5 Key Things that Flow Chemistry Makes Possible

It is a well known moment - the conference weary chemist laden with bags of brochures stops in front of the vendor's booth and asks

"OK, what could I do with your equipment that I cannot already do now ?"

For a modern high performance flow chemistry system vendor, the answer is

"Quite a few things, actually !"

Some of the most important of these are summarised below.

They are

- Reduced Reaction Times
- Reproducibility and Scaleup
- Improved Selectivity
- Control of Exotherms
- Use of Dissolved Gaseous Reagents

Reduced Reaction Times

Because flow chemistry can be performed at very high pressures, temperatures can be far above the normal boiling point of the solvents at atmospheric conditions (see below). High temperatures generally make for shorter reaction times and this can speed exploratory and optimisation work enormously, and makes for highly productive processes when the time comes for scaleup.

For thermally mediated reactions, continuous flow reactors and batch microwaves are found to give similar results. (However, temperature is more precisely controlled in the flow reactor leading to safer and more straightforward scale-up.)

	100 psi (6.89 bar)	**200 psi (13.79 bar)**
THF	137 °C	171 °C
CH_2Cl_2	102 °C	130 °C
EtOH	137 °C	163 °C
EtOAc	145 °C	175 °C

Solvent Boiling points vs Pressure.

Reproducibility and Scaleup

Because a properly designed † flow system offers very good reproducibility across wide range of flow rates, it is possible to prove and optimise a reaction at a tiny scale and then scale up from mg to gram scale with almost no further development work.
This means not only a huge amount of time saved, but also that usage of expensive reagents at the optimisation stage can be minimised.

Once a method is proven at small scale, the synthesis can be pretty much repeated on demand at the required scale.

Eventual handover to process groups for larger scale-up may be far easier when the initial synthesis is developed in a flow system, reducing the overall time to market considerably.

† It should go without saying that flow and temperature must be accurately known. Temperature must be measured at the reactor, not on some nearby component, and pump performance should be monitored rather than simply assumed to be as requested.

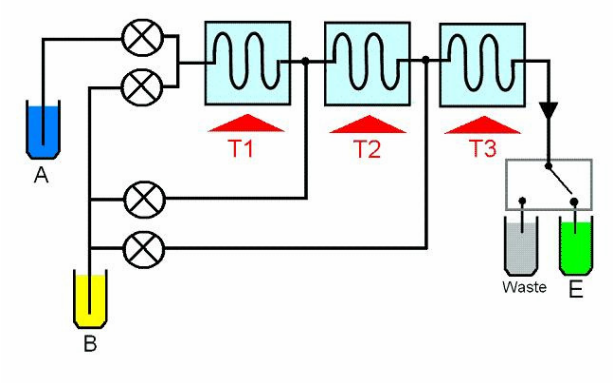
See **www.vapourtec.co.uk/applications**
Application Notes 1-4 - Optimisation and Scaleup

Improved Selectivity

With a batch reaction, raw reagents swirl around with partly reacted reagents and fully reacted products in a fashion that varies both with respect to time and space in the reactor.
For reactions that are sensitive to relative concentrations of the reagents, the result can be in effect a distribution of a range of outcomes (including unwanted over-reacted products), and the distribution can vary with different reaction scales or reactor flask geometries. Mixing is therefore a reaction variable, but not one that is easy to control or reproduce at a different scale.

With flow, however, raw reagents meet at the initial mixing point and mixing is complete within seconds. At any point along the reactor thereafter the concentration of each of the components is invariant with time, so the same output emerges at the end whether the reaction is run for minutes or left running for hours. In addition to reproducibility, this often results in better selectivity.

Initial flow conditions can be optimised to prevent over reaction, or reagents can be brought in stepwise at several points along the reactor.



Partial Addition for improved selectivity

See **www.vapourtec.co.uk/applications**
Application Note 15 - Bromination of Ketones

Control of Extreme Exotherms or Unstable Intermediates

There are some reactions that are simply not safe to do above a certain scale in a round bottomed flask, because the evolved heat (or potential evolved heat in the event of decomposition) cannot be removed fast enough to control the reaction. And even reactions which MAY fall into this category often require calorimetric analysis first just to be on the safe side.

But with a flow approach, the capacity for heat transfer is far greater and so these reactions can be carried out safely at almost any scale. They can also be speeded up by superheating.

Reactions with unstable intermediates are also safer with flow because the amount of intermediate in existence at any one time is small, and it need not exist for long before being consumed, so is less likely to decompose anyway.

See **www.vapourtec.co.uk/publications**
A modular flow reactor for performing Curtius rearrangements as a continuous flow process

See **www.vapourtec.co.uk/applications**
Application Note 12- Weinreb Amidation

Reactions featuring dissolved gaseous reagents

There are some reactions which require such volatile reagents that they are in effect gases dissolved in another carrier solvent (examples include ammonia, dimethylamine). Normal practice with these reagents is either to run the reactions cold (with correspondingly long reaction times) to keep the gases in solution long enough, or else to use quite involved equipment (a bomb reactor with a purged then pressurised headspace above the reaction mixture).

Such reactions are quite straightforward in a flow chemistry system. Reagents are fed into the pressurised system before the temperature is raised and they are then fully contained with no reactor headspace all the way through the reaction. At the elevated temperatures that this makes possible, such reactions can be performed safely in minutes where the alternative batch approach could take hours.

Other advantages of the Vapourtec flow approach ...

"Automatability"

It would be unfair to say that batch chemistry cannot be automated, but it is clear that automating flow is both easier and far more cost effective.

Imagine, for example, a fully automated batch system that could run a sequence of 50 reaction variants unattended, where each reaction involved several steps (including perhaps the use of a solid supported catalyst, or a pressurised superheated reaction), and where the products of each reaction were captured in vials and made available for use as reagents in subsequent reactions if required.

Now, imagine the cost, the fume hood space and the likely setup effort for a batch system like this. Yet there would still be reactions that were simply not safe to carry out unattended.

For the Vapourtec R Series system, the scenario described above uses basic off the shelf functionality.

Monitoring and Data Recording

It is useful to be able to run a reaction, achieve a successful result, and know that

- All the reaction setup details are automatically recorded ready to file in the electronic lab notebook, along with key variable measurements through the reaction
- The reaction details could be shared with someone else in a different lab with similar equipment who could then repeat the reaction (perhaps at a different scale) and get the same results.

When this level of data recording is automatically happening for every reaction all the time, with no extra effort, the chemist really can concentrate on innovating and optimising the chemistry.