CHEMTRIX

Flow Reactor Technology

A Flexible Tool for Reaction Optimisation & Chemical Production

Dr Charlotte Wiles

RSC – Practical Continuous Flow Technology
Munich, Germany

June 2013

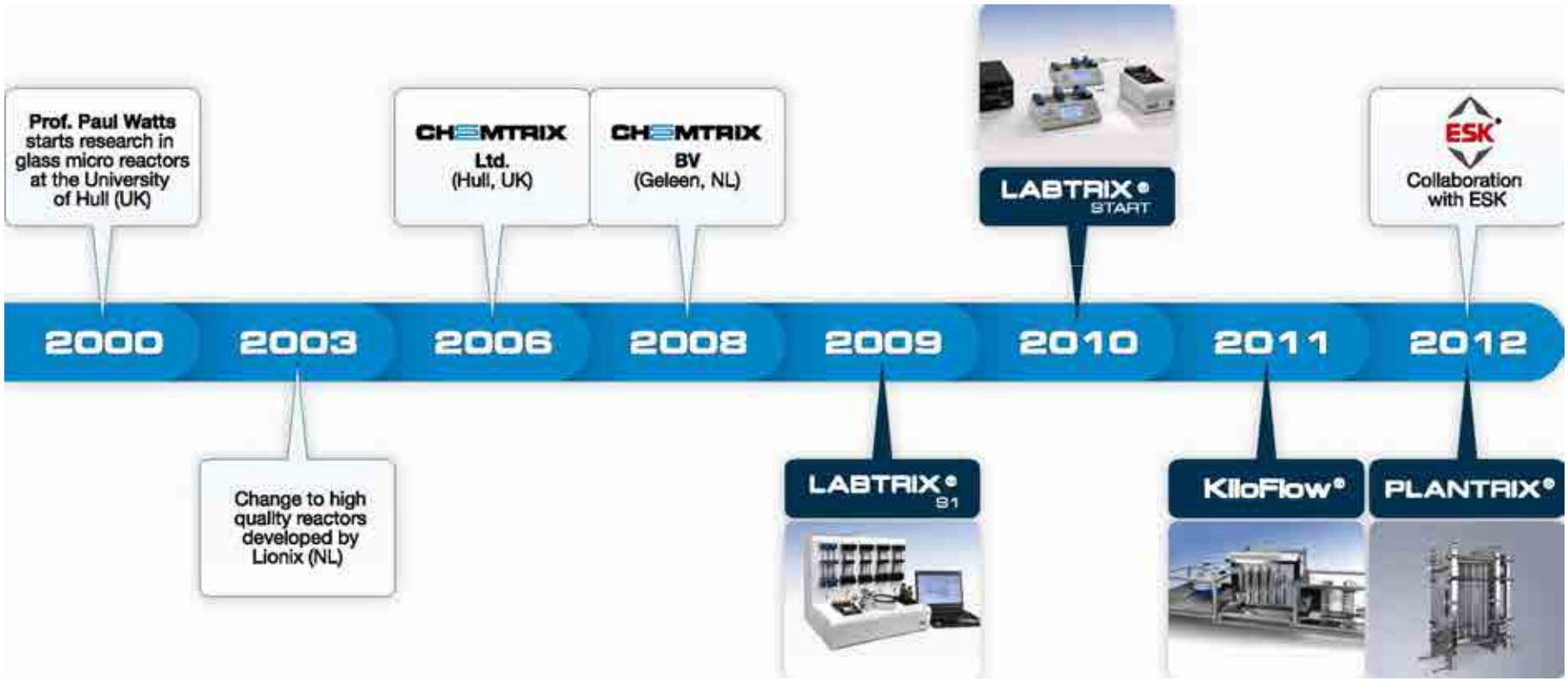
Strategic Partner of ESK

Presentation Overview

1. Introduction to Chemtrix & Flow Chemistry
2. Products at the Lab Scale
   - Applications of the Technology
   - 13,000 x Scale-up
3. Products for Production Scale
   - Customer Examples of Flow Chemistry in Production
4. Summary

Strategic Partner of ESK

Chemtrix Company History



More than 12 years experience in Flow Chemistry

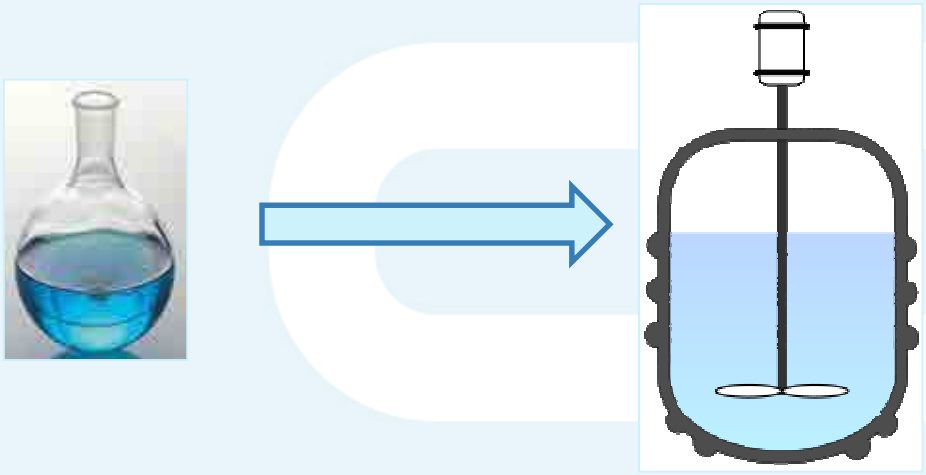
Conventional Synthetic Methodology:
Challenges and Limitations

CHEMTRIX

- If we look to how synthetic chemistry has been taught and performed, little has changed over the past century, with all chemists being familiar with **standard glassware** and equipment

Batch Reactions:

- In batch reactions parameters such as time, temperature, stoichiometry, order of addition and solvent are investigated with the aim of increasing yield and product purity
- If more product is required then a **larger vessel** is normally employed



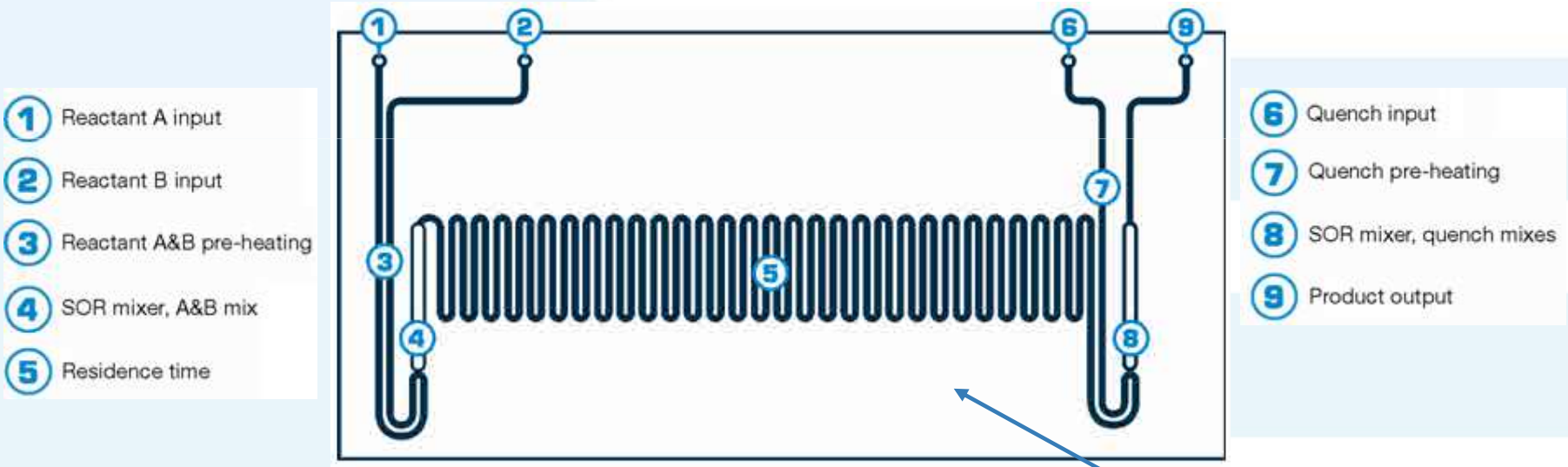
- Changes in **surface to volume ratio** mean that differences in thermal and mass transfer occur and reactions often need to be re-optimised

Fundamentals of Flow Chemistry:
How are Flow Reactions Performed?

CHEMTRIX

Solutions of reagents are pumped into a reactor, where they are;

- Heated or cooled ahead of mixing
- Reacted for specified period of time - based on volume of reactor & flow rate



- Quenched *in-situ* (where needed)
  - To stabilise product & prevent decomposition
- Collected for batch isolation & purification (where needed)

Chemtrix deliver glass or SiC flow reactors

Innovative Technology:
Scalability & System Flexibility at all Stages

CHEMTRIX

DISCOVERY

Labtrix® (µg to mg's)

-20 to 195 ºC

- Rapid reactions
- Efficient evaluation
- mg consumption
- Parameter accuracy
- New chemical entities

DEVELOPMENT

KiloFlow® (g to kg's)

-15 to 150 ºC

- Rapid up-scaling
- Process validation
- kg Production in a lab
- New process windows
- Flexible production

PRODUCTION

Plantrix® (kg to ton's)

-30 to 200 ºC

- Facile up-scaling
- Forbidden chemistry
- Safe production
- High quality products
- Cost effective

Labtrix®:
Flow Chemistry Method Development

CHEMTRIX

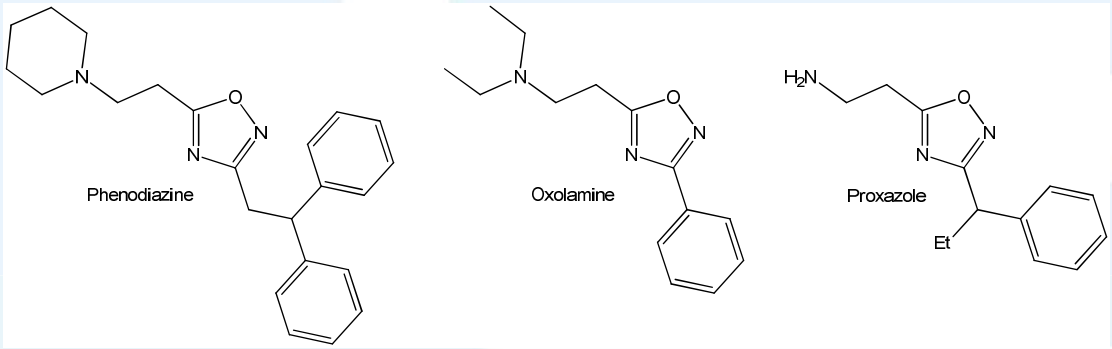
- Increased safety
- Generate reliable & reproducible data
- Access to new chemical possibilities
- Fast method development
- Minimal use of raw materials
- High flexibility
- Easy to use
- Scalable flow chemistry methods

Rapid Reaction Optimisation using Labtrix®:

Design of Experiment

CHEMTRIX

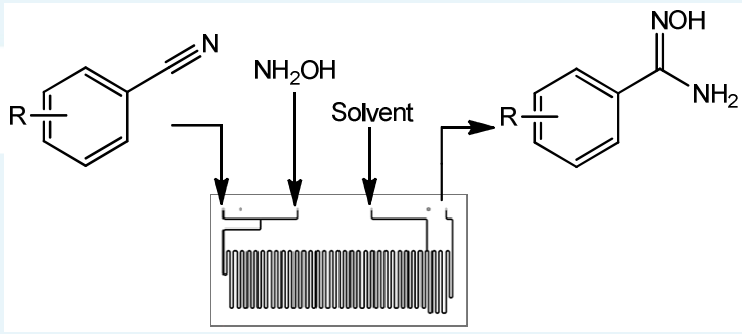
Sanofi (Budapest) with Budapest University of Technology & Economics employed Labtrix®-S1 to develop a process for the large-scale synthesis of amidoximes



Due to the hazards associated with the use of hydroxylamine, a 'safety concerned reagent', a metal-free system was required

To reduce the time taken to optimise the reaction conditions, the authors employed Design of Experiment (DoE) using three factors;

1. Reactor temperature (75-125 ºC)
2. Hydroxylamine equiv. (1-7)
3. Residence time (1 to 9 min)



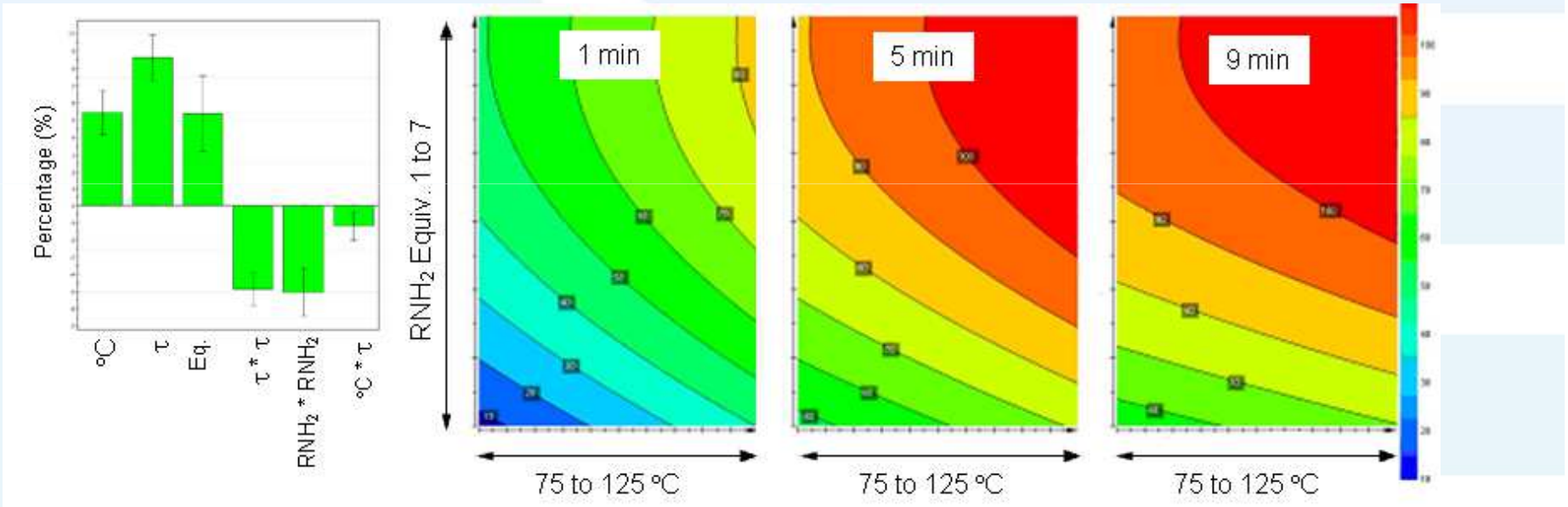
Rapid Reaction Optimisation using Labtrix®:

Design of Experiment

CHEMTRIX

Performing flow experiments, defined by the DoE (MODDE 9.0) software, within the automated micro reactor platform, Labtrix®-S1 (Figure 1) gave;

- Co-efficient & contour plots

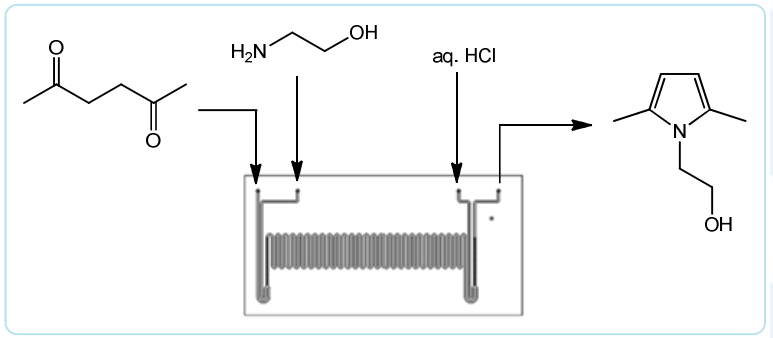


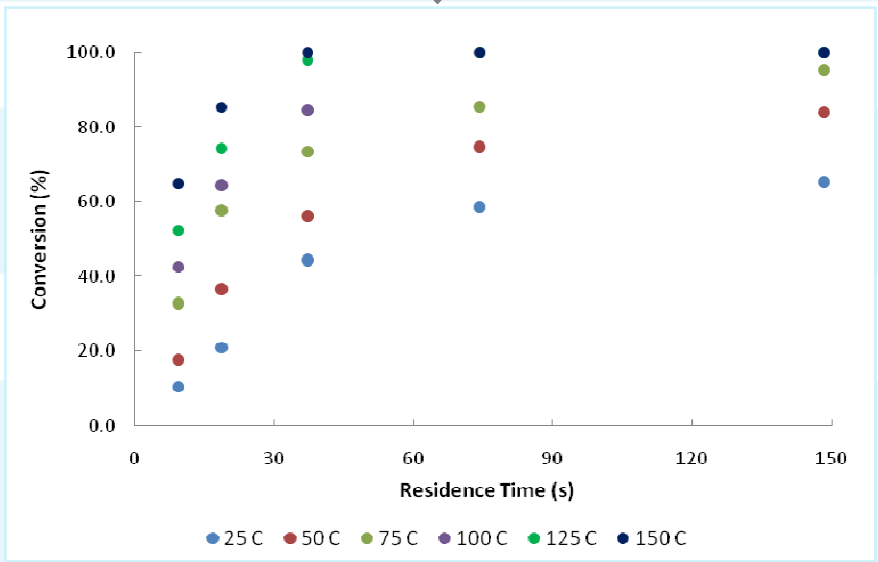
- High temperature (125 ºC) & moderate hydroxylamine **1** excess (4.0 equiv.)
- Moderate temperature (100 ºC) & large excess of hydroxylamine **1** (7.0 equiv.)

→ Using this information, the reaction was scaled x450 to prepare the aldoxime

Org. Proc. Res. Dev., **2012**, *16* (11), 1717–1726.

Extraction of Kinetic Data using Labtrix®





Plot kinetic curves

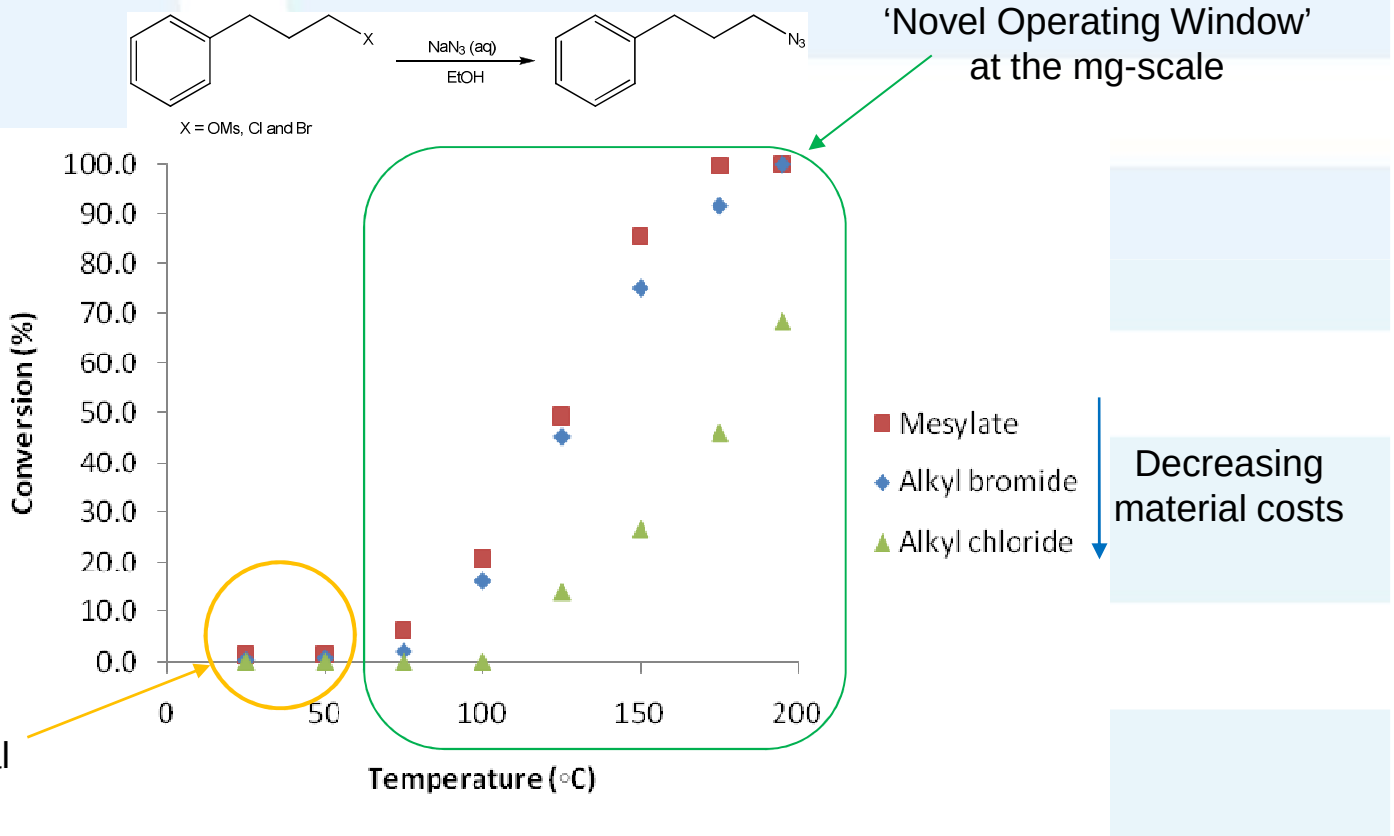
Determine reaction order and rate constant

Throughput at 418 mg h^{-1} (10 µl reactor)

Continuous Azidation using Labtrix®:
Manipulation and Formation of Hazardous Materials

CHEMTRIX

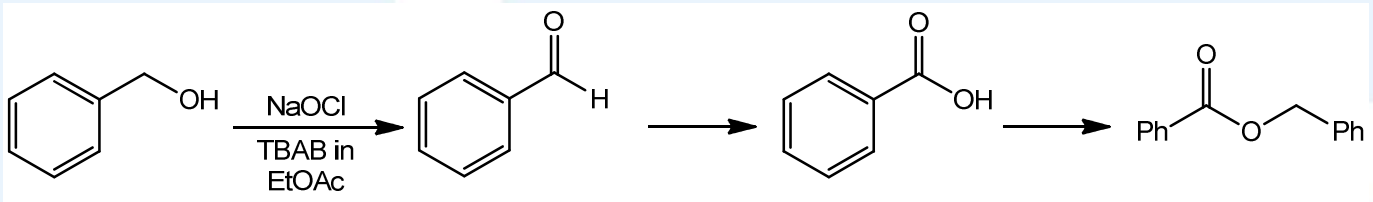
- Employing 0.66 M (EtOH) alkyl precursor and 0.66 M (50:50 aq. EtOH) NaN_3, the effect of temperature on the reaction was investigated at a residence time of 30 s



  - Using OMs derivative, azide obtained at a throughput of 79 mg h^{-1} @195 ◦C

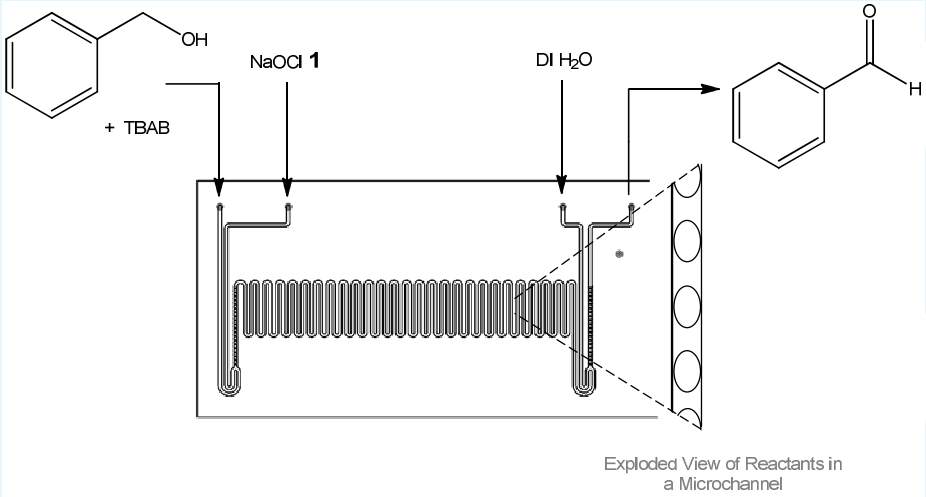
Selective Oxidation of 1º Alcohols in Labtrix® Flex: Sodium Hypochlorite

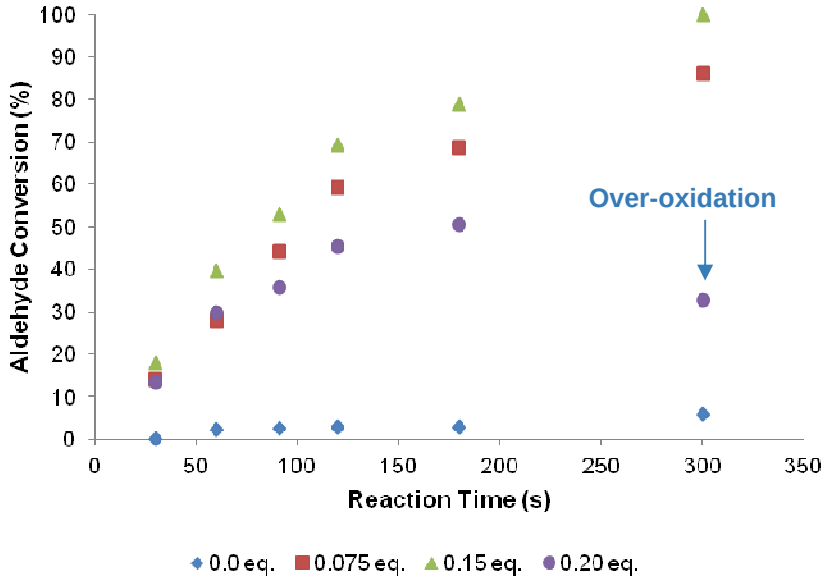
Whilst the oxidation of 1º alcohols is a fundamental transformation, concomitant over-oxidation is problematic in batch



Reaction Conditions:

- Alcohol (0.82 M) in EtOAc and NaOCl (13 wt %)





- 0.15 eq. TBAB optimal phase transfer catalyst
  - @ 50 ºC Throughput = 17.2 mg h^{-1}

KiloFlow®

The Turn-key Kilolab in your Fumehood

CHEMTRIX

- Scalability
- Increased safety
- Efficient & flexible production
- Turnkey system with small footprint
- Different levels of process control

Facile Up-scaling from Labtrix® to KiloFlow®:
No Re-optimisation Required

CHEMTRIX

KiloFlow® is a modular, **scalable** flow reactor system that can support up to **Phase 3**

- Giving you access to a **pilot plant** within a standard laboratory fume hood

KiloFlow® Product Portfolio has a;

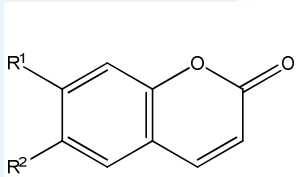
- Large working range
  - **-15 to 150 ºC**
- Flexible production volume of
  - 0.012-6.0 l h^{-1} (up to **140 l day^{-1}**)
- Small footprint
- Glass meso reactors
  - Low pressure drop & efficient mixing allows method transfer from Labtrix®

	Specific Area S/V (m^2/m^3)	Global Heat Transfer Coefficient U ($W.m^2.K$)	U x (S/V) ($kW/m^3.K$)
KiloFlow® Heat Exchange (water/Kryo, 1.70 m/s)	4081	800	3265

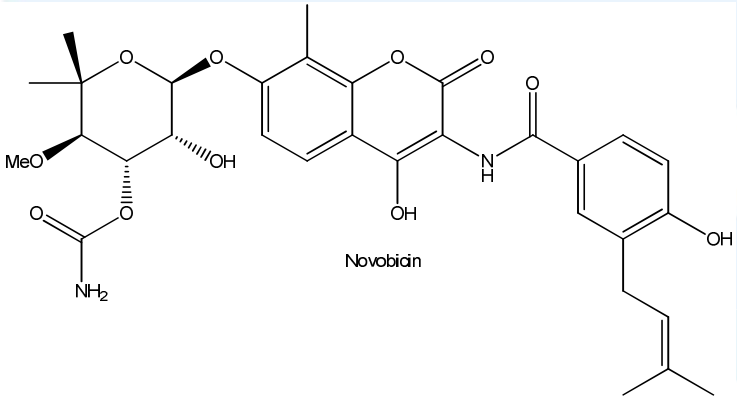
Production using KiloFlow® Basic:
Synthesis of 1-(2-Methyl-2*H*-chromen-3-yl)ethanone

CHEMTRIX

Finding application in the pharmaceutical, agrochemical & flavours/fragrance sectors, coumarins are of significant interest to researchers



R^1/R^2 = H; Coumarin
R^1 = OH, R^2 = H; Umbelliferone
R^1 = OH,R^2 = OH; Esculetin
R^1 = OH, R^2 = OMe; Scopoletin

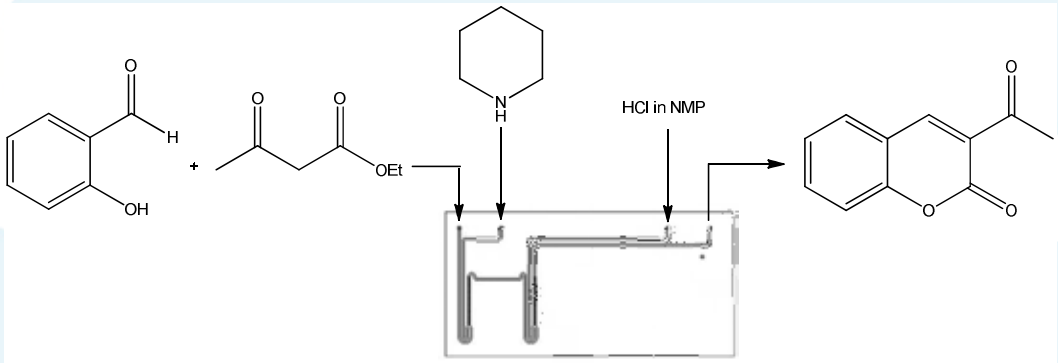


Novobicin

Using the condensation of salicylaldehyde and ethyl acetoacetate in the presence of an organic base, the synthesis of 3-acetylcoumarin was optimised in Labtrix®

<u>Optimal Conditions:</u>

- 60 s reaction time
- 125 C reactor temperature
- 0.4 eq. piperidine
- MeCN reaction solvent

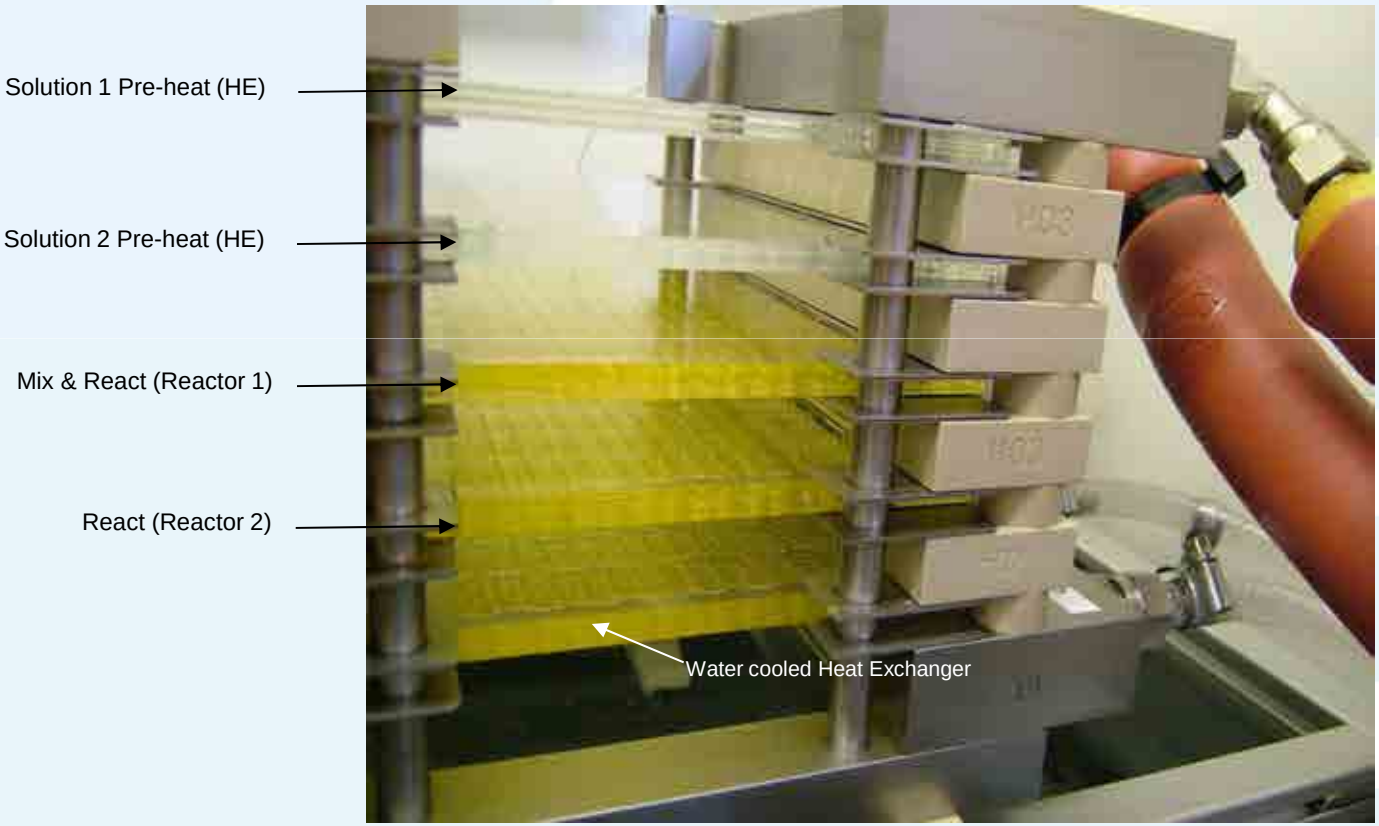


1 µl Reactor volume (3221) consumed 5.4 mg h^{-1}

Production using KiloFlow® Basic:
Synthesis of 1-(2-Methyl-2*H*-chromen-3-yl)ethanone

CHEMTRIX

Translating the optimal conditions to KiloFlow® Basic (Reactor Volume = 13 ml)



Operating for 5.2 h, **369.6 g** of 1-(2-methyl-2*H*-chromen-3-yl)ethanone was obtained

- After aq. extraction (98.2 % yield)

Production using KiloFlow® Basic:
Synthesis of 1-(2-Methyl-2*H*-chromen-3-yl)ethanone

CHEMTRIX

13,000 x scale-up without;

- Parameter re-optimisation
- Change in product quality

Turn-key Flow Platform for;

- mg-scale optimisation to Kg production

Production using KiloFlow® Basic:
Synthesis of *N*-(4-Phenylthiazol-2-yl)acetamide

The following conditions were selected for application in KiloFlow® Basic;

- 1.0 M (1:1) in NMP/MeOH, 40 s at 75 ºC → With no quench

- Operating for 8.5 h, 10 litres reaction mixture processed
- Product isolated by precipitation

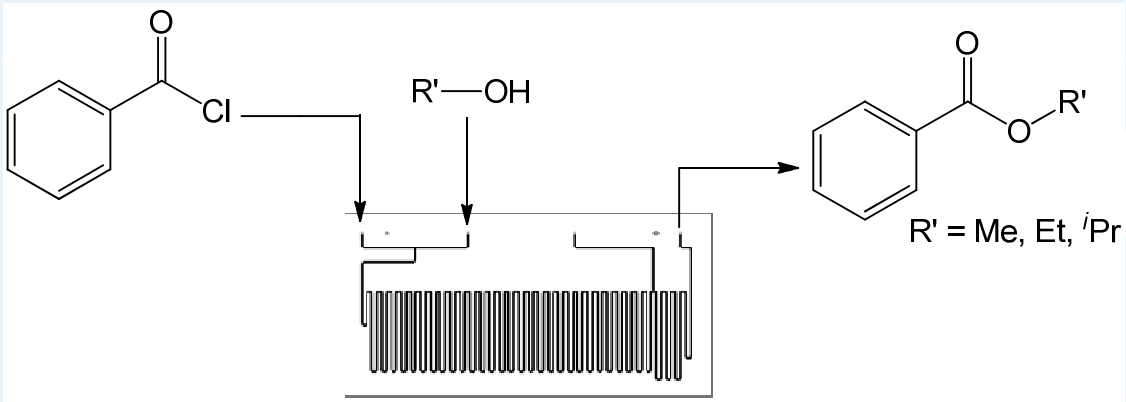
→ **1.08 kg** *N*-(phenylthiazol-2-yl)acetamide (**127 g/h**)

Production using KiloFlow® Basic:
Amidation Reactions using Acid Chlorides

Finding application in the fine chemical industry as flavours & fragrances or as protecting groups in the pharmaceutical industry, esters are important compounds

Investigating their direct formation from acid chlorides, Stevens and co-workers [1] at the University of Gent developed an efficient method of ester production

Optimised in Labtrix® (10 µl), transferred to KiloFlow® (13.8 ml) for material production



The following conditions were selected for application in KiloFlow® Basic;

- Neat benzoyl chloride & MeOH at 100 °C (300 s)

→ Operating for 4 h, **528 g** methyl benzoate (**2.2 g min^{-1}**) produced

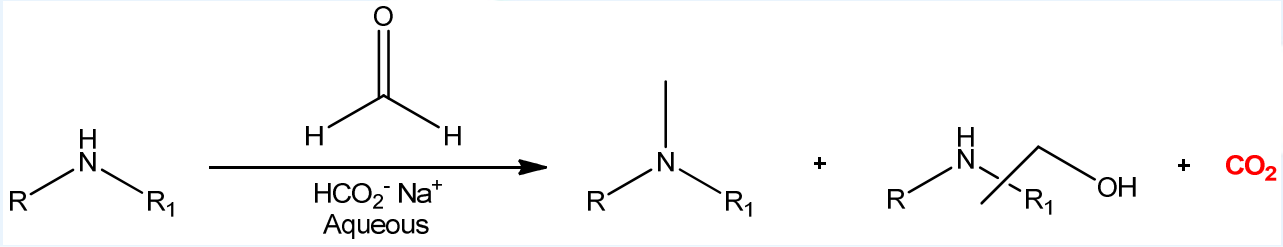
- Product isolated by removal of excess MeOH

[1] Stevens *et al. Green Chem.*, 2012, **14**, 2776.

Customer Appraisal of KiloFlow®:
Janssen Pharmaceutica NV & Iolitec GmbH

In addition to our own appraisal, the systems have been employed by;

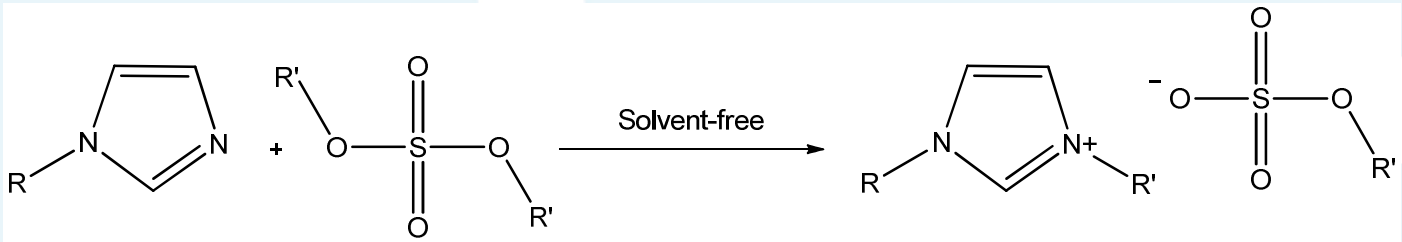
Janssen Pharmaceutica NV (part of J&J Company) Eschweiler Clarke Reaction:



Drivers:

- Safety: Outside the operating conditions **safely** attainable in batch reactors, CO_2 ↑
- Reduce **by-product** formation from 10 to 2.5 %

Iolitec GmbH: Ionic Liquid Synthesis



Driver:

- **Control** reaction exotherm to maintain product quality & **process safety**

Plantrix® made of EKasic® Silicon Carbide
Efficient Industrial Production & Superior Chemical Flexibility

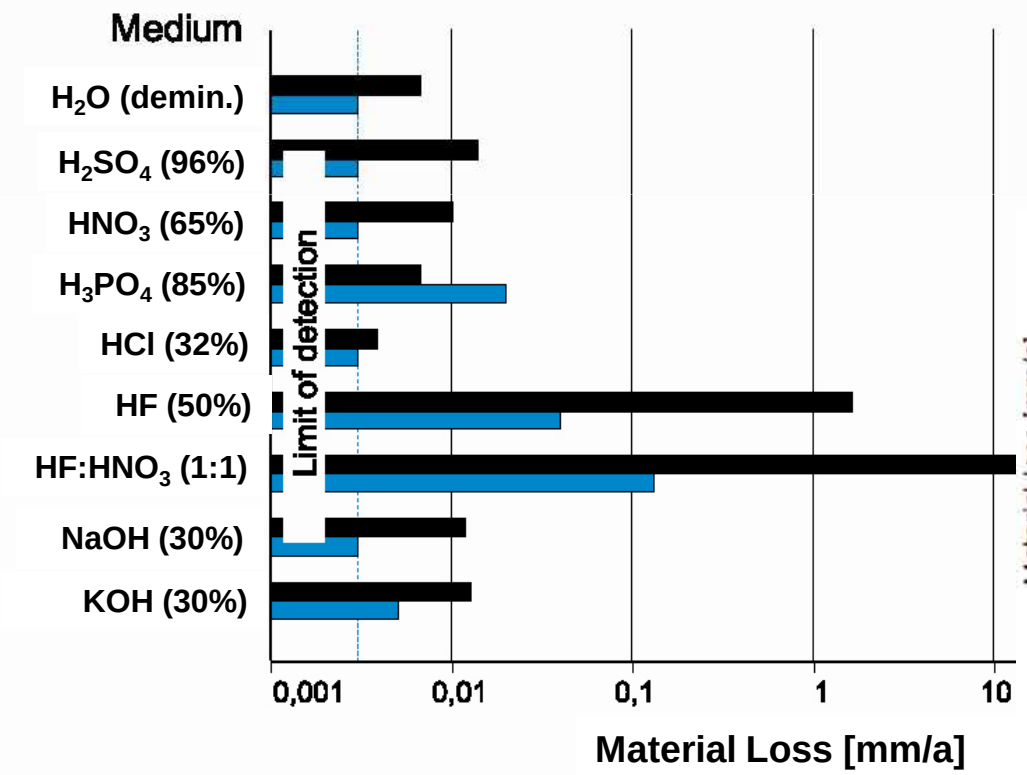
CHEMTRIX

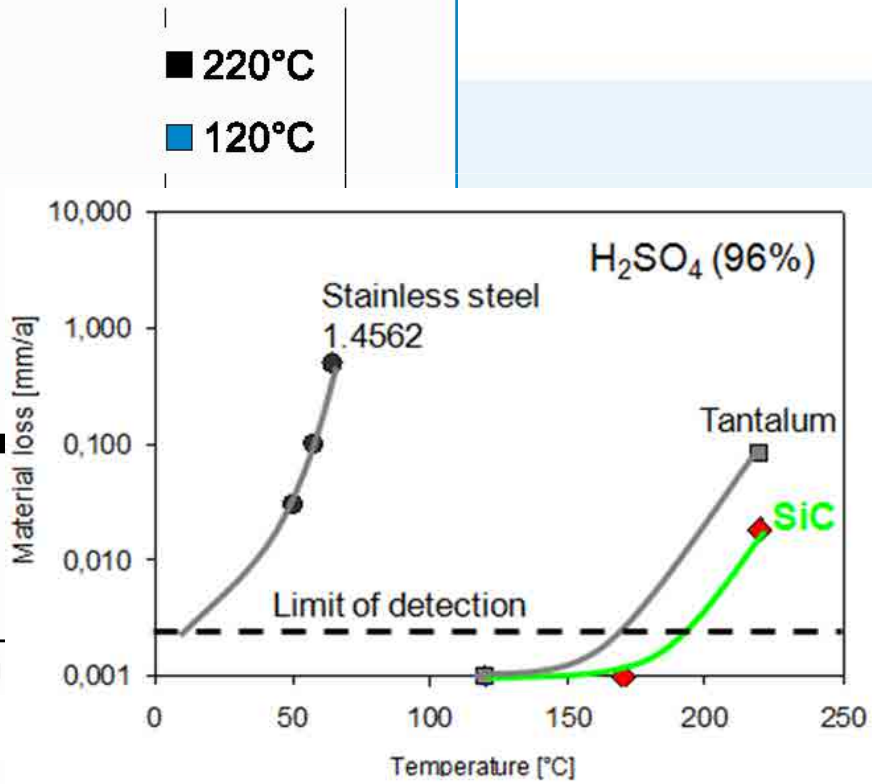
- High productivity
- High chemical flexibility
- Less scale-up risk
- Handling of solids
- Increased safety
- Environmental friendly production
- Small footprint

EKasic® Material Properties:
High Chemical Resistance

CHEMTRIX

Corrosion resistance of EKasic® Silicon Carbide





Plantrix® Industrial Flow Reactor:
Specifications

CHEMTRIX

Plantrix® MR260

Plantrix® MR500

Specification	Plantrix® MR260	Plantrix® MR500
Channel Dimensions (mm)	2.0 x 2.0	3.5 x 3.5
Temperature Range (°C)	-30 to 200	-30 to 200
ΔT (Service - Process) (°C)	< 70	< 70
Maximum Operating Pressure - Service Fluid (bar)	6	6
Maximum Operating Pressure - Process Fluid (bar)	25 (< 100 °C) 16 (≤ 200 °C)	25 (< 100 °C) 16 (≤ 200 °C)
Module Dimensions (mm)	110 x 260	200 x 500

Plantrix® Industrial Flow Reactor:
Customer Application

CHEMTRIX

DSM uses ESK Micro Reactors made of EKasic® (SiC) in a pharmaceutical production plant

Innovative Technology:
Flow Reactor Benefits

CHEMTRIX

1. Safe Use of Extreme Reaction Conditions

- Efficient mixing
- Excellent thermal control
- Process intensification of hazardous reactions

2. Reduced Development Time

- Small hold-up volume
- Rapid reaction optimisation
- Minimal scale-up steps

3. Improved Process Control

- High level of reaction control
- Process reproducibility
- Quality by Design (QbD)

4. Reduced Production Costs

- Increased product quality
- Reduced safety investments
- Higher unit productivity

✓ Efficiency

✓ Quality

✓ Safety

Contact Details

Dr Charlotte Wiles (CTO)
Chemtrix BV
The Department of Chemistry
The University of Hull
HU6 7RX
United Kingdom

e-mail: c.wiles@chemtrix.com

Tel: +44 1482 466459

Please find details of our publications, application notes and white papers on our website www.chemtrix.com