Micro Process Technology for Holistic Process Intensification
- From Ex-Ante Cost/Eco-Efficiency Considerations via Scaling Out to Novel Process Windows

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GATEWAYS STAND FOR OPENNESS AND ENTRANCE INTO NEW WORLDS

Miyajima Torii – Miyajima Island, next to Hiroshima

Torii is commonly found at the entrance or within a Shinto shrine, where it symbolically marks the transition from the sacred to the profane.
NEW HORIZONS – FUTURE FACTORY CONCEPTS

„Changing customer needs“
„Exploit the full potential of micro process technologies“
„Develop new production concepts, new start-up and shut-down strategies“
„More fast and flexible future production strategies“

NMP Large Scale EU Projects, started 2009-2010

„New, intensified process and plant concepts for speeding up market penetration, for enhancing the product life-cycle and improving sustainable production“
Volume: ~17 Mio €; funding: 11.0 Mio €, 30% industry
15 partners – Coordinator: IMM

- Sugar oxidation hydrogenation (Abo Akademi)
- Epoxidation (Mythen)
- Biodiesel production (Chemtex)
- Ammonia production (ITI Energy)
- Polymer chemistry reaction 1 (Evonik-Degussa)
- Polymer chemistry reaction 2 (Evonik-Degussa)
Process intensification: New processes & plants with step-change performance shift

Application of decision support and optimisation tools

Knowledge
Costs & Sustainability

“Early bird” – ex-ante
Simplified Life-Cycle and Cost Analysis (SCLA)

“Do not lock the stable door after the horse has bolted”

Degree of freedom
Apparatus & Processing

R & D Scale up Production

Stage of development

Freedom of choice, knowledge
SOME PI CRITERIA
- HIERARCHICALLY GROUPED

“Be holistic"

- Society / Environmental
- Company / Economy
- Plant / Process
- Reaction / Reactor

Footprint – Land use

Transport – use of local feedstock

Emissions

Toxicity

Cost (cap/op)

Depreciation

Safety – Plant operational time

Price (product)

Energy

Productivity

Flexibility

Selectivity

Reactivity

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BE HOLISTIC – HAND-IN-HAND DEVELOPMENT OF REACTOR DESIGN AND CHEMISTRY

March 2010

µ-Mixing

FASTNESS OF REACTIONS

µ-Heat exchange

Metal/halogen exchange, Grignard ketone addition

Low-T Grignard

Nitrations,

peptide couplings

10⁻² 10⁻¹ 1

10

100

1000

10,000

Process protocol times in organic textbooks

LONZA-class A (8%)

LONZA-class B (9%)

‘LONZA-class D’ (81%)

SN2 reactions

Many, many reactions

Intrinsic chemistry *

Effective chemistry

Conv-Mixing

Conv-Heat exchange

µ-Mixing

µ-Heat exchange

Intensified chemistry

Intrinsic chemistry *

Norbert P. Wijffels

MCPT: MASS & HEAT TRANSFER

Case Study 1: 2-Methylbenzimidazole Formation

Kinetic Study

\[
\text{NH}_2 \quad + \quad \text{COOH (excess)} \quad \xrightarrow{\text{neat (1 M)}} \quad \text{rt-200 °C} \quad \rightarrow \text{NH}
\]

Arrhenius Plot

- Activation energy: \( E_a = 73.43 \text{ kJ/mol} \)
- Pre-Exponential factor: \( A = 3.1 \times 10^8 \)

NOVEL PROCESS WINDOWS

- Heterogeneous catalytic routes
  - Routes bridged by intermediates
  - One flow ('pot') multi-step route
  - Direct one step synthesis

- Alternative heating (MW)
- Pressurized ex-reflux processes
- Ex-cryogenic processes

- New chemical transformations
  - Routes at much elevated temperature
  - Routes at much elevated pressure
  - Routes in the explosive or thermal runaway regime
  - Routes at much increased concentration or even solvent-free

- Process integration and simplification
- Mixing all at once
  - Catalyst-free
  - Reduced process expenditure

- Hazardous reactants
  - Thermal runaway regime
  - Ex regime

- Solvent-free
  - Solvent-less
  - Alternative solvents (IL, SCF)

German NPW Research Cluster: 7 projects


March 2010
Chemistry Under Extreme or Non-Classical Conditions

Edited by
Rudi van Eldik and Colin D. Hubbard

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Background: High Temperature/Pressure Flow Chemistry in Steel Capillary Reactors

Reactor Combining HPLC and GC Parts

Chemistries
- Redox chemistry
- Radical reactions
- Ester pyrolysis
- Degradation of cellulose and chitin
- Supercritical conditions

Selected References (J. O. Metzger, 1978-1991)
Comparable yields were obtained for the continuous process, but with much shorter reaction times:

→ Reaction time reduction at best up to 2000 times; increase in space-time yield by factor 440


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PROCESS INTENSIFICATION: INCREASE IN SPACE-TIME YIELD BY HIGH-p,T PROCESSING


Batch (1 l)
2 h – 7200 s
20 kg/(m³ h)
1 t / a

4 t / a
64200 kg/(m³ h)
4 s
Flow chem (9 ml)

→ Reaction time reduction at best up to 2000 times; increase in space-time yield by factor 3200

Residence time (s)
- 140°C, (initial)
- 200°C, aq (initial)
- 200°C, aq
- 250°C, aq
- 200°C, IL BMIM-HCl

Elevated temperature

Yield (%)

- Total flow rate (ml/h)
- OH
- KHCO₃ (aq)

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GOOD MICROREACTORS STILL NEEDED
... FOR SCALE-OUT

Yield 2,4-DHBA [%]

- 1/16 in. capillary, 200 °C, 35 bar
- dedicated µ-reactor, 206-219 °C, 35 bar
- dedicated µ-reactor, 200 °C, 70 bar
- dedicated µ-reactor, 220 °C, 70 bar
- nondedicated µ-reactor, 220 °C, 35 bar

Residence time [s] (reciprocal)

- 15500
- 20300
- 34450
- 38250
- 225 g/h
- 200 g/h
- 175 g/h
- 90 g/h

STY [kg/m³h]

- 25-fold productivity
- gas formation, intermittent flow

Productivity

GOOD MICROREACTORS STILL NEEDED
... FOR SCALE-OUT
INCREASE IN REACTIVITY VS. SELECTIVITY

Capillary reactor, O.D. 1/8 inch 35 bar

Yield 2,4-DHBA and 2,6-DHBA [%]

Residence time [s] (reciprocal)

- 2,4-DHBA, 160°C
- 2,4-DHBA, 180°C
- 2,4-DHBA, 200°C
- 2,6-DHBA, 160°C
- 2,6-DHBA, 180°C
- 2,6-DHBA, 200°C
<table>
<thead>
<tr>
<th>Heating</th>
<th>Solvent</th>
<th>Aqueous</th>
<th>Ionic liquid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>CH-A-KS</td>
<td>CH-IL-KS</td>
<td></td>
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<tr>
<td>Microwave</td>
<td>M-A-KS</td>
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</tbody>
</table>


**Faysal Benaskar (TUe)**
**Internship at IMM**

**HCO$_3^-$ donating ionic liquids**
'Footprint' - distinct LCA (and costing) patterns; determining factors: here, energy and raw materials

REACTION TIME IS DETERMINING FACTOR NO. 1

Fast reaction processing has much better global warming potential
→ Efficient use of reactor capacities is prime issue for eco-efficient processing

Multi Criteria Decision Support

Multiobjective Optimisation (MO)


March 2010
‘Lukewarm’ ex-cryogenico processes –
MOFFAT-SWERN OXIDATION

\[
\begin{align*}
\text{SO} + (\text{CF}_3\text{CO}_2)_2\text{O} & \rightarrow \text{S}^+\text{OCOCF}_3 \\
\text{R'}\text{R} & \rightarrow \text{R'}\text{R} \\
\text{S} & + \text{R'}\text{R} \rightarrow \text{R'}\text{R} \\
\text{base} & \rightarrow \text{R'}\text{R} \\
\end{align*}
\]

1st Step
2nd Step
3rd Step

- Batch: very low temperatures (<-50°C)
- Microreactor: temperatures between -20 and 20°C
- Microreactor yields >> batch yields (e.g. 95% opposed to 20%) at very short residence times of 0.01 s

Mannosylation of diisopropylidene galactose with mannosyl trichloroacetimidate

- **Batch:** good yields at -60°C and 213 s
- **Microreactor:** same yield at -35°C and 25.7 s

‘Scalding hot’ pressurized ex-reflux processes – BROMINATIONS

- High temperature: core-substitution
- 0°C: 20% side-chain bromination
- 190°C: side-chain bromination
- Higher conversion (40% to 95%) with temperature and pressure

**COPPER-FREE SONOGASHIRA COUPLING**

- Green process: water-mediated, without organic solvents
- Copper-free process without specific ligands for Pd catalyst
- Nearly quantitative yield at 0.1–4.0 s, 250°C and 16 MPa
- Even at 0.035 s: yield was >96% yield, but decreased to 1.5% at 0.012 s

NEWMAN-KUART REARRANGEMENT

O-(2-nitrophenyl)-N,N-dimethylthiocarbamate to S-(2-nitrophenyl)-N,N-dimethylthiocarbamothioate

- Scale-up prohibited in multi-purpose plants > 140°C
- Safe operation in microreactors > 200°C
- Yield near 100% at 170°C > yield by laboratory equipment (90%)

Continuous Flow Newman-Kwart Rearrangement

Kinetic Analysis (HPLC)

- Alternative solvents
- Elevated temperature

Flow processing:
- 100-330 °C, 60-80 bar
- 1 mL min⁻¹ flow rate
- 4 mL coil
- Residence time 4 min
Reduction with TTMSS, tris(trimethylsilyl)silane of various alcohol-derived thiocarbonyl derivatives in superheated toluene at 130°C with 5 min.

- Reduction of deoxy sugars at excellent yield (>90%)
- No toxic or chlorinated solvents such as CCl₄
- Process simplicity as compared to literature procedure
- Enhanced reactivity and changes in stereochemistry / cis/trans selectivities

Full conversion and 82% yield within 8 min at 270 °C and 70 bar as opposed to reaction times of several days in conventional equipment

CORE AND SIDE-CHAIN BROMINATIONS WITH ELEMENTAL BROMINE

meta-nitrotoluene  toluene  thiophene

reaction speed

formation of gaseous hydrogen bromide

Br₂ [ml/h] / Educt [ml/min]:

18.6 / 42.8  24.5 / 49.8  18.4 / 28.4

Solvent-free
THIOPHENE BROMINATION

Solvent-free

- Figure of merit: optimum for formation of 2,5-dibromothiophene
- Therefore processing at molar ratios of 2

2-BrT
2,5-DiBrT
2,3,5-TriBrT
2,3,4,5-TetraBrT


T = 0°C
Pure bromine
• Large heat releases – in batch addition of reactants drop per drop over 24h – micro-reactor operation needs only some minutes (1.6 – 29 min)

• Large increases in space-time yield by micro-flow processing (8 – 652 x, based on g /ml h\(^{-1}\))


Alternative solvents

BECKMANN REARRANGEMENT
– NYLON 6 INTERMEDIATE

Process simplification: elimination of need for acid at increased reaction speed

ESTERIFICATIONS IN SUPERCritical ALCOHOLS

Esterification

\[
\text{Ph} \quad \text{O} \quad \text{Et} \xrightarrow{\text{scMeOH}} \quad \text{Ph} \quad \text{O} \quad \text{Me}
\]

350°C, 180 bar

18 min


Transesterification

\[
\text{Ph} \quad \text{O} \quad \text{H} \xrightarrow{\text{scEtOH}} \quad \text{Ph} \quad \text{O} \quad \text{Et}
\]

330°C, 180 bar

12 min


Process simplification: no catalyst used – high ionic product of SCFs

T_c = 239°C; p_c = 81 bar.
Dedicated fluorinations with diethyl-amino-sulfur trifluoride (DAST), (1-chloro-methyl-4-fluoro-1,4-diazo-niabicyclo-[2.2.2]octane), bis(tetra-fluoroborate) (Selectfluor®), and trimethylsilyl trifluoromethane (TMS-CF3, Ruppert’s reagent)

- **DAST**: volatile, reacts violently with water and readily undergoes dismutation to SF₄ and (Et₂N)₂SF₂
- Nucleophilic fluorination, electrophilic fluorination and trifluoromethylation
- Purities >95% & yields up to 95%, eliminating purification
- Superheated processing with rate acceleration

• Al-catalyst highly pyrophoric and difficult to handle in larger volumes
• Aluminium–amide intermediate is unstable at elevated temperatures
• Batch: 16 h; combined microwave and microreactor operation at 2 min
• Applied for the synthesis of rimonabant and efaproxiral at 49% yield
• Rimonabant is anti-obesity drug & central cannabinoid receptor antagonist

• Nitration of phenol: catalyzed by nitrous acid and not by the nitronium ion
• Autocatalytic behaviour

Even at small batch scale (1 l) thermal runaway with 55 K increase
• Hot-spot in microreactor only 5 K
• Micro processing with largely increased purities (batch: up to 25%, micro-flow: up to 79%), and higher yields (batch: up to 32%, micro flow: up to 77%)
• Micro processing at concentrated conditions, almost solvent-free and without H₂SO₄ or CH₃CO₂H

IMPROVEMENT OF PRODUCT QUALITY - IONIC LIQUID SYNTHESIS

Conventional, discontinuous manufacture
- Unsufficient heat transfer in vessel -> undesired temperature increase -> product coloration, slowing down of processing
- Large volumina of hazardous reactants

Continuous microreactor processing
- Much improved heat transfer -> faster process, no coloration
- Reduction of reactor volume (= safety gains)
Initial lab rig
Micromixer/tube set-up

- Continuous processing
- Reduction of reaction time down to minutes

Optimised reactor parameters
The reactor set-up has been implemented in the demonstration facility erected at and by RWTH Aachen.

Continuous 36 h operation performed successfully.
Zunächst war der 20 kg/d Reaktor des IMM integriert, später wurde dieser und der folgende RWTH-Reaktor durch den 100 kg/d Gesamtreaktoraufbau des IMM ersetzt.
SCALE-OUT CONCEPTS FOR FALLING FILM MICROREACTORS

DO SCALED-OUT FFMRs BEHAVE THE SAME?
TEST BY CO₂ ABSORPTION IN ALKALINE SOLUTION

Operation conditions: 1 M NaOH 0.5 – 1.6 (5 – 16) ml/min; CO₂: 6.22 (62.2) ml/min diluted with N₂ 35 (350) ml/min; co-current operation mode

- Performance kept from FFMR-LARGE to STACK-1x-FFMR-LARGE
- Basic reactor design thereby proved
PILOT FALLING FILM MICROREACTORS IN PILOT PLANTS AT EVONIK-DEGUSSA


BMBF-Projekt µ.Pro.Chem

Falling film microreactor of IMM for pilot scale

Ozone generator

Ozone decomposition unit
ACHIEVED: THROUGHPUT INCREASE BY FACTOR 100x; FACTOR 1000 UNDERWAY

Validated numbering-up concept

Outlook: first steps towards even larger scale reactors have been done

March 2010
• Be holistic – complete process development view

• Exploit fast kinetics – chemistry is not slow, but is slow made

• Process intensification - new processing – evaluation tools

• Flow chemistry: micro and milli processing tools in cascaded manner

• Scaling-out: numbering-up at micro and smart scaling-up at milli level

• Production flow chemistry is there – future factories need to be developed