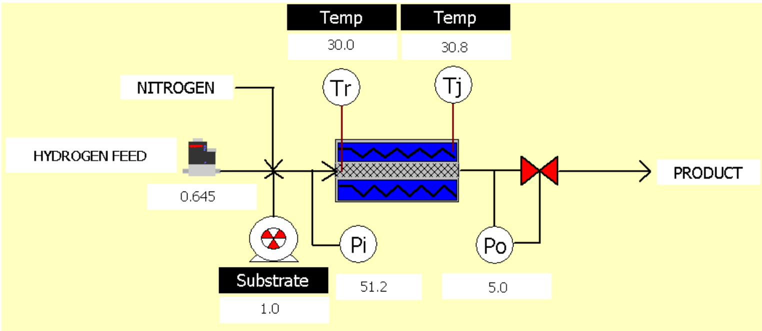
FlowCAT - continuous flow reactor system for hydrogenation screening and small scale production



Dr Jasbir Singh

(Jsingh@helgroup.com)

HEL Ltd, England

2nd Symposium on Continuous Flow Reactor Technology for Industrial Applications,
3-4 October, 2010
Paris

HEL Limited London, England

HEL Inc NJ, USA

HEL China Beijing

HEL Italia Milan

HEL India Mumbai

Terminology in catalytic reactions

- **Homogeneous catalysis**
- **Heterogeneous catalysis**
- **Fixed bed or Plug Flow (continuous) and stirred/Batch reactors**

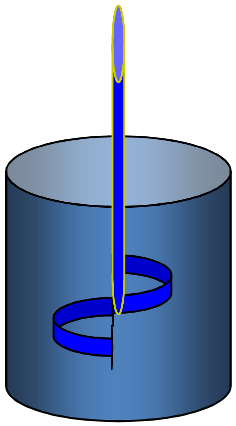
Fixed Bed is special case of continuous flow type.

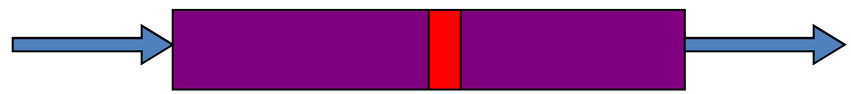
Terminology in catalytic reactions

- **Homogeneous catalysis**
- **Heterogeneous catalysis**
- **Fixed bed or Plug Flow (continuous) and stirred/Batch reactors**

Fixed Bed is special case of continuous flow type.

Crude Mathematical equivalence of flow and batch reactors

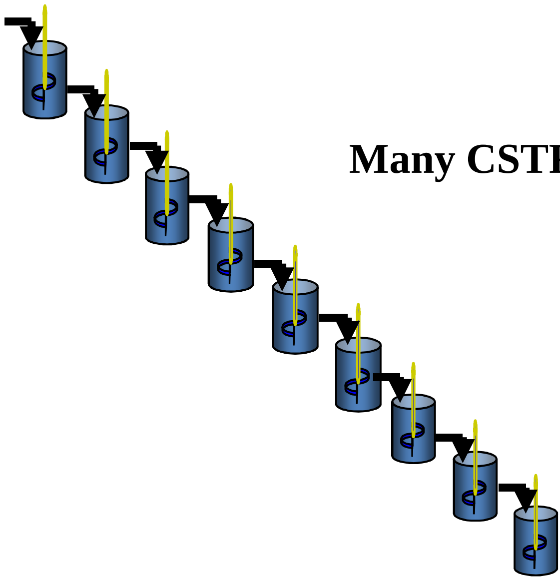




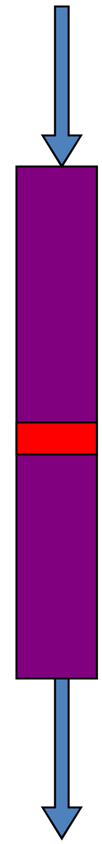
Batch Time **Residence Time = Volume/flow rate**

Equivalence – time in batch reactor equates to position down plug flow.
Changing flow rate changes residence time: corresponds to batch time.

Closer Mathematical equivalence of Reactors



Many CSTRs in series



Co-Current feeds

PFR (plug flow)

Vertical orientation (top-to-bottom)

Lab-scale flow Systems – Screening and Prep-scale

Screening

•Catalyst in small cartridge, very high catalyst loading
• Conversion limited by hydrogen solubility (at high conc.)
• Typical throughput 1+ g/day

H-cube (Thales-nono) well established in this field. Limited to hydrogenations and to screening applications only.

Prep-scale

• Traditional “tubular” reactor
• “Trickle flow” mode demonstrated
• High conversion far exceeding solubility limit
• Typical throughput 100+g/day

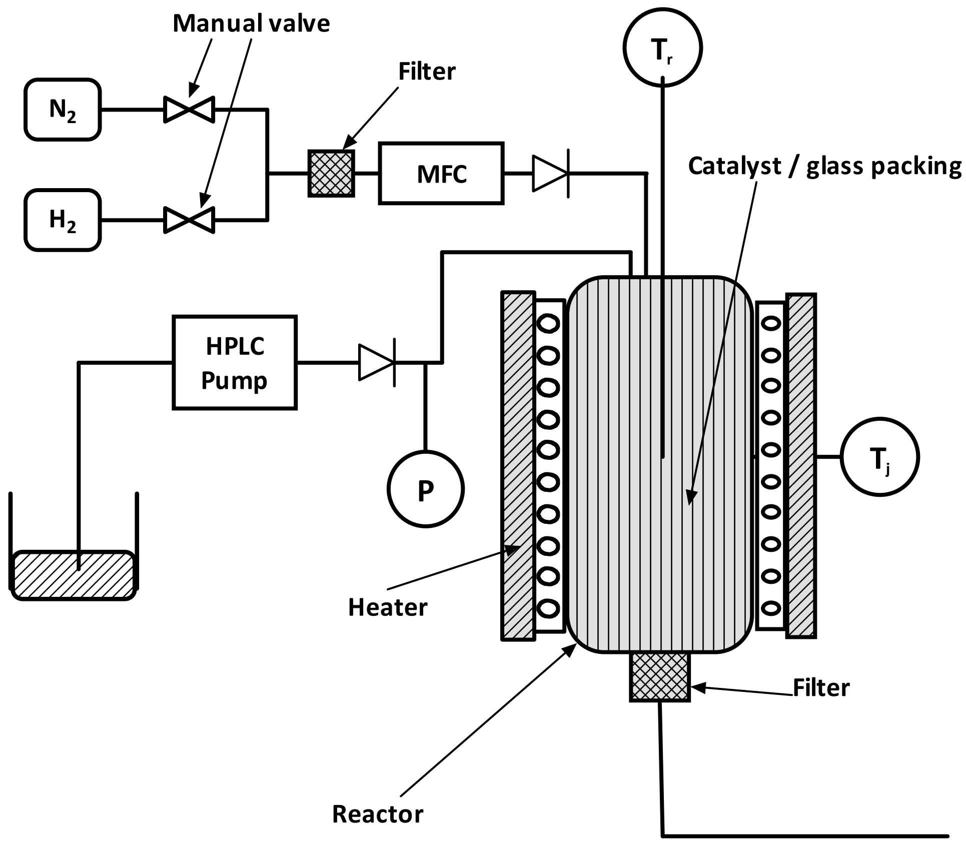
No fully automated product established up to now.

FlowCAT Package

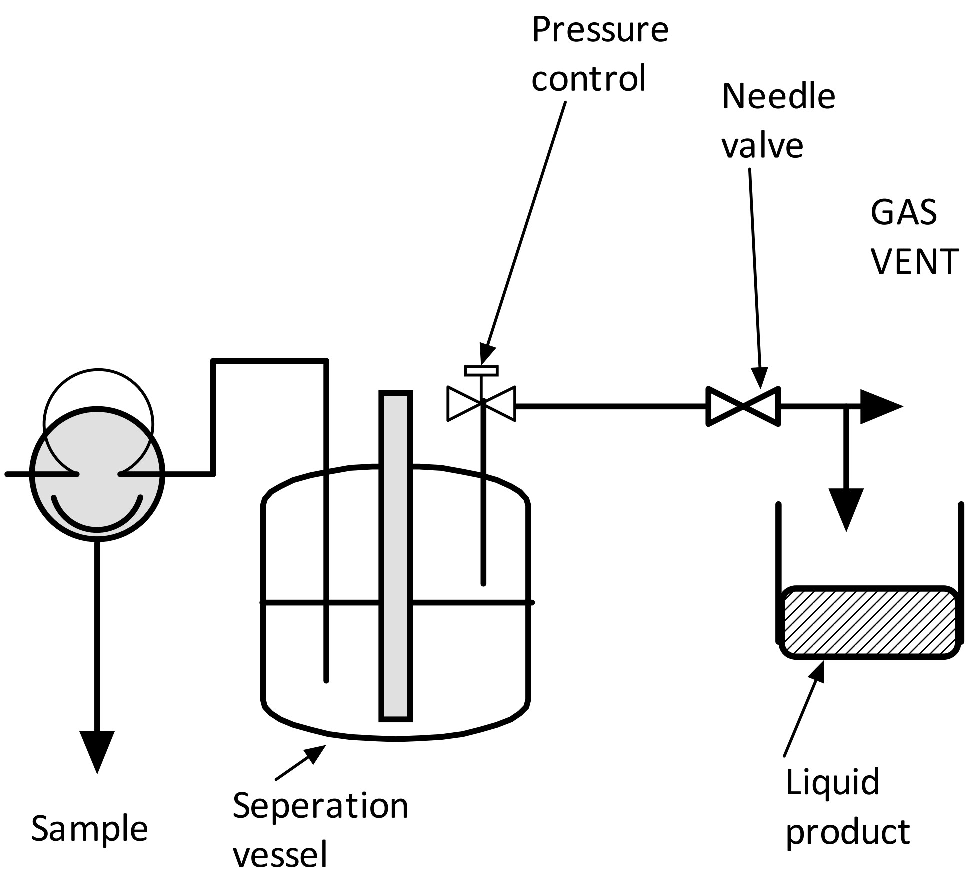
- Developed to bridge screening and prep-scale needs
- Not limited to hydrogenations
- Fully software controlled
- Does not require high pressure expert for operation

Trialled at length by Pfizer for hydrogenation applications.
Some results to follow.

flowCAT Feed Section



flowCAT Product Sampling and Collection



FlowCAT Typical Specification

- Standard lengths: 15cm (6")
- Two standard int. diameters: ½" (12mm) or ¼" (6mm)
- Volumes : 2.8ml, 12ml (in hot zone, approx).
- Standard ovens: heated lengths 10 cm
- 100bar/300C standard (higher temperature/pressure options)
- One liquid and one gas feed standard, other combinations possible.

Not limited to hydrogenations

Not limited to heterogeneous catalytic reactions

Flow Capacity of Tubular Reactors

Very wide range of flows are possible, subject to pump range and pressure drop across reactor.

Gas and liquid flow rate determines:

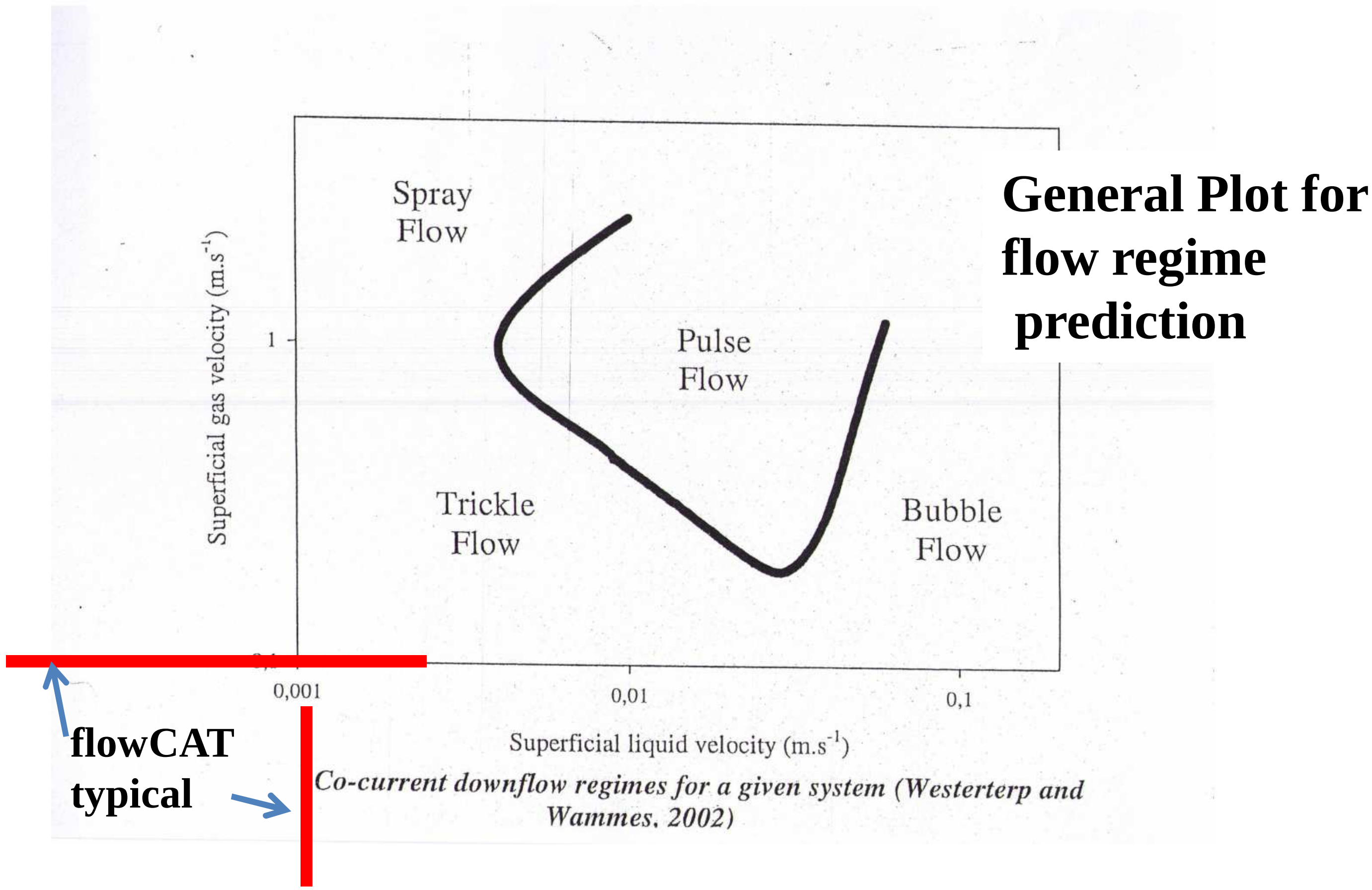
- the “pattern” of flow
- Gas/liquid mixing and contact with catalyst
- Conversion
- Ease of scale up

Flows rates widely selected to favour that “trickle bed” mode.

Trickle Bed Flow Regime

Most common mode of operation for tubular fixed bed reactors

- **Fixed bed of inert and catalyst pellets, former occupying large volume (50% or more)**
- **Co-current downward flow of gas and liquid**
- **Leads to gas dispersed, liquid continuous phases around solids**



Co-current downflow regimes for a given system (Westerterp and Wammes, 2002)

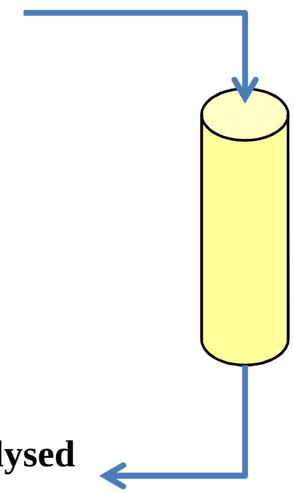
HEL

flowCAT performance Testing

$$C_6H_5NO_2 + 3H_2 \longrightarrow C_6H_5NH_2 + 2H_2O$$

Hydrogenation of (4%) nitrobenzene to aniline

Hydrogen plus
Nitrobenzene/solvent
G/L vol. ratio 20 (100max, gas at NTP)
Hydrogen excess typically 1.83 x stoich.

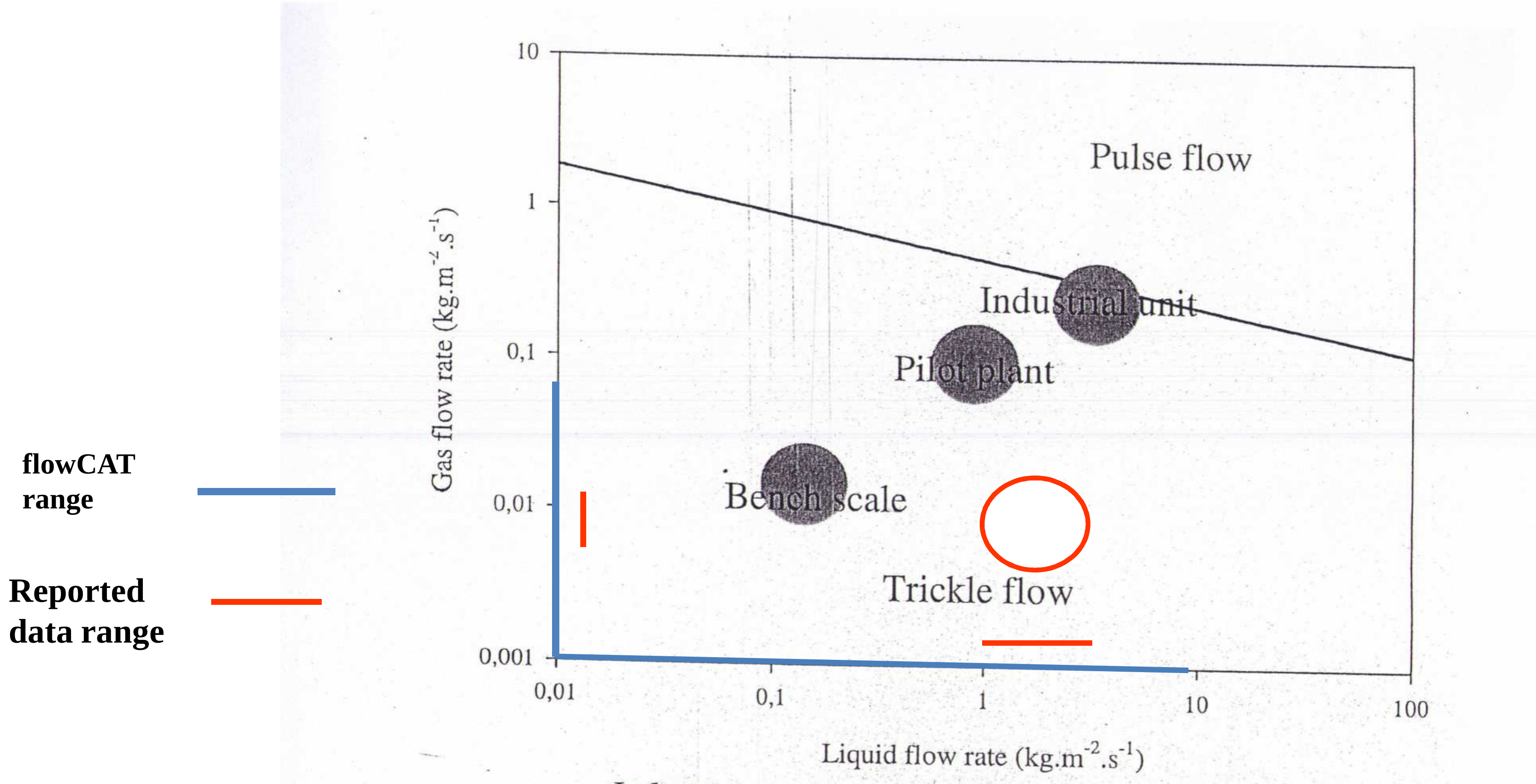


0.25” internal dia.
Temperature 30 deg C
1% Pd/C mixed with glass beads
4ml packed volume (30% voids)
Catalyst mass 0.1g (0.2 and 0.4g alternates)

Product (Aniline), analysed by GC

Trickle Bed Flow – Lab Reactors

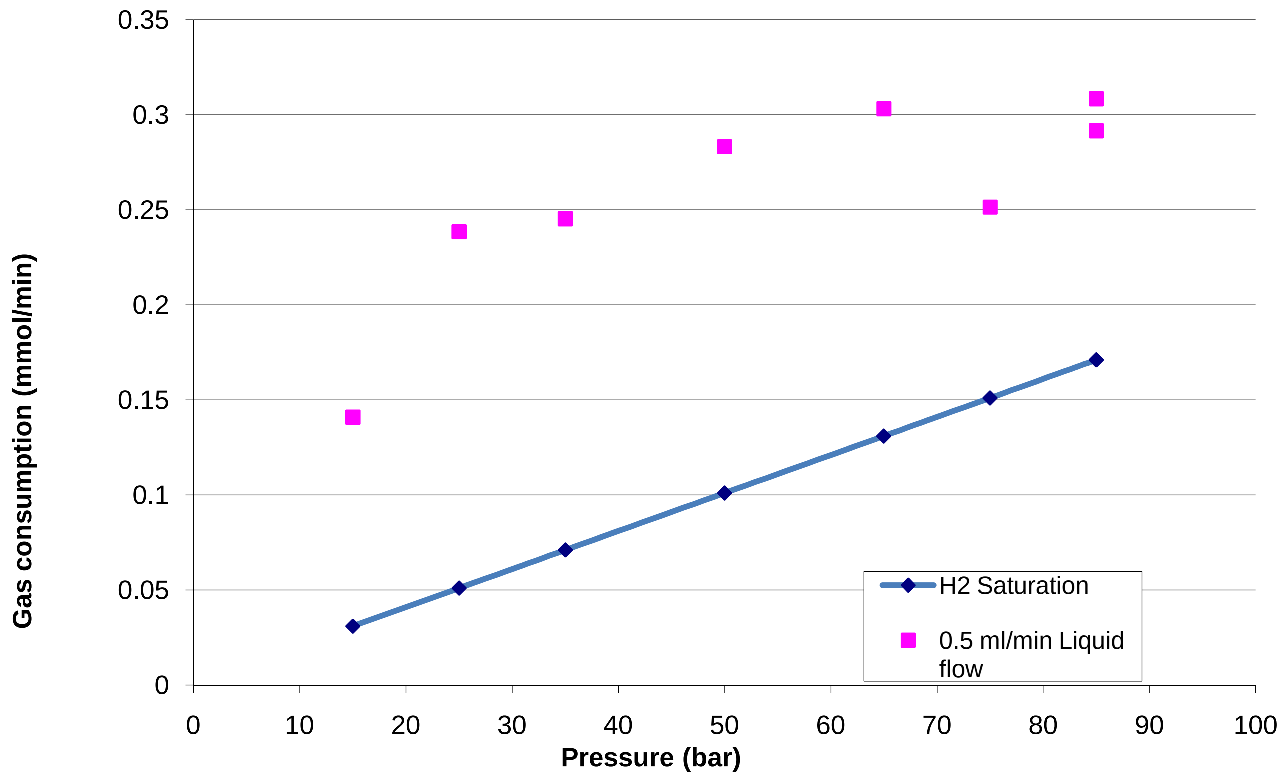
Diagram below shows likely position of bench scale flow reactors



Industrial and pilot plants regimes (Sie and Krishna, 1998)

Hydrogen consumption with pressure

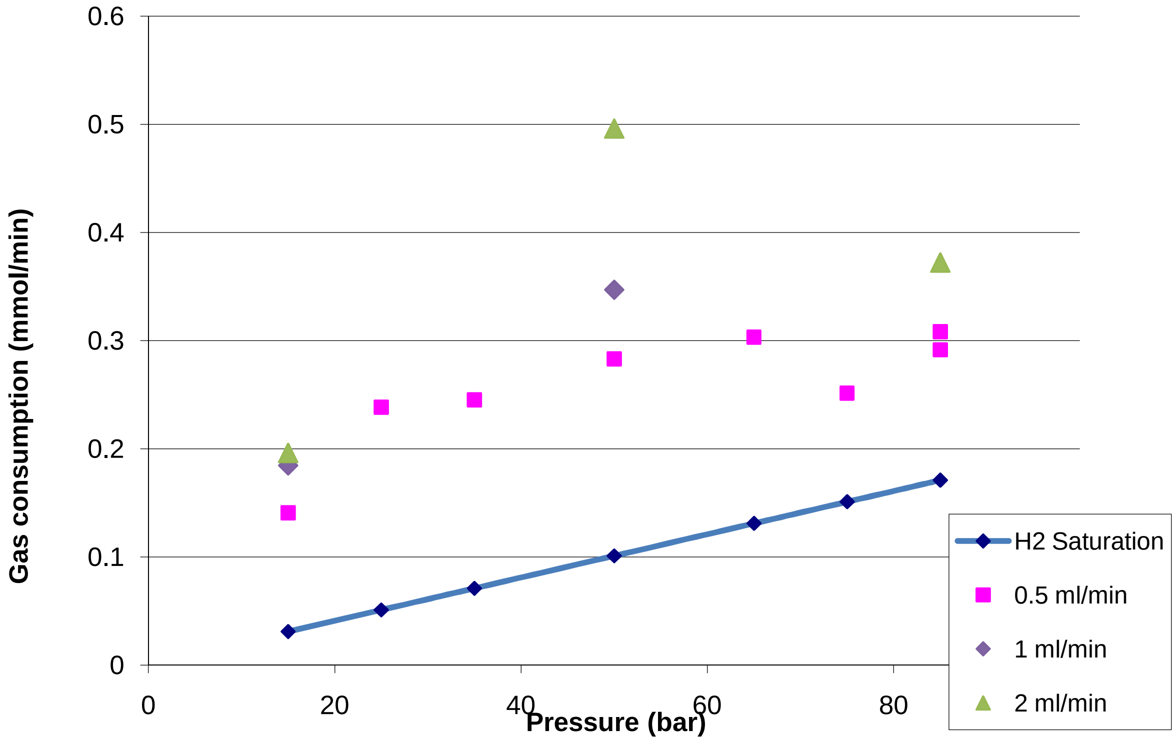
Hydrogenation of nitrotoluene to aniline



Hydrogen 1.83 x stoichiometric
(= 20 n ml/min)
Catalyst loading 0.1g
Bed volume 4ml (30% void)

Hydrogen consumption with at different substrate flows

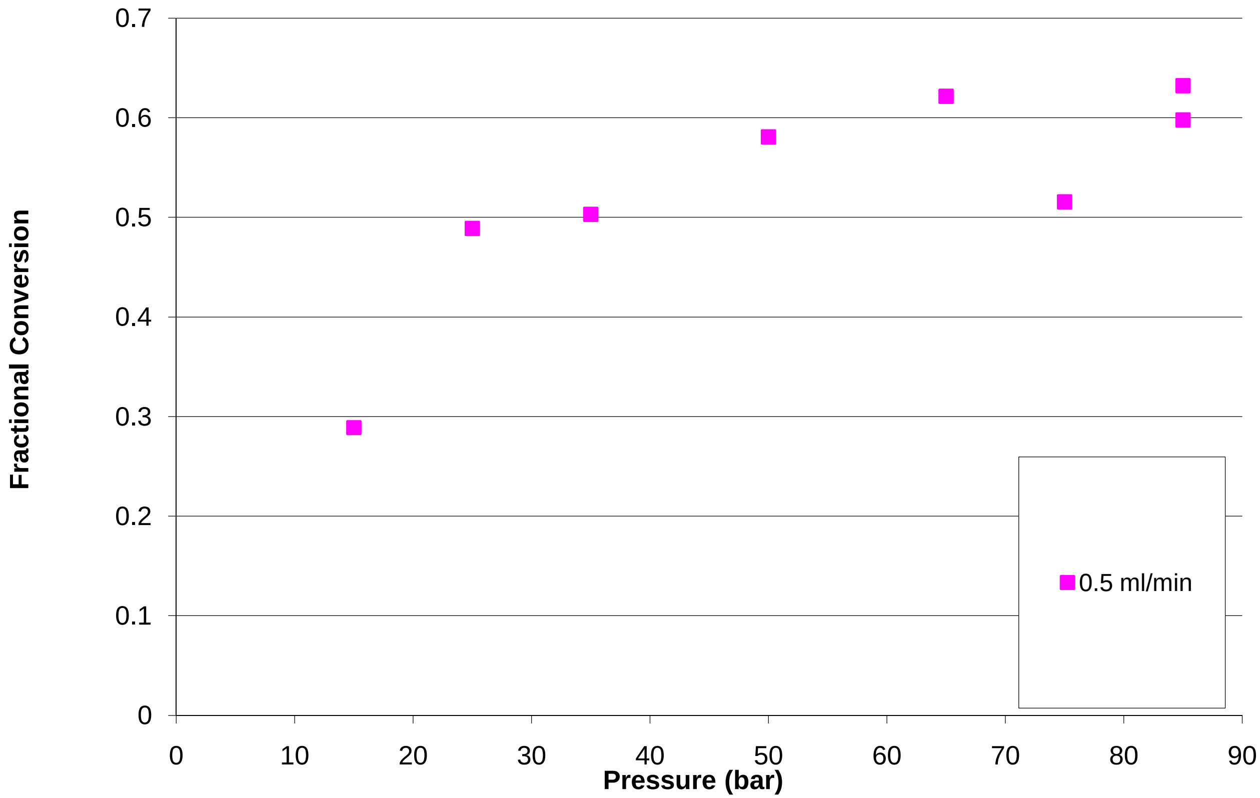
Hydrogenation of nitrotoluene to aniline



Hydrogen 1.83 x stoichiometric
(= 20 to 80 n ml/min)
Catalyst loading 0.1g
Bed volume 4ml (30% void)

Fractional conversion with pressure

Hydrogenation of nitrotoluene to aniline

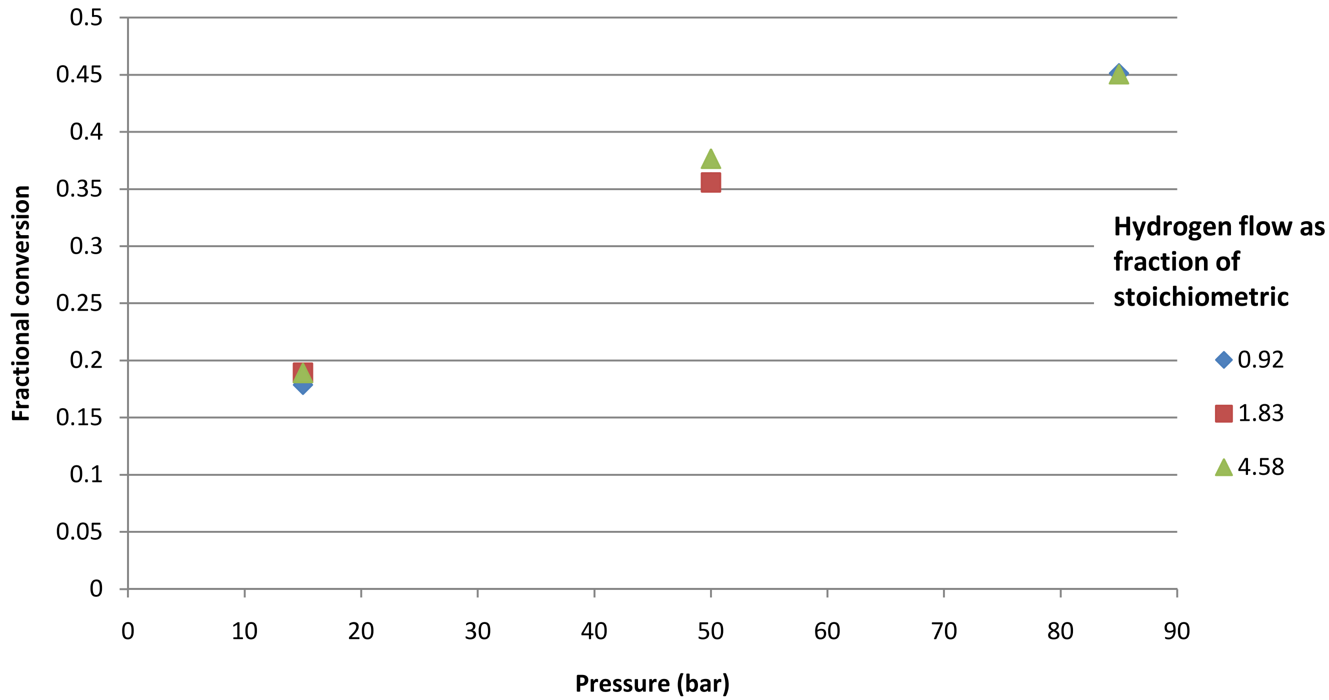


Liquid flow = 0.5ml/minuite
(residence time approx 2.4 mins)
Hydrogen 1.83 x stoichiometric
(= 20 n ml/min)
Catalyst loading 0.1g
Bed volume 4ml (30% void)

H·E·L

Conversion at different gas flows

Hydrogenation of nitrotoluene to aniline



Liquid flow 1ml/minute
Catalyst loading 0.1g
Bed volume 4ml (30% void)

Comparison with Stirred Reactor Data

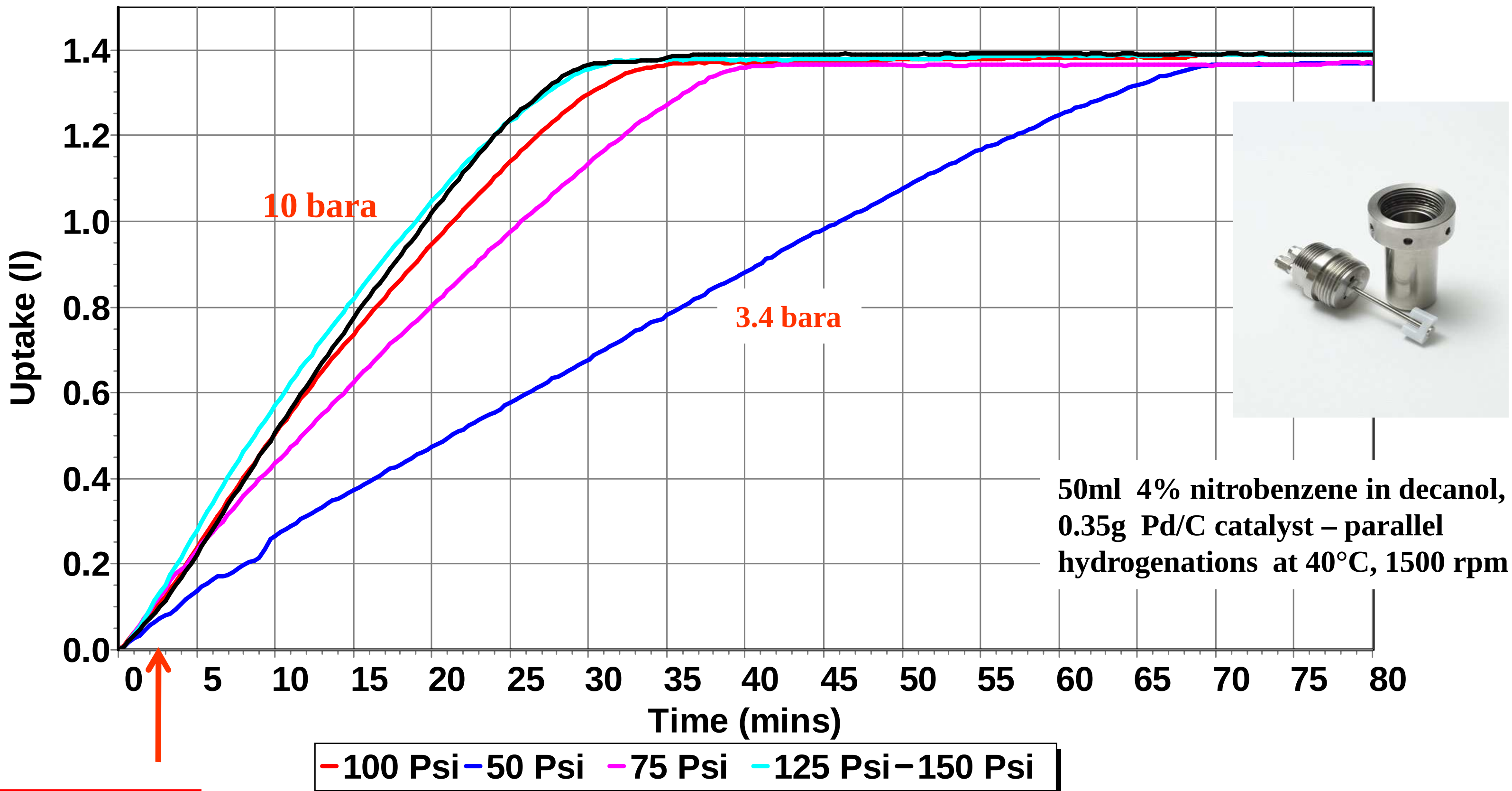
HP Chemscan
8 x 16ml reactors

Auto-MATE
4 x 100-300ml HP reactors

AUTOLAB
1000ml HP glass reactor

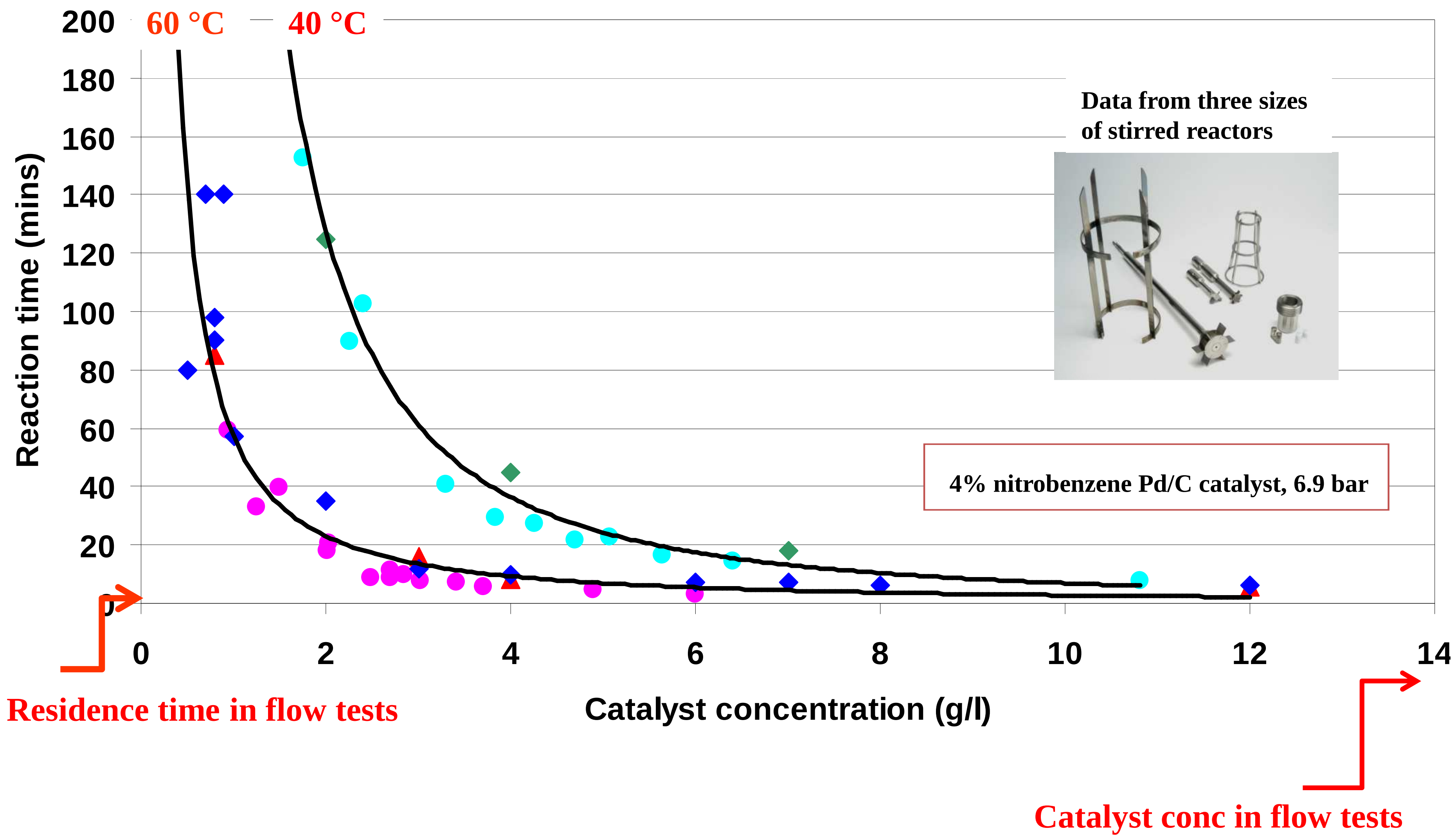
HYDROGENATION 100ml stirred HP auto-MATE

Catalyst loading approx 1/100th of flow reactor



Typical residence time in flow tests

Time to 100% conversion in stirred reactors (5 to 500ml)



Hydrogenation Screening?

H-cube

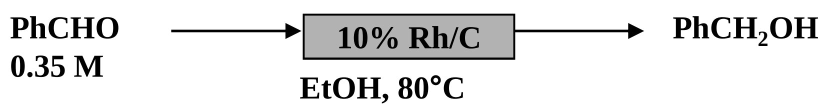
• Hydrogen generation in situ – safety advantage
• Low flow only, limited to screening at low conc or small scale compound prep (eg med chem)

flowCAT

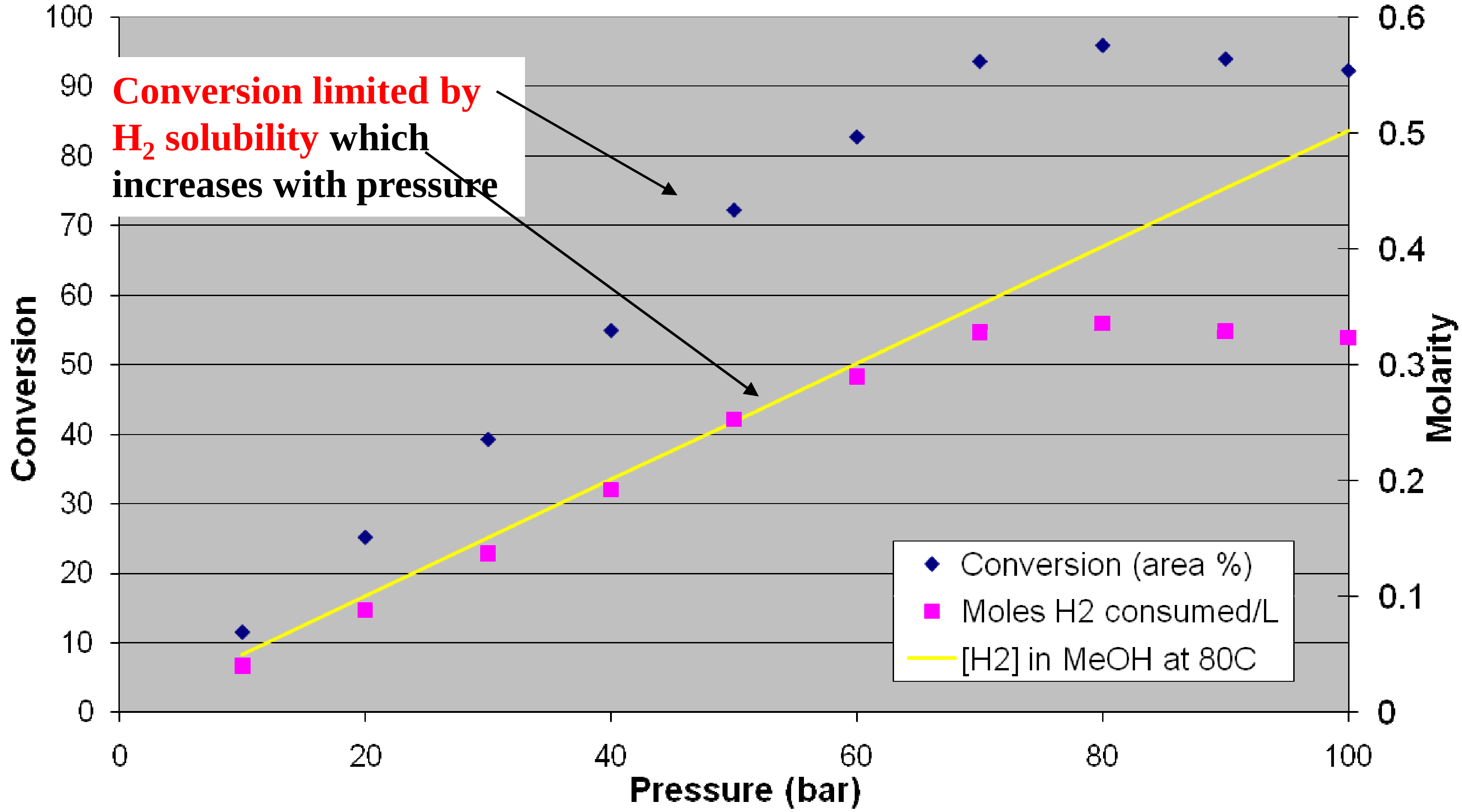
• Needs hydrogen supply – less safe potentially
•Low flow version feasible, cartridge designs being tested
•Already in use for prep-scale work
Can flowCAT be adapted for screening?

.

Screening with H-cube: Conversion Limited by hydrogen solubility

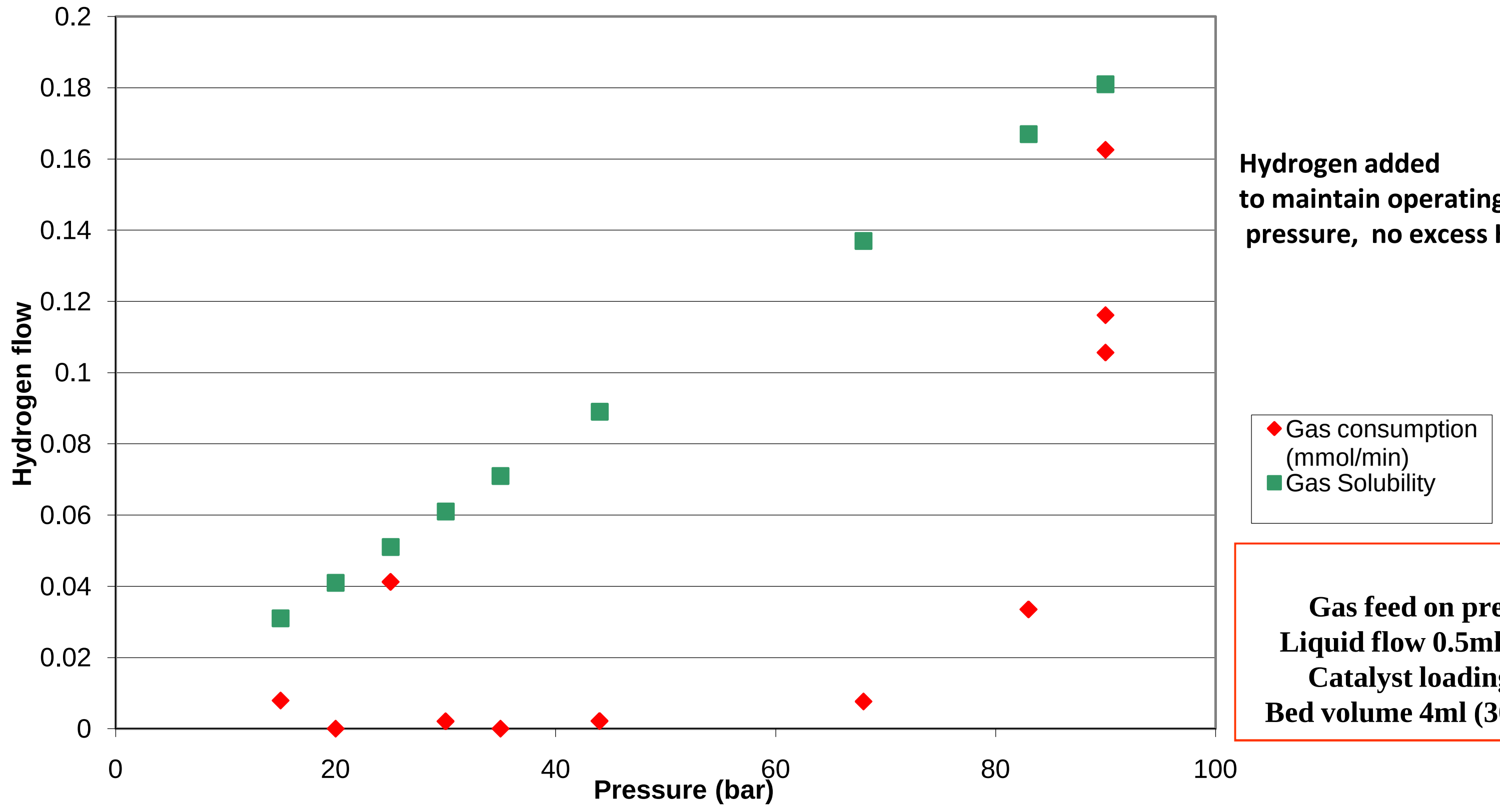


(courtesy J Hawkins, Pfizer Inc, August 2010)



Conversion Limited by Solubility - flowCAT

Hydrogenation of nitrotoluene to aniline



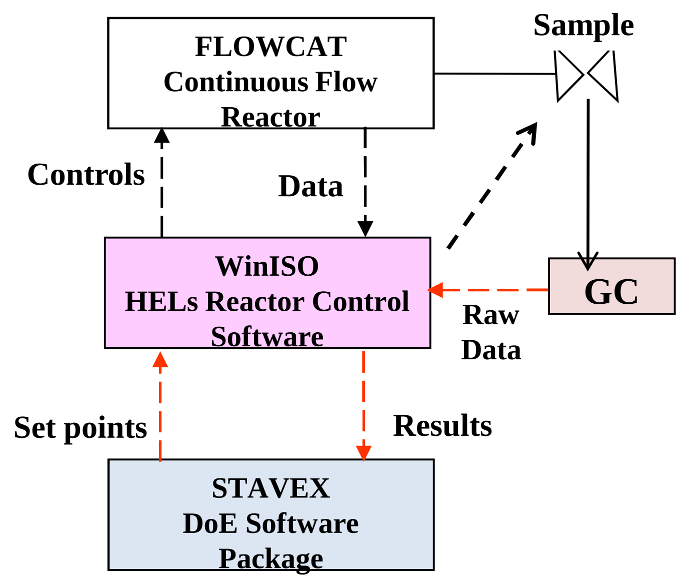
Hydrogen added to maintain operating pressure, no excess H2

Gas feed on pressure
Liquid flow 0.5ml/minute
Catalyst loading 0.1g
Bed volume 4ml (30% void)

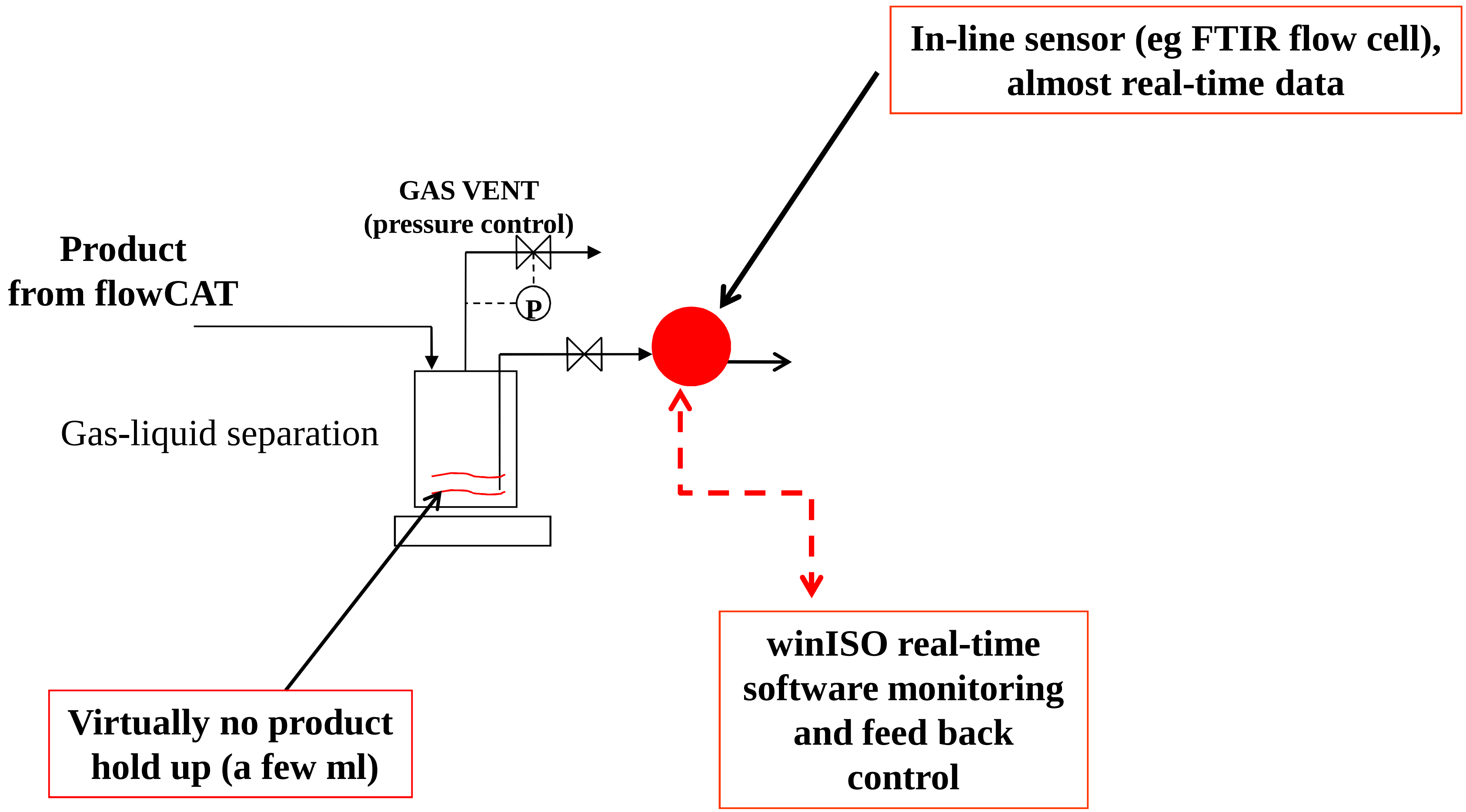
H·E·L

flowCAT in commercial R+D

- Controlled by commercial, well established software/electronics, fully developed
- Ideal for process development and large enough for prep-scale production
- Possible to integrate with DOE package and optimise totally automatically.



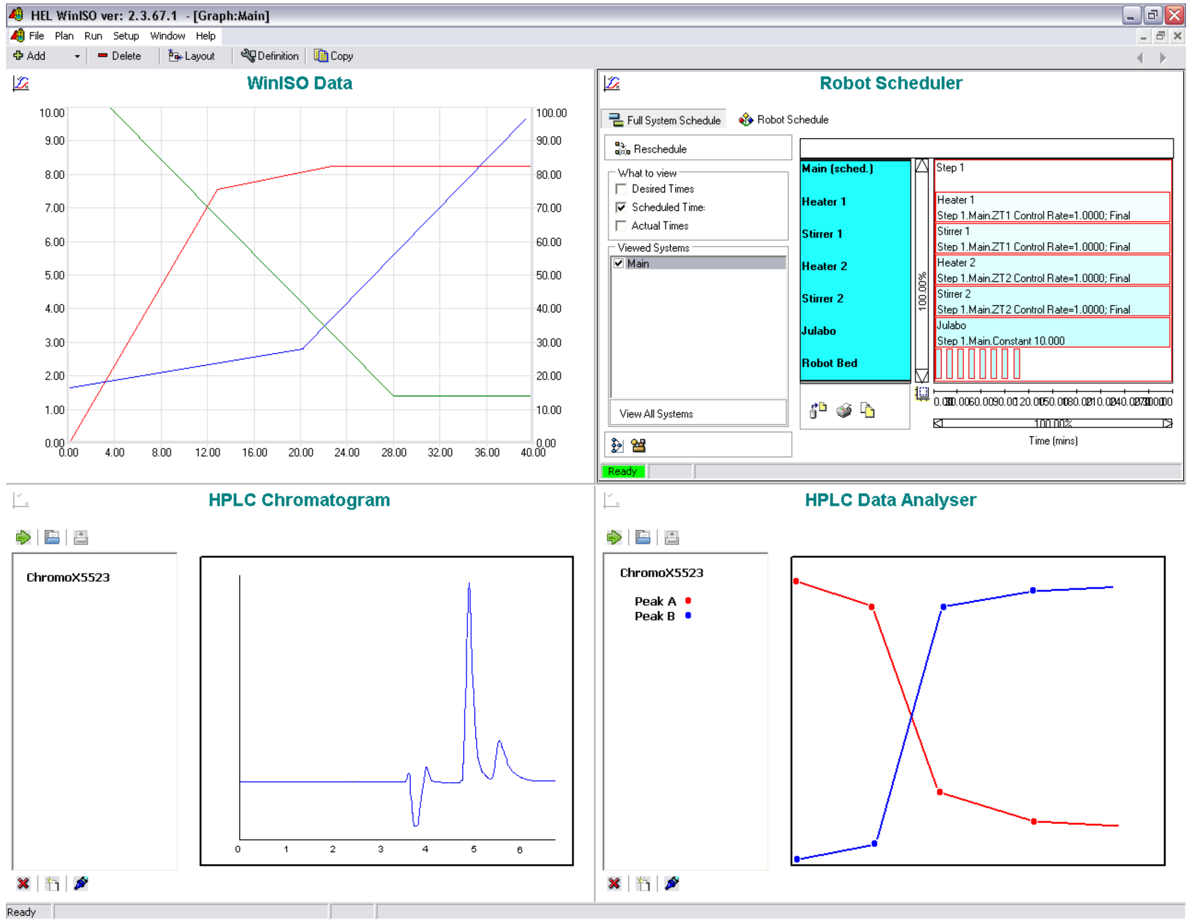
PAT integration - Real-time monitoring and feed back control



Integrating Process/Analytical Data

process data

schedule



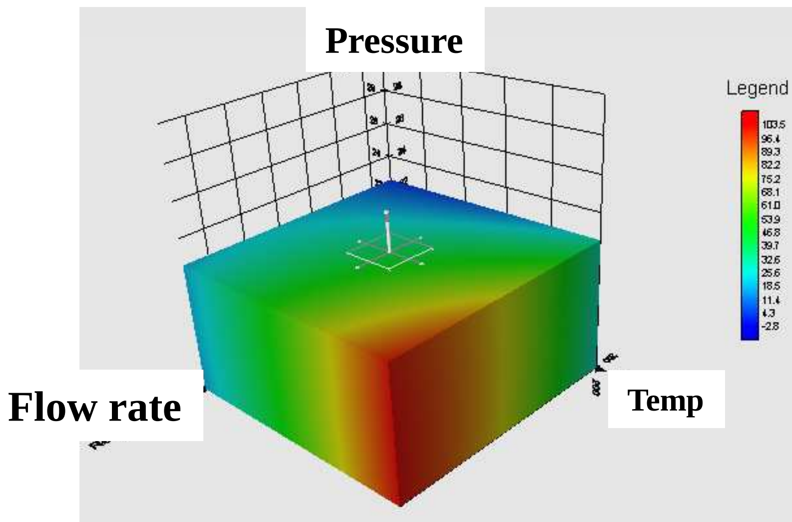
chromatogram

data analyser

better chemistry - faster

Process Development Examples using DOE

- Samples can be taken at <u>each</u> change of operating condition
- Wide range of conditions can be tested, sequentially, without operator involvement (no need to clean reactor after each change)
- Integrated with Stavex software

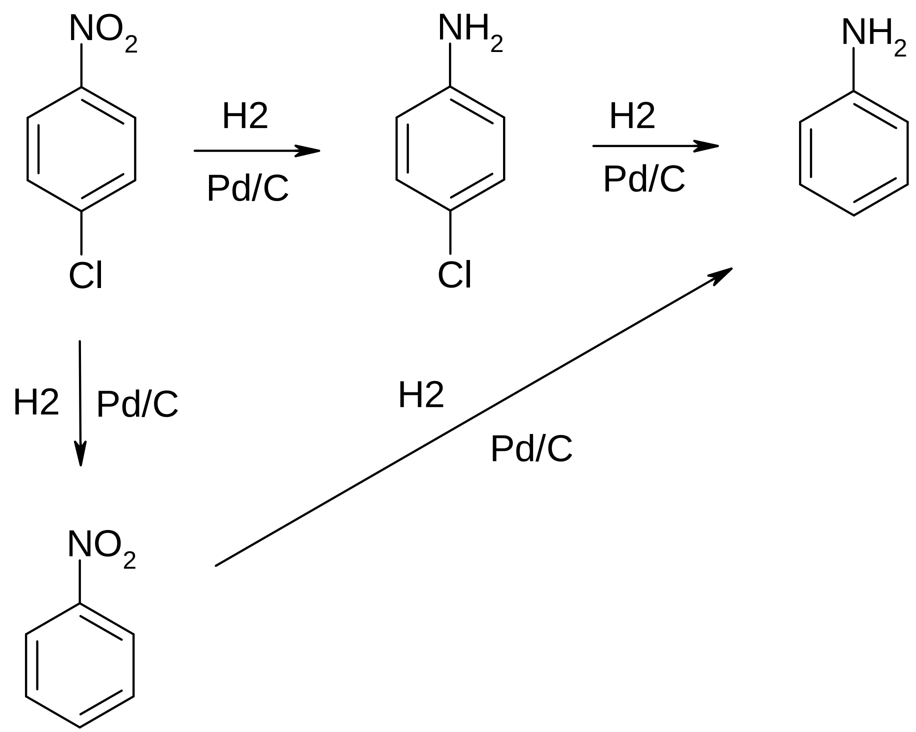


STAVEX software

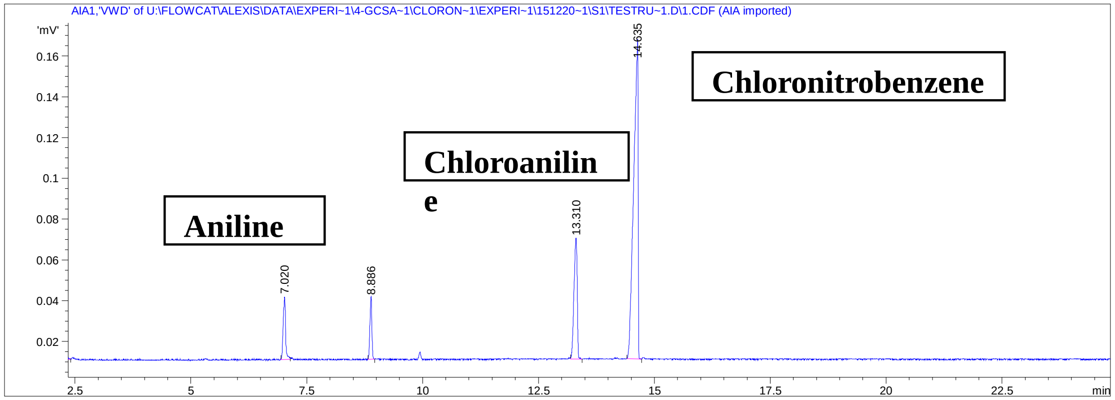
better chemistry - faster

H·E·L

EXAMPLE 2: Conversion of chloronitrobenzene to chloroaniline



GC Traces: chloronitrobenzene to chloroaniline



Fractions: 55.8% chloronitrobenzene

15.2% chloroaniline 6.1% aniline

Conditions:P=5bar T=22ºC

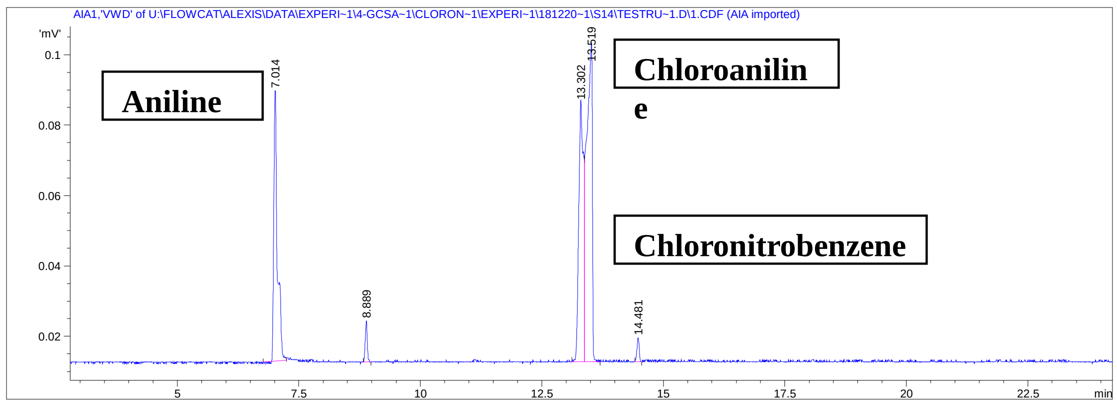
Residence time=0.5min

Fractions: 24% chloronitrobenzene

43.4% chloroaniline

24.2% aniline

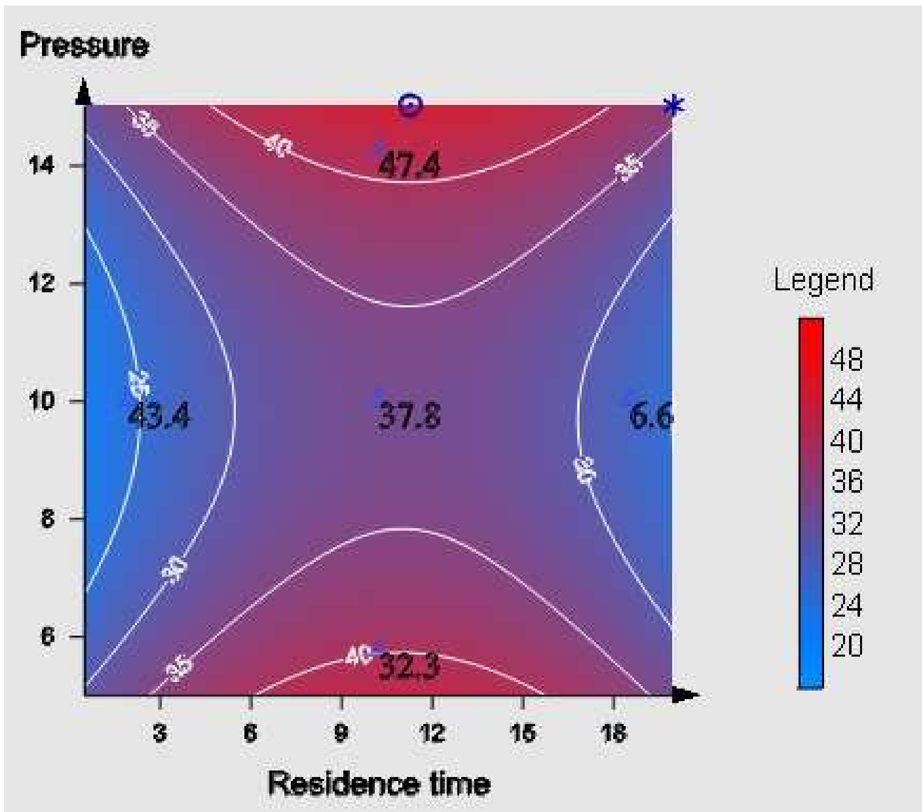
Conditions:P=10bar T=61ºC
Residence time=1.96min



better chemistry - faster

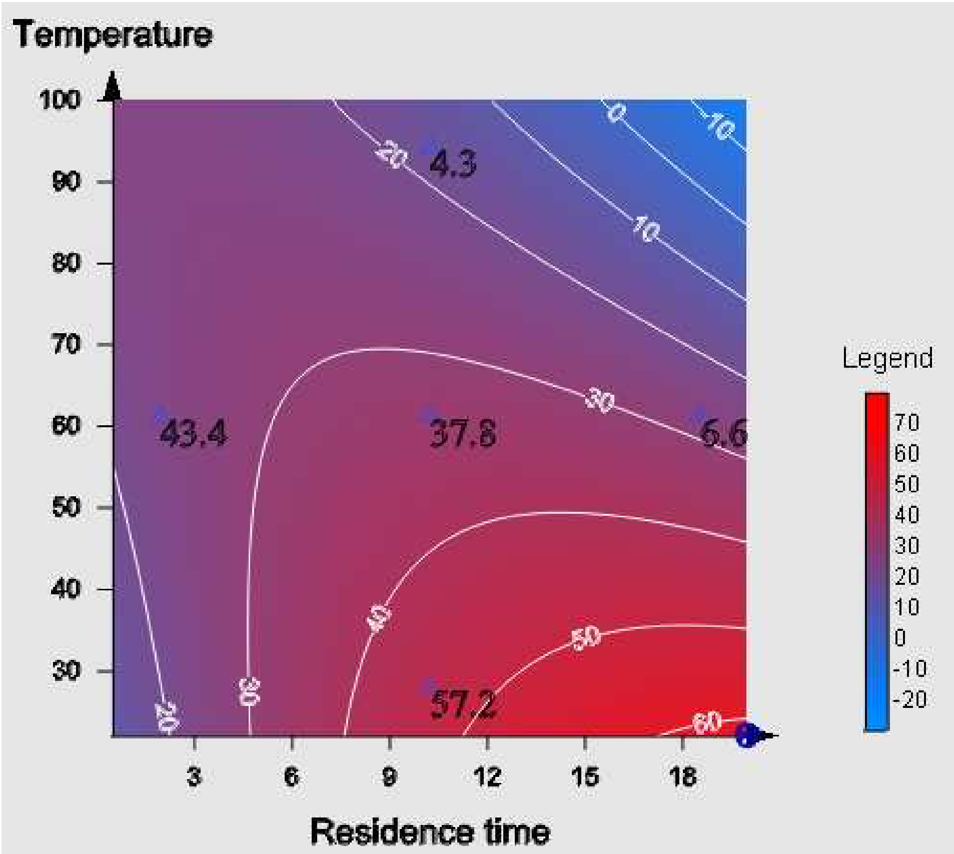
H·E·L

chloronitrobenzene to chloroaniline (Pressure-residence time)



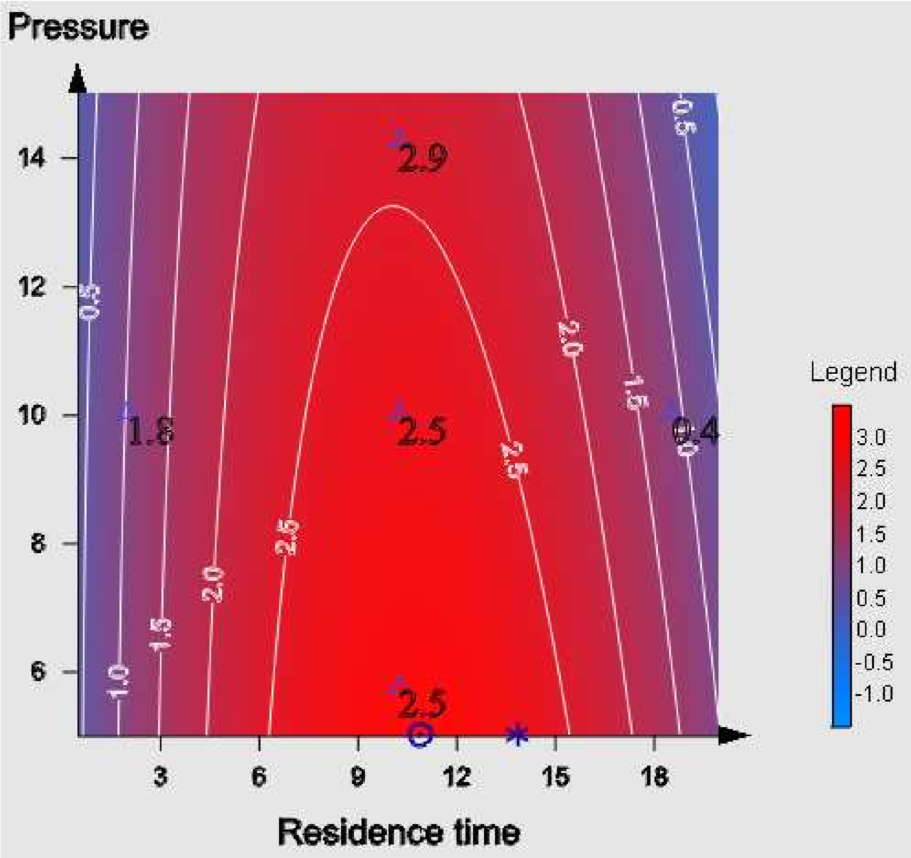
Low and high pressures yield the better conversions at medium residence times

chloronitrobenzene to chloroaniline (Temp – residence time)



- **Chloroaniline reacts to yield aniline at high temperatures**
- **Conversion favoured by low temperatures and high residence times**
- **Wrong range of conditions selected – go back!**

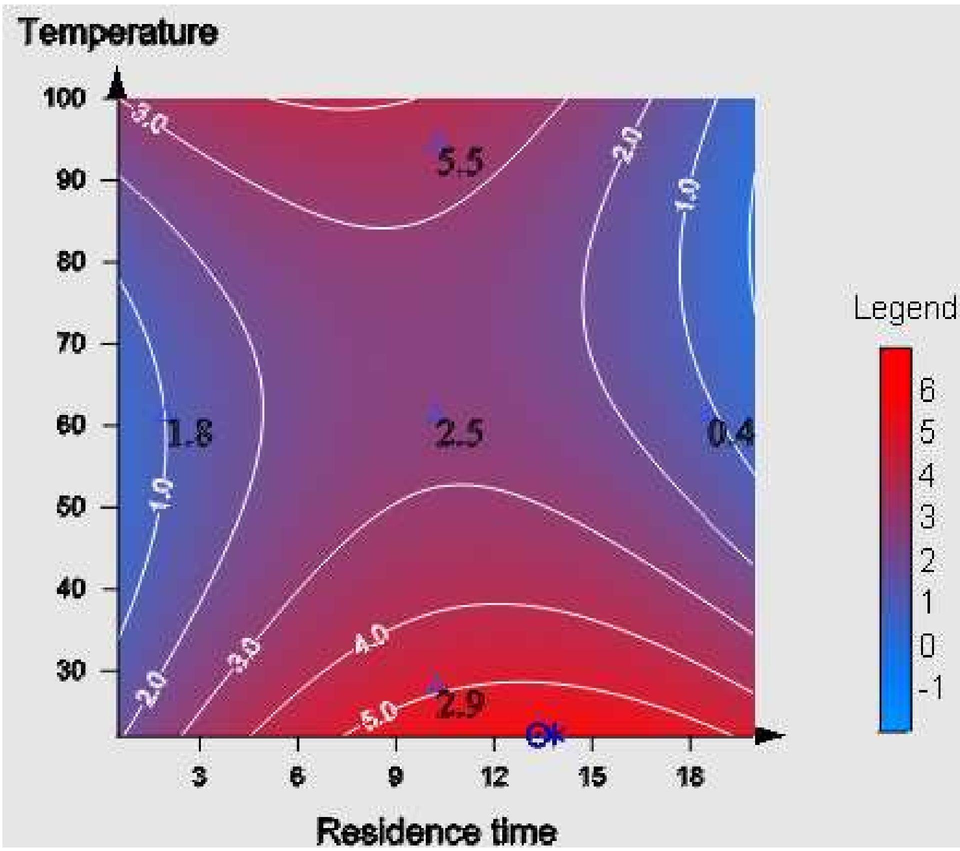
chloronitrobenzene to chloroaniline (Pressure – residence time)



- mid-range residence time favours chloroaniline

- High or low residence time favours aniline

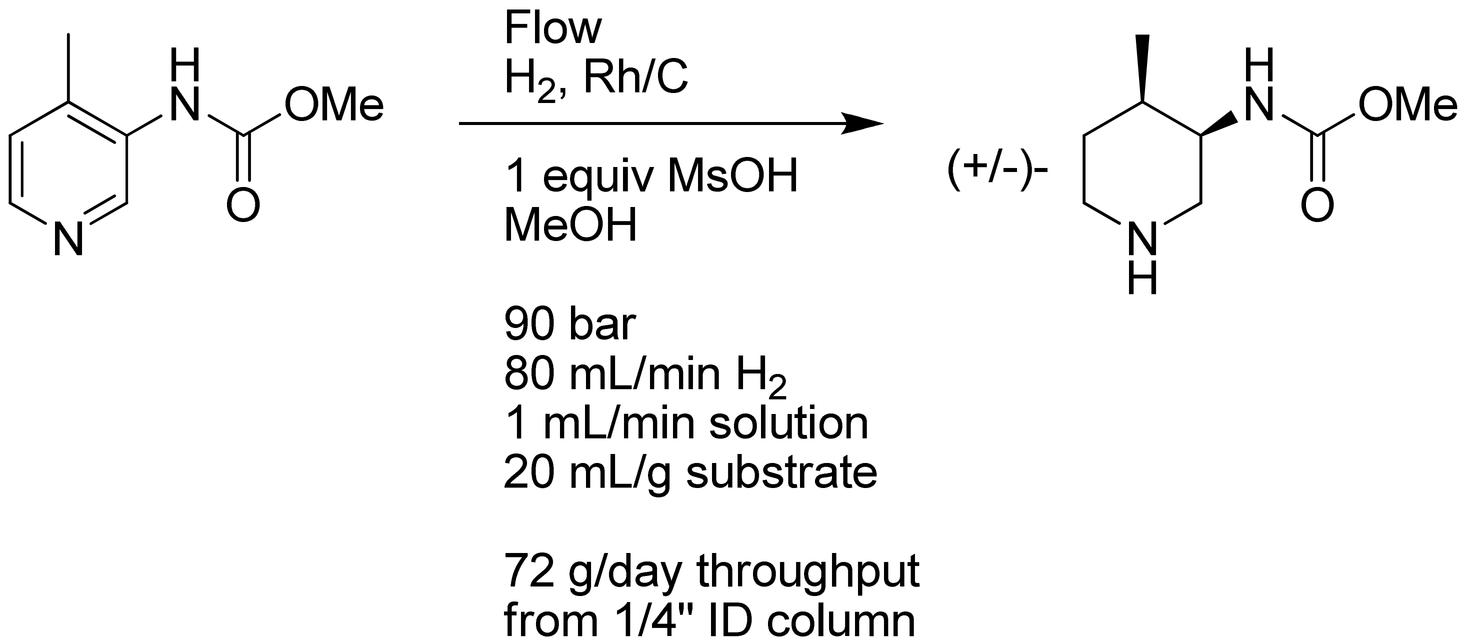
chloronitrobenzene to chloroaniline (Temp – Residence time)



- **Mid-range residence time and low temperature favours high yield chloraniline**

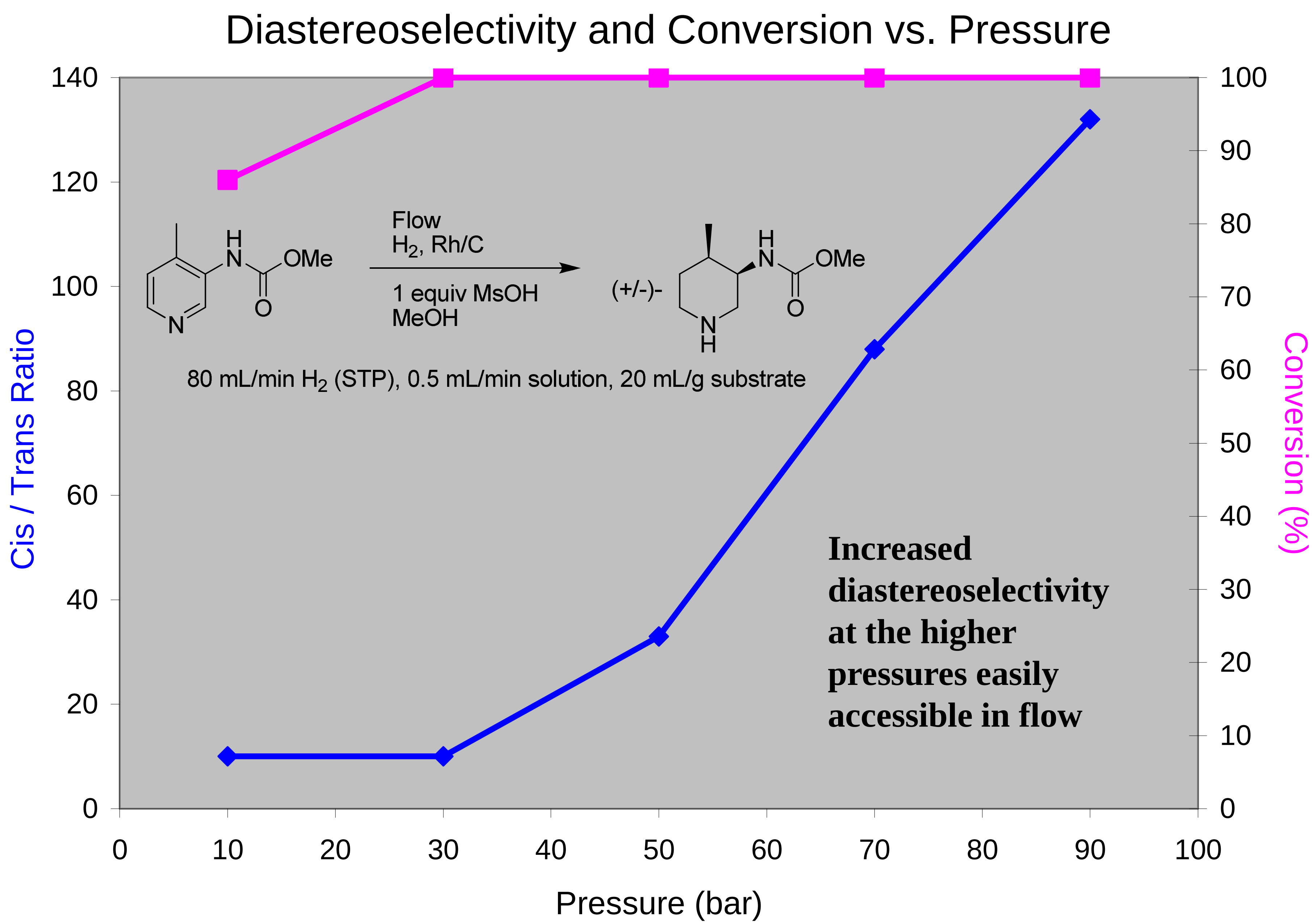
- **Aniline favoured by high or low residence time**

Sterioselectivity through flowCAT Process Control



- **100 g hydrogenated with 1 g of catalyst which was still active**

(Example courtesy J. Hawkins, Pfizer Inc, August 2010)



Diastereoselectivity and Conversion vs. Pressure
Flow
H2, Rh/C
1 equiv MsOH
MeOH
(+/-)-
OMe
80 mL/min H2 (STP), 0.5 mL/min solution, 20 mL/g substrate
Increased diastereoselectivity at the higher pressures easily accessible in flow
Cis / Trans Ratio
Conversion (%)
Pressure (bar)
0
10
20
30
40
50
60
70
80
90
100
120
140

flowCAT - CONCLUSIONS

• Bench-scale flow system, industrially proven development

• Wide range of operating conditions

• Controls all important variables and reports progress in real time.

• Full integration of third party sensors for PAT

•Low flow version feasible, cartridge designs being tested

•Already in use for prep-scale work

.