UNIVERSITY OF LEEDS

The development of continuous multi-phase reactions (and separations)

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Talk Summary

- Multi-phase systems
- Continuous stir tank reactors
- Continuous liquid-liquid separation
- Automated optimization

Multi-phase systems in processes

- Multi-phase means: combinations of gas(es) liquid(s) and solid(s)
- Applies to reaction, separation or both.
- Unit operations – reaction, distillation, crystallisation, extraction, filtration, drying…
- Process efficiency is sought during development to reduce cost, maximise productivity and minimise waste.
- Intensification often results in solids as reactant, intermediate or product solubility limits are exceeded or solid additives are required (catalysts, adsorbents, inorganics etc).

- The majority of chemical manufacturing processes involve multi-phase systems.
- Efficient mixing is required

Thermopedia - 10.1615/AtoZ.m.multiphase_flow

Mixing

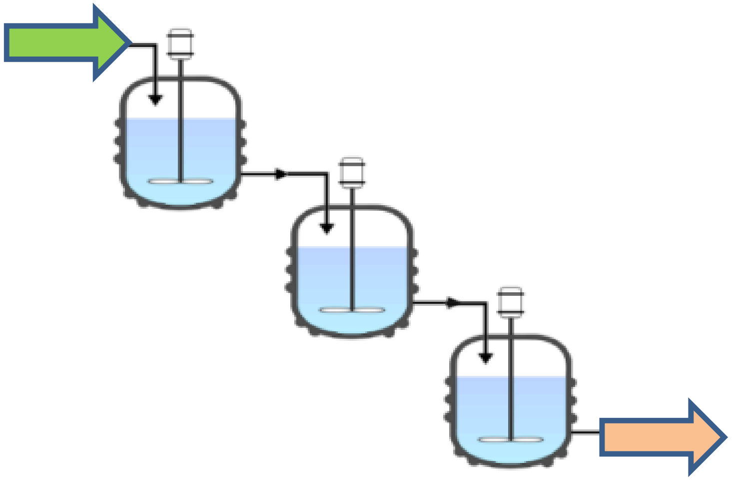
- Batch manufacturing using stirred tanks is an industry standard due to its flexibility for unit operations and handling multi-phase systems.
- Impellor/reactor design is important in ensuring efficient mixing
- Active mixing results in efficient mass transfer but requires energy input.

On the other hand….

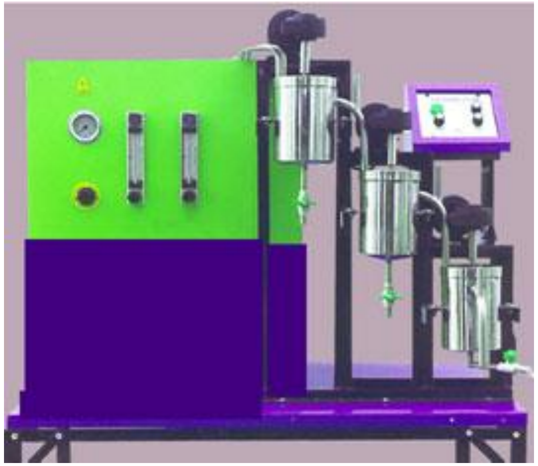
- Continuous flow systems commonly employ pipes that operate most easily with mono-phase fluids (gas or liquid).
- Unless very high flow rates are used the energy input is low making multi-phase mixing difficult.
- If multi-phase systems are used, mixing is required and can be provided by the flow rate or static mixers or tortuous paths.

Lab-scale equipment to enable continuous process development

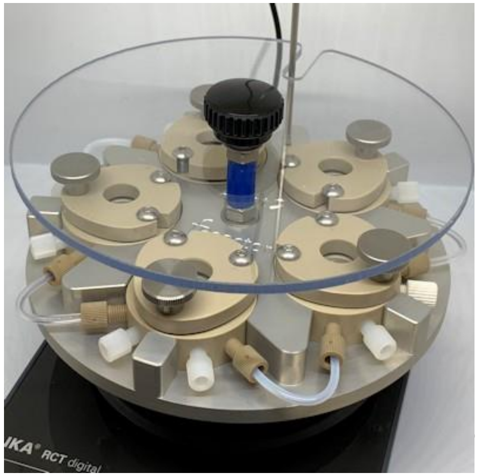
Cascade continuous stirred tank reactor
- Active mixing
- Thermal control



Original lab-scale device: 3*1 litre cascade CSTR



*f*Reactor™



www.freactor.com
[Flow Chemistry - fReactor CSTR Flow Chemistry Platform - Asynt]()

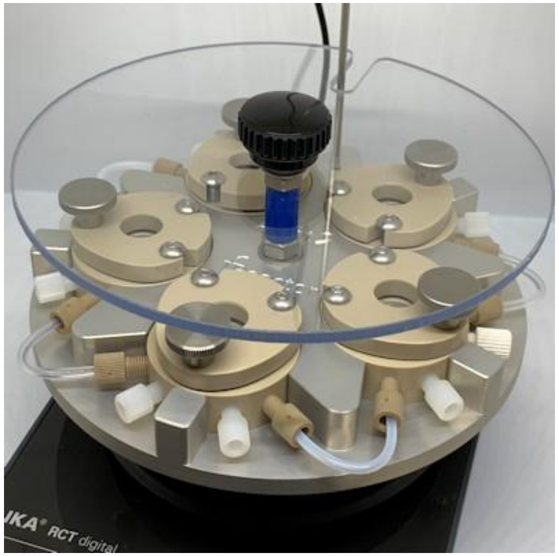
CSTRs and fReactor design

*f*Reactor available from Asynt

Can be used in batch or continuous mode

2 ml per reactor.
Also available 7.5 ml version and made 0.4 ml

Made of PEEK, resistant to most solvents, Hastelloy version available



Viton gasket with three nuts to maintain even pressure for seal. Easy to remove lid for washing.

Glass window Pressure to 8 bar Safety shield removable.

Sits on a standard hot plate stirrer.
Active mixing with magnetic flea and heating max 130degC

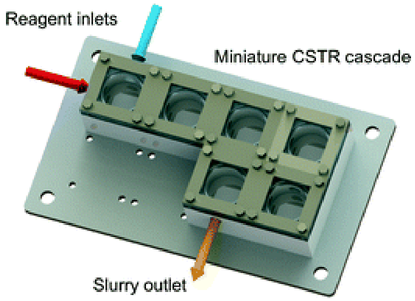
Each reactor daisy-chained with 2.5mm PTFE tube HPLC fittings

Extra ports for probes
(e.g. temp., pressure) or additional feed or outflow.

- Alternative CSTR designs

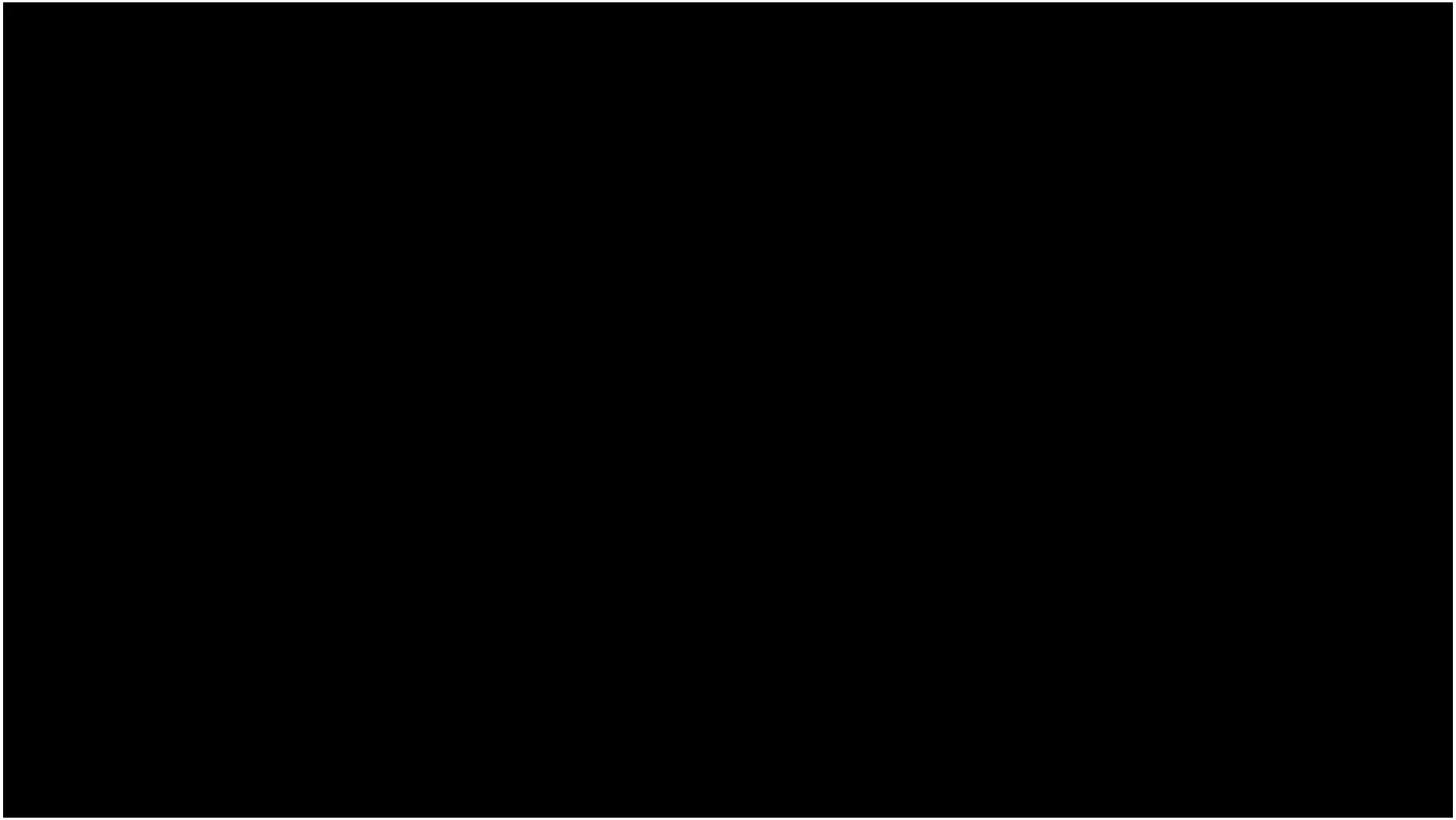
AMTech ACR Coflore

SABRe from StoliChem



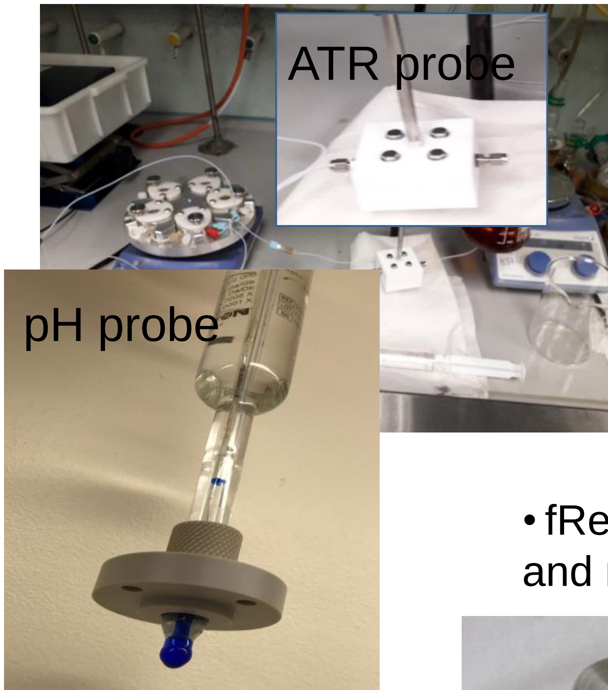
Y. Mo, K. Jensen
React. Chem. Eng., 2016,**1**, 501-507

Active vs Passive Mixing

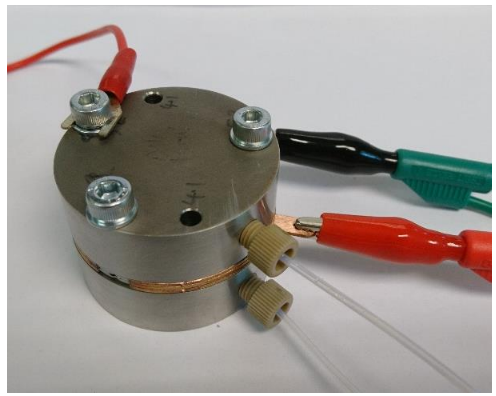


fReactor variations

- Process Analytical Technology

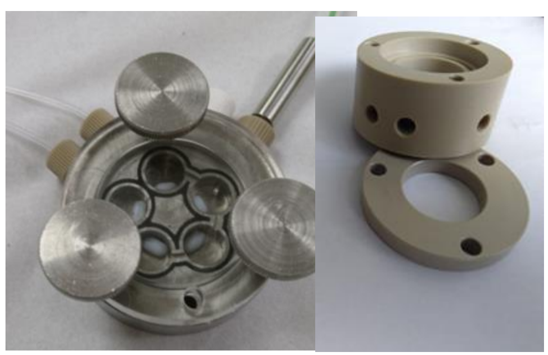


- Continuous flow electrochemical reactor

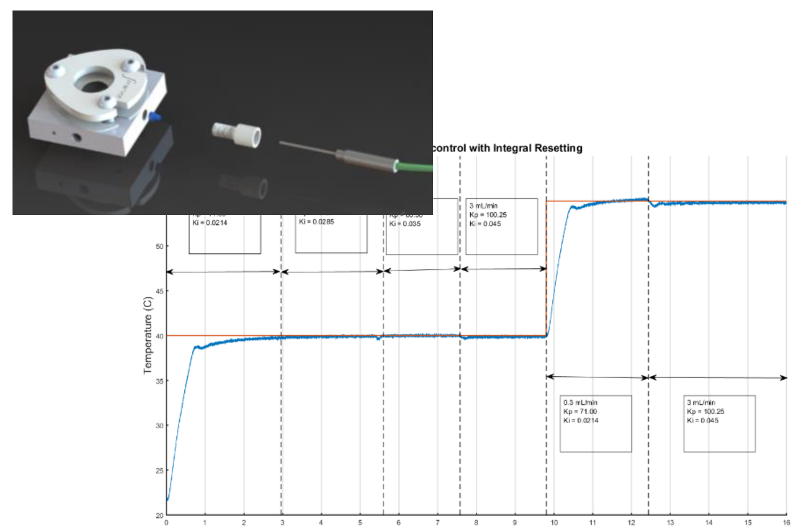


- Continuous multi-phasic flow photochemical reactor

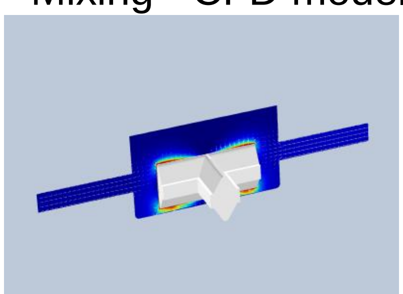
- fReactor mini 5*0.4mL and maxi 7.5 mL



- Direct heating cartridge for accurate and gradient temperature control

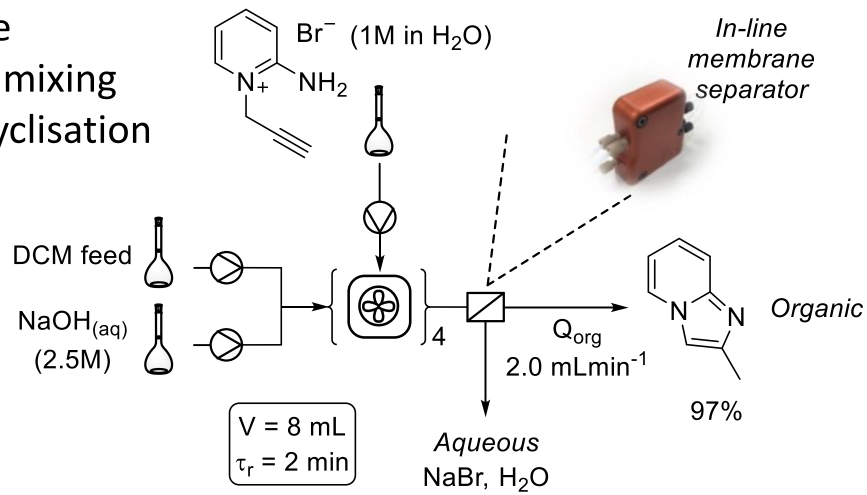


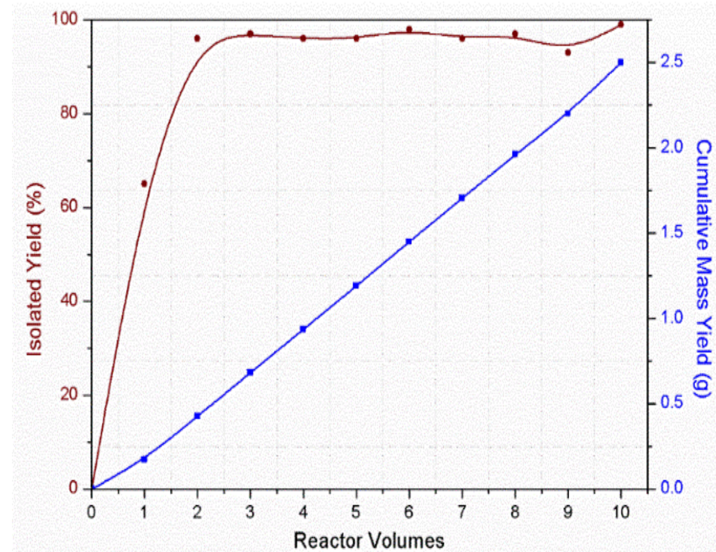
- Mixing - CFD model



Liquid-liquid (L-L) reactions

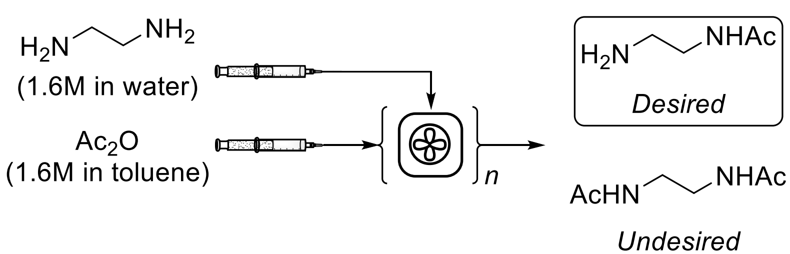
L-L bi-phase
- Intense mixing
- Rapid cyclisation





M. Chapman, N. Kapur, A.J. Blacker *et al*, *Org. Proc. Res. Dev.* 2017, 21(9), 1294-1301

L-L bi-phase
- productive acylation



Undergraduate student data

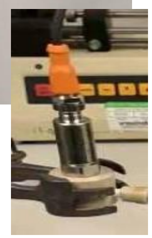
No. CSTRs (n)	τ_{res} (min)	Conversion (%)[a]/ Selectivity (%)	Productivity ($gL^{-1}h^{-1}$)
Batch	20	53/20	51
5	30	83/84	173

M. Bayana, M.; A.J. Blacker, A.D. Clayton, K..E. Jolley, R. Labes, C.J. Taylor, W. Reynolds, *J. Flow Chem.* 2020.
DOI:10.1007/s41981-020-00114-5

Lab scale continuous flow hydrogenations

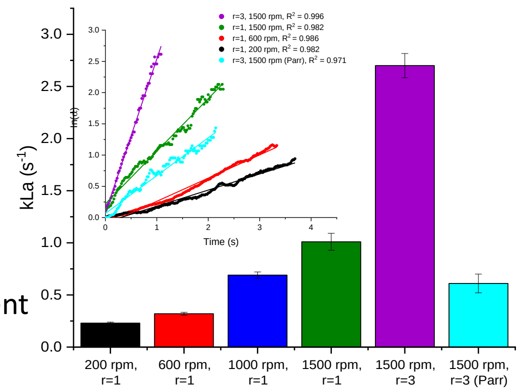
- G-L-S Pd/C catalysed hydrogenation of nitrobenzene at 9 bar H_2

Reactor pressurised with H_2 in syringe

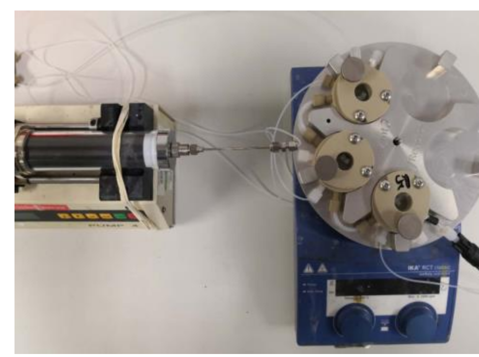


On-line pressure measurement

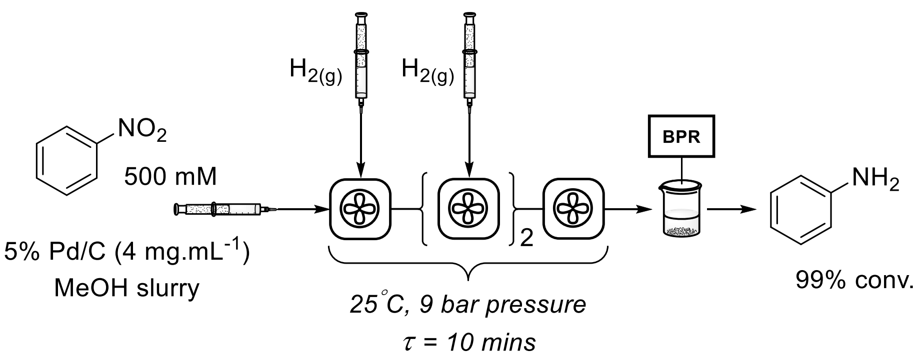
Parallel batch for kinetic studies



Reconfigure for continuous flow



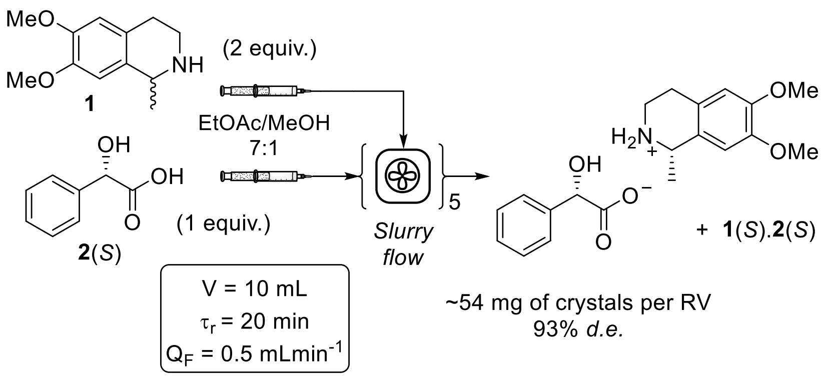
- Effect of mixing speed on hydrogenation rate
- Direct measurement of mass transfer coefficient K_La

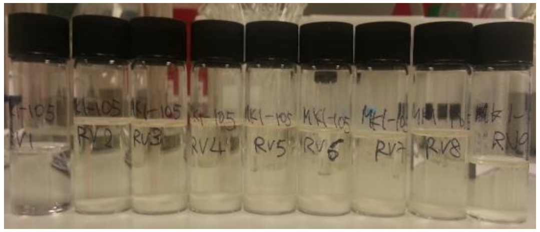


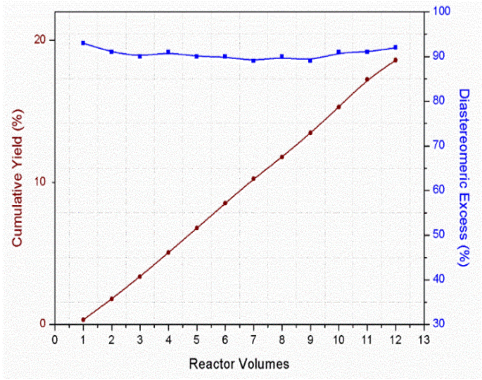
Guan, F.; Kapur, N.; Sim, L.; Taylor, C. J.; Wen, J.; Zhang, X.; Blacker, A. J., *React.Chem.Eng.* **2020,** *5* (10), 1903-1908

Continuous Crystallization

- S-L System: Diastereomeric (reactive) crystallisation – τ_{res} = 20-60 min

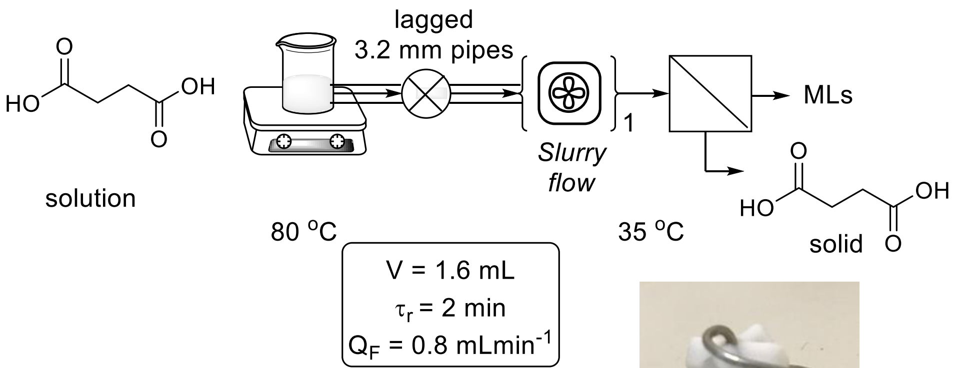






M. Chapman, N. Kapur, A.J. Blacker *et al*, *Org. Proc. Res. Dev.* 2017, 21(9), 1294-1301

- S-L System: Cooling crystallisation – τ_{res} = 2 min



Steady-state achieved
Blockage after >10 RV

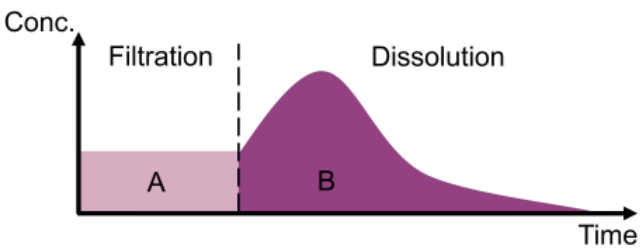
Paddle stirrer
to reduce crystal attrition

Jack Taylor – unpublished data

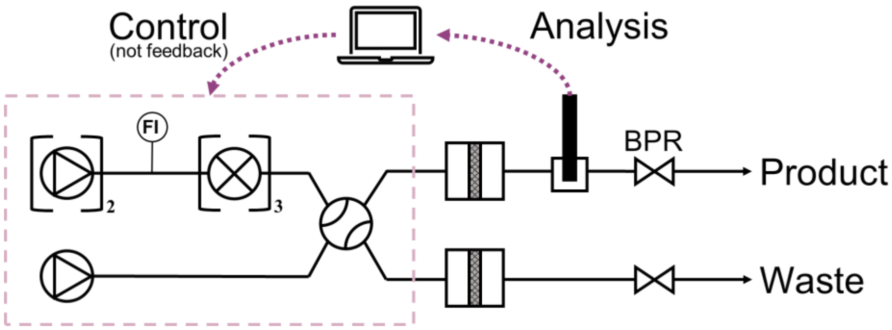
Continuous Crystallization

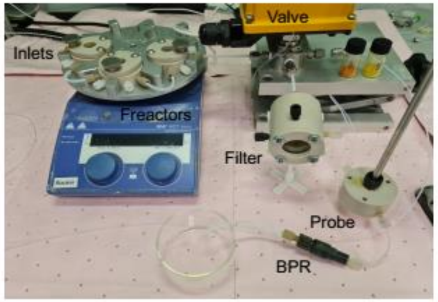
- S-L System: Anti-solvent crystallisation
- In-line filtration and on-line UV/vis analysis

- Determination of solid mass recovery

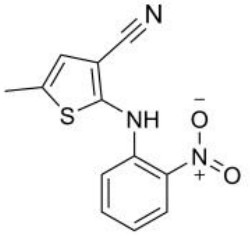


A = amount left in solution (mother liquor)
B = amount of solid dissolved from filter (overall yield)
A+B = total amount (reaction yield)





System



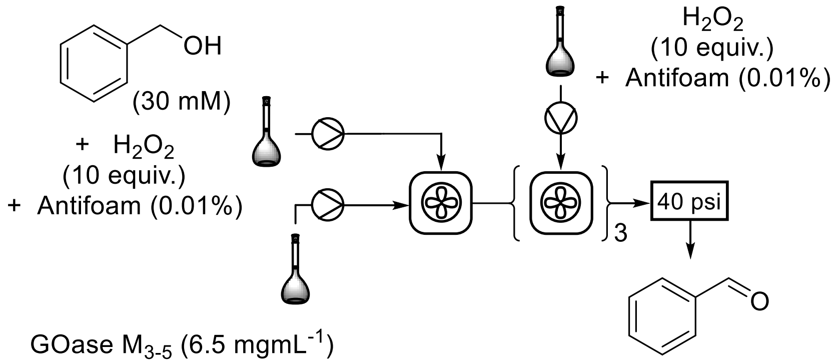
ROY
5-Methyl-2-((2-nitrophenyl)amino)-3-thiophenecarbonitrile

- Link to automation enables process development to improve mass recovery /purity

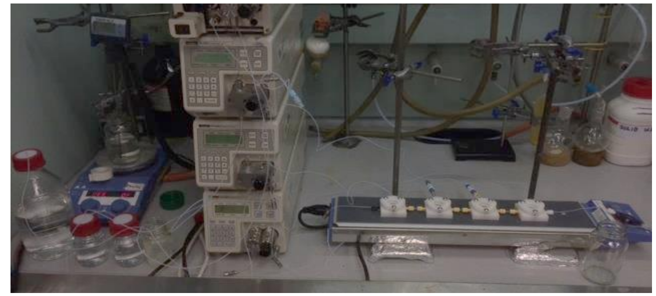
Joe Marsden – unpublished work

Accelerated bio-oxidation

- G-L system: galactose oxidase alcohol oxidation mediated by water supersaturated oxygen



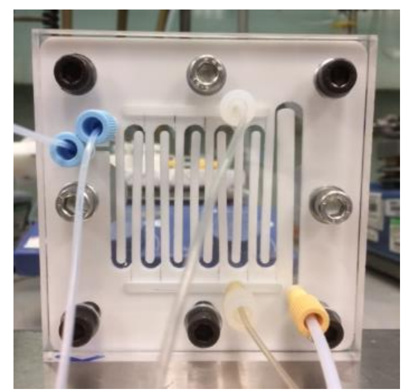
GOase $M_{3\text{-}5}$ (6.5 $mgmL^{-1}$)
HR-peroxidase (0.1 $mgmL^{-1}$)
Catalase (0.15 $mgmL^{-1}$)
$CuSO_4$ (0.1$mgmL^{-1}$)



fReactor informed design of multi-point injection reactor

τ_{res} (min)	No. CSTRs	H_2O_2 feeds (equiv.)	GOase loading ($mgmL^{-1}$)	Conversion (%) /productivity ($gL^{-1}h^{-1}$)
13	4	3 (3)	6.5	70
13	4	3 (5)	6.5	84
26	4	3 (5)	6.5	86
26	4	3 (10)	6.5	95/1.7
13*	4	3 (10)	15.0	92/6.9
8.7	-	11 (3)	15.0	97

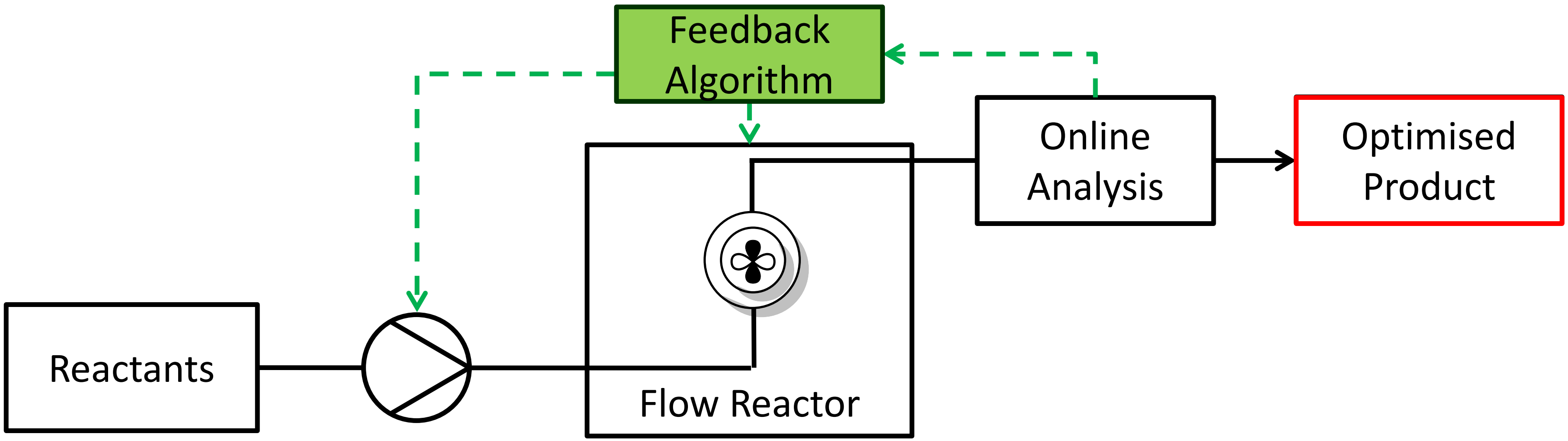
Conversion (%) determined by HPLC analysis at steady-state. *60 mM substrate.



- Productivity increased to 11.3 $gL^{-1}h^{-1}$ (272 $gL^{-1}d^{-1}$)
- Product solubility becomes the limit, with solid blocking the reactor

M. Chapman, N. Kapur, A.J. Blacker *et al. Angew. Chem*. 2018, 57(33), 10535-10539

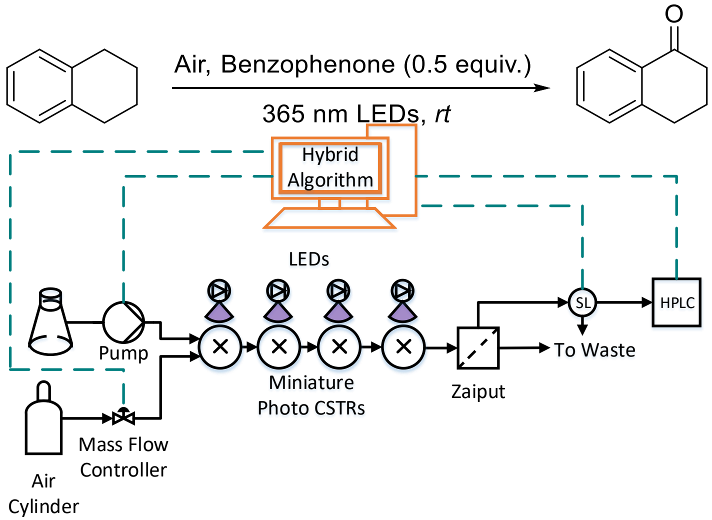
Automated development using lab scale continuous flow



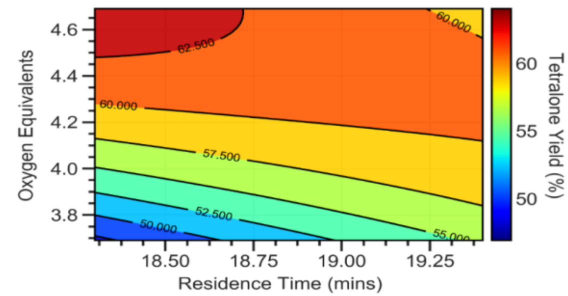
- Rapid optimisation technique for continuous and discrete input variables and multi-factor evaluation (output) functions
  - Days/hours rather than weeks
- A variety of local and global optimisation algorithms available
- The data can be used for statistical/kinetic models
- Optimum is verified by experiment

R. A. Bourne *et al.*, *Org. Process. Res. Dev.*, 2011, **15**, 932

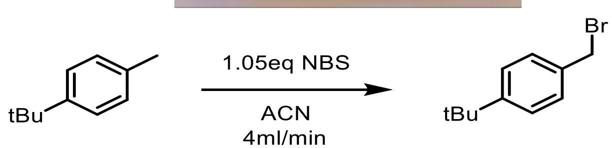
G-L and S-L continuous flow photochemistry



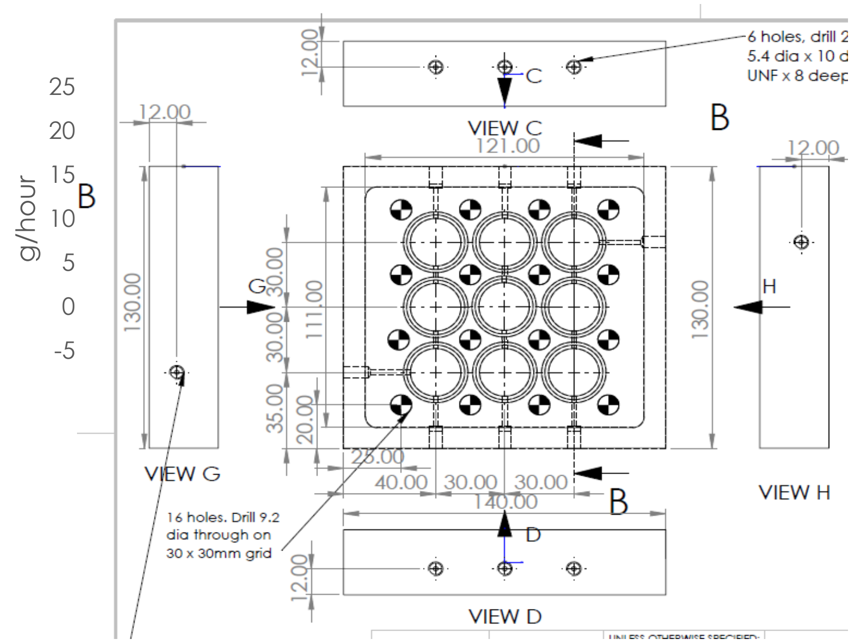
A.D. Clayton *et al, Chimia* 2019, 73, 817-822



- reduced residence time (18.3 *cf.* 45 minutes)
- air is a safer source of oxygen compared to oxygen
- benzophenone is a more accessible than TBADT - even at 0.5 equivalents



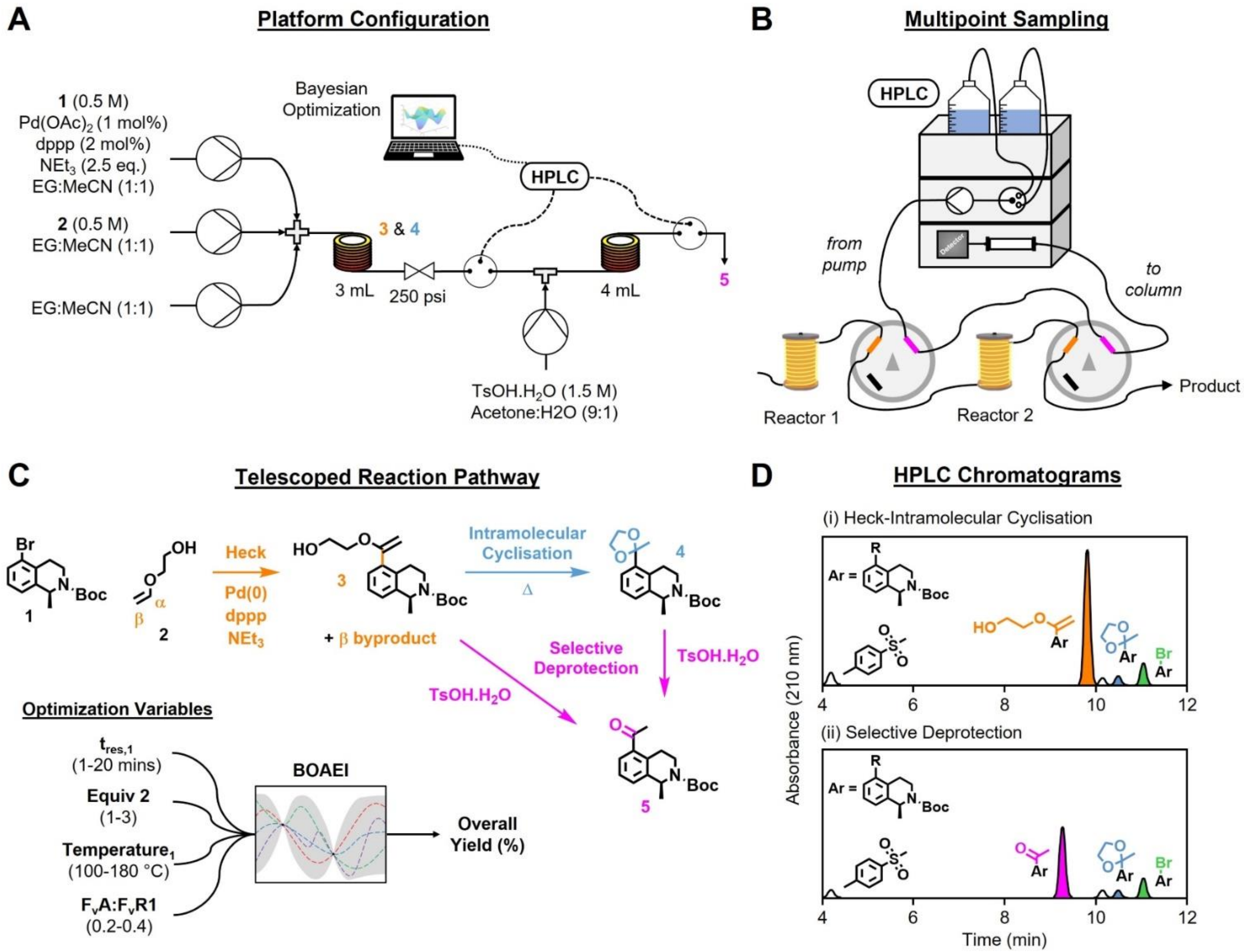
72% conv; 96% selectivity;
63g/hour



Photo*f*reactor scale-up design

Francis et al *Org. Proc. Res. Dev.,* 2022, 26, 1, 215-221

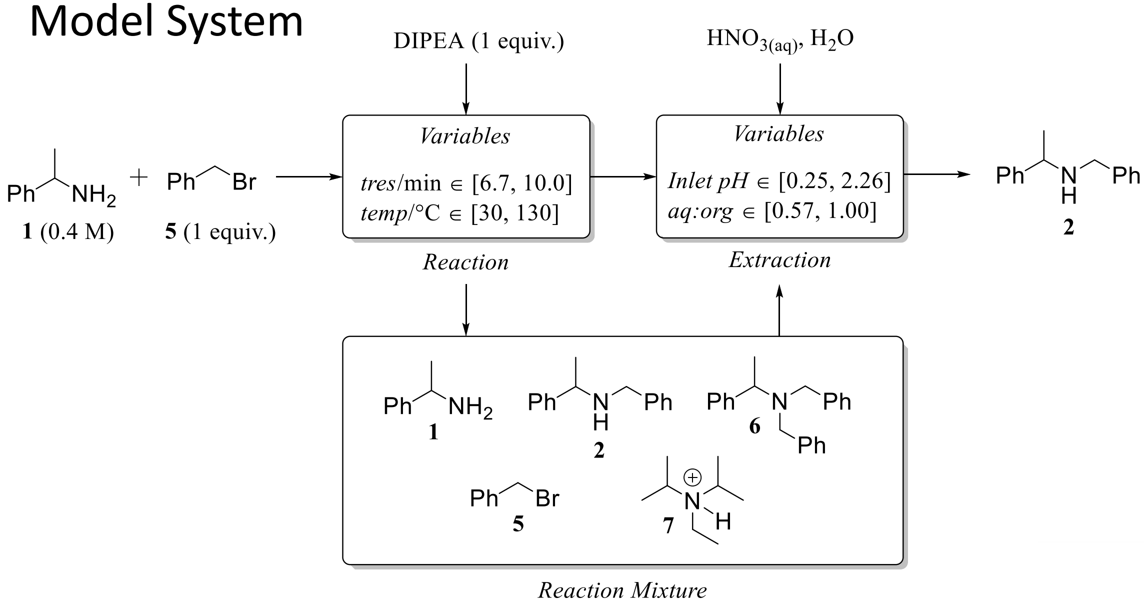
Auto-optimised telescoped reaction

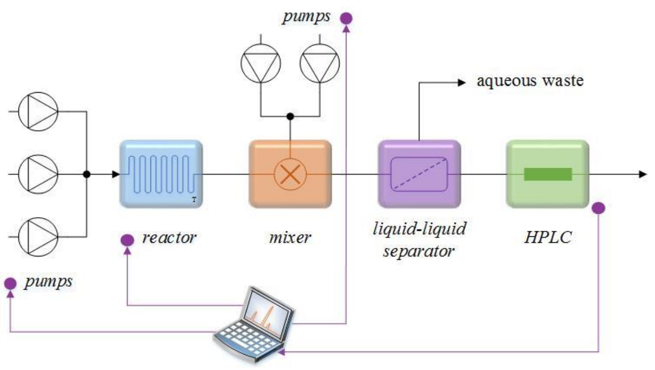


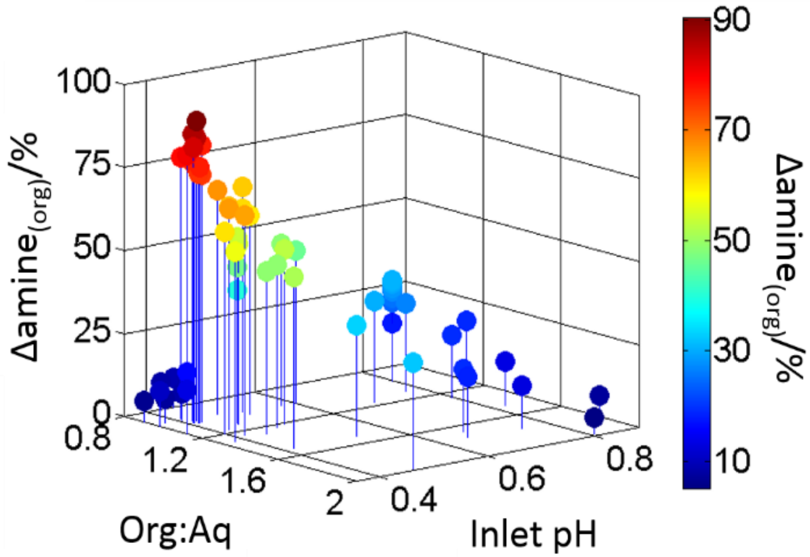
Clayton *et al* *Angew. Chem.* **2023**, *135*, e202214511

Black box optimisation of reaction-extraction

- Model System

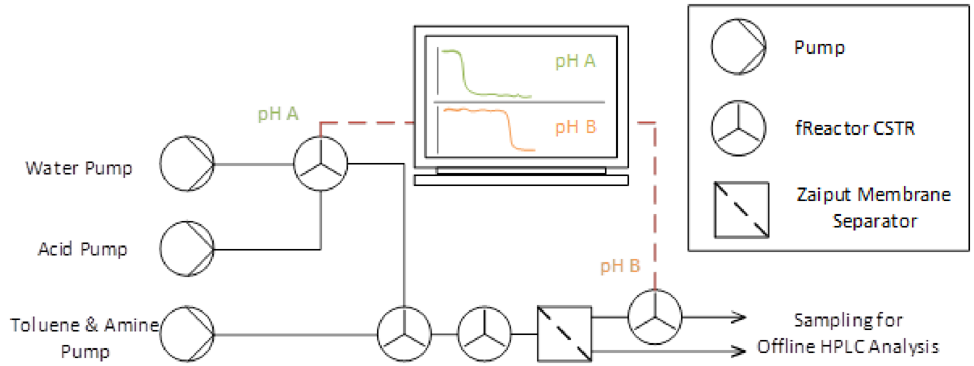


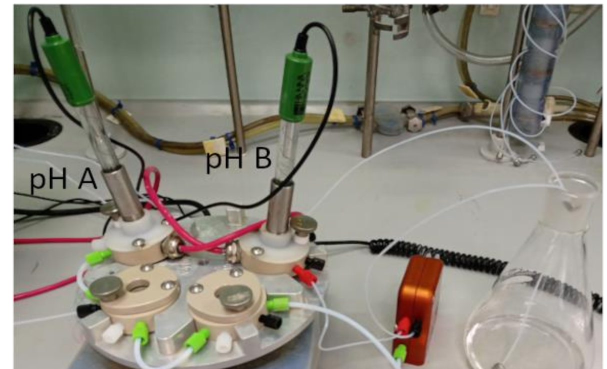




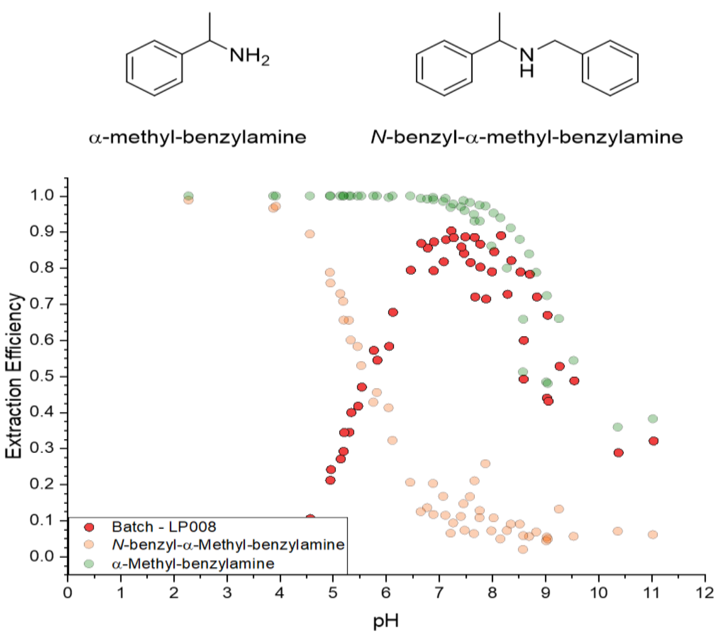
A.D.Clayton, Luke A.Power, W.R.Reynolds, C.Ainsworth, D.Hose, M. F.Jones, T.W.Chamberlain, A.J.Blacker, R.A.Bourne
J. Flow Chem., **2020** (10),199–206

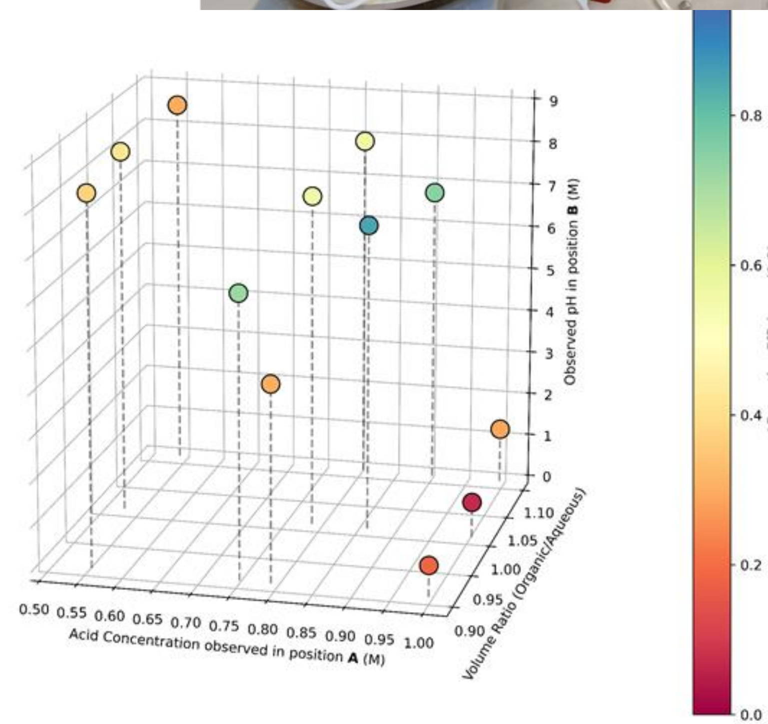
Optimum pH and phase ratio for selective extraction of one of two amines





Amine separation - comparison

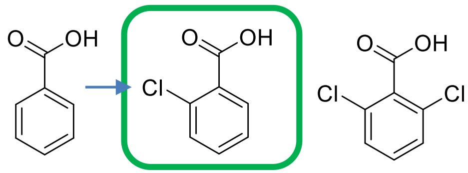




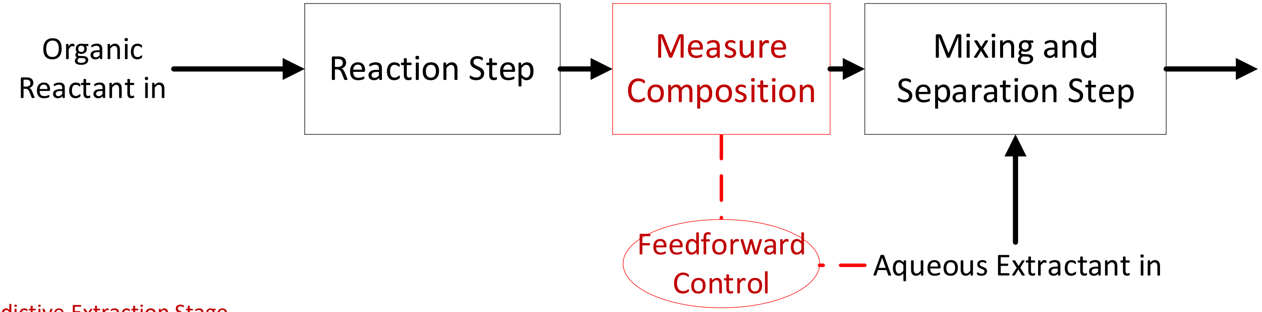
Power *et al React. Chem. Eng.*, 2021,6, 1806-1810; Clayton *et al J. Flow Chem.*, 2020(10),199–206

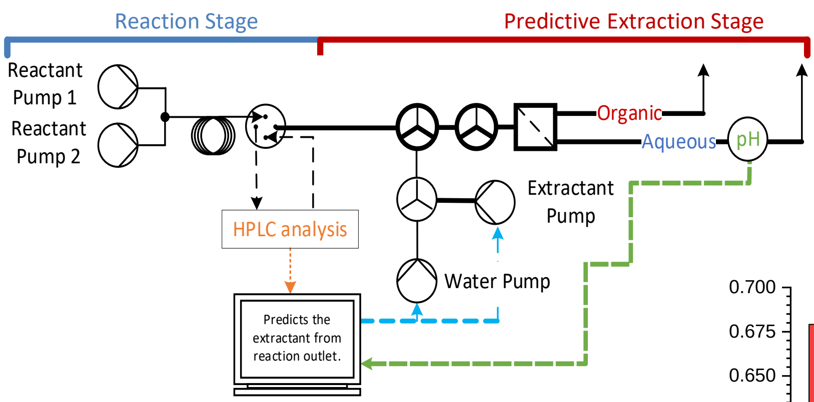
Feedforward control for pH selective extraction

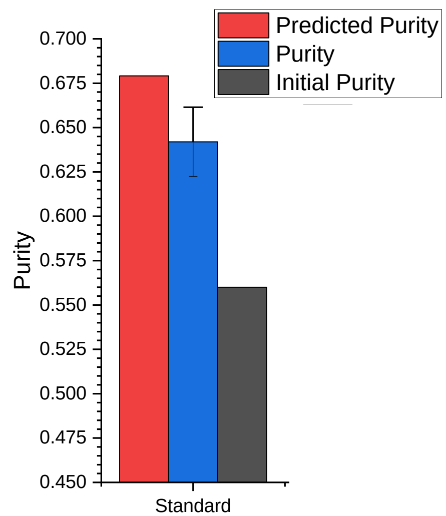
- Synthetic reaction mixture

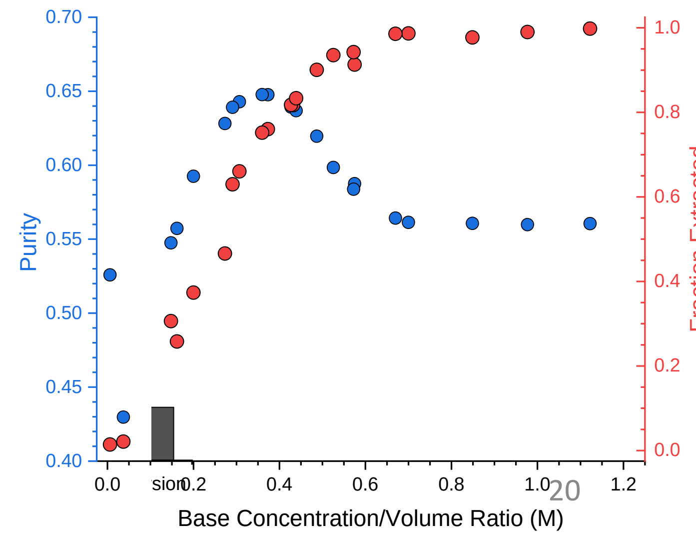


30% 55% 15%



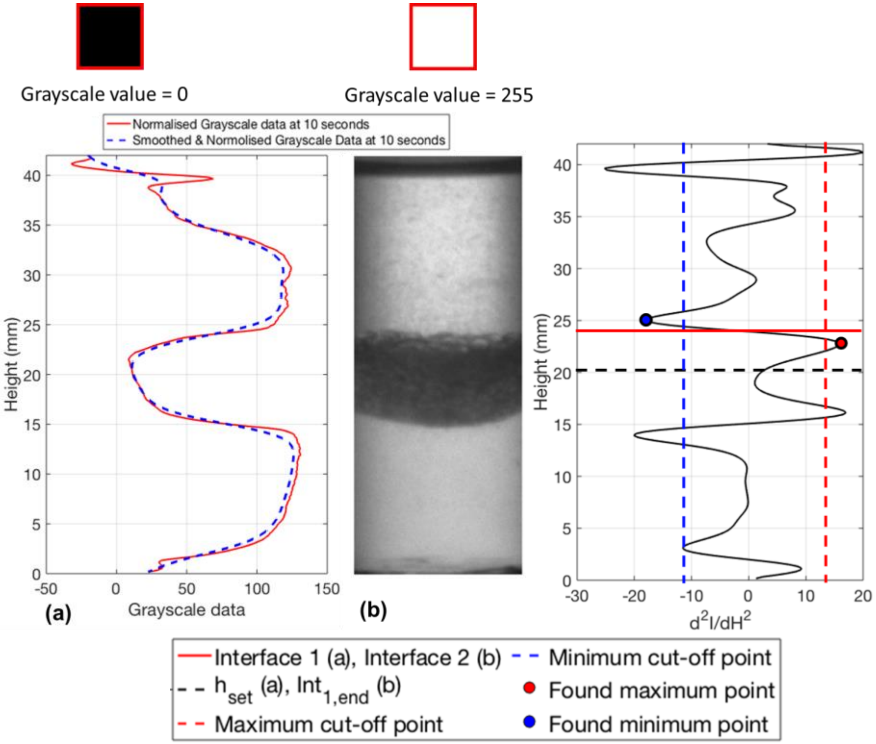


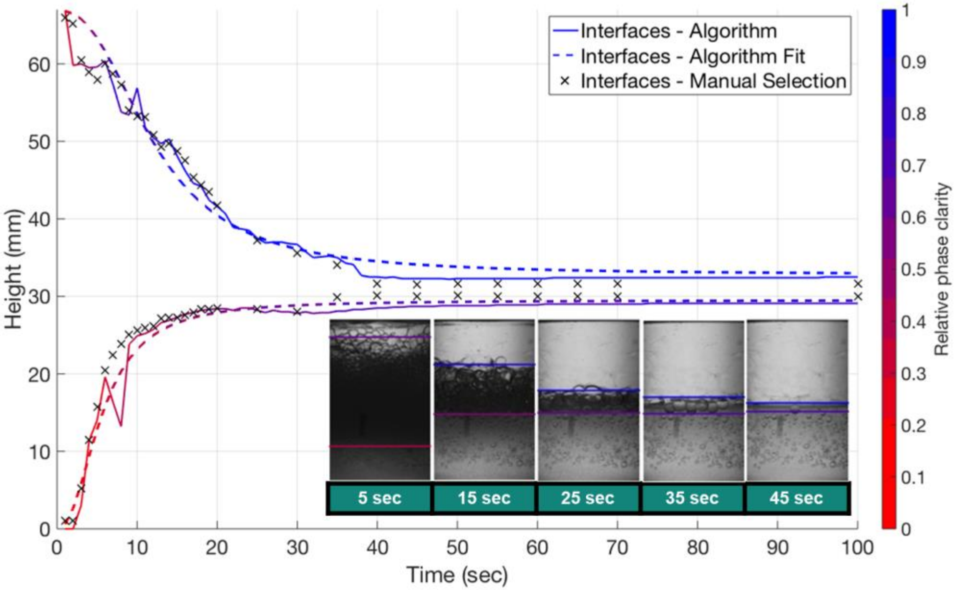




Luke Power – unpublished work

Quantification of L-L Separation

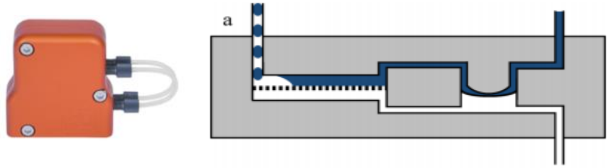




Daglish et al *Org.Proc. Res. Dev.* 2023 2c00357

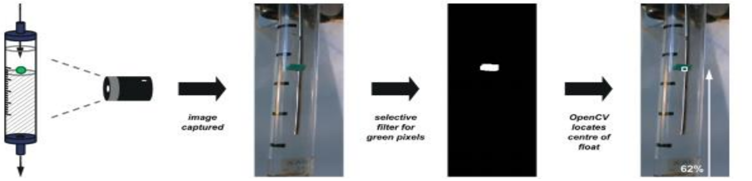
Continuous Separation: L-L Separator Design

- Zaiput – membrane separation



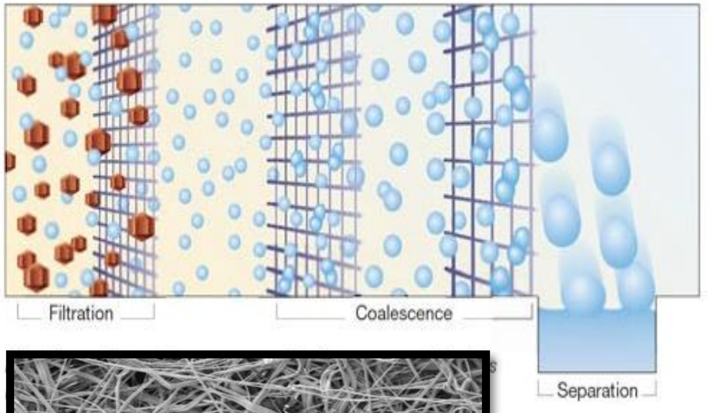
L. Yang *et al, Ind.Eng. Chem. Res*. **56** (2017), 42, 12184-12191.

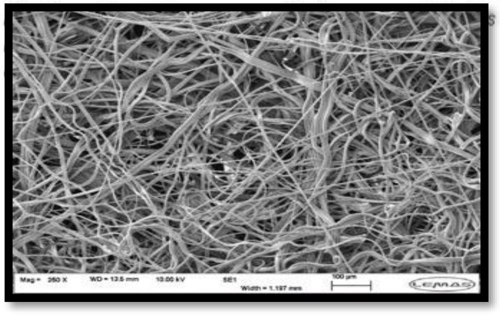
- Gravity separation

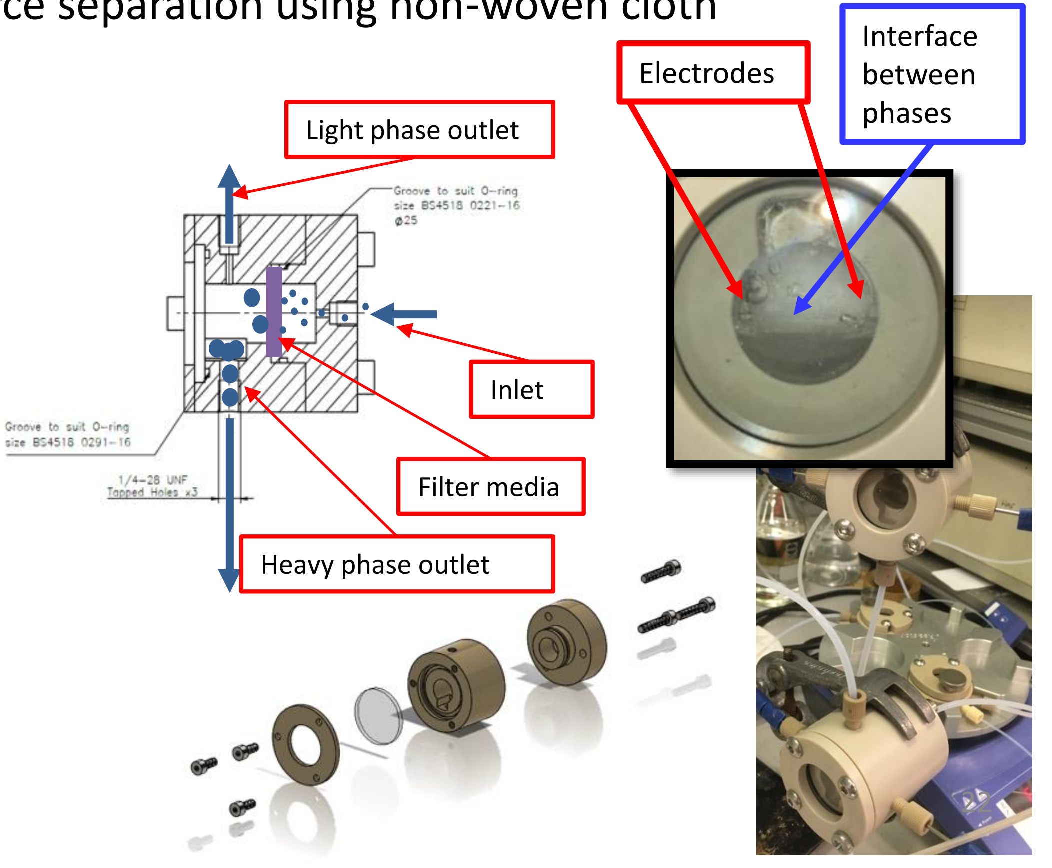


S. V. Ley *et al* Org. Syn. **9** (2013), 1051-1072.

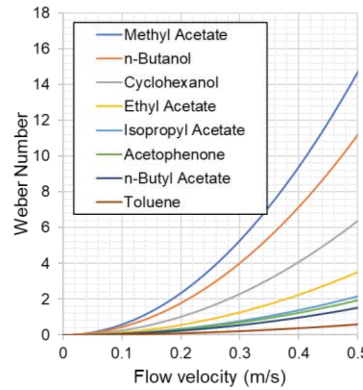
- Coalescence filtration - capillary force separation using non-woven cloth

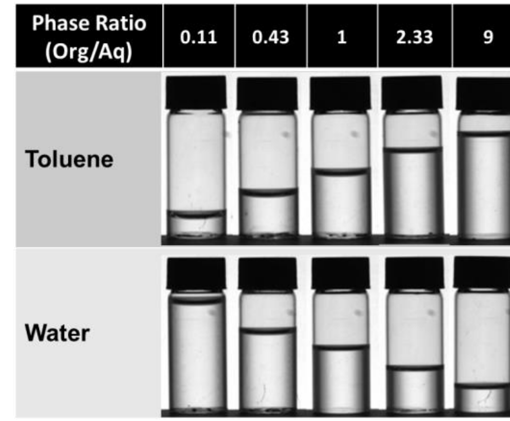


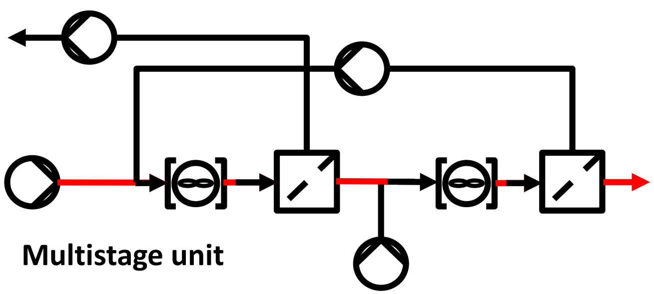




Coalescence filtration: single and multi-stage separator design







Multistage unit

Counter-current arrangement

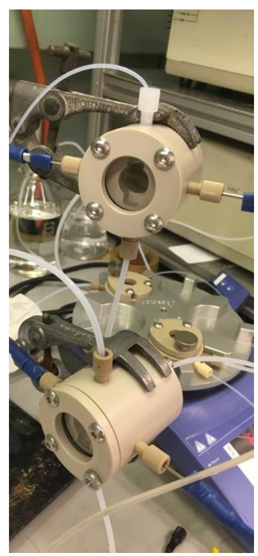
Small volume per stage

Versatile applications

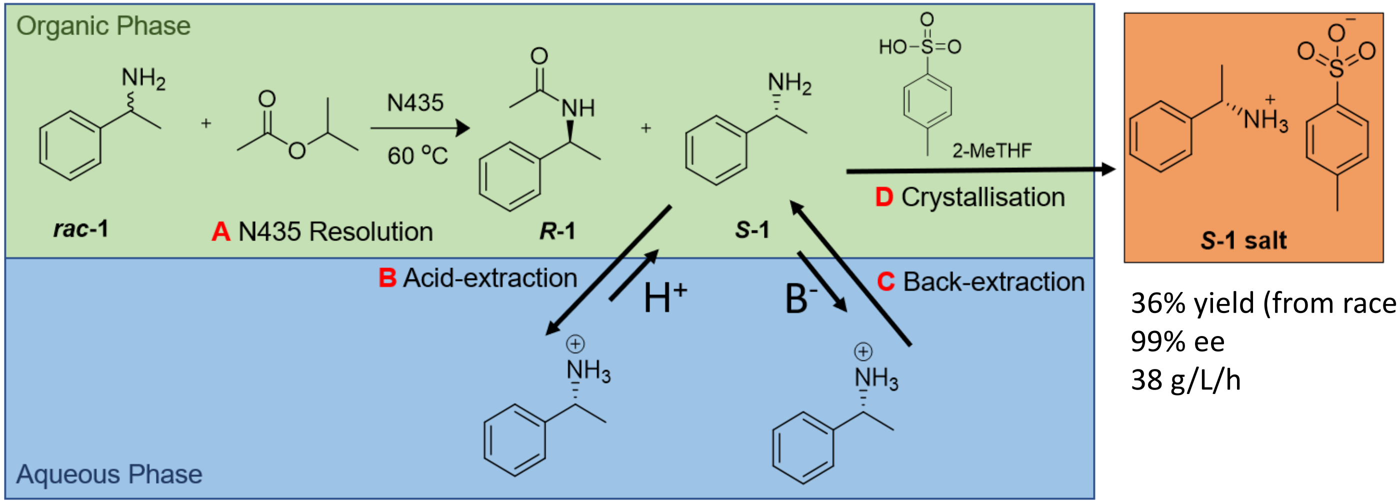
Aqueous phase

Organic phase

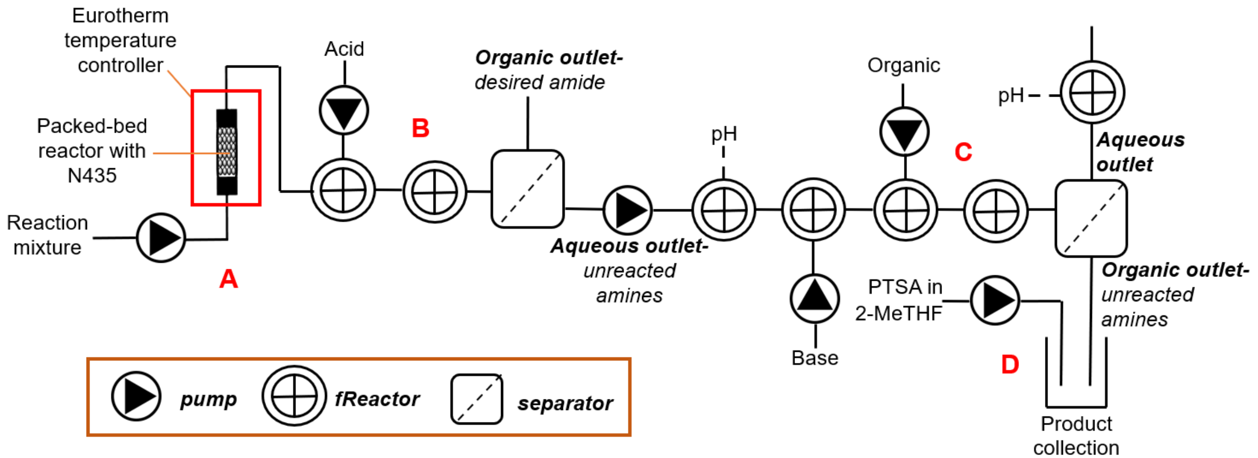
Mixed phases



Integrated continuous reaction, work-up and purification of a chiral amine salt



36% yield (from racemate)
99% ee
38 g/L/h



Bethan Rowley, Lisa Thompson – unpublished results

Summary

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Use of cascade CSTR's (fReactors) has been demonstrated with a variety of gas-liquid-solid systems

Equipment and methods for continuous separation of gas-liquid, solid-liquid and liquid-liquid have been presented

The use of on-line measurement and automated control systems allows rapid development and optimization of processes

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