Benchmark of Micro Reactor Applications in Organic Synthesis

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Organische Synthesen in Mikrostrukturreaktoren
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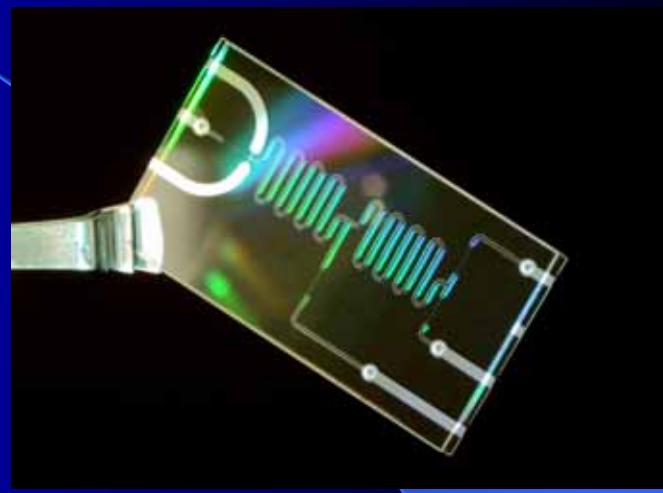
THE UNIVERSITY OF HULL

Continuous ‘Flow’ Reactors

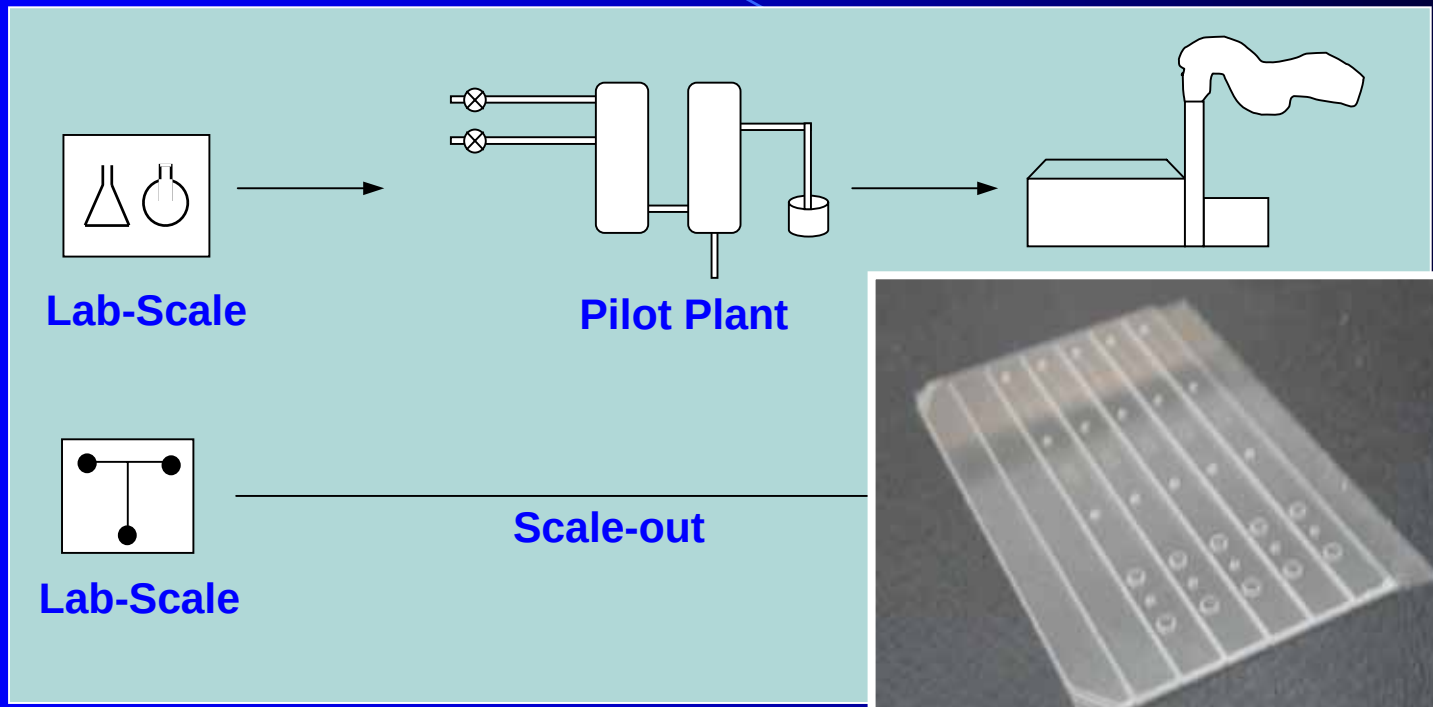
- ‘Micro’ reactors
  - Defined as a series of interconnecting channels formed in a planar surface
  - Channel dimensions of 10-300 μm
- ‘Flow’ reactors
  - Dimensions > 300 μm (up to 5 mm)
- Various pumping techniques available
  - Hydrodynamic flow
  - Electroosmotic flow
- Fabricated from polymers, metals, quartz, silicon or glass
- Why glass?
  - Mechanically strong
  - Chemically resistant
  - Optically transparent



LioniX

CHeMTriX

Production Technology



Scale-up:

Re-optimised at each stage

Costly and time consuming

Scale-out:

Numbering-up/replication

Cost effective and flexible

Requires reproducibility within single reactors

Chem. Commun., 2007, 443

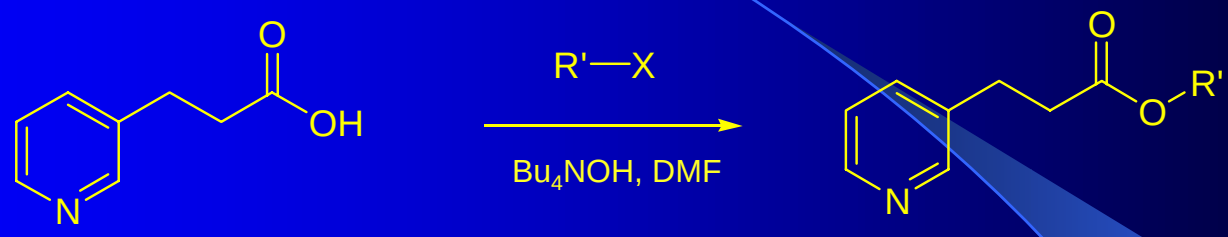
PET Radiosynthesis

- Positron emission tomography (PET) is a radiotracer imaging technique used to provide quantitative information on physiological and biochemical phenomena *in vivo*
- Applications in clinical research and drug discovery
- Two of the most desirable radioisotopes are:
  - ^{11}C ($t_{1/2}$ 20.4 minutes)
  - ^{18}F ($t_{1/2}$ 109.7 minutes)
- Syntheses must be conducted within 2-3 half-lives
- Aims of miniaturisation:
  - Produce the desired quantity of radiotracer (< 1 mg) at point of use
  - Reduced reaction times will produce the product with enhanced specific activity
  - The PET ligand will have greater sensitivity *in vivo*

Collaboration with NIH, Washington DC

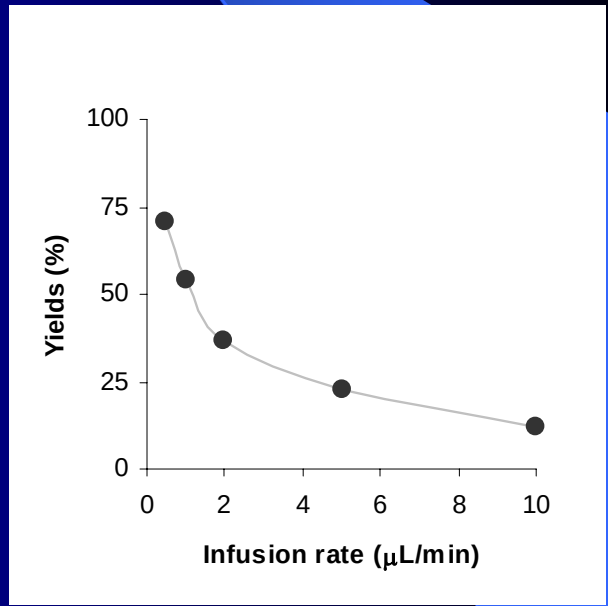
PET Chemistry

- Reaction of 3-(3-pyridinyl)propionic acid



CH_3I or $^{11}CH_3I$
FCH_2CH_2OTs or $^{18}FCH_2CH_2OTs$

- Reaction optimised with $^{12}CH_3I$ (10 mM concentration) at RT
- Hydrodynamic flow (syringe pump)
- Reaction with $^{11}CH_3I$
  - At 0.5 μl/min flow rate RCY 88%
- Reaction of $^{18}FCH_2CH_2OTs$ at 80 ^{o}C
  - At 0.5 μl/min flow rate RCY 10%

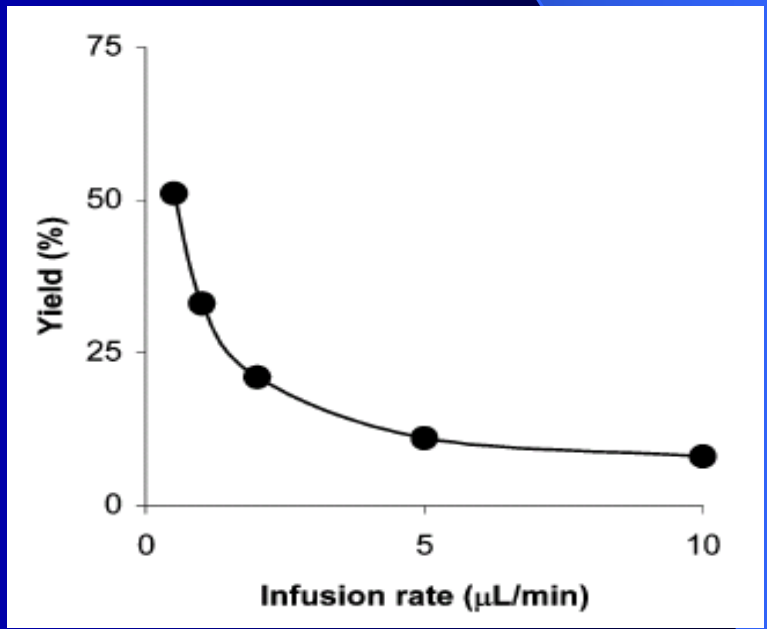


Lab Chip, 2004, **4**, 523

PET Chemistry

- Esterification reaction

- Reaction with $^{11}CH_3I$ (10 mM concentration) at RT
  - RCY 65% at 0.5 μl/min flow rate
- Product isolated by preparative HPLC

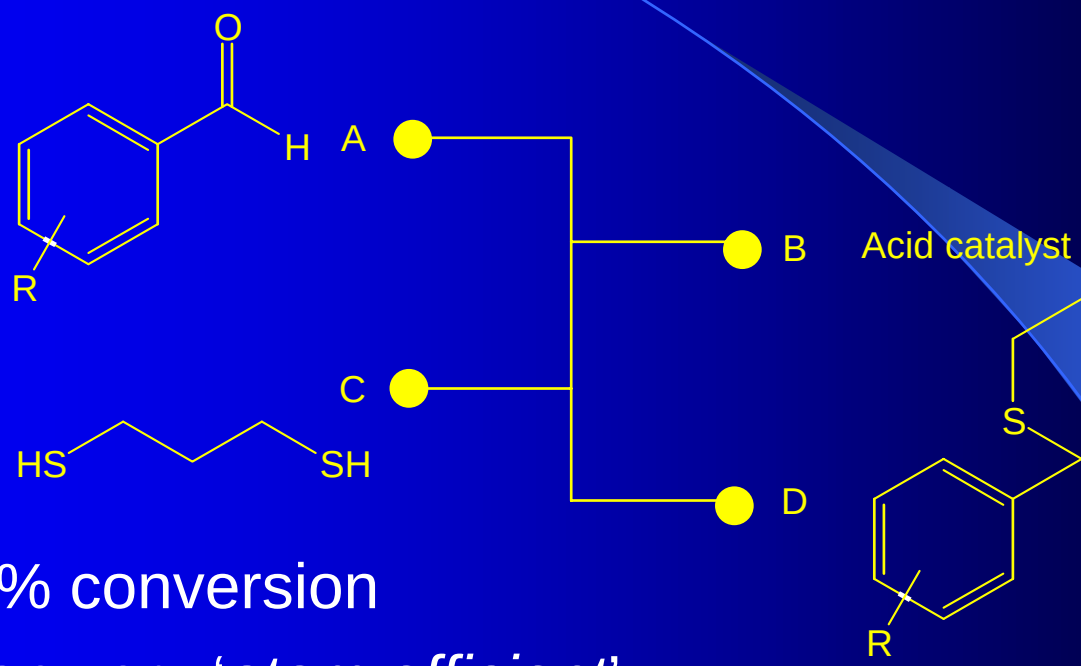


Lab Chip, 2004, **4**, 523

J. Lab. Compd. Radiopharm., 2007, **50**, 597

Dithiane Synthesis

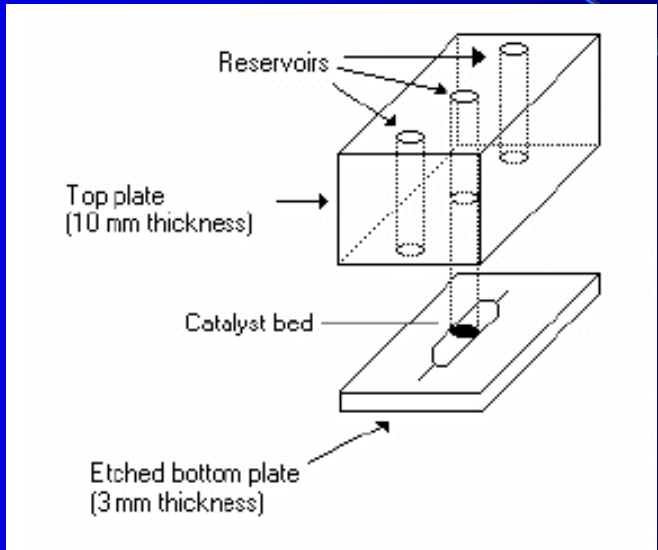
- 1:1 Ratio of reagents (0.5 M) in MeCN



- *ca.* 99 % conversion
- Reaction very '*atom efficient*'
- BUT product contaminated with acid!!
- Also product mixture contains residual (< 1 %) thiol
  - Traditional solvent extraction needed
  - This clearly reduces the advantages of flow reactors

Functionally Intelligent Reactors

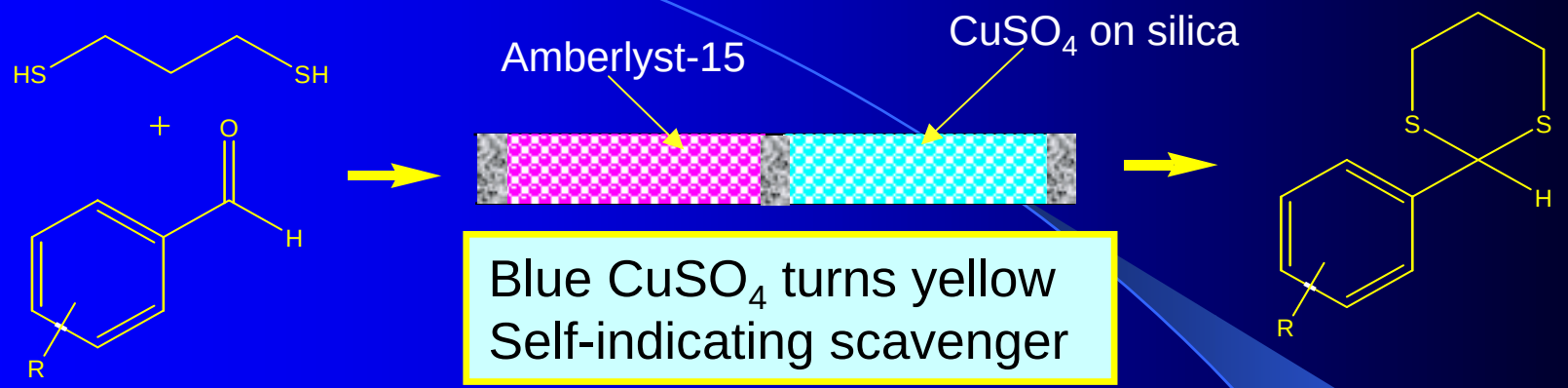
- Fabricate reactors which enable catalysts and/or supported reagents to be spatially positioned



- Removes problem of acid contamination
- Reproducible synthesis:
  - Supported reagents deteriorate with time in batch reactions as a result of physical damage and/or loss
  - Reagents last longer in micro reactions as they suffer less damage in flow reactors

Tetrahedron, 2004, **60**, 8421

Dithiane Synthesis with Scavenger



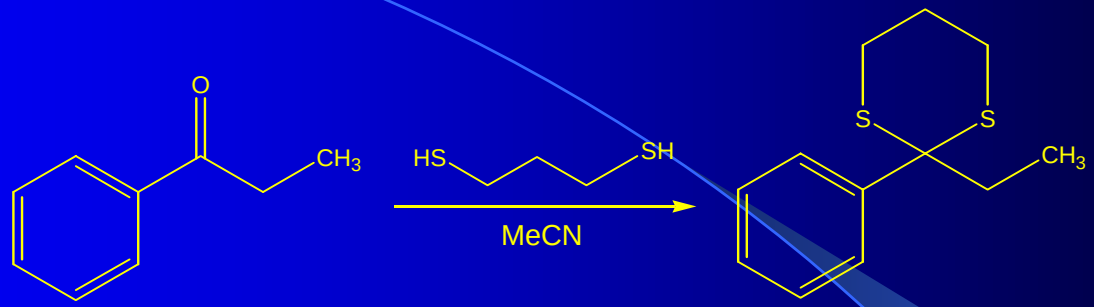
Blue $CuSO_4$ turns yellow
Self-indicating scavenger

Aldehyde	Flow Rate/μl min^{-1}	Conversion/%	Yield/%
4-Bromobenzaldehyde	61.4	99.99 (0.005)[a]	99.92
4-Chlorobenzaldehyde	61.7	99.99 (0.003)	99.91
4-Cyanobenzaldehyde	65.4	99.99 (0.002)	99.94
4-Biphenylcarboxaldehyde	63.0	99.99 (0.001)	99.97
4-Methylbenzaldehyde	70.0	99.99 (0.001)	99.97
4-Benzyloxybenzaldehyde	61.1	99.99 (0.002)	99.22
2,4-Dihydrobenzaldehyde	58.9	99.99 (0.003)	99.90
Methyl-4-formyl benzoate	60.4	99.99 (0.008)	99.82
2-Furaldehyde	67.9	99.99 (0.001)	99.92

[a] Numbers in parentheses represent % RSD

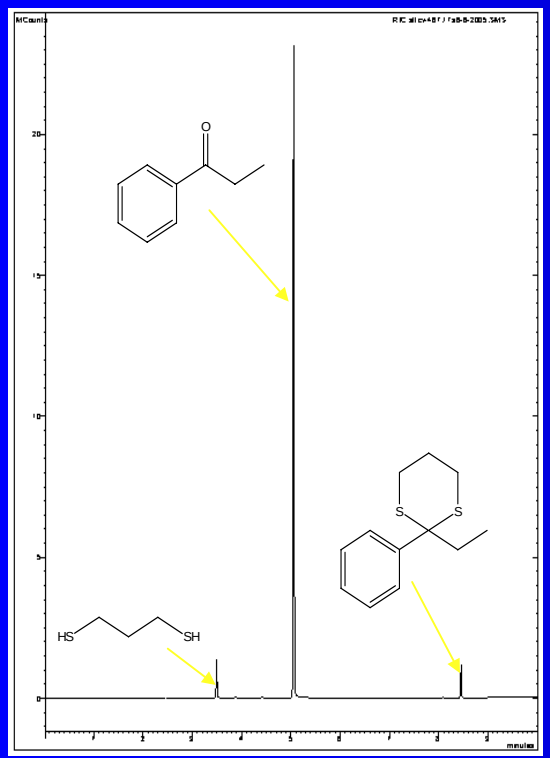
Tetrahedron Lett, 2007, **48**, 7362

Synthesis of Thioketals

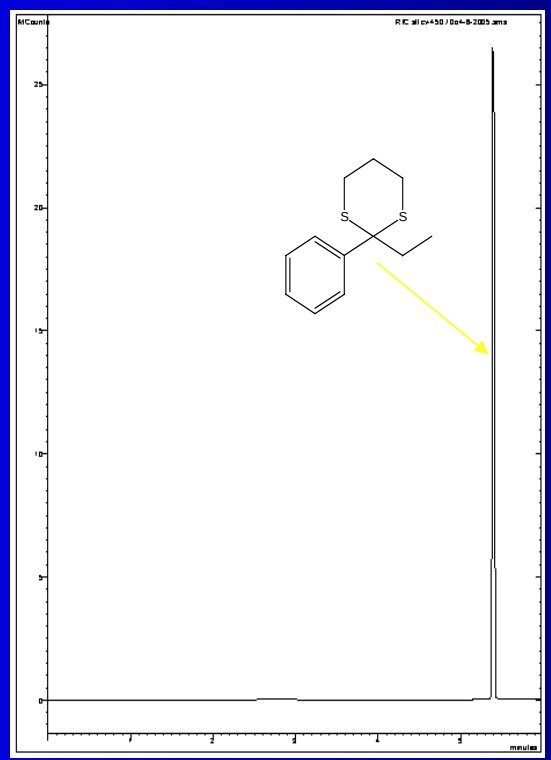


- Kinetically less favourable than acetalisation

Batch (24 hrs)



Flow Reactor

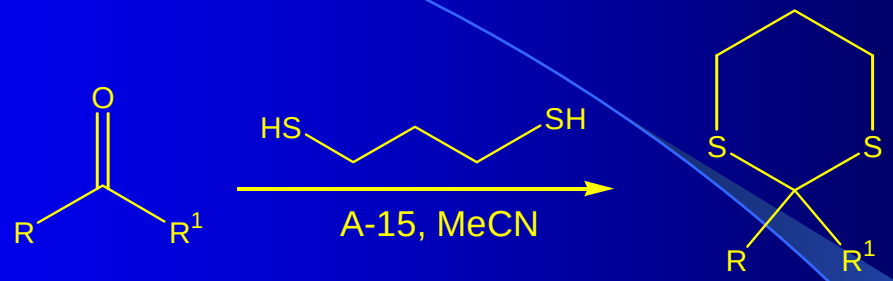


Flow Reactor Results:

- % RSD = 0.004
- n = 6
- Flow rate = 40.4 μl min^{-1}
- Conversion = 99.94 %

Tetrahedron Lett, 2007, **48**, 7362

Thioketalisation Results



Ketone	Flow Rate/μl min^{-1}	Conversion/%	Yield/%
Acetophenone	41.5	99.99 (0.004) [a]	99.57
Cyclohexanone	42.2	99.99 (0.003)	99.62
Butyrophenone	41.6	99.99 (0.005)	99.90
4-Methylacetophenone	42.0	99.99 (0.001)	99.91
4-Nitroacetophenone	40.9	99.99 (0.004)	99.95
2-Methylcyclohexanone	41.6	99.99 (0.001)	99.96
Cyclopentanone	43.0	99.99 (0.001)	99.91
4-Aminoacetophenone	40.3	99.99 (0.001)	99.93
4-Hydroxyacetophenone	41.9	99.99 (0.0004)	99.90

[a] Numbers in parentheses represent % RSD

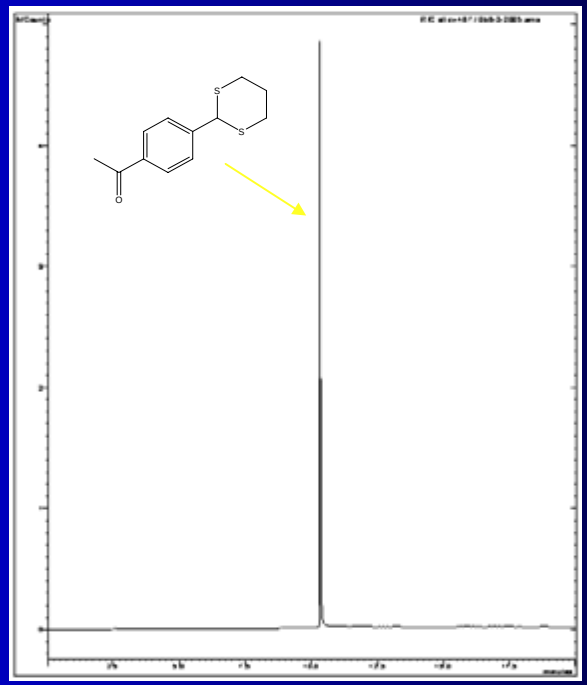
Chemoselective Thioacetalisation

Question: What would happen if the compound to be protected contained both a ketone and an aldehyde?

4-Acetylbenzaldehyde

Desired product

Stirred Reactor 24 hr

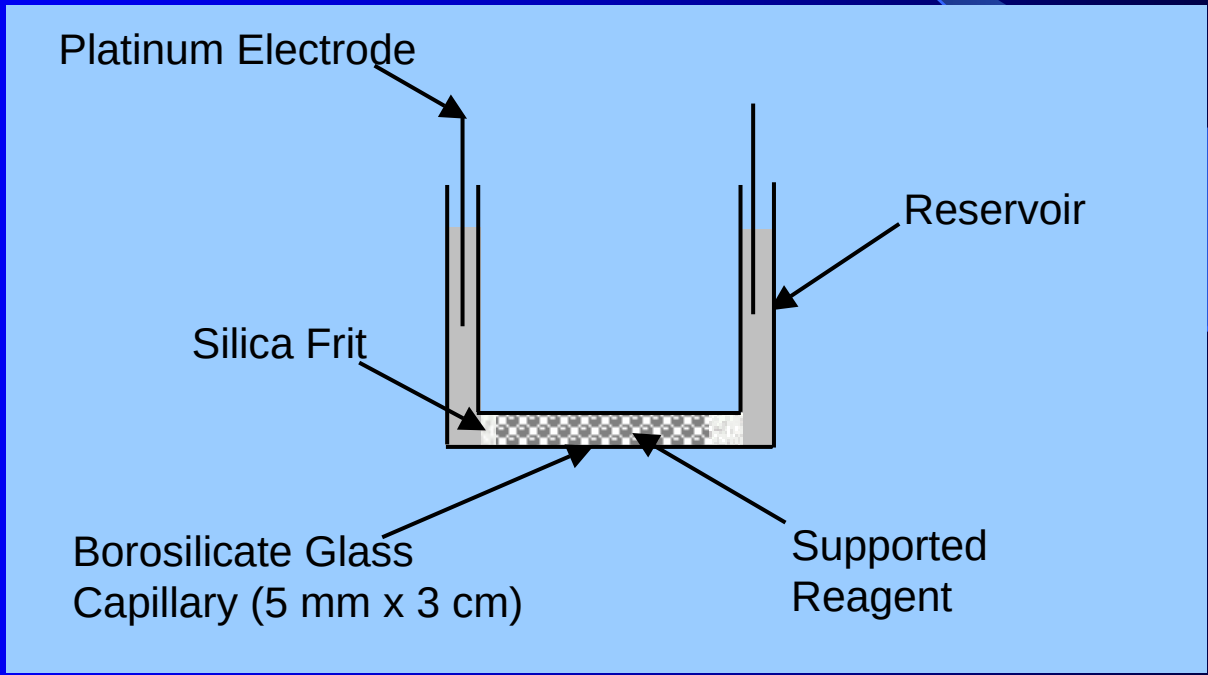


Flow reactor (65 μl min^{-1})

Tetrahedron Lett, 2007, **48**, 7362

Scaling Up Scale-Out!

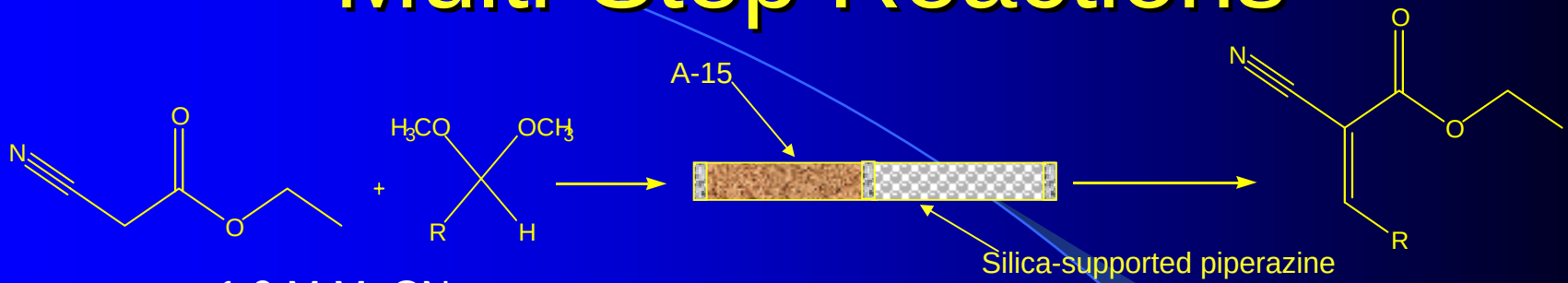
- In '*open capillaries*' EOF only operates in channels up to *ca.* 300 μm
- In '*packed*' micro reactors flow rate was faster even when the channel was bigger!!



- 5 mm wide catalyst bed (3 cm length)
- Typically prepare 1g/hour of analytically pure product

Chem Commun, 2007, 966

Multi-Step Reactions



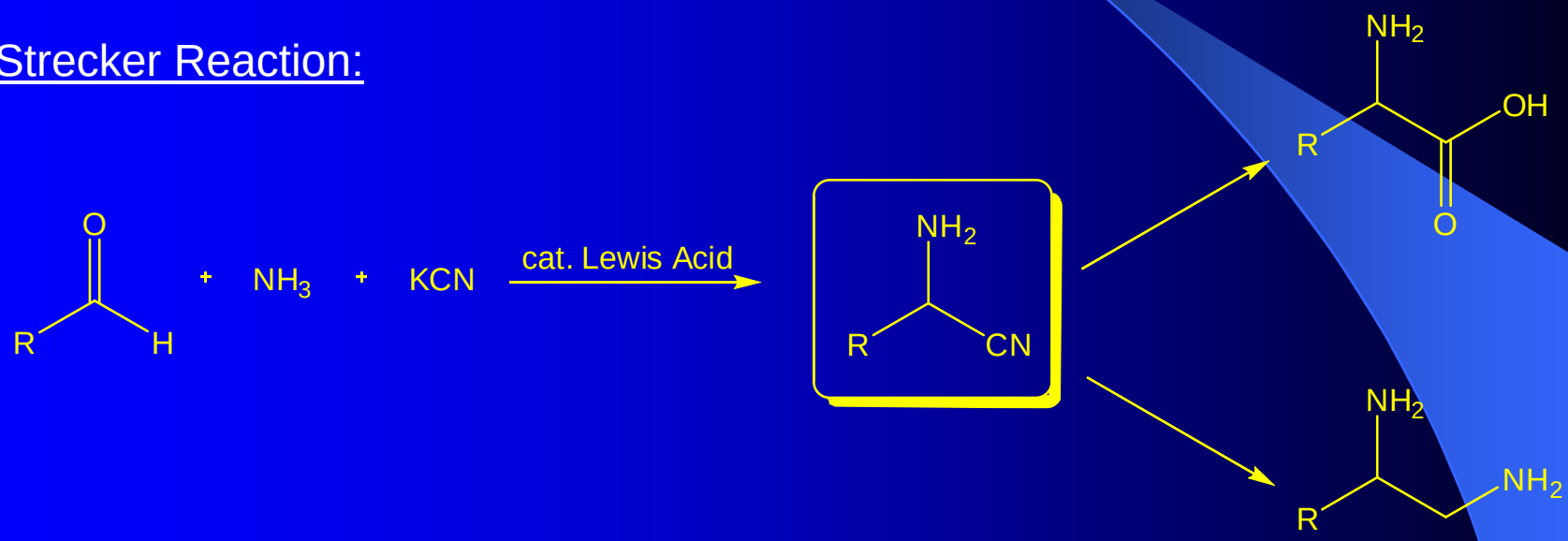
Aldehyde	Conversion (%)	Actual Yield (g)	Yield (%)
Benzaldehyde	99.99	0.0150 g	99.4
4-Bromobenzaldehyde	99.99	0.0338 g	99.8
4-Chlorobenzaldehyde	99.99	0.0277 g	99.6
4-Cyanobenzaldehyde	99.99	0.0284 g	99.7
2-Naphthaldehyde	99.99	0.0298 g	99.8
Methyl-4-formyl benzoate	100.0	0.0253 g	99.7
4-Benzyloxybenzaldehyde	99.99	0.0219 g	99.1
Nitrothiophenecarboxaldehyde	99.99	0.0238 g	99.7
3,5-Dimethoxybenzaldehyde	99.99	0.0213 g	99.5

Lab Chip, 2007, **7**, 322

Synthesis of α-Aminonitriles

- Synthesis of non-proteinogenic α-amino acids
  - Novel, efficient syntheses are required
  - Low yields/selectivities often observed

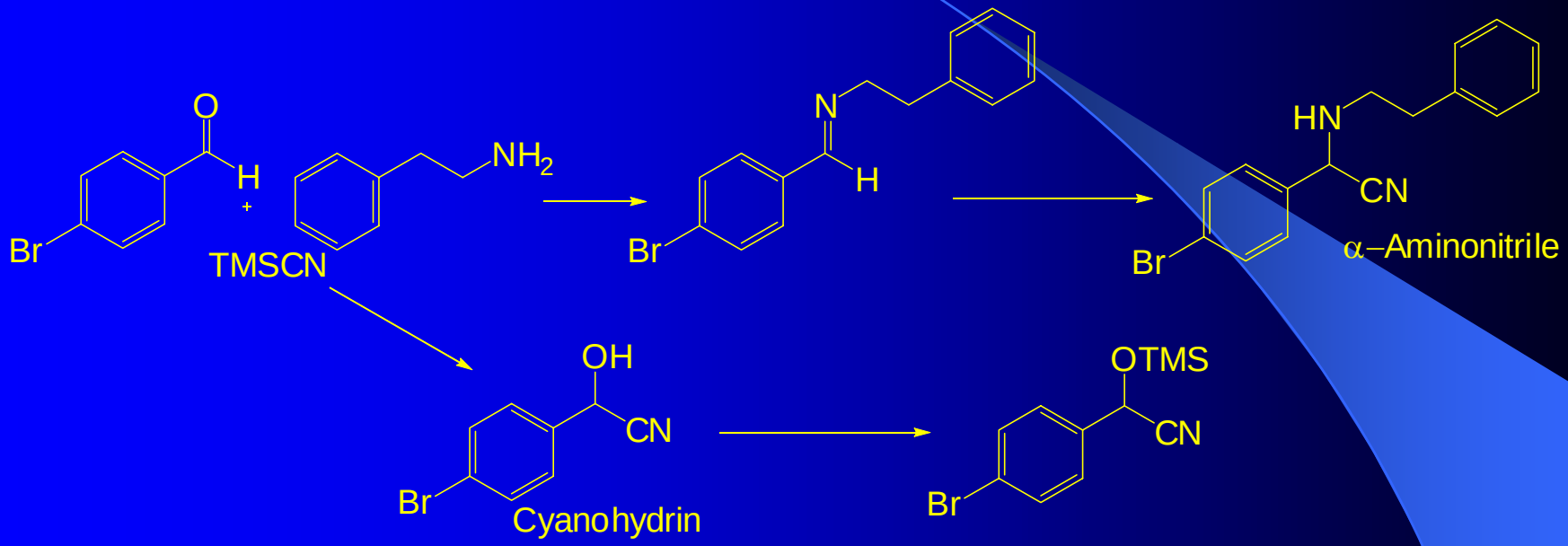
Strecker Reaction:



- Multi-component reaction, useful for the synthesis of thiadiazoles, imidazoles, diamines and α-amino acids
- Catalysts include; $InCl_3$, $BiCl_3$, KSF clay, $Sc(OTf)_3$, Cs(II)-salt, Pt-salt
- Reaction times in the range of 24 to 48 hr
  - Moderate yields (55 to 95 %)

Disadvantages: Strecker Reaction

Side Reactions:

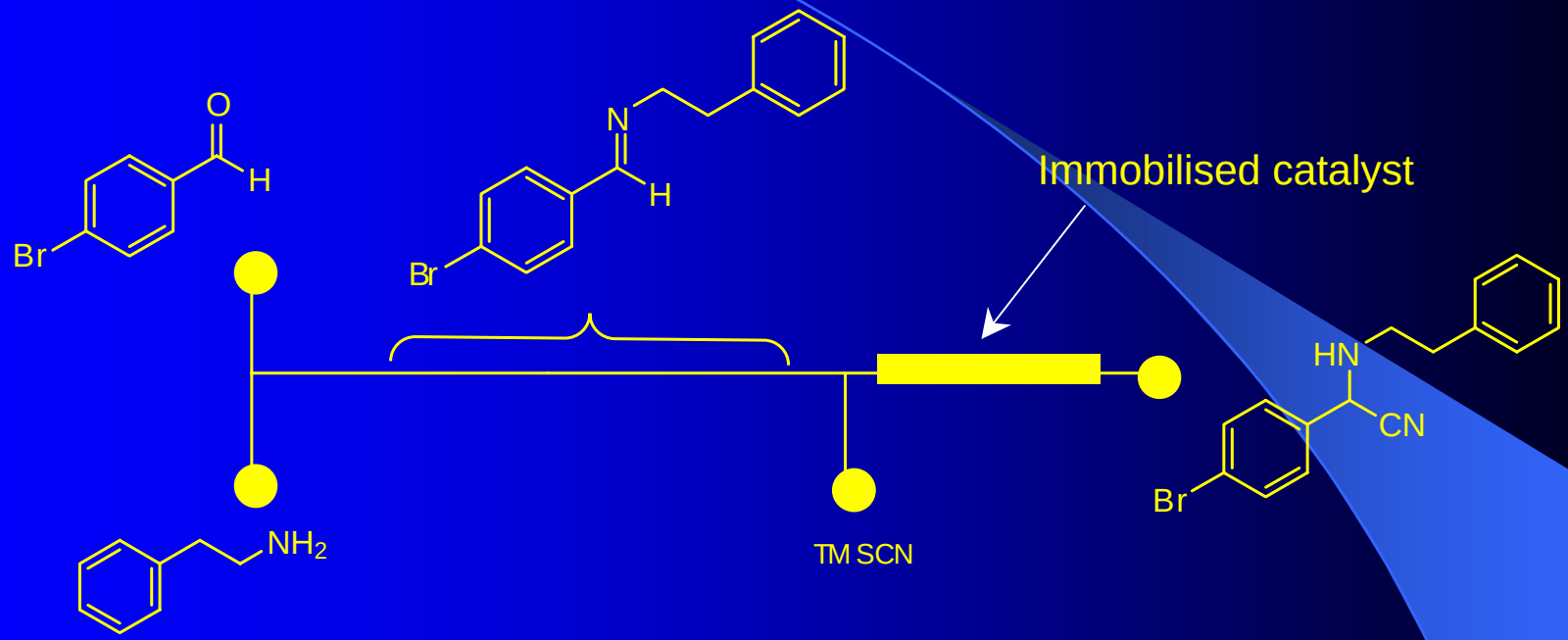


- Low yields, complex reaction mixtures
  - Laborious purification required

Expensive Catalyst:

- Difficult to recover and recycle

Continuous Flow Synthesis



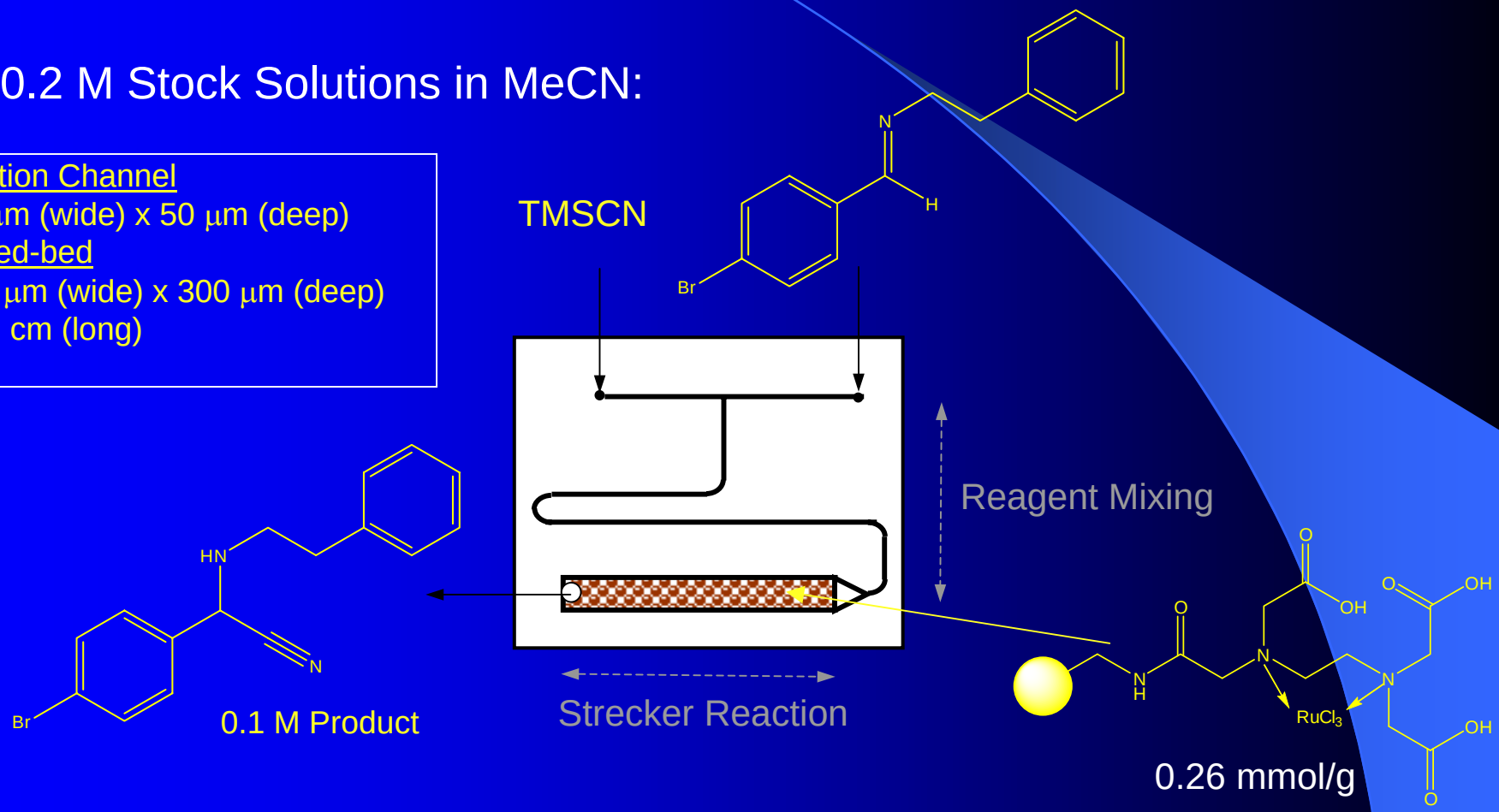
Aims of Flow Reaction:

- Enable optimisation of imine formation
  - To minimise or prevent cyanohydrin formation
- Employ a stoichiometric quantity of TMSCN and amine
- Recycle catalyst efficiently
  - Reduce degradation due to absence of stirring

Continuous Flow Nucleophilic Addition to Imine

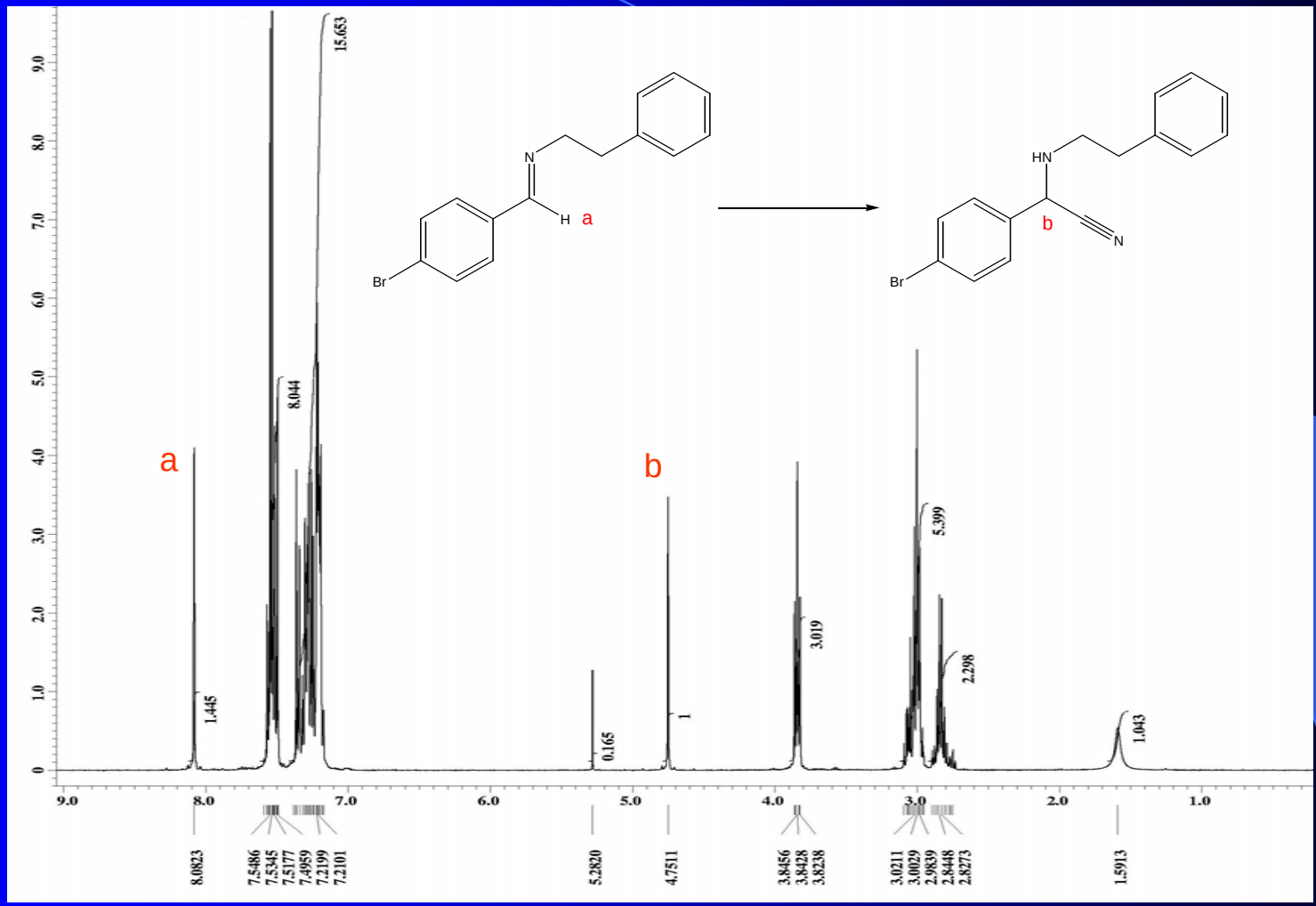
0.2 M Stock Solutions in MeCN:

<u>Reaction Channel</u>
150 μm (wide) x 50 μm (deep)
<u>Packed-bed</u>
3000 μm (wide) x 300 μm (deep)
x 2.1 cm (long)



- Remove solvent and dissolve residue in $CDCl_3$, analyse by ^1H NMR

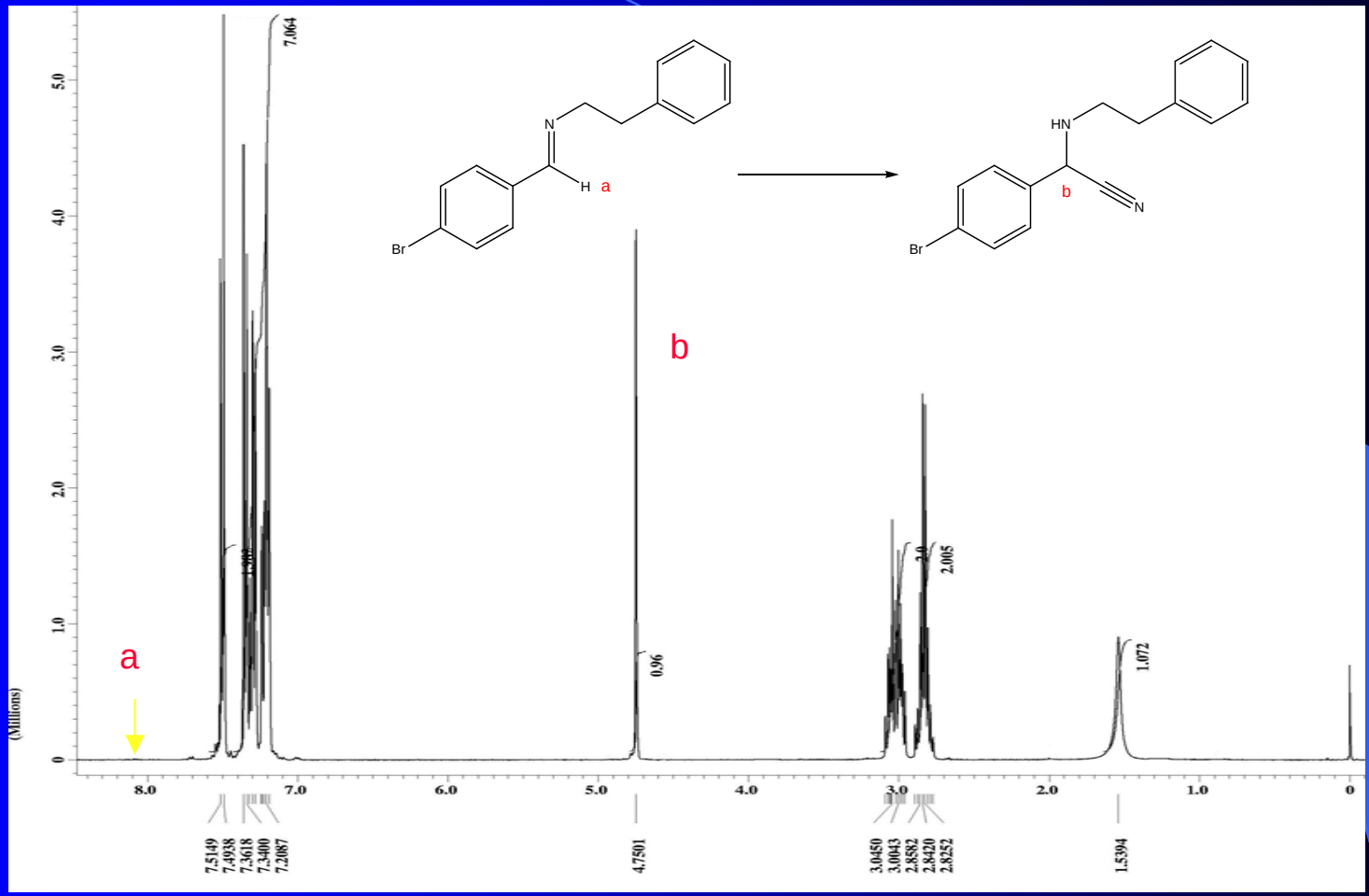
Results: Pre-formed Imine



Reaction Conditions:

- Total flow rate = 100 μl min^{-1}, 41 % conversion (unoptimised)

Optimised Results



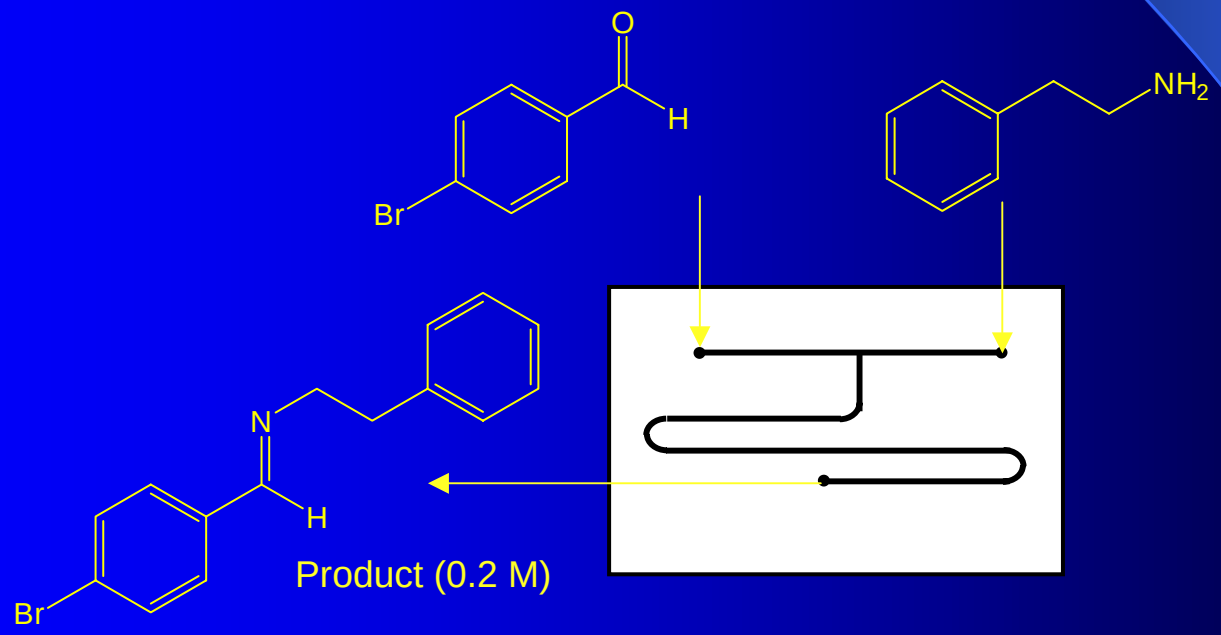
Reaction Conditions:

- Total flow rate = 5.0 μl min^{-1}, 100 % conversion
  - Product also evaluated by MS, IR and CHN analysis to confirm purity

Flow Synthesis of Imines

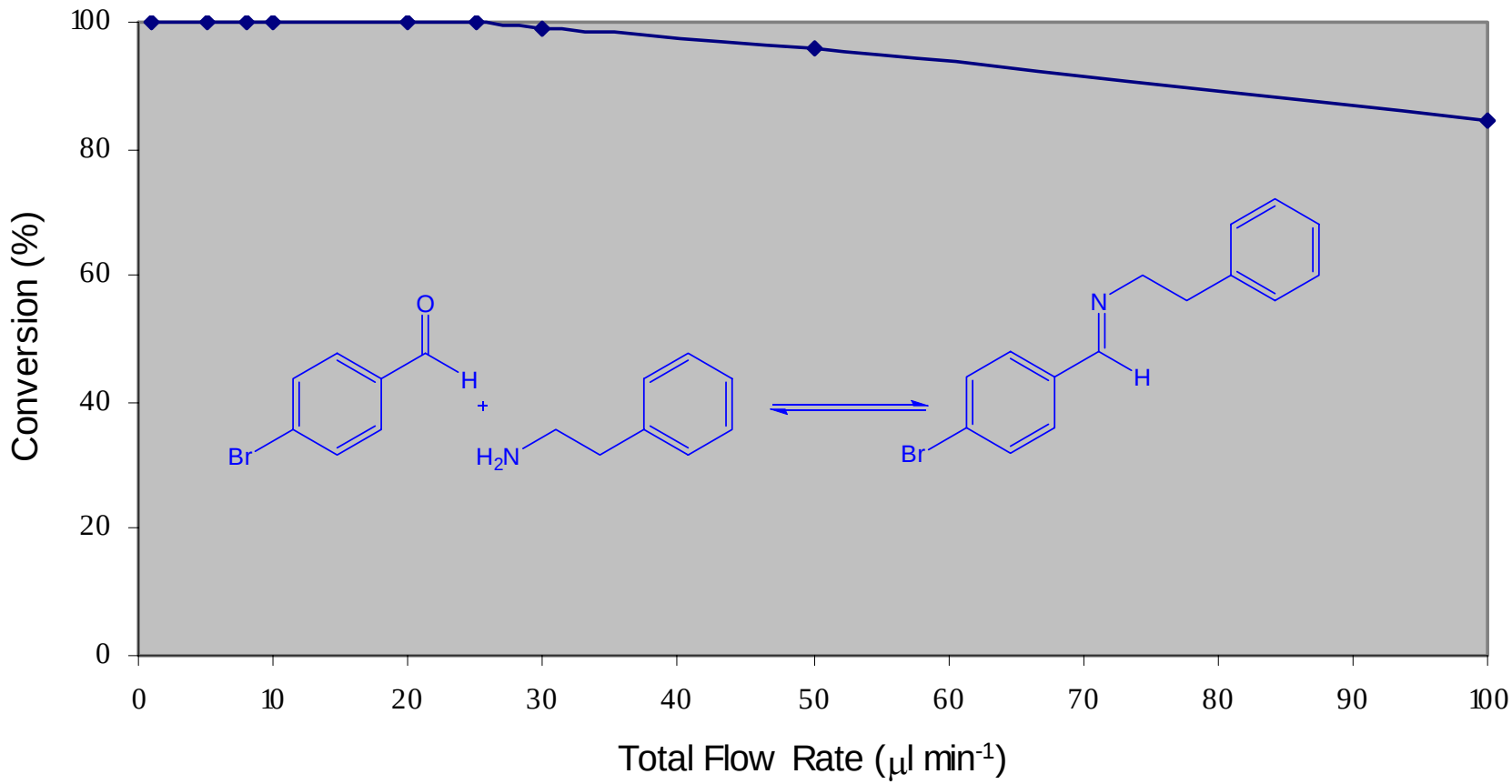
Reaction Conditions:

- 0.4 M Stock Solutions in MeCN
- Micro Channel Dimensions = 150 μm (wide) x 50 μm (deep)



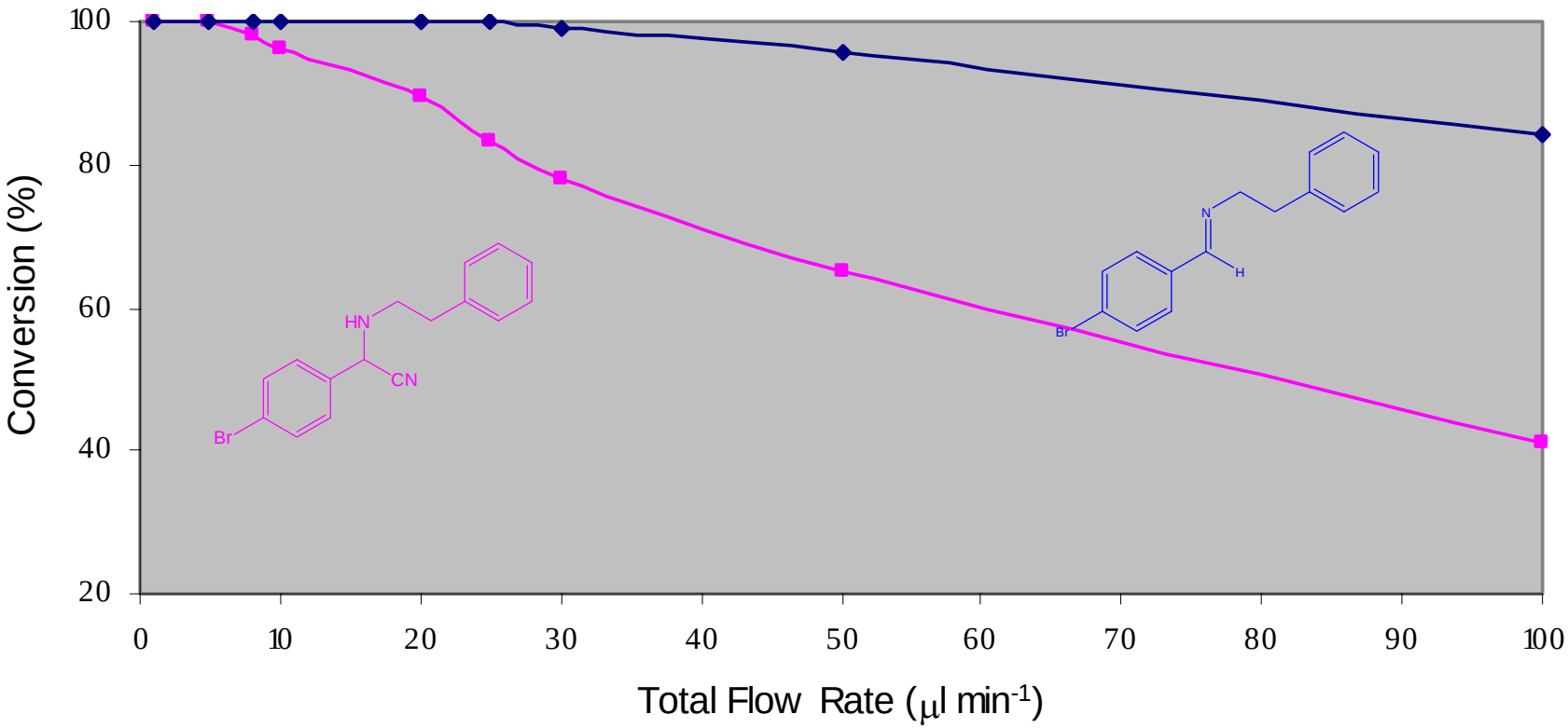
- Reaction products analysed, off-line, by GC-MS
  - Identify optimal conditions for imine formation

Optimisation of Imine Formation



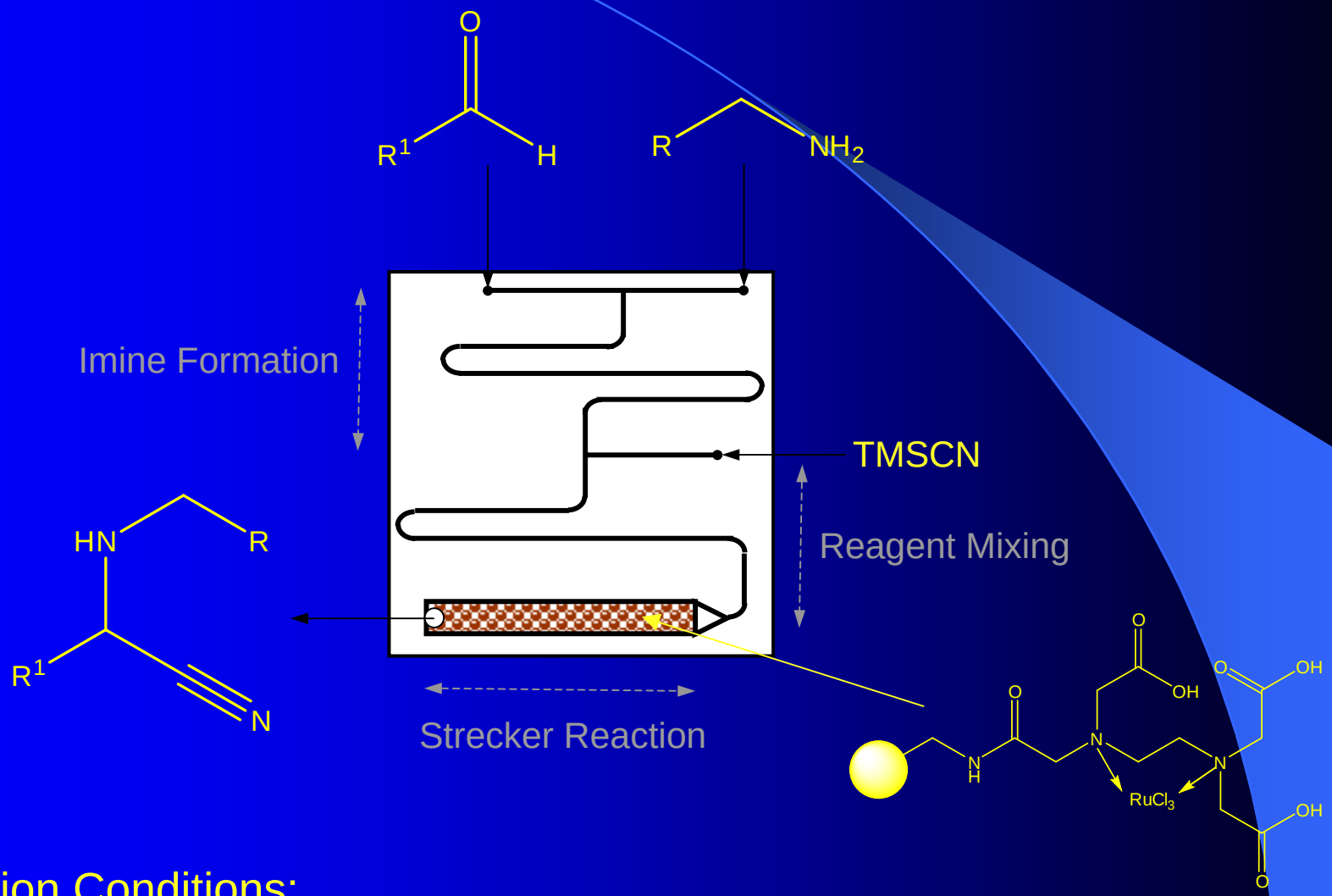
Conversion calculated wrt. residual 4-bromobenzaldehyde

Comparison of Reaction Steps



- Optimal conditions for both reactions = Total flow rate < 5.0 μl min^{-1}
  - Conversion calculated wrt. residual imine

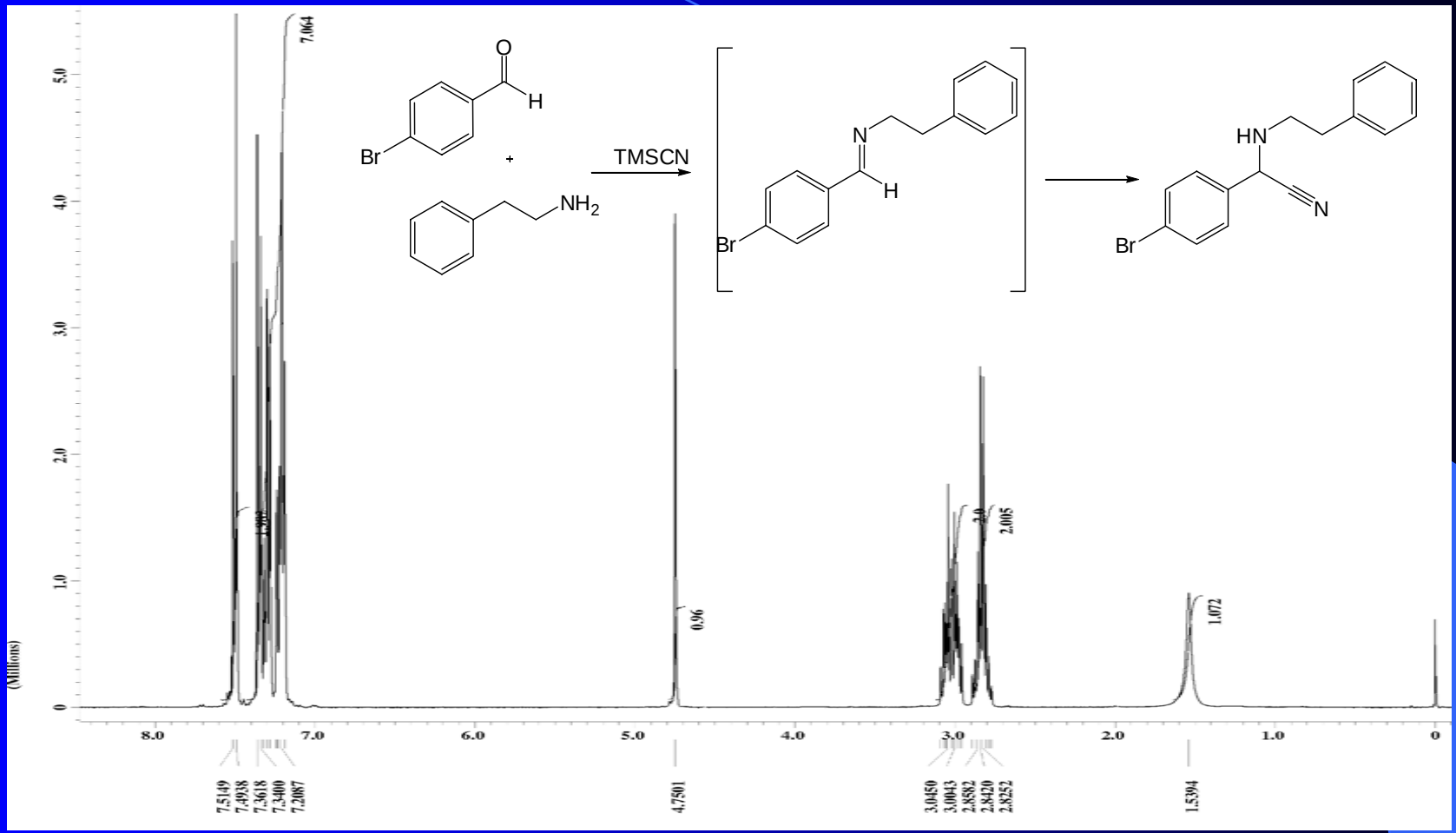
Combined Micro Reactor Design



Reaction Conditions:

Total flow rate 5.0 μl min^{-1}, 0.4 M aldehyde and amine, 0.2 M TMSCN

Multi-Step Reaction: NMR Analysis



Flow: Quantitative Conversion (by NMR), 99.9 % Yield, 9.45 mg hr^{-1} (5.0 μl min^{-1})

Batch: 64.9 % Conversion, stirred for 24 hr (1.5 eq. TMSCN)

Evaluation of Catalyst Recycling and Leaching in a Micro Reactor

4-Bromo-phenyl-phenethylamino-acetonitrile:

- 0.1 mmol of α-aminonitrile synthesised using 2.6 x 10^{-3} mmol of PS-$RuCl_3$
  - Turnover number of 38 for a single reaction
- In addition to efficient catalyst recycling, it is pharmaceutically important that minimal heavy metals are found in the resulting product

ICP-MS Analysis:

  - Stirred Batch Reaction: 440 ppm Ru
  - Micro Reaction: No observable difference from the blank (MeCN)
- Confirms that minimal catalyst degradation is observed in flow reactors, *cf*. stirred/shaken batch vessels
- Affording an analytically purer product that obtainable using traditional reactor methodology

Use of Polymer Supported $ScOTf_2$

Advantages vs. PS-$RuCl_3$:

- Higher loading commercially available (0.60 mmol g^{-1})
- Greater tolerance to H_2O
- Effective activation of imines

Reaction Conditions: Amine and aldehyde (0.4 M), TMSCN (0.2 M) in MeCN

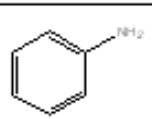
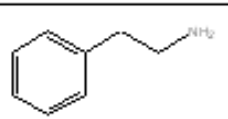
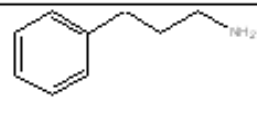
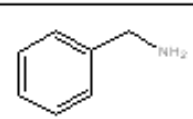
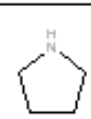
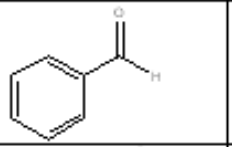
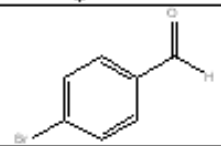
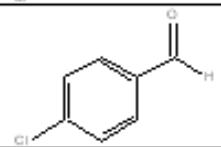
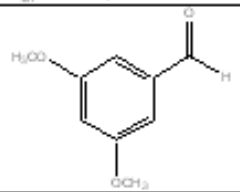
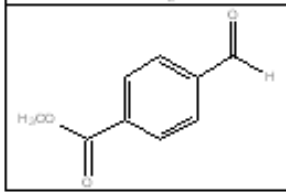
Entry	Flow Rate [a] ($\mu l\ min^{-1}$)	Conversion (%) PS-$RuCl_3$	Conversion (%) PS-$ScOTf_2$
1	5	100.0	100.0
2	10	95.2	100.0
3	20	85.9	95.4
4	40	36.3	84.6
5	100	25.9	36.3

Increasing Residence Time

[a] Total flow rate (based on delivery of reagents from 3 inputs)
[b] Calculated based on ^1H NMR integration of the crude product

5 x 5 Array of α-Aminonitriles

Using PS-ScOTf$_2$: Amine and aldehyde (0.4 M), TMSCN (0.2 M) in MeCN

					
	99.90 % 10.0 µl min^{-1} 0.0125 g hr^{-1}	99.85 % 10.0 µl min^{-1} 0.0142 g hr^{-1}	99.69 % 10.0 µl min^{-1} 0.0150 g hr^{-1}	99.97 % 10.0 µl min^{-1} 0.0133 g hr^{-1}	99.87 % 20.0 µl min^{-1} 0.0223 g hr^{-1}*
	99.88 % 10.0 µl min^{-1} 0.0173 g hr^{-1}	99.90 % 10.0 µl min^{-1} 0.0189 g hr^{-1}	99.74 % 10.0 µl min^{-1} 0.0197 g hr^{-1}	99.93 % 10.0 µl min^{-1} 0.0181 g hr^{-1}	99.77 % 20.0 µl min^{-1} 0.0318 g hr^{-1}*
	99.72 % 10.0 µl min^{-1} 0.0146 g hr^{-1}	99.89 % 10.0 µl min^{-1} 0.0162 g hr^{-1}	99.89 % 10.0 µl min^{-1} 0.0170 g hr^{-1}	99.94 % 10.0 µl min^{-1} 0.0154 g hr^{-1}	99.73 % 20.0 µl min^{-1} 0.0264 g hr^{-1}*
	99.93 % 10.0 µl min^{-1} 0.0161 g hr^{-1}	100.0 % 10.0 µl min^{-1} 0.0178 g hr^{-1}	99.99 % 10.0 µl min^{-1} 0.0188 g hr^{-1}	99.93 % 10.0 µl min^{-1} 0.0169 g hr^{-1}	99.69 % 20.0 µl min^{-1} 0.0295 g hr^{-1}*
	100.0 % 10.0 µl min^{-1} 0.0160 g hr^{-1}	99.93 % 10.0 µl min^{-1} 0.0176 g hr^{-1}	99.94 % 10.0 µl min^{-1} 0.0185 g hr^{-1}	99.80 % 10.0 µl min^{-1} 0.0168 g hr^{-1}	99.79 % 20.0 µl min^{-1} 0.0295 g hr^{-1}*

Run time = 2.5 hr, except for * where run time = 1.25 hr

Conclusions

- Micro reactors allow the rapid optimisation of reactions
  - High-throughput synthesis
  - Combinatorial and library synthesis
- Immobilised reagents (and enzymes) allow the synthesis of analytically pure compounds
- Micro reactors are suitable for a wide range of reactions
- Micro reactors generate products in:
  - Higher purity
  - Higher conversion
  - Higher selectivity
- *In situ* formation of reagents
- *In situ* purification of products

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