dioxide.

A similar concept was later demonstrated by the Kappe group where they used lithium bis(trimethylsilyl)amide (LiHMDS) or lithium diisopropylamide (LDA) solutions to achieve the lithiation of terminal alkynes or heterocycles. The lithiation was shown to happen very rapidly (~0.5 seconds at room temperature) but they opted for a ~3 second residence time after which the lithiated substrate was carboxylated with carbon dioxide through a T-mixer. In order to stabilize the CO\textsubscript{2} flow, the gas was preheated at 65 °C before going through the mass flow controller (Scheme 20). Additionally a water quench was introduced before the back pressure regulator to dissolve any small amounts of precipitate formed during the reaction. Using the optimised conditions a number of alkynes were carboxylated generally giving very good yields (66-90% yields, 8 examples). A couple of examples gave no results due to problems encountered with the reactor clogging. The carboxylation of some additional heterocycle substrates was also demonstrated using the same set-up with LDA giving moderate to good yields (43-86% yields, 6 examples). Clogging issues were also observed despite the water quench but were overcome by changing to a dilution mixture of water and acetic acid (10:1).
Scheme 20: Flow set-up for the carboxylation of lithiated species using CO$_2$ gas.

The Jamison group have taken this approach a step further and shown the feasibility of quenching the intermediate lithium carboxylate with another organolithium to form unsymmetric ketones (Scheme 21). Peristaltic pumps were used to pump the organolithium species (kept between 0 and 20 °C due to their instability) at a low concentration (0.1 M in THF) to prevent issues of precipitation and potential reactor clogging. For some substrates, a degasser was used to remove the excess CO$_2$ before the organolithium quench to prevent symmetric ketone by-product formation. The sequence was shown to be general for most substrates giving good to excellent yields (40-92% yields, 18 examples).
Scheme 21: Flow set-up for the synthesis of unsymmetric ketones using CO₂ gas.

Another interesting transformation also reported by the Jamison group involves the synthesis of cyclic carbonates through a bromine-catalysed conversion of CO₂ and epoxides in continuous annular flow (Scheme 22). A mixture of N-bromosuccinimide (NBS) and benzoyl peroxide (BPO) was used to form bromine, which activates the epoxide to nucleophilic attack. Substrates with aliphatic and aromatic substituents generally resulted in good to excellent yields (72-90% yields, 7 examples) with moderate yields being achieved for substrates with olefinic substituents (51-58% yields, 3 examples). Even though the authors postulate that the alkene pendant group might be interfering with the active catalyst, they do not report any bromination occurring on the alkene.
Scheme 22: Micro-flow synthesis of cyclic carbonates through bromine-catalysed conversion of CO₂ and epoxides.

Recently the continuous flow synthesis of 2,4,5-trifluorobenzoic acid (96) was reported through the Grignard reaction of 2,4,5-trifluorobromobenzene (95) and subsequent CO₂ trapping (Scheme 23) using a falling film microreactor (FFMR) (Figure 3). The use of ethylmagnesium bromide as a Grignard exchange reagent was used due to the stability of the reagent, allowing the authors to conduct the reaction at 30 °C. As part of the study, the size of the T-mixer was investigated to avoid blockage of the system due to precipitation. An inner diameter of 1200 µm was found to be optimal which prevents clogging and still allows for efficient mixing. Although the authors describe an efficient way of forming the carboxylic acid through this set-up, the FFMR used has one drawback; the maximum flow rate is 0.83 mL/min and thus achieving high space-time yields is a challenge.
Scheme 23: Use of a FFMR for the synthesis of 2,4,5-trifluorobenzoic acid (96) as a continuous process.

The use of fluorine gas in flow
Fluorine gas is a very corrosive and hazardous gas. To minimise working volumes and enhance safety, flow protocols for fluorine gas started as early as the 1990s. Three basic reactor designs have been used. The falling film microreactor was the first one to be explored by researchers at the Institut für Mikrotechnik (IMM) in Germany. IMM also developed a microbubble reactor for conducting direct fluorinations in flow. In addition the Durham Fluorine Group has developed a continuous laminar flow reactor for fluorine based reaction chemistries. All three reactors are very similar in design to other gas-liquid flow reactors shown above (Figures 2-3). However, certain required modifications in terms of the construction materials used for the main reactor as well as for seals and contacts need to be carefully considered for their resistance to fluorine gas or oxidation.59

Direct fluorination of organic substrates
Flow protocols employing fluorine gas have been developed under two main headings, principally for either selectively fluorinating organic substrates or for performing oxidation
Within the former group the electrophilic fluorination of aromatic systems is relatively well represented in the literature. The substrate specificity varies widely from simple fluorination of toluene through to more advance aromatic systems possessing several electron donating groups where polyfluorination becomes an issue (Scheme 24). Likewise electron deficient aromatics and heteroaromatics including several benzaldehyde derivatives have also been investigated (Scheme 25).

**Scheme 24:** Continuous flow fluorination of several aromatic systems.
Scheme 25: Continuous flow fluorination of benzaldehydes.

The continuous flow fluorination of 1,3-dicarbonyl systems is reported to proceed with good selectivities and in good to excellent yields (68-91%, 9 examples). An investigation towards an industrial scale continuous flow fluorination of 1,3-dicarbonyl systems, revealed that a productivity of 200 g/h could be reached with a commercial flow reactor. This methodology was applied to the formation of 4-fluoro-3,5-dimethylpyrazole derivatives from the corresponding monofluorinated 1,3-diketo compound via condensation with hydrazine derivatives (Scheme 26).
Scheme 26: Two step flow synthesis of 4-fluoro-3,5-dimethylpyrazole derivatives through direct fluorination of 1,3-dicarbonyl substrates.

The continuous flow, direct fluorination, of various anilines has been reported by the Sandford group to yield the corresponding \( N,N \)-difluoroaniline products which were highlighted as versatile starting materials for additional synthesis (Scheme 27).\(^{64}\) A laminar flow reactor was used for these transformations to furnish the perfluoro products in moderate to good yields (54-71% yields, 4 examples). These were isolated in crude form after extraction with DCM and could be purified via silica chromatography. The authors remark that even though similar compounds are sometimes unstable and potentially explosive, these isolated products were stable enough for the work-up and purification procedure used albeit still treated as potential explosives.
Scheme 27: Continuous flow synthesis of N,N-difluoroanilines using fluorine gas.

**Fluorine as an oxidant**

The strong oxidising power of fluorine can be utilised in oxidations. A mixture of fluorine, water and acetonitrile rapidly forms the adduct HOF·MeCN which is a strongly electrophilic oxygen transfer agent (Scheme 28). However, as this is not a very stable compound at room temperature, forming it in flow and directly consuming it is highly desirable. An *in situ* flow generation method was used for the epoxidation of several alkenes in moderate to excellent yields (38-99% yields, 9 examples).65 Additionally, the oxidation of various amines (80-95% yields, 8 examples) and anilines (51-95% yields, 13 examples) to the respective nitro groups was also disclosed.66 The direct oxidation of alcohols was achieved by directly using fluorine as an oxidant without forming the HOF·MeCN adduct was also shown (Scheme 29).67
Scheme 28: The use of *in situ* generated HOF.MeCN in flow for the epoxidation of alkenes (top) and oxidation of amines (bottom).

![Scheme 28](image)

Scheme 29: Oxidation of secondary alcohols using fluorine gas in flow.

**The use of oxygen gas in flow**

With the recent move towards even more environmentally friendly and sustainable oxidation chemistry, metal oxidants like permanganate and chromium(VI) compounds are receiving less attention. Oxygen is however considered to be a good alternative either alone or in conjunction with various promoting catalysts.

As an early example, the Glaser-Hay coupling in continuous flow was reported by the Ley group, with oxygen being used to re-oxidise the copper catalyst. A conventional ‘tube in tube’
module was used to pre-saturate the solvent with oxygen which was then mixed with an additional liquid substrate stream containing the copper(I) complex and the terminal alkyne (Scheme 30). A polymer-supported thiourea scavenger cartridge was used post reaction to remove the copper catalyst from the flow stream with an additional polymer-supported sulfonic acid cartridge to sequester the $N,N,N',N'$-tetramethylethane-1,2-diamine (TMEDA) base facilitating direct in-line purification. A range of aromatic and aliphatic terminal alkynes gave 1,3-butadiynes in moderate to excellent yields (49-100% yields, 11 examples).

**Scheme 30:** Glaser-Hay coupling in continuous flow using oxygen to reoxidise the copper catalyst.

Oxygen has also used in continuous flow aerobic anti-Markovnikov Wacker oxidation. Optimisation of the reaction temperature, oxygen pressure and water content was performed to achieve a good conversion and selectivity towards the desired aldehyde product. The reaction was successfully performed on a selection of styrenes possessing both electron withdrawing as
well as electron donating groups, in good yield (56-80%, 12 examples) and good to excellent selectivities (from 77:2:14 to 92:2:3 [A:B:C – Scheme 31]). Some further optimisation on the set-up was performed to demonstrate a scale-up of the reaction (96 mmol over 6 h) with the addition of an extra ‘tube in tube’ reactor placed in series to achieve better oxidation of the copper catalyst (Scheme 31).

Scheme 31: Anti- Markovnikov Wacker oxidation of alkenes using oxygen in flow.

The air-promoted oxidation of 2-benzylpyridine derivatives to their corresponding 2-benzoylepyridines has been reported by the Kappe group employing propylene carbonate as a solvent (Scheme 32). A microreactor was used with oxygen (delivered as atmospheric air) added through a T-mixer to give plug flow with the gas addition being supplied through a mass-flow controller. A high temperature (200 °C) and low residence time (13 min) combination was used to give the oxidation products in good yields (69-83% yields, 3 examples).
Scheme 32: Aerobic oxidation of the 2-benzylpyridine derivatives to their corresponding 2-benzoylepyridines in flow.

The Kocsis group have made use of the X-Cube™ to deliver oxygen for a number of industrial relevant oxidations and N-alkylation reactions (Scheme 33). The oxidation of indoline and 1-phenylethanol were used for the optimisation reactions in continuous flow with a range of catalysts, oxidants, solvents, temperatures and flow rates being evaluated. Subsequently the derived conditions were used to convert a small collection of alcohol substrates to the corresponding ketones or aldehydes in good yields (80-92%, 8 examples). The optimisation of the N-alkylation reaction using alcohols was performed in moderate yields (47-64% yields, 6 examples) employing activated Raney nickel as a catalyst for the oxidation of the alcohol in a ‘borrowing hydrogen’ step. The intermediate imine formed, through the condensation of the amine and aldehyde, was then reduced by the ‘borrowed’ hydrogen.
Scheme 33: Oxidation of alcohols using oxygen in flow (top) and N-alkylation of alcohols using oxygen in continuous flow (bottom).

The Kirschning group have used oxygen gas delivered through a conventional ‘tube in tube’ reactor to oxidise allylic and benzylic alcohols using gold-doped superparamagnetic nanostructured particles as the catalyst (Scheme 34). The gold catalyst was immobilised on MAGSILICA® which facilitates inductive heating at medium frequency induction (25 KHz). Using this set-up no over-oxidation was observed which is encountered when the same process is conducted in batch. Unfortunately, this set-up worked best with benzene as the solvent as other solvents such as methanol, ethyl acetate, acetonitrile and dichloromethane did not give full conversion. Toluene gave full conversions but produced by-products derived from the oxidation of the methyl group, making the purification more difficult.
**Scheme 34:** Oxidation of allylic and benzylic alcohols using oxygen as the oxidant and gold-doped superparamagnetic nanostructured particles as catalysts under inductively-heated flow conditions.

The continuous flow synthesis of carboxylic acids through the aerobic oxidation of aldehydes was reported by the Favre-Réguillon group using a plug flow approach (Scheme 35).\textsuperscript{74} The process was run at ambient temperature with 5 bar of oxygen pressure without any added metal catalysts. This was claimed to cleanly (98% purity) generate the carboxylic acids in high yields (61-91% yields, 4 examples). The aerobic oxidation of the aldehydes goes through a free radical chain reaction to form the corresponding peracid which reacts with the remaining aldehyde to produce a tetrahedral adduct (similar to the Criegee intermediate in the Baeyer-Villiger reaction). The tetrahedral adduct then rearranges, through a migration of hydrogen or alkyl group from the aldehyde to give the corresponding carboxylate. The authors also described how through the use of EPR spectroscopy and spin trap methodology,\textsuperscript{75} they could show that their process goes through a free radical auto-oxidation pathway which was initiated by a trace amount of overoxidised aldehyde present in the starting materials at ppm levels.
Scheme 35: Metal free oxidation of aldehydes to form carboxylic acids using oxygen in flow.

The synthesis of functionalised phenols using aerobic oxidation of Grignard substrates has been reported as a continuous flow procedure again using a plug flow system to deliver the oxygen.\textsuperscript{76} The effect of temperature and system pressure were studied for the oxidation of phenylmagnesium bromide. Ultimately, a combination of 14 bar pressure and -25 °C was used to deliver a near quantitative conversion to the corresponding phenol in 3.4 minutes. These conditions were then applied to a wider range of Grignard reagents with electron-rich systems forming the corresponding phenols in moderate to good yields (57-87%, 13 examples). The corresponding electron-deficient substrates required elevated temperatures (-10 °C to 25 °C) but also gave comparable yields (53-81%). Some heteroaryl magnesium reagents were also tested, with thiophene and benzothiophene giving the ketone derivatives (24% and 32% yields respectively). Other heteroaryl magnesium reagents gave the expected phenol products (47-86% yields, 3 examples). This transformation was also utilised for the preparation of ortho-functionalised phenols in an integrated three-step continuous process using compressed air instead of pure oxygen (Scheme 36). A number of substrates were prepared with a residence time of 14 minutes in combined yields of 33-55% for the 8 examples studied.
Scheme 36: Integrated flow system for the synthesis of ortho-functionalised phenols using air in flow.

The C-H activation of indoles via a cross-dehydrogenative coupling was reported in a segmented flow reactor (Scheme 37). The oxygen has a similar role as in the earlier example of the oxidative Heck reaction reported in a dual-channel microreactor. During the optimisation phase the authors reported that better conversions were obtained when the reactor size was doubled and the flow rate was maintained rather increasing the residence time by decreasing the flow rates. This was highlighted as being due to better mixing in the segmented flow path when higher flow rates were applied, ensuring efficient palladium reoxidation. Using optimised conditions a number of vinyl indoles were synthesised in moderate to excellent yields (27-92%, 15 examples). The choice of solvent, DMSO, was based on the solubility of the palladium catalyst and its propensity to decrease palladium black formation which could ultimately block the tubular reactor. Although practical at these small lab scales the use of DMSO is not ideal for scale-up due to the difficulty of its removal and so this process would require reaction
reengineering before being more widely applicable. Additionally, the authors did not mention any use of back pressure regulators/pressure control, which would be essential to maintain a stabilised flow when scale up is required.

![Scheme 37: Pd(II)-catalysed cross-dehydrogenative Heck reaction using oxygen gas in flow as an oxidant to reoxidise the palladium catalyst.](image)

An iron-catalysed aerobic nitro-Mannich reaction was published by the Polyzos group which affords a direct $\alpha$-$C(sp^3)$-H functionalisation of $N$-aryl tetrahydroisoquinolines. The oxygen was delivered through a conventional ‘tube in tube’ reactor with a stainless steel tube reactor being used as a residence time unit and to heat the flow stream (Scheme 38). A back pressure regulator was placed just after the ‘tube in tube’ reactor which precludes in-line degassing. The reaction was quenched by dropping the liquid stream onto 2 equivalents of triethylamine which enabled isolation of the products in moderate to good yields after conventional purification (31-77%, 15 examples).
Scheme 38: Iron-catalysed aerobic nitro-Mannich reaction with oxygen gas as an oxidant in flow.

The biocatalytic production of catechols was demonstrated through a 2-hydroxybiphenyl 3-monooxygenase (HbpA) catalysed conversion of 2-hydroxybiphenyl to 3-phenylcatechol using a conventional ‘tube in tube’ to deliver an oxygen feed. Although the authors showed a number of optimisation steps to increase the gas transport into the solution, when the transformation was carried on an 80 mmol scale, only a 5% isolated yield was obtained, indicating that the enzyme catalyst employed was the limiting aspect of the process.

The use of oxygen in flow photochemistry has also been extensively reported. The addition of singlet oxygen to α-terpinene (141) to yield anthelmintic ascaridole (142) was realised using Rose Bengal as the sensitiser in a micro-chip reactor equipped with a 20 W tungsten lamp. The oxygen stream was introduced as a laminar flow (Scheme 39). A direct comparison of the flow process with the batch process using a 500 W tungsten lamp shows a higher yield obtained for the flow process (85% vs 67%) but a lower productivity for the flow reactor (1.5 mg/h vs 175 mg/h). On the other hand, as the flow process should have a linear scalability, higher productivities could be achieved by multiple reactors in parallel rather than direct reactor scaling.
**Scheme 39:** Micro-flow preparation of anthelmintic ascaridole 142.

Recently, the photo-oxidation of 4-substituted toluene derivatives was described using a microchip reactor and oxygen delivered as a segmented flow using 2-tert-butylanthraquinone (143) as a photosensitiser (Scheme 40). Even though the yields obtained in flow were comparable to batch (30-83% yields) much shorter reaction times were needed - between 12 and 36 h were needed to achieve similar yields in batch.

**Scheme 40:** Photo-oxidation of 4-substituted toluene derivatives using oxygen in micro-flow.

The oxidation of (-)-β-citronellol, using a borosilicate glass-loop microreactor with a diode array as a light source, was demonstrated in the synthesis of the fragrance rose oxide, with Rose Bengal as an oxygen sensitiser. However, the reaction time needed for reasonable conversion on a 1 mmol scale (400 min) was deemed too long for the reactor to be used for efficient scale up.
The use of a TiO$_2$ deposited photocatalyst within the channels of a flow microreactor has received attention for the oxidative degradation of para-chlorophenol,$^{85}$ toluene,$^{85}$ phenol$^{86}$ and methylene blue.$^{86}$ Other synthetically useful transformations were also reported such as the oxidation of $\alpha$-terpinene (141) to yield ascaridole (142),$^{87}$ oxidation of L-methionine to the corresponding sulfoxide,$^{87}$ for the oxidation of $\beta$-citronellol$^{88}$ and the oxidation of allylic alcohols for the synthesis of the antimalarial artemisinin (Scheme 41).$^{89}$ The concept of this reactor is similar to that of the ‘tube in tube’ reactors but employing a poly(dimethylsiloxane) (PDMS) membrane separating the two channels allowing oxygen to permeate through the membrane and saturate the reaction mixture (Figure 7).

Scheme 41: Flow photo-oxidation of allylic alcohols for the synthesis of artemisinin using a PDMS membrane reactor.
The photochemical rearrangements of an N-oxide moiety has been used for the synthesis of 4-substituted quinolone derivatives (Scheme 42). Oxygen was used as a triplet quench to suppress the [2+2]-dimerisation of the quinolones. This gave the desired quinolones (151-154) in good to excellent yields (72-99% yield, 4 examples), which were superior to the equivalent batch reactions. The flow reactor was built from a double coiled tubular reactor (Duran tube 7 mm, coil outer diameter: 75 mm, height: 200 mm, internal volume: 150 mL) placed in the middle of a Rayonet (RPR-100) photoreactor equipped with 16 lamps of fixed wavelength. The oxygen was bubbled through the solvent to pre-saturate the solution. The authors claimed this approach could be used to deliver gram scale quantities of products. They also used the same set-up for the
synthesis of quinolones with tethered alkenes at the 4-position which enabled subsequent intramolecular [2+2] cycloadditions.\textsuperscript{91}

\begin{center}
\begin{tabular}{c}
\chem{\text{X}} \chem{\text{R}} \chem{\text{Y}} \\
\text{N} \\
\text{O} \\
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{c}
\chem{X} \chem{R} \chem{Y} \\
\text{N} \\
\text{O} \\
\end{tabular}
\end{center}

\textbf{Scheme 42:} Photochemical rearrangement of N-oxides to quinolones.

The high solubility of molecular oxygen in supercritical carbon dioxide (scCO\textsubscript{2}) has been exploited in the oxidation of citronellol (155) using 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (TPFPP, 156) as a photosensitiser (Scheme 43).\textsuperscript{92} Oxygen was delivered through a Rheodyne dosage unit and mixed with the scCO\textsubscript{2} before mixing with a solution of 155 in dimethyl carbonate (DMC) (1:1 \textit{v:v}). The combined stream was then passed through a second micro-mixer before it was passed into a sapphire cell equipped with four 1000 lumen LEDs. Complete consumption of 155 was achieved with 52\% selectivity to 157 and 48\% to 158 at a flow rate of 0.1 mL/min (1:1 \textit{v:v} DMC:155), 1.0 mL/min of scCO\textsubscript{2} and 2 equivalents of O\textsubscript{2} at 180 bar. Although supercritical carbon dioxide was completely miscible with oxygen in all proportions used,\textsuperscript{93} it is not the ideal solvent for most organic compounds which can limit its use as a solvent for flow chemistry.\textsuperscript{94}
Scheme 43: Photo-oxidation of citronellol in flow using scCO₂.

The oxidation of citronellol has also been reported by the Seeberger group using oxygen in a segmented flow regime with tetraphenylporphyrin (TPP) as the photosensitiser. In their set-up (Scheme 44), the system could deliver up to 2.5 mmol/min of product. The same set-up was also used for the photo-oxidation of other substrates to show the scope of the method developed including the flow synthesis of the anti-malaria drug artemisinin. A modified version of this set-up using 420 nm LED lamps was subsequently applied to the transformation of amines to α-cyanoepoxides through an oxygen based oxidation (Scheme 45) and the photo-oxidative cyanation of secondary amines to give 161-163 and primary amines to give 164-167 using singlet oxygen (Scheme 46).
Scheme 44: Photo-oxidation of citronellol using oxygen in a segmented flow regime.

Scheme 45: Photo-oxidation of amines for the synthesis of α-cyanoepoxides.

Scheme 46: Photo-oxidative cyanation of primary and secondary amines using singlet oxygen.

The application of other gases in flow: Ozone
Like carbon monoxide and hydrogen, ozone is a very reactive and thus hazardous gas. Nevertheless, it is very atom efficient and has a high oxidative potential similar to that of...
chlorine making it useful for several transformations most commonly directed at the oxidative cleavage of alkenes. Flow chemistry offers a safer way for the use of ozone in the laboratory, which if optimised properly, can also be used at larger scales. An early example showcasing the proof of principle for O$_3$ oxidation in flow was demonstrated by the Jensen group. They described in detail how a multi-channelled microreactor was built up with 48 pressure drop regions and 16 reaction channels which ensures a uniform distribution of gas and liquids throughout the channels. The ozone was generated through an electric discharge in a commercial ozoniser from 95% O$_2$ balanced with 5% N$_2$. An annular flow was observed when the microreactor contained posts while a slug flow regime was obtained with microreactors containing no posts (Figure 8). Even though the report primarily concentrates on the engineering of the multichannel microreactor and its physical properties, the group demonstrated ozonolysis by exploring three model reactions: the oxidation of triethyl phosphite (Table 7), octylamine and 1-decene (Table 8).

![Microreactor with posts and Microreactor without posts](image)

Figure 8: Cross section of the microreactor showing a comparison of reactor with posts and reactor without posts under multiphase flow.
Table 7. Ozonolysis of triethyl phosphite in multichannel reactors with and without microfabricated posts.

<table>
<thead>
<tr>
<th>Microreactor</th>
<th>[P(OEt)$_3$] (mol/L)</th>
<th>O$_3$/O$_2$ (%)</th>
<th>Q$_G$ (sccm)$^a$</th>
<th>Q$_L$ (sccm)$^a$</th>
<th>No. of ozone equiv.</th>
<th>Contact time (s)</th>
<th>Conversion of reactant (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posts</td>
<td>0.247</td>
<td>5.6</td>
<td>2.5</td>
<td>0.05</td>
<td>0.51</td>
<td>1.25</td>
<td>48.1</td>
<td>95.1</td>
</tr>
<tr>
<td>Posts</td>
<td>0.247</td>
<td>5.76</td>
<td>3.8</td>
<td>0.05</td>
<td>0.79</td>
<td>0.83</td>
<td>81.0</td>
<td>94.9</td>
</tr>
<tr>
<td>Posts</td>
<td>0.247</td>
<td>5.87</td>
<td>4.7</td>
<td>0.05</td>
<td>1.00</td>
<td>0.67</td>
<td>97.0</td>
<td>98.1</td>
</tr>
<tr>
<td>Posts</td>
<td>0.247</td>
<td>6.06</td>
<td>9.1</td>
<td>0.05</td>
<td>1.99</td>
<td>0.35</td>
<td>100.0</td>
<td>98.2</td>
</tr>
<tr>
<td>Posts</td>
<td>0.247</td>
<td>5.96</td>
<td>9.3</td>
<td>0.10</td>
<td>1.00</td>
<td>0.34</td>
<td>100.0</td>
<td>98.7</td>
</tr>
<tr>
<td>No posts</td>
<td>0.244</td>
<td>6.02</td>
<td>1.3</td>
<td>0.0138</td>
<td>1.04</td>
<td>2.42</td>
<td>51.4</td>
<td>84.1</td>
</tr>
<tr>
<td>No posts</td>
<td>0.244</td>
<td>6.16</td>
<td>5.0</td>
<td>0.055</td>
<td>1.02</td>
<td>0.63</td>
<td>47.6</td>
<td>87.6</td>
</tr>
<tr>
<td>No posts</td>
<td>0.244</td>
<td>6.56</td>
<td>10.0</td>
<td>0.11</td>
<td>1.09</td>
<td>0.31</td>
<td>45.7</td>
<td>89.1</td>
</tr>
<tr>
<td>PTFE$^b$</td>
<td>0.247</td>
<td>5.53</td>
<td>5.0</td>
<td>0.05</td>
<td>1.00</td>
<td>0.63</td>
<td>23.6</td>
<td>86.3</td>
</tr>
</tbody>
</table>

$^a$ sccm – cm$^3$/min at standard conditions (273.15 K and 1 atm). $^b$ PTFE tubing 0.778 mm i.d. and 109 mm length (= inner volume of microreactor with posts). Q$_G$ = Gas flow rate; Q$_L$ = Liquid (ethyl acetate) volumetric flow rate.

Table 8. Oxidation of Amine and Alkene with multichannel microreactor with posts.$^a$

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Reactant concentration (mol/L)</th>
<th>O$_3$/O$_2$ (%)</th>
<th>Q$_G$ (sccm)$^a$</th>
<th>Q$_L$ (sccm)$^a$</th>
<th>No. of ozone equiv.</th>
<th>Contact time (s)</th>
<th>Conversion of reactant (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octylamine</td>
<td>0.105</td>
<td>6.16</td>
<td>10</td>
<td>0.088</td>
<td>2.99</td>
<td>0.32</td>
<td>98.7</td>
<td>79.7</td>
</tr>
<tr>
<td>1-decene</td>
<td>0.280</td>
<td>7.26</td>
<td>10</td>
<td>0.116</td>
<td>1.00</td>
<td>0.31</td>
<td>63.0</td>
<td>100.0</td>
</tr>
<tr>
<td>1-decene</td>
<td>0.280</td>
<td>7.39</td>
<td>10</td>
<td>0.0589</td>
<td>2.00</td>
<td>0.32</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>1-decene</td>
<td>0.280</td>
<td>6.63</td>
<td>10</td>
<td>0.035</td>
<td>2.99</td>
<td>0.32</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

$^a$ P(OEt)$_3$/EtOAc was added from the quencher inlet for consumption of remaining ozone and reduction of ozonide to produce aldehyde.

The use of a conventional ‘tube in tube’ reactor for ozonolysis in flow was later reported by the Innovative Technology Centre (ITC).$^{17b}$ A basic solvent screen to evaluate solubility was first performed by following the kinetics and efficiency of ozone bleaching of Sudan-red 7B, with methanol showing the fastest rate of bleaching. A number of alkene substrates were subsequently oxidised in good to excellent yields (57-95% yields, 11 examples) showing the scope of this
process in flow. To help with the purification process, the crude reaction mixture was immediately quenched using a polymer-supported triphenylphosphine reagent suspended in methanol. The same team also made use of flow ozonolysis as part of the synthesis of 7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (169). In this case the ozone was delivered through a T-mixer in a wavy-annular flow manner to a wide bore tube serving as a residence tube (Scheme 47). A similar system was also used as part of the flow-based synthesis of 2-aminoadamantane-2-carboxylic acid.

Scheme 47: Flow ozonolysis of substrate 168 as part of the formation of 7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde 169.

The use of a commercial flow ozonolysis reactor, the O-Cube™, was exemplified by the Kappe group (Table 9). The reactor could be operated at temperatures of between -25 °C to room temperature and at 0.2-2.0 mL/min flow rates. The instrument uses an O₂ gas cylinder which is connected to an inbuilt O₃ generator with the O₂ flow being supplied at a maximum flow rate of 20 mL/min. An internal analyser quantifies the O₃ generated which is then mixed with the substrate stream. For optimum temperature control, the stream of substrate was continuously cooled before and after being mixed with O₃. The ozonide formed is then quenched with a chemical quenching stream (i.e. triphenylphosphine) which is supplied via an independent pump to an in-line mixer. The ozonolysis of a number of styrene substrates was reported to give very
good yields (72-91%, 4 examples). The authors also showed the ozonolysis of \( \beta \)-pinene in 70% yield, 1,1-diphenylprop-2-yn-1-ol in 86% yield and octan-1-amine to give the corresponding nitroalkane in 73% yield.

**Table 9:** Flow ozonolysis using the O-Cube\textsuperscript{TM}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R\textsubscript{1}</th>
<th>R\textsubscript{2}</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Product (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>MeOH</td>
<td>25 °C</td>
<td>1 mL/min</td>
<td>NaBH\textsubscript{4}/MeOH</td>
<td>0.7 mL/min</td>
<td>90</td>
</tr>
<tr>
<td>b</td>
<td>Me\textsubscript{2}CO</td>
<td>0 °C</td>
<td>1 mL/min</td>
<td>5% H\textsubscript{2}O/Me\textsubscript{2}CO</td>
<td>0.7 mL/min</td>
<td>91</td>
</tr>
<tr>
<td>c</td>
<td>Me\textsubscript{2}CO</td>
<td>25 °C</td>
<td>1 mL/min</td>
<td>5% H\textsubscript{2}O/Me\textsubscript{2}CO</td>
<td>0.7 mL/min</td>
<td>84</td>
</tr>
<tr>
<td>d</td>
<td>Me\textsubscript{2}CO</td>
<td>15 °C</td>
<td>1 mL/min</td>
<td>5% H\textsubscript{2}O/Me\textsubscript{2}CO</td>
<td>0.7 mL/min</td>
<td>72</td>
</tr>
</tbody>
</table>
The routine use of flow ozonolysis in industrial application is still in its infancy but is certainly due to receive greater attention as alternative oxidation systems involving heavy metals such as chromic acid and permanganate salts become even less acceptable options. Some steps towards scaled use of ozone have already been conducted. For example, Lonza have built a continuous flow process for ozonolysis of some of their intermediates which is capable of processing over 0.5 tonnes of product per day.\textsuperscript{103} A set-up for bench scale flow ozonolysis was also devised which is an exact scale down of the plant system and uses a gas-liquid loop reactor equipped with a micro Venturi injector.

**The use of ammonia in flow**

The Paal-Knorr pyrrole synthesis using ammonia delivered through a conventional ‘tube in tube’ module and reacting with 1,4-diketones was reported to proceed efficiently as a continuous flow process (Scheme 48).\textsuperscript{104} The system was calibrated using an in-line titration of ammonia against bromocresol green as an indicator. This colorimetric indicator determined the ammonia concentration in the liquid flow and showed that a longer residence time and a lower temperature increases the ammonia concentration in the solvent. Additionally, an increase in ammonia concentration was observed when changing from dimethoxyethane to methanol as the reactor solvent.
Scheme 48: Continuous flow Paal-Knorr pyrrole synthesis using gaseous ammonia.

The synthesis of thioureas using gaseous ammonia in flow was also reported with excellent yields achieved from the corresponding isothiocyanates.\(^{104}\) A substrate scope was performed on both arylisothiocyanates (99% yields, 9 examples) and alkylisothiocyanates (99% yields, 6 examples). The protocol was then applied as part of the continuous flow synthesis of fenetizole (174) (Scheme 49).\(^{105}\)

Scheme 49: Continuous flow synthesis of fenetizole using ammonia gas.
**The use of ethylene in flow**

The palladium catalysed Mizoroki– Heck-type cross-coupling reaction of aryl iodides and ethylene gas for the formation of functionalised styrenes has been conducted as a continuous flow process.\textsuperscript{106} In the presence of the JohnPhos ligand and tetra-n-butylammonium iodide (TBAI) as an additive using 15 bar of ethylene led to the best conversions. Generally, good yields were obtained (43-85%, 10 examples) but substrates possessing an electron withdrawing group gave lower yields. In addition a small selection of aryl bromo substrates and heteroaryl iodides were tested but in general these failed to give good yields under the standardised conditions.\textsuperscript{50b} The method was used as part of the two-step telescoped process for the formation of predominately branched aldehydes through a Rh-catalysed hydroformylation of the intermediate styrenes (Scheme 50).\textsuperscript{50} A change in the co-solvent used, from $N,N$-dimethylformamide to methanol, resulted in a further improvement to the process and higher overall yields (68-95%, 9 examples) even for substrates that previously gave low yields.\textsuperscript{50b}
Scheme 50: Two-step telescoped process for the formation of predominately branched aldehydes through a Rh-catalysed hydroformylation of the styrenes using ethylene and Syngas in flow.

The [2+2] cycloaddition of the chiral cyclohexenone 175, with ethylene gas was demonstrated by the group of Kakiuchi (Scheme 51). The ethylene gas was delivered as a segmented flow stream through a FEP tube wrapped around a quartz immersion well with a 500 W medium pressure mercury lamp. The diastereomeric excess (d.e.) of the desired product 176, was found to be highly temperature dependent, consequently a cooling bath was used for the flow process to maintain the reaction temperature. At -78 °C a 52% d.e. was obtained in the flow process which was superior to the batch protocol (47% d.e.).
Scheme 51: [2+2] Photo-cycloaddition of the chiral cyclohexanone 175 using ethylene gas.

The use of diazomethane in flow
The continuous small scale generation and use of diazomethane in flow has attracted a significant amount of interest because of its synthetic utility as an efficient methylating agent coupled with its extreme explosive and toxic nature. The Kim group have devised a protocol for the in situ generation of diazomethane (182) from N-methyl-N-nitroso-p-toluenesulfonamide (diazald, 181) in the presence of KOH. The freshly prepared diazomethane is passively transported across a poly(dimethylsiloxane) (PDMS) membrane into a second parallel flow channel (Table 10) where it is immediately consumed in a reaction. A similar approach has also been used by the Kappe group to form α-chloroketone analogues as basic building blocks of antiretroviral agents in varying yield 55-82% (8 examples) over three steps (Scheme 52).
Table 10: Continuous *in situ* generation, separation, and reaction of diazomethane using a PDMS membrane reactor.

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Flow rate (µL/min)</th>
<th>KOH + Diazald flow rate (µL/min)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Daily output (mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Substrate Image]</td>
<td>4</td>
<td>10</td>
<td>![Product Image]</td>
<td>&gt;99</td>
<td>2.88</td>
</tr>
<tr>
<td>2</td>
<td>![Substrate Image]</td>
<td>1</td>
<td>4</td>
<td>![Product Image]</td>
<td>&gt;99</td>
<td>0.72</td>
</tr>
<tr>
<td>3</td>
<td>![Substrate Image]</td>
<td>1</td>
<td>4</td>
<td>![Product Image]</td>
<td>81</td>
<td>0.58</td>
</tr>
<tr>
<td>4</td>
<td>![Substrate Image]</td>
<td>1</td>
<td>4</td>
<td>![Product Image]</td>
<td>90</td>
<td>0.65</td>
</tr>
</tbody>
</table>

[a] Diazomethane was generated in the bottom channel by flowing solutions of diazald (1.0 M in DMF) and KOH (2.0 M in water containing 0.01% aliquat 336) with the same flow rate. Substrates were introduced to the top channel in DMF (0.5 M solution).
Scheme 52: Flow-synthesis of α-chloroketone analogues using in situ formed diazomethane delivered through a ‘tube in tube’ reactor.

The use of chlorine gas in flow
Chlorine gas is not normally encountered in many lab based synthetic transformation due to its toxicity and strong oxidising power. The use of chlorine in microflow allows for a safer way of using this dangerous gas in small quantities. The photochlorination of toluene-2,4-diisocyanate (190) has been demonstrated using a falling-film microreactor (FFMR) (Figure 3). The residence time was varied by changing the flow rate of the isocyanate 190 solution from 0.12 mL/min (equating to a residence time of 13.7 s) to 0.57 mL/min (4.8 s). As shown in Table 11 an increase in conversion from 30% to 81% was achieved at higher residence times but a lower selectivity for the desired product 191 was also observed (79% to 67% selectivity). The construction material for the FFMR was also studied. A microreactor made from iron instead of nickel was used to study the effect of a Lewis acid on the reaction (FeCl₃ is formed by chlorination of the iron plate) with a drop in selectivity towards the desired product (191) occurring (50% selectivity at 80% conversion) when such a microreactor was used.
Table 11: Photochlorination of toluene-2,4-diisocyanate (190) in a FFMR at various flow rates.α

<table>
<thead>
<tr>
<th>Flow rate (mL/min)</th>
<th>Conversion (%)</th>
<th>Selectivity of 191 (%)</th>
<th>Selectivity of 192 (%)</th>
<th>Space time yieldb (mol/L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td>81</td>
<td>67</td>
<td>5</td>
<td>321</td>
</tr>
<tr>
<td>0.23</td>
<td>55</td>
<td>80</td>
<td>5</td>
<td>401</td>
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<tr>
<td>0.38</td>
<td>41</td>
<td>79</td>
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<td>393</td>
</tr>
<tr>
<td>0.57</td>
<td>30</td>
<td>79</td>
<td>12</td>
<td>398</td>
</tr>
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α 32 microchannels (600 µm x 300 µm x 64 µm). b referred to the film volume in the microchannels.

The use of acetylene gas in flow
The direct use of acetylene gas has to our knowledge only been reported by the Zhang group in which they used it to prepare the ethynyl-Grignard reagent (193) which was further reacted with various carbonyls to form propargylic alcohols.111 A FFMR was used and after some optimisation, the authors reported a set of conditions, overcoming noted precipitation issues, which gave the desired propargylic alcohols in excellent yields and selectivities (Scheme 53). The highest impact on selectivity came from changing the flow rate, which was ascribed to the change in the thickness of the falling films which improves the gas-liquid contact and mass transfer. A change in the molar ratio of EtMgBr and aldehyde from 1:1 to 2:1 improved the
conversion from 57% to 100%. Ultimately, the optimised conditions were used to synthesis a number of propargylic alcohols which were obtained in excellent yields (87-96% yields, 17 examples) including an example which involved benzophenone, obtained in 58% yield.

Scheme 53: Synthesis of propargylic alcohol and analogues in micro-flow using acetylene gas delivered through a FFMR.

The use of formaldehyde in flow
Kunz and co-workers described the use of a conventional ‘tube in tube’ reactor in the synthesis of N-methylamino acids (NMOs). The two step synthesis of NMOs, originally described by Freidinger et. al., involves the formation of oxazolidinones which are then subjected to reduction conditions to achieve the ring opening step to yield the desired NMO. Using a pressure resistant vessel, paraformaldehyde was heated to form formaldehyde which was passed through the ‘tube in tube’ reactor for the formation of the oxazolidinone (Scheme 54). The Fmoc-alanine (194) and a catalytic amount of p-toluenesulfonic acid in acetonitrile were pumped through the reactor at 3 mL/h with a back pressure regulator of 1 atmosphere needed to keep the formaldehyde from degassing. This afforded the N-Fmoc-L-4-methylazolidin-5-one (195) in...
91% yield. Even though the second step was also reported to be performed in flow, the two could not be telescoped in one continuous process as the excess formaldehyde was found to quench the triethylsilane used in the ring opening step. However, this could be potentially avoided if a subsequent ‘tube in tube’ reactor under reduced pressure was to be applied after the first step to remove the excess formaldehyde from solution prior to it entering to the reductive step.

**Scheme 54:** Flow synthesis of oxazolidinone (195) for the formation of NMOs using formaldehyde in a ‘tube in tube’ reactor.

**Conclusion**
The use of gases in continuous flow has increased access to several chemistries which were deemed either too dangerous to be conducted at large scales in batch chemistry, or not efficient enough to be used due to the high pressure requirements of the gases. Flow chemistry of gaseous reaction has not currently resulted in the invention of new chemistries but has rather made existing reactions more feasible. It has been shown that most of the synthetic gases (CO, CO₂, O₂, H₂, C₂H₂, C₂H₄, CH₂O, F₂, O₃, Cl₂, CH₂N₂ and NH₃) can be employed in various flow reactors. Several new and now commercially available lab based gas delivery modules have been described and exemplified. It appears no one module can be used for all the gas-liquid flow
application and there is a requirement to select the best fit reactor for each specific use. For example, a ‘tube in tube’ reactor and a segmented flow reactor tend to be more suitable if the reaction is scaled up to multigram-kilos scale, while annular flow reactors and other microchip reactors are better suited for rapid small scale screening.

Even though a lot of gas-liquid transformations have been optimised to be used in continuous flow, we believe that there are still a large number of transformations yet to be tested. This will eventually lead to a shift into a greener, safer way of doing gas-liquid reactions, both in academia and ultimately in industrial settings.

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