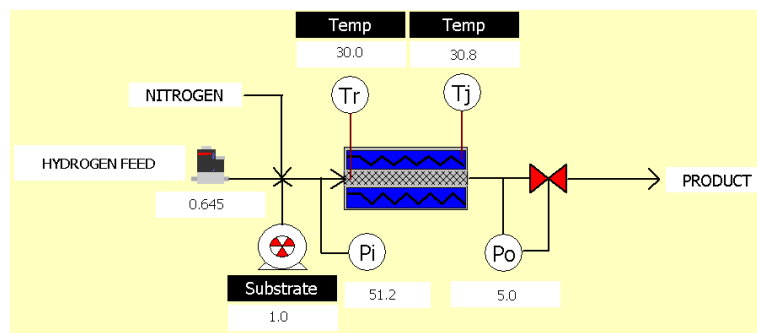


FlowCAT - continuous flow reactor system for hydrogenation screening and small scale production



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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.

better chemistry - faster



Terminology in catalytic reactions

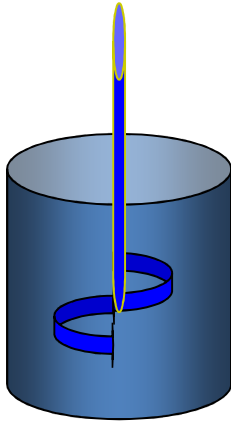
- ▲ **Homogeneous catalysis**
- ▲ **Heterogeneous catalysis**
- ▲ **Fixed bed or Plug Flow (continuous) and stirred/Batch reactors**

Fixed Bed is special case of continuous flow type.

better chemistry - faster



Crude Mathematical equivalence of flow and batch reactors



Batch Time



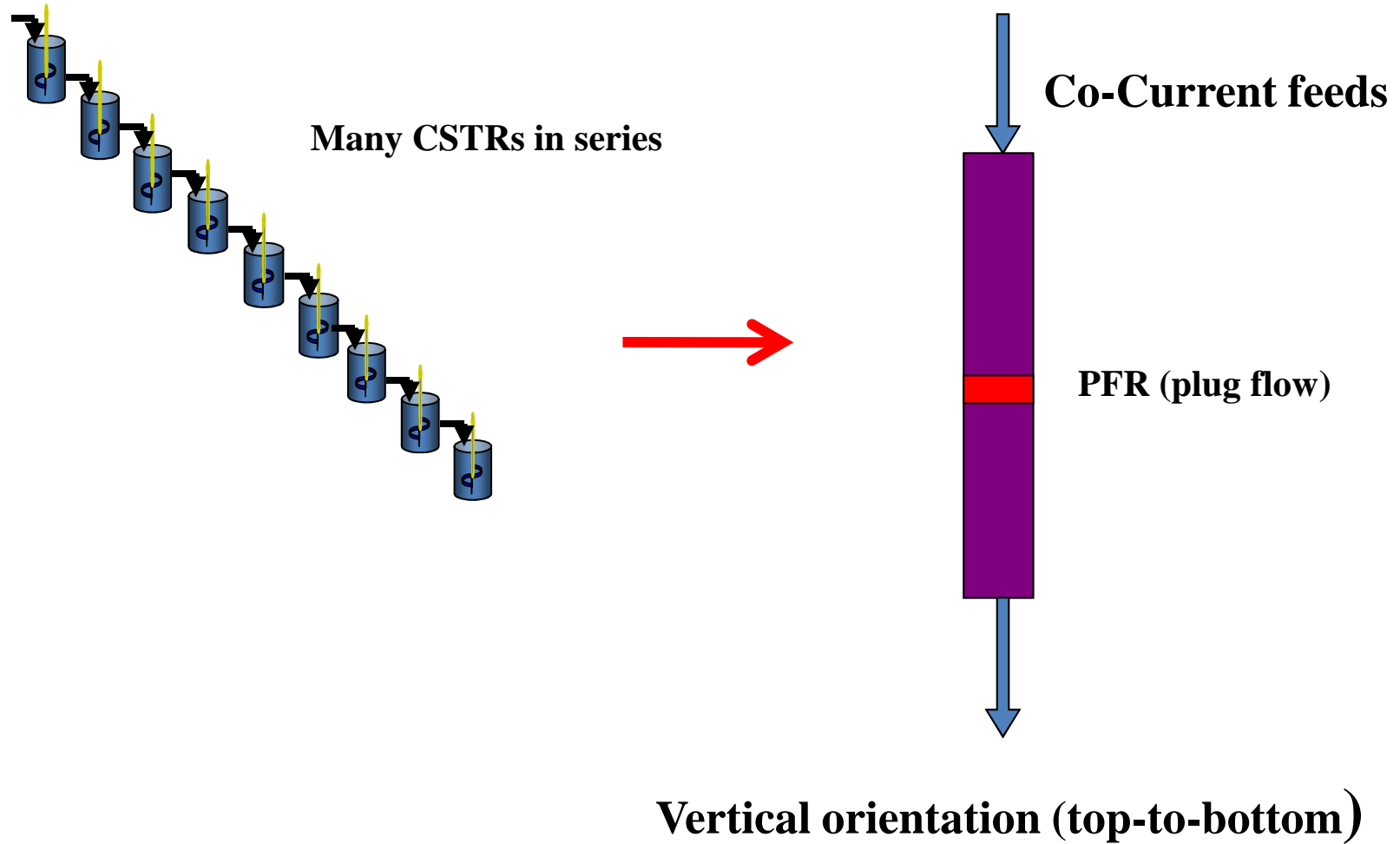
Residence Time = Volume/flow rate

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

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Closer Mathematical equivalence of Reactors



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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.

better chemistry - faster



FlowCAT Package



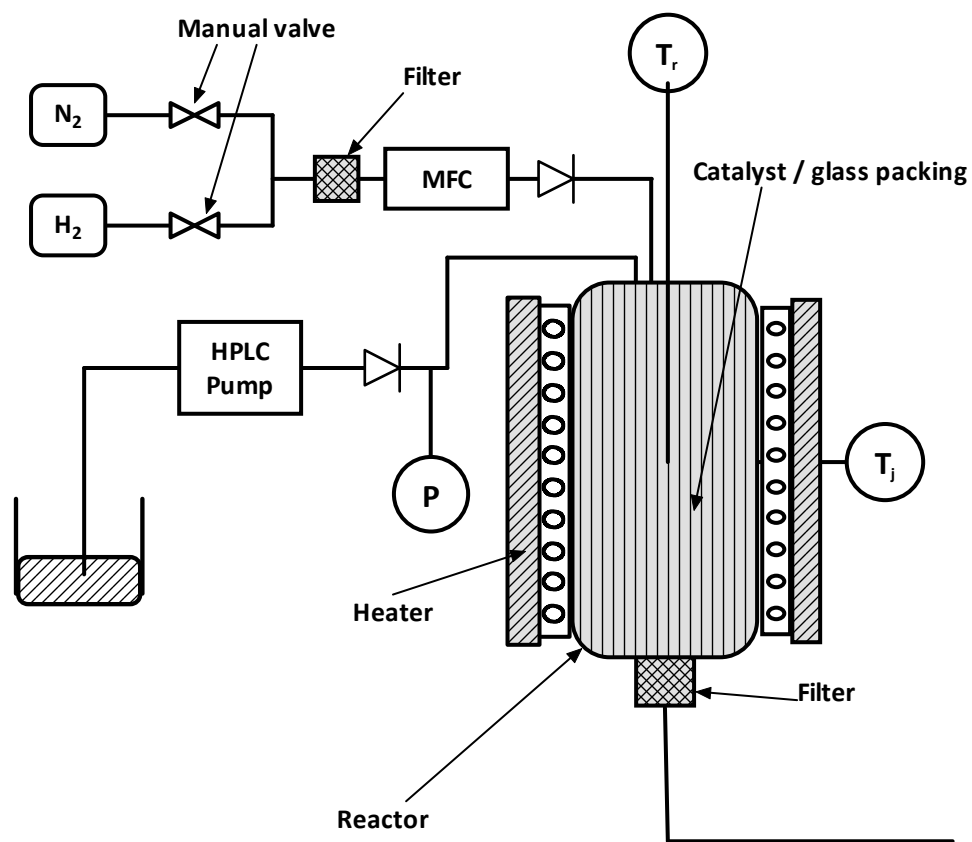
- Developed to bridge screening and prep-scale needs
- Not limited to hydrogenations
- Fully software controlled
- Does not require high pressure expert for operation

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

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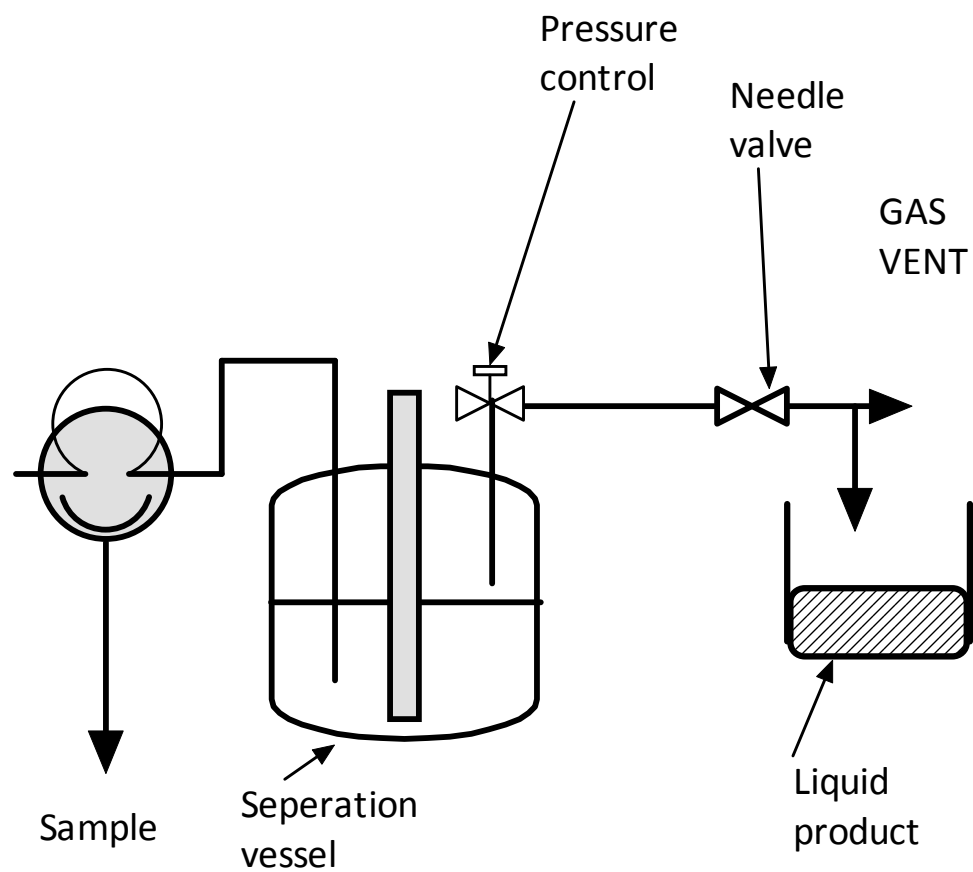
flowCAT Feed Section



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flowCAT Product Sampling and Collection



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FlowCAT Typical Specification

- **Standard lengths: 15cm (6")**
- **Two standard int. diameters: 1/2" (12mm) or 1/4" (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

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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.

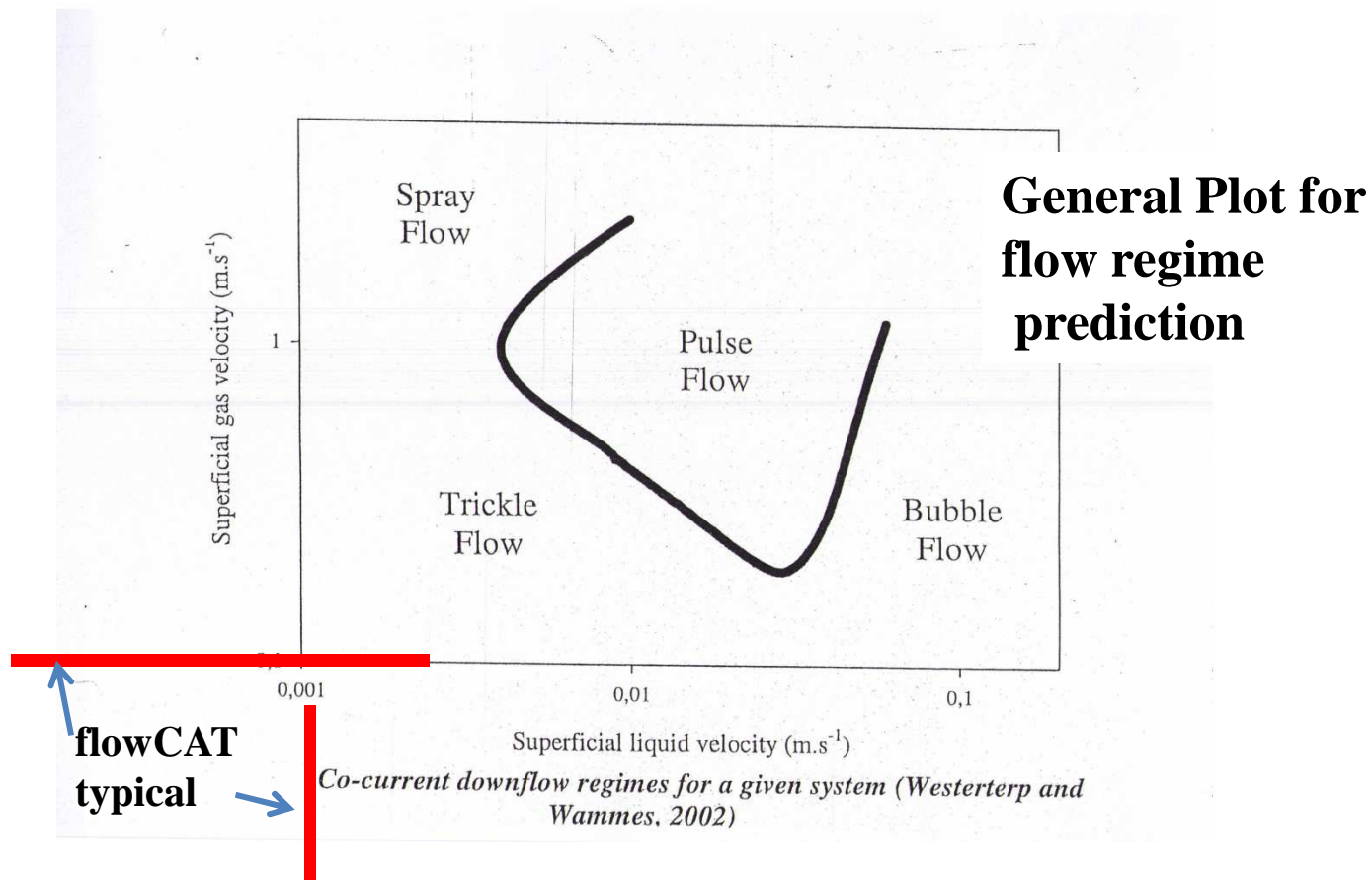
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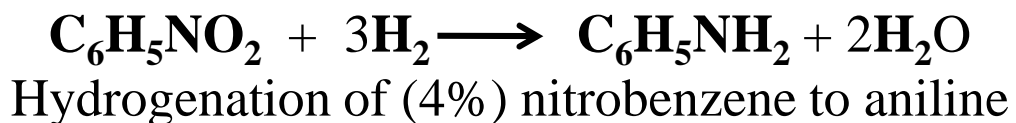
Trickle Bed Flow Regime

Most common mode of operation for tubular fixed bed reactors

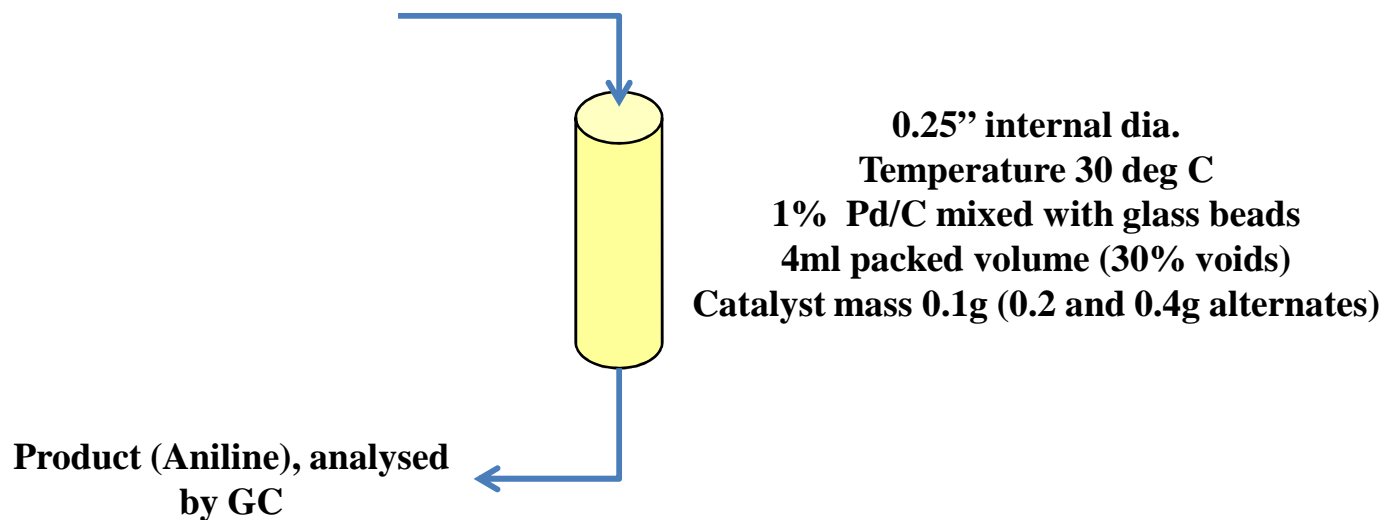
- ▲ Fixed bed of inert and catalyst pellets, former occupying large volume (50% or more)
- ▲ Co-current downward flow of gas and liquid
- ▲ Leads to gas dispersed, liquid continuous phases around solids



flowCAT performance Testing



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

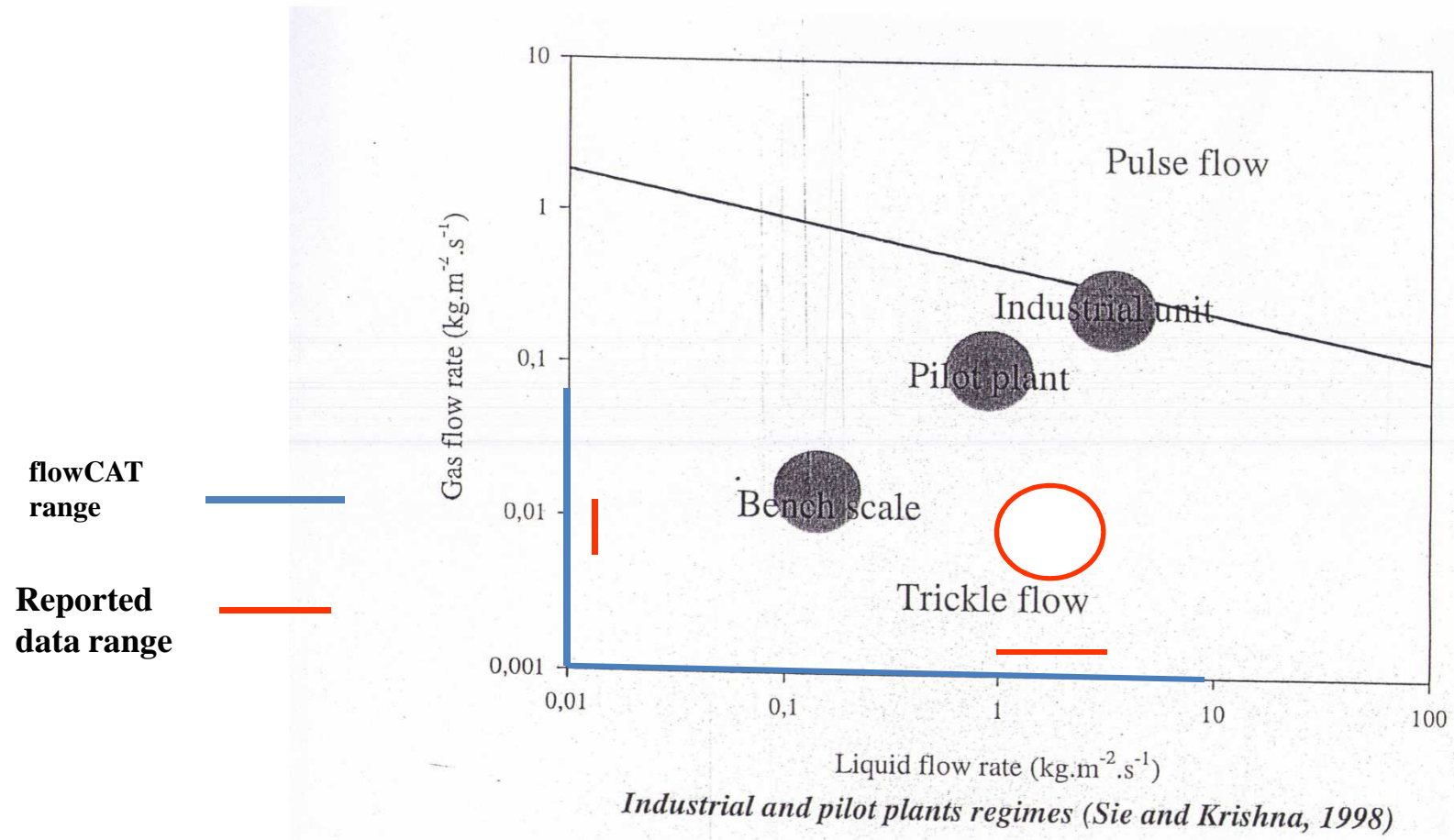


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Trickle Bed Flow – Lab Reactors

Diagram below shows likely position of bench scale flow reactors

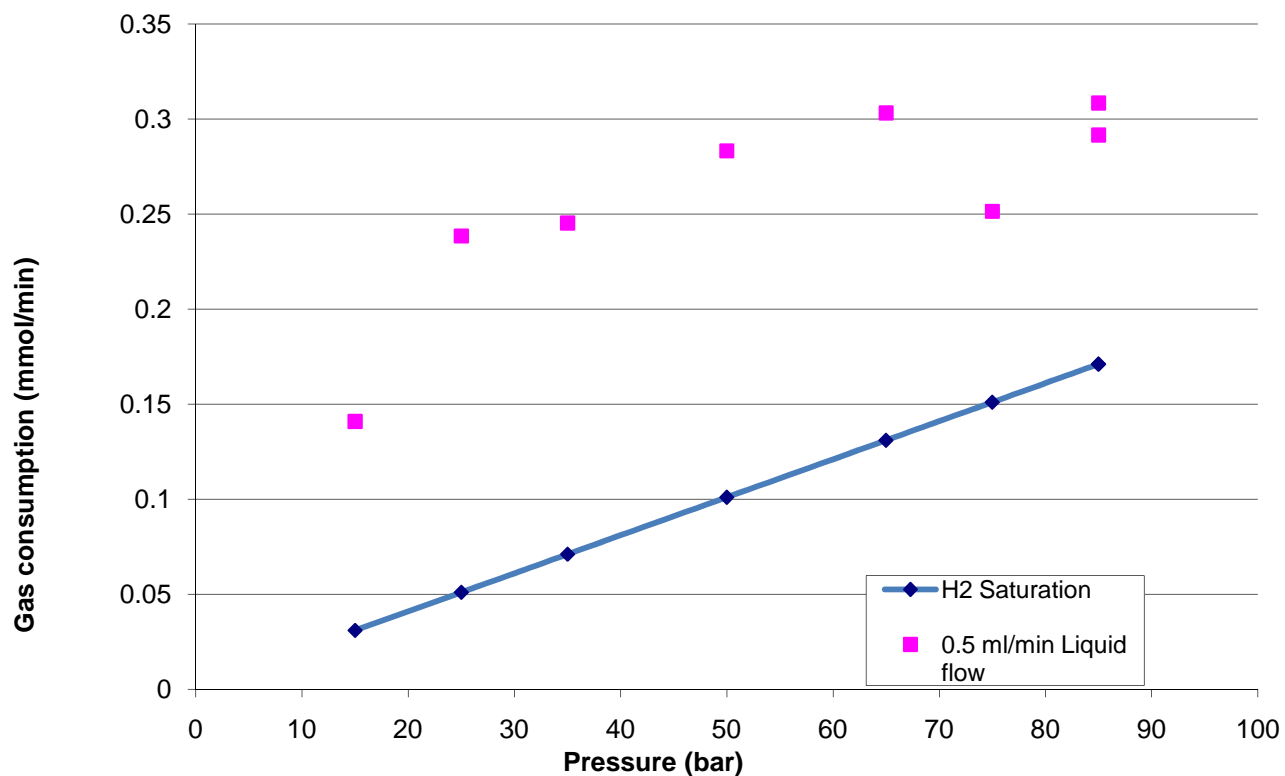


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Hydrogen consumption with pressure

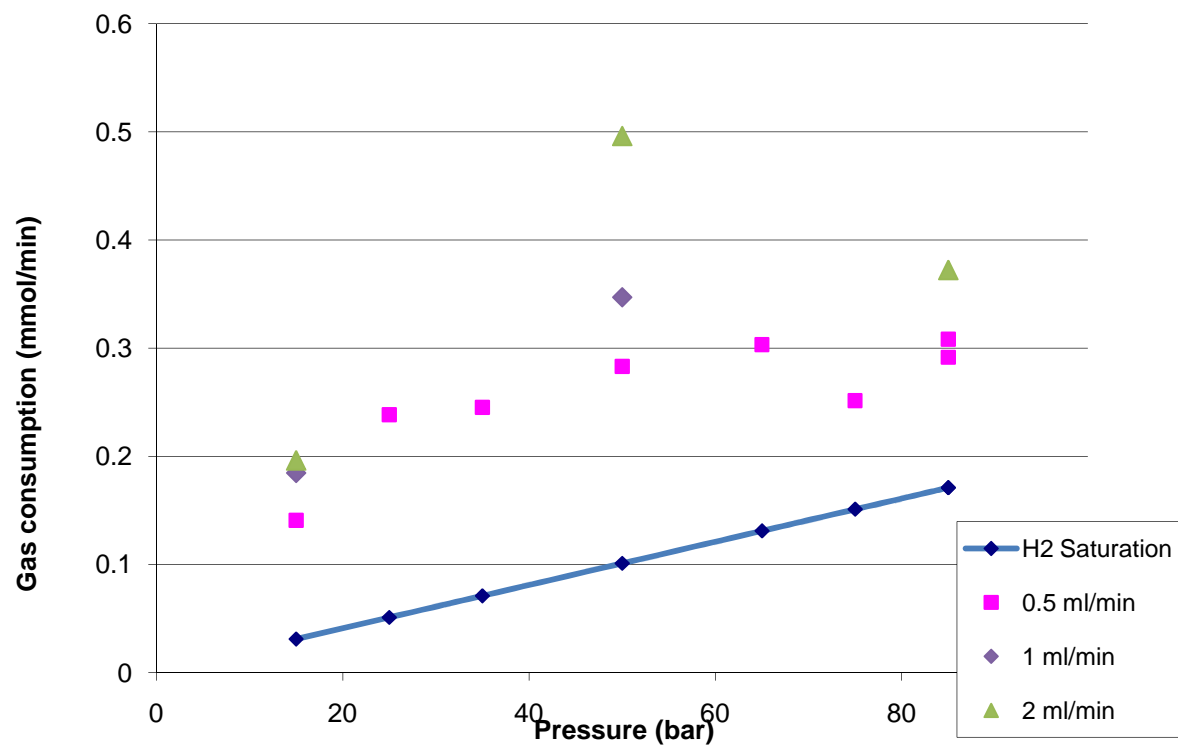
Hydrogenation of nitrotoluene to aniline



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

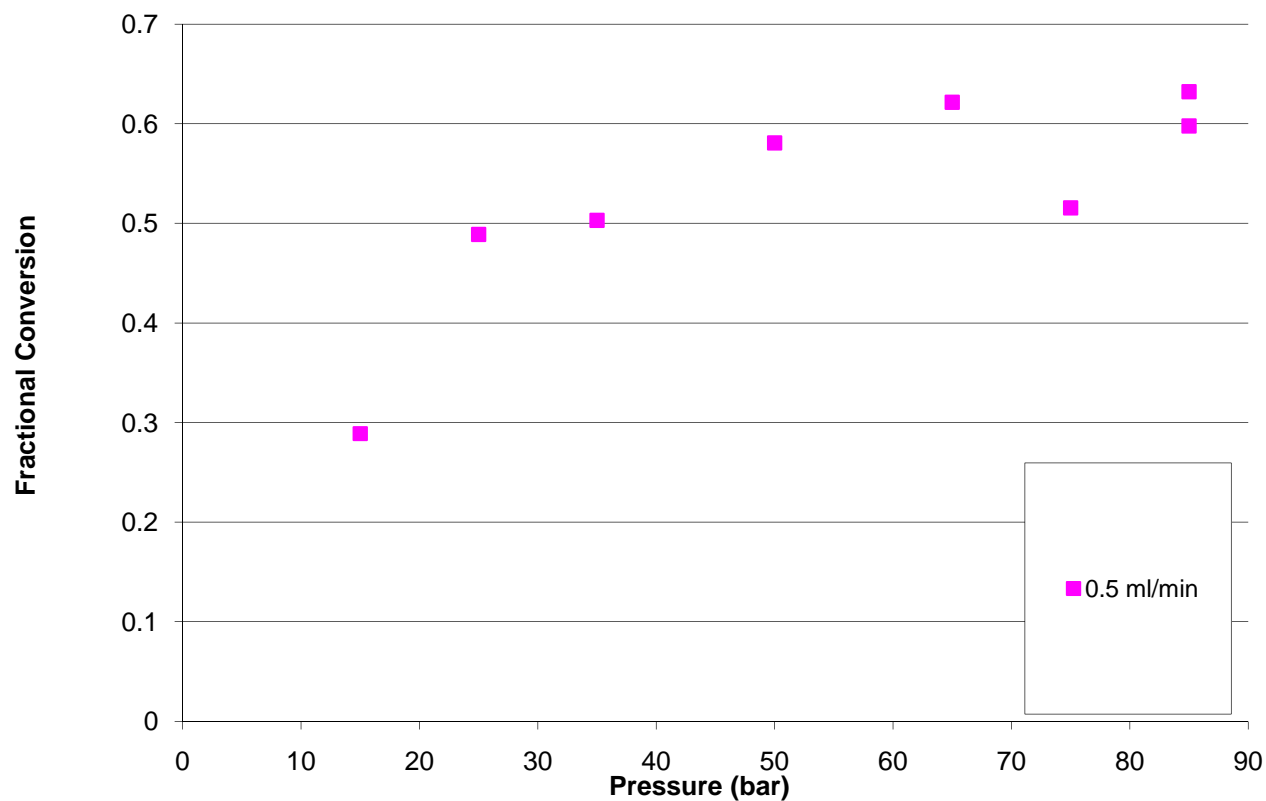
Hydrogenation of nitrotoluene to aniline



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

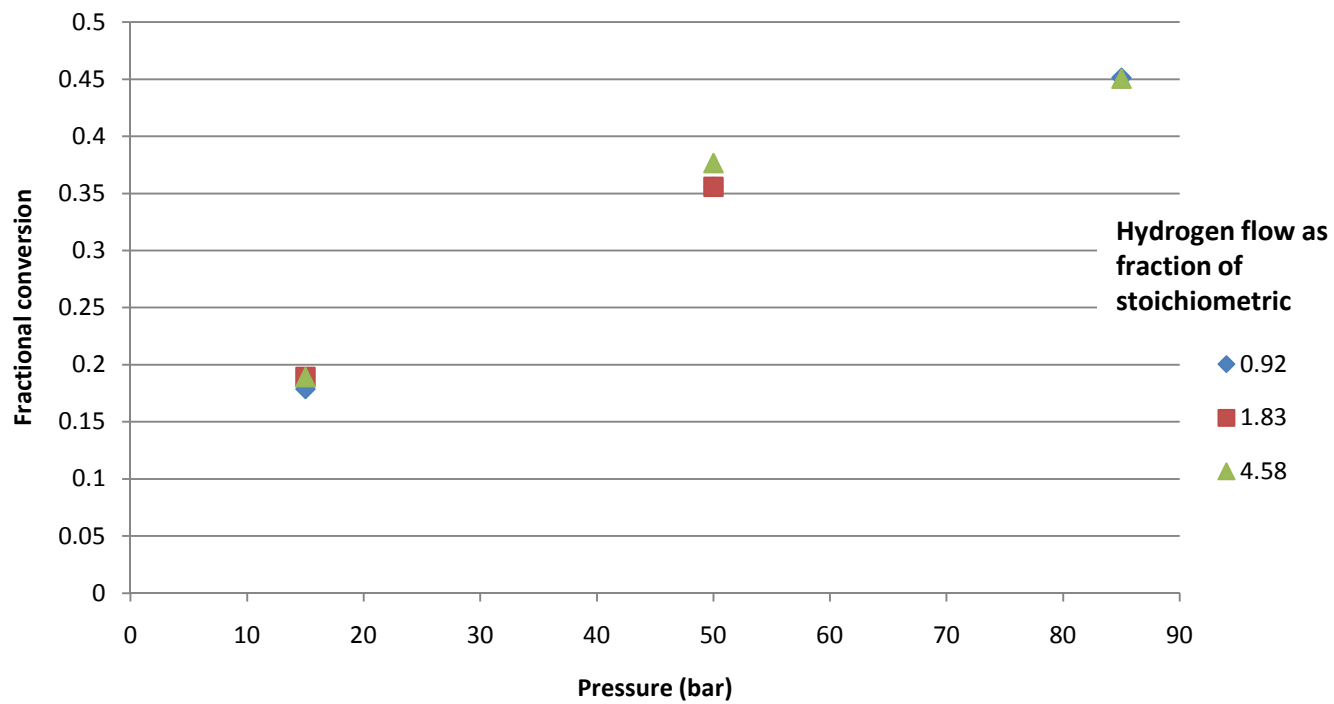


Liquid flow = 0.5ml/minuite
(residence time approx 2.4 mins)
Hydrogen 1.83 x stoichiometric
(= 20 n ml/min)
Catalyst loading 0.1g
Bed volume 4ml (30% void)



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 Chemsan
8 x 16ml reactors



Auto-MATE
4 x 100-300ml HP reactors



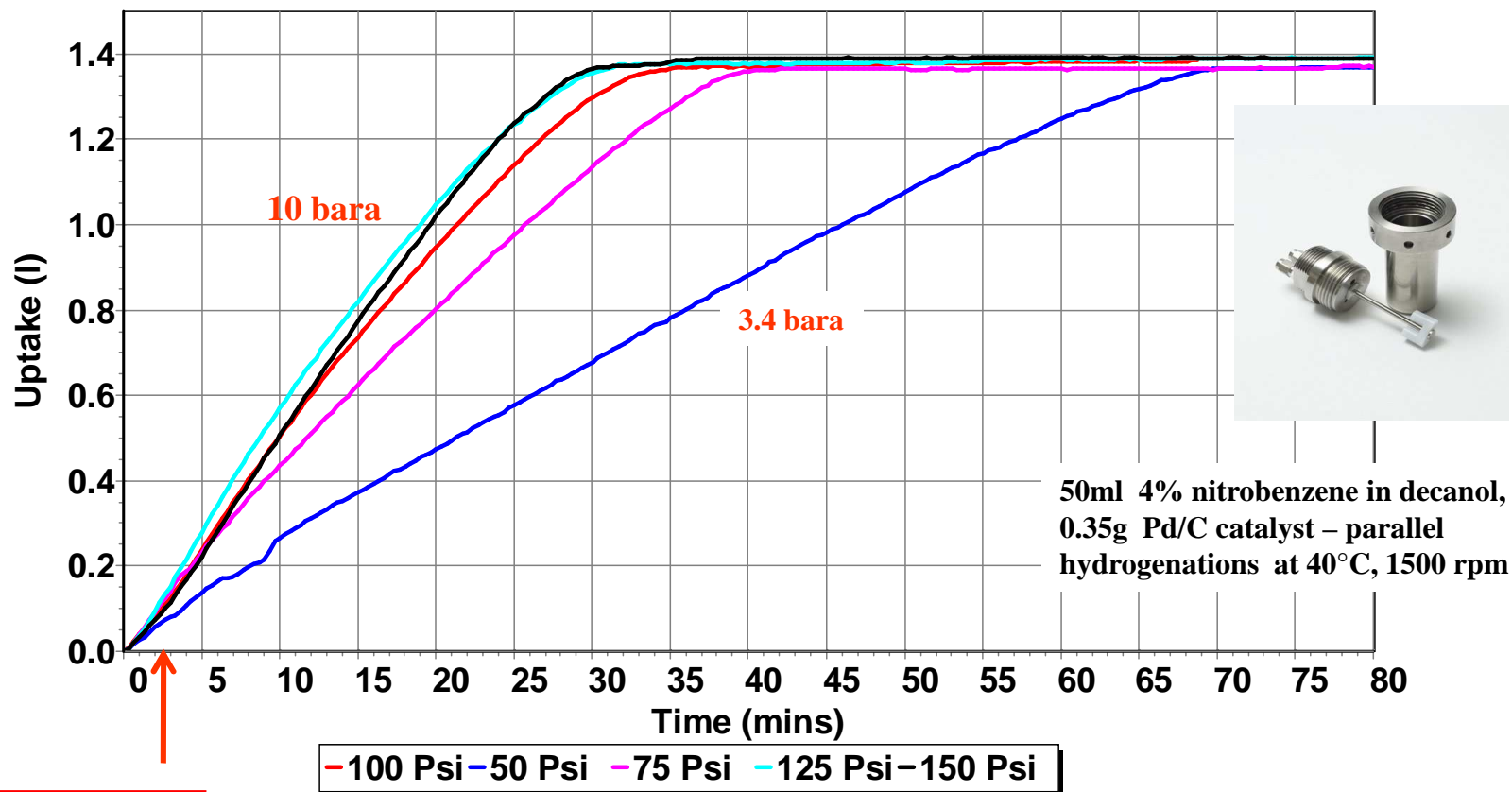
AUTOLAB
1000ml HP glass reactor

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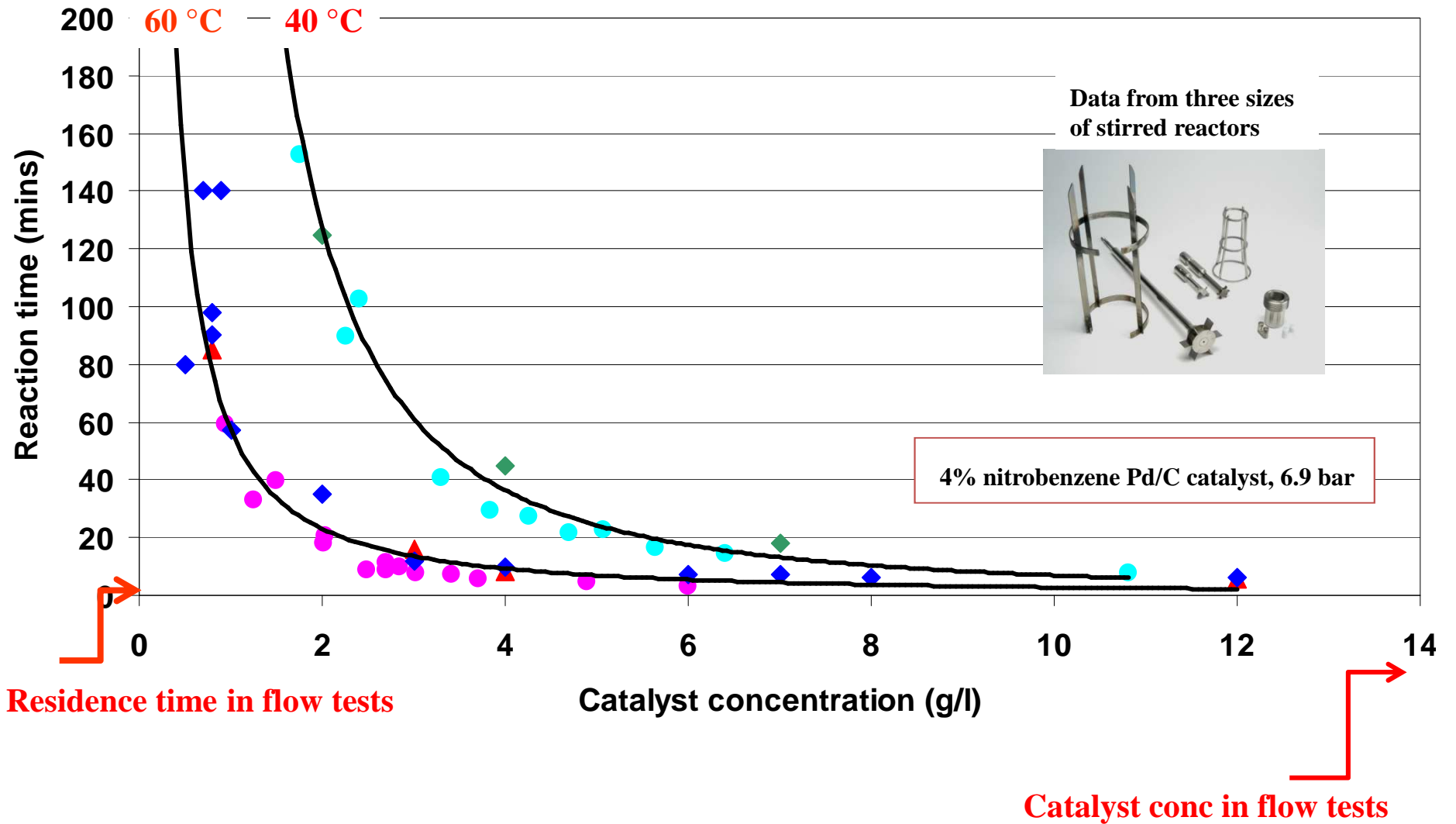
HYDROGENATION 100ml stirred HP auto-MATE

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

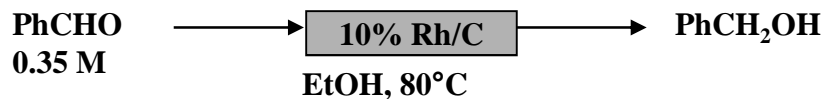
Can flowCAT be adapted for screening?

.

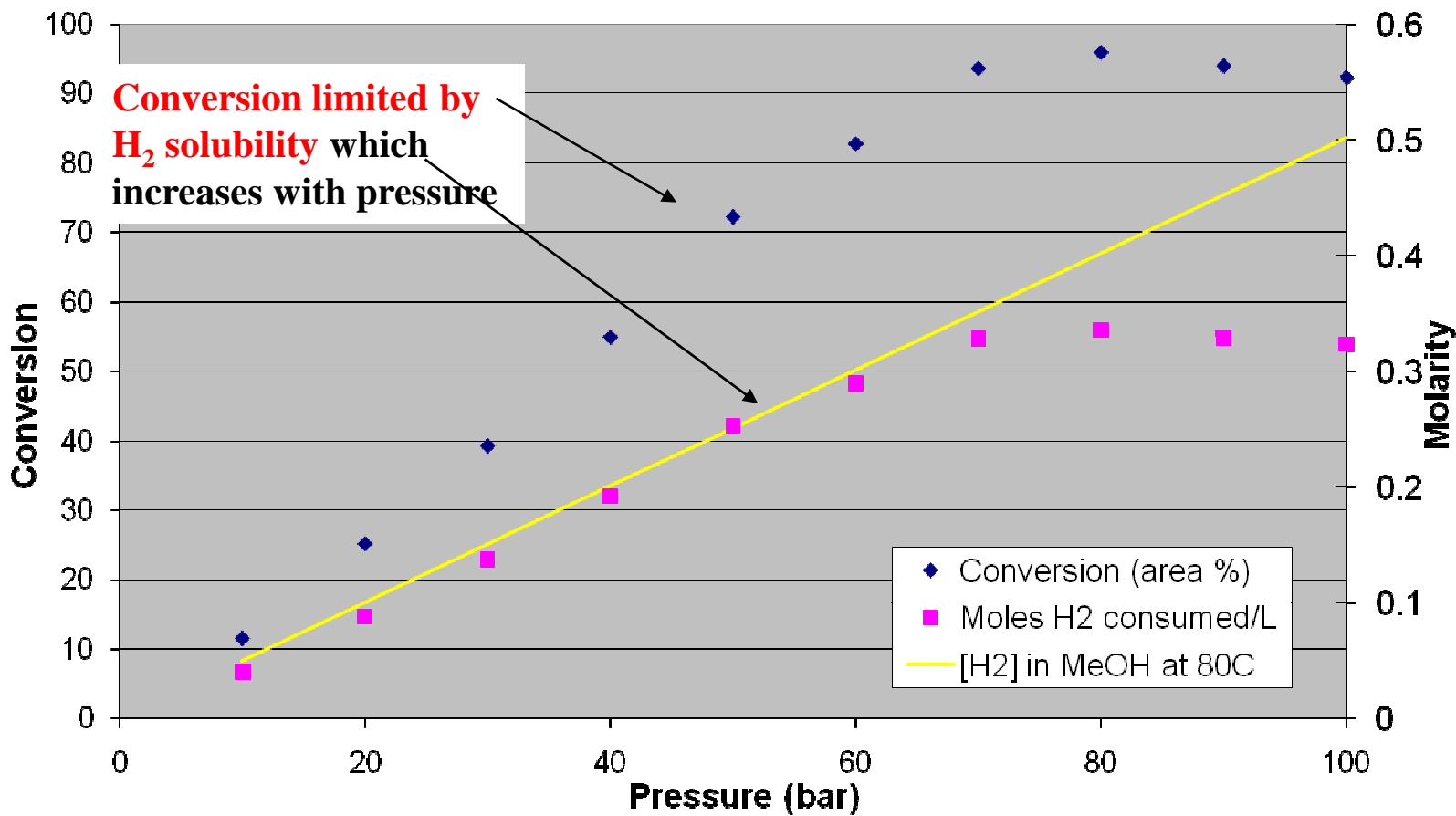
better chemistry - faster



Screening with H-cube: Conversion Limited by hydrogen solubility

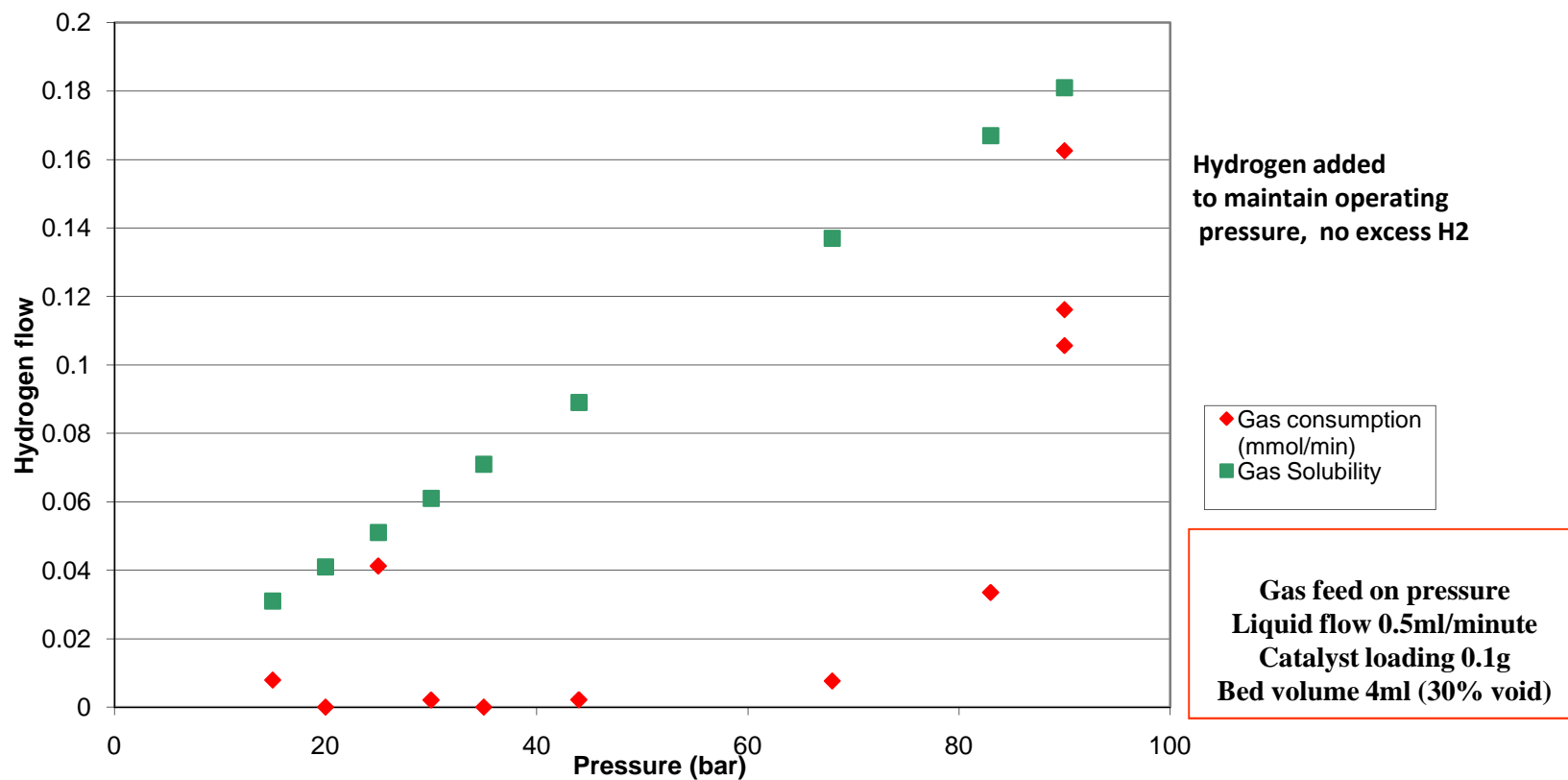


(courtesy J Hawkins, Pfizer Inc, August 2010)



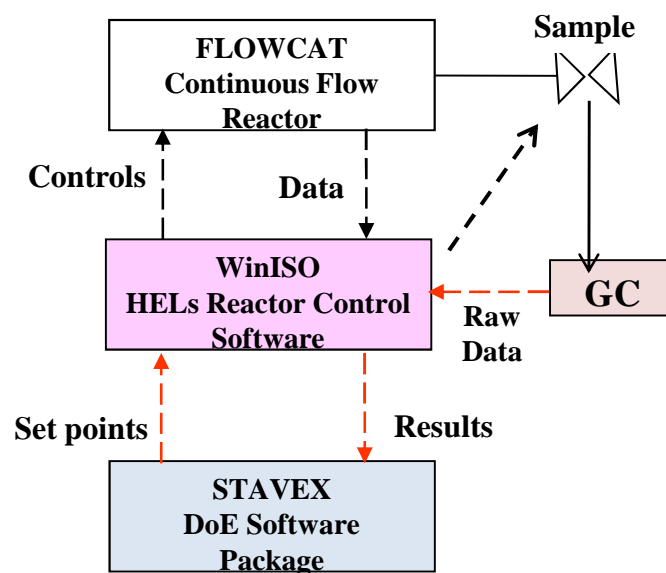
Conversion Limited by Solubility - flowCAT

Hydrogenation of nitrotoluene to aniline



flowCAT in commercial R+D

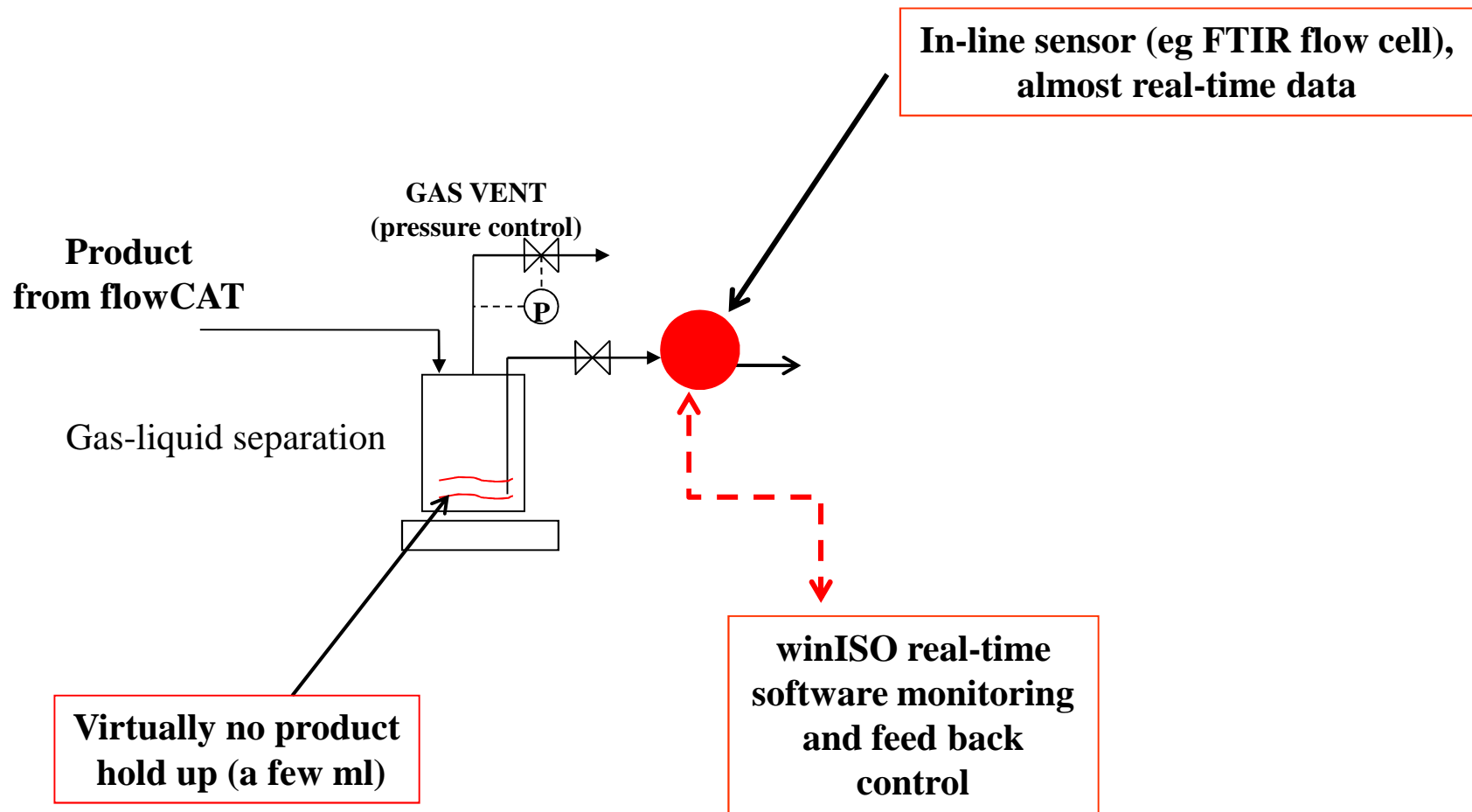
- Controlled by commercial, well established software/electronics, fully developed
- Ideal for process development and large enough for prep-scale production
- Possible to integrate with DOE package and optimise totally automatically.



better chemistry - faster



PAT integration - Real-time monitoring and feed back control

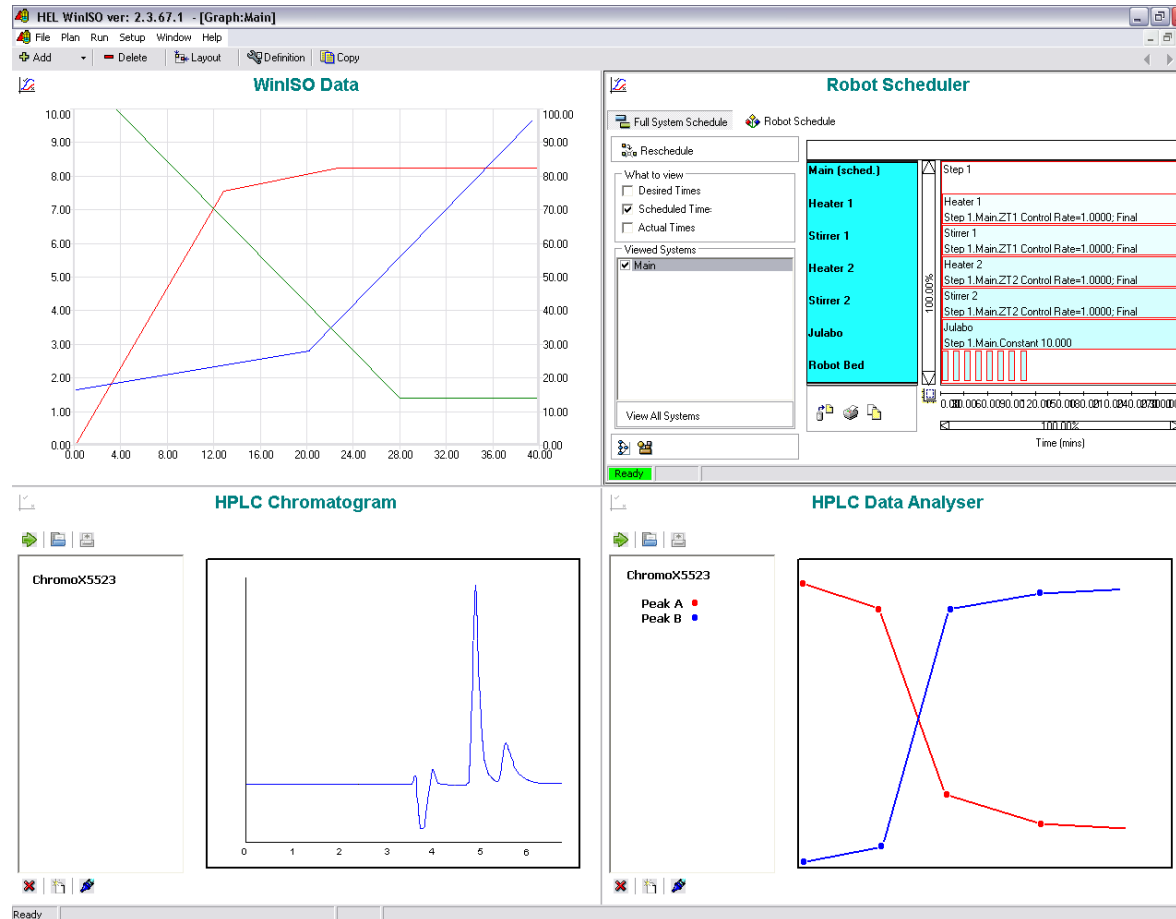


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Integrating Process/Analytical Data

process data



schedule

chromatogram

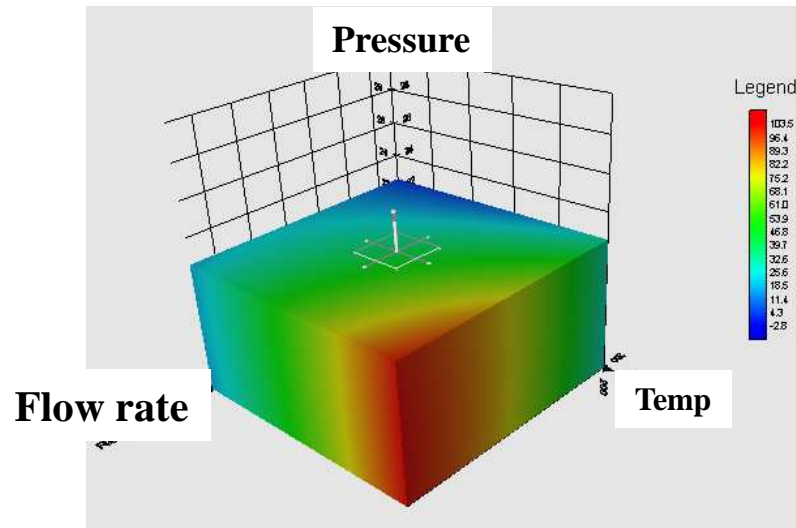
data analyser

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Process Development Examples using DOE

- Samples can be taken at each 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

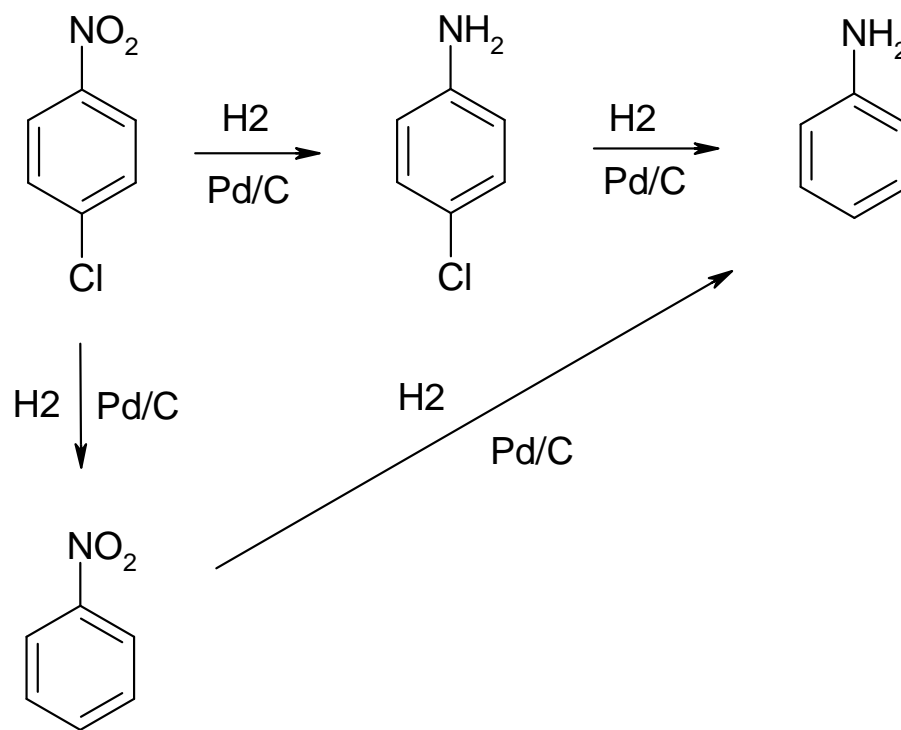


STAVEX software

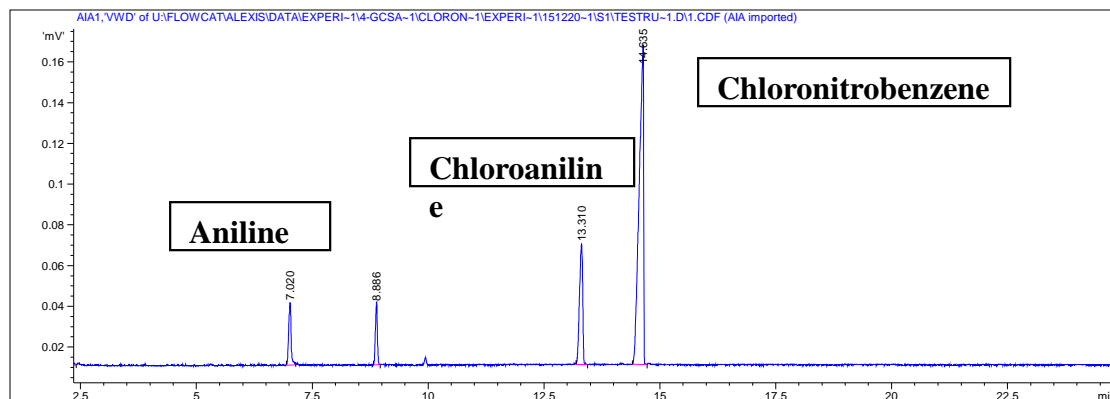
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EXAMPLE 2: Conversion of chloronitrobenzene to chloroaniline

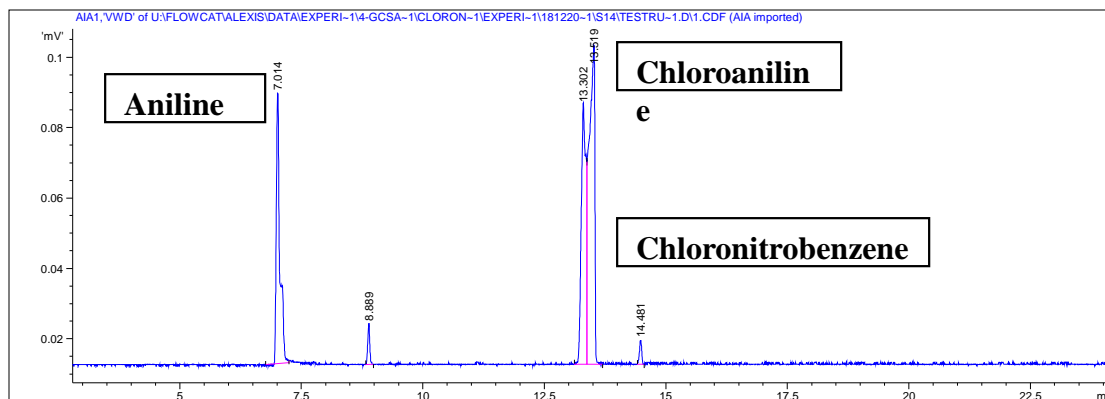


GC Traces: chloronitrobenzene to chloroaniline



**Fractions: 55.8% chloronitrobenzene
15.2% chloroaniline 6.1% aniline**
Conditions: P=5bar T=22°C
Residence time=0.5min

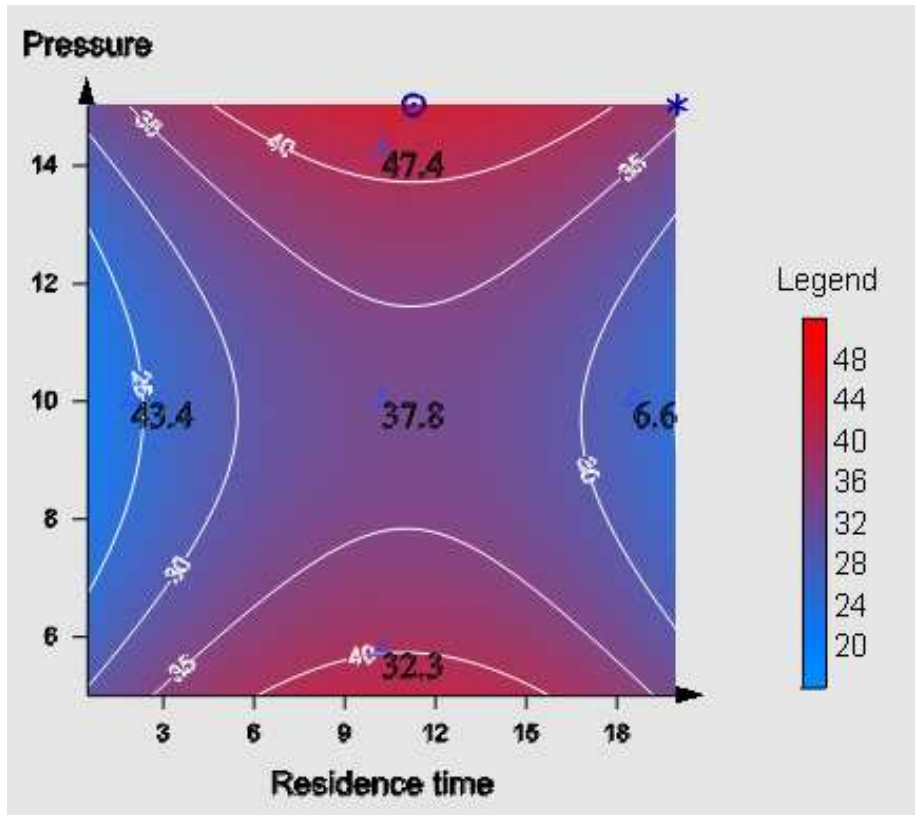
**Fractions: 24% chloronitrobenzene
43.4% chloroaniline
24.2% aniline**
Conditions: P=10bar T=61°C
Residence time=1.96min



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chloronitrobenzene to chloroaniline (Pressure-residence time)

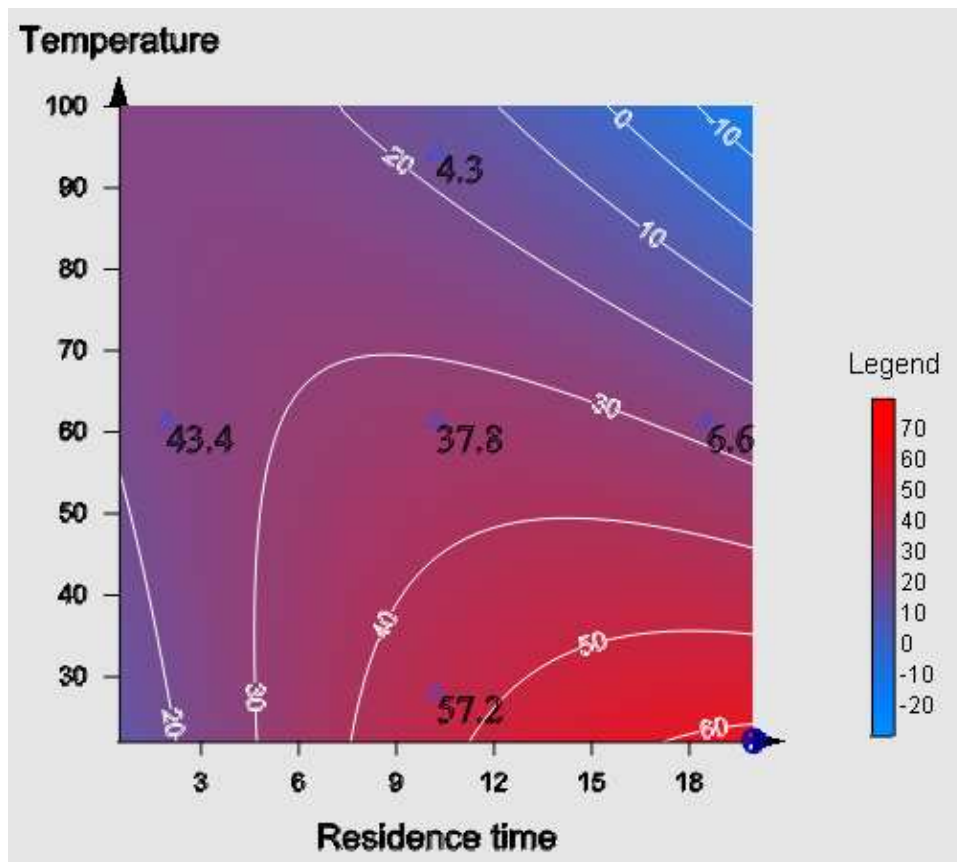


**Low and high pressures
yield the better conversions
at medium residence times**

better chemistry - faster



chloronitrobenzene to chloroaniline (Temp – residence time)

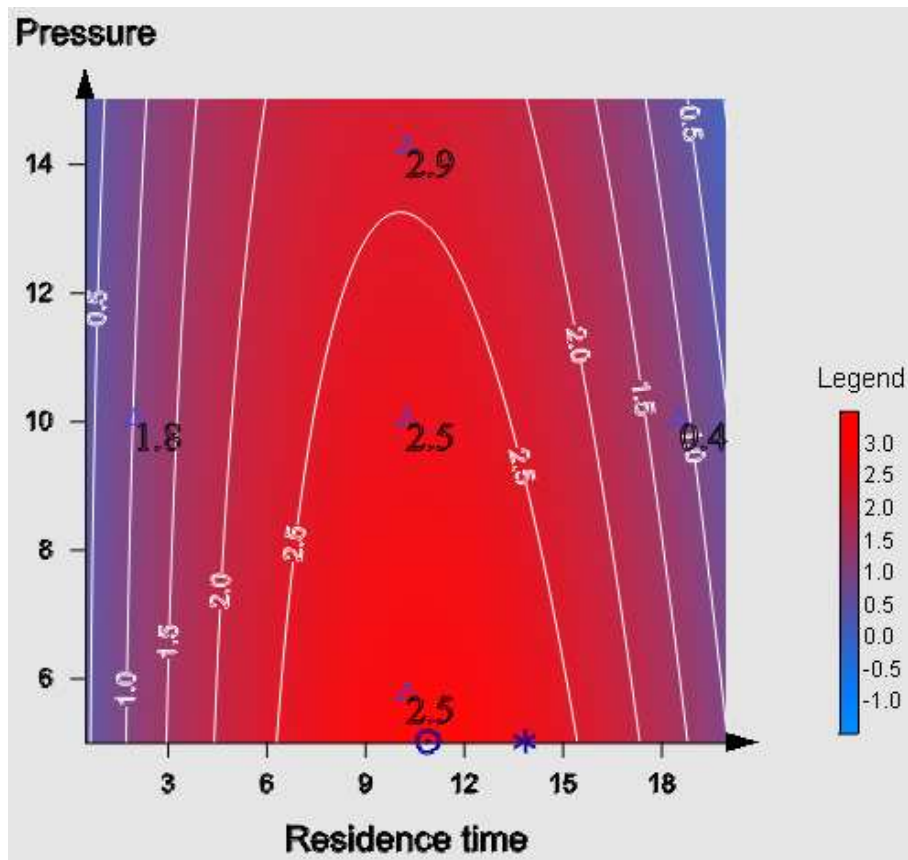


- Chloroaniline reacts to yield aniline at high temperatures
- Conversion favoured by low temperatures and high residence times
- **Wrong range of conditions selected – go back!**

better chemistry - faster



chloronitrobenzene to chloroaniline (Pressure – residence time)



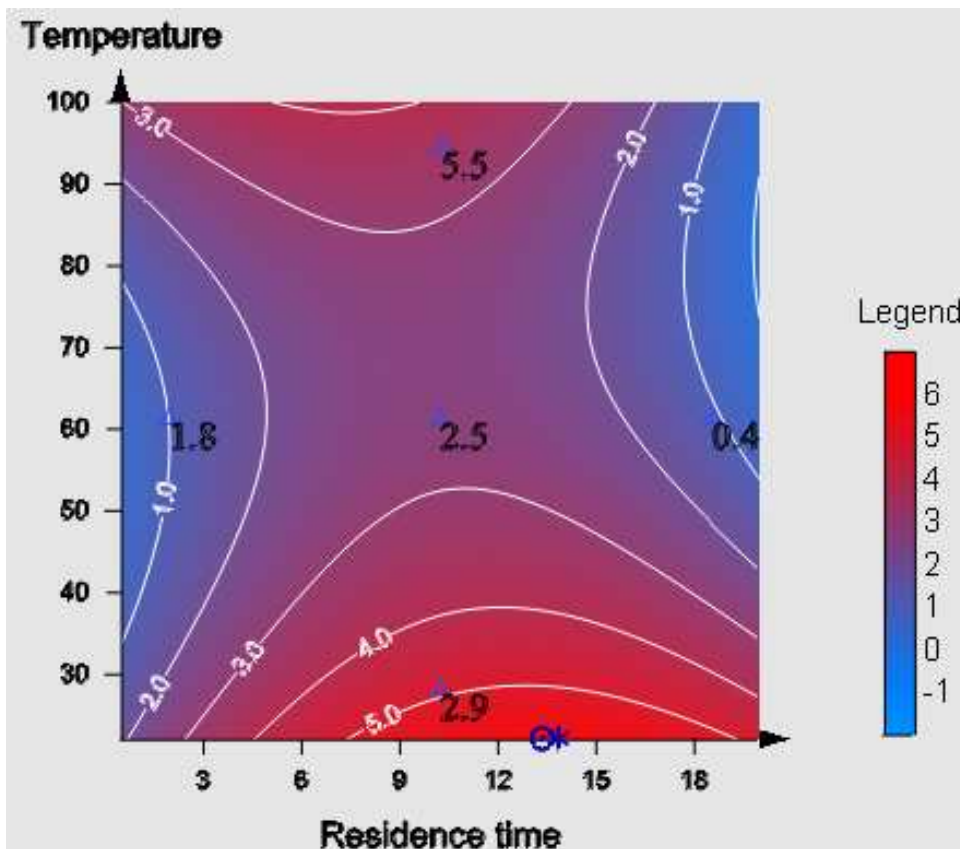
- mid-range residence time favours chloroaniline

- High or low residence time favours aniline

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chloronitrobenzene to chloroaniline (Temp – Residence time)



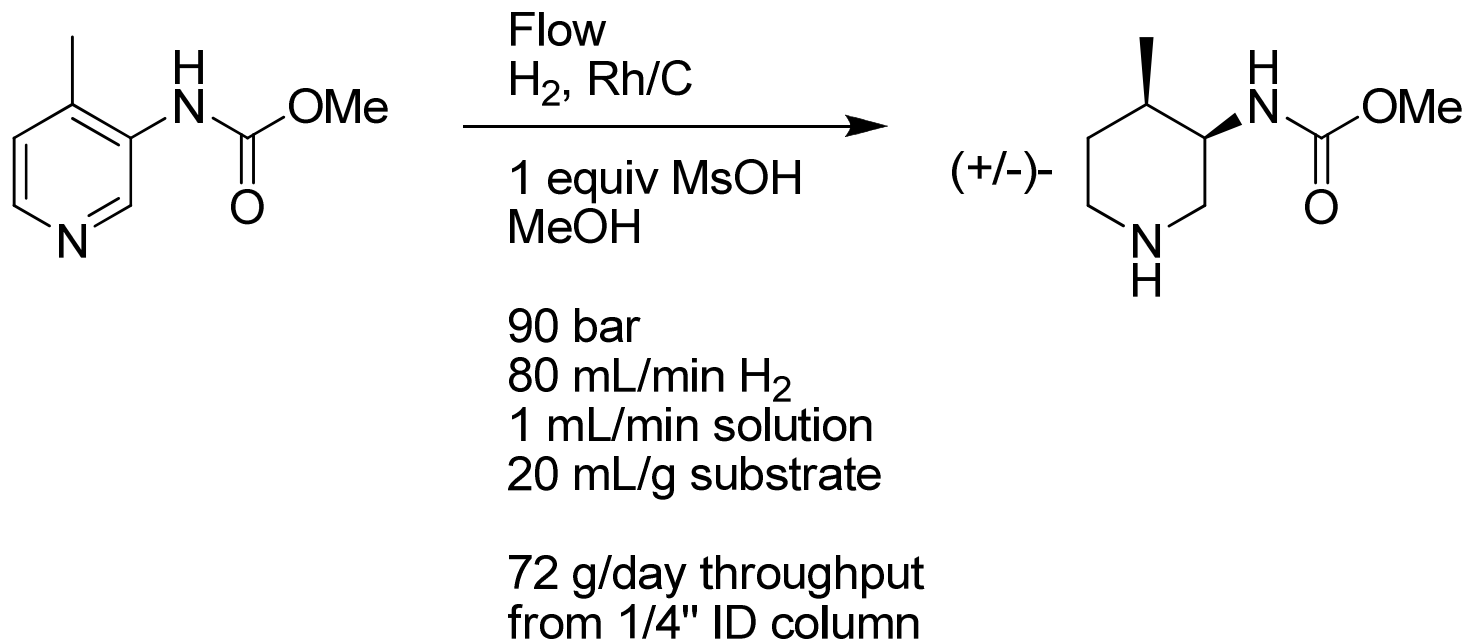
- Mid-range residence time and low temperature favours high yield chloroaniline

- Aniline favoured by high or low residence time

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H·E·L

Stereoselectivity through flowCAT Process Control



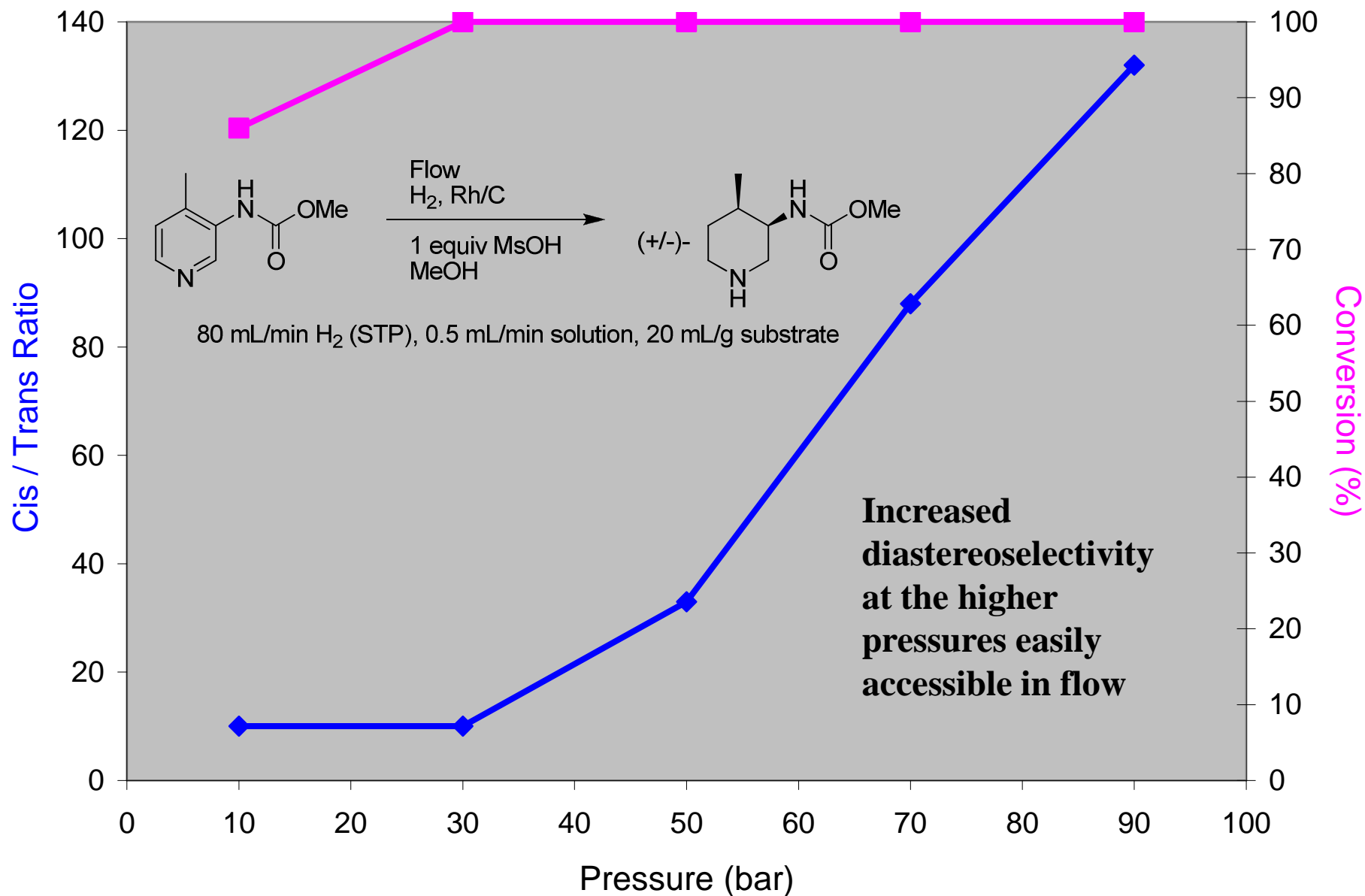
- 100 g hydrogenated with 1 g of catalyst which was still active

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

better chemistry - faster



Diastereoselectivity and Conversion vs. Pressure



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

better chemistry - faster

