Enhanced Chemical Synthesis in Micro Reactors

Paul Watts

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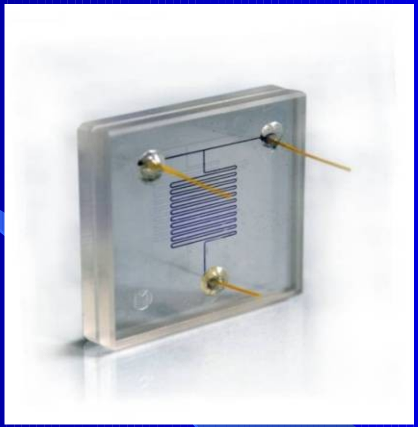
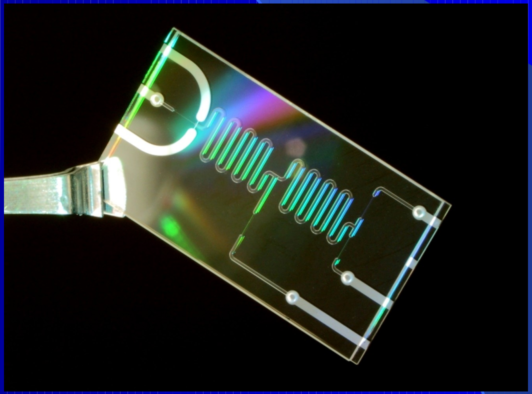
THE UNIVERSITY OF HULL

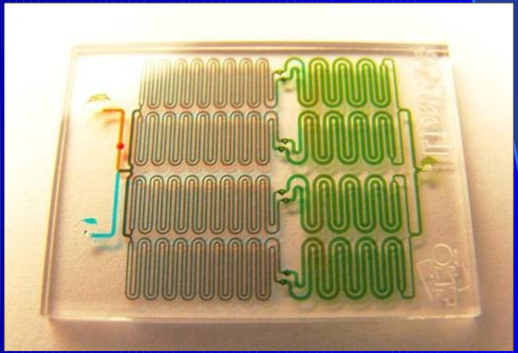
CHEMTRIX

Flow Reactors

- ‘*Micro*’ reactors
  - Defined as a series of interconnecting channels formed in a planar surface
  - Channel dimensions of 10-300 μm
  - Very small dimensions result in very fast diffusive mixing
  - Rapid heat transfer
  - High throughput experimentation
- ‘*Flow*’ (or meso) reactors
  - Dimensions > 300 μm (up to 5 mm)
  - Mixing much slower
  - Throughput higher
  - More useful when packed with catalysts
- Fabricated from polymers, metals, quartz, silicon or glass
- Why glass?
  - Mechanically strong
  - Chemically resistant
  - Optically transparent



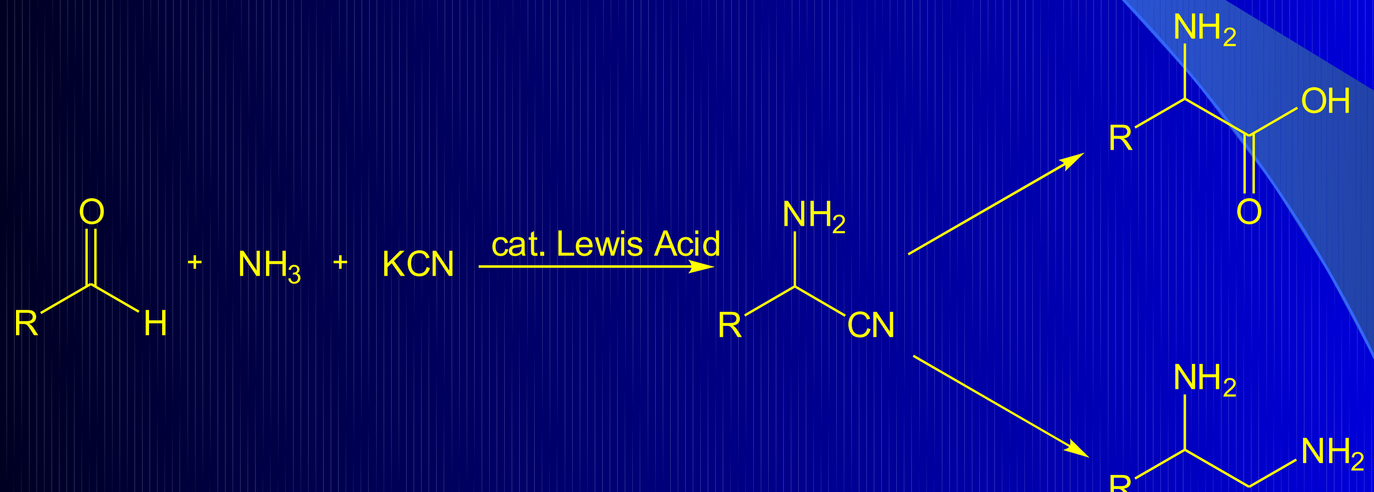




Synthesis of α-Aminonitriles

- Synthesis of non-proteinogenic α-amino acids
  - Novel, efficient syntheses are required
  - Existing techniques efficient for aryl imine substrates
    - Low yields/selectivities for aliphatic derivatives

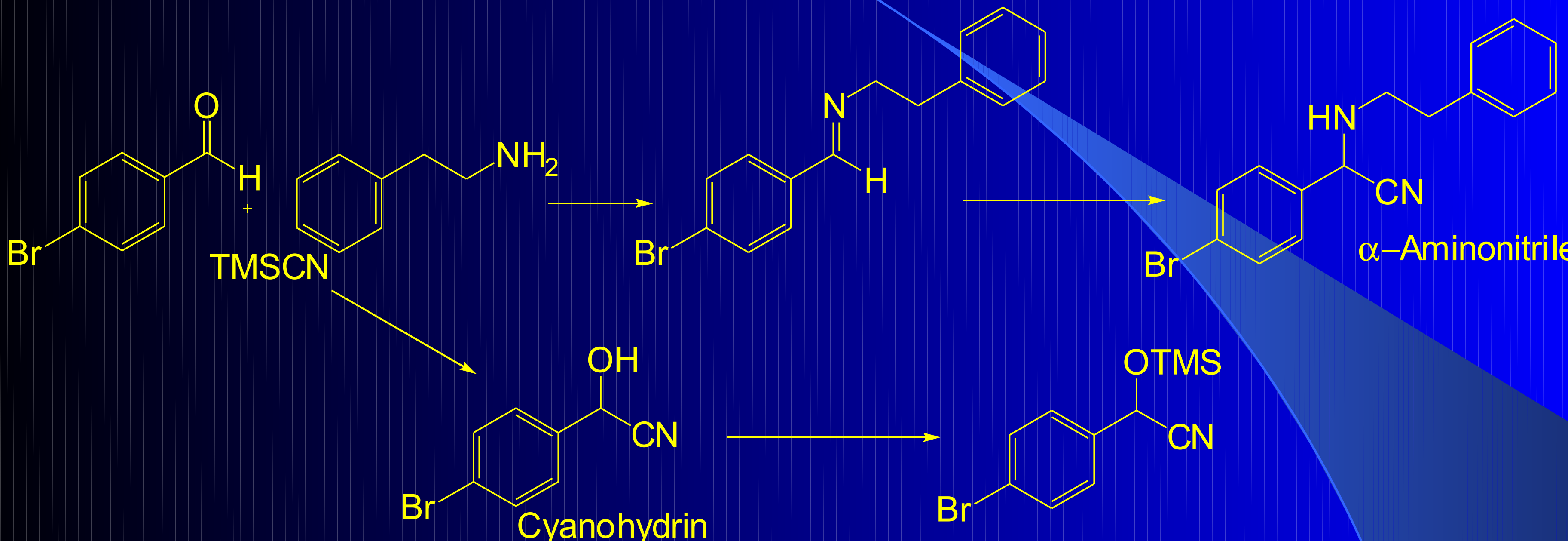
<u>Strecker Reaction</u>



- 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

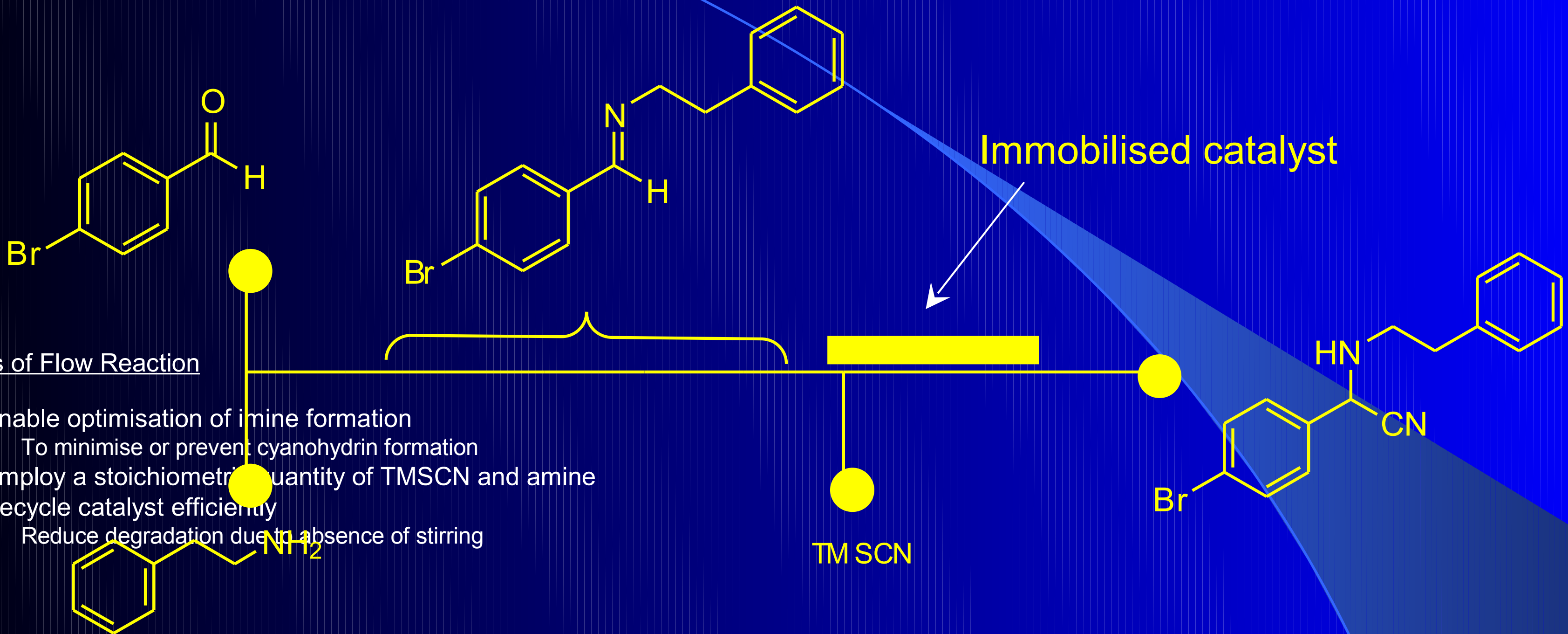


- Low yields, complex reaction mixtures laborious purification required
  - Problematic with aromatic aldehydes due to slow imine formation

Expensive Catalyst

- Difficult to recover and recycle
- Generation of acidic waste

Continuous Flow Synthesis



<u>Aims of Flow Reaction</u>

- 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

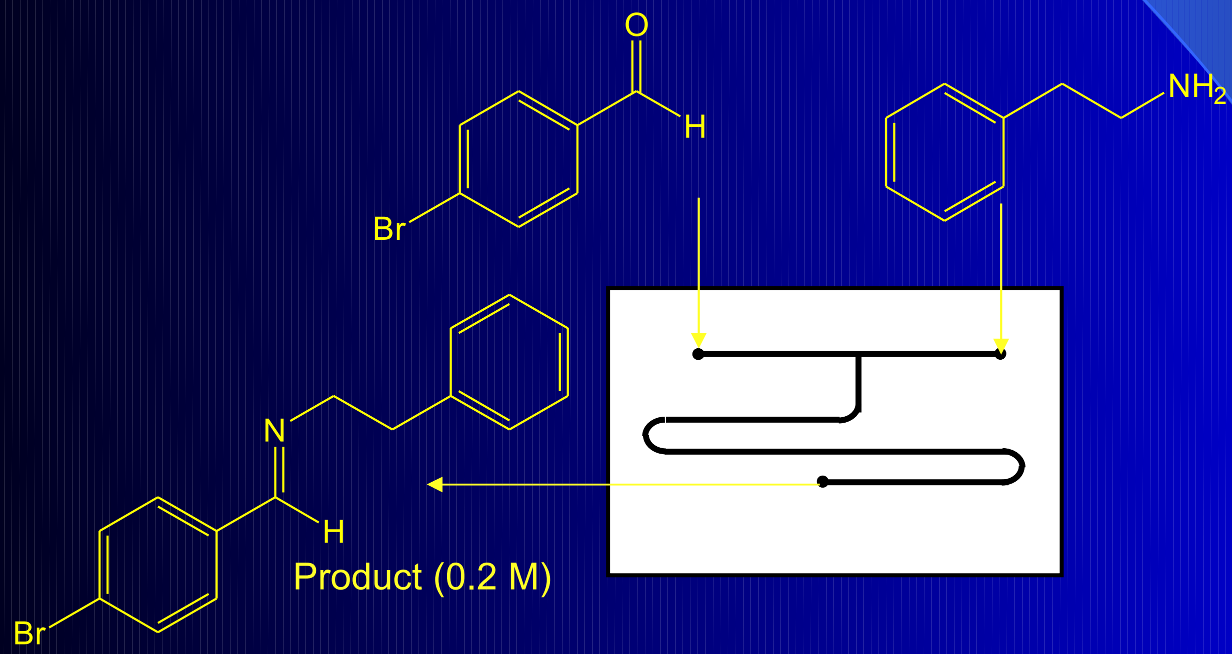
Lab Chip, 2007, **7**, 322

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

Flow Synthesis of Imines

Reaction Conditions

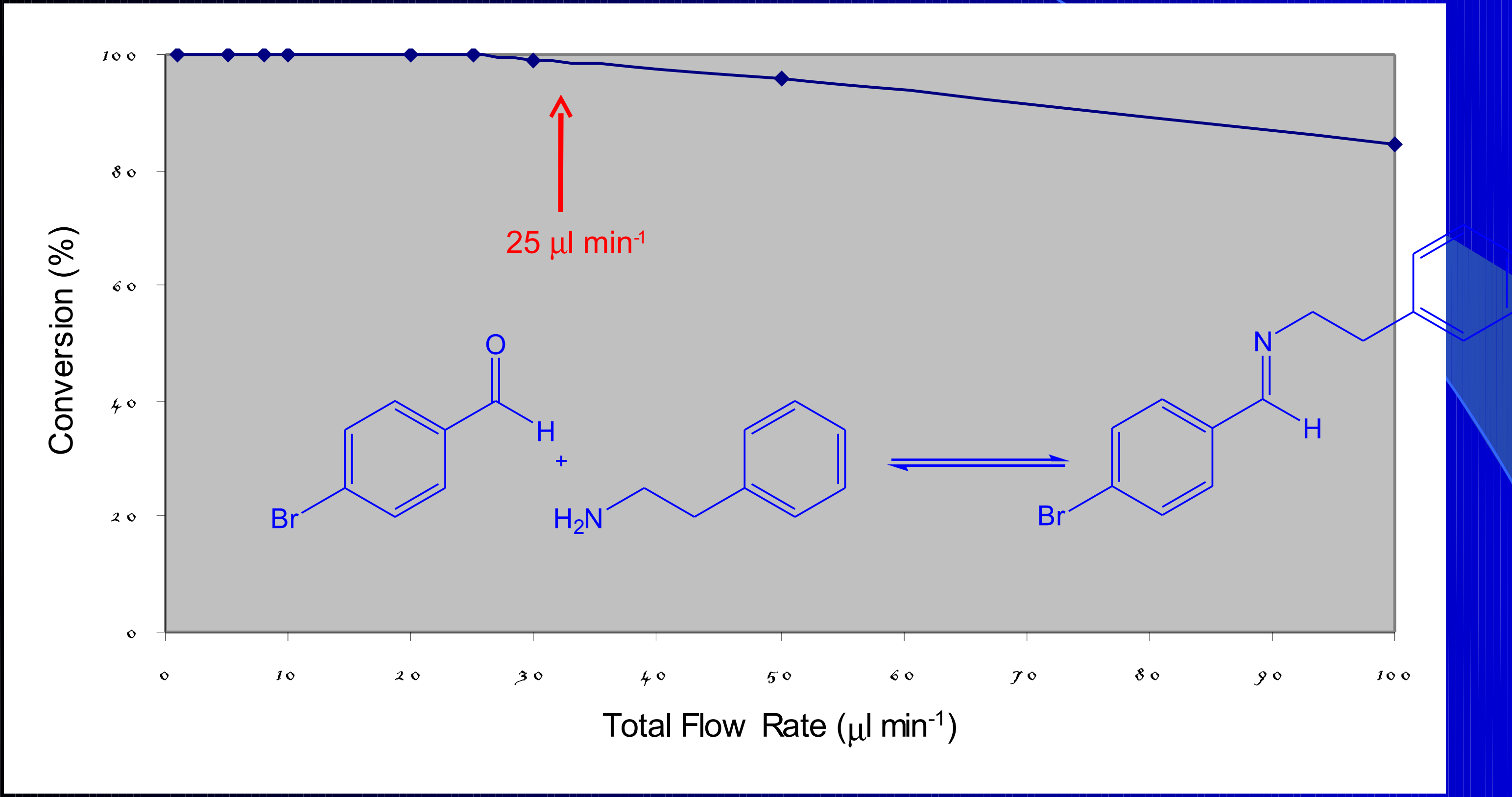
- 0.4 M Stock Solutions in MeCN
- Micro Channel Dimensions = 150 μm (wide) x 50 μm (deep)



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

Optimisation of Imine Formation

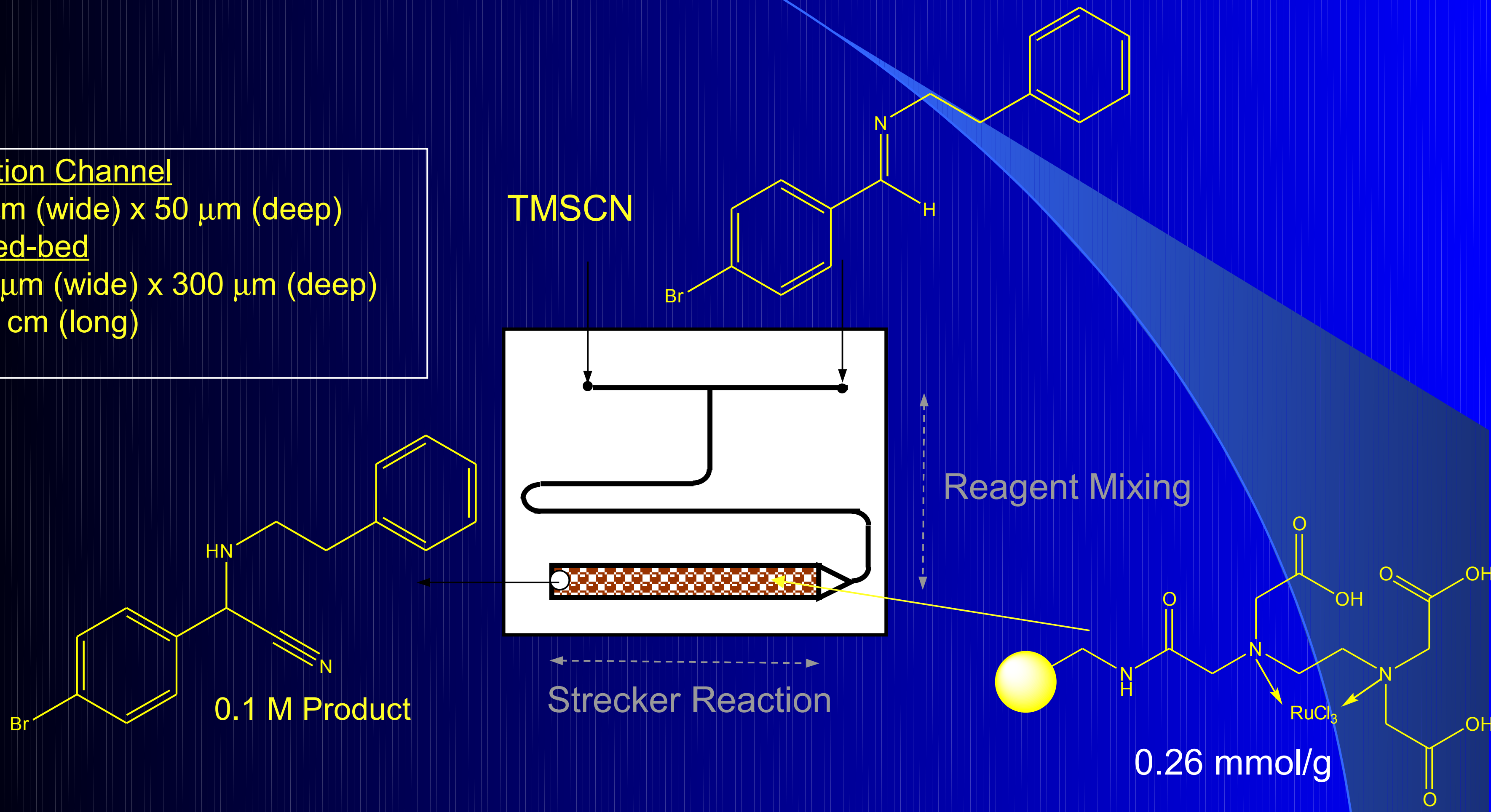
- '*Micro' reactors* allow rapid optimisation of reaction conditions



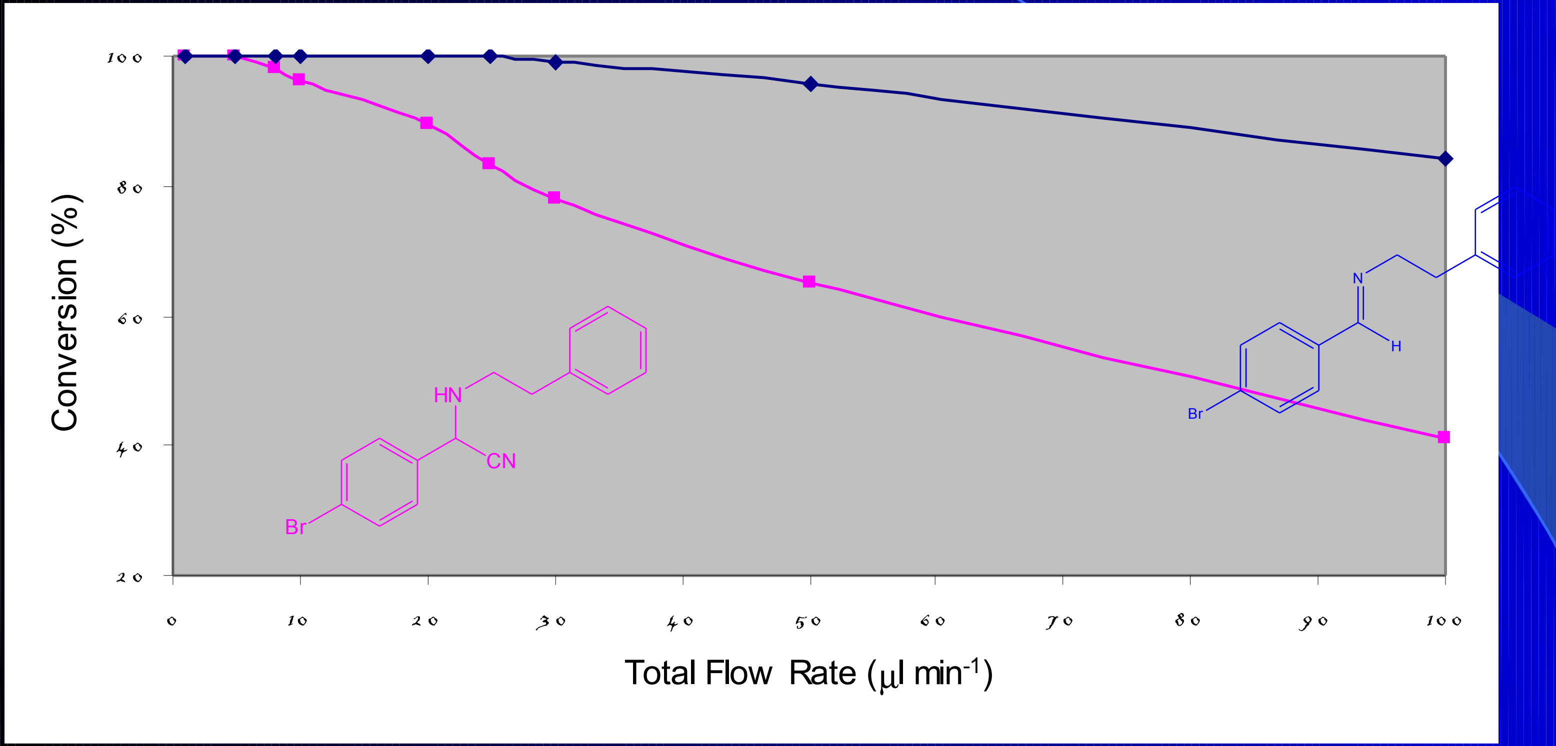
Conversion calculated wrt. residual 4-bromobenzaldehyde

Continuous Flow Addition to Imine

<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)

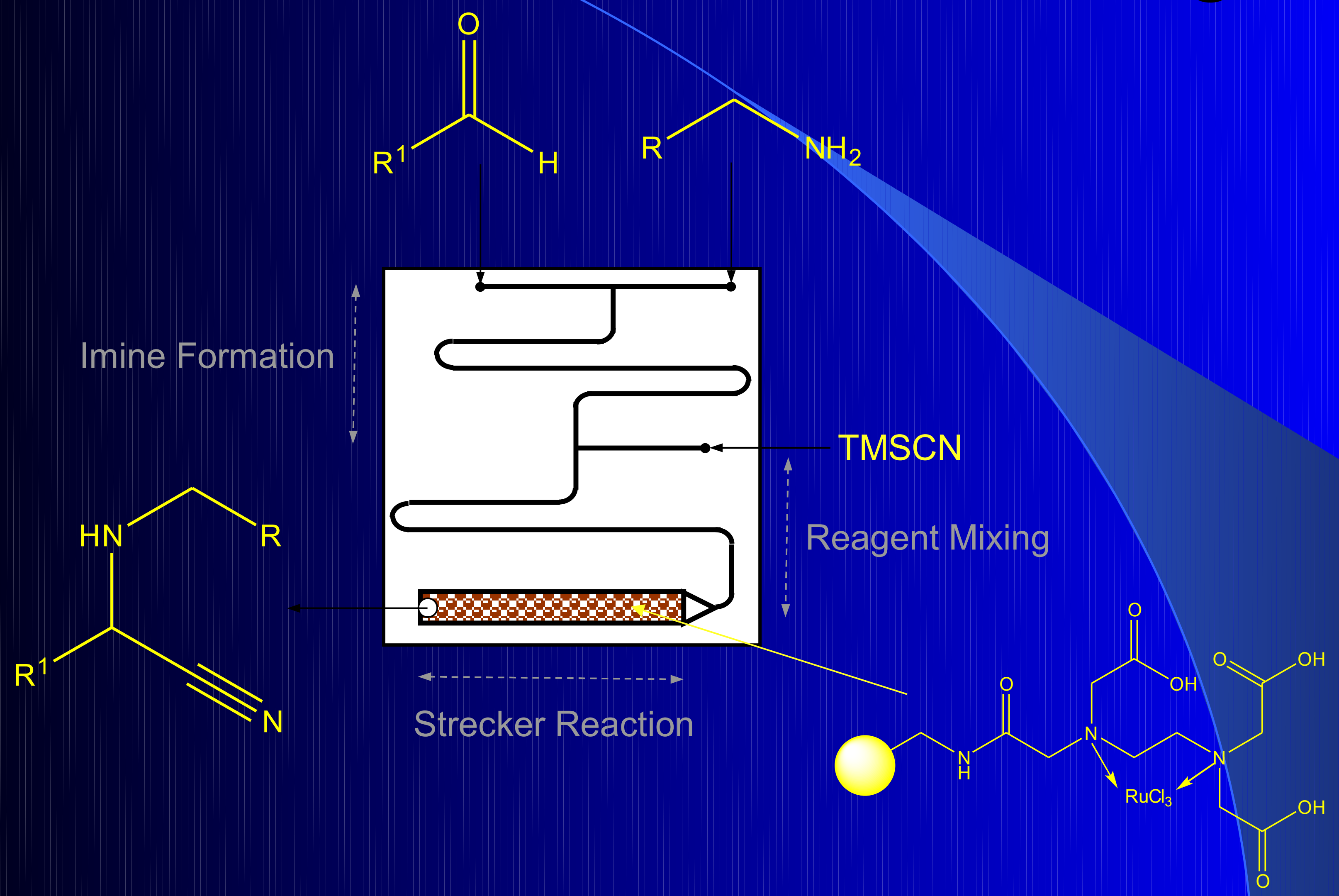


Comparison of Reaction Steps



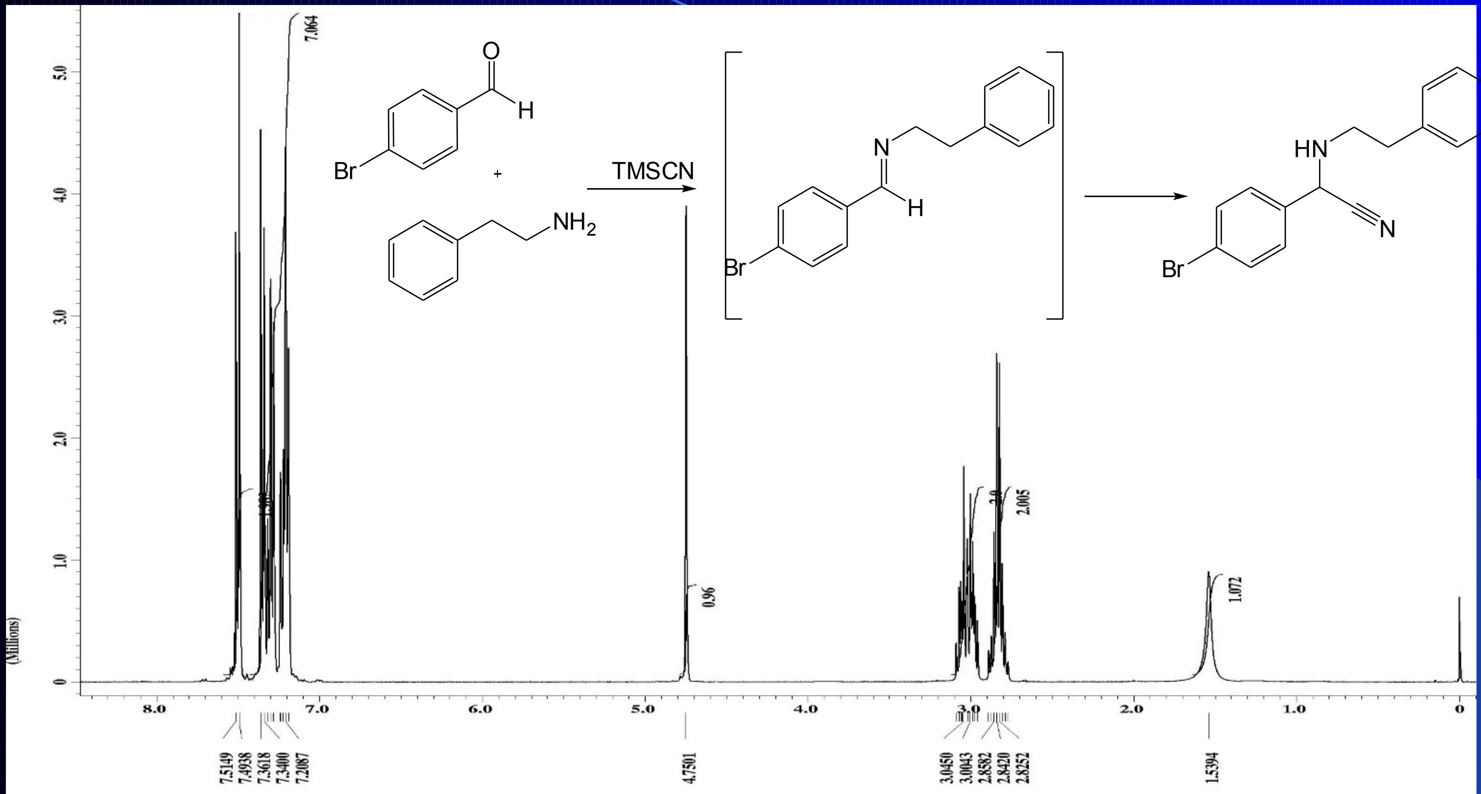
- Optimal conditions for both reactions = Total flow rate < 5.0 μl min-1
  - Conversion calculated wrt. residual imine

Combined Micro Reactor Design



<u>Reaction Conditions:</u> Total flow rate 5.0 µl min-1, 0.4 M aldehyde and amine, 0.2 M TMSCN

Multi-Step Reaction



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

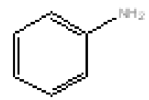
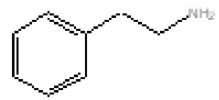
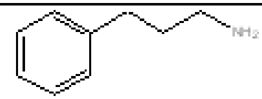
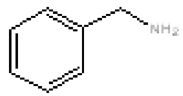
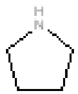
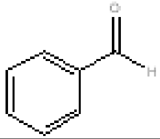
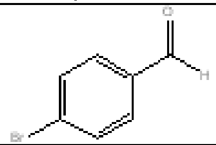
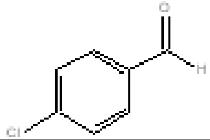
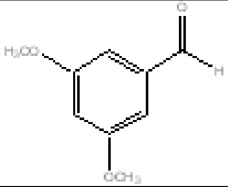
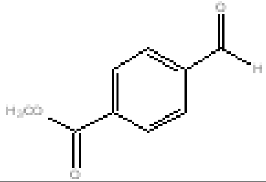
Batch: 64 % Conversion, stirred for 24 hr (1.5 eq. TMSCN)

ICP-MS Analysis:

- Stirred Batch Reaction: 440 ppm Ru
- Micro Reaction: No observable difference from the blank (MeCN)

5 x 5 Array of Products

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*}

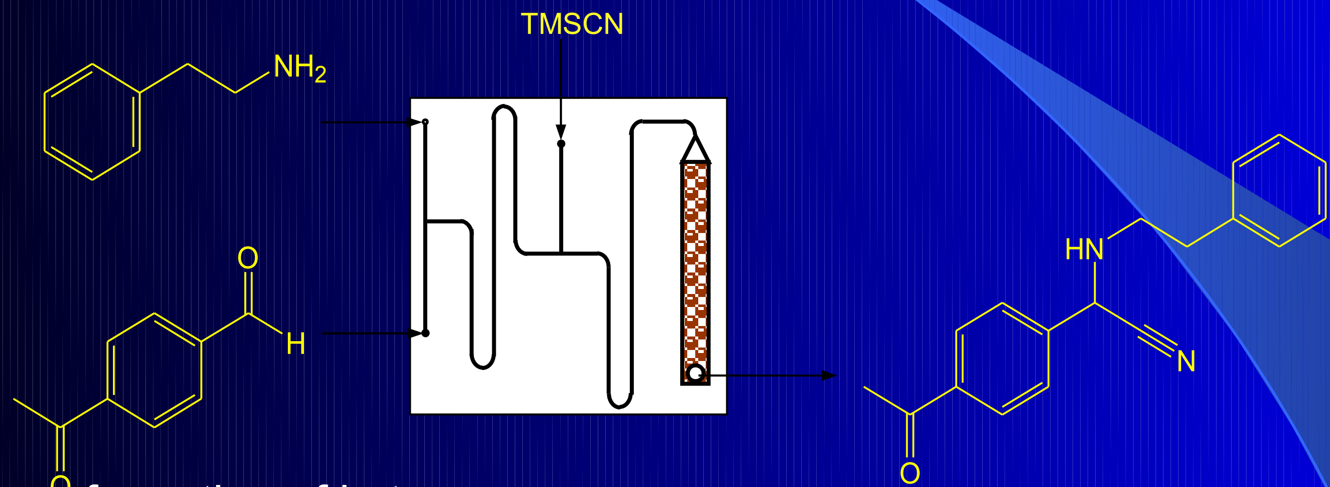
- Librar

OPRD, 2008, **12**, 1001

Eur. J. Org. Chem., 2008, 5597

Reaction of Bifunctional Compounds

- Would ketones react under these conditions?



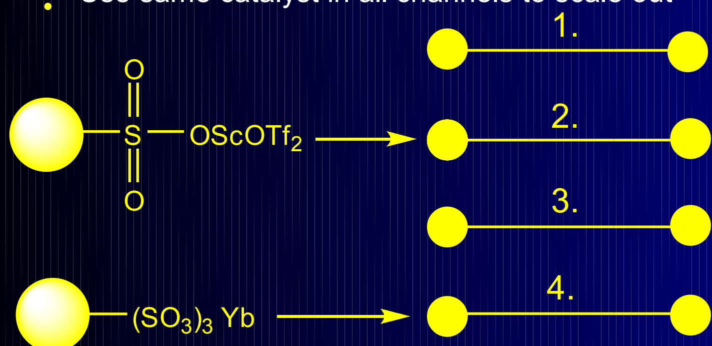
- No trace of reaction of ketone

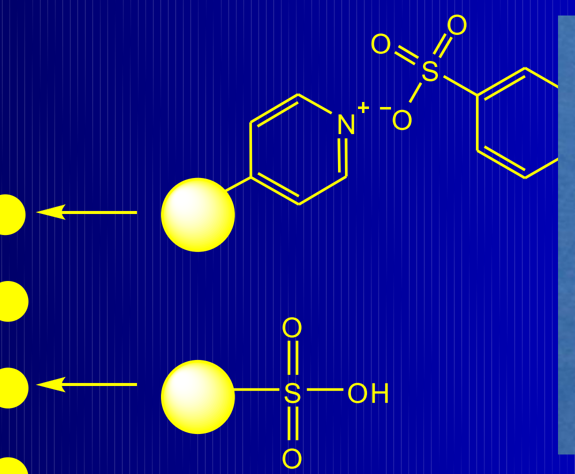
Chemoselective for aldehydes, no reaction of the ketone moiety!!

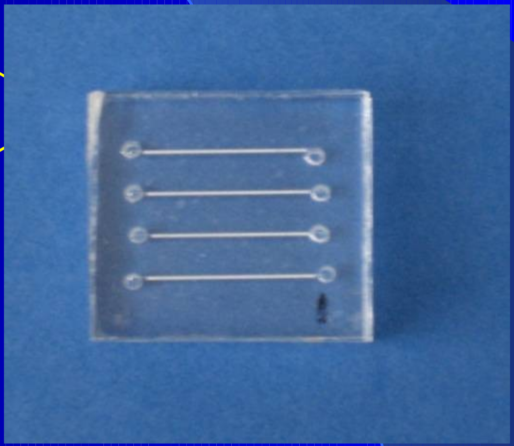
Eur. J. Org. Chem., 2008, 5597

HT Catalyst Screening

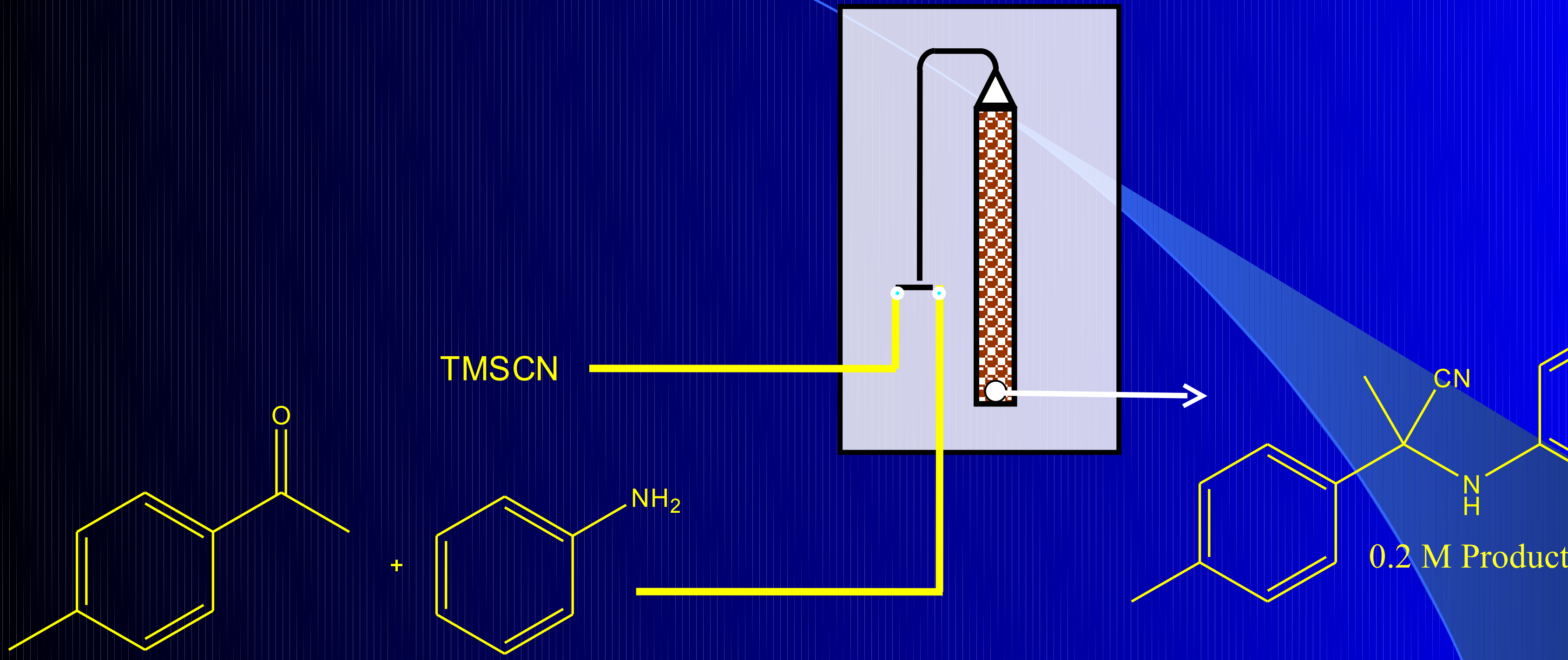
- Catalyst immobilisation techniques:
  - Microencapsulation
  - Ion exchange
  - Covalent immobilisation
- Which catalyst supported material?
  - Must not swell in organic solvents
- Use same catalyst in all channels to scale out







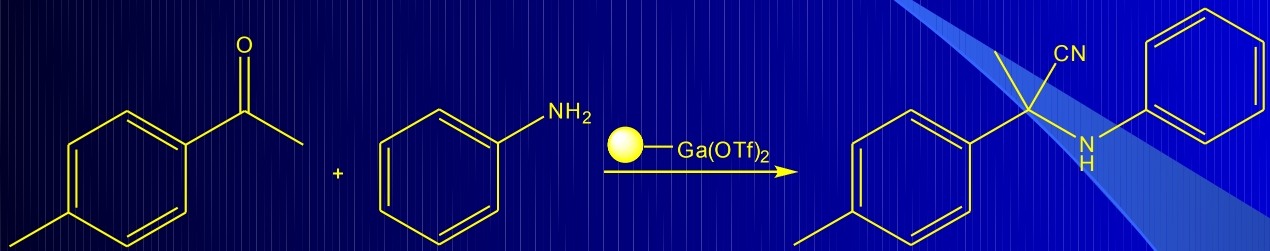
Immobilised $Ga(OTf)_3$ Catalysis



Reaction Conditions

- Packed-bed containing 10 mg of PS-$Ga(OTf)_2$
  - 1.1 x 10^{-2} mmol of Ga
- 0.4 M in DCM stock solutions of all reagents
  - Pressure-driven flow

Evaluation of PS-Ga(OTf)$_2$ by Continuous Flow

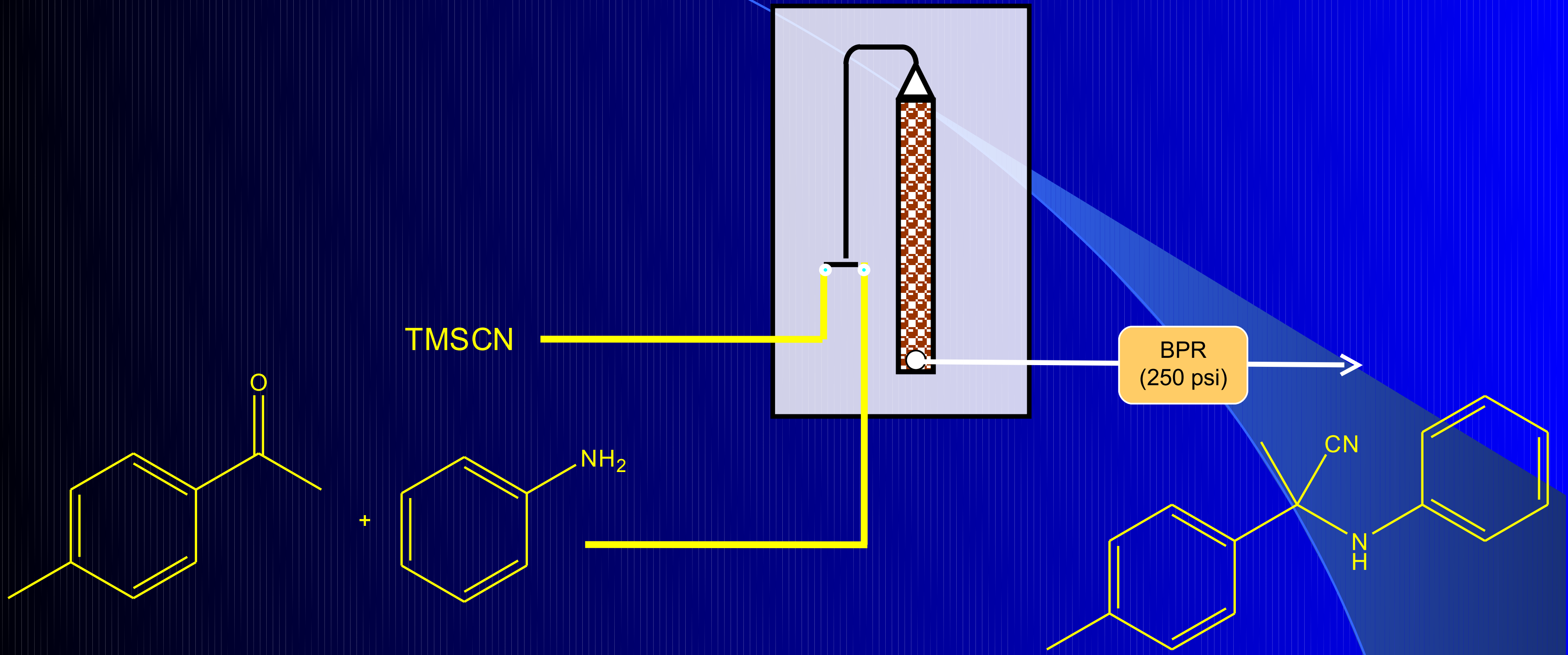


Flow Rate (μl min^{-1})	Conversion (%)	Theoretical Throughput (mg h^{-1})
20	25.6	13.6
10	40.8	10.8
5	52.3	7.0
1	89.1	2.4

Increasing purity
Decreasing productivity

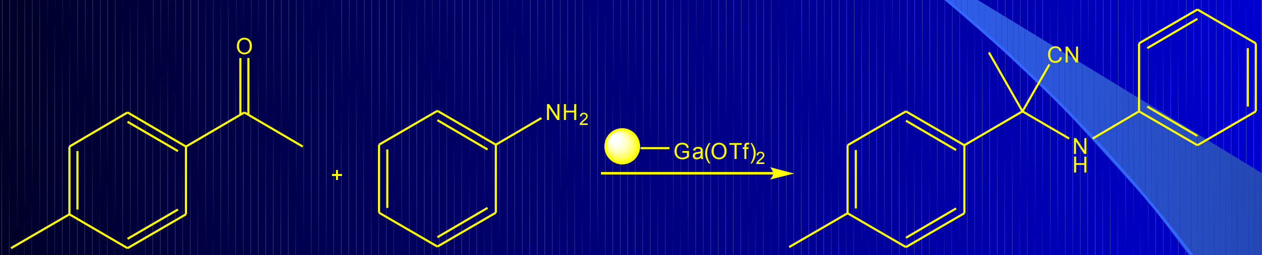
- Reducing the flow rate further to attain quantitative conversion is undesirable, alternatives;
  - Reduce reactant concentration (would also reduce throughput)
  - Increase reaction temperature

Increased Reaction Temperature



- Dry-heated the reactor on an aluminium block using a hotplate
  - Integrated a BPR to prevent boiling of the reaction mixture and solvent
- ICP-MS analysis of reaction products

Effect of Reaction Temperature on Throughput



Flow Rate (µl min^{-1})	Temperature (°C)	Conversion (%)	Theoretical Throughput (mg h^{-1})
20	RT	25.6	14.5
20	30	76.2	43.1
20	40	100.0	56.6
20	50	100.0	56.6

Increasing purity
Increasing productivity

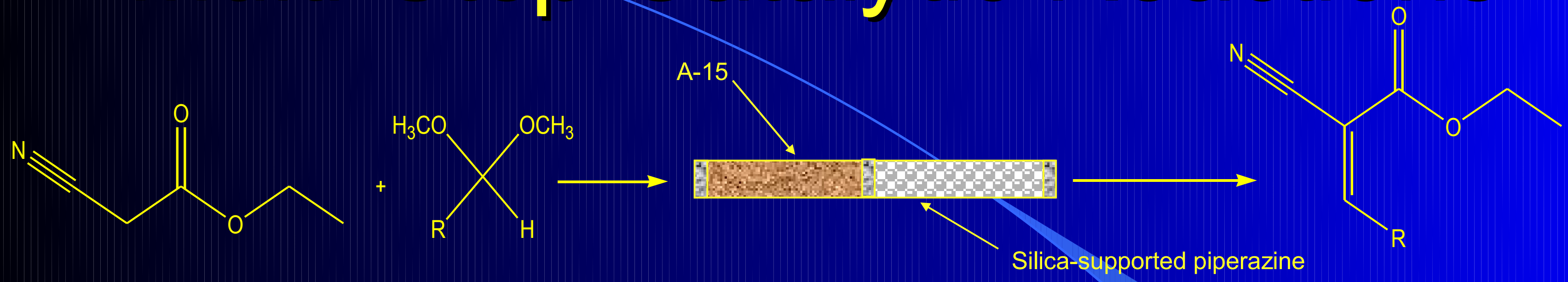
- Elevated reactor temperature = enhanced purity and increased throughput
- Residence time *ca.* 1 min
- No leaching of Ga detected at higher temperatures

Reaction Array of Ketones

- Products isolated in high yield and purity
- Throughputs greater than 50 mg/hr
- Library of 10 compounds prepared (Catalytic turnover > 850)
- Ga also a better catalyst for the aldehydic Strecker reaction

Ke

Multi-Step Catalytic Reactions



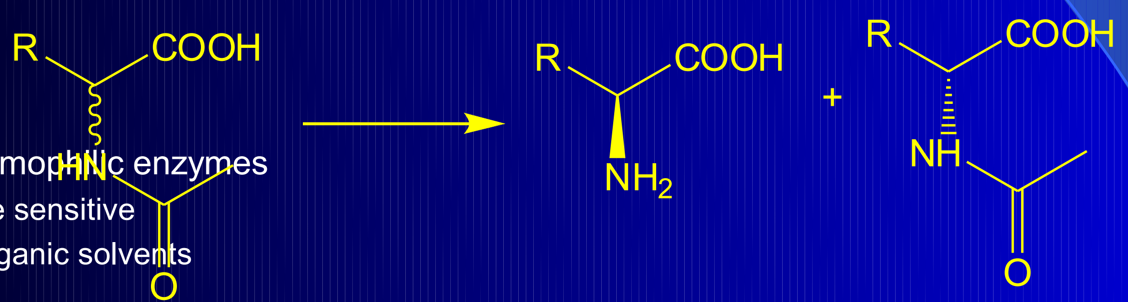
Aldehyde	Conversion (%)	Actual Yield (g)	Yield (%)
Benzaldehyde	99.99	0.0150 g	99.4
4-Bromobenzaldehyde	99.99	0.0338 g	99.8
4-Cyanobenzaldehyde	99.99	0.0284 g	99.7
2-Naphthaldehyde	99.99	0.0298 g	99.8
Methyl-4-formyl benzoate	100.0	0.0253 g	99.7
4-Benzyloxybenzaldehyde	99.99	0.0219 g	99.1
Nitrothiophenecarboxaldehyde	99.99	0.0238 g	99.7
4-Methylbenzaldehyde	99.99	0.0284 g	99.3

- 20 examples

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

Enzyme Reactors: L-Aminoacylase

- Cloned thermophilic enzyme
    - L-Aminoacylase
        - *Thermococcus litoralis*
        - Optimum temperature 85 ºC
        - Hydrolysis of *N*-acylamino acids
        - More importantly chiral resolutions:



N-Acetyl-DL-amino acid

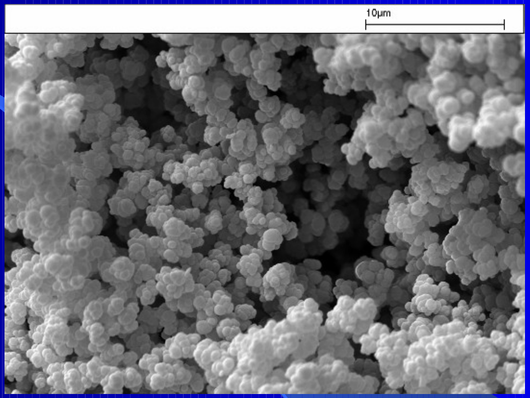
L-Amino Acid

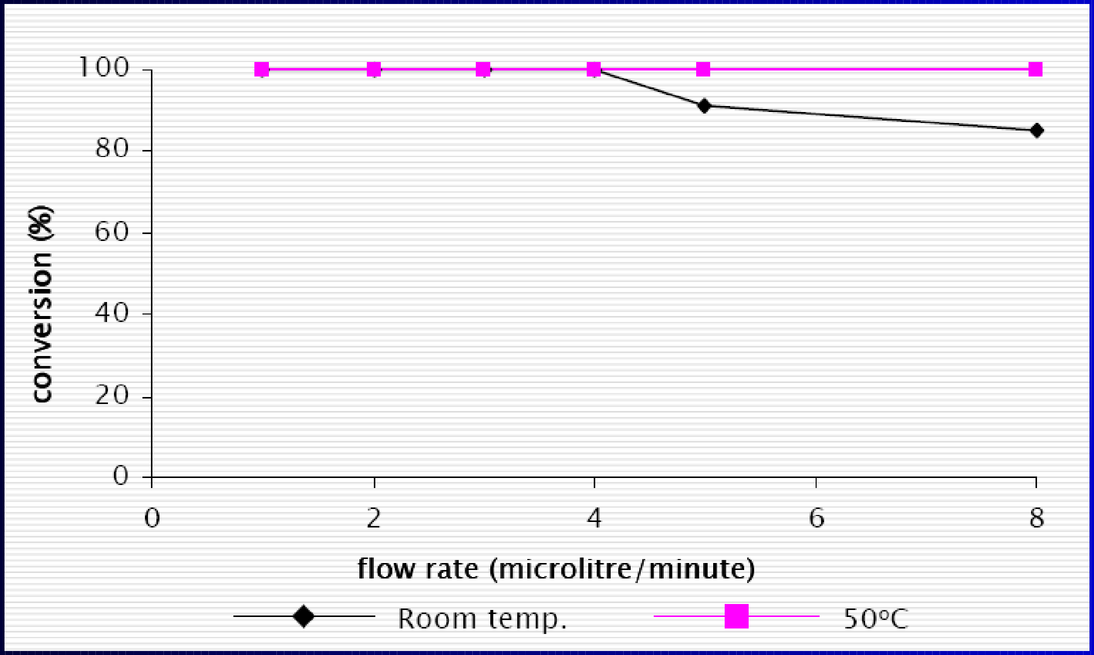
N-Acetyl-D-amino acid

- Advantages of thermophilic enzymes
    - Less temperature sensitive
    - More stable in organic solvents
    - Longer lasting

Effect of Flow Rate on Conversion

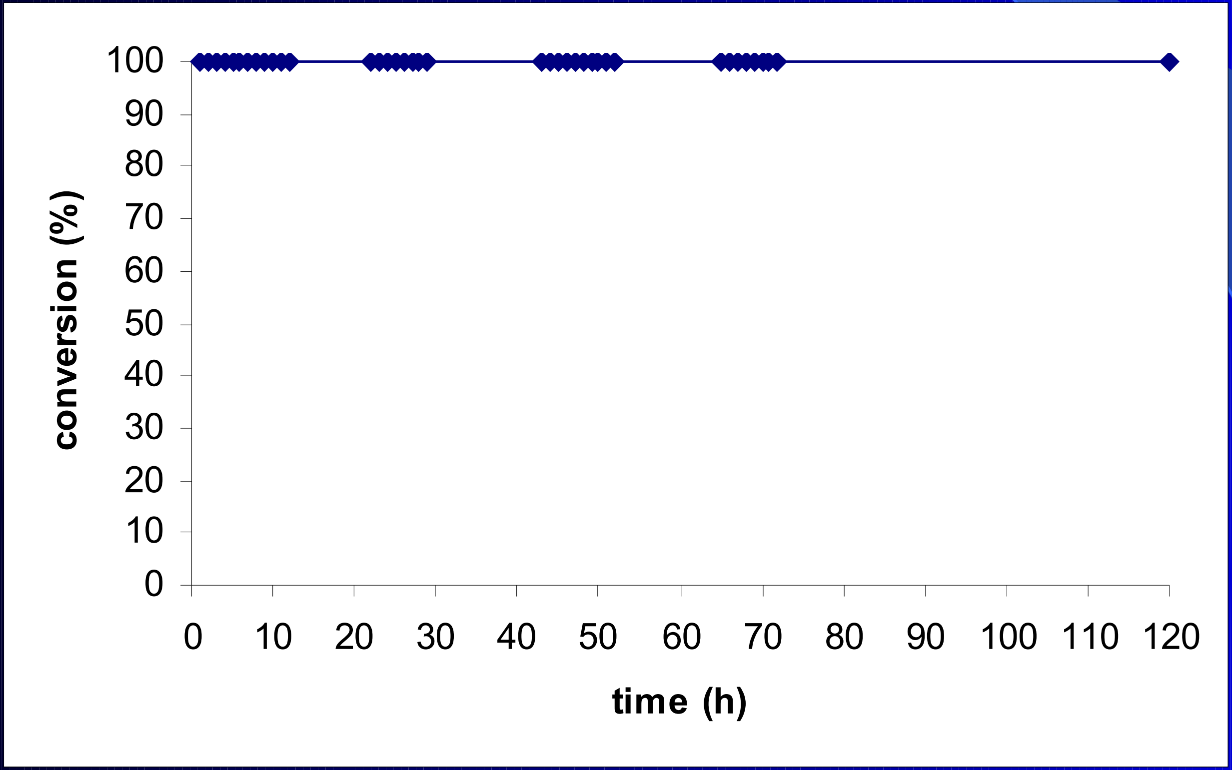
- Immobilisation of enzyme onto monolith
  - Flow rate 1 μl min^{-1}, 3 hr, RT
- Reaction conditions
  - Room temperature and 50 ^{o}C
  - 10 mmol/L benzoyl-L-phenylalanine in TRIS buffer





Enzyme Stability

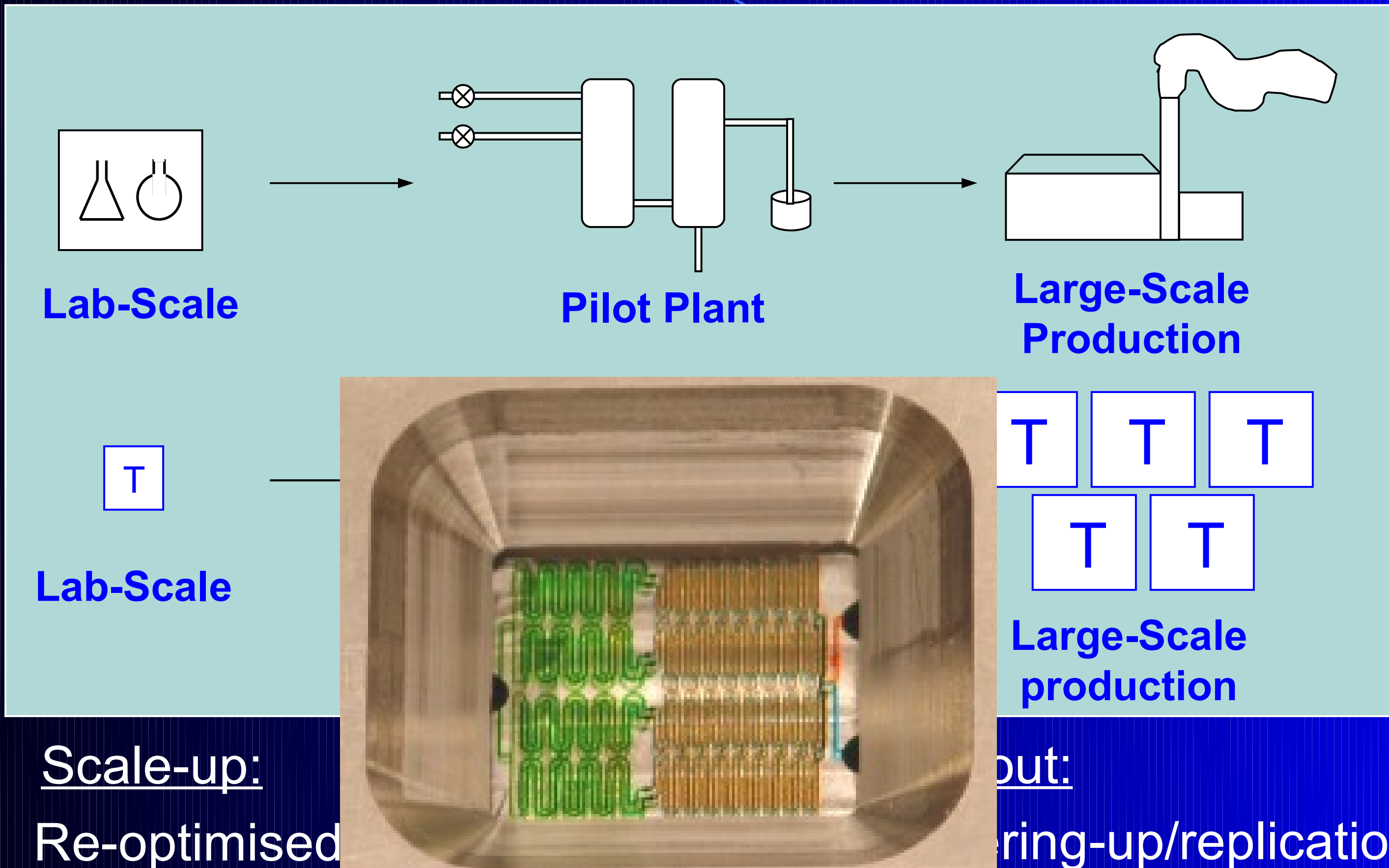
- Experimental conditions
  - Temperature 50 °C
  - 10 mmol/L benzoyl-L-phenylalanine in buffer
  - Flow rate 1 μl/min



Substrate Screening

Amino acids	Substrate conversion (%)
N-Benzoyl-L-phenylalanine	100.0
N-Benzoyl-D,L-phenylalanine	50.0
N-Acetyl-L-phenylalanine	100.0
N-Chloroacetyl-L-phenylalanine	100.0
N-Benzoyl-L-threonine	68.3
N-Benzoyl-L-leucine	52.2
N-Acetyl-L-tyrosine	33.3
N-Acetyl-L-tryptophan	7.0

Production Technology



Scale-up:

Re-optimised

Costly and time consuming

out:

ering-up/replication

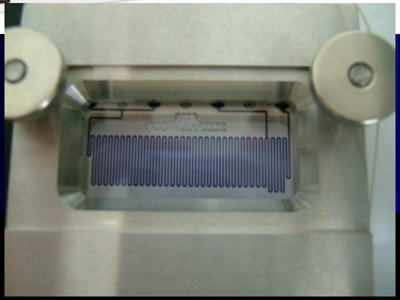
Cost effective and flexible

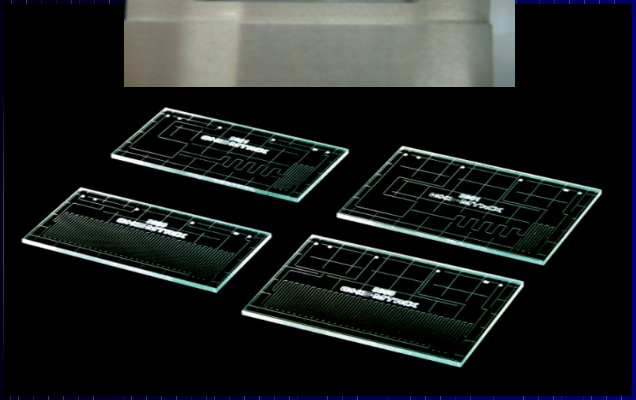
Requires reproducibility within single reactors

Chem. Commun., 2007, 443

Labtrix

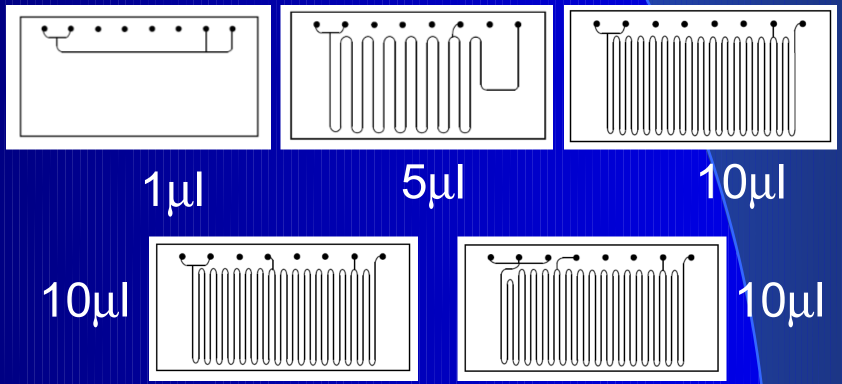
- Reaction optimisation and small scale synthesis





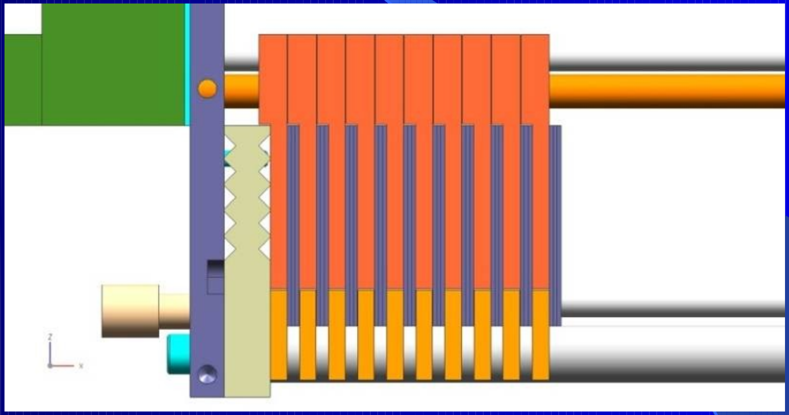
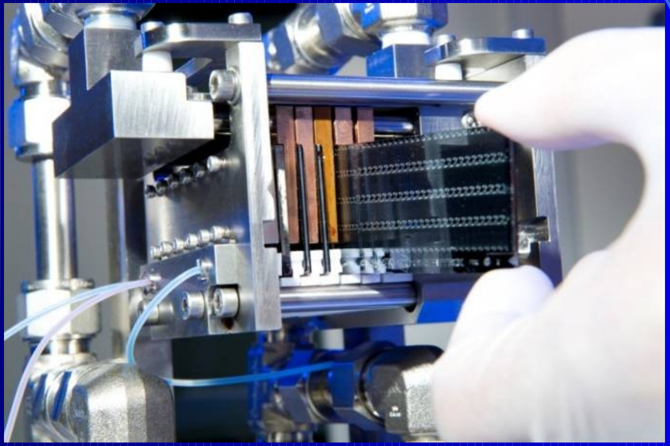
<u>Features</u>

- Syringe pumps
- Automated sample collection and control (flow, temperature)
- Tests at pressures of 20 bar and temperatures of -20 to 200°C
- Standard interchangeable chips delivered with product, multi-input.



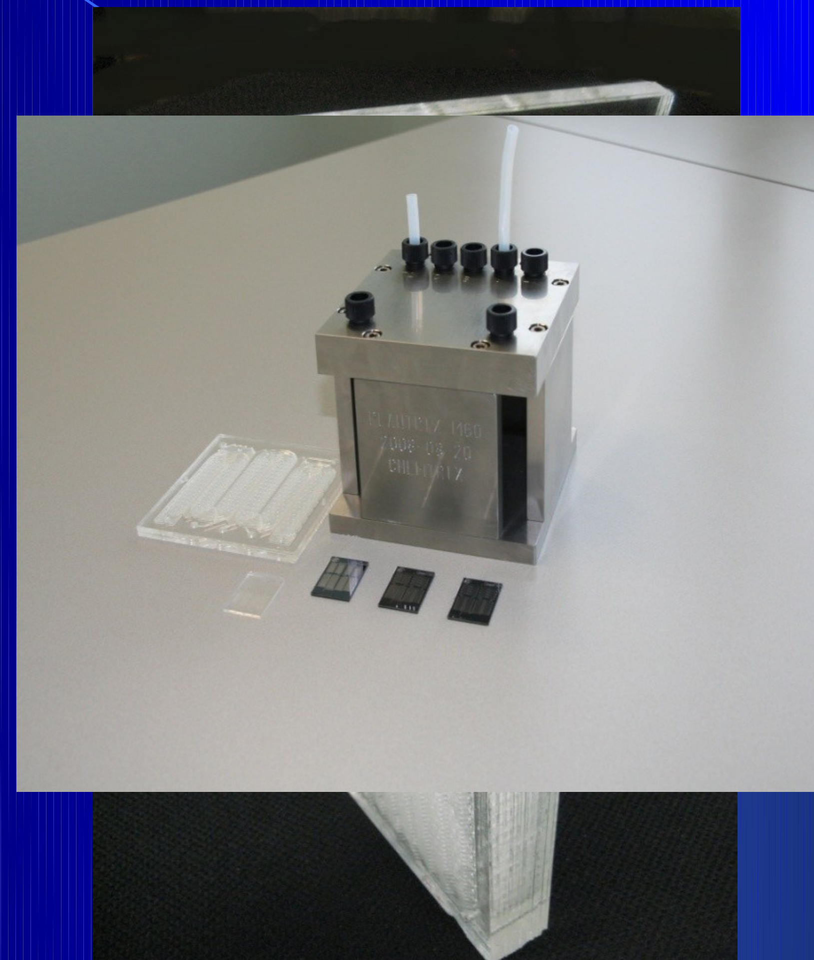
Protrix Technology

- Medium scale production *via* parallelisation
- Fast capacity increase without upscaling
  - Collaboration with TNO

Large Scale Production - Plantrix

- What are the limits of parallelisation?
  - 20 Tonne production P/A need several million chips!!
- Channel dimensions must be bigger
- 6 layer chip
  - 2 reactor layers
  - 2 heat transfer layers
  - 5 ml reactor volume
- 20 layer chip
  - 9 reactor and heat transfer layers
  - 22 ml reactor volume



Conclusions

- Micro reactors allow the rapid optimisation of reactions
  - Rapid process development
  - High-throughput synthesis
- Immobilised catalysts allow the synthesis of highly pure compounds
  - Support material very important
  - Only small quantities of catalyst needed
  - Minimal catalyst leaching (Ru, Sc and Ga)
- Micro reactors generate products in:
  - Higher purity
  - Higher conversion
  - Higher selectivity
- Equipment for scale-up being developed

Chem. Commun., 2007, 443-467

Research Workers and Collaborators

- Current group members
- Dr. Charlotte Wiles
- Dr. Bongkot Ngamsom
- Dr. Joe Dragavon
- Dr. Vicki Hammond
- Gareth Wild
- Tamsila Nayyar
- Julian Hooper
- Linda Woodcock
- Haider Al-Lawati
- Ben Wahab

- Past group members
- Dr. Nikzad Nikbin
- Dr. Ping He
- Dr. Victoria Ryabova
- Dr. Vinod George
- Dr. Leanne Marle
- Mairead Kelly

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- Astra Zeneca
- EU FP6
- Yorkshire Concept