syrris

Why Perform Chemistry in Flow?

Why perform chemistry in flow?

Overview

- Faster reactions
- Safer reactions
- Faster reaction optimisation
- Reaction conditions not possible in batch
- Reactions are usually more selective
- Scale up is easier in flow than batch
- Easy integration of reaction analysis
- Reactions are easier to work-up in flow

Explanations

How does flow chemistry achieve faster reactions?

- It is much easier to pressurize flow reactors
- Higher pressures enable higher temperatures
- Higher temperatures result in faster reaction rates

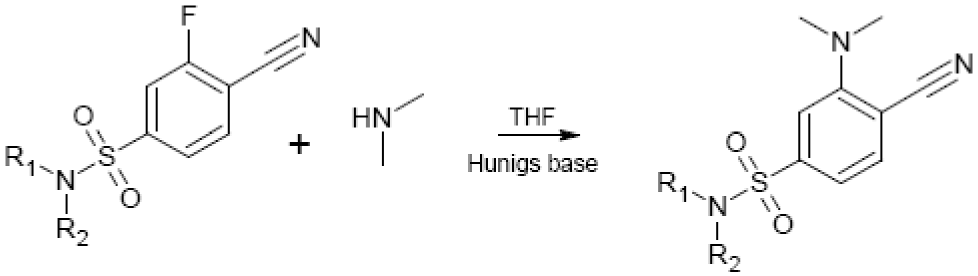
$$k = Aexp\left[-\left(\frac{E_a}{RT}\right)^{\beta}\right]$$

- Example:
  - Syrris products can pressurize to 20bar
  - This means the boiling point of solvents increase by 100-150C

Solvent	1 bar	7 bar	17 bar
Dichloromethane	41°C	109°C	153°C
Methanol	65°C	138°C	185°C
Water	100°C	181°C	231°C

  - **The Arrhenius rate law tells us that reactions are 2 x faster for every 10C rise**
  - **Therefore 100C rise =2x2x2x2x2x2x2x2x2x2 faster (over 1000x faster)**

Example – super-heating in flow



In batch:

- Incomplete reaction using batch chemistry despite 1 week of reflux
- Yield of the reaction was poor.

In flow:

- It was possible to superheat the THF up to 140ºC
- Optimisation: reaction time, reaction temperature and equivalents of reagents were varied for each of the two reactions
- 100% conversion achieved for a variety of substrates at 140ºC with 1h residence time.

Tibotec, Johnson & Johnson (Belgium)

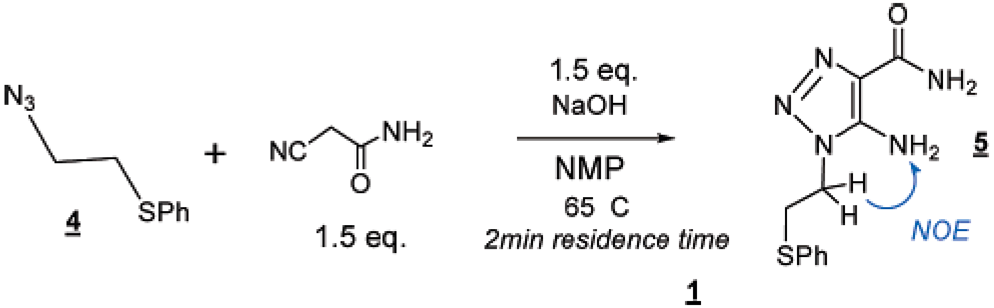
Why does flow chemistry enable safer reactions?

- The quantity of reaction occurring at any one time is minimised
- The surface area:volume ratio is1000s times higher in a flow reactor

- Example:
  - If a 10L batch reactor explodes, this has serious consequences
  - The same 10L can be passed through a 10ml flow reactor, ensuring that only 10ml is reacting at any time
  - For a fast reaction e.g.1 min reaction this only takes an overnight run
  - **In this case the risk is 1/1000!!!**

Example – safer reaction in flow

- Triazole synthesis at Wyeth



- Hazard: azide compound. Use in medium and large scale is prohibited
- β-azidoethyl phenyl sulfide: bp =65ºC, TSU showed exotherm at 155ºC
- “Continuous-flow reactions have the potential to be much safer than batch reactions, as only a small amount of reactive and potentially hazardous material is heated or converted to product at any given time.”

R. Tinder, T. Storz, *Org. Process Res. Dev.*, **13**, 2009

How can flow perform reaction optimization faster?

- In a flow reactor it is extremely easy to vary:
  - Reaction time
    - Vary total flow rate
  - Reaction temperature
    - Low thermal mass
  - The ratio of reagents
    - Vary flow rate ratio
  - Concentration
    - Vary solvent stream
- One reaction is flushed out by the next (separated by a solvent) therefore only one reactor is used.

- **This means 50-100 reaction conditions can be investigated with just 15mins set-up time**

Example – quick optimisation in flow

- Optimisation of thiazole synthesis at Burnham Institute

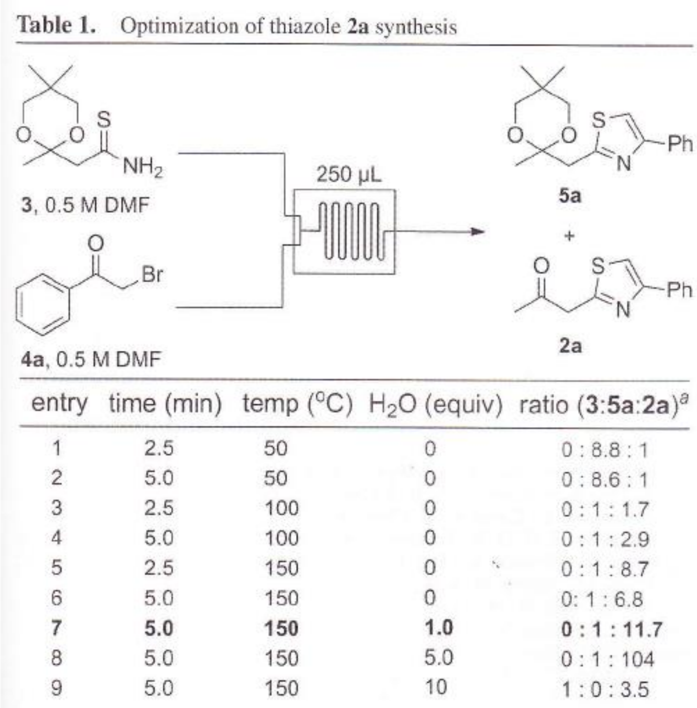


Table 1. Optimization of thiazole **2a** synthesis

entry	time (min)	temp (°C)	H_2O (equiv)	ratio (**3**:**5a**:**2a**)[a]
1	2.5	50	0	0 : 8.8 : 1
2	5.0	50	0	0 : 8.6 : 1
3	2.5	100	0	0 : 1 : 1.7
4	5.0	100	0	0 : 1 : 2.9
5	2.5	150	0	0 : 1 : 8.7
6	5.0	150	0	0: 1 : 6.8
7	**5.0**	**150**	**1.0**	**0 : 1 : 11.7**
8	5.0	150	5.0	0 : 1 : 104
9	5.0	150	10	1 : 0 : 3.5

- Varying residence time, temperature and water equivalent
- Optimum conditions identified in 9 experiments and 37.5 min total experiment time

N. Pagano, N. D. P. Cosford, *J. Flow Chem.* 2011

How can flow chemistry achieve reaction conditions not possible in batch?

- Mixing happens by diffusion
  - This is much, much faster and more reliable than in batch

- Because the reactors are pre-heated/pre-cooled, the reaction can change temperature almost instantly

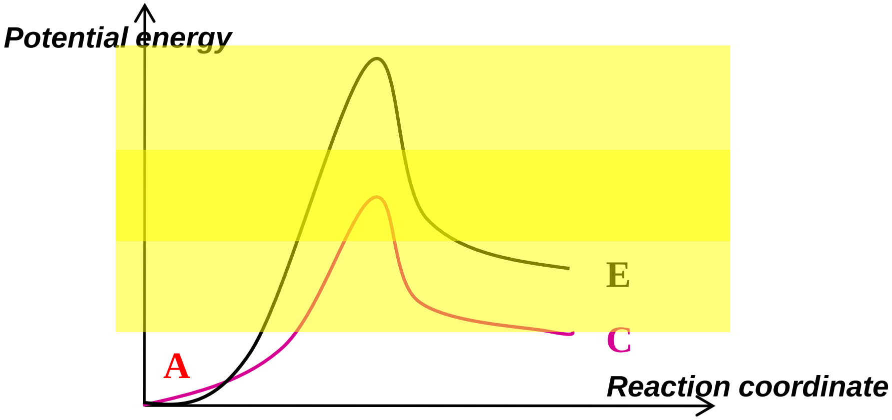
- Example 1
  - Heat up and cool down times are much faster than a microwave , therefore ultra hot, ultra fast reactions are easily possible

- Example 2
  - Deprotonate a substrate at low temperature, then add a nucleophile and instantly heat to a high temperature

How can flow reactions be more selective?

- Poor selectivity comes from variations in temperature, concentration and addition /stirring rates

- Due to a high surface area:volume rato and diffusion mixing, flow chemistry offers:
  - Excellent temperature control
  - Minimal concentration gradient

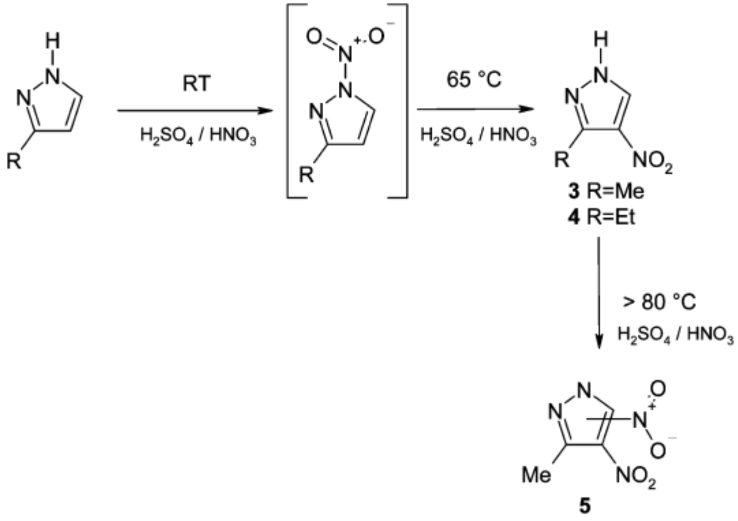


- **Flow enables much better selectivity**

Example – cleaner reaction in flow

- Nitration of pyrazoles at AstraZeneca

Scheme 2. Temperature-dependent pyrazole nitration



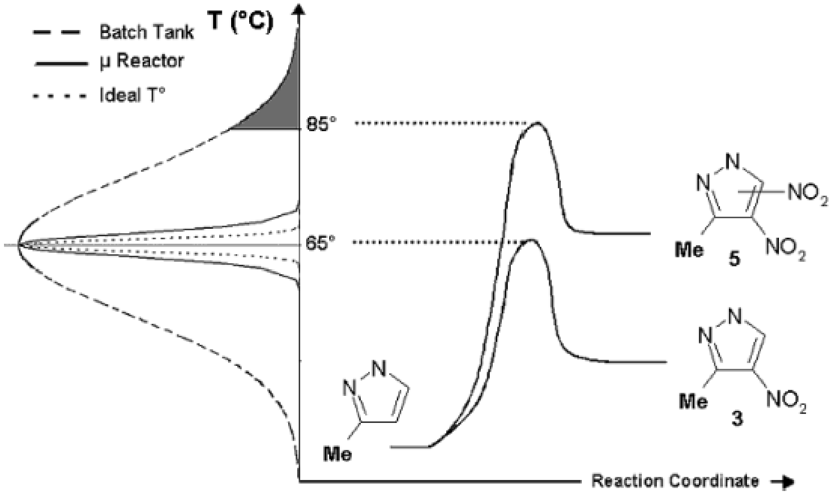


Figure 4. Temperature population in a batch reactor vs a microreactor and impact on byproduct generation.[2]

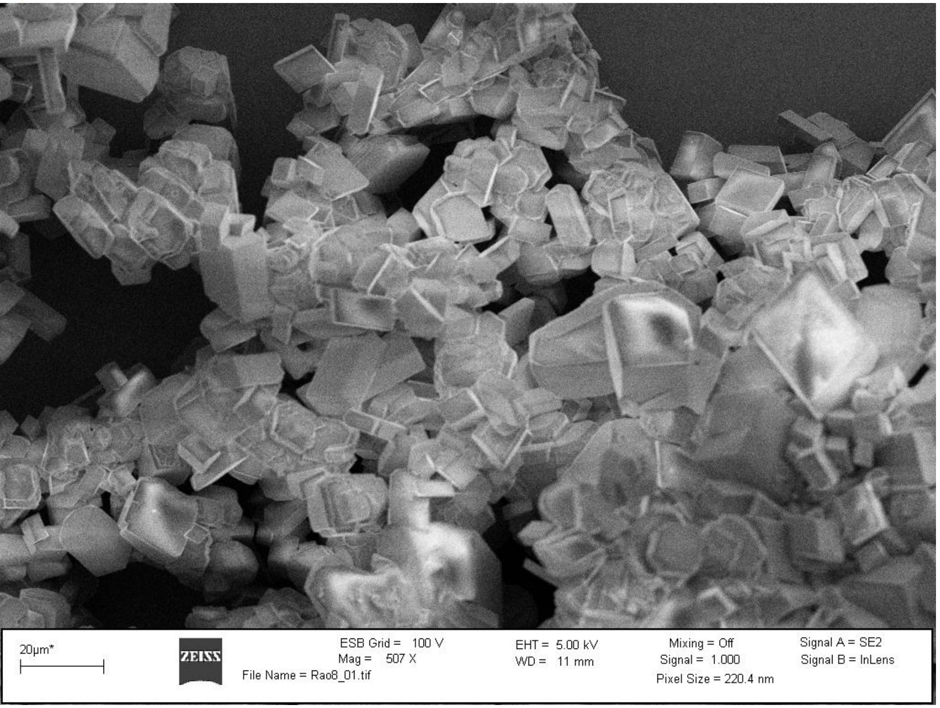
- “In the case of a hazardous reaction, the risk of an incident is minimised as the accumulation of potentially dangerous intermediates is avoided.”

J. Pelleter, F. Renaud, *Org. Process Res. Dev.*, 2009

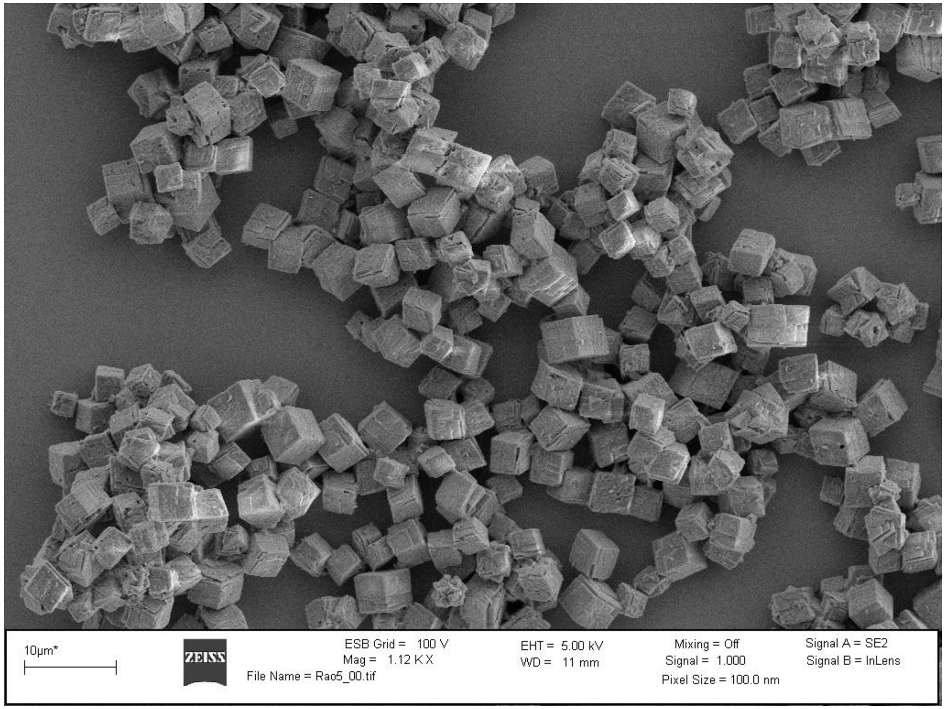
Example – better control in flow

- Reaction of $CaCl_2$ and Na_2CO_3 to synthesize $CaCO_3$ in batch and flow
- Exactly the same concentration, temperature and reaction/residence time
- Quality and reproducibility clearly much higher in flow than batch

Batch



Flow

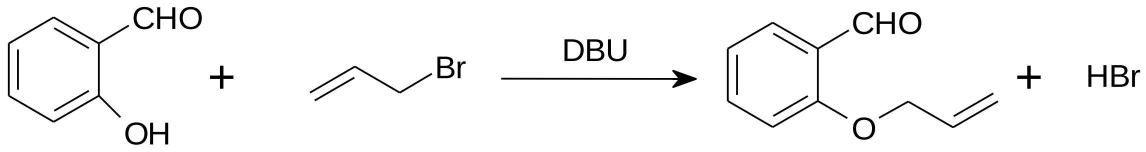


Why is scale-up easier in flow chemistry?

- For 10x or 100x scale up
    - It is possible to flow for longer to make more product
    - E.g. from the same tap you can fill a cup or a bath
- For 1000x +
    - The fundamental principles of a higher surface area to volume ratio means that scaling up flow will reduce the heat transfer effect
    - The ability to use static mixers means that mixing is faster and more reproducible
- **Flow saves time and money scaling up reactions**

Scale Up Example

- Synthesis of Salicylaldehyde allyl ether
- Reaction used by Ley group to demonstrate their Micro Capillary Flow Disc Reactor and the FRX FLLEX (Flow Liquid-Liquid EXtraction)

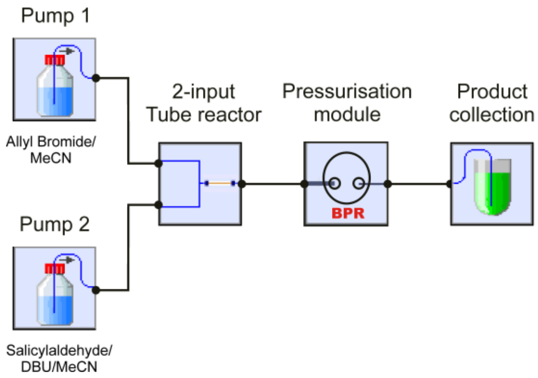


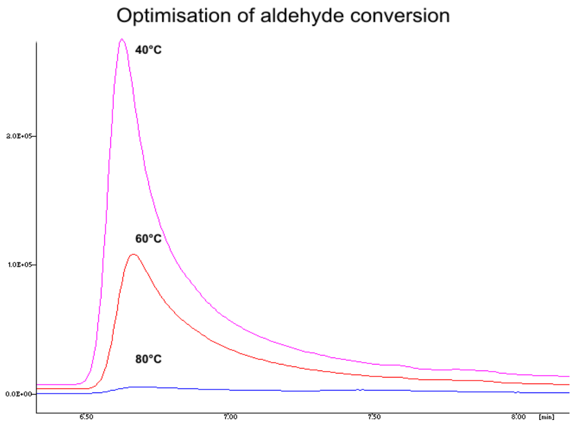
- Published reaction conditions were room temperature in MeCN for 113mins
- Work up involved dilution with EtOAC and wash with $HCl_{(aq)}$ using the FRX FLLEX

[1] Ley et al. Org. *Process Res. Dev*, 2007, **11** (3), 399-405.

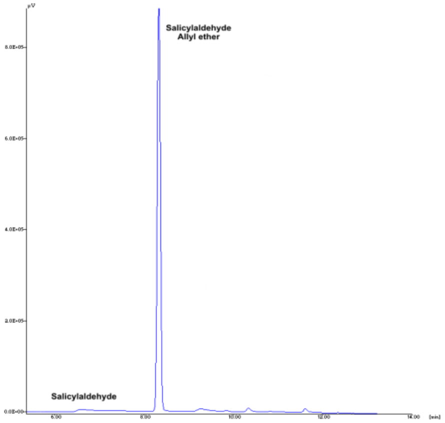
Optimisation and Scale Up

- Reaction was optimized and scaled to a 16ml reactor
  - Residence time reduced from 113min to 13.3min
  - Conversion remained high (97%)
  - Reaction ran overnight





Parent depletion during optimizaton



Product Formation

- **Result was 376g of Crude Product (at 97% yield from HPLC)**

How is reaction analysis made easier?

- To analyse multiple reactions in batch chemistry requires multiple probes (one per reactor).

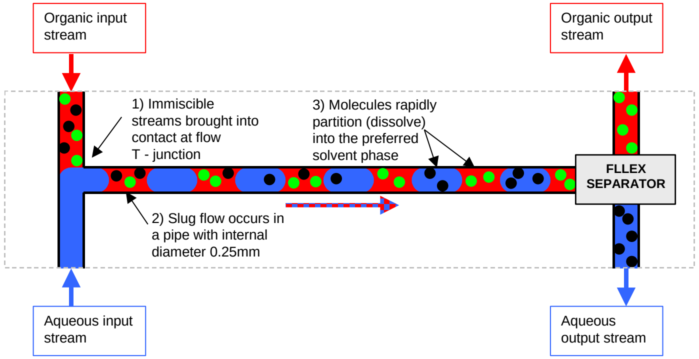
- In flow chemistry, many different reactions can flow “under” the same probe.
  - The Sampler and Dilutor can automatically divert a tiny amount of each reaction for analysis

- In flow chemistry, the reaction automatically moves to the analytical system because it is flowing

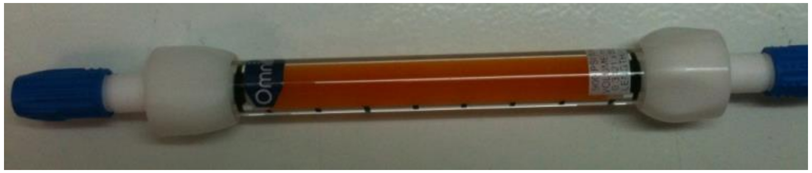
Why is reaction work-up easier in flow?

- Batch chemistry relies on a separate operation to perform a work-up e,g. aqueous work-up, filtration or solid phase scavenging

- Because the reaction is already mobile flow chemistry offers in-line (integrated) work-up:
  - Flow liquid-liquid extraction (FLLEX)



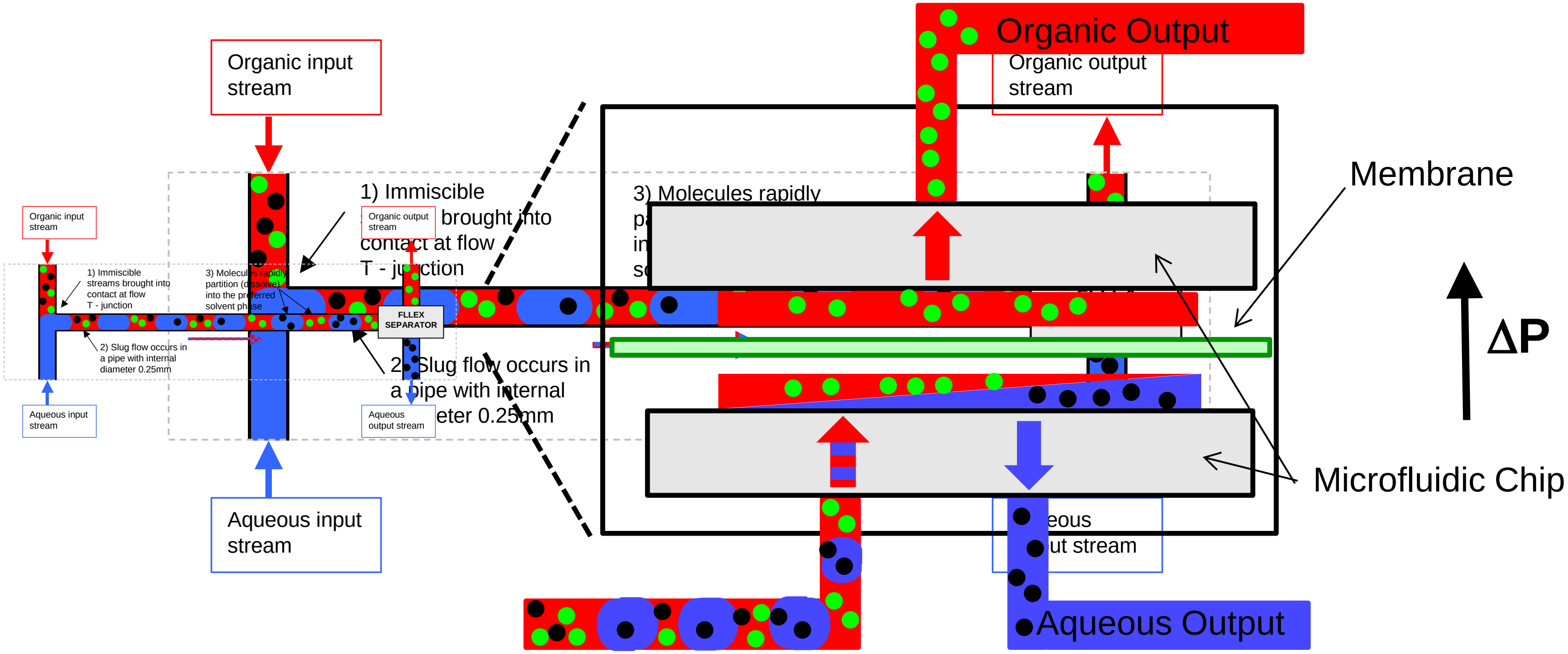
  - Solid phase reagents/scavengers/filtration



Liquid Liquid Extraction (FLLEX)

Step 2. Separation

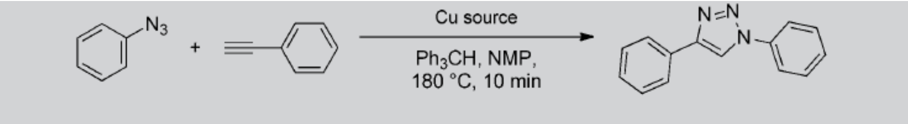
Step 1. Extraction



- Diffusion of molecules (extraction) between slugs occurs rapidly, < 3 secs
- Separator, based on hydrophobic membrane, results in continuous flow of worked up product
- Separation of solvent pairs not typically thought of a practical e.g. THF and Aqueous

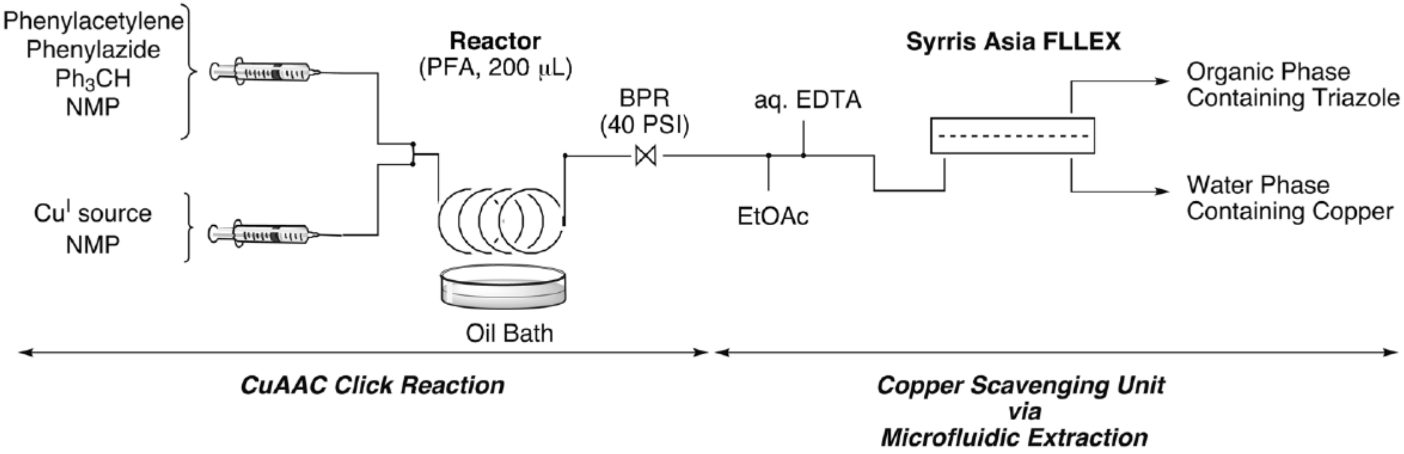
Syrris FLLEX as Copper Scavenging Unit

- Cu-catalyzed azide–alkyne cycloaddition reaction (CuAAC) (Click Chemistry)



Entry	Reactor type[b]	Cu catalyst (amount)	Yield [%][c]
1	Cu tube	–	51
2	PFA tube	$Cu(CH_3CN)_4BF_4$ (2.5 mol%)	91
3	PFA tube	$[Cu(phen)(PPh_3)_2]NO_3$ (1 mol%)	92 (88)[d]
4	PFA tube	$[Cu(phen)(PPh_3)_2]NO_3$ (0.5 mol%)	73

- CuAAC reaction is an ideal candidate for flow chemistry as high temperature required and intermediate azide formed pose an explosion hazard.



Noel, Hessel (Technical University of Eindhoven)
ChemSusChem, 2012, *703–1707*

University of Eindhoven – FLLEX - Copper Scavenging Unit

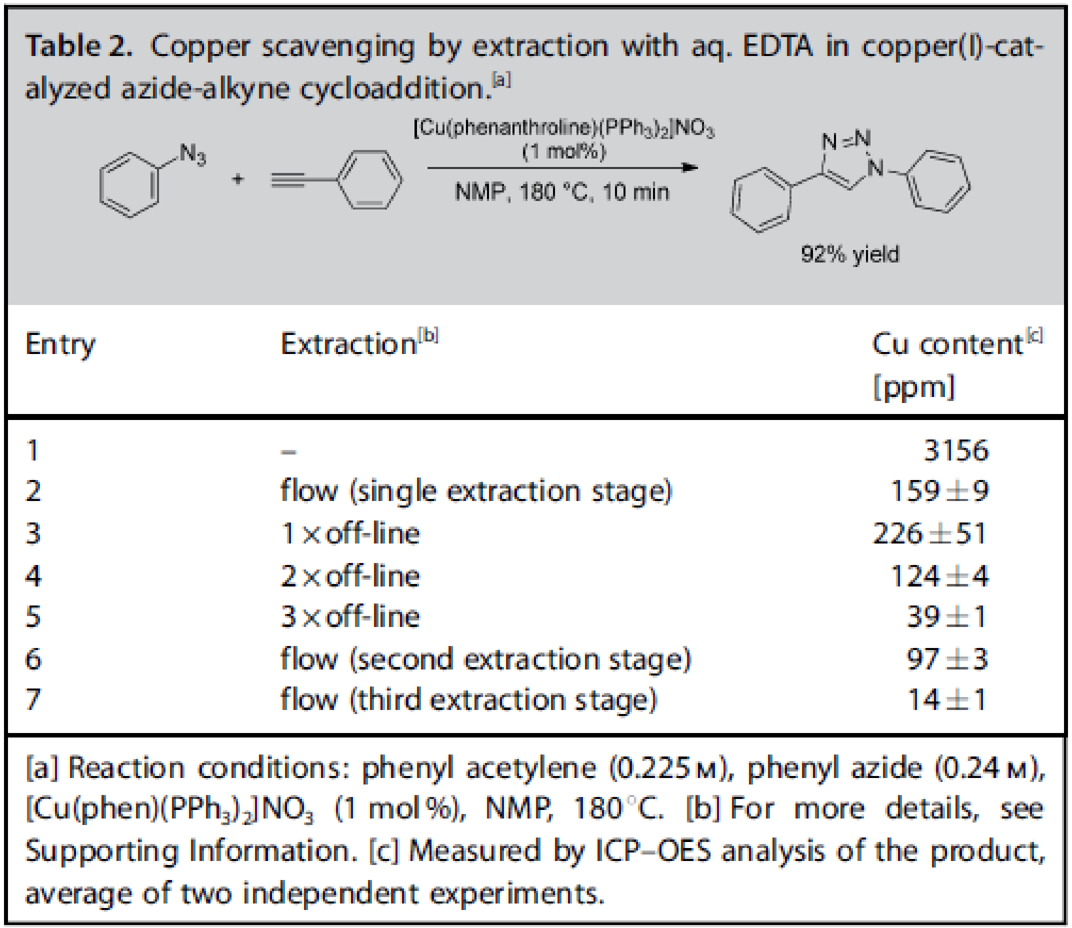


Table 2. Copper scavenging by extraction with aq. EDTA in copper(I)-catalyzed azide-alkyne cycloaddition.[a]

Entry	Extraction[b]	Cu content[c] [ppm]
1	–	3156
2	flow (single extraction stage)	159 ± 9
3	1 × off-line	226 ± 51
4	2 × off-line	124 ± 4
5	3 × off-line	39 ± 1
6	flow (second extraction stage)	97 ± 3
7	flow (third extraction stage)	14 ± 1

[a] Reaction conditions: phenyl acetylene (0.225 M), phenyl azide (0.24 M), $[Cu(phen)(PPh_3)_2]NO_3$ (1 mol %), NMP, 180 °C. [b] For more details, see Supporting Information. [c] Measured by ICP–OES analysis of the product, average of two independent experiments.

<u>RESULTS</u>:

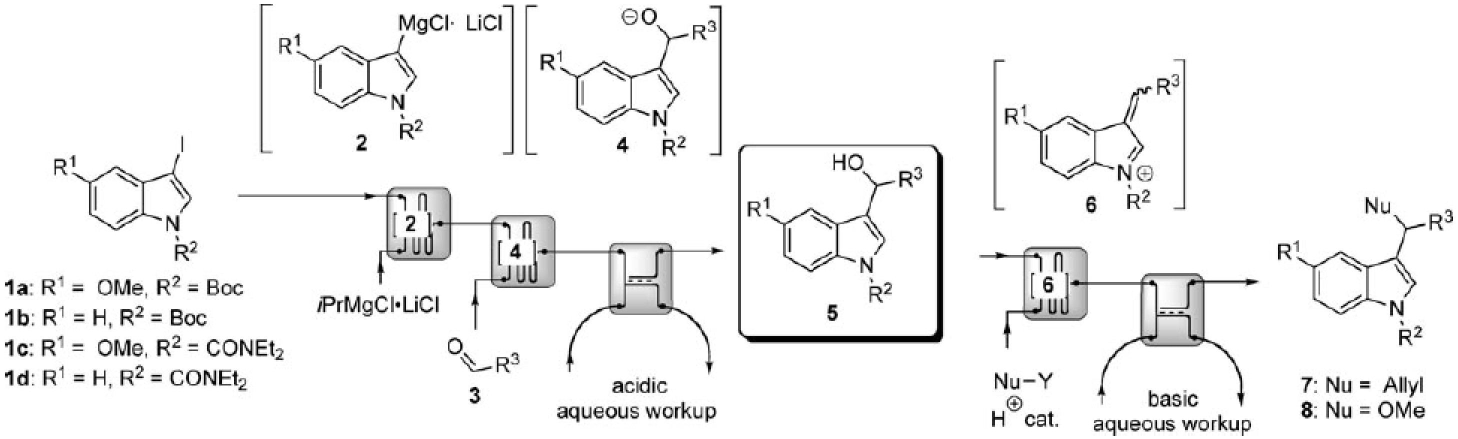
- The copper content could be effectively reduced to 119ppm in a single equilibrium extraction stage using Reaction flow/aq EDTA/EtOAc = 1/7/5

Figure 5. Collection of the two phases after phase separation in continuous flow: aqueous phase containing EDTA, copper, and NMP (left vial), and the organic phase containing triazole (right vial).

Note: The amount of copper allowed in API is 15ppm.

Example – work-up in flow

- 3-Hydroxymethylindoles synthesis by O’Shea et al.



Scheme 1. Multi-step strategy for the continuous-flow synthesis of 3-hydroxymethylindoles **5** and their conversion to **7** and **8** by acid-catalysed nucleophilic substitution.

- “Our current goal is to develop automated, sequentially performed homogeneous reactions with in-line continuous liquid–liquid extraction of the products”

T. Tricotet, D. F. O’shea, *Chem. Eur. J.* 2010,

Summary of flow chemistry benefits

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Any questions?