



UNIVERSITY OF LEEDS

Multi-phase continuous flow bio- and chemo- catalysed transformations

Prof. John Blacker

j.blackler@leeds.ac.uk

iPRD

Institute of Process Research and Development

- Introduction to flow reactors
- Lab-scale multi-phasic continuous flow fReactors and examples
- Meso-scale flow reactors
- Conclusions

Commercially Available Flow Reactors

- Commercial flow reactors costly £10-50k
- Consist of pump(s), tube(s), detector, automation



Uniqlisq FlowSyn



Vapourtec R-Series



Vapourtec E-Series



FutureChemistry FlowStart Evo



Chemtrix Labtrix



Syrris Asia



Accendo Propel



Advion NanoTek



ThalesNano H-Cube Pro

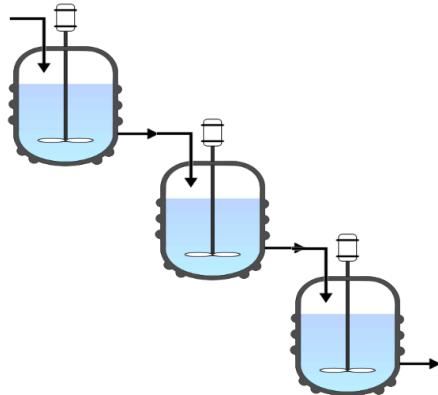


Sigma-Aldrich Microreactor Explorer

- Limited to homogenous reactions: need to dilute the reaction until all is soluble

Continuous Stirred Tank Reactor (CSTR)

Is there another way to carry out continuous multi-phase reactions with long residence times?

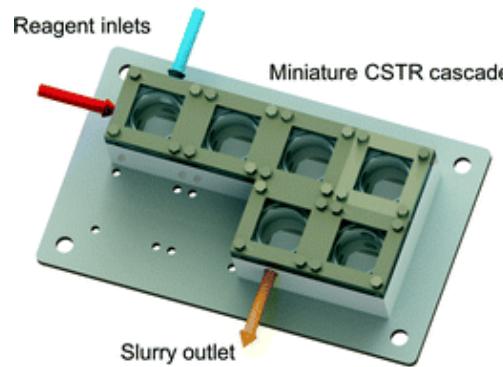


3*1 litre scale cascade CSTR

- Requires kg's of SM's
- Unsuitable for testing reactions
- Need for Lab-Scale CSTRs



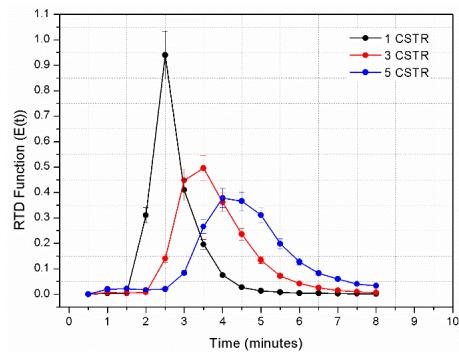
AMTech ACR Coflore



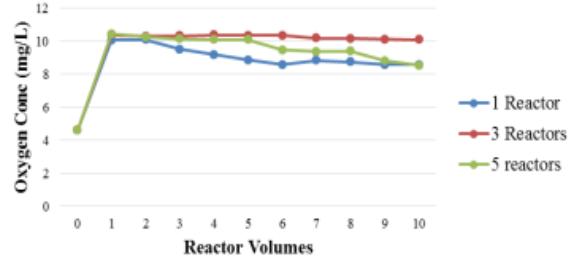
Y. Mo, K. Jensen
React. Chem. Eng., 2016, 1, 501-507

Freactor: Lab-scale Cascade CSTR

- Simple and flexible design
- -10-130 °C made of Delrin (solvent resistant)+Steel
- Magnetic stirring @ 16rps
- Glass observation window
- Low cost
- On-line blog : www.iprd.leeds.ac.uk
- Commercialisation in collaboration with Asynt Ltd.



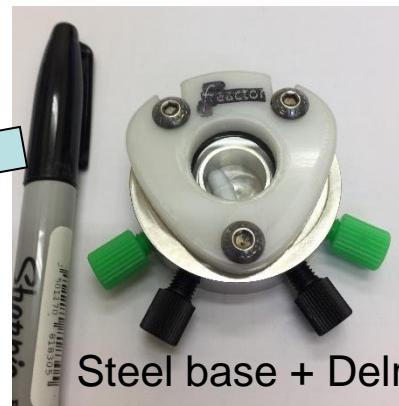
Residence time distribution
Oxygen Mass Transfer 1ml/min



Mass transfer rate



5 cm; volume = 2mL/reactor



Steel base + Delrin top



Meso-Scale Reactors in iPRD

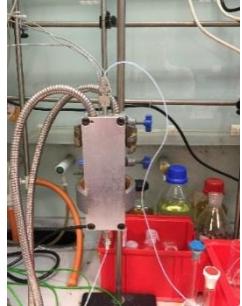
- Multi-phasic reactions (tubular, CSTR)
- Slow kinetics (CSTR)
- Medium - fast kinetics (tubular, CSTR)
- Energy management (plate)
- Defined mixing (laminar, turbulent)
- Potential for closed loop control



Variable residence time static mixed reactor
For multi-phasic medium to fast reactions



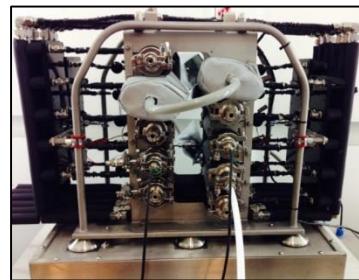
High pressure
trickle-bed
reactor for
gas-liquid
contacting



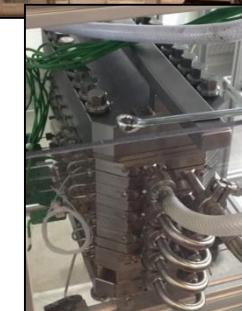
Heated fixed-bed
catalyst in HPLC tube



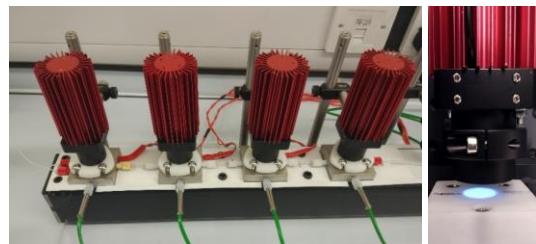
2-stage high pressure cascade CSTR for
multiphasic medium rate reactions



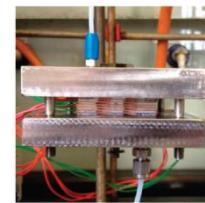
AMTech Coflore Reactor
temperature-zoned cascade
CSTR with rocking-motion mixing



Alfa-Laval plate reactor for
multi-phasic fast reactions



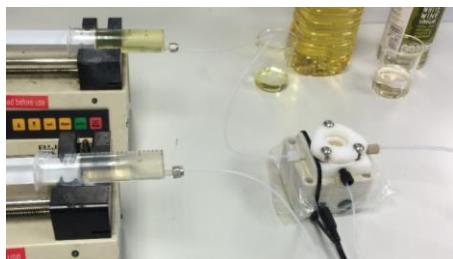
Continuous multiphasic photochemical reactor



Stacked plate flow electrochemical reactor

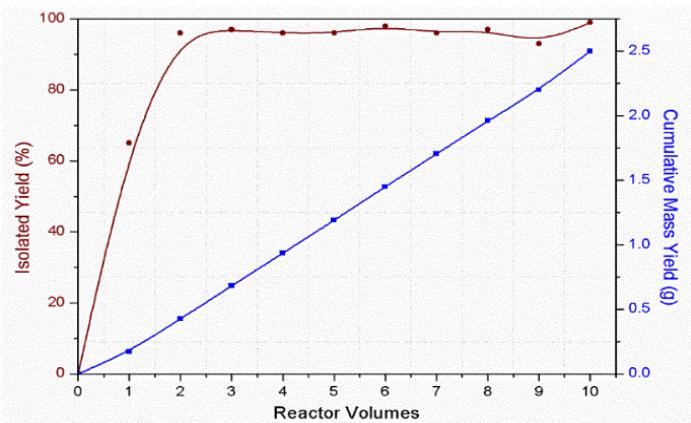
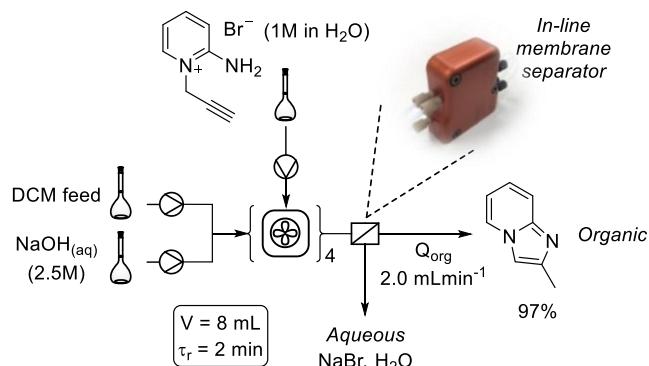
Examples of Liquid-liquid (L-L) reactions

L-L bi-phase
- emulsion

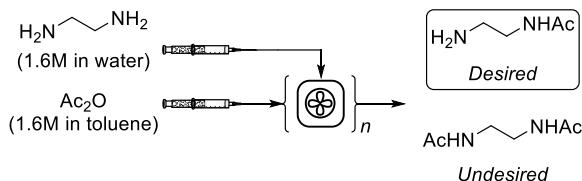


outflow that has been mixednot mixed

L-L bi-phase
- rapid cyclisation



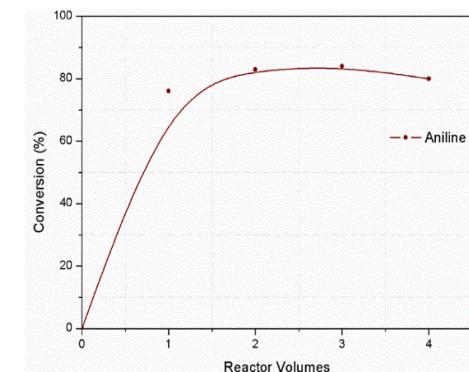
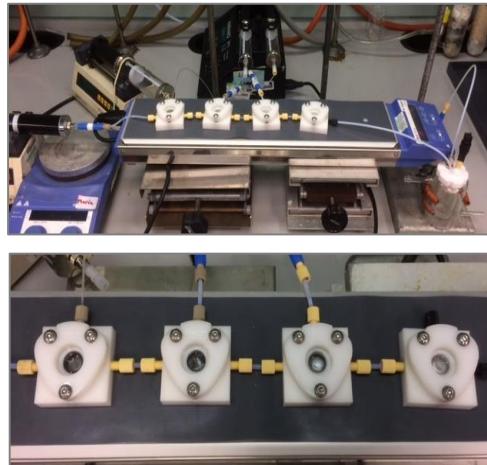
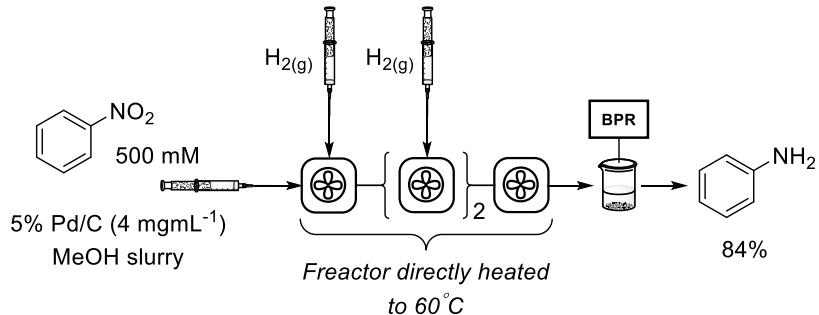
L-L bi-phase
- productive acylation



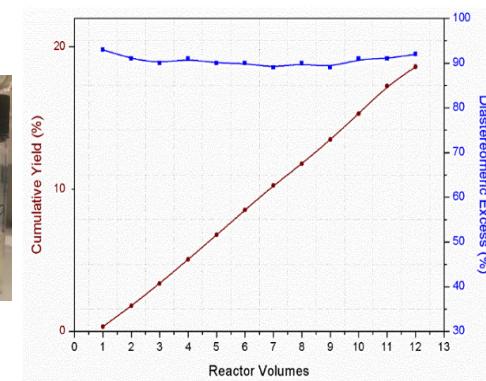
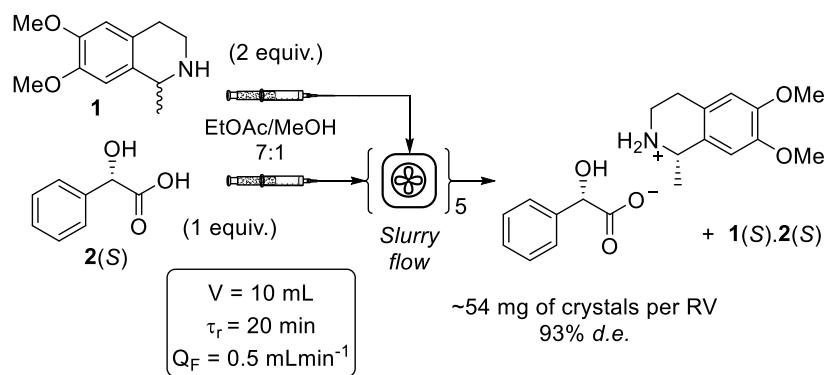
No. CSTRs (n)	τ_{res} (min)	Conversion (%) ^a /Selectivity (%)	Productivity ($\text{gL}^{-1}\text{h}^{-1}$)
Batch	20	53/20	51
5	30	83/84	173

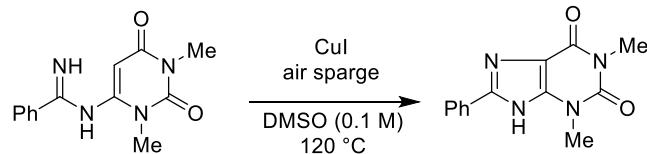
Examples of Continuous G-S-L and S-L Reactions with long residence times

- Pd/C Catalysed Hydrogenation of Nitrobenzene – $\tau_{\text{res}} = 180 \text{ min}$



- Diastereomeric crystallisation – $\tau_{\text{res}} = 20 \text{ min}$

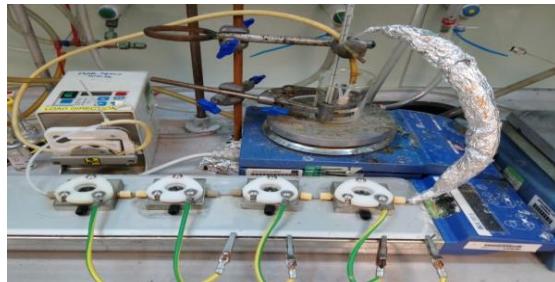
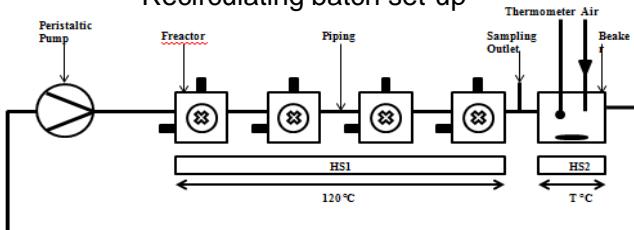




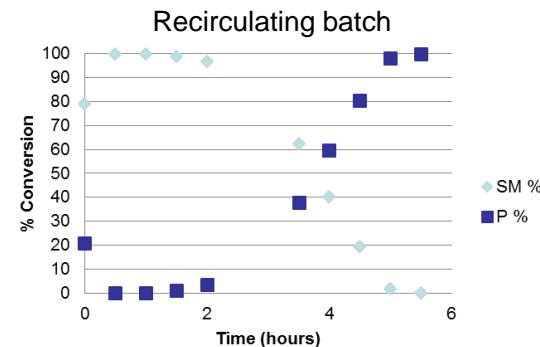
- Freactors enable multi-phase mixing
- Filter at in-let to retain product and enable Cu recycle

- SM = 0.1 M in DMSO @ 120°C (above Fpt)
- 0.58 mL/min τ_{res} = 14 min
- Product poorly soluble - accumulates in reservoir
- CuI (50 mol%) recirculated 20 times equivalent to 2.5 mol% CuI
- Safety - O₂ saturated DMSO at 80°C in reservoir (below Fpt)

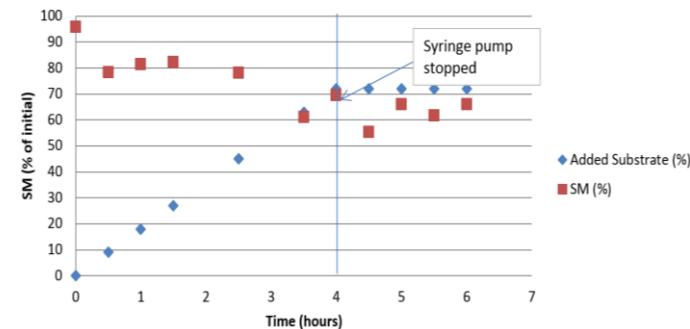
Recirculating batch set-up



Example: Continuous, Aerial (O₂) Cu-catalysed C-H activation at 120°C

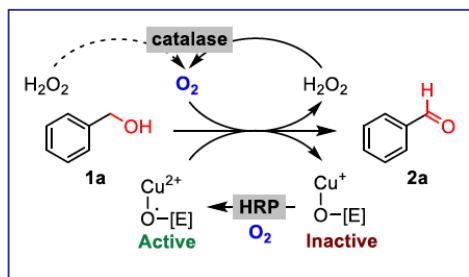


Continuous SM feed

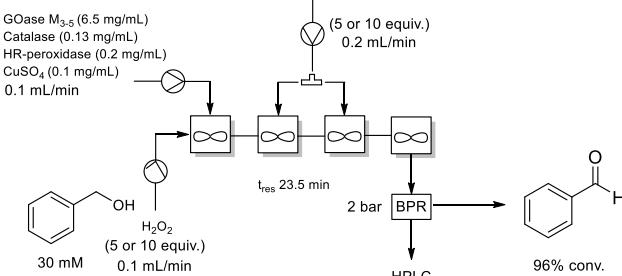


Example G-L Reaction: Continuous Oxidase Biotransformation of Alcohol to Aldehyde

- Oxidase enzymes are O_2 mass transfer limited
- Use H_2O_2 / catalase to generate high $[O_2]$ soluble

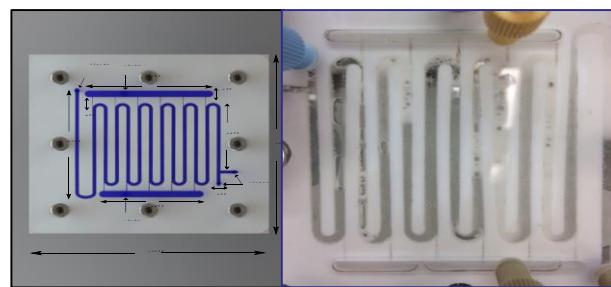
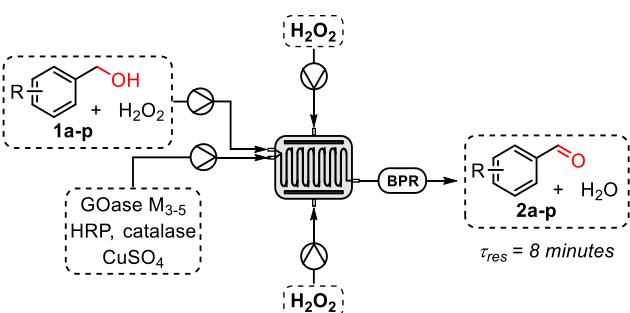


Freactor set-up

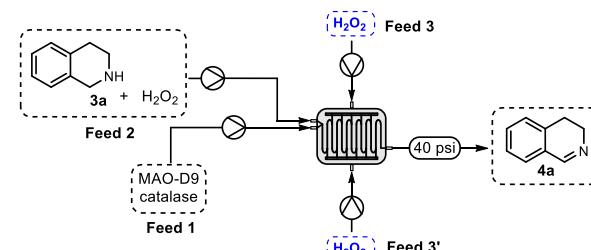
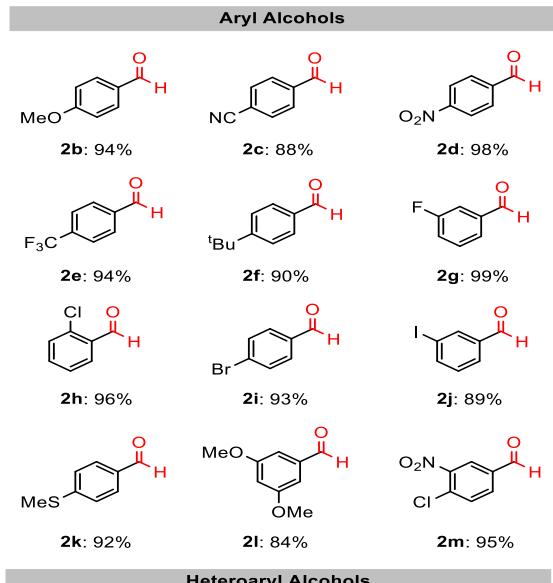


GOase CFE (mgmL ⁻¹) ^[a]	H_2O_2 equiv. (# feeds) ^[b]	CSTRs (n)	t_{res} (min)	Conv. (%)
0.5	2(1)	1	11	5
6.5	4(1)	1	11	40
6.5	4(2)	2	11	64
6.5	10(3)	3	13	84
6.5	10(4)	4	26	95
15	10(4)	4	13	92
6.5	0(0)	4	26	18

Multi-point injection reactor

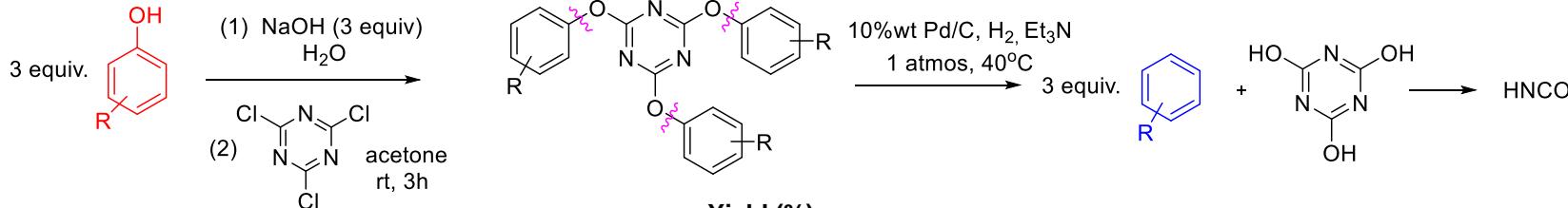


[Substrate]/mM	t_{res} (min)	H_2O_2 (equiv.)	Conv (%)
30	12	10	>99
30	8.7	10	>99
30	8.7	3	97
90	12	10	95*



Productivity increased to $11.3 \text{ gL}^{-1}\text{h}^{-1}$

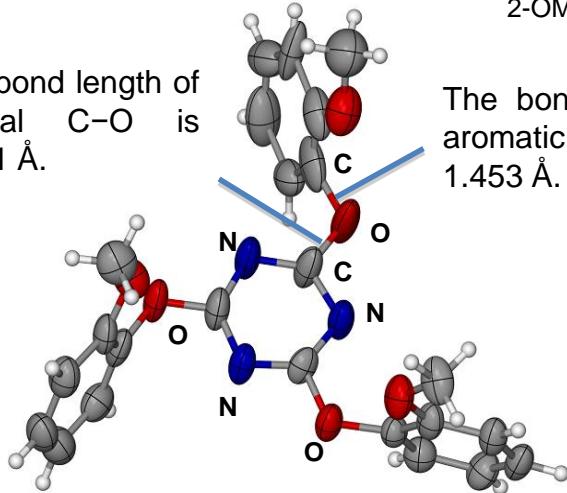
Cyanuric chloride: Cost Effective Reagent for Aromatic Deoxygenation



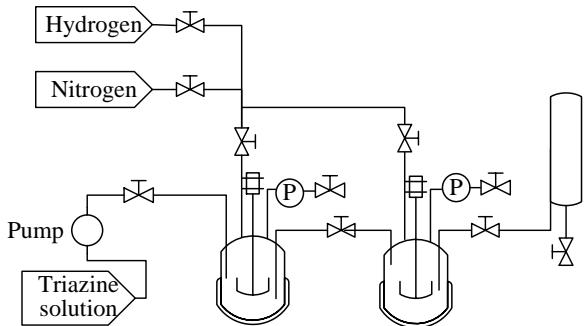
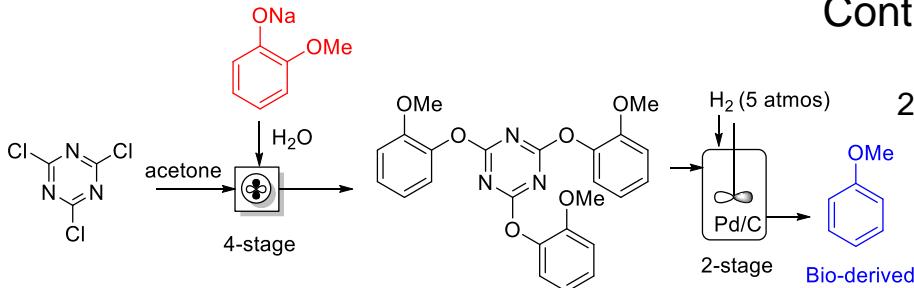
R	Yield (%)		Yield (%)
H	89	benzene	10
2-OMe	94	anisole	86
3-OMe	92	anisole	68
4-OMe	92	anisole	68
4-CHO	85	benzyl alcohol	30
2-OMe, 4-CHO	62	3-methylanisole	14
2-CO ₂ Me	22	methyl benzoate	10
2-OMe, 4-CO ₂ Me	10	methyl 3-methoxybenzoate	12
2-CO ₂ H	76	benzoic acid	21
2-OMe, 4-CO ₂ H	71	3-methoxybenzoic acid	58

The bond length of central C-O is 1.361 Å.

The bond length of aromatic C-O is 1.453 Å.

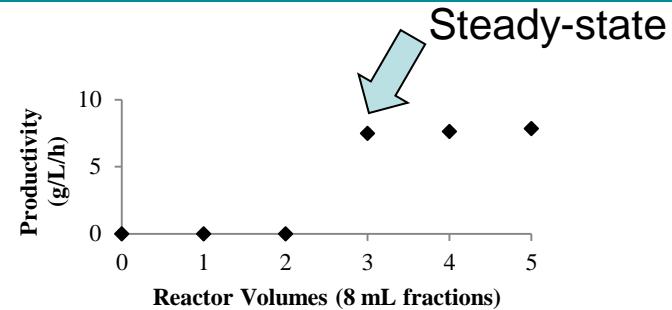


Example: Continuous Flow Deoxygenation of Guaiacol to Anisole



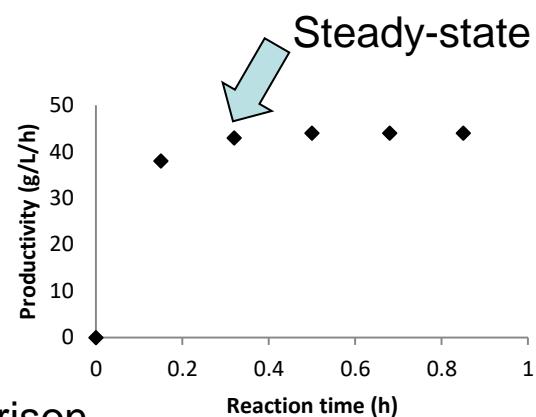
Continuous stage 1

τ_{res} 8 min;
20°C, 16% conv.



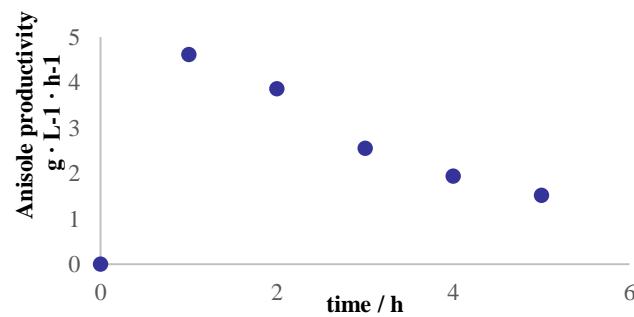
Continuous stage 2

10% Pd/C; τ_{res} 8 min;
5bar H_2 ; 50°C,
>95% conv.

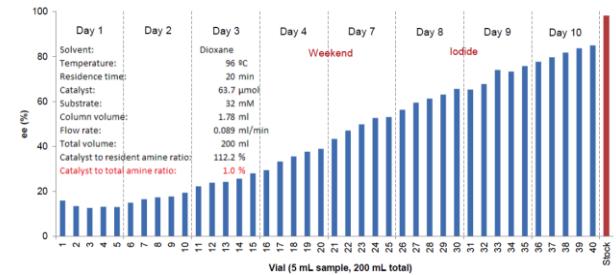
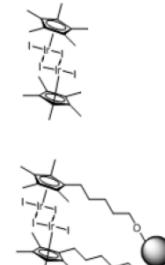
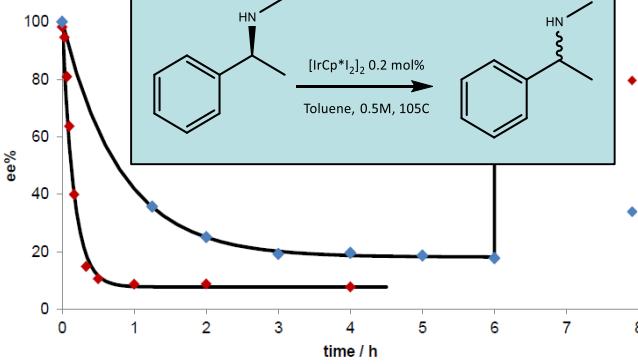
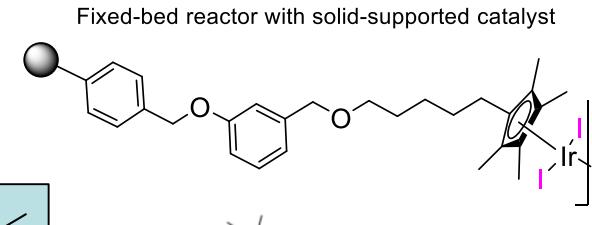
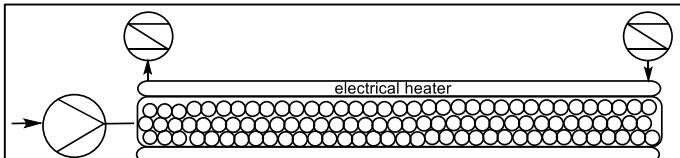
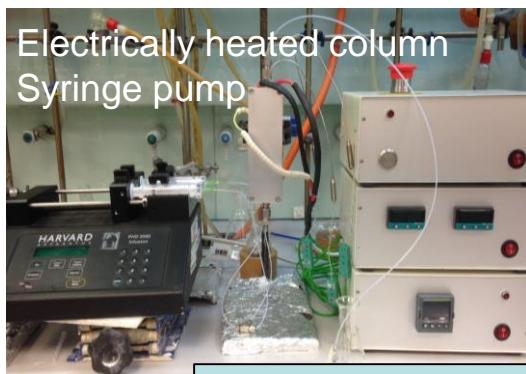


Batch stage 2 comparison

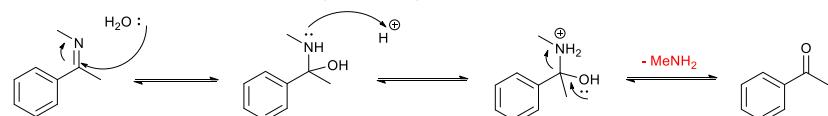
- Decreasing productivity due to catalyst deactivation by cyanic acid



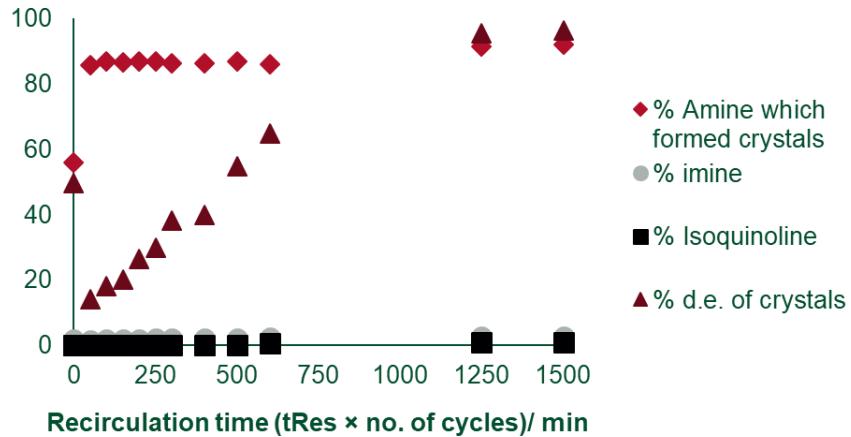
- η^5 -5 ligand-metal coordination – stable, no leaching (<1 ppm over extended use)
- Cost effective - achieved TON of >1,500
- Applicable to Rh, Ru and other Cp-coordinated metals
- Design enables ligand variation
- Deactivation mechanism understood



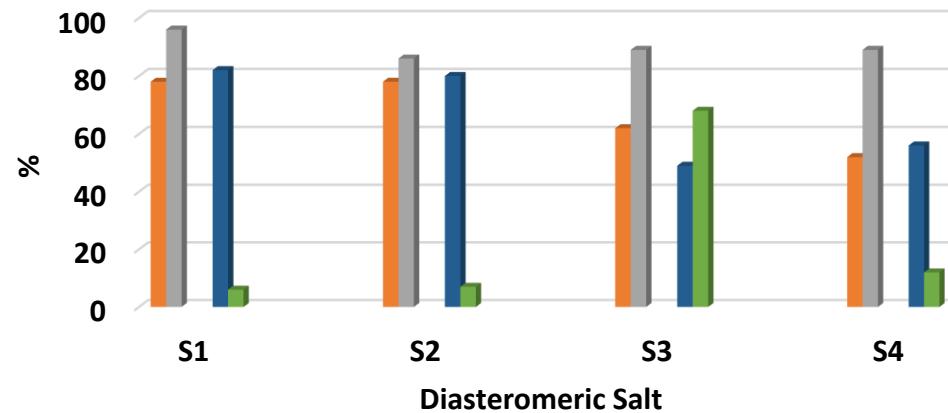
- 10 days continuous racemisation.
- Deactivation rate = 6.5% / day
- Deactivation by methylamine (via imine hydrolysis)



Resolution-Racemisation-Recycle (R^3)



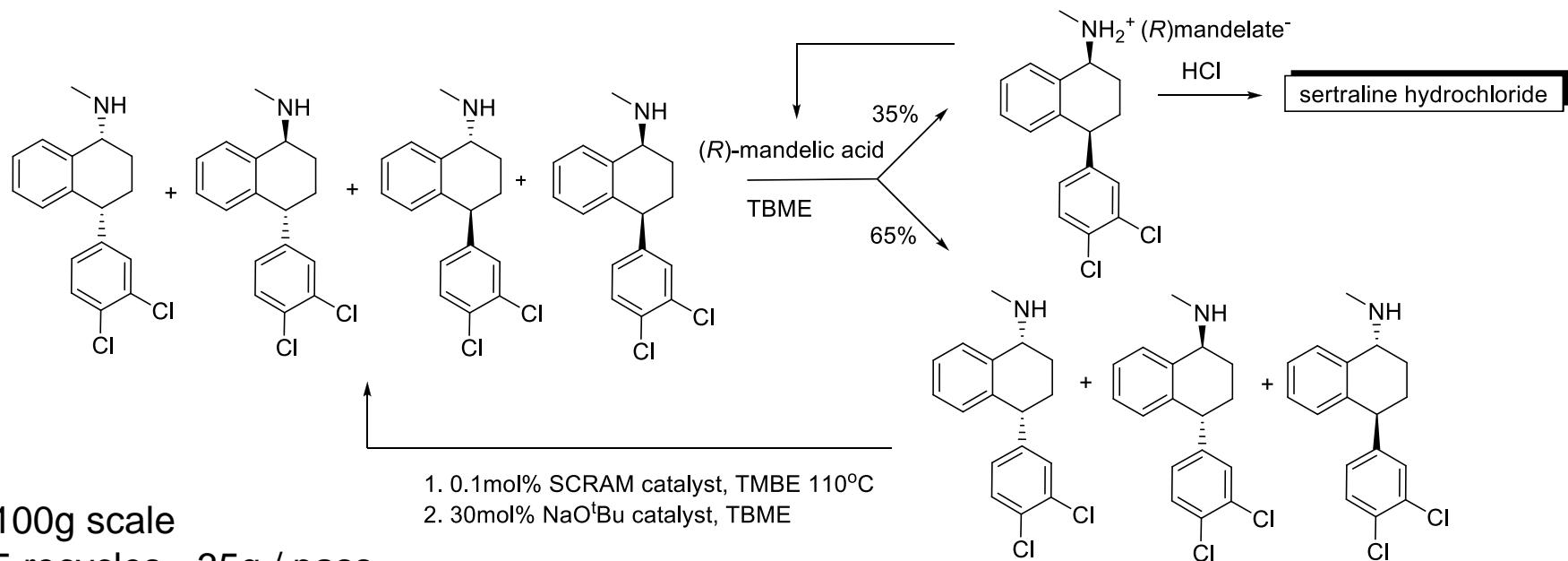
█ Yield (R^3) █ d.e. (R^3)
█ Yield (Resolution only) █ d.e. (Resolution only)



System	Amine	Chiral acid
S1		
S2		
S3		
S4		

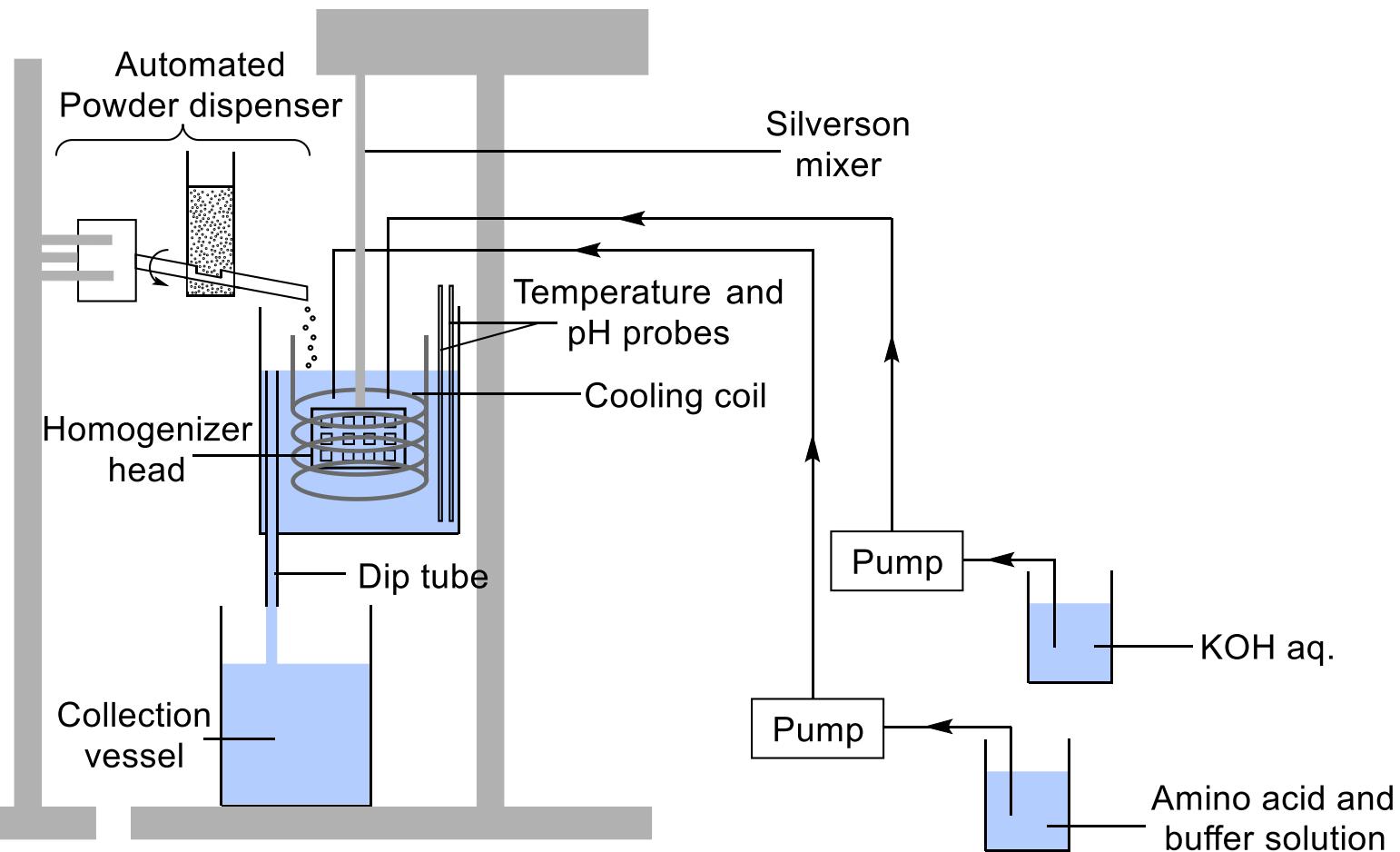
R³ Process to Make Sertraline

- Active Pharma Ingredient appx \$110/kg,
- Sertralone is \$12/kg so recycle needs to be <\$12/kg !
- To recover waste racemisation of both chiral centres required
- Iridium needs to be <10ppm in API



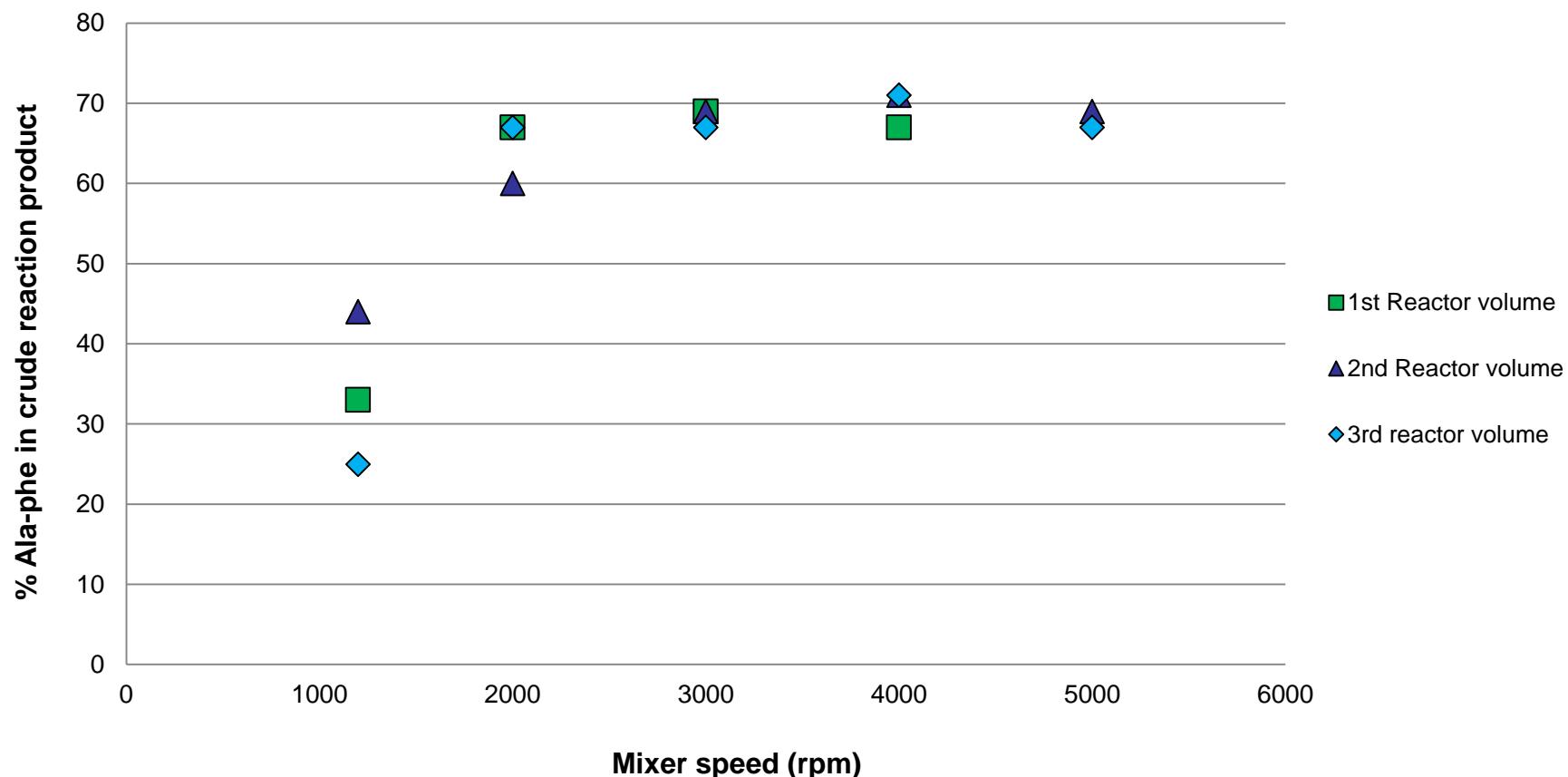
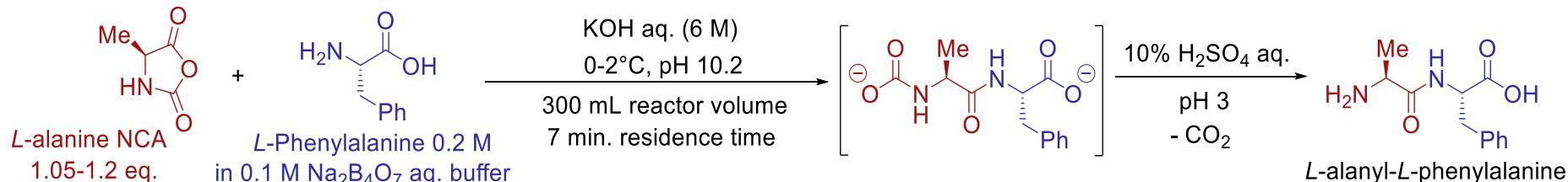
- 100g scale
- 5 recycles - 35g / pass
- 175g >95% purity product
- API <10ppm Iridium, 99% catalyst recovery
- <1kg waste/ kg product

Reactor design

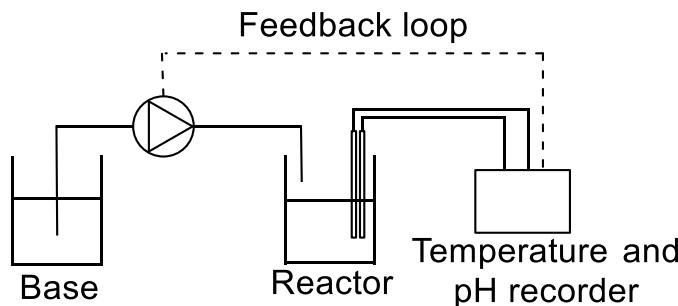


Reaction conditions

Mixer speed:

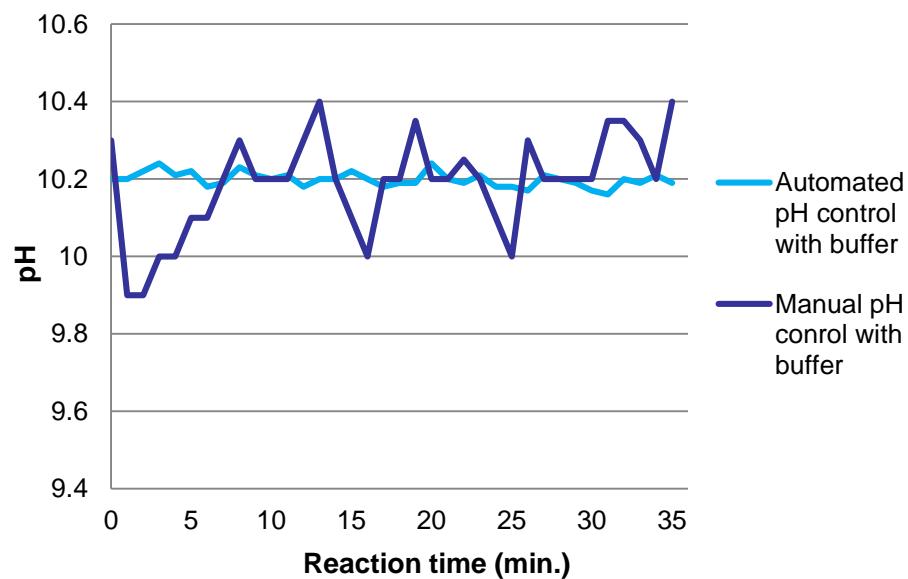


Automated pH control

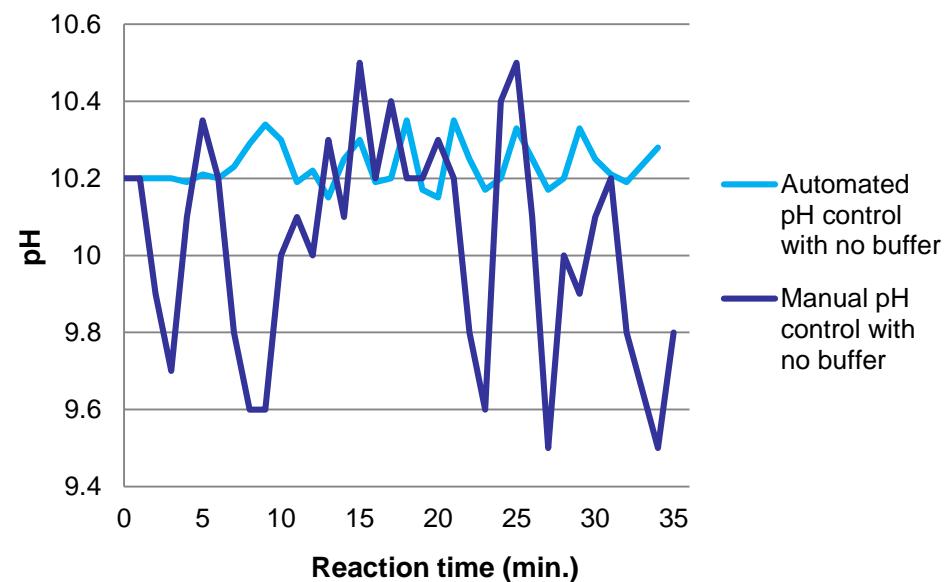


- Simplify reaction process.
- Improved consistency and precision of pH value: beneficial for less stable NCAs.
- Improve product yield.
- Reduce side product formation.

pH control – reactions with buffer:

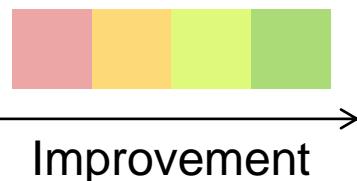


pH control - reactions without buffer:



Green reaction metrics

Metric	Merrifield solid phase synthesis ¹	Merck solution phase synthesis ²	Continuous flow synthesis with buffer ³	Continuous flow synthesis without buffer ³
Yield (%)	54	70	90	80
Reaction mass efficiency (%)	8.47	56.68	63.54	57.12
Atom economy (%)	24.89	84.3	82.1	85.7
Solvents	DMF	Water	Water	Water
Health and safety	DMF	Na ₂ B ₄ O ₇	Na ₂ B ₄ O ₇	Pass
Total mass intensity	850.35	268.64	48.24	31.3
Mass intensity: reaction chemicals	290.2	25.5	3.31	2.36
Reactor	Batch	Batch	Flow	Flow



1. *J. Am. Chem. Soc.* 1963, **85**, 2146-2154.
2. *J. Am. Chem. Soc.* 1967, **89**, 3415-3425.
3. Optimum reaction conditions from this project

Conclusions

- Lab-scale cascade CSTRs are useful in a variety of multi-phase continuous flow reactions
- Examples of L, L-L, G-L, S-L, G-S-L in reaction and work-up
- Enable testing of reactions at lab-scale to determine whether larger scale is viable
- Their versatility makes useful alternative to the round-bottom flask
- Multi-phase flow reactions can give higher productivity and enable unsafe reactions
- Sequential reactions (phenol deoxygenation) and Recirculating reaction (R^3 CIDT process)

Acknowledgements

Prof. Nik Kapur

Dr Richard Bourne

Dr Bao Nguyen

Dr Maria Kwan

Dr Mike Chapman

Dr Katie Jolley

Dr Will Reynolds

Dr Ibrahim Moaty

Dr James McManus

Adam Clayton

Lisa Thompson

Carlos Gonzalez

Ffion Abraham, Martyn Fordham, Kerry Elgie



Martin Jones, Mark Purdie, Rachel Munday



Katherine Wheelhouse



Prof. Bert Maes

Prof. Nick Turner



Engineering and Physical Sciences
Research Council

