



# **FlowCAT – a versatile continuous flow reactor system focusing on reactions under elevated pressure and/or involving heterogeneous catalysis.**

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## 1 Introduction

An upsurge in catalytic activity, primarily in relation to hydrogenation reactions, is widely recognised in the pharmaceutical and related industries. In the last couple of years, there has also been an increasing interest in flow chemistry, quite new to the pharmaceutical and fine chemicals industry though well established in other sectors, especially petrochemical and refining. This has highlighted the need for a research scale apparatus which enables high pressure flow chemistry to be conducted safely by chemists who are neither specialists in pressure equipment nor flow processes.

The FlowCAT is introduced as such a device, small scale high pressure flow reactor unit ideally suited to heterogeneous catalysis under pressure but able to handle all-liquid chemistries even down to atmospheric pressure. In pharmaceutical context, the system is targeted at post med-chem and discovery stages though the ability to produce fairly large amounts of sample lends itself to these early stages too. In the chemical industry generally, it is a research scale unit that allows easy and successful scale-up.

## 2 FlowCAT Reactor system

### **2.1 Flow chemistry – general features and benefits**

Flow reactors have the advantage over stirred vessels that fluids can be pumped through the reactor and hence even for relatively large production rates the reactor is often just a pipe rather than a big cylindrical vessel with a voluminous inventory. This is especially true if the reaction rate is fast and hence the reactants can be passed through the “pipe” at a high flow rate enabling the reactor to be even smaller.

The safety and energy advantages of flow reactors follow from the reduced inventory and much simpler hardware. From a process viewpoint too there are advantages as the simple pipe can be used at higher pressure and temperature if necessary, allowing more extreme conditions to be realised without excessive cost.

Flow reactors can be used in all sorts of configurations the simplest being to take a coiled length of metal or plastic tube which is held at a controlled temperature. This is ideal for

some situations especially in the laboratory but the one most commonly found is tubular design which may be only 5-20cm long with machined ends and diameter large enough to take powder catalyst if necessary. This is often but is relatively short held vertically within a heated zone and feeds introduced from the top and product withdrawn from the bottom. Where the catalyst is a powder, this is normally held in position to form a solid pack, “packed bed”, through which the reactants flow.

## 2.2 Design Features of FlowCAT

The most common (research-scale) version of the FlowCAT is a bench top unit about the size of an HPLC analyser and is shown in figure 1. The design is intended firstly to be compact and secondly for operator's ease of use – thus it can fit into normal (and busy) laboratory fume hoods and be used by operators with few tools and little training. For example the heating jacket opens up easily to give access to the reactor, the outlet pipe at the bottom is normally just a push on fit, and the reactor itself can be screwed off the head without breaking any of the connections as the head is held in position.

*Figure 1 :  
Standard FlowCAT set up*



Tubular reactors are either 6mm (1/4”) or 12mm (1/2”) diameter though can be larger and the length is normally 15cm of which 10cm is the temperature controlled (hot) region. This gives a maximum hot zone reaction volume of approximately 3 and 12ml respectively. These specially machined reactors can be easily replaced by coiled tubing and used in the heated zone where the chemistry favours this alternative reactor type.

The system includes an innovative back-pressure regulator which is unusually small and permits pressure control without any alteration regardless of whether the reaction products are all liquid, all gas or a two-phase mixture. The feed system is also versatile and can be adapted to applications that require different combinations of liquid and gas feeds.

## 2.3 FlowCAT Controls

The FlowCAT unit is software controlled with independent control of feed rates, working pressure and temperature and the mimic diagram of the set up for the standard configuration used for example for hydrogenations, is shown in figure 2. This shows one controlled gas and one liquid feed plus a manual nitrogen purge. The feeds are preheated and then pass through the main body of the reactor and the product then leaves the high pressure section after passing through the back pressure control valve.

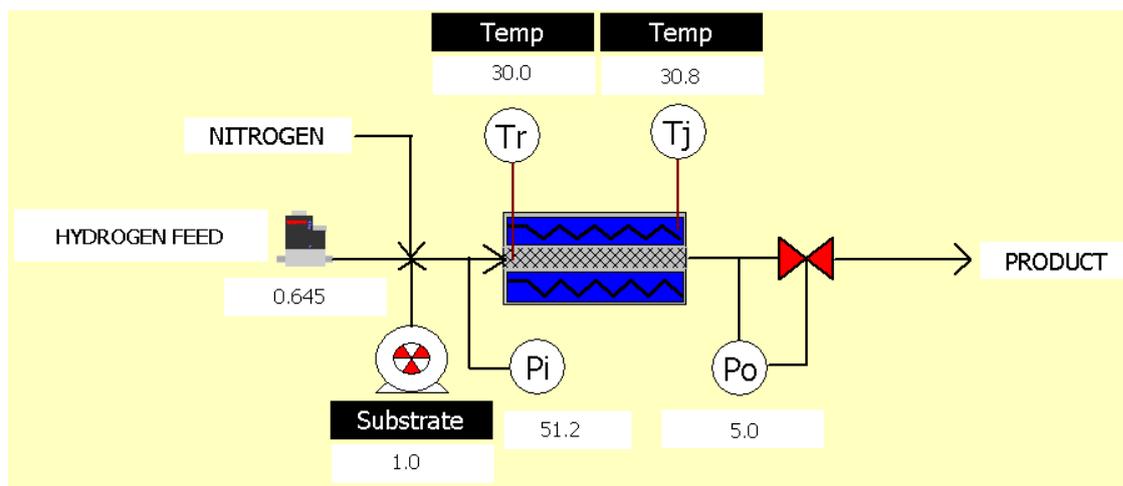


Figure 2: Mimic of standard FlowCAT set up for hydrogenation

A totally different set up is shown in figure 3 where there are three separate gas feeds and one liquid, and these involve some pre-treatment before entering the reactor. The reactor itself actually has no catalyst packing and the product is analysed in real-time by means of an analyser piped upstream of the pressure control valve. The analyser readings are accessed and displayed in real-time along with process data.

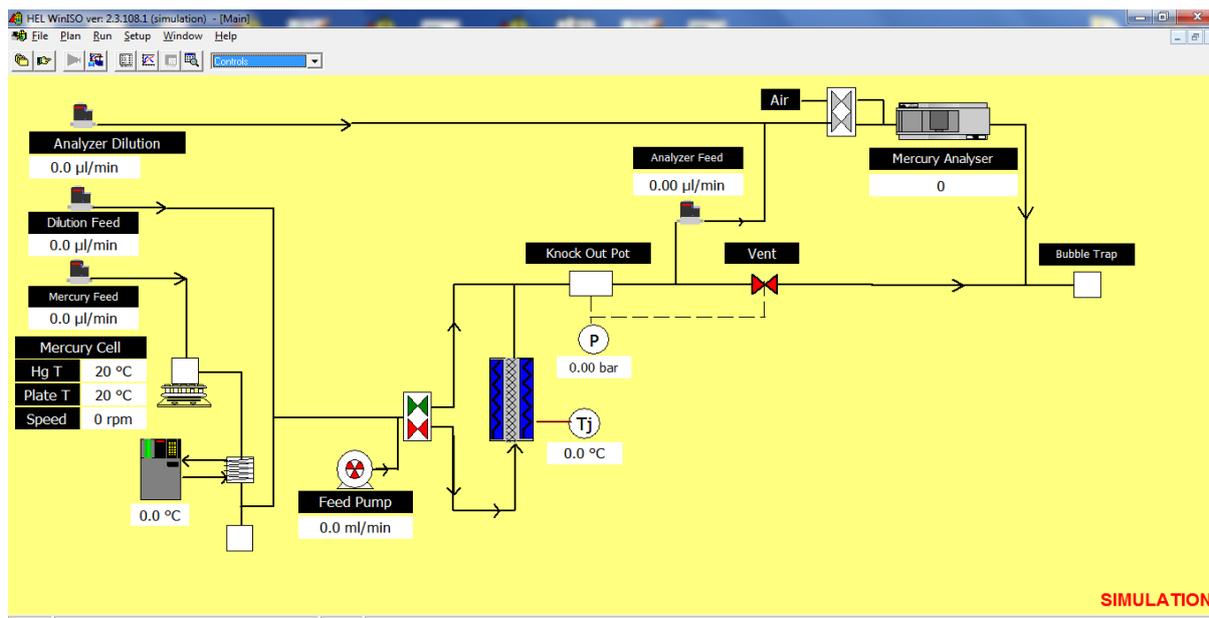
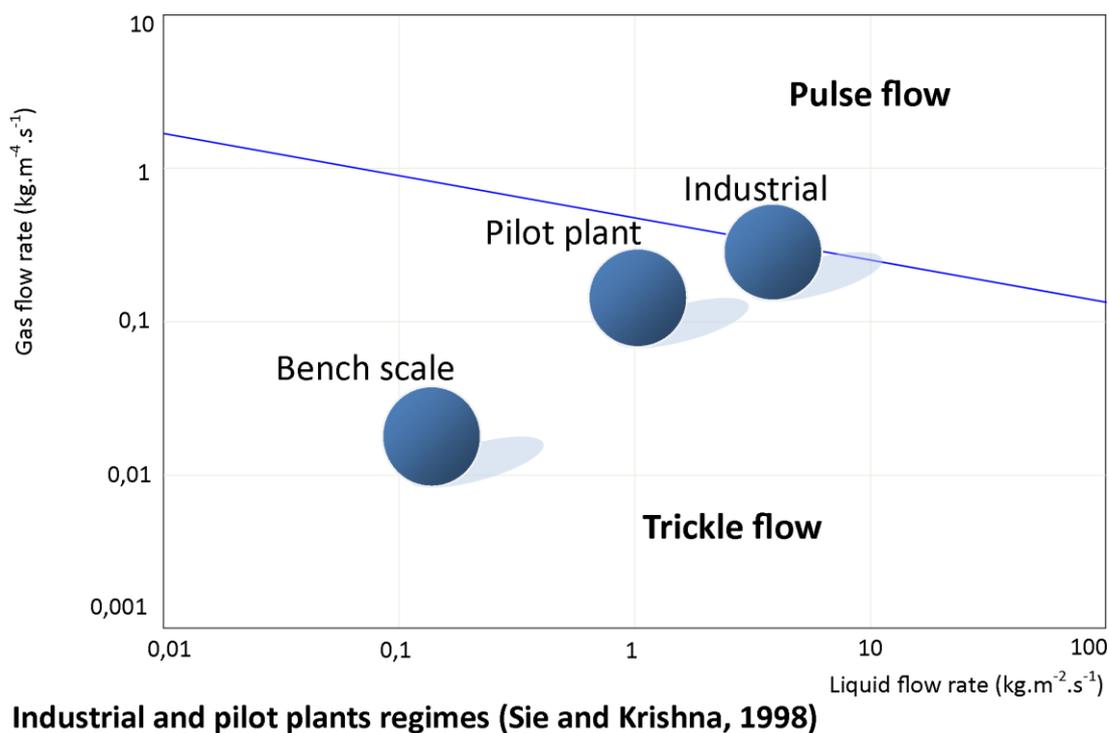


Figure 3: Example of Modified set up with on-line product analyser

## 2.4 Operating window – trickle flow region

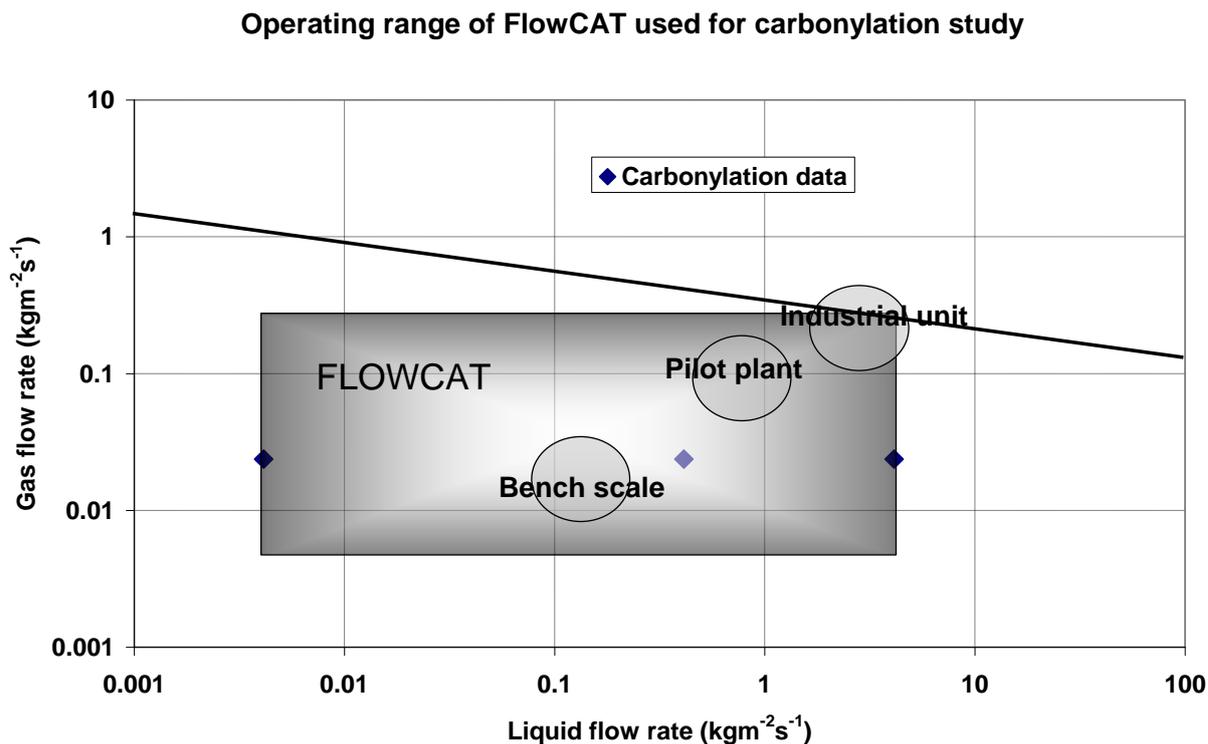
In principle, any flow rate of gases and liquids can be passed through a given reactor provided the pumps can overcome the pressure drop. In reality, best performance is obtained if the flow pattern is what is called “trickle-flow” and this also then can be used as the basis for scale-up. The ranges of gas and liquid flows which will lead to trickle-flow are shown on figure 4 (which also indicates the flow pattern at rates beyond the trickle-flow band).



*Figure 4 : Flow pattern in packed tubular reactors at different flow rates*

Figure 5 shows the trickle-flow region in more detail but also plotted is the region occupied by the standard FlowCAT (and as an illustration, the data points for the carbonylation reaction studies reported in section 5 of this article are also marked).

Loading of solid catalyst to the reactor is also an important part of operation and reproducibility of results. It is common practice to have a top section packed with inert particles (such as glass beads) which helps to preheat and mix the feeds. The reaction section itself also can contain inerts mixed with catalyst particles, thus helping to spread a given amount of catalyst over a bigger volume which assists with temperature control and gives more reproducible results.



*Figure 5: Working range of standard FlowCAT to give trickle flow*

### 3 Hydrogenation of nitrobenzene

The first reaction presented is the hydrogenation of nitrobenzene to aniline using 1% Pd on carbon catalyst (around 0.1g) mixed with glass beads (around 400 micron diameter). Most of the experiments were done at 30°C, using substrate/solvent flow rate of 0.5ml/minute and 20 litre/minute of hydrogen, corresponding approximately to 1.83 times stoichiometric of the gas. Taking into account the volume occupied by the inert beads, the void space available for reactant flow was around 1.2ml and therefore, the residence time is around 2.4 minutes.

The results are plotted in figure 6, where the amount of hydrogen consumed is plotted at different working pressures. Also shown is the solubility of hydrogen in the solvent at different pressures; clearly, the consumption is not limited by solubility. The gas consumption values in fact correspond to substrate conversion of around 20% at the lowest pressure rising to around 60% at 90bar.

To increase conversion, temperature could be increased and residence time could be increased (for example by reducing the liquid flow rate). These changes could be made while the reactor is still working, without any need to stop the experiment and change the equipment. This is one great advantage compared with batch reactors where the system would need to be dismantled, reactors washed, cleaned and reloaded with freshly weighed catalyst before different conditions could be attempted.

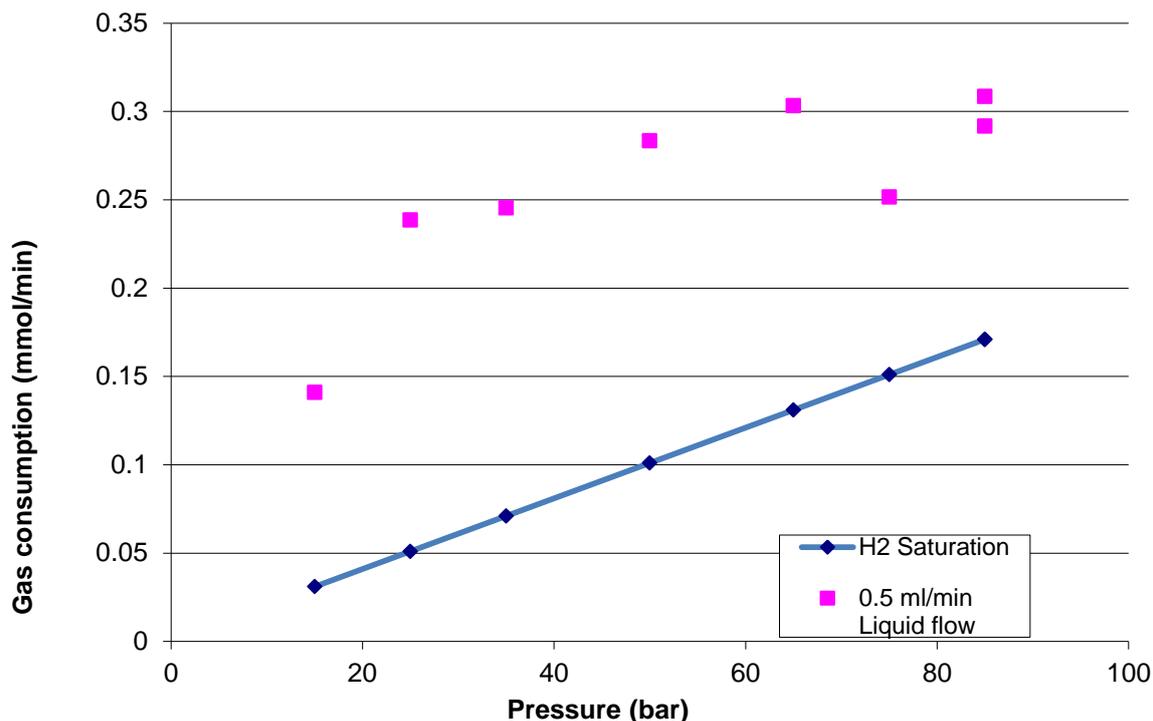
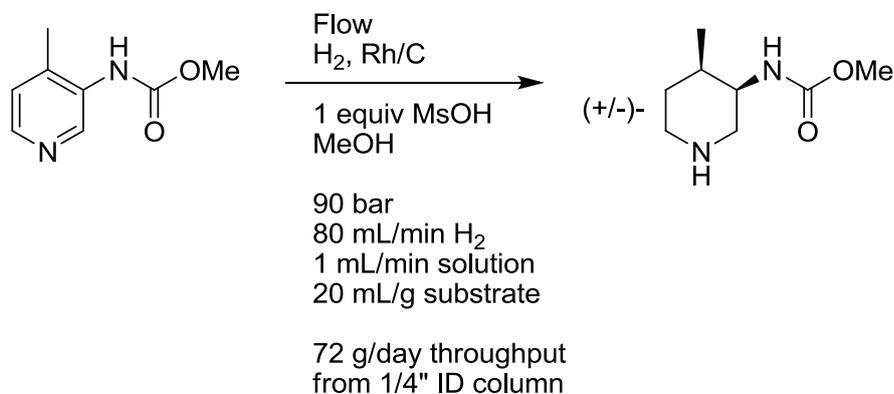


Figure6: Hydrogenation of nitrobenzene to aniline at different pressures

If flow rate is reduced to increase conversion, then of course throughput is compromised. In order to avoid this, it would be possible to reduce the amount of inert packing to free up more space or alternately switch to a larger diameter reactor.

#### 4 Stereoselective hydrogenation

Pfizer pharmaceutical company reported the benefits of using the FlowCAT to perform a hydrogenation where stereoselectivity control was important and they showed that control of the cis to trans ratio in the product could be tuned by adjusting the pressure. The chemistry in question is summarised in below and the results they achieved which show the “tuning” capability with a flow reactor is plotted in figure 7.



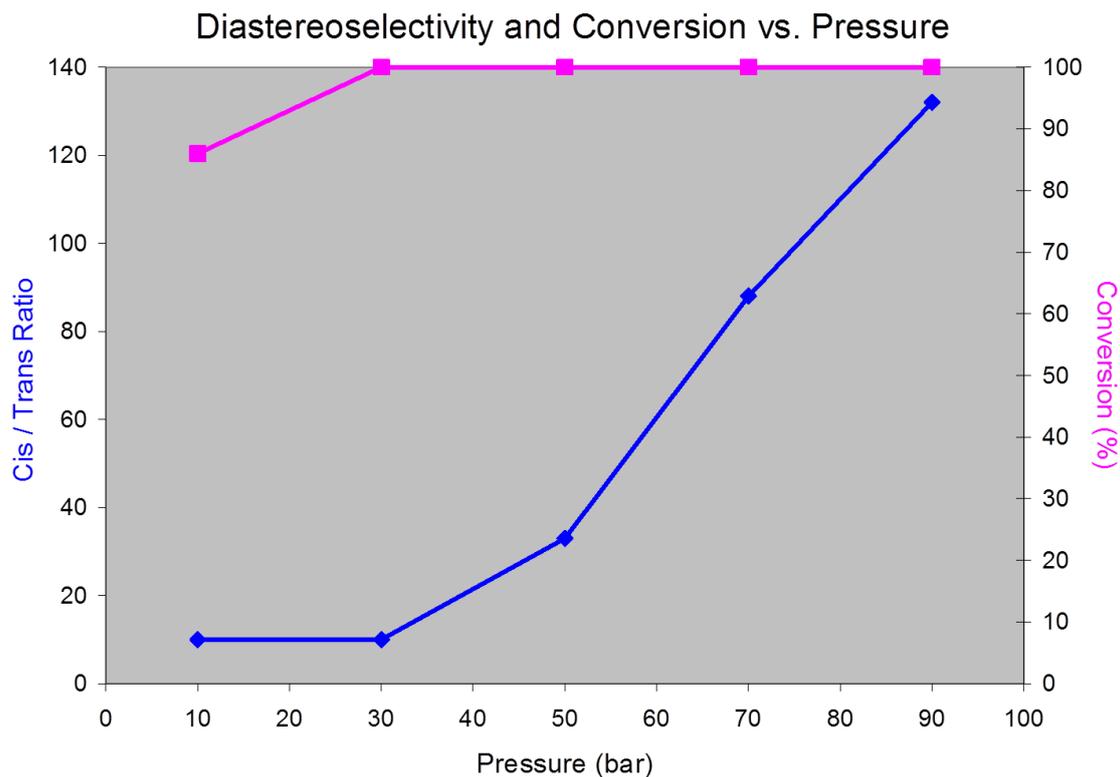
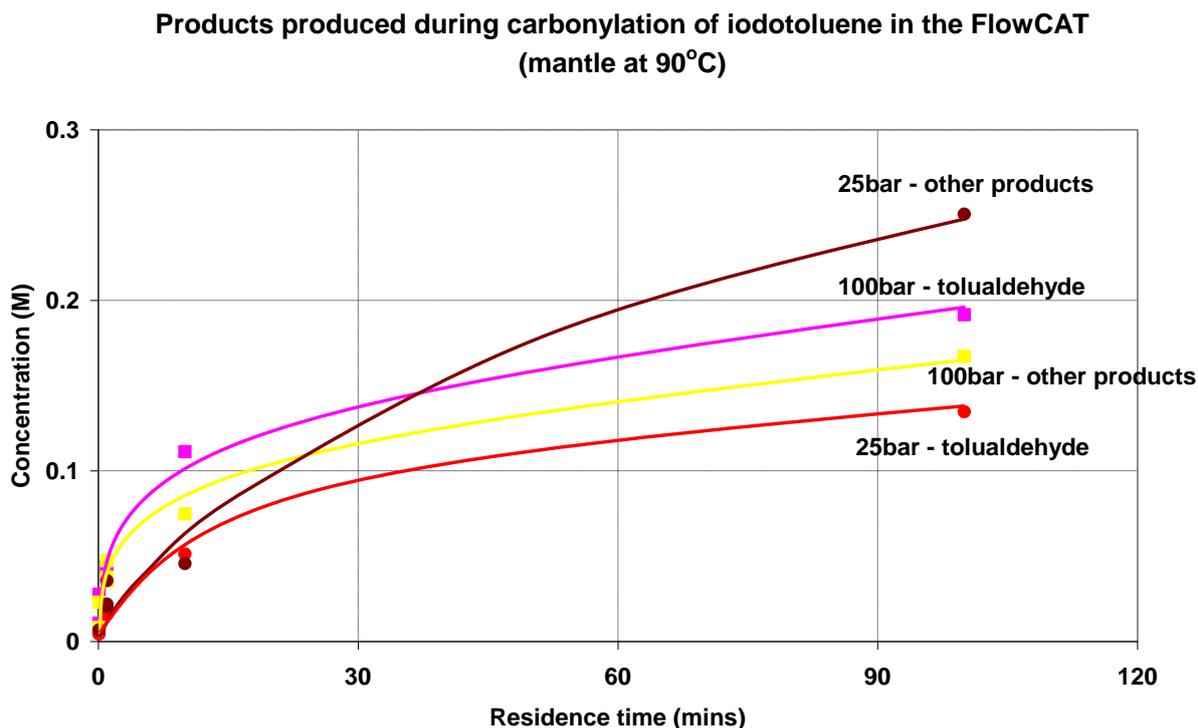


Figure 7: Pfizer data for a stereoselective hydrogenation in FlowCAT (J Hawkins, 2010)

### 5 Carbonylation of Iodotoluene

While hydrogenation reactors are very common in some industries other chemistries that involve gaseous reactants with solid catalysts, such as oxidation and polymerisation, can be accommodated equally well. Another example is carbonylations, a reaction which is commercially important and quite difficult to perform. To demonstrate this on the FlowCAT, carbonylation of iodotoluene to tolualdehyde was attempted using 0.72 molar solution of the substrate in triethylsilane and triethyleamine using a Palladium catalyst supported on polymer, supplied by Johnson Matthey.

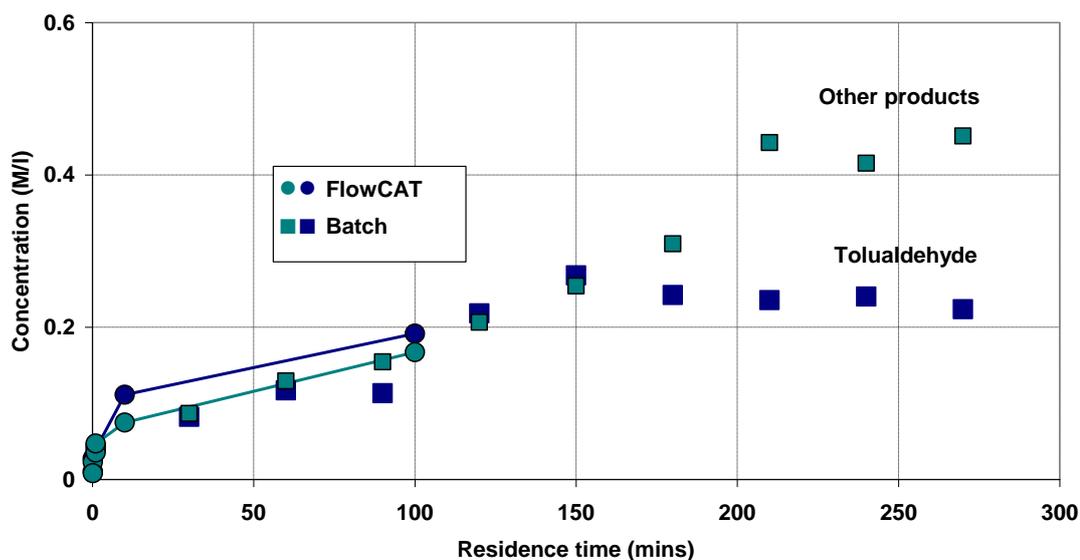
The chemistry is highly non-selective and results of some experiments in FlowCAT at 90C are summarised in figure 8. The molar concentration in the product stream is plotted at different residences times (ie liquid flow rates) with the CO flow kept constant. This shows that at 25bar pressure, conversion is relatively low and the amount of desired product (toluadehyde) is much less than the amount of by-products. If the pressure is raised to 100bar, the situation is seen to improve considerably where the by-product amount is much reduced and the desired product increased.



*Figure 8: Carbonylation reaction in FlowCAT at two different pressures*

The same reaction was also performed in a small batch reactor at the same conditions and the results of the two systems are compared in figure 9. This shows that in fact the product slate under batch and flow conditions is quite similar. Additional batch experiments were performed at higher reaction times than on the FlowCAT and it seems that this does not favour the chemistry, certainly after around 150 minutes increasing amount of by-product is formed at the expense of the desired product.

**Concentrations of products during carbonylation of Iodotoluene in the  
FlowCAT and a batch reactor with similar catalyst mass (at 90°C, 100bar)**

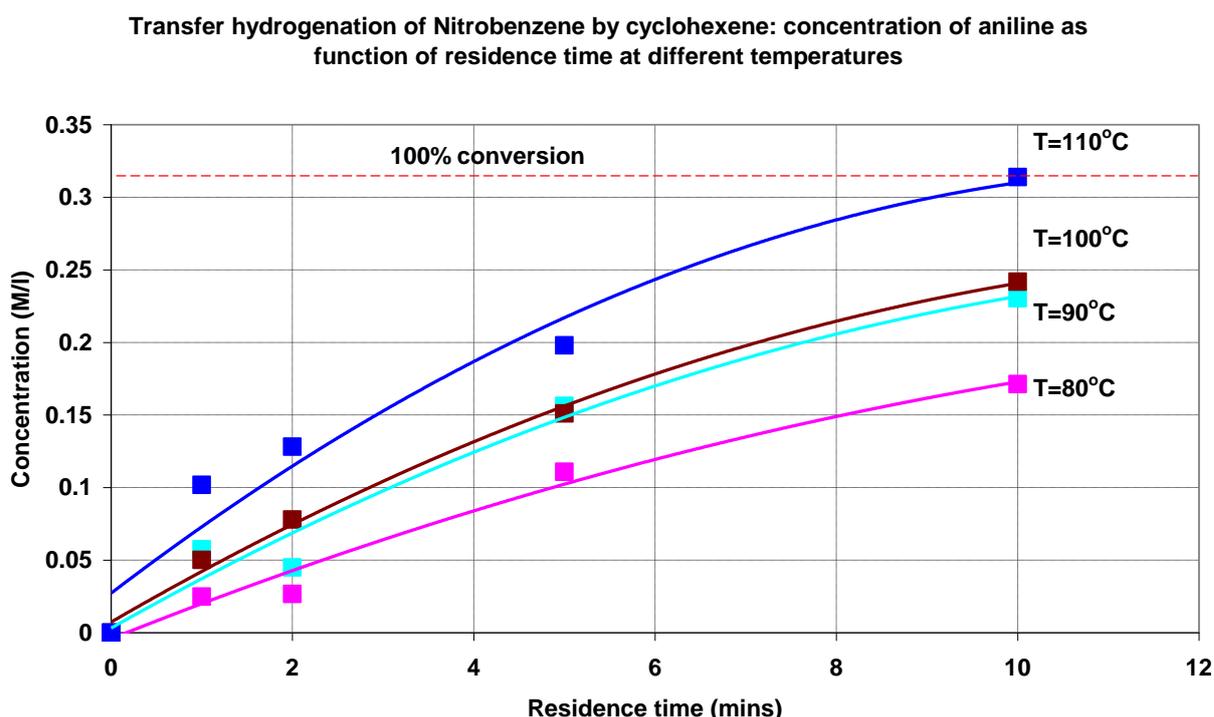


*Figure 9: Comparison of batch and continuous flow carbonylations*

## 6 Liquid-liquid reaction in Tubular reactor

It is also quite simple to perform reactions on the FlowCAT that do not involve a gaseous reactant and this was illustrated by studying the transfer hydrogenation of nitrobenzene to aniline using cyclohexene as a transfer molecule.

This is a much easier reaction than the carbonylation and selectivity is nearly 100%. With a back pressure of 2bar, temperatures of between 80 and 110C were studied at different residence times up to 10 minutes. The results (figure 10) show that in fact 100% conversion is achieved at these conditions.

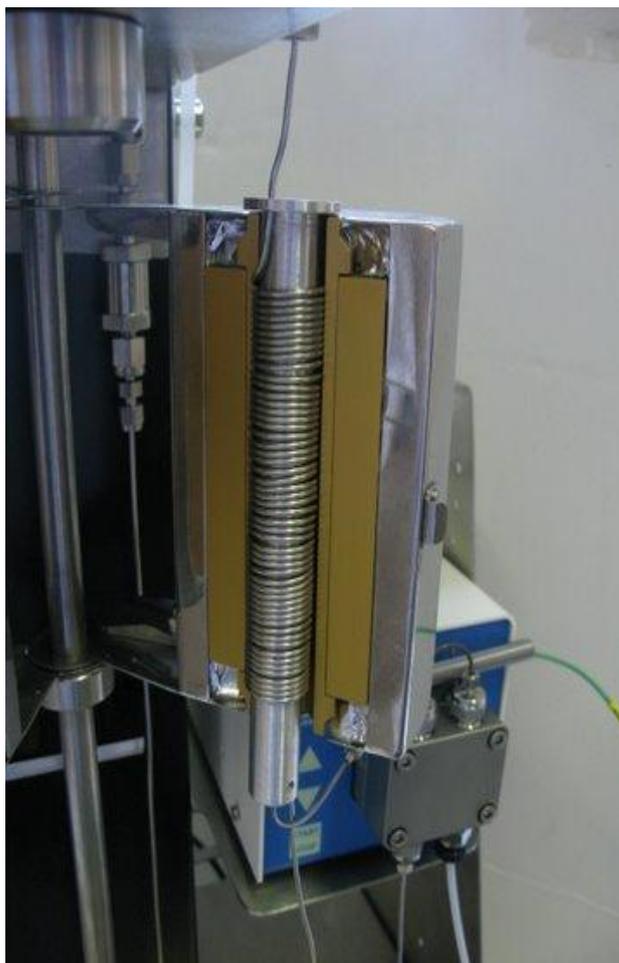


*Figure 10: Liquid-liquid reaction involving transfer hydrogenation*

## 7 Liquid-liquid reaction in coiled tube reactor

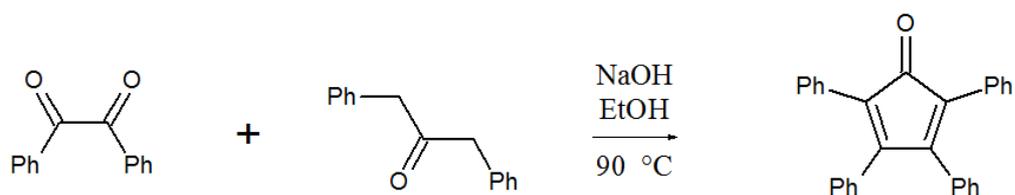
The standard tubular reactors used in the previous examples are limited when very fast reactions are performed as the only way to achieve a long residence time is slow down the feed rate and this is limited both by the pump and eventually poor mixing and heat transfer.

The alternative is to use 1/16" or 1/8" diameter piping which can be coiled to fit the heating zone. These can be easily fitted to replace the tubular reactors and hence common synthesis reactions at atmospheric or elevated pressure can be performed easily. Photographs of such a set up with 1/8" stainless steel tubing is shown below. This is held inside the same heating jacket as the tubular reactors previously and product leaving the pipe can be under pressure or simply by gravity.



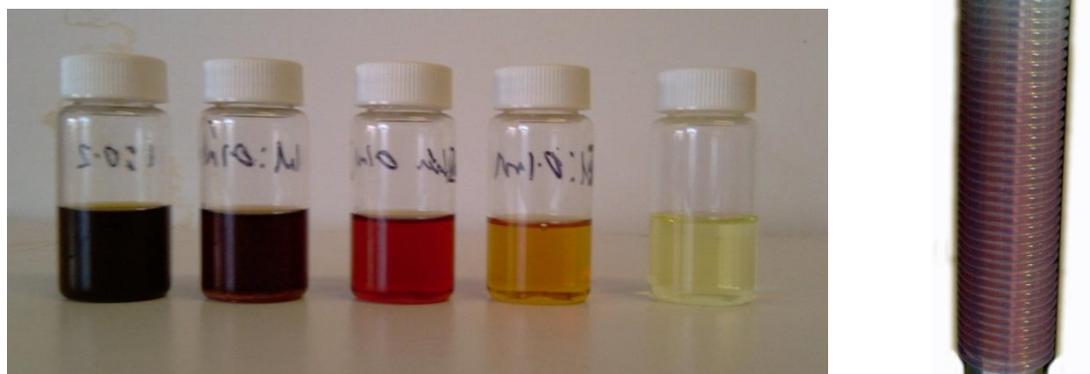
*Figure 11 Coiled Stainless Steel Tube Reactor inside heated jacket*

The utility of this arrangement is illustrated by an interesting condensation reaction between diphenylacetone and benzyl in the a basic environment (typically NaOH):



The feed mixture is a very pale green and product becomes progressively darker with conversion, eventually becoming an intense purple. Several runs were performed at different flow rates with the temperature held at 90C and the amount of caustic fixed and the product collected. The results are shown below with the fresh feed being on the right and then moving left the residence times are 2,4,6 and 12 minutes.

The same reaction was also performed in a PTFE coiled reactor and the change in colour is shown in the right hand photograph.



*Figure 12 Products at due to different reaction times and PTFE coiled reactor showing colour change with conversion*

## 8 Chemistry under super-critical conditions

One of the advantages of flow reactors is that very high pressures can be achieved at relatively low cost and much more safely than in stirred vessels. This opens up the possibility of using novel solvents that can have exceptional properties at conditions where the solvent is supercritical. An important example is CO<sub>2</sub> which at modest conditions of pressure and temperature starts to behave most unusually. For example hydrogen becomes totally miscible with supercritical CO<sub>2</sub> and reactions then become much faster as the normal solubility barriers associated with common liquid solvents, which slow down the chemistry, suddenly disappear.

Even in its standard form FlowCAT can handle this type of chemistry, the only additional hardware needed is a booster compressor for CO<sub>2</sub> as this gas is normally available at relatively low pressure.

## 9 Conclusions

The utility of a versatile, research scale flow reactor has been demonstrated with numerous reactions. In addition, the FlowCAT is extremely simple to and opens up the possibility of doing pressure reactions, including hydrogenations, in normal laboratories by chemists who are not specialists in pressure equipment.

The flowCAT allows all manner of chemistries to be studied interchangeably with virtually no change in set up being necessary. Feeds of all liquid, all gas and mixtures of gas and liquid are possible and the same is true for products.

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