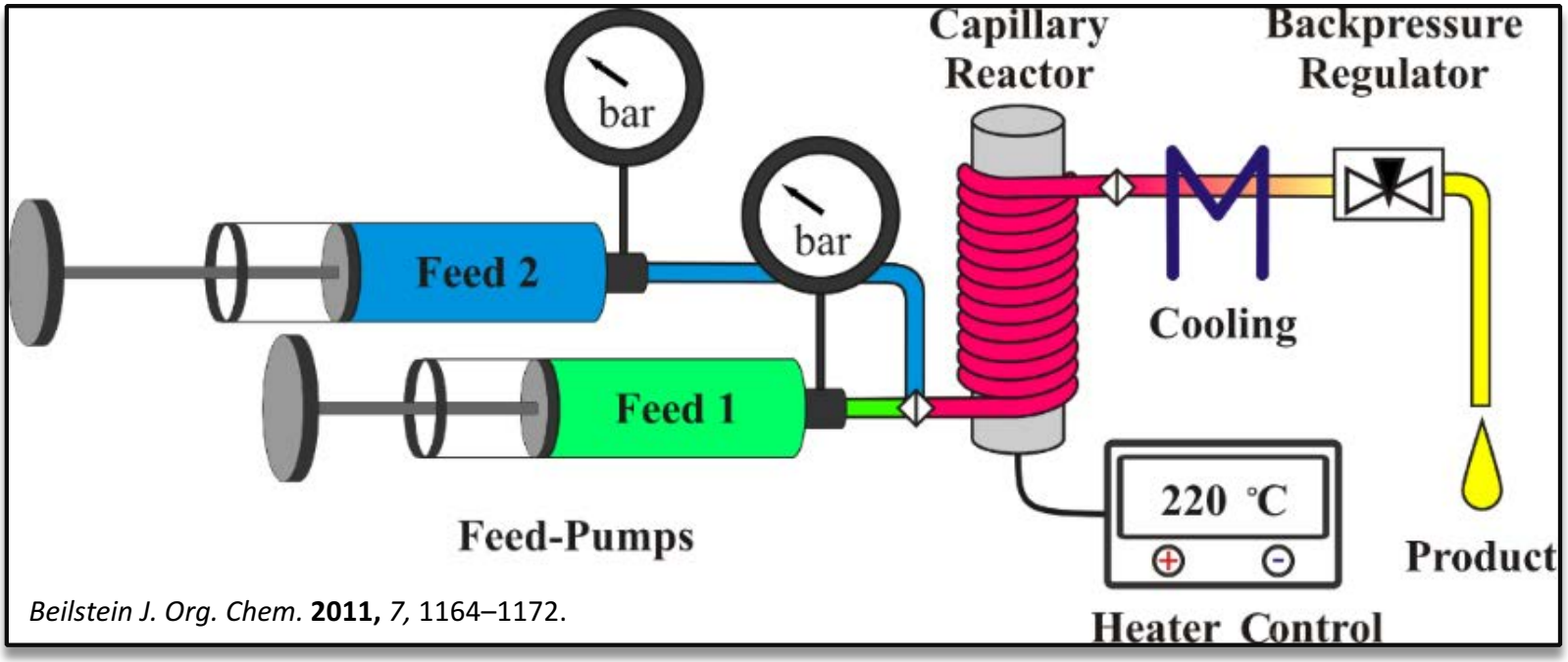


Beilstein J. Org. Chem. **2011,** *7,* 1164–1172.

Flow Chemistry Applications in Organic Synthesis

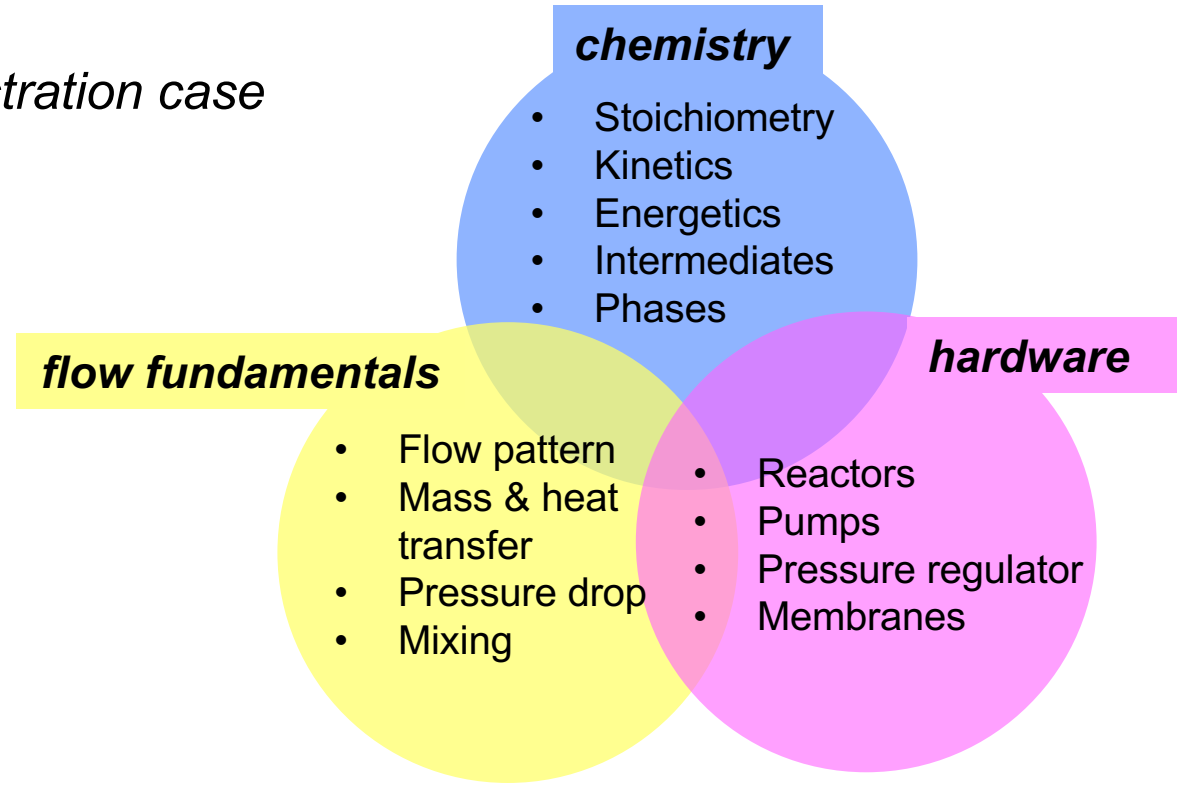
Jan. 24th, 2017

Malek Ibrahim

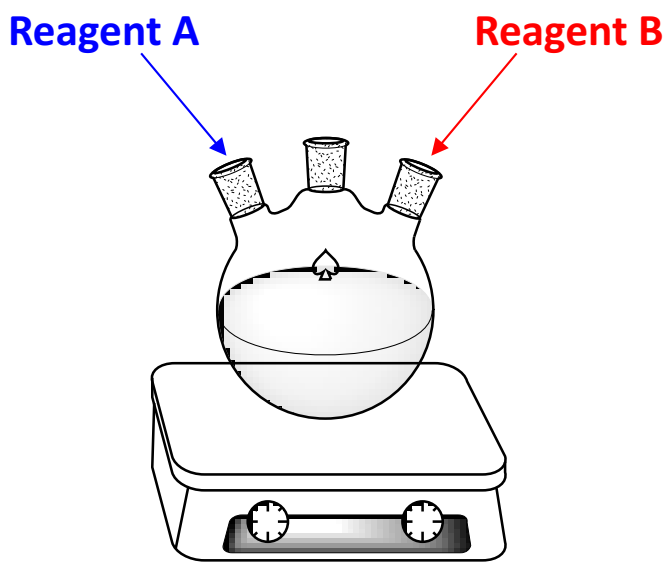
Group meeting

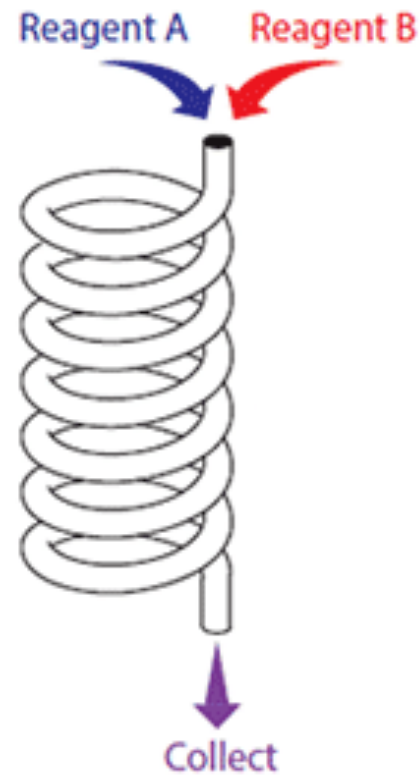
Outline

- *Batch vs. flow chemistry*
- *Advantages of flow chemistry*
- *Fundamentals of flow dynamics*
- *Pressure in flow chemistry*
- *Reactor Configurations*
    - *Tube-in tube gas reactor*
    - *Packed bed reactor*
    - *Microchannel reactor & Flash chemistry*
- *Solid handling*
- *Total synthesis demonstration case*



Batch vs. Flow Chemistry





Batch:

Instantaneous addition of reagents to a container (reactor) fitted with means of temperatures/pressure control and mixing

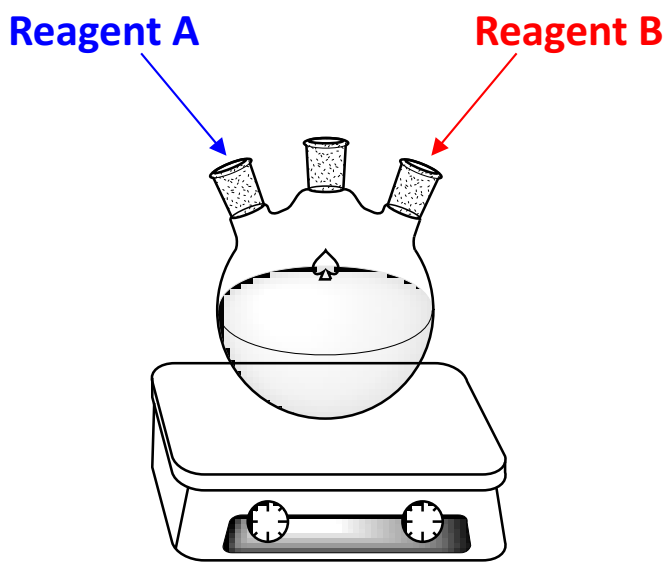
Mixing and conditions control are applied for the desired reaction time followed by workup

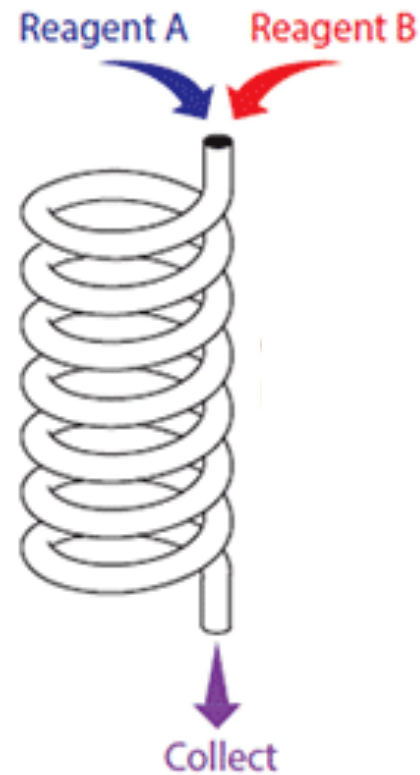
Flow:

Continuous addition of reagents to a reactor (tube, vessel, autoclave…) using pumps or compressors

Reaction time is the time the reaction medium spend inside the reactor (residence time)

Batch vs. Flow Chemistry





Key factors:

- *mixing*
- *temperature*
- *time*

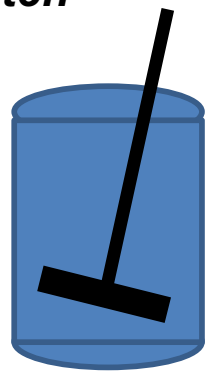
Variable parameters across time and space, unsteady state; concentration and temperature time gradient

- *flow rate (or residence time)*
- *temperature*
- *pressure*

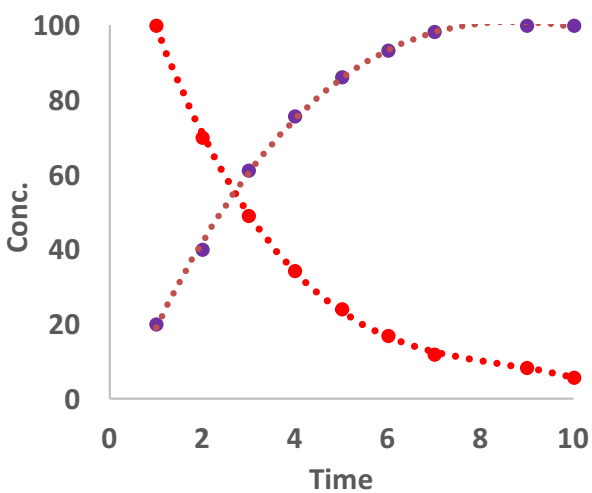
Steady state operation, constant parameters across reaction time, each molecule reacts under the same conditions

Reactor Models

Batch



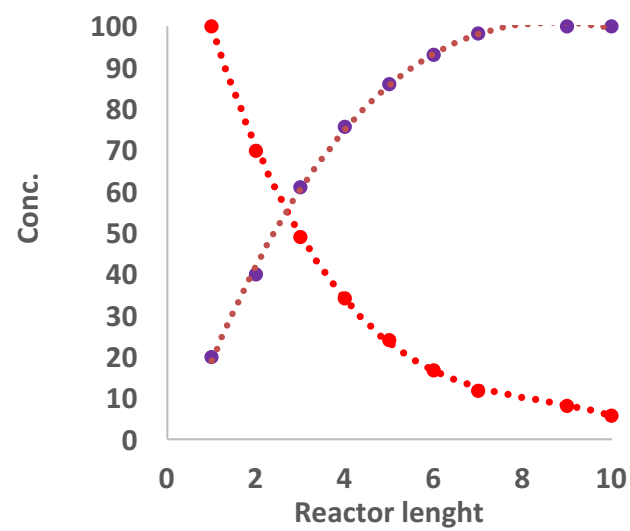
- *Variable concentration with time*
- *Variable reaction rate with time*



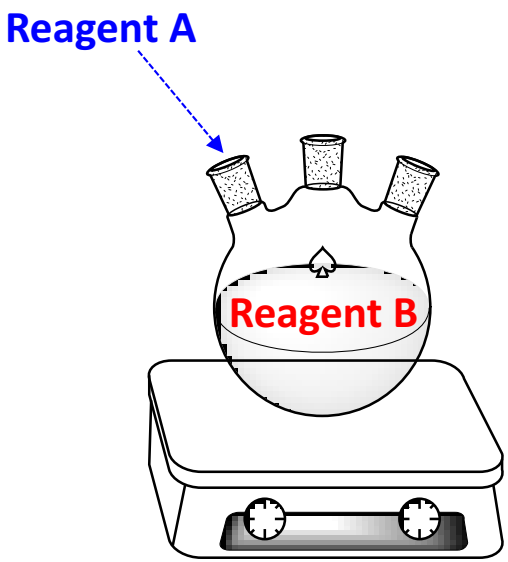
Plug flow reactor (tubular)

Plug Flow Reactor (tubular)

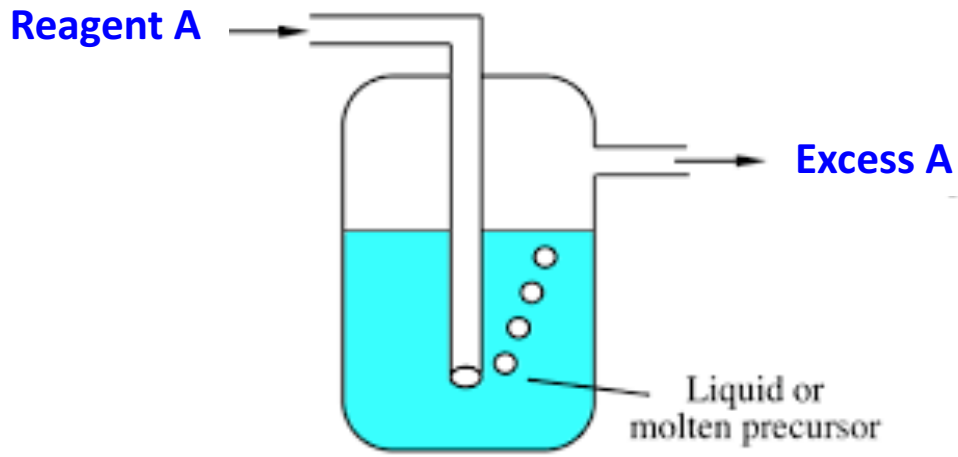
- *Continuous flow*
- *Steady state*
- *Concentration changes across reactor length*
- *Neglects conc. gradient in axial direction and back mixing*



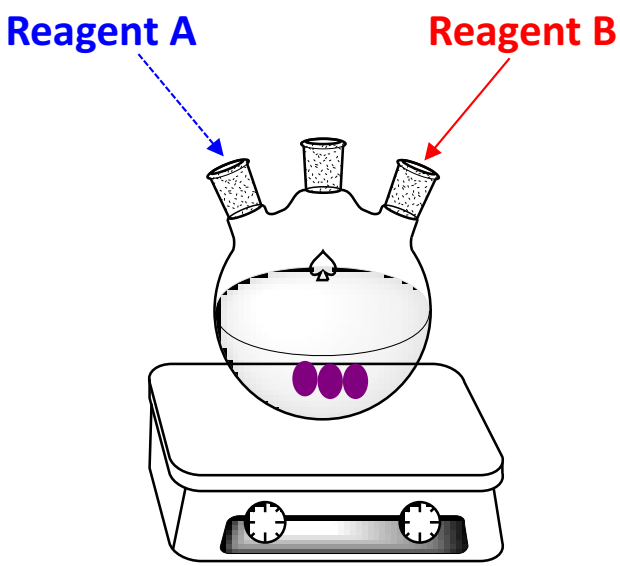
Special case: semi-batch chemistry



Slow liquid addition



Gas bubbling



Slow solid dissolution or precipitation

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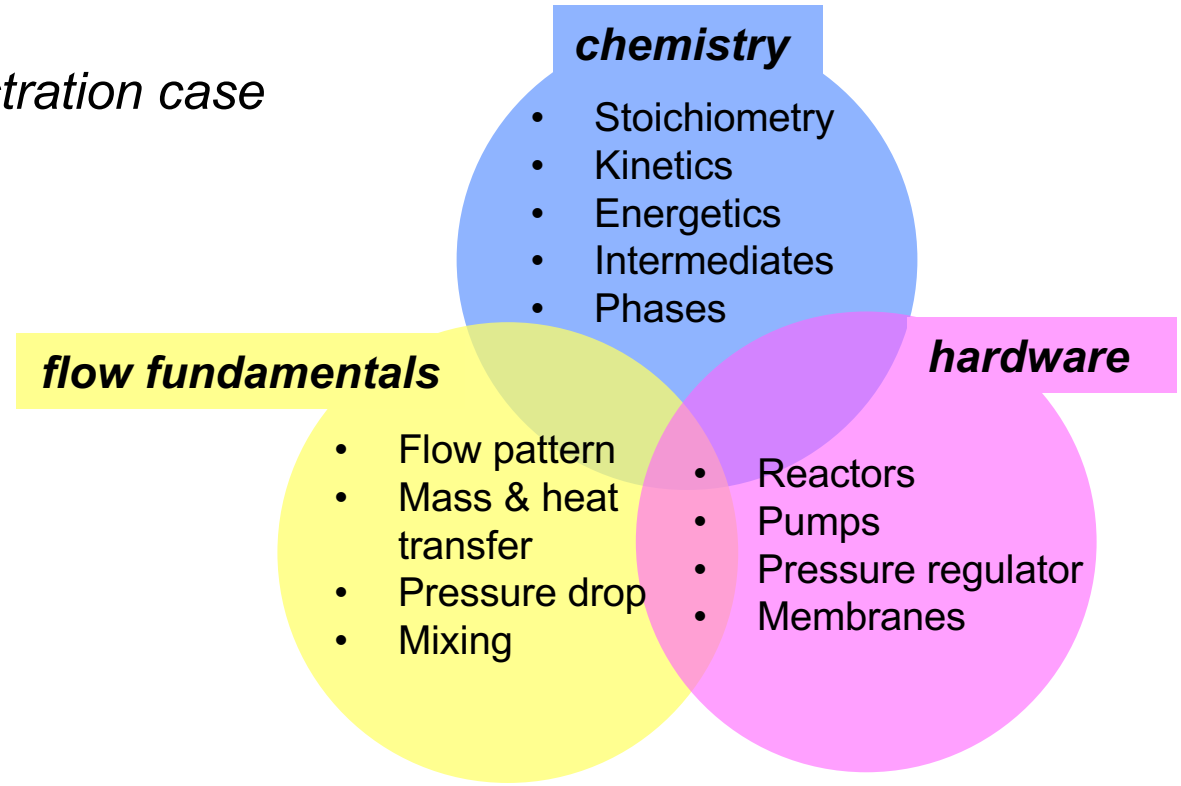
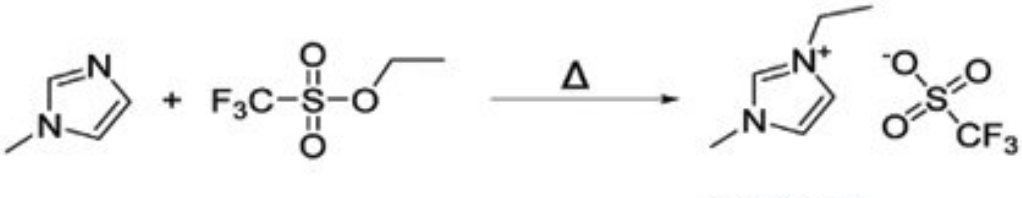
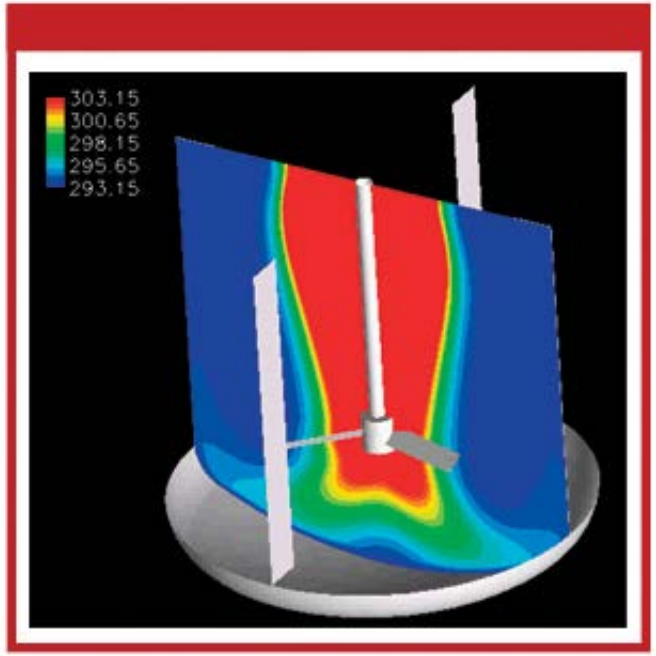


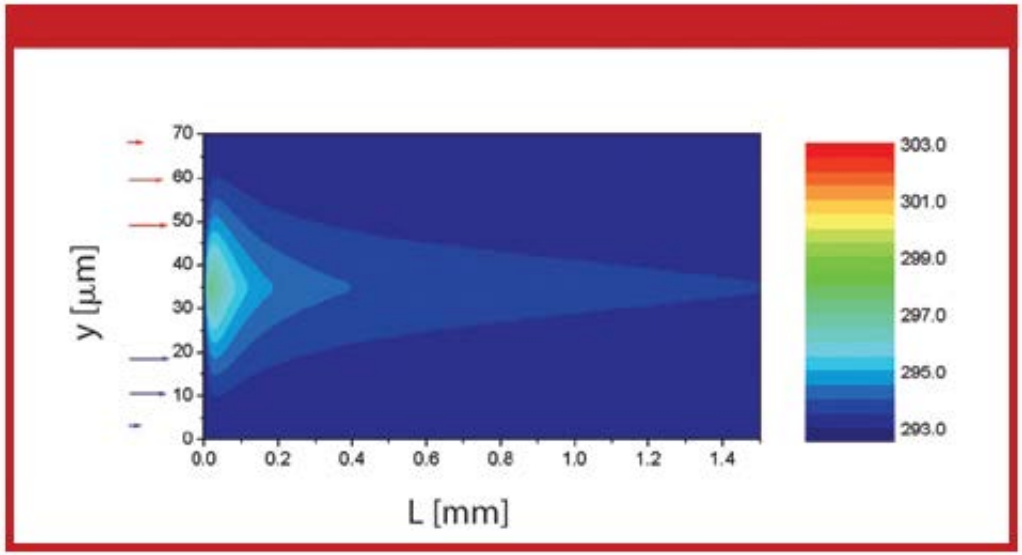
Advantages of flow chemistry

- Ionic liquid formation is highly exothermic
- Optimized batch operation had 10 °C gradient and yields brown product due to side reactions triggered by high temperature



- Enhanced mixing in PFR drastically mitigated the exothermic, less than 3 °C gradient





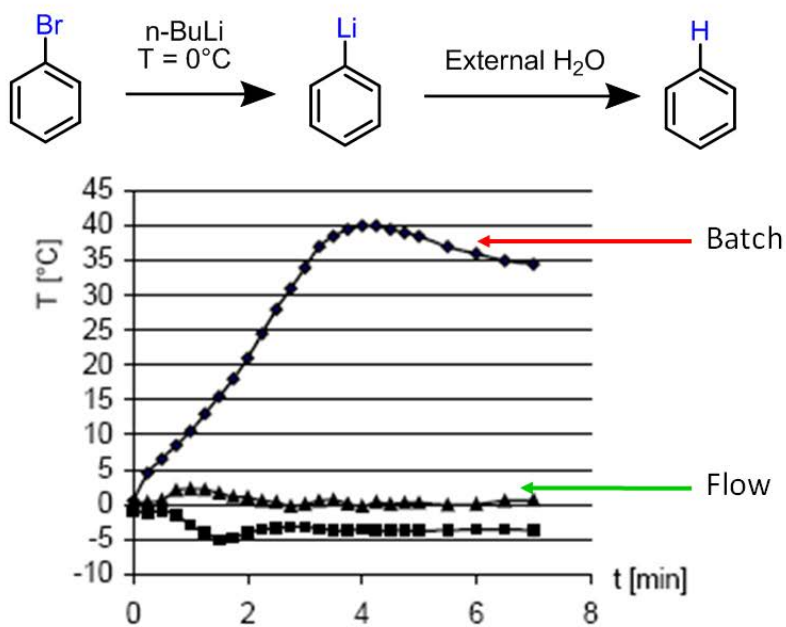
- Batch: <96% purity
- Plug Flow: >99% purity

Pharmaceutical Technology Volume 2009 Supplement, Issue 5

Enhanced heat transfer: managing exothermic rxn

- Other exothermic reactions include lithiation, nitration, and ozonolysis
- Temperature runaway forms a safety and selectivity concern in these cases
- Lower than needed temperature (-78 ^{o}C) is often applied to account for inefficient heat dissipation in batch mode

Heat out under batch and flow conditions

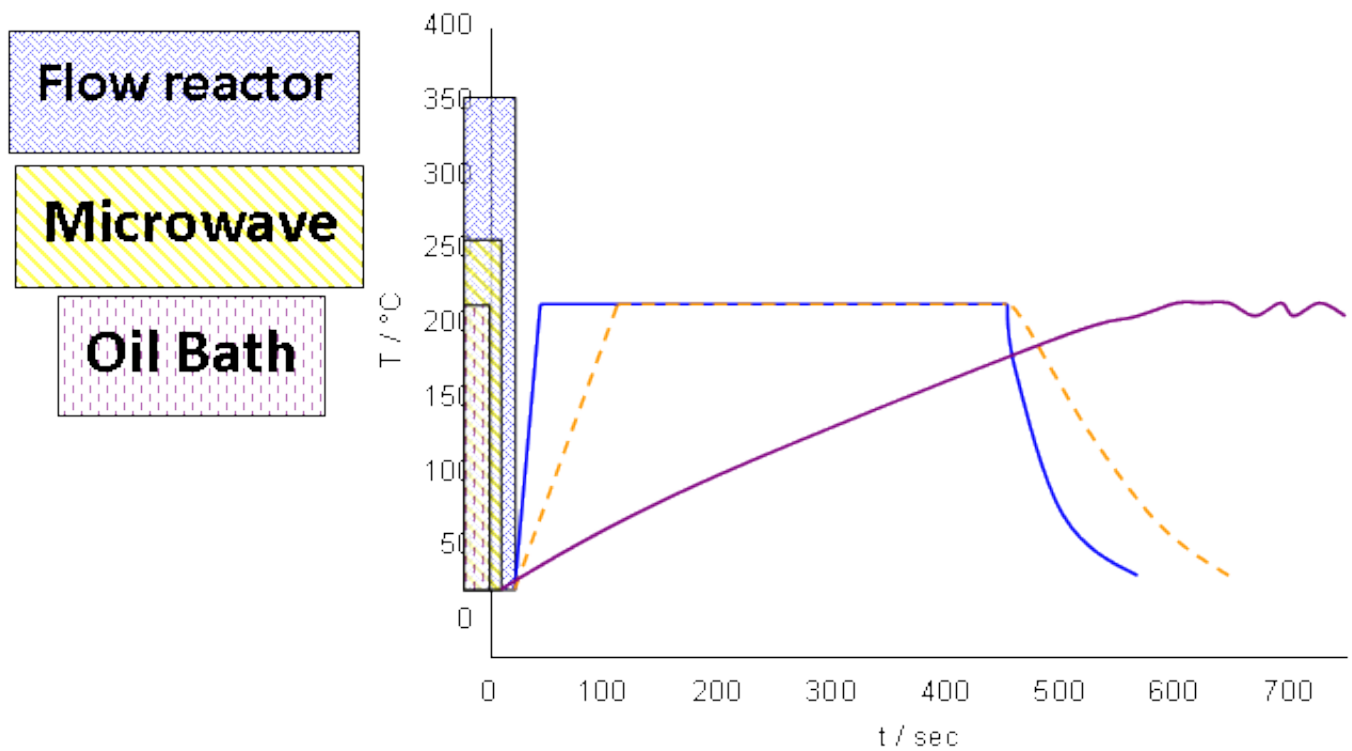


- Batch experiment shows temperature increase of 40°C.
- Flow shows little increase in temperature.

http://thalesnano.com/flow-university/how-flow-chemistry-can-benefit-you

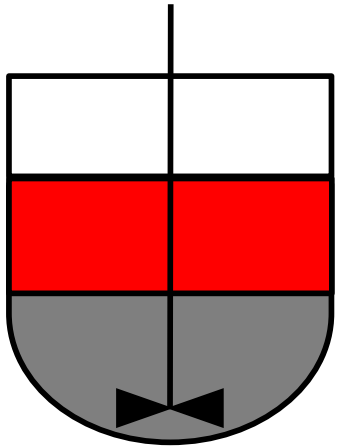
Temperature control

- Higher surface area/volume ratio in flow tubular reactor; better heat transfer
- Reactions cool down or heat up extremely rapidly (faster than a microwave)
- By pressurising, flow reactors can operate at temperatures above the typical boiling point of reactions
  - This enables easy superheating of reactions e.g. 100ºC to 150ºC above reflux temperatures



http://thalesnano.com/flow-university/how-flow-chemistry-can-benefit-you

Biphasic reaction in batch vs. flow

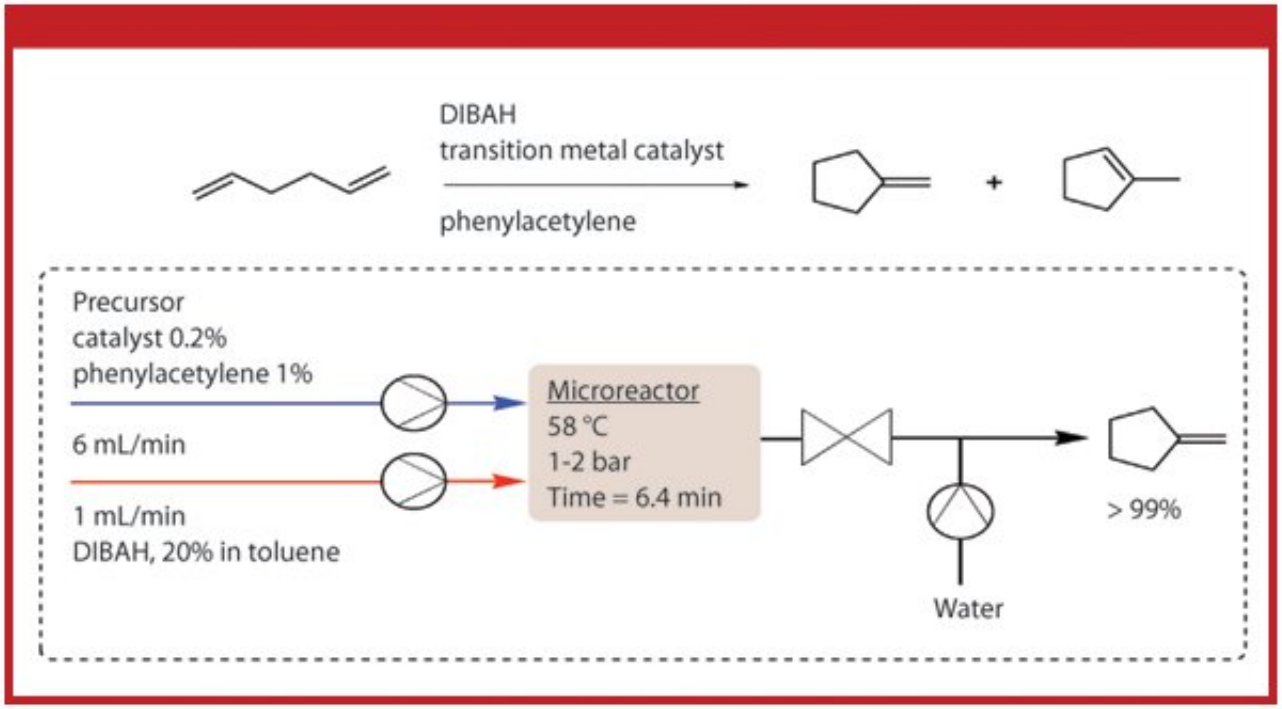


	Batch	Flow
• Scaling	☹	☺
• Surface Area	☹	☺
• Gravity	✓	✗
• Mass transfer	☹	☺
• Emulsion	☹	☺

- Flow Chemistry is ideal for biphasic liquid reactions
- Flow Chemistry is very suitable for aqueous work-up

Pressure in flow chemistry

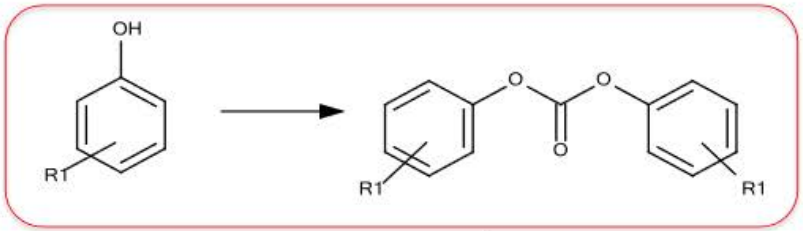
Ring closure in synthesizing exomethylenecyclopentane: advantage of additional pressure in flow chemistry



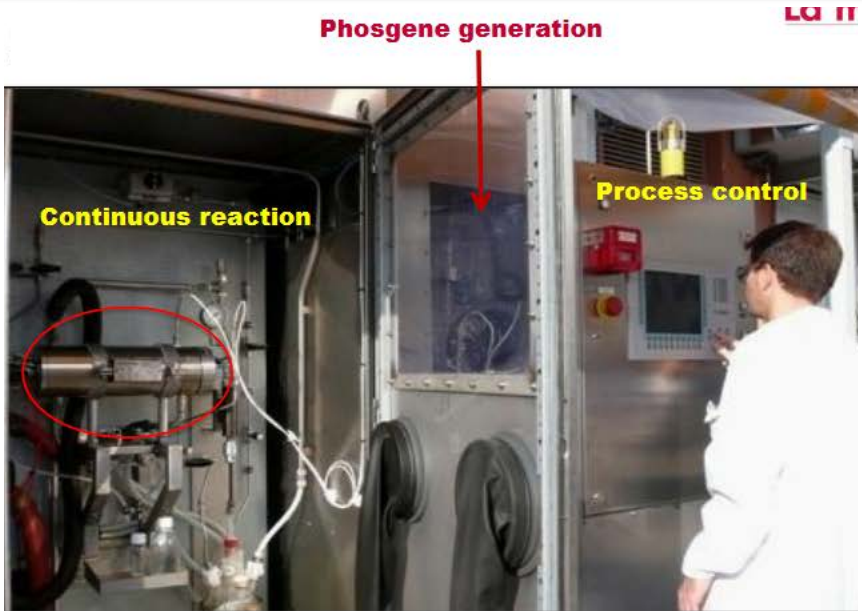
- Optimum operation temperature for catalyst activation is higher than s.m. boiling point (55 C at 1 atm)
- Pressurized higher temperature batch reactor gives a difficult to separate mixture of isomers
- Flow reaction under elevated pressure (2 bar) allows for smooth operation at >55 C >99% product selectivity at multikilogram scale

Pharmaceutical Technology Volume 2009 Supplement, Issue 5

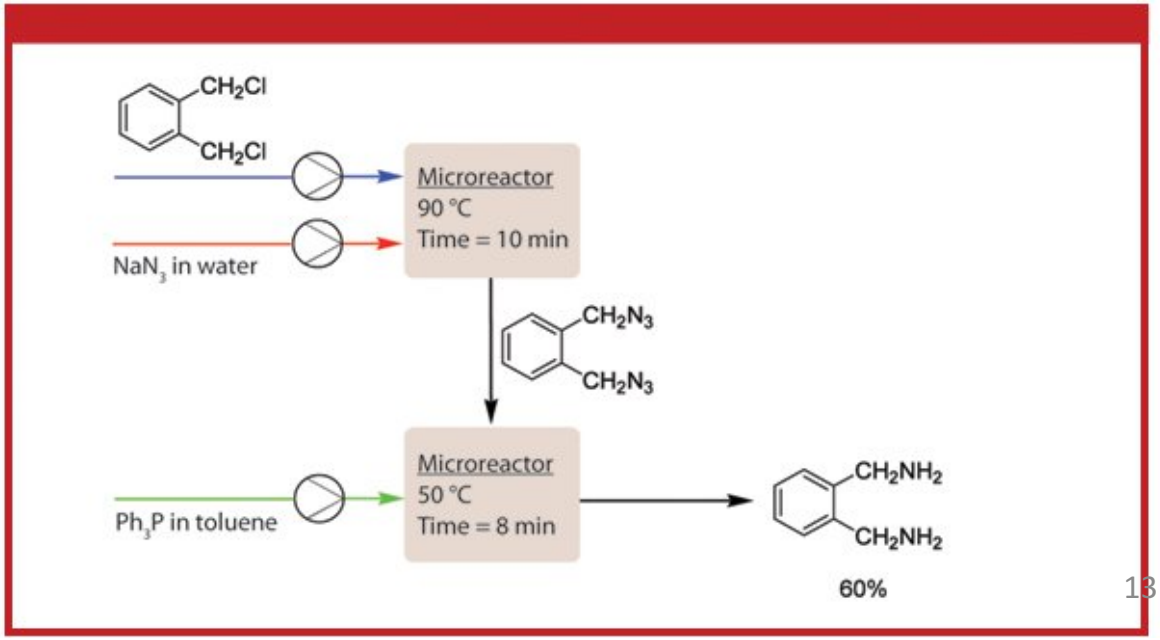
Handling dangerous reagents



Temperature	*35-45°C*
Pressure $COCl_2$	*0 bar*
Phosgene Excess	*5% mole*
Residence Time	*0.2min*
Productivity	*16 kg/h*
Conversion	*complete*



http://www.chemspeceurope.com



Pharmaceutical Technology Volume 2009 Supplement, Issue 5

Advantages of flow chemistry

- Better mixing, enhanced heat and mass transfer
- Better conditions control
- Better reproducibility
- Easier automation
- Easier conditions screening & optimization
- Safer operation
- Quality control
- Less waste

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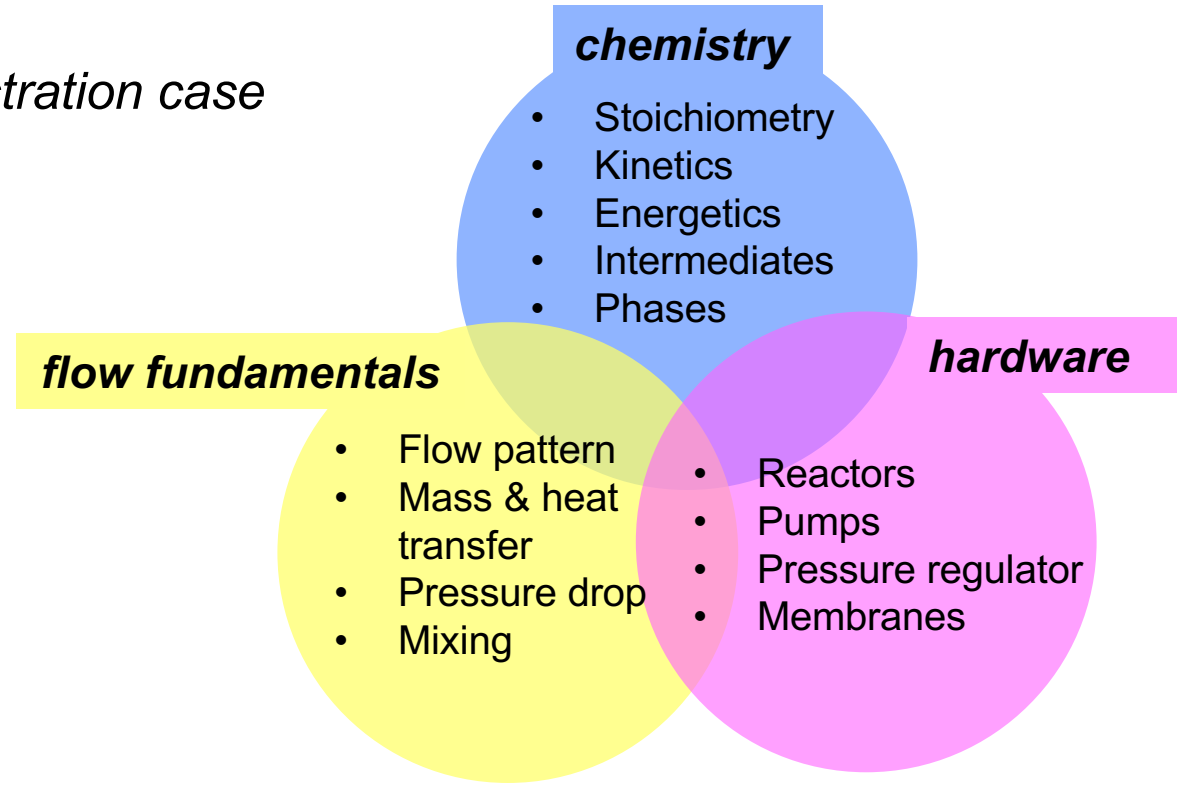
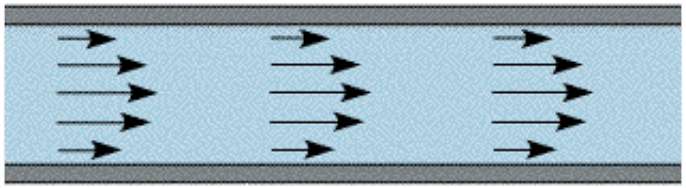


Fluid Flow patterns: monophasic flow

- Flow pattern depends on flow rate, density, viscosity and tube diameter
- Knowing flow pattern is essential for estimating pressure drop, and heat and mass transfer

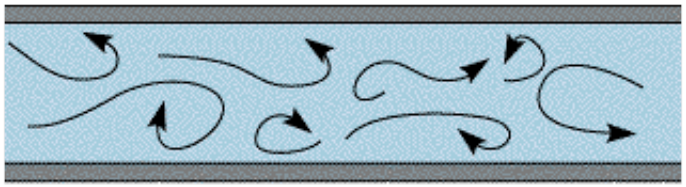
Flow pattern can be determined from Reynold's number (dimensionless number) $\mathrm{Re} = \frac{\rho V L}{\mu}$

Laminar



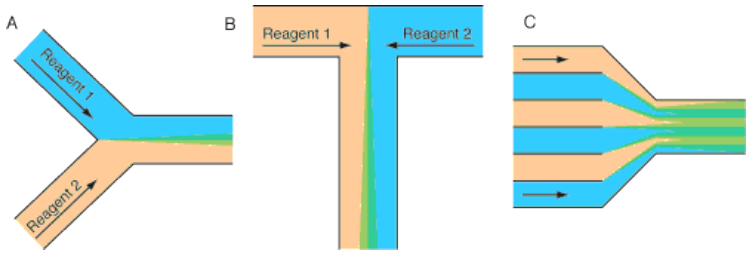
Re < 2300
smooth, occurs when fluid flows in parallel lines, low velocity or high viscosity

Turbulent

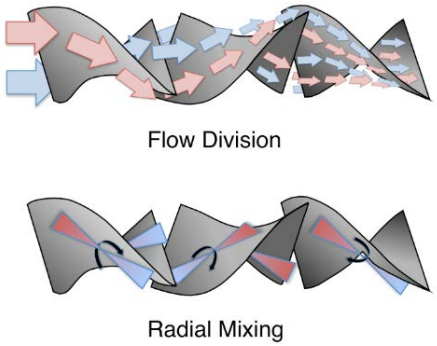


Re > 4000
Irregular, occurs when flow is characterized by eddies, high velocity

Mixing



Diffusion driven



Can be enhanced by static mixers

Factors affecting flow rate

Residence Time = Reactor Volume / Flow Rate

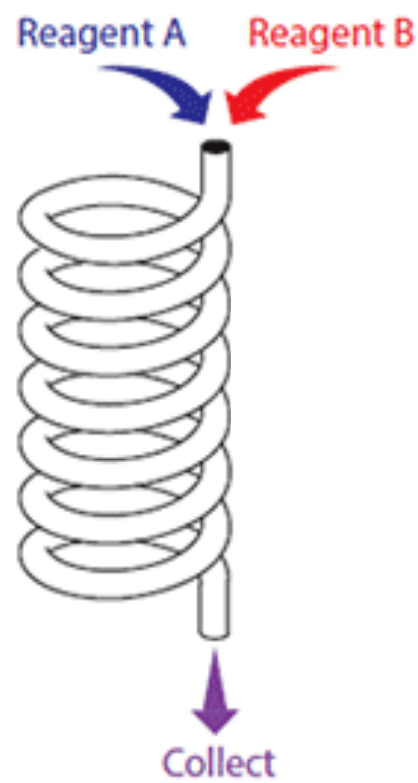
Residence time needs to be long enough to allow complete conversion, but…

- very low flow rate harms mixing and heat transfer efficiency
- very long reactor causes high pressure drop

Residence time, mixing and heat transfer, and pressure drop all need to be optimized to set flow rate and reactor dimensions for a system

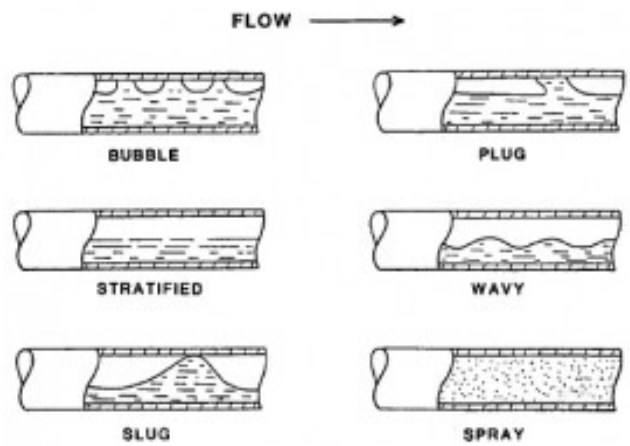
Darcy's equation: $\Delta p = \lambda \, (l / d_h) \, (\rho \, v^2 / 2)$

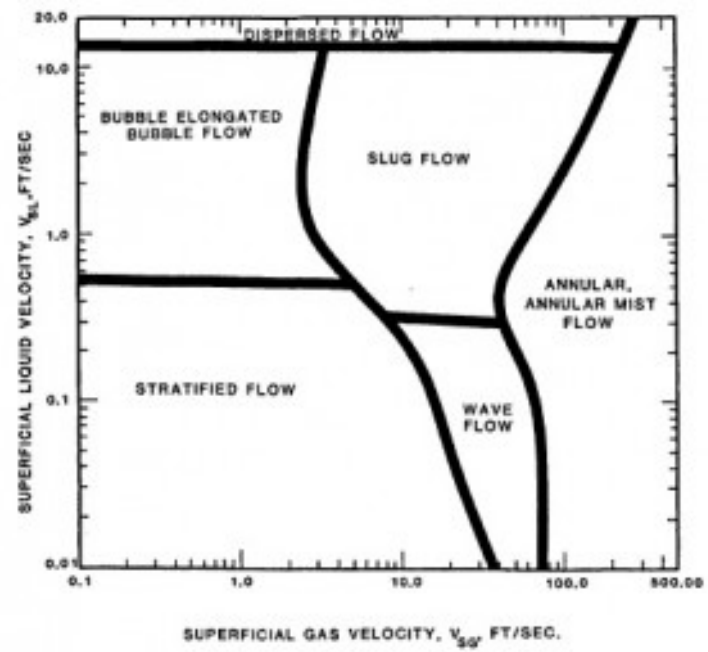
Δp = *pressure loss (Pa, N/m^2)*
λ = *Darcy friction factor*
l = *length of tube (m)*
v = *velocity (m/s)*
d_h = *tube diameter (m)*
ρ = *density (kg/m^3)*



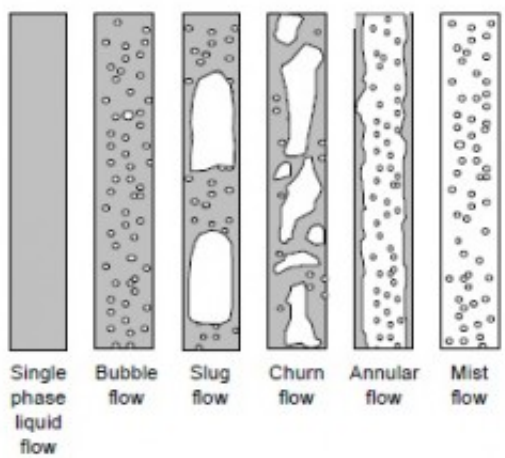
Fluid Flow patterns: biphasic flow

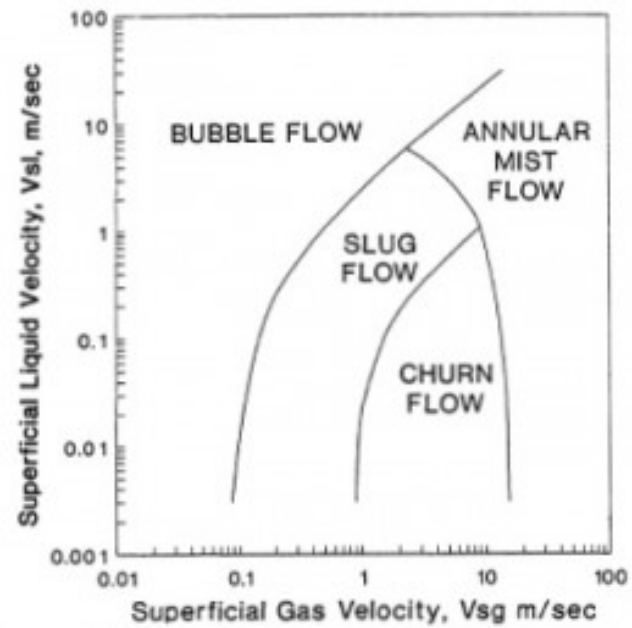
Horizontal pipe





Vertical pipe





http://www.ingenieriadepetroleo.com/flow-regimes-in-horizontal-and-vertical-pipes.html

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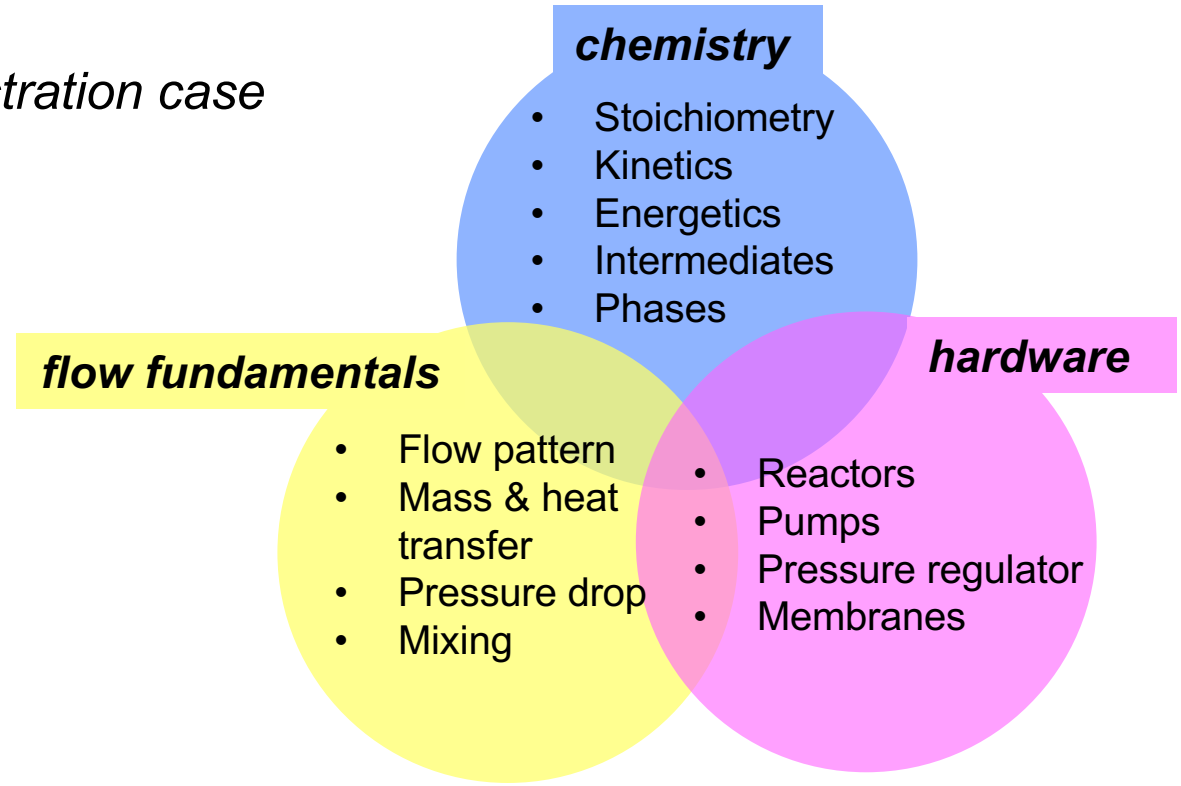


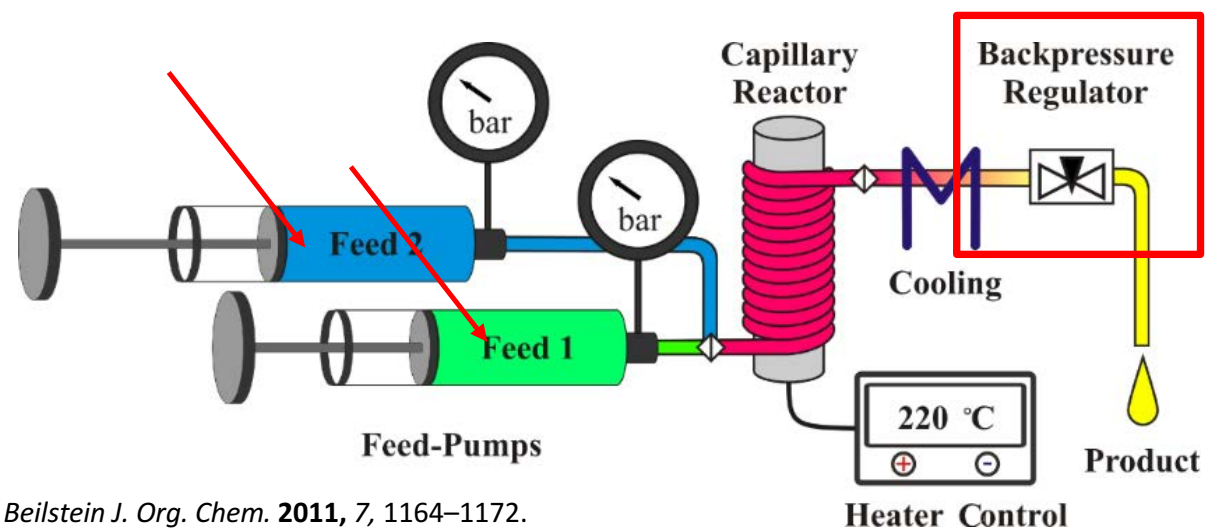
Pressure in flow chemistry

Pressure is needed to drive flow and overcome friction

Higher pressure can be applied to:

- prevent evaporation of volatile reagents
- operation above solvent bp
- enhance gas-liquid mixing
- increase gas residence time

Pressure is provided through pumps or compressors and controlled via Back Pressure Regulator (bpr)

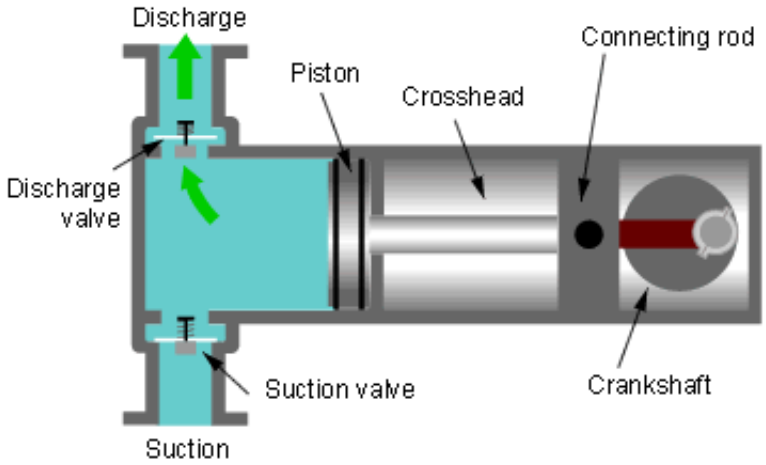


Beilstein J. Org. Chem. **2011,** *7,* 1164–1172.

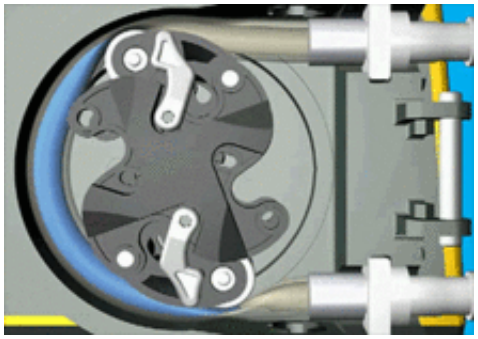
Pumps

Used to deliver reproducible quantities of solvents and reagents

- Reciprocating: single or dual acting
- Peristaltic pump
- Centrifugal pump
- Syringe pump



Pump selection depends on delivery pressure and material aggressiveness

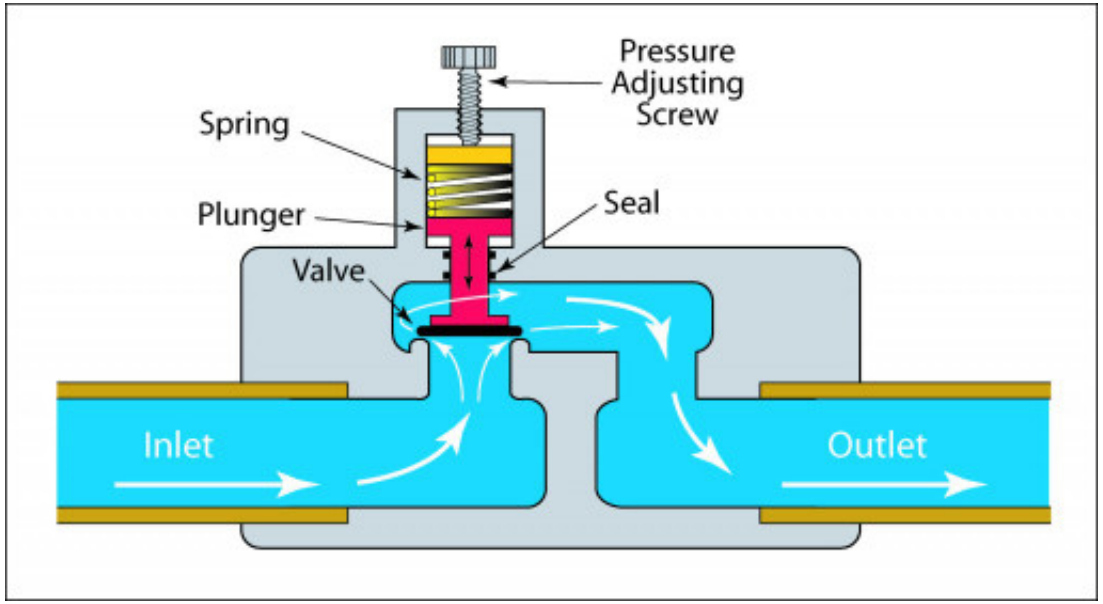


https://www.quora.com/What-is-the-difference-between-a-plunger-and-a-piston

Back Pressure Regulator

Unlike the more common pressure reducing regulators, the orifice opening of back pressure regulator is adjusted to control the inlet “upstream” pressure not the outlet

BPR can be controlled automatically to maintain constant pressure



https://www.equilibar.com/back-pressure-regulators/how-it-works/bpr-definition
https://blog.lesman.com/2016/01/18/regulators-101-pressure-vs-back-pressure

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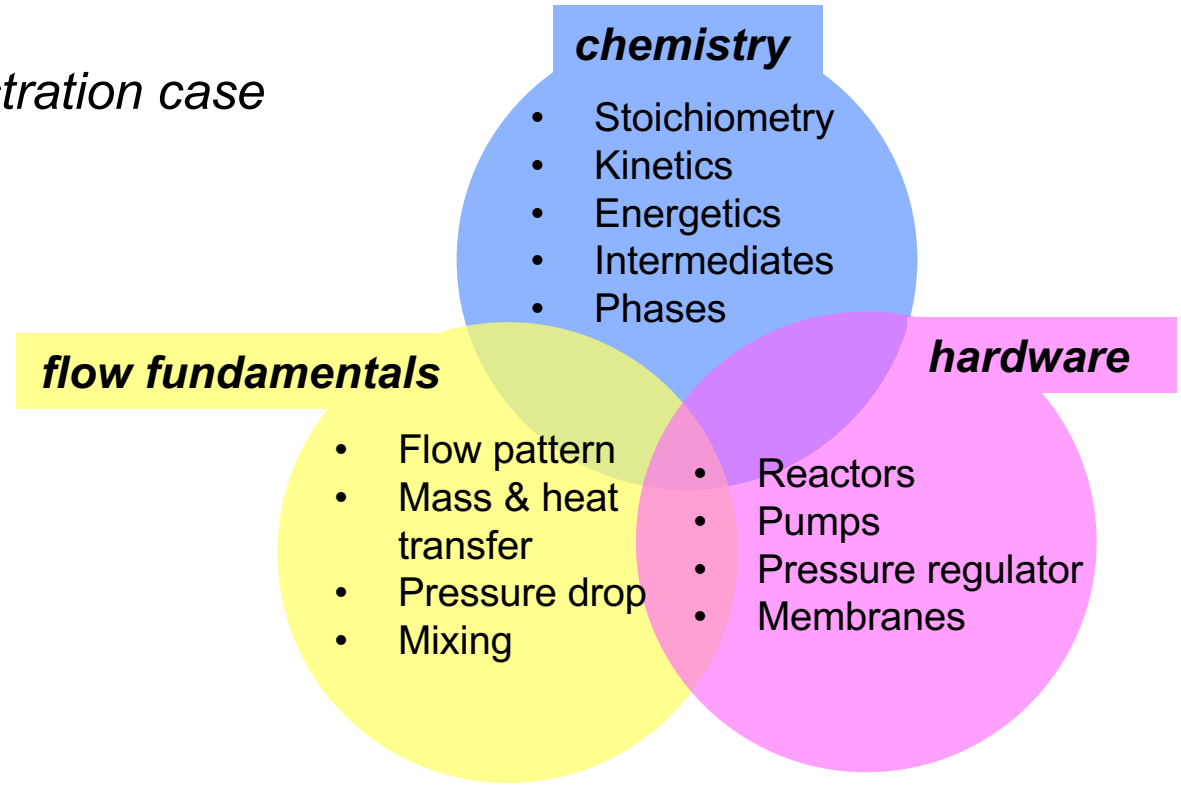


Design calculations

Help researcher B to design a tubular reactor for his chemistry:

- Flow rate 0.1 ml/min
- Fluid density 950 kg/m^3, viscosity 0.92*10^{-3} Ns/m^2
- Required residence time 5 min
- Knowing that researcher B wants to keep his flow turbulent for mass transfer reasons and has a pump with a maximum pressure delivery of 200 psi

Assume that pressure drop can be estimated $\Delta p = 0.01(v^2 (l / d)$

$Re = \rho v d / \mu$

Turbulent Re >4000

Δp = pressure loss psi
l = length of tube (m)
v = velocity (m/s)
d = tube diameter (m)
ρ = density (kg/m^3)
μ = viscosity (Ns/m^2)

Commercial bench scale flow Reactors

Gas reactor
(http://www.cambridgereactordesign.com/)

Trickle bed reactor
(http://www.helgroup.com/)

Microchip reactor unit
(http://www.chemtrix.com/)

Syringe pumps
(http://syrris.com/)

Gas reactor platform
(http://www.thalesnano.com/)

Reaction platform
(http://www.uniqsis.com/)

Cryogenic reactor unit
(http://www.cambridgereactordesign.com/)

Reaction platform
(https://www.vapourtec.com/)

Reaction platform
(http://www.amtechuk.com/)

http://www.organic-chemistry.org/topics/flowchemistry.shtm

Rate of hydrogenation

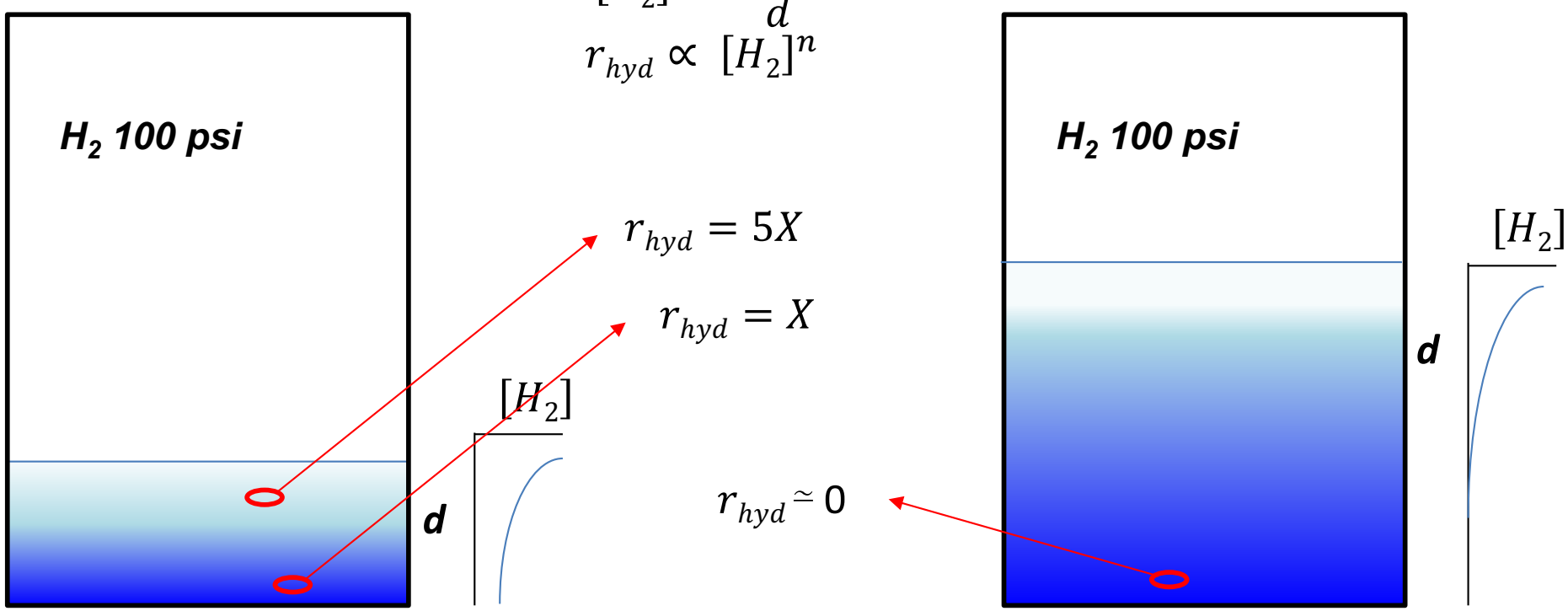
…equals the rate at which the slowest step occurs

this step can be a chemical step (bond formation or breaking), or a mass transfer step.

In some cases the reaction can be limited by mass transport rendering the actual kinetics not relevant to the product formation rate

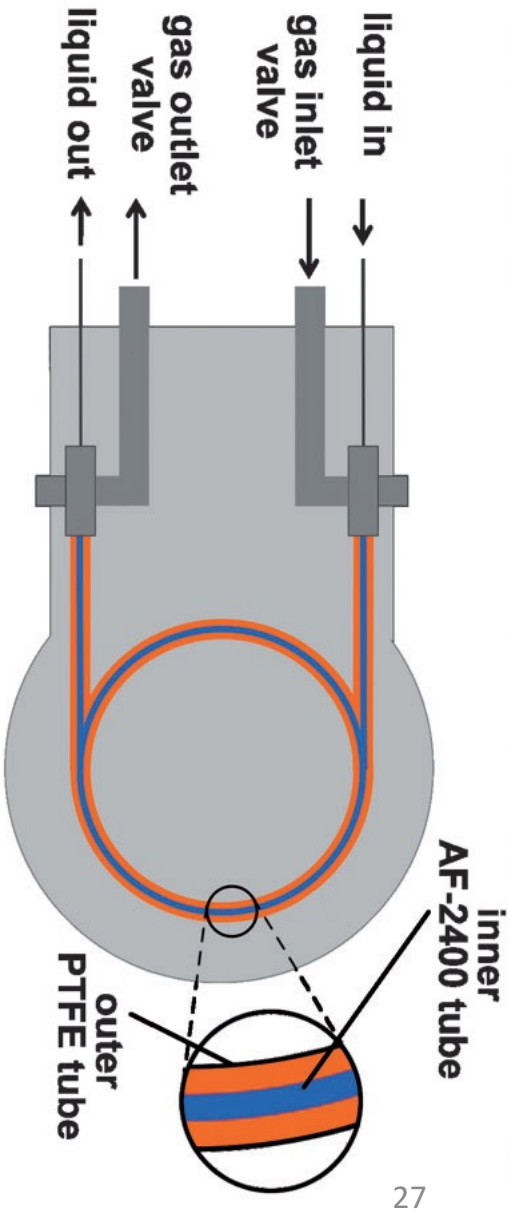
$$[H_2] \propto \frac{P_{H2}}{d}$$

$$r_{hyd} \propto [H_2]^n$$



Gas Reactor: tube in tube with membrane

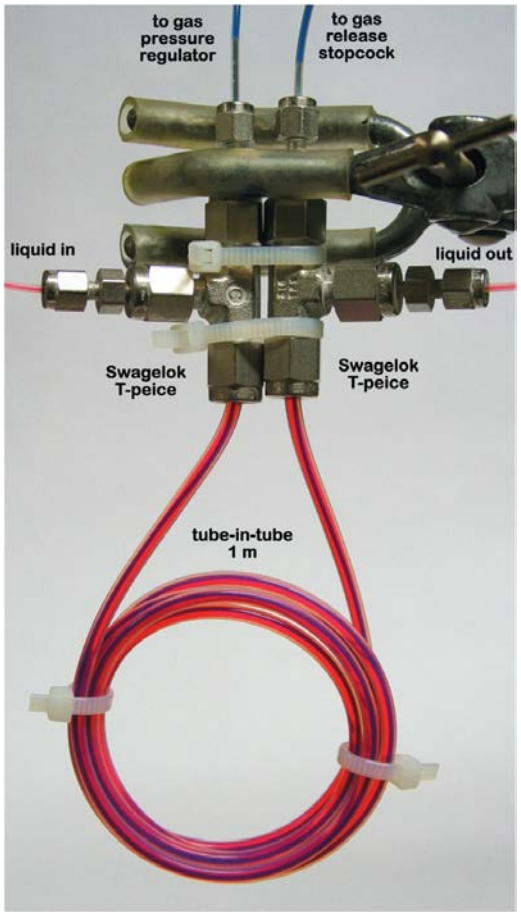
- Designed for enhanced gas-liquid mixing at minimum gas usage
- The inner tube is made of a gas-permeable material The membrane material needs to withstand swelling by solvent and chemical attack (silicon PDMS or Teflon AF 2400 membrane)
- The outer tube is made of a non-permeable rigid material
- Applications: ozone, hydrogen, carbon dioxide, carbon monoxide, ethylene, oxygen…



Cranwell, P. B.; O'Brien, M.; Browne, D. L.; Koos, P.; Polyzos, A.; Pena-Lopez, M.; Ley, S. V. Org. Biomol. Chem., 2012, 10, 5774

Gas Reactor: tube in tube with membrane

- Designed for enhanced gas-liquid mixing at minimum gas usage
- The inner tube is made of a gas-permeable material The membrane material needs to withstand swelling by solvent and chemical attack (silicon PDMS or Teflon AF 2400 membrane)
- The outer tube is made of a non-permeable rigid material
- Applications: ozone, hydrogen, carbon dioxide, carbon monoxide, ethylene, oxygen…



Four different flow configurations:

- Liquid flows through the inner or the outer tube
- Gas flows in the other tube co- or countercurrent with the liquid

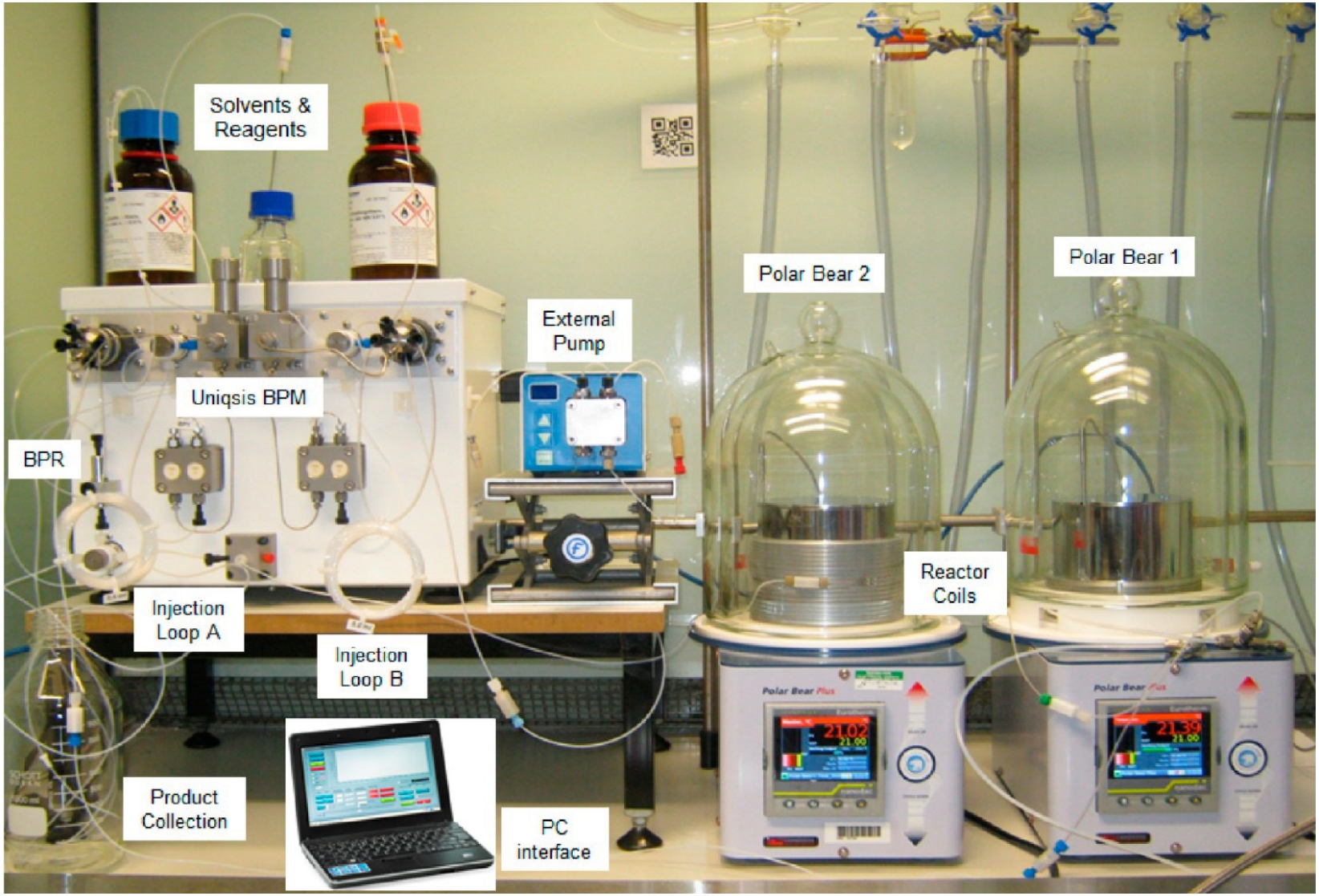
for 2 m length:

volume of liquid = 2.45 cm^3
volume of gas = 1.01 cm^3
surface area of AF-2400 exposed to liquid = 62.83 cm^2
surface area of AF-2400 exposed to gas = 50.27 cm^2

volume of liquid = 1.01 cm^3
volume of gas = 2.45 cm^3
surface area of AF-2400 exposed to liquid = 50.27 cm^2
surface area of AF-2400 exposed to gas = 62.83 cm^2

Cranwell, P. B.; O'Brien, M.; Browne, D. L.; Koos, P.; Polyzos, A.; Pena-Lopez, M.; Ley, S. V. Org. Biomol. Chem., 2012, 10, 5774

Gas Reactor: tube in tube with membrane

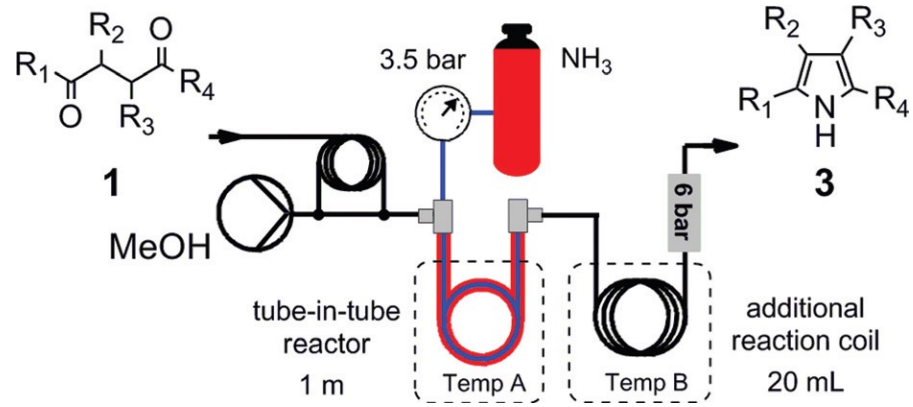


Pastre, J. C.; Browne, D. L.; O'Brien, M.; Ley, S. V., Org. Process Res. Dev. **2013,** *17* (9), 1183-1191.

Tube in tube reactor: Teflon reactor for pyrrole synthesis

Paal-Knorr reaction of 1, 4 diketone with ammonia

- Volatility of ammonia makes heated batch reaction often not reproducible and inconvenient
- Gas flow through the inner membrane tube made of Teflon AF-2400
- High temperature is needed for reaction but low temperature is favoured for ammonia permeation
- Dual coil pressurized system



Entry	Temp A.[a](°C)	Temp B.[b](°C)	Flow rate (mL min^{-1})	Conversion[c] (%)
1	0	80	0.4	48
2	0	100	0.4	62
3	0	100	0.3	87
4	0	110	0.3	100
5	0	120	0.3	51[d]
6	25	120	0.3	50

Cranwell, P. B.; O'Brien, M.; Browne, D. L.; Koos, P.; Polyzos, A.; Pena-Lopez, M.; Ley, S. V. Org. Biomol. Chem., 2012, 10, 5774

Tube in tube reactor: reaction with in-line purification

Oxygen assisted Glaser-Hey Coupling to afford 1.3 butadiene

- Three different injection pumps for substrate, catalyst, additive, and solvent
- Two different coiling at different temperatures for gas loading and reaction
- Two different packed columns downstream in series to remove catalyst and additive respectively

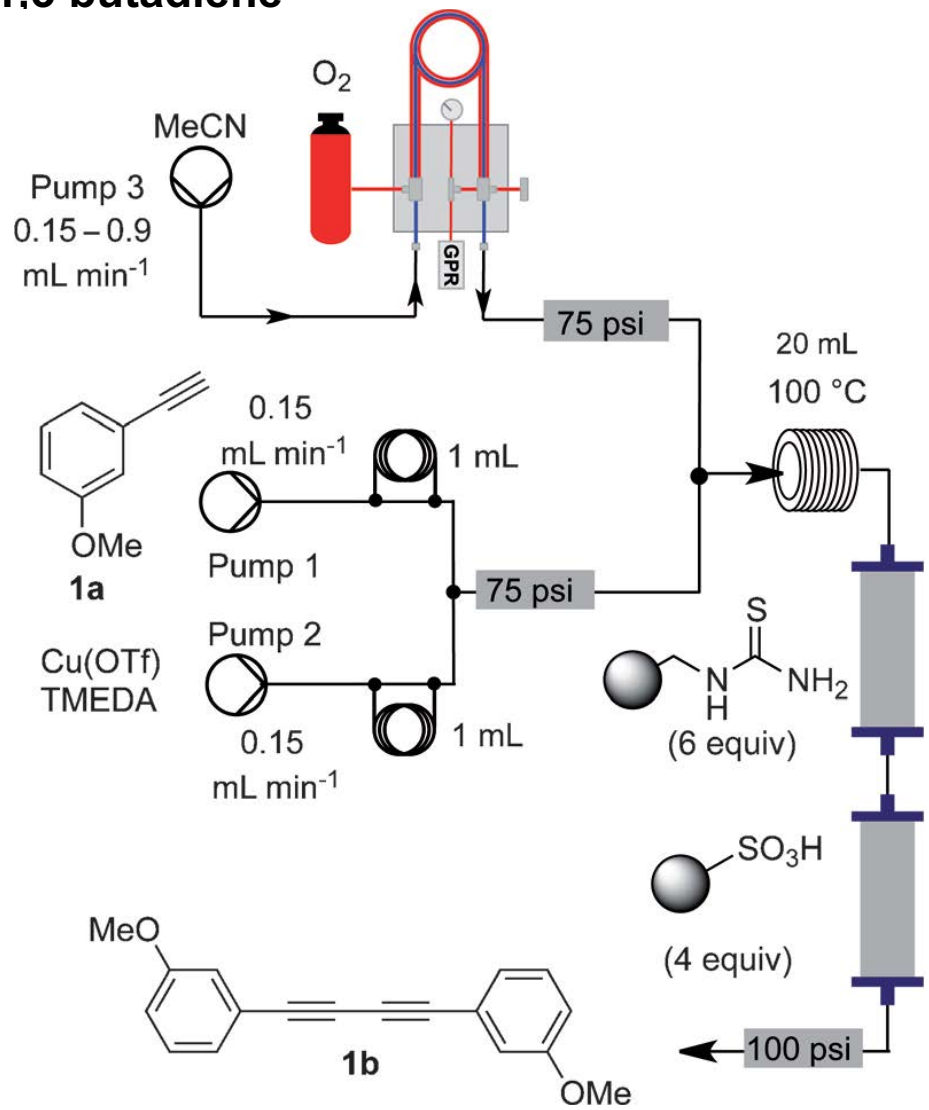


Table 1. Influence of reaction parameters on the Glaser–Hay coupling of 3-ethynyl anisole to afford 1.

Entry	T [°C]	P [bar]	Flow rate pump 1 [mL min^{-1}]	Flow rate pump 2 [mL min^{-1}]	Flow rate pump 3 [mL min^{-1}]	Conv.[a] [%]
1	25	8	0.15	0.15	0.3	54
2	25	8	0.15	0.15	0.6	69
3	25	8	0.15	0.15	0.9	71
4	40	4	0.15	0.15	0.9	76
5	40	8	0.15	0.15	0.9	87
6	100	8	0.15	0.15	0.15	98
7	100	8	0.15	0.15	0.6	100

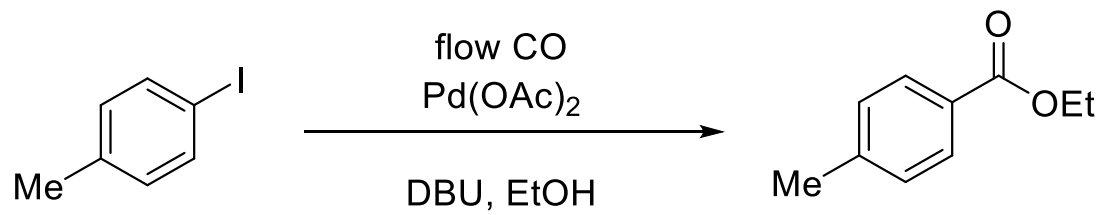
[a] Determined by ^{1}H NMR.

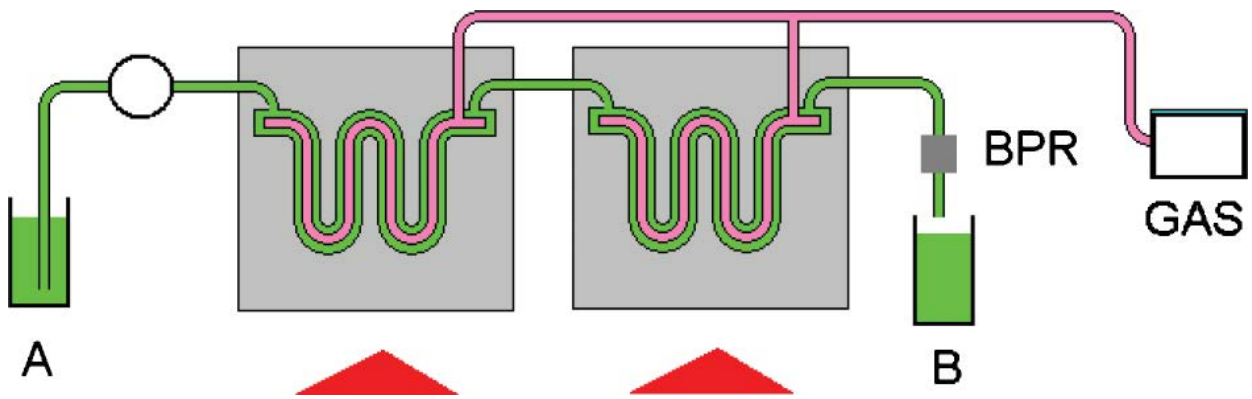
Petersen, T. P.; Polyzos , A.; O'Brien, M.; Ulven, T.; Baxendale, I. R.; Ley, S. V. *ChemSusChem* **2012,** *5* (2), 274-277.

Tube in tube reactor: simultaneous gas and heat addition

Alkoxycrabonylation of aryl halide with CO at 120 °C

- Liquid flow in outer tube made of stainless steel for efficient heat supply and control
- Gas flow through the inner membrane tube
- Countercurrent flow of CO with two CO inlets at 180 psi allows for 97% yield with no excess CO being used
- Protocol was applied for other substrates and scaled up





Mercadante, M. A.; Leadbeater, N. E. Org. Biomol. Chem., 2011, **9**, 6575

Commercial bench scale flow Reactors

Gas reactor
(http://www.cambridgereactordesign.com/)

Trickle bed reactor
(http://www.helgroup.com/)

Microchip reactor unit
(http://www.chemtrix.com/)

Syringe pumps
(http://syrris.com/)

Gas reactor platform
(http://www.thalesnano.com/)

Reaction platform
(http://www.uniqsis.com/)

Cryogenic reactor unit
(http://www.cambridgereactordesign.com/)

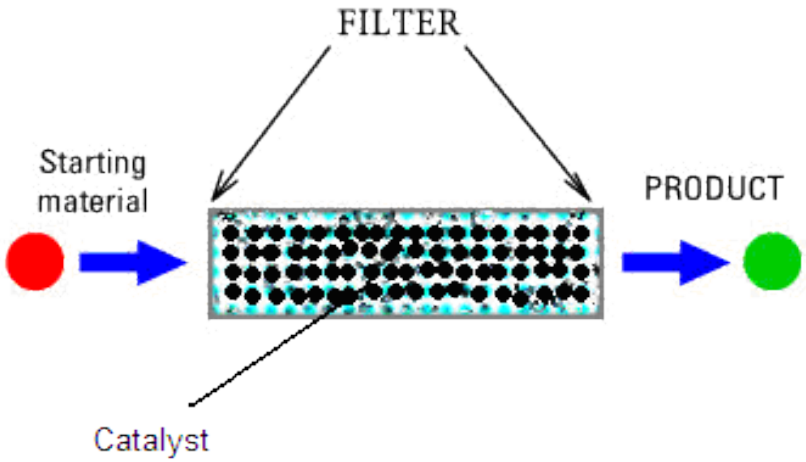
Reaction platform
(https://www.vapourtec.com/)

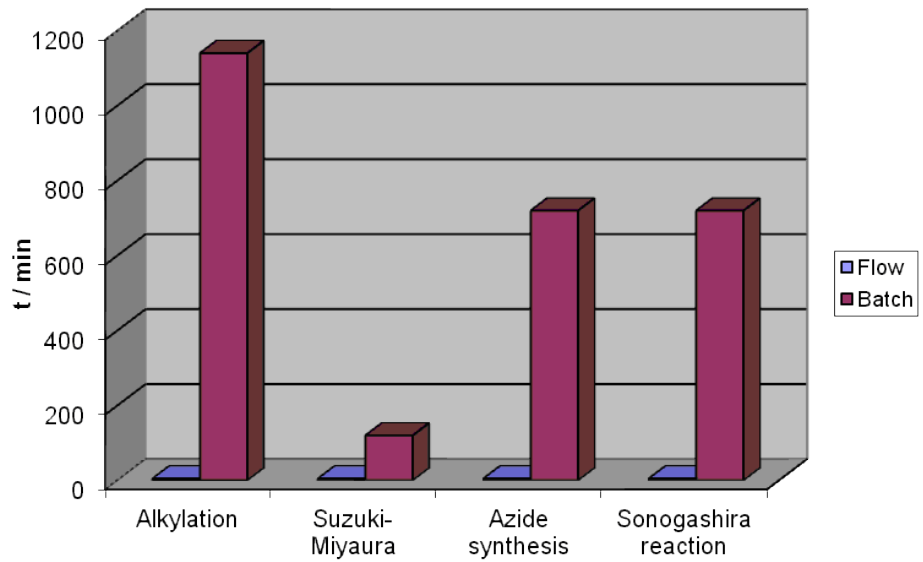
Reaction platform
(http://www.amtechuk.com/)

http://www.organic-chemistry.org/topics/flowchemistry.shtm

Packed bed reactor: solid-liquid reactions

- Reactants flow through a fixed bed of solid heterogeneous/immobilized catalyst or reagent
- Much higher catalyst concentration when compared to batch for the same amount of catalyst
- Forcing the fluid reagent to flow through catalyst particles drastically enhances catalyst/reactant mixing
- Increase in rates by orders of magnitude
- Shorter reaction time, less temperature or catalyst loading can be achieved



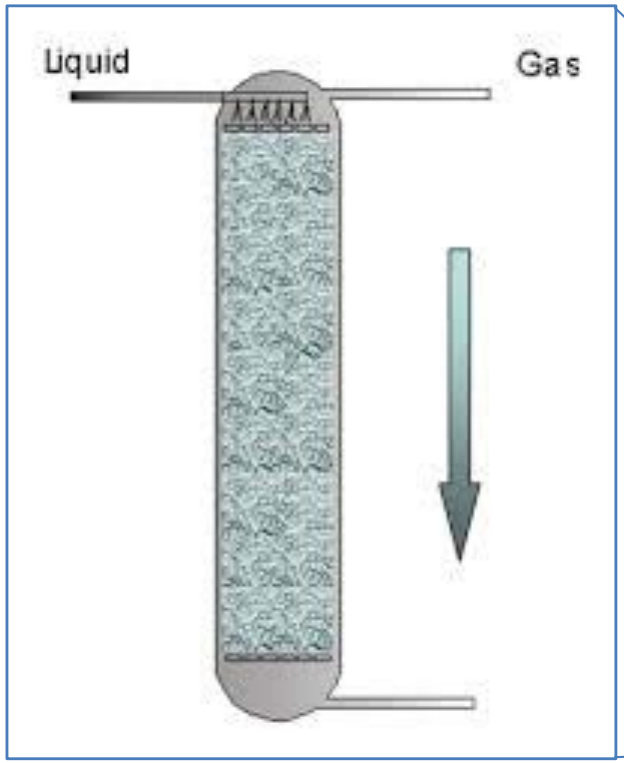


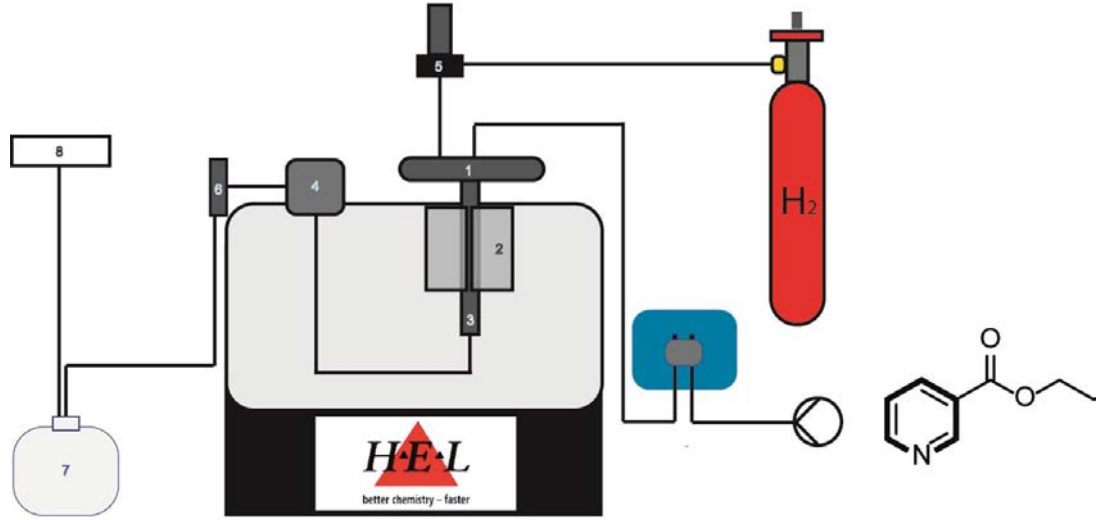
http://thalesnano.com/flow-university/how-flow-chemistry-can-benefit-you

Trickle bed reactor: triphasic reactor

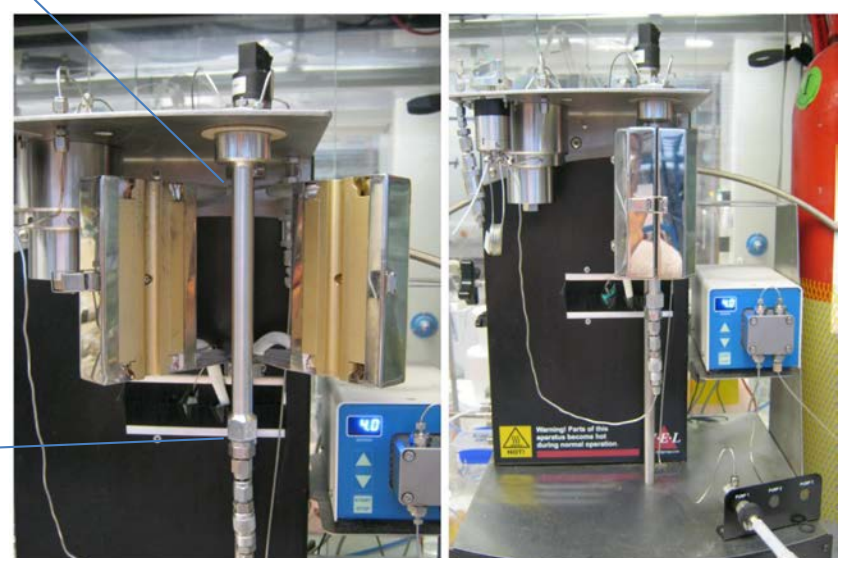
Gas-solid-liquid reactions

- Catalyst solid bed is confined in reactor
- Liquid flows from top to bottom by gravity
- Gas can flow co- or countercurrently w.r.t liquid





1. Liquid/gas mixing zone
2. Heating jacket
3. Trickle bed
4. Liquid/gas separator
5. Mass flow controller
6. Pressure release valve
7. Collection vessel
8. H_2 Venting



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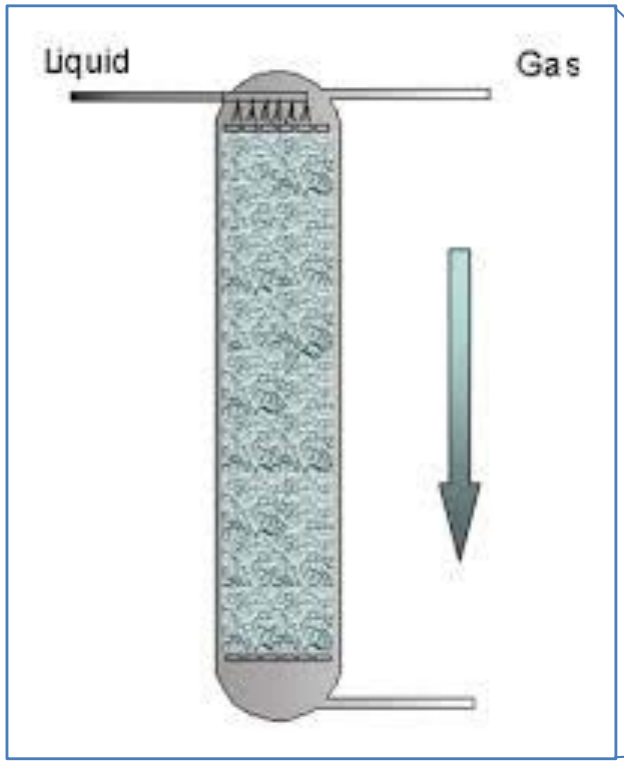
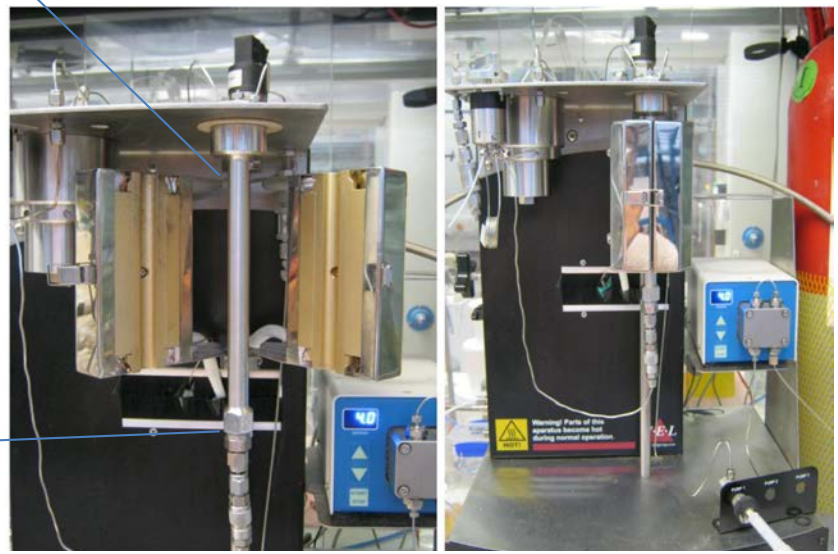
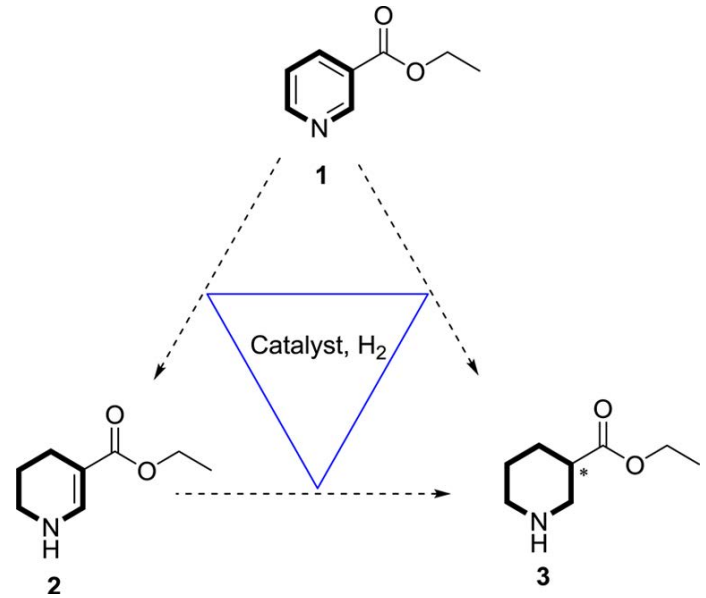


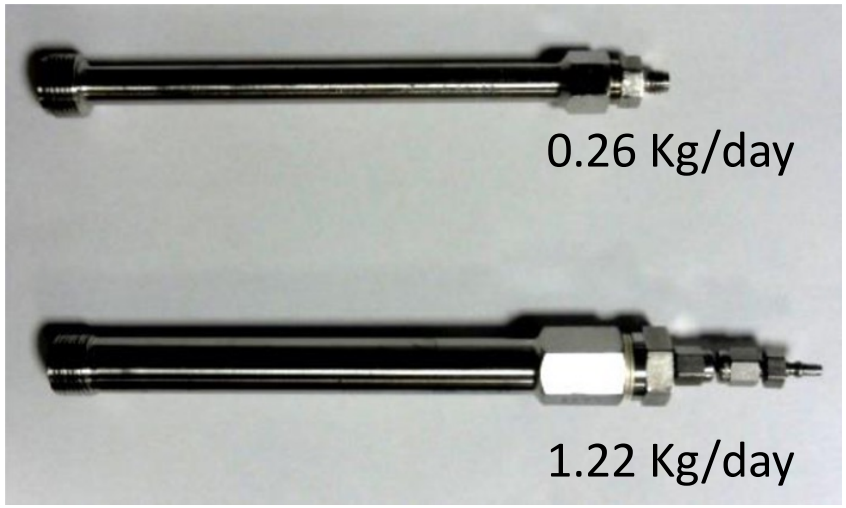
The catalyst particle size plays a crucial role in reactant mixing and flow pattern
Particles smaller than 0.1 mm dia causing flow blockage while particles bigger than 0.25 mm dia casing flow channelling

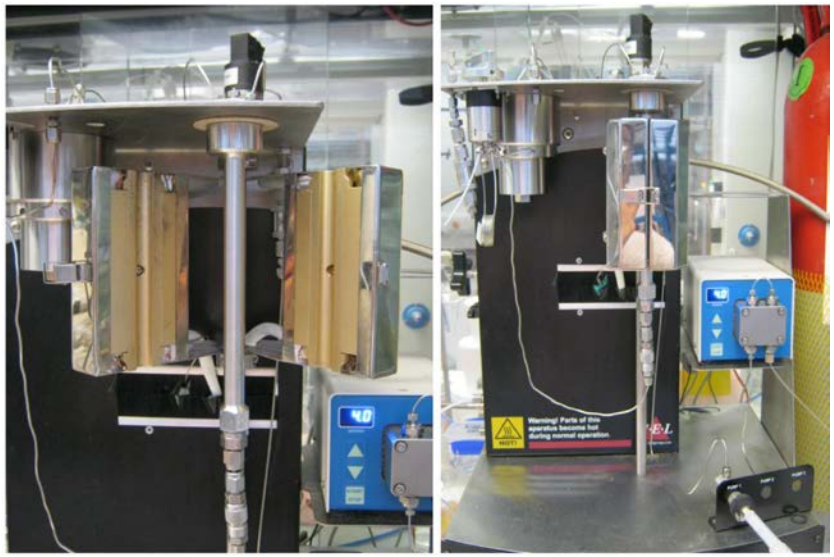


Trickle bed reactor: selective hydrogenation

- Batch reactor at 100 psi hydrogen and 38 h: 74% yield of **2** maximum
- TBR reactor at 300 psi hydrogen and minutes reaction time: 90% yield of **2**
- Efficient scale up was achieved by simply using a larger diameter reactor
- Increasing temperature above 100 C and hydrogen pressure to 1500 psi switchs product selectivity to 90% yield of **3** without further modifications







Ouchi, T.; Battilocchio, C.; Hawkins, J. M.; Ley, S. V. Org. Process Res. Dev. **2014,** *18* (11), 1560-1566.

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Reaction platform
(http://www.uniqsis.com/)

Cryogenic reactor unit
(http://www.cambridgereactordesign.com/)

Reaction platform
(https://www.vapourtec.com/)

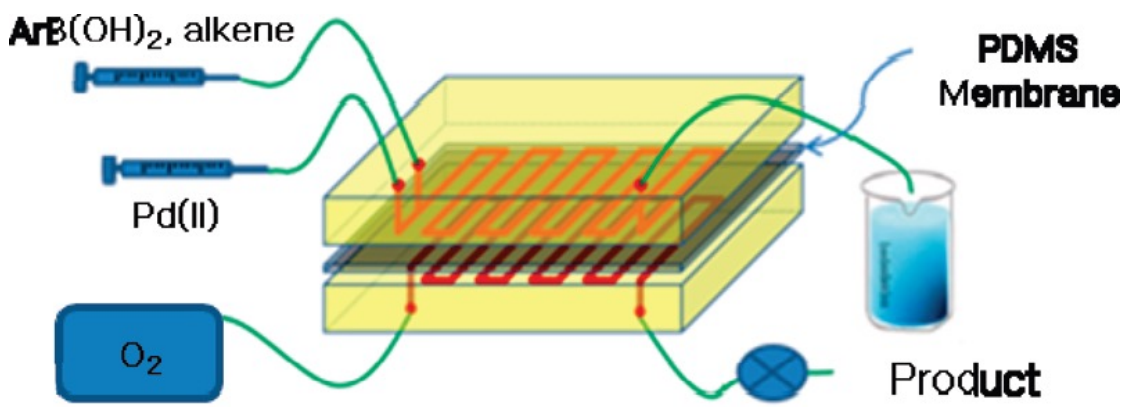
Reaction platform
(http://www.amtechuk.com/)

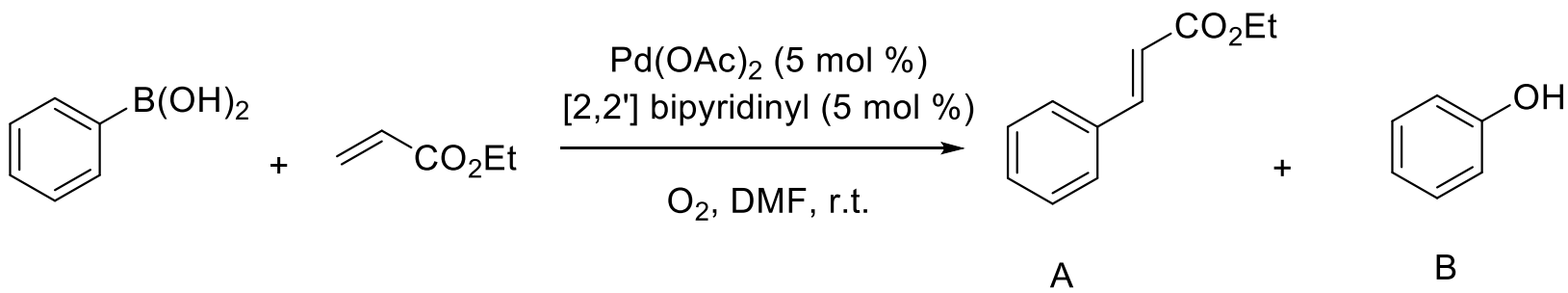
http://www.organic-chemistry.org/topics/flowchemistry.shtm

Dual Channel microreactor: oxidative Heck reaction

A thin gas permeable membrane is sandwiched between two PDMS slabs, the engraved microchannel in each of the slabs facing the other microchannel across the thin PDMS membrane. The microchannel in one of the slabs is used for liquid flow, while the other microchannel across the thin membrane is used for gas flow.

- Better gas-liquid contact
- Enhanced control of gas flow
- Difficult to fabricate reactor



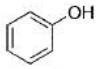
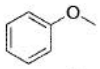
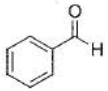
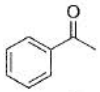
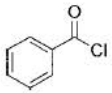
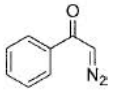


	12 h batch	30 min DC
Yield A:B %	69:24	82:8

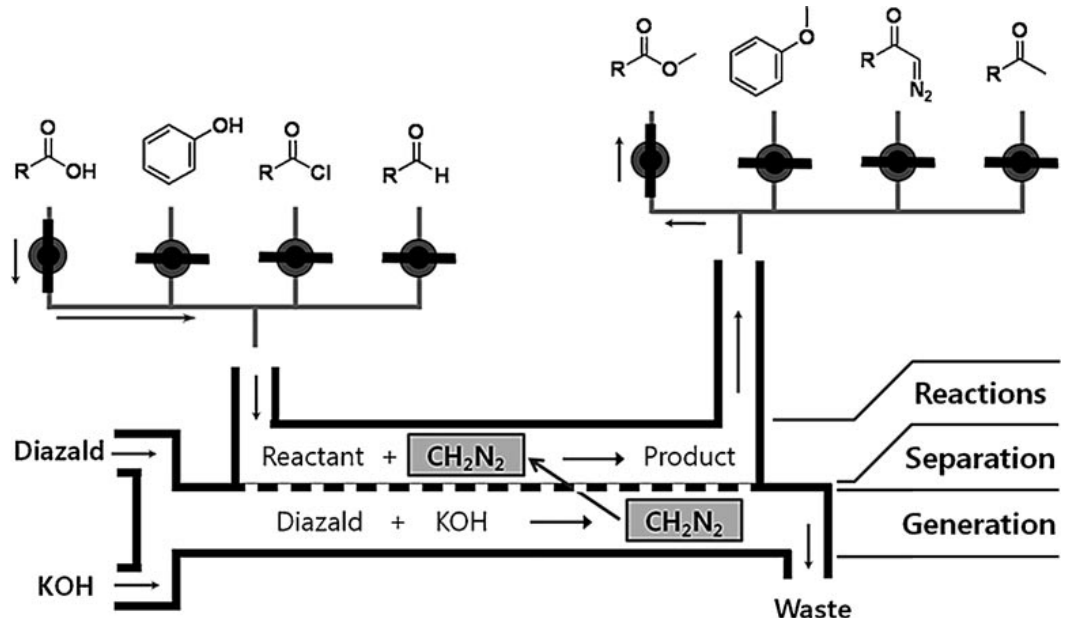
Park, C. P.; Kim, D.-P J. Am. Chem. Soc. **2010,** *132* (29), 10102-10106.

Dual Channel microreactor: handling diazomethane

- Diazomethane is odourless, toxic, carcinogenic, and explosive gas
- Insitu generation of dizomethane mitigates problems associated with its handling
- The use of DC reactor with PDMS membrane allows for insitu generation of anhydrous diazomethane from aqueous solution without dangerous distillation or drying
- Suitable for wide range of applications even the moisture sensitive Arndt-Eistert synthesis

Entry	Substrate	Flow rate [μL min^{-1}]	KOH + Diazald flow rate [μL min^{-1}]	Product	Yield [%][b]	Daily output [mmol]
1		4	10		> 99	2.88
2		1	4		> 99	0.72
3		1	4		81	0.58
4[c]		1	4		90	0.65

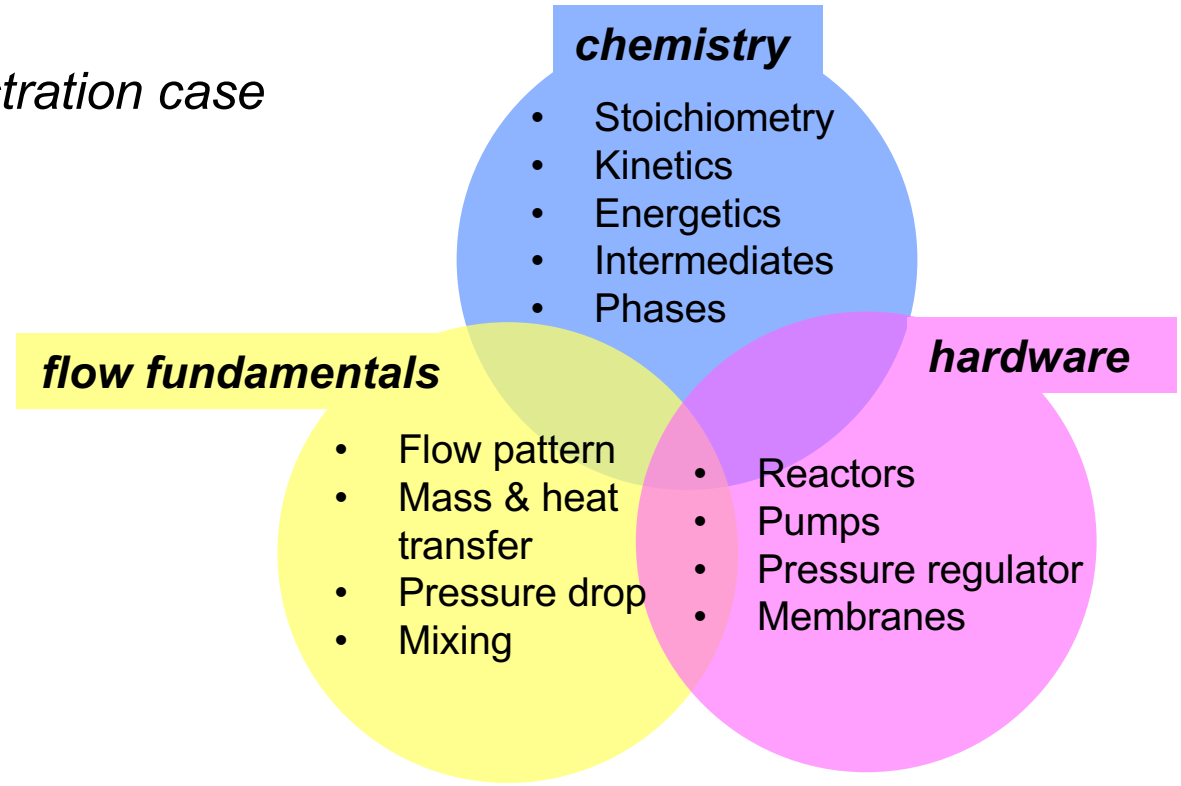
[a] Diazomethane was generated in the bottom channel by flowing solutions of diazald (1.0 M in DMF) and KOH (2.0 M in water containing 0.01 % aliquat 336) with the same flow rate. Substrates were introduced to the top channel in DMF (0.5 M solution). [b] Yields were determined by GC/MS analysis using an internal standard. [c] Arndt–Eistert synthesis.



Park, C. P.; Kim, D.-P., Dual-Channel Microreactor for Gas–Liquid Syntheses. *Journal of the American Chemical Society* **2010,** *132* (29), 10102-10106.

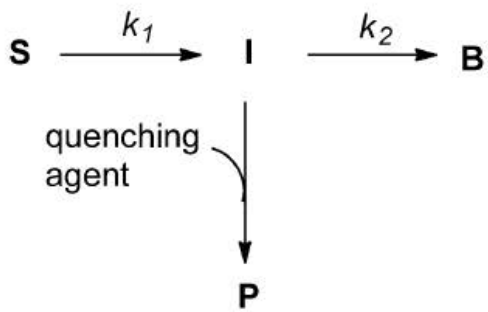
Outline

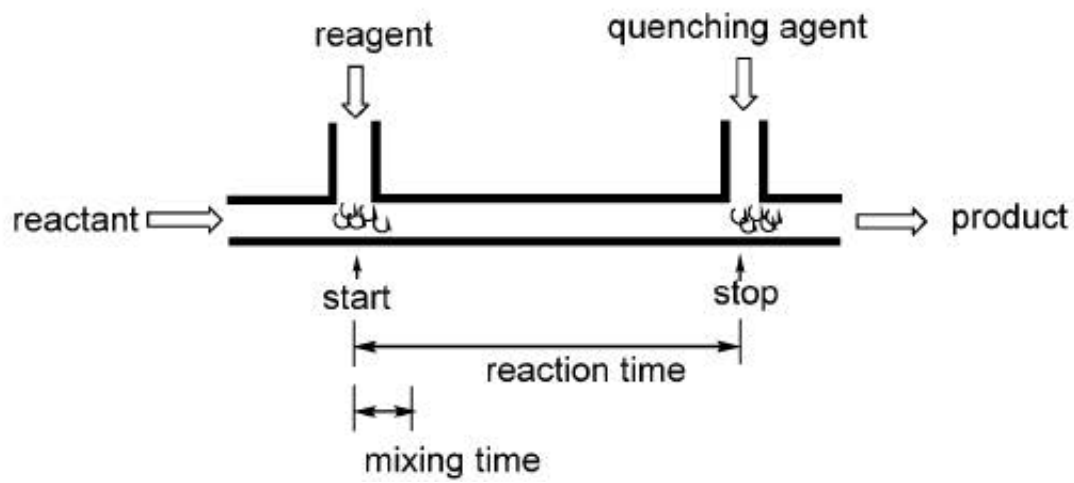
- *Batch vs. flow chemistry*
- *Advantages of flow chemistry*
- *Fundamentals of flow dynamics*
- *Pressure in flow chemistry*
- *Reactor Configurations*
    - *Tube-in tube gas reactor*
    - *Packed bed reactor*
    - *Microchannel reactor* & ***Flash chemistry***
- *Solid handling*
- *Total synthesis demonstration case*



Flash Chemistry: capture the unstable intermediate

- Extremely fast reactions (millisecond reaction time) leading to unstable intermidiates could be carried out effectively with high resolution reaction time control
- Microreactors are needed to minimize mixing to reaction time ratio and allow for precise reaction time control in Flash chemist





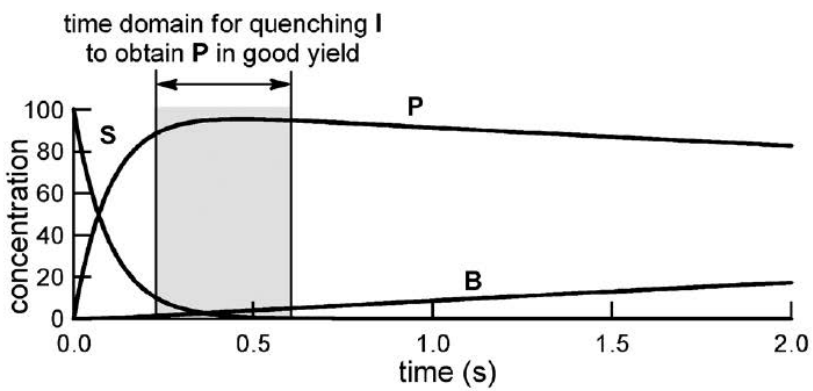
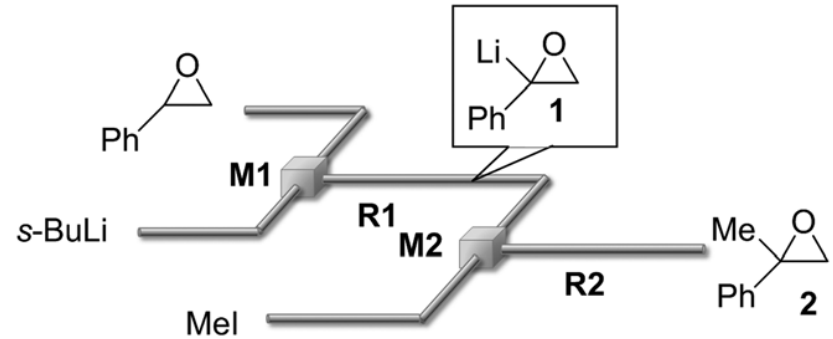


Fig. 6 A variation of the concentrations of reaction components against time (k_1 = 10 s^{-1} and k_2/k_1 = 0.01).

Yoshida, J.-i.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013,** *49* (85), 9896-9904.

Flash Chemistry: capture the unstable intermediate

- In a conventional batch reactor the use of s-BuLi in the absence of TMEDA caused decomposition even at - 98 °C.
- A flow microreactor enables us to conduct the transformation at higher temperatures such as ca. - 70 °C.



- By choosing an appropriate residence time for quenching (addition of iodomethane), the methylated product was obtained in a high yield.

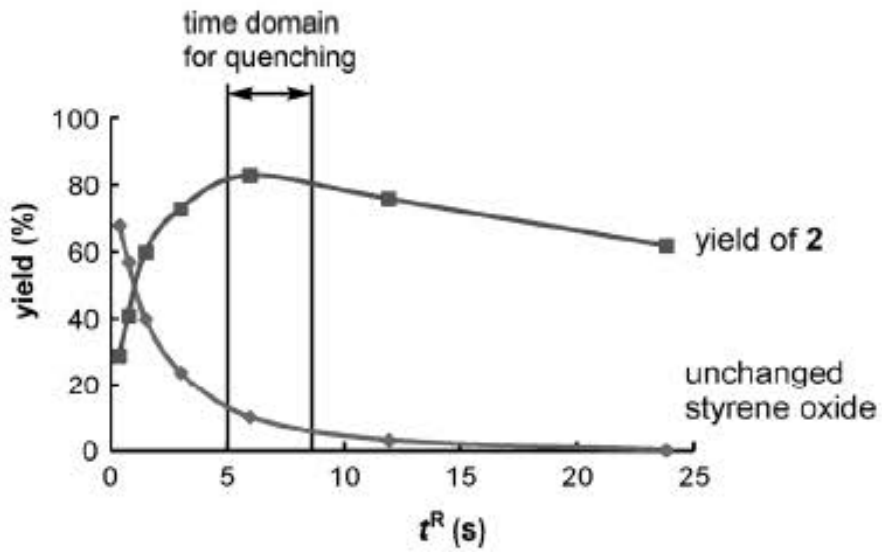
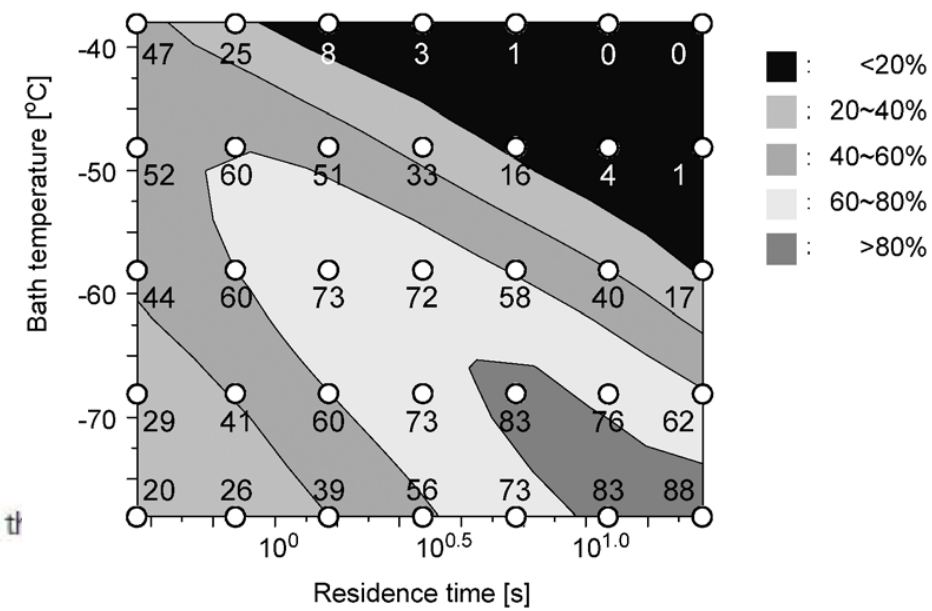


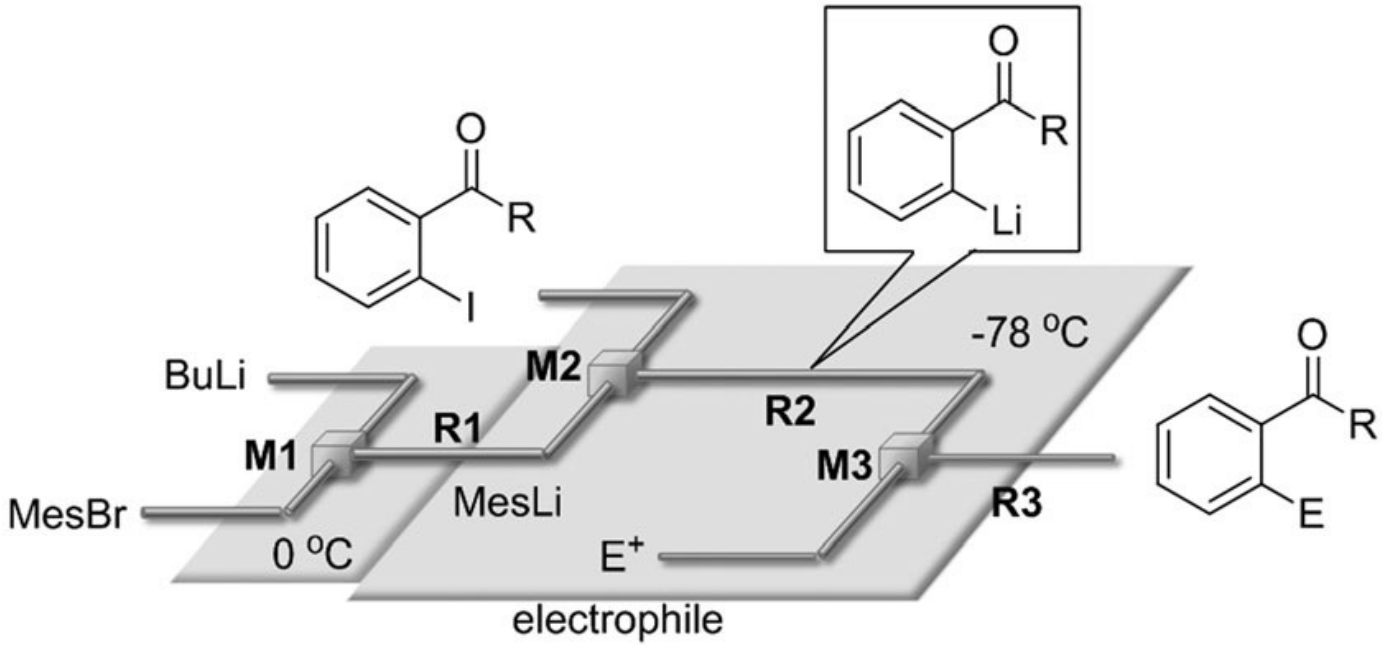
Fig. 8 Plots of the amount of unchanged styrene oxide and the yield of th methylated product against the residence time (t^R) at −68 °C.



Yoshida, J.-i.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013,** *49* (85), 9896-9904.

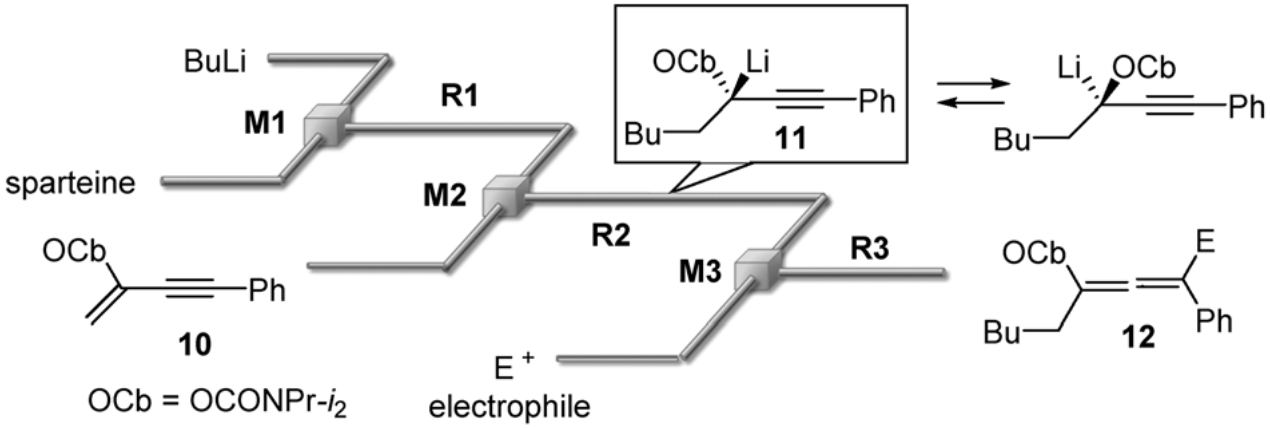
Flash Chemistry: Protecting group-free synthesis

- Unprotected ketone carbonyl groups can potentially survive in organolithium reactions within a very short reaction time
- Efficient reaction of electrophiles including aldehydes, chloroformates, and isocyanates with lithiated unprotected ketones was achieved at residence time of 0.003 s or less.
- Longer residence times lead to decomposition of the aryllithium species to give by-products such as dimeric compounds.

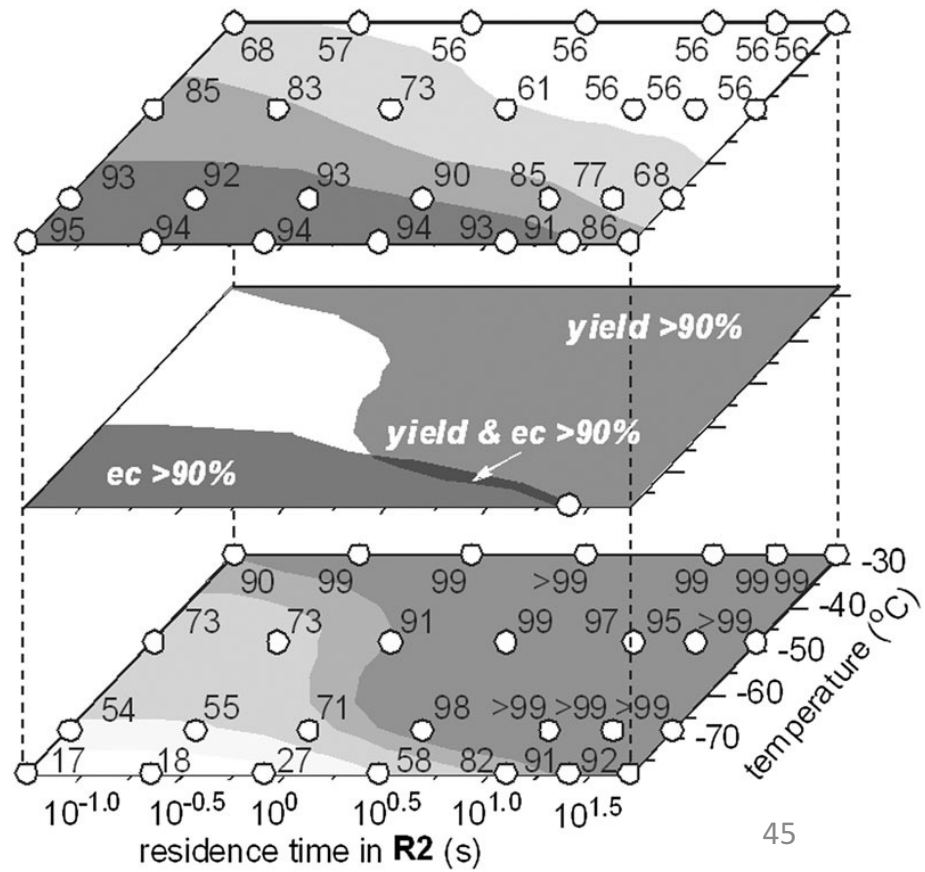


Yoshida, J.-i.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013,** *49* (85), 9896-9904.

Flash Chemistry: asymmetric synthesis

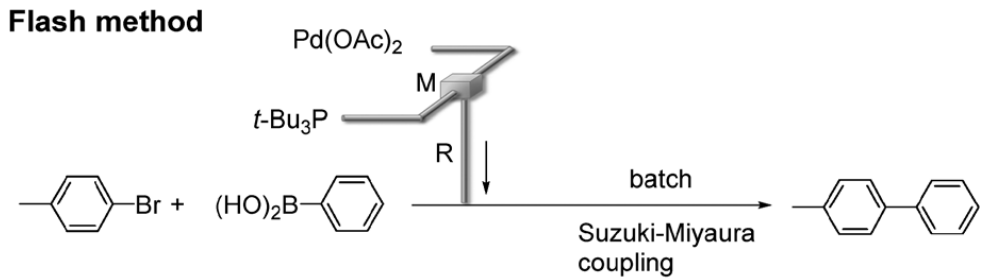


- Flow microreactor systems enable the rapid generation of configurationally unstable organometallics…
- and allow their reaction with electrophiles before they epimerize
- 91% yield and 91% ee vs 60% max. ee in batch

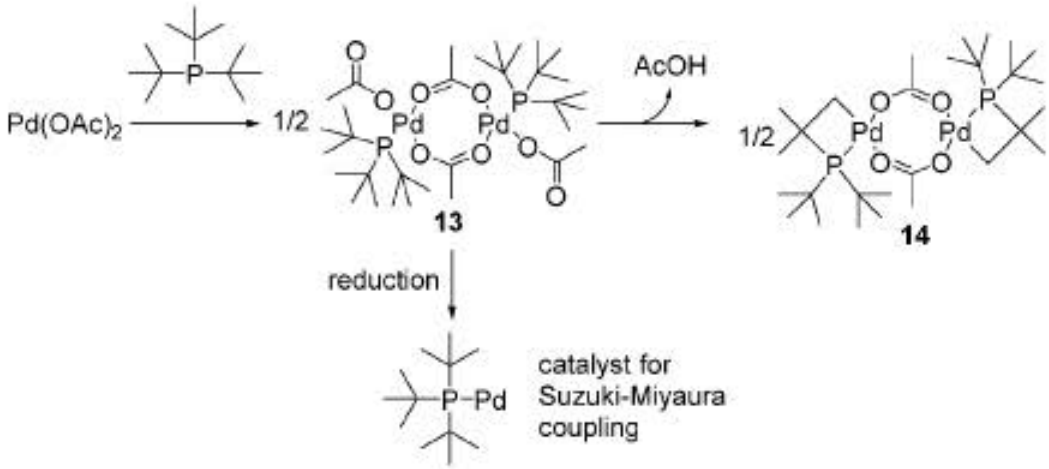


Yoshida, J.-i.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013,** *49* (85), 9896-9904.

Flash Chemistry: catalyst generation

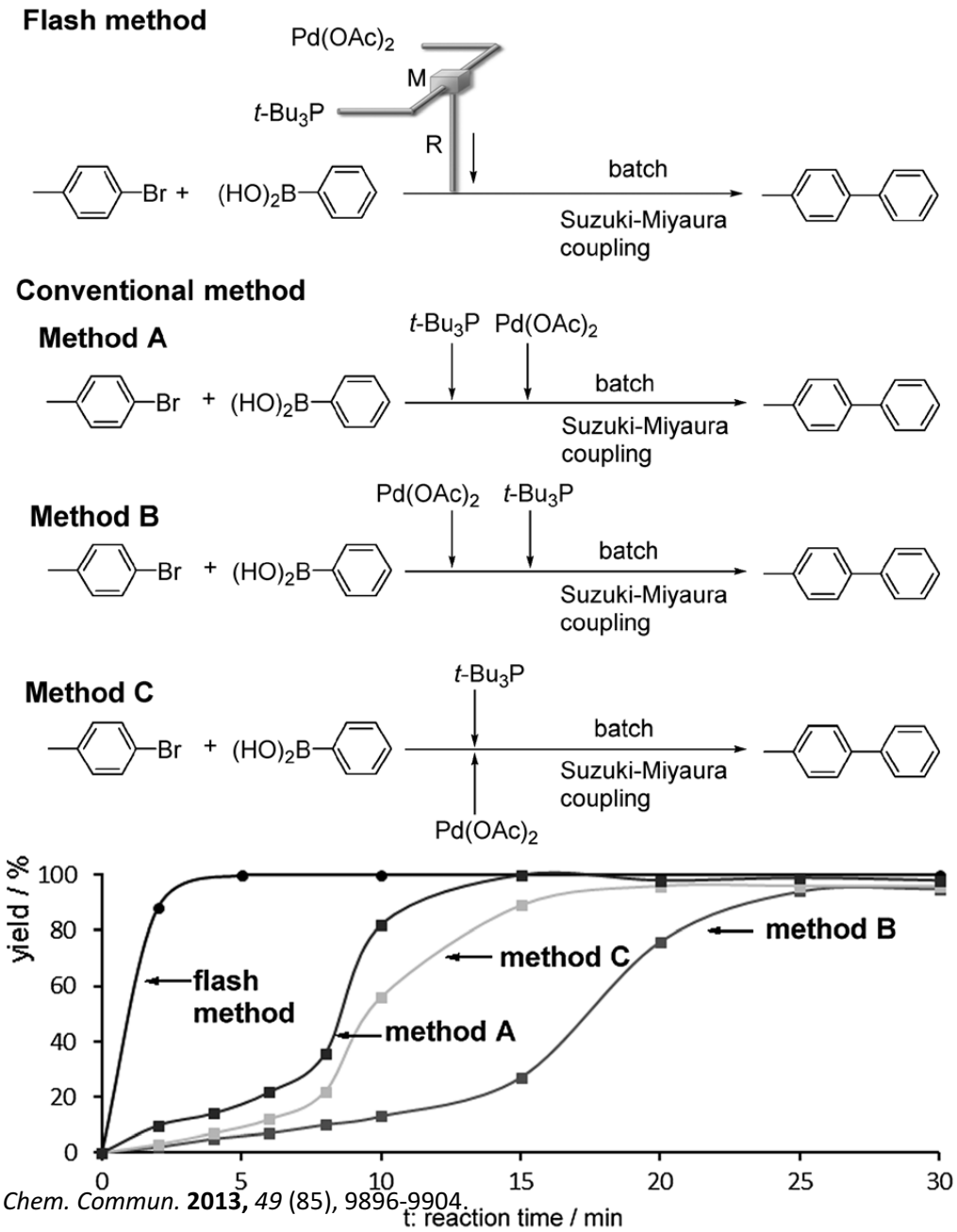


- Coordinatively unsaturated [Pd(0)L] species are highly reactive towards oxidative addition of aryl halides (ArX) to produce [Pd(Ar)X(L)], a key intermediate in the Suzuki-Miyaura coupling
- [Pd(0)L] is highly unstable and its generation at high concentrations is very difficult.
- The flash method involving 1 : 1 mixing of Pd(II) and L in a flow microreactor enables the generation of [Pd(II)L] species in the absence of coupling substrates.
- [Pd(II)L] species is transferred, before it decomposes, to a reaction vessel for coupling reactions, where it may be reduced to give highly reactive [Pd(0)L]. Rt =0.65 s



Yoshida, J.-i.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013,** *49* (85), 9896-9904.

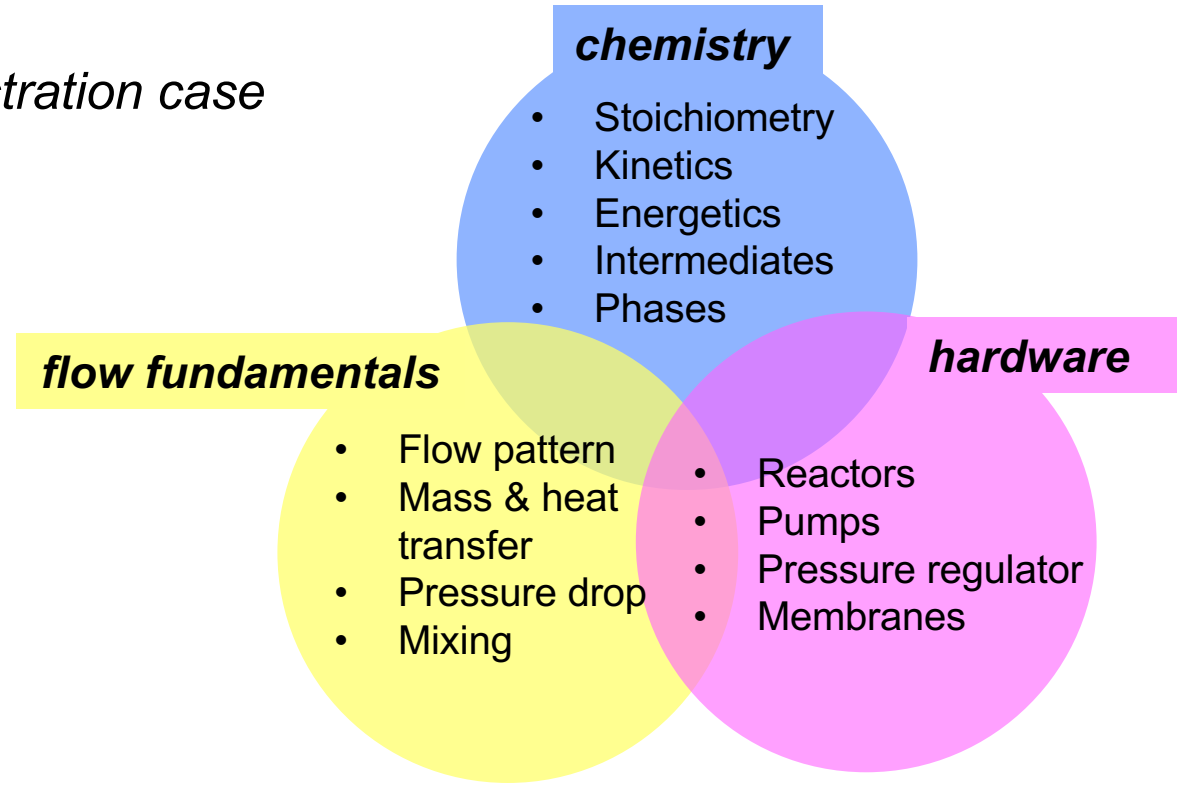
Flash Chemistry: catalyst generation



Yoshida, J.-i.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013,** *49* (85), 9896-9904.

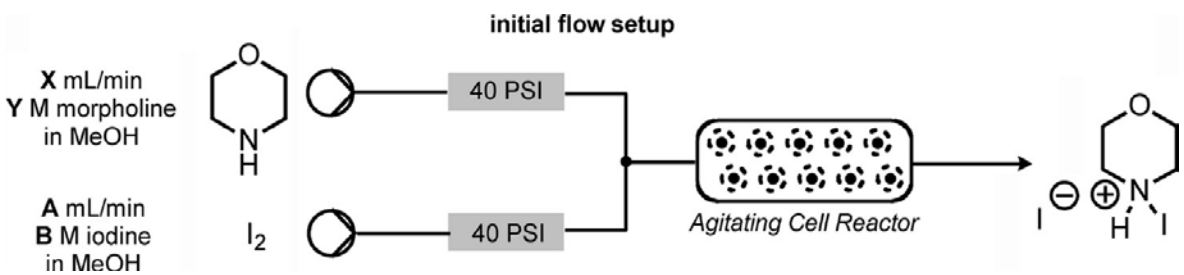
Outline

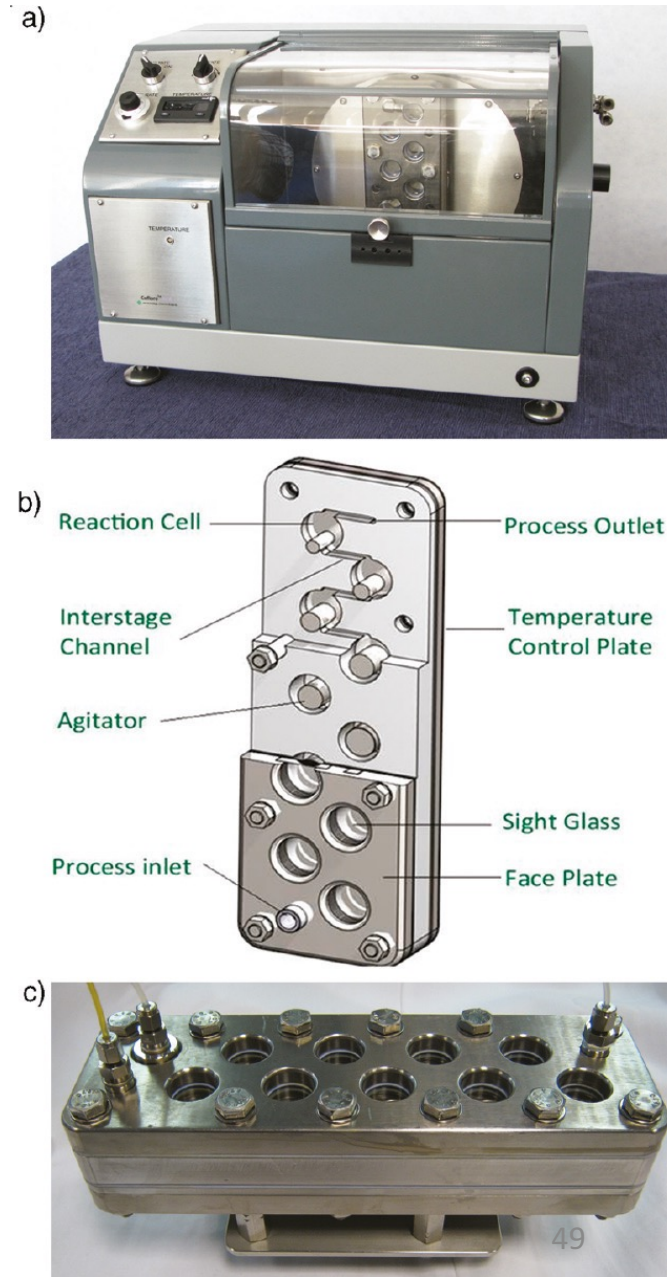
- *Batch vs. flow chemistry*
- *Advantages of flow chemistry*
- *Fundamentals of flow dynamics*
- *Pressure in flow chemistry*
- *Reactor Configurations*
    - *Tube-in tube gas reactor*
    - *Packed bed reactor*
    - *Microchannel reactor & Flash chemistry*
- ***Solid handling***
- *Total synthesis demonstration case*



Common drawback: solid formation

- Solids in flow reactors cause blockages
- The ability to tolerate solids varies greatly
  - ratio between channel diameter and particle size
  - velocity of the reaction
- The use of solid reagents is typically easiest by isolating them in a “column” and flowing the reaction in solution through the packed column
- Solution to solids issues is often a chemistry solution:
  - Add co-solvents to increase solubility of products
  - Reduce concentrations of reaction
- Or use of specially designed reactors





Browne, D. L.; Deadman, B. J.; Ashe, R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev.*, 2011, 15 (3), pp 693–697

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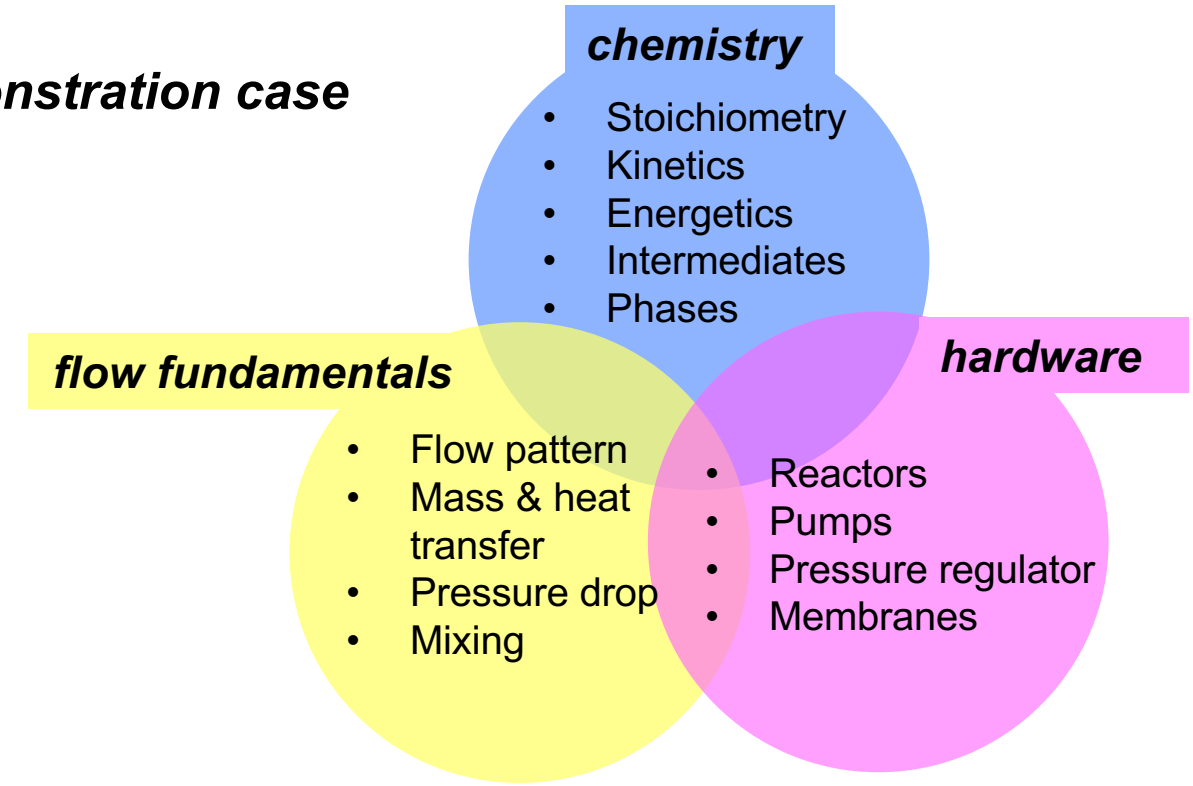
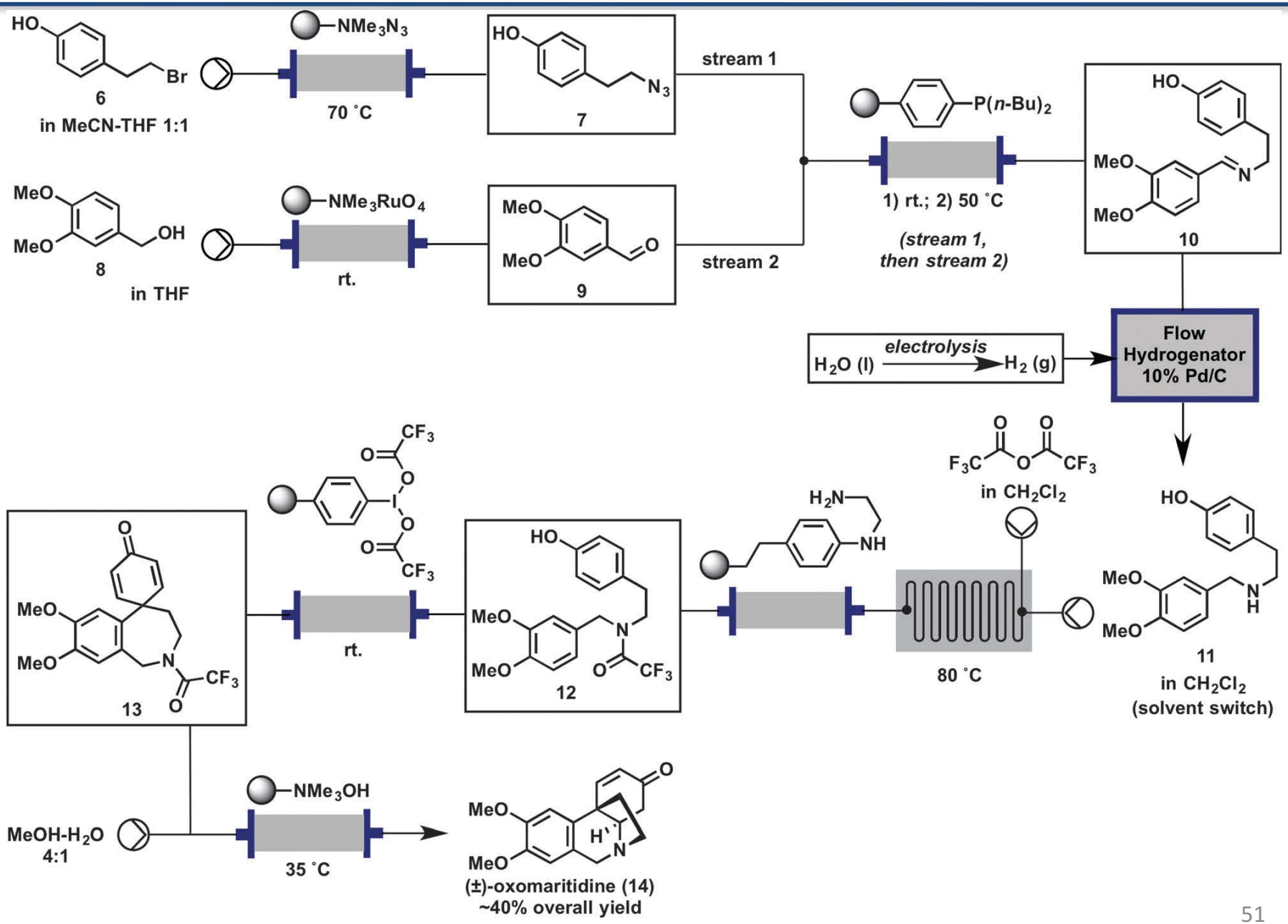


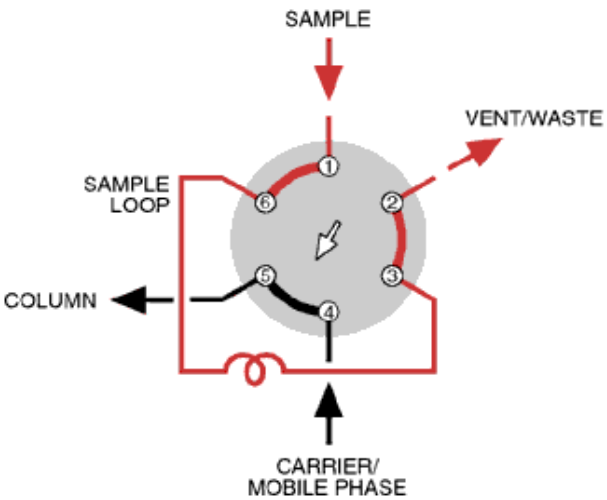
Natural Product Synthesis: Oxomaritidine



I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby and G. Tranmer, Chem. Commun., 2006, 2566–2568..

Analytical techniques in flow chemistry

- Several analytical methods can be integrated for online measurements such as IR, Uv-vis…
- Automated sampling valves used to deliver samples to other methods; GC, MS, IR



http://www.vici.com/support/app/app11j.php

http://www.siphotonics.com/Pages/UV_Vis_Spectrophotometer_Flow_Cells.html

http://www.mt.com/in/en/home/products/L1_AutochemProducts/ReactIR/flow-ir-chemis.html

Conclusion

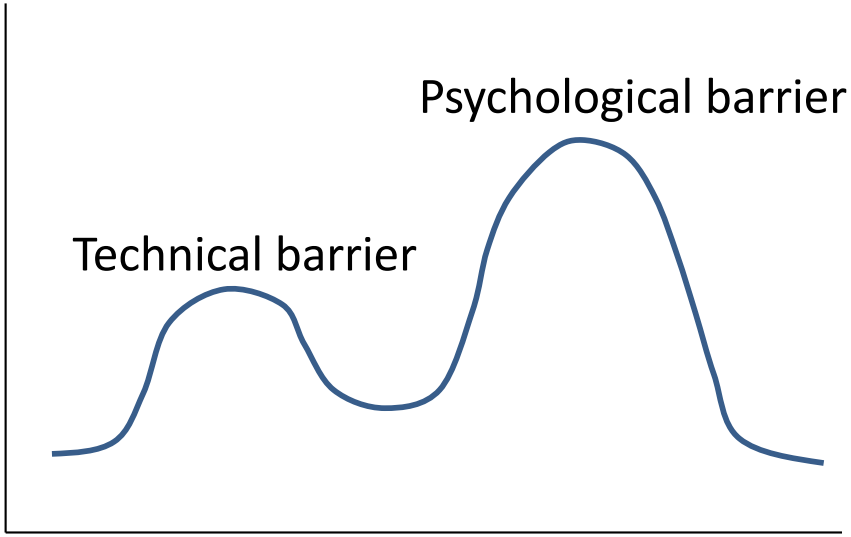
Flow Chemistry:

- Better mixing, enhanced heat and mass transfer
- Better conditions control, efficient handling of unstable intermediates
- Better reproducibility, easier scale-up

Several reactor designs for different reactive systems

Demonstrated to effectively perform multistep total synthesis

Disruptive technology, not meant to replace a skilled organic chemist but to allow more time for experiment design and analysis



Useful resources

Societies and Forums:
http://www.flowchemistrysociety.com/
http://www.flowchemistrysociety.com/journal_of_fc.php
http://www.flowchemistrytks.com/index.html

Research groups:
Ley Group, Univ. of Cambridge
http://www.leygroup.ch.cam.ac.uk/
Kappe Group, Uni Graz schafft Fortschritt
https://homepage.uni-graz.at/de/oliverkappe/
Yoshida Group, Koyto University
http://www.sbchem.kyoto-u.ac.jp/yoshida-lab/en/index.php?research
Jamison Group, MIT
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Technology providers:
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