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NOVEL PROCESS WINDOWS

Doors to More Cost-Efficient and Environmentally Benign Processes and New Products

DBU Workshop “Novel Process Windows”
Osnabrück, 10.12.09

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Chemical Micro and Milli Process Technologies

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Technical Chemistry

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– ACS-Novel Chemistry / Microwaves / Microreactors / Flash Chemistry

Novel Process Windows

– Concept and Research Cluster

Applications and Demonstrations

– Literature review

Cost and Environmental Impacts

– Cost and Life-Cycle Analysis

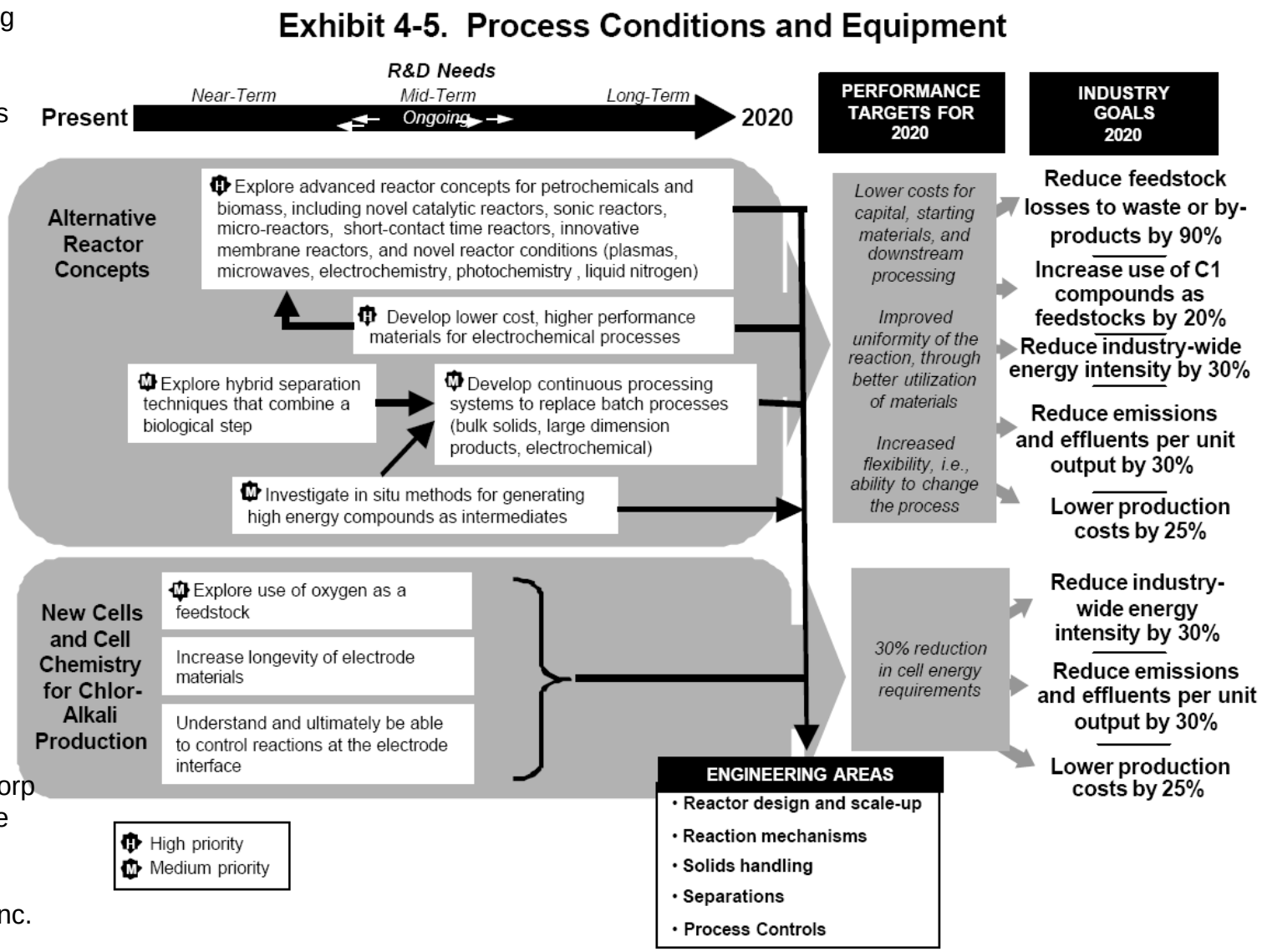
Dissemination & Exploitation

- Conferences, Symposia, Research Projects, Products

- **Starting Position**
  - **ACS-Novel Chemistry / Microwaves / Microreactors / Flash Chemistry**

NEW CHEMISTRY ROADMAP, ACS - JOE ZOELLER, EASTMAN KODAK, 2001

A.E. Staley Manufacturing
ARCO Chemical
AGA Gas
Air Products & Chemicals
Akzo-Nobel
Autoclave Engineers
BCI
BF Goodrich
Biofine
BOC Gases
Celanese
Cryo Dynamics
Degussa
DOW Chemical
DOW Corning
DuPont
Eastman Chemical
Electrolux
Eltron Research Inc.
Fedegari Autoclavi
Ford Motor Company
Genentech
GE Plastics
Global Technologies
Great Lakes Chemical Corp
Green Chemistry Institute
Isopro International
Itochu Aviation
Kellogg, Brown & Root, Inc.
…



Chemistry Under Extreme or Non-Classical Conditions

Edited by

Rudi van Eldik and Colin D. Hubbard

EARLY LITERATURE REVIEWS - HIGH PRESSURE CHEMISTRY

$$\ln k(p) = a + b \cdot p$$

$$\ln k(p=0) = a; \quad \Delta V^{\neq} = -b \cdot R \cdot T$$

$$\ln k(p) = a + b \cdot p + c \cdot p^2$$

$$\ln k(p=0) = a; \quad \Delta V^{\neq} = -b \cdot R \cdot T; \quad \Delta\beta^{\neq} = c \cdot 2 \cdot R \cdot T$$

$\Delta\beta^{\neq} - (\partial \Delta V / \partial p)_1$ (compressibility coefficient of activation)

$$\ln [k(p)/k(p=1)] = a \cdot p + b \cdot p/(1 + c \cdot p)$$

$$\Delta V^{\neq} = -(a + b) \cdot R \cdot T$$

$$\ln [k(p)/k(p=1)] = a \cdot p + b \cdot \ln (1 + c \cdot p)$$

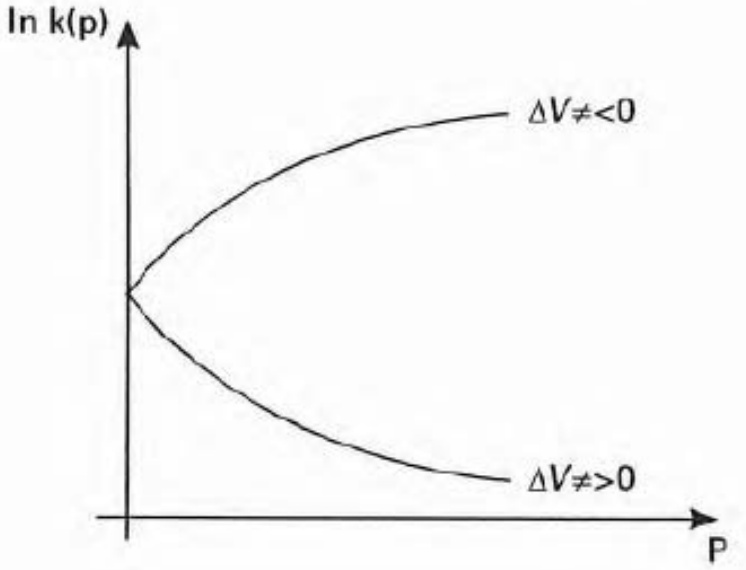
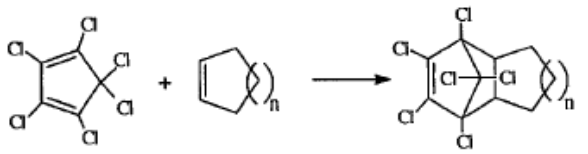


Table 3.3 The pressure-dependence of rate constants; the maximum values of rate retardation and acceleration are calculated for four different values of the activation volume $\Delta V^{\neq}$ at 25 °C.

	$k(p)/k$ (1 bar) = exp[$-\Delta V^{\neq}/RT \cdot (p - 1\ \text{bar})$] $\Delta V^{\neq}$ ($cm^3\ mol^{-1}$)			
p (kbar)	+10	−10	−20	−30
1	0.67	1.5	2.2	3.4
3	0.30	3.4	11	38
5	0.13	7.5	56	420
7	0.06	17	280	4800
10	0.02	56	3200	180000



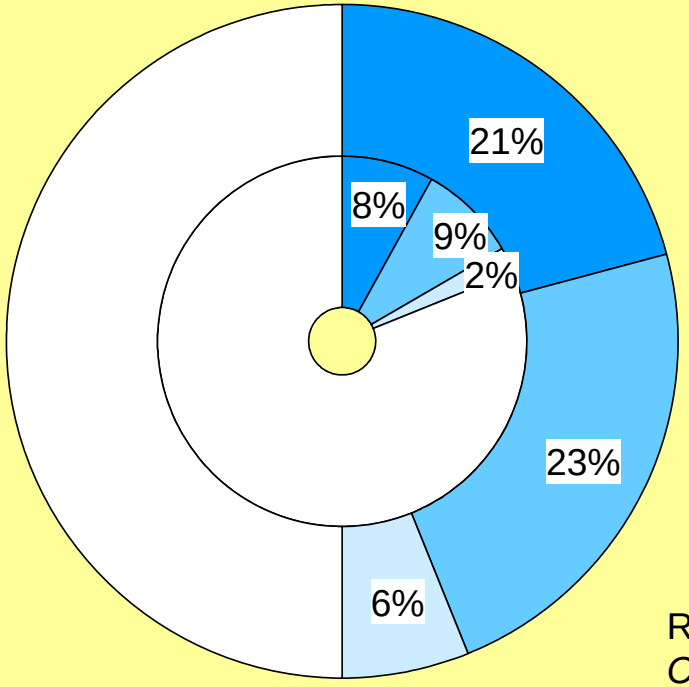
n	Cycloalkane	$\Delta V^{\neq}$ [a]	ΔV^{a}	Θ [b]	$\Delta S^{\neq}$ [c]	$\Delta H^{\neq}$ [d]
1	Cyclopentene	− 34.9	− 33.2	1.05	− 49	12.3
2	Cyclohexene	− 33.4	− 34.3	0.97	− 51	14.8
3	Cycloheptene	− 27.4	− 35.6	0.76	− 38	15.8
4	Cyclooctene	− 25.8	− 34.5	0.75	− 31	18.5
6	Cyclodecene	− 22.6	− 35	0.65	− 33	20.3
	Norbornene	− 28.6	− 33.3	0.86	− 42	14.8

F.-G. Kärner, M. K. Diedrich, A. E. Wigger, 3. Effect of pressure on organic reactions in: Chemistry under extreme or npn-classical conditions. (eds. R. van Eldik, C. D. Hubbard) 1997, John Wiley & Sons, New York

SUITABILITY OF REACTIONS

Classification of 86 reactions campaigns carried out at Lonza

Lonza



- Type A reactions
- Type B reactions
- Type C reactions
- Remaining

Big circle:
based on kinetics only

Small circle:
based on kinetics & phases

- **50% of the reactions to benefit from a continuous process**
- **63% not suited to current micro reactors due to solid carriage**

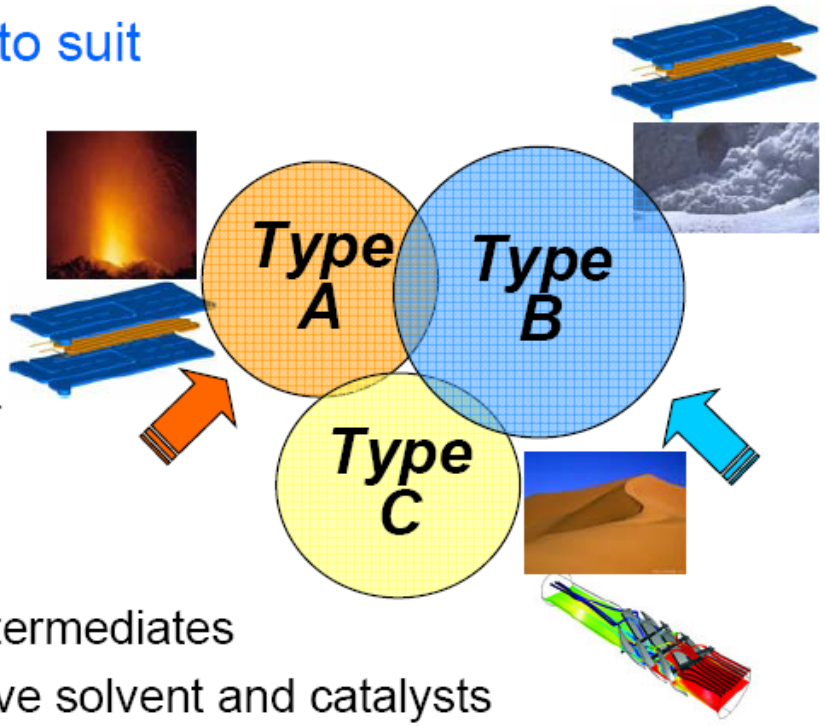
Roberge, D.M., Ducry, L., Bieler, N., Cretton, P., Zimmermann, B. *Chem. Eng. Tech.* **28**, 3 (2005) 318-323

- **Type A reactions: very fast, < 1 s; mixing controlled**
- **Type B reactions: rapid, 1 s to 10 min; kinetically controlled**
- **Type C reactions: slow, > 10 min; safety and quality issues**

Shifting reactions to suit Microreactors

Reactions can be designed to suit microreactor technology:

- Increased concentration
  - harsher reaction conditions
  - fast reactions
- Increased temperature
- Adjusted residence time RT



- Hazardous reagents and intermediates
- Expensive, but more effective solvent and catalysts
- Controlled educt quality, filtering, avoid impurities and particles

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MICROWAVE ENCASED PROCESSING

{50-130°C; 1 bar; 2-8 h} — **Conventional lab batch**

↓

{>200°C; >50 bar; <1 s} — **High-p,T microreactor protocol**

'alike gas-phase chemistry'

$k = A \exp(-E_a/RT)$

$A = 4 \times 10^{10}$ mol^{-1} s^{-1}
$E_a = 100$ kJ mol^{-1}

Temperature [°C]	27	77	127	177	227
Rate constant k [s^{-1}]	1.6×10^{-7}	4.8×10^{-5}	3.5×10^{-3}	9.9×10^{-2}	1.43
Time (90% conversion)	68 days	13.4 h	11.4 min	23.4 s	1.61 s

from: Kappe, C.O., Stadler, A. *Microwaves in Organic and Medicinal Chemistry*, Vol. **25** in: Methods and Principles in Medicinal Chemistry (eds.: Mannhold, R., Kubinyi, H., Folkers, G.) Wiley-VCH (2005) pp. 94-95.

→ **following the routes of microwave assisted continuous synthesis (MAOS)**

Organ, M.G., Mayer, S., Lepifre, F., M'Zemba, B., Kathri, J. *Mol. Diversity* **7** (2003) 211-227.

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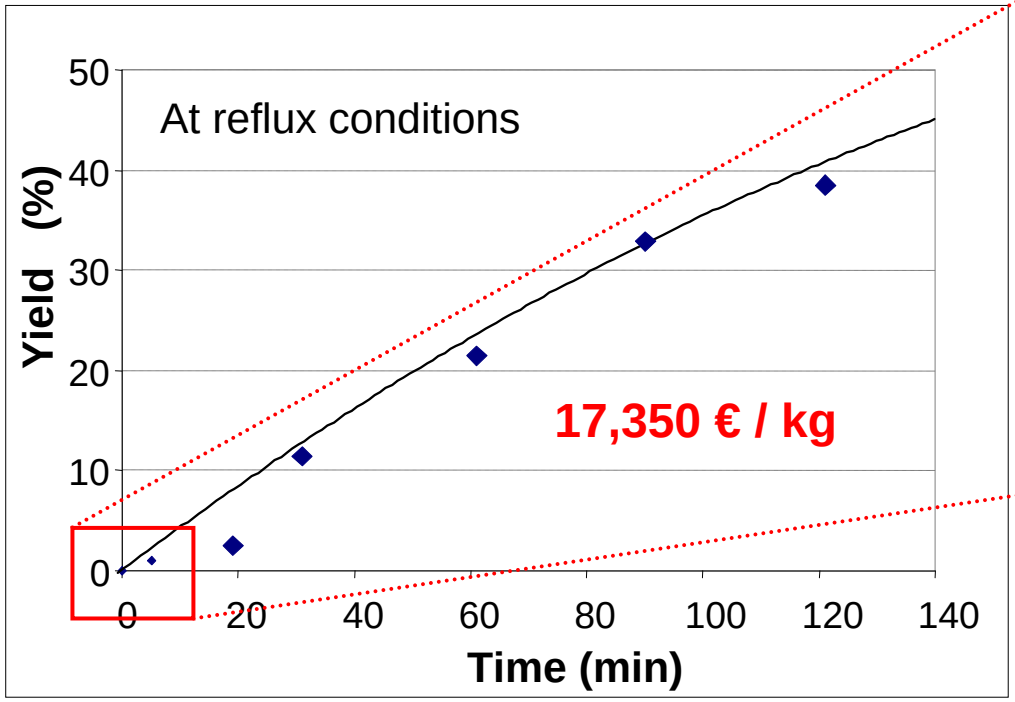
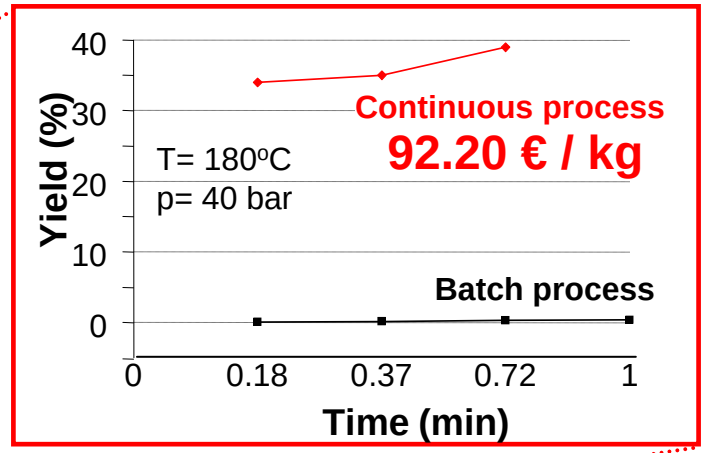
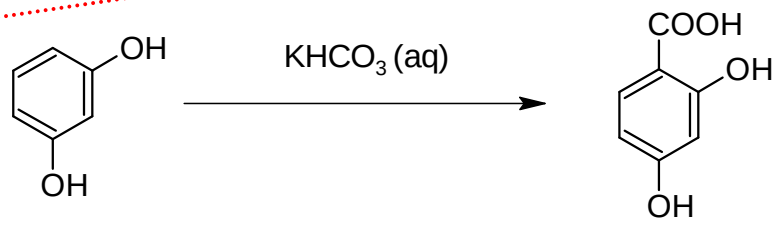
KOLBE-SCHMITT SYNTHESIS: SPEED-UP OF REACTION BY HIGH-p,T PROCESSING

Aldrich sales price 160 € / kg







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

V. Hessel, C. Hofmann, P. Löb, J. Löhndorf, H. Löwe, A. Ziogas *Org. Proc. Res. Dev.* **9**, 4 (2005) 479-489

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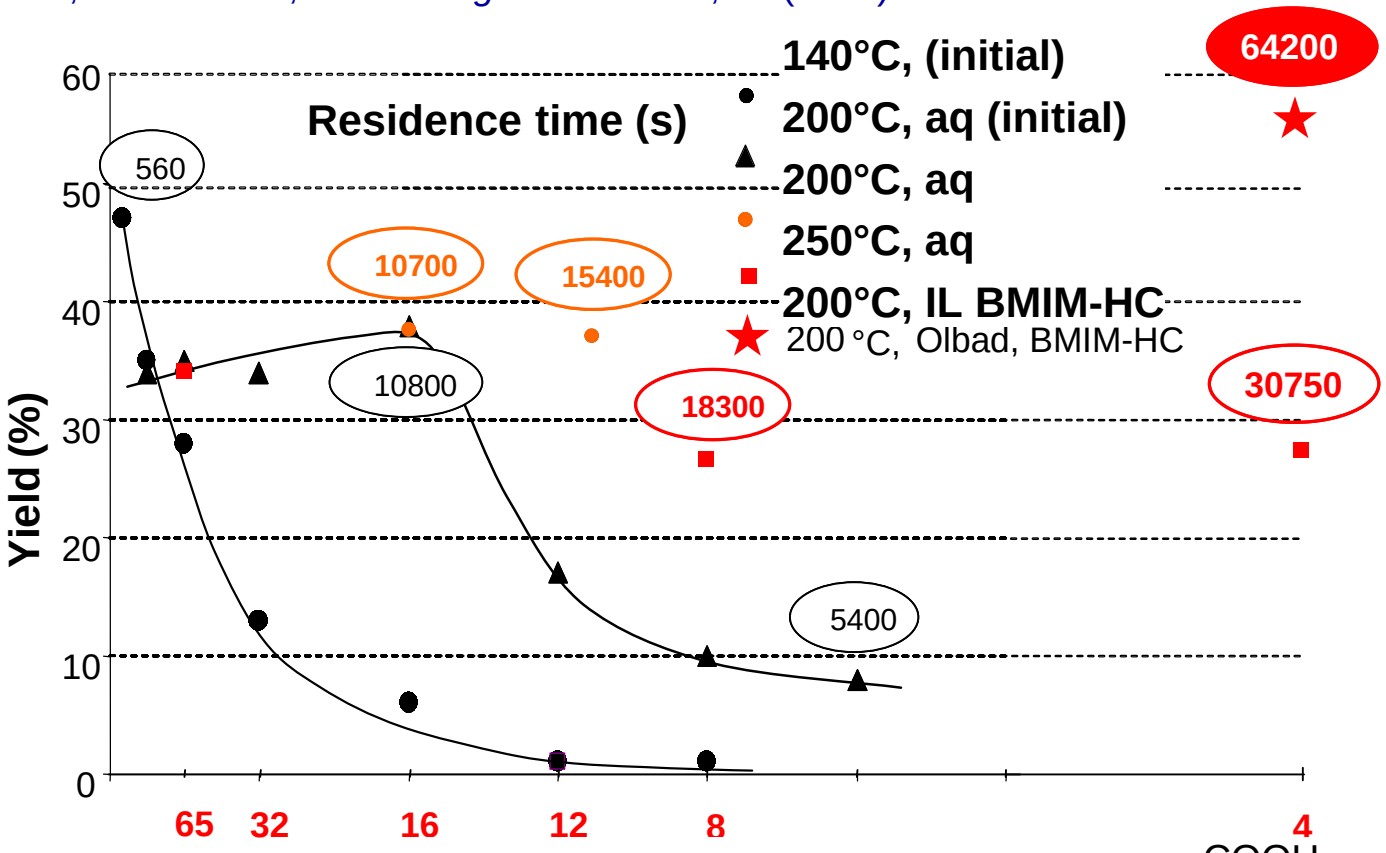
PROCESS INTENSIFICATION: INCREASE IN SPACE-TIME YIELD BY HIGH-p,T PROCESSING

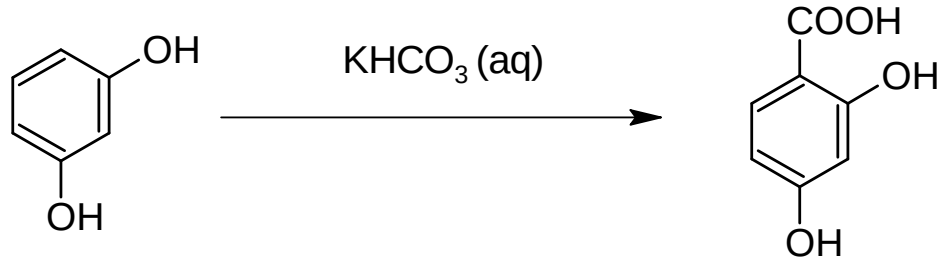
V. Hessel, C. Hofmann, P. Löb, J. Löhndorf, et al. *Org. Proc. Res. Dev.* **9**, 4 (2005) 479-489.
V. Hessel, U. Krtschil, P. Löb, A. Stark, et al. *Org. Proc. Res. Dev.* **13**, *5* (2009) 970-982.
U. Krtschil, V. Hessel, A. Stark, D. Reinhard, *Chem. Eng. Technol.* **32**, 11 (2009) 1774-1789.

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**



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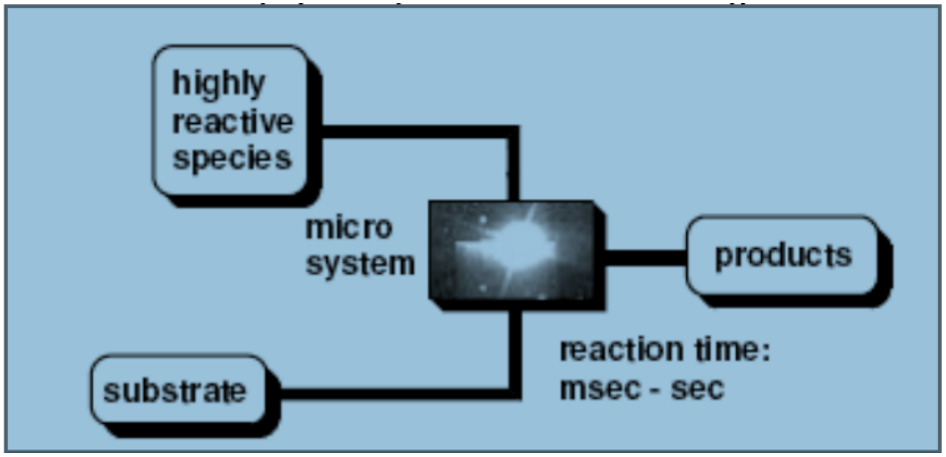
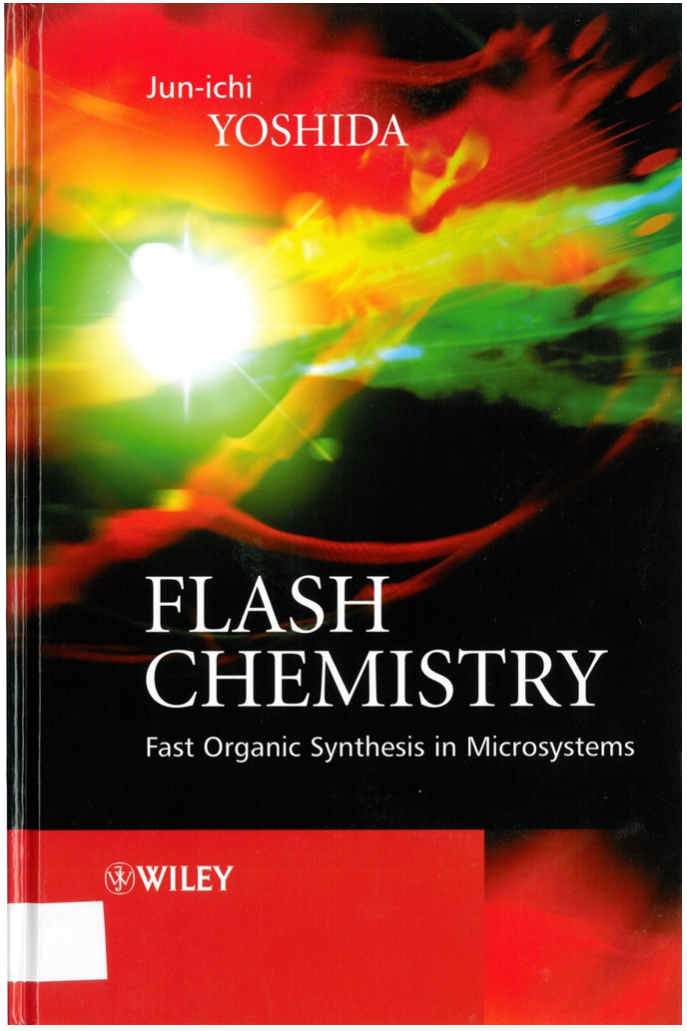
FLASH CHEMISTRY – COMPLEMENTARY TO NOVEL PROCESS WINDOWS

J.-i. Yoshida, A. Nagaki, T. Yamada, "Flash Chemistry: Fast Chemical Synthesis by Using Microreactors", *Chemistry - A European Journal* **14**, 25 (2008) 7450 – 7459.



- **CET Special Issue**
  „Novel Process Windows; in 11/09
- **International DBU Workshop**
  „Novel Process Windows"; in December 10, 2009
- **Topical book**
  „Novel Process Windows", Wiley-VCH; in 2010

Jun-ichi Yoshida, Kyoto University



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December 2009

Novel Process Windows

– Concept and Research Cluster

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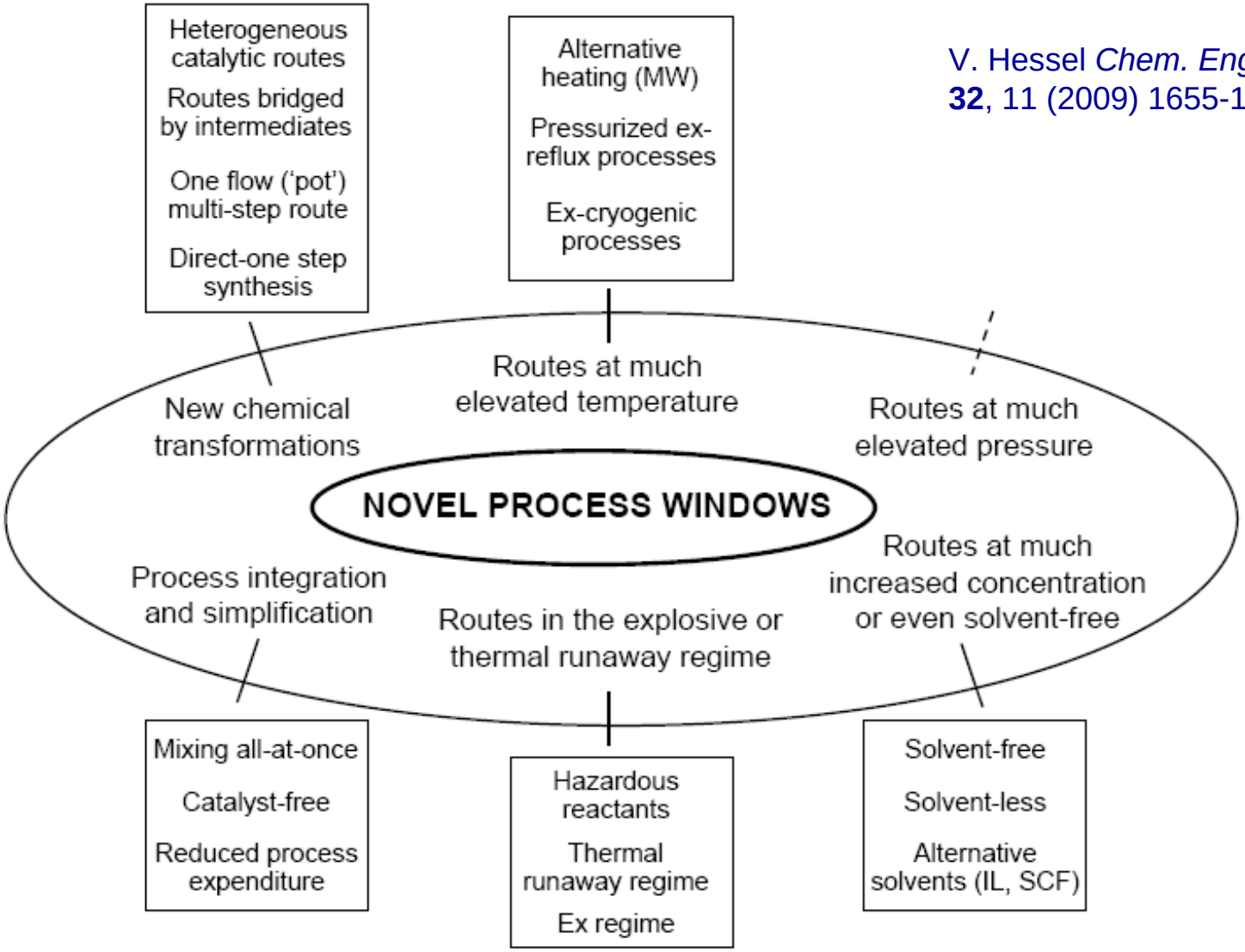
NOVEL PROCESS WINDOWS



V. Hessel *Chem. Eng. Technol.* **32**, 11 (2009) 1655-1681.

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DBU RESEARCH CLUSTER
NOVEL PROCESS WINDOWS (April 2007)

Mission

Novel process windows with regard to pressure, temperature, concentration

Sustainable chemical processes by temperature stable, pressurised microreactors

Technical Targets

- **High energy efficiency**
- **Minimisation of waste**
- **Clean and inherently safe product makign**
- **Safe and low-emission syntheses**
- **Process intensification (e.g. increase in space-time yield)**

Relevant Topics

- **High-temperature & high-pressure conti routes, e.g. for functionalisation of alkanes**
- **Syntheses in explosive and thermal runaway regimes**
- **Solvent-less and free syntheses**
- **Multi-step syntheses with immediate conversion of instable intermediates**

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PROJECT CLUSTER ‚NOVEL PROCESS WINDOWS' AT DBU

Forschungscluster „Novel Process Windows"

DBU Deutsche Bundesstiftung Umwelt

New products via new process windows

- OLED materials
- Phenols by Kolbe-Schmitt synthesis
- Chitosan for Pharmaceuticals
- High pressure amination of hydrocarbons
- New ink materials

guided and accompanied by LCA & cost analyses

\+

- **KONAROM, sugar melts**
- **CORA, H_2O_2 via membranes**

Universities in co-operation with industry:

- Jenpolymers Ltd
- Sigma-Aldrich
- Heppe Medical Chitosan GmbH,
- Pelikan PBS GmbH &CoKG
- ASD GmbH, JTT

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- **Applications and Demonstrations**
  - **Literature review**

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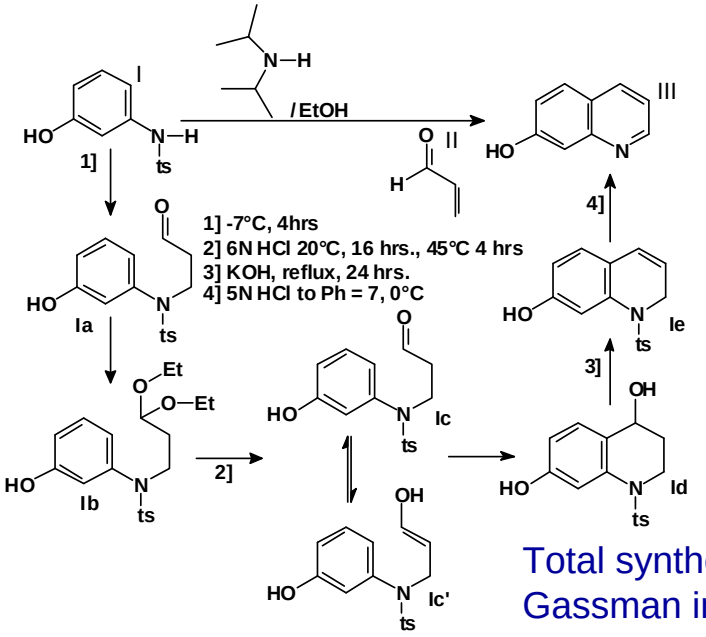
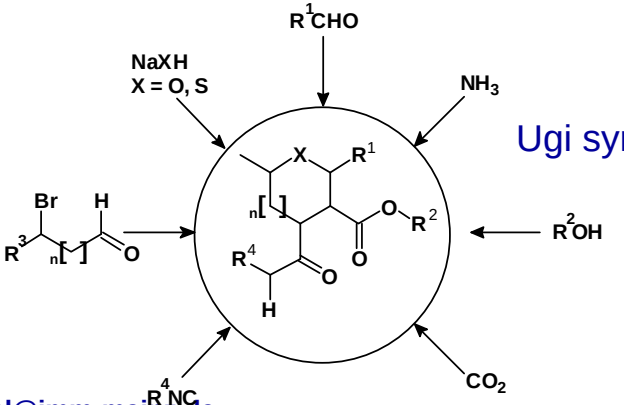
One-flow ('pot') multi-step route instead of multiple step-wise processing

Famous telescoping syntheses



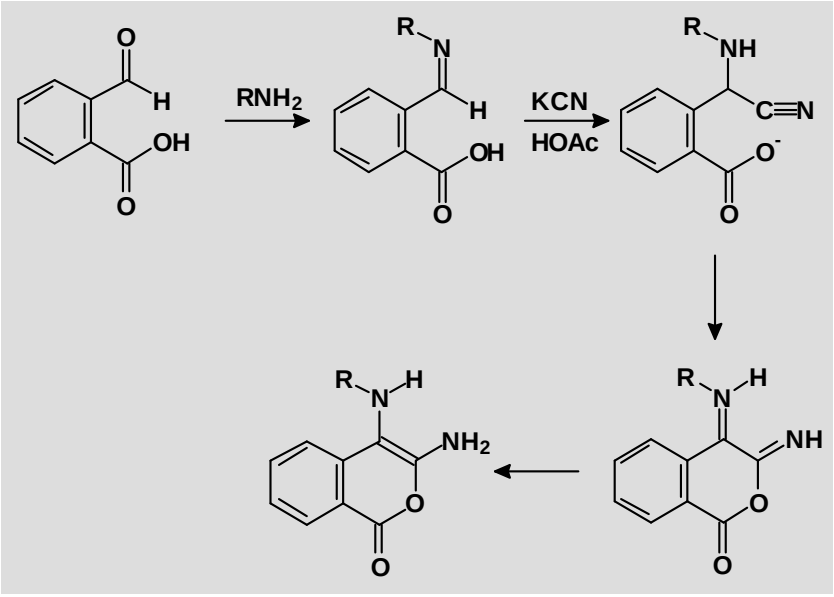
Total synthesis of tropinone - Gassman indole synthesis



Ugi synthesis

New chemical transformations

3,4-diamino-1H-isochromen-1-ones synthesis in microreactor



- **Moderate to good yields up to 66%.**
- **In situ generated HCN produced from KCN was directly consumed**

D. R. J. Acke, C. V. Stevens, *Green Chem.* **9** (2007) 386–390.

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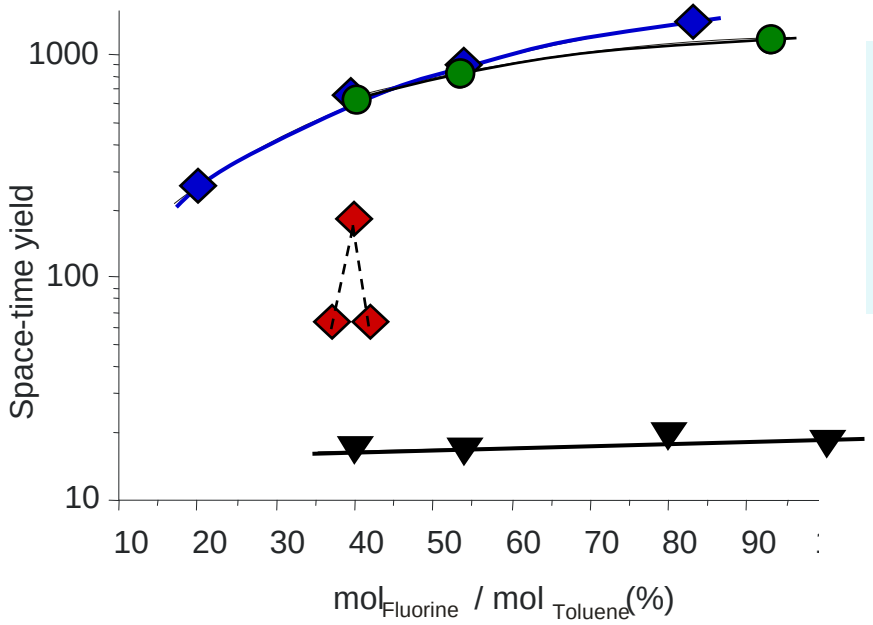
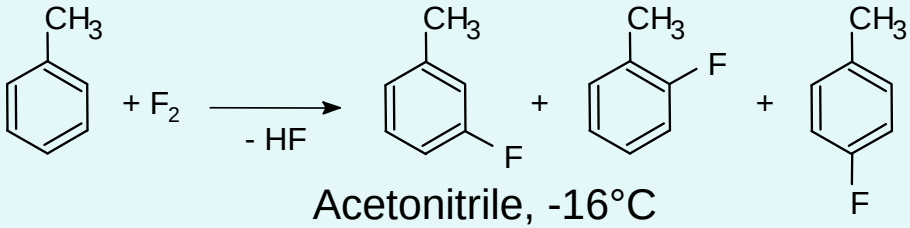
SPACE-TIME YIELD – THE REDUCTION OF RESIDENCE TIME

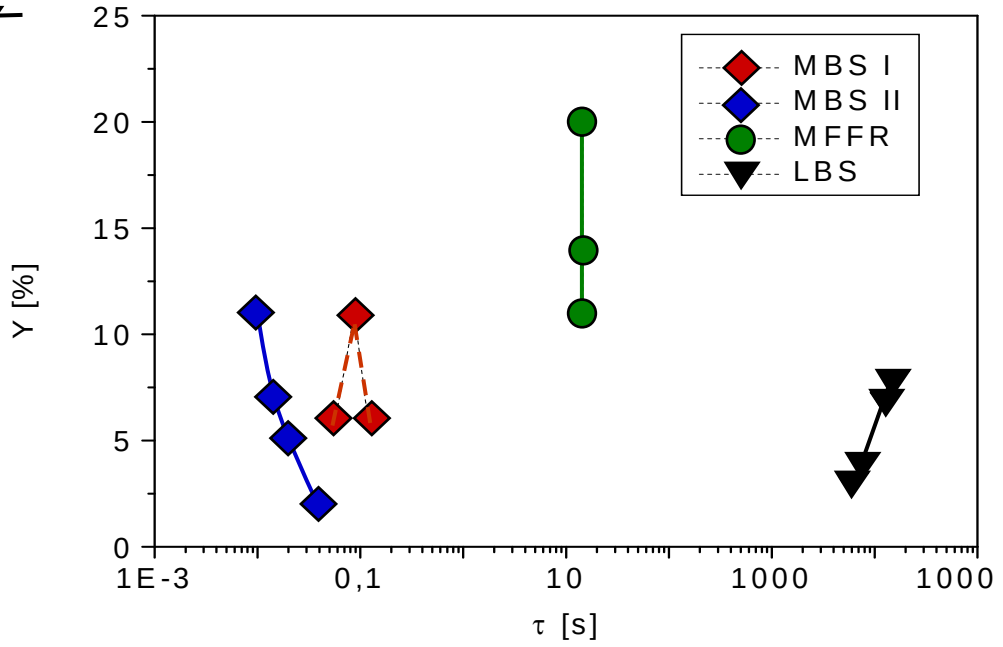
Reaction volume = Active channel volume



New chemical transformations



Jähnisch, K., et al..; *J. Fluorine Chem.* **105**, 1 (2000) 117



- **Significant enhancement of space-time yield for the micro-structured reactors compared to the laboratory bubble column**

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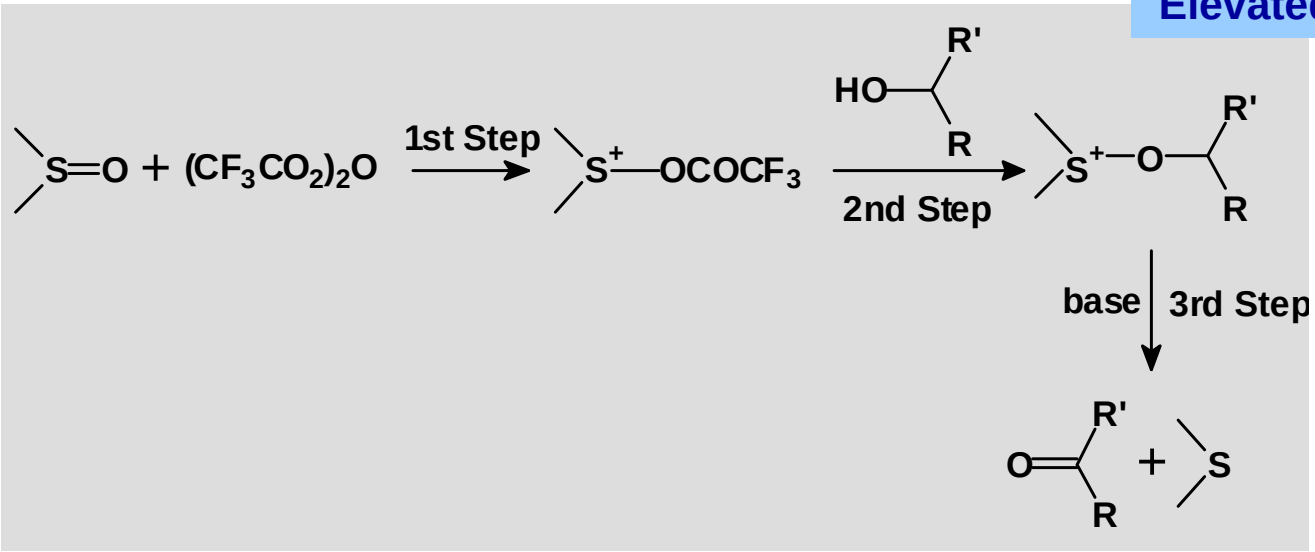
‘Lukewarm’ ex-cryogenico processes – MOFFAT-SWERN OXIDATION

Elevated temperature

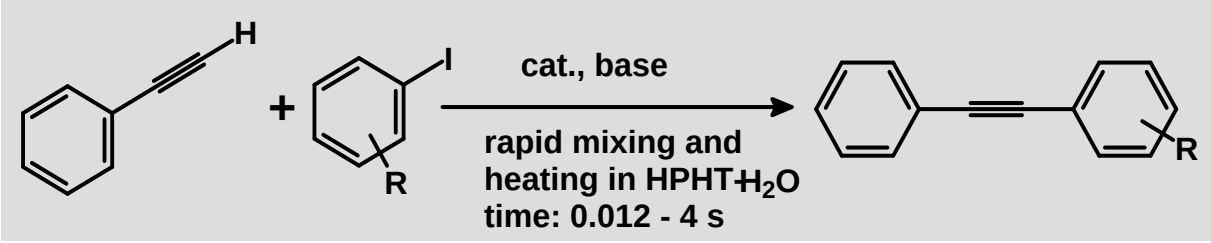


- **Side reaction: the Pummerer rearrangement**
- **Processing in batch reactors at very low temperatures (<-50°C)**
- **Processing in a microreactor at temperatures between -20 and 20°C**
- **Three-reaction process - a cascade with the same number of micromixers**
- **Microreactor yields much higher than batch yields (e.g. 95% opposed to 20%) at very short residence times of 0.01 s**

T. Kawaguchi, H. Miyata, K. Ataka, K. Mae, J.-i. Yoshida, *Angew. Chem. Int. Ed.* 44 (2005) 2413 –2416.

COPPER-FREE SONOGASHIRA COUPLING

Elevated temperature

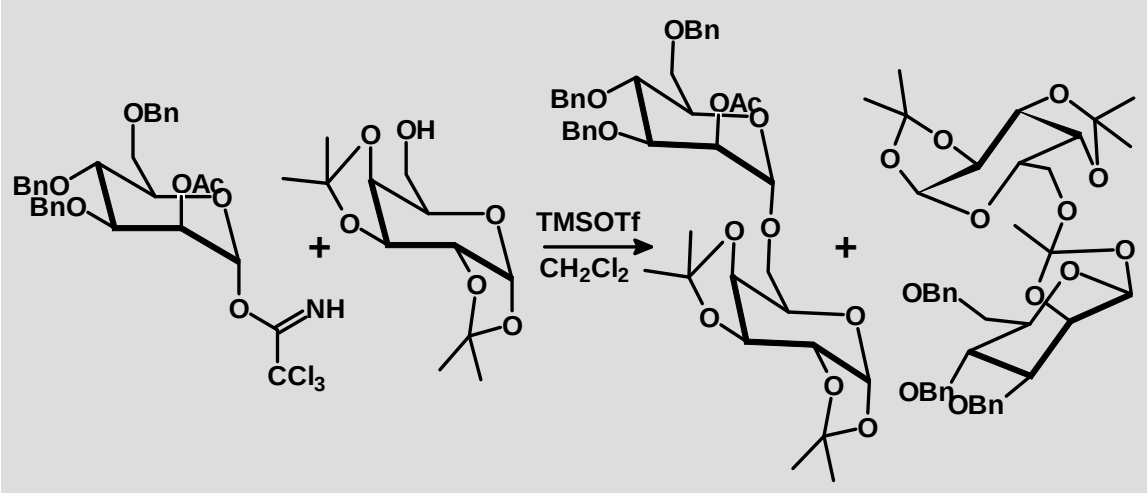


- **Green process: water-mediated, without organic solvents**
- **Step-by-step rapid mixing and heating**
- **Copper-free process without specific ligands for Pd catalyst**
- **High-pressure and high-temperature water micro processing**
- **Nearly quantitative yield for only 0.1–4.0 s at 250°C and 16 MPa**
- **Even at 0.035 s, yield was >96% yield, but decreased to 1.5% at 0.012 s**
- **No homocoupling**

H. Kawanami, K. Matsushima, M. Sato, Y. Ikushima, *Angew. Chem. Int. Ed.* **46** (2007) 5129 –5132.

GLYCOSYLATIONS

Elevated temperature



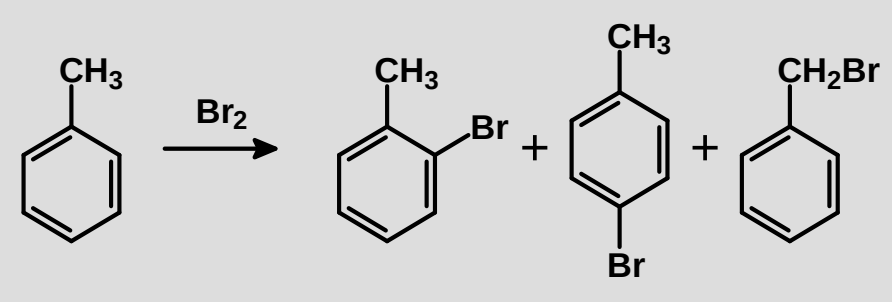
Mannosylation of diisopropylidene galactose with mannosyl trichloroacetimidate

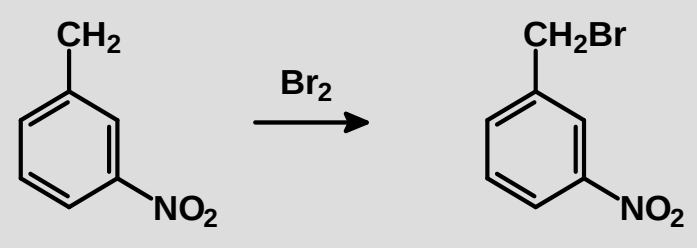
- **Batch: good product yields from -60 to -40°C, with some orthoester formation; the optimum being at -60°C and 213 s.**
- **Microreactor: nearly the same yield at -35 °C and 25.7 seconds**

D. M. Ratner, E. R. Murphy, M. Jhunjhunwala, D. A. Snyder, K. F. Jensen, P. H. Seeberger, *Chem. Commun.* **2005**, 578–580.

‘Scalding hot’ pressurized ex-reflux processes – BROMINATIONS

Elevated temperature





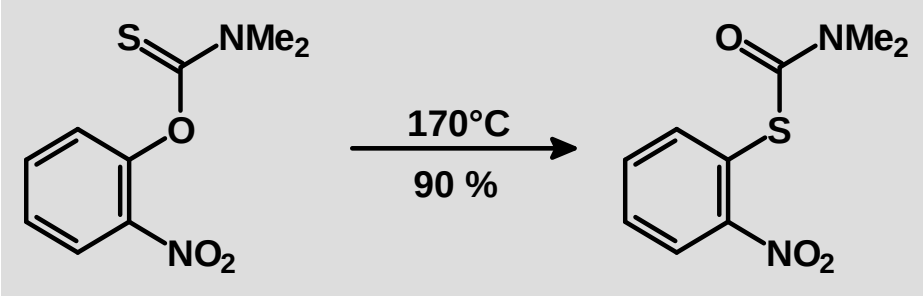
- **At high temperature, nearly all brominated species were core-substituted**
- **At 0°C, side-chain bromination with a selectivity still below 20%**

- **At 170, 1.9 min and 190°C, 2.4 min, side-chain bromination to benzyl bromide**
- **Higher conversion (40% to 95%) with temperature and pressure**

P. Löb, H. Löwe, V. Hessel, *J. Fluorine Chem.* **125**, 11 (2004) 1677-1694.

NEWMAN-KUART REARRANGEMENT

Elevated temperature



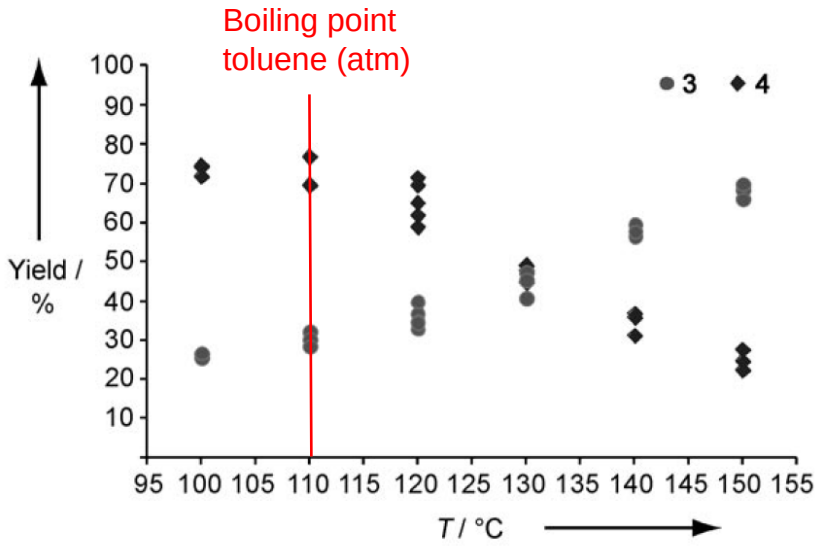
O-(2-nitrophenyl)-N,N-dimethylthiocarbamate to S-(2-nitrophenyl)- N,N-dimethylthiocarbamothioate

- **Industry's multi-purpose plants have upper temperature limit of 140°C**
- **Standard microstructured reactors proved safe operation at above 200°C**
- **Yield of nearly 100% at 170°C > yield by laboratory equipment (90%)**

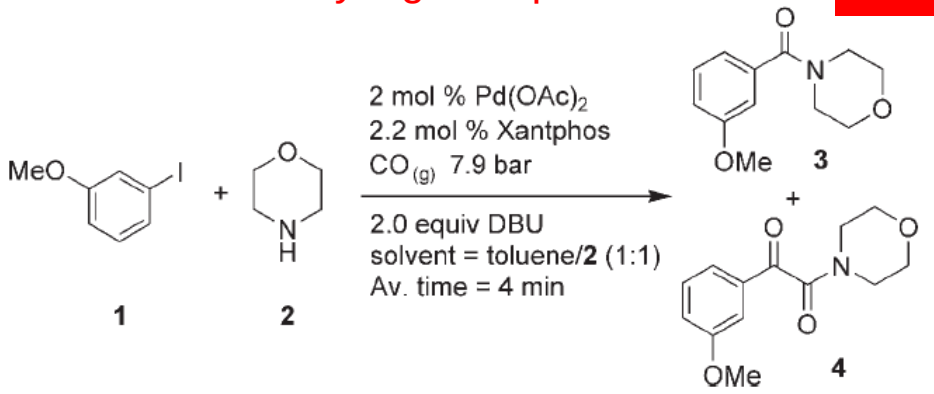
X. Zhang, S. Stefanick, F.J. Villani, *Org. Process Res. Dev.* **8**, 3 (2004) 455.

HIGH-p,T WINDOWS FOR TUNING α-KETOAMIDE / AMIDE SELECTIVITY

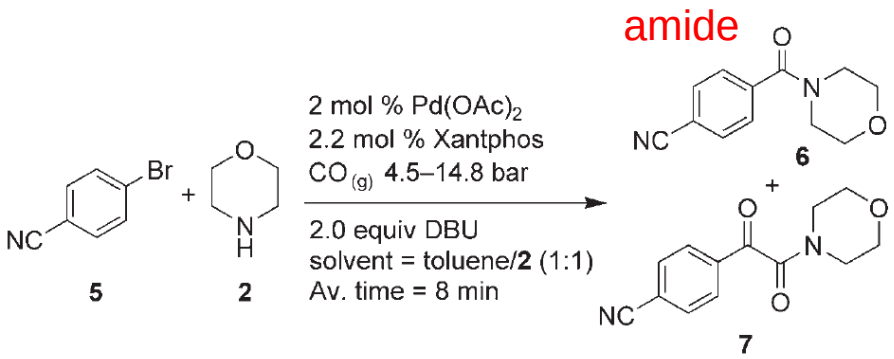
Murphy, Martinelli, Zaborenko, Buchwald, Jensen *Angew. Chem. Intl. Ed*. **119**, 10 (2007) 1764-1767

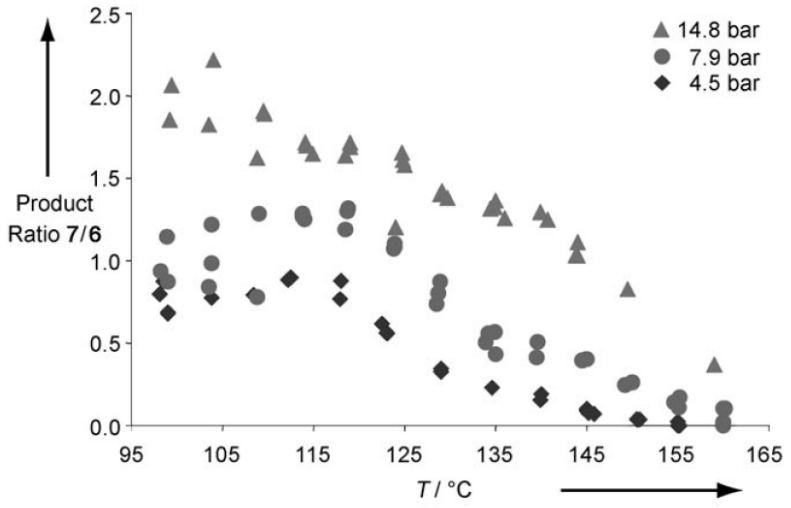


favoured by high temperature ← **amide**



favoured by high pressure (CO) ← **α-ketoamide**



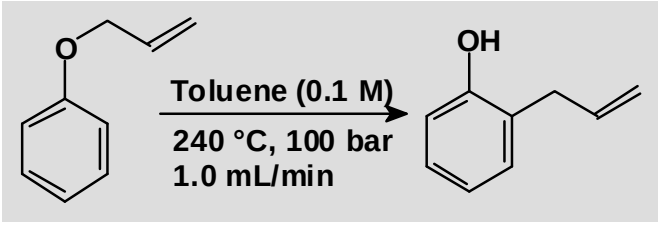


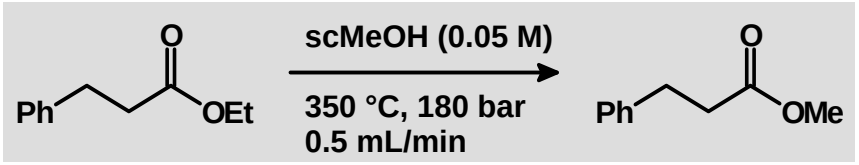
HIGH-T FLOW ORGANIC SYNTHESIS

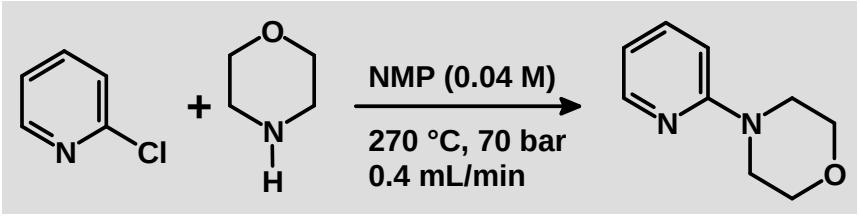
Elevated temperature

- **Extended study concerning high-temperature flow organic synthesis**
- **Stainless steel microtubular flow reactor, up to 350°C and 200 bar.**
- **Lower boiling solvents in or near supercritical state with same extreme experimental environments as high-boiling solvents at reflux or under sealed-vessel MW conditions**

Diels–Alder reaction, Newman-Kwart rearrangement, Fischer indole synthesis, Claisen rearrangement, supercritical transesterification, and nucleophilic aromatic substitution (SNAr) of 2-halopyridines with amines







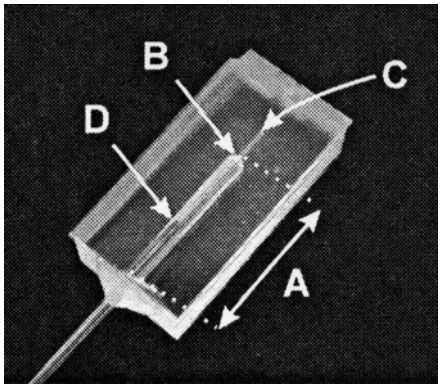
Full conversion and 82% yield within 8 min for direct amination of 2-chloropyridine with morpholine at 270 °C and 70 bar as opposed to reaction times of several days in conventional equipment

hessel@imm-mainz.de

T. Razzaq, T. N. Glasnov, C. O. Kappe, *Eur. J. Org. Chem.* **2009**, 1321–1325. **December 2009**

HIG-PRESSURE AMINATIONS

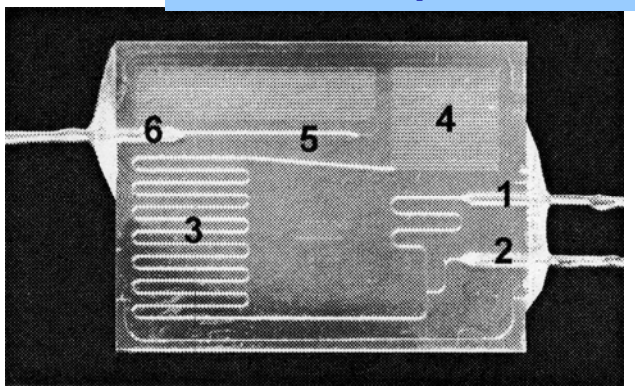
Capillary microreactor →



Fiber-based chip interface

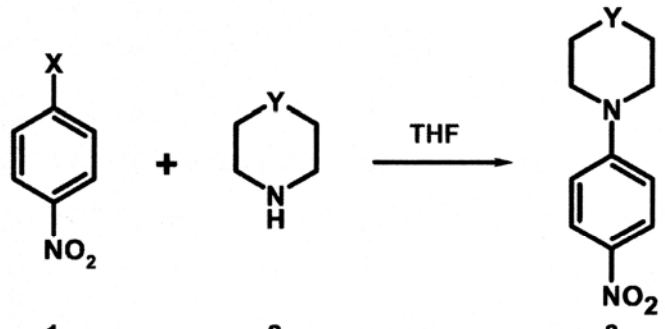
→

Elevated pressure



Glass high-pressure microreactor

Nucleophilic aromatic substitution



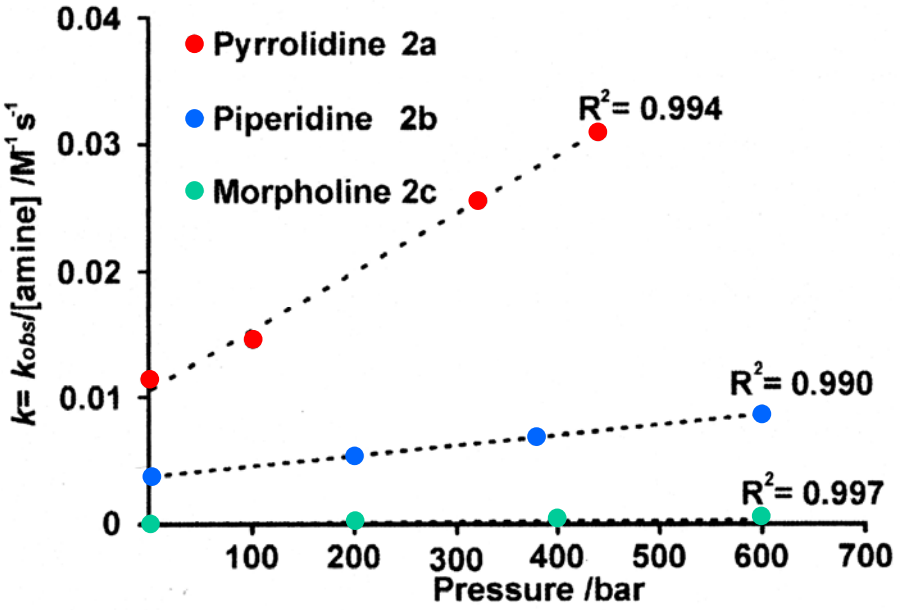
1

a X = F
b X = Cl
c X = Br

2

a Y = --
b Y = CH_2
c Y = O

3



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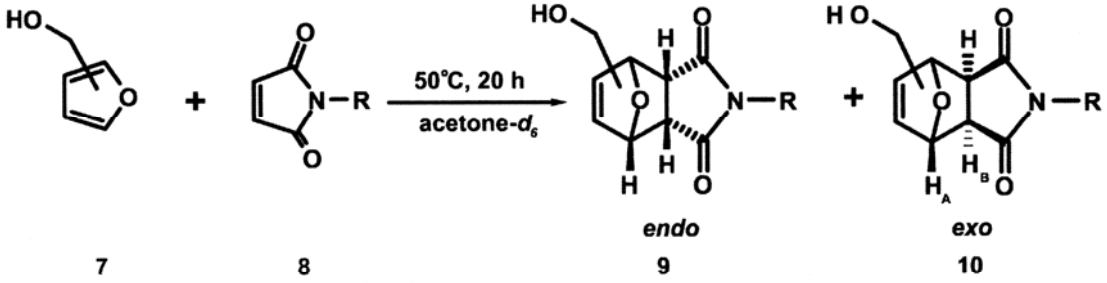
HIGH-PRESSURE DIELS-ALDER REACTIONS

Stereoselectivity of Diels-Alder reactions



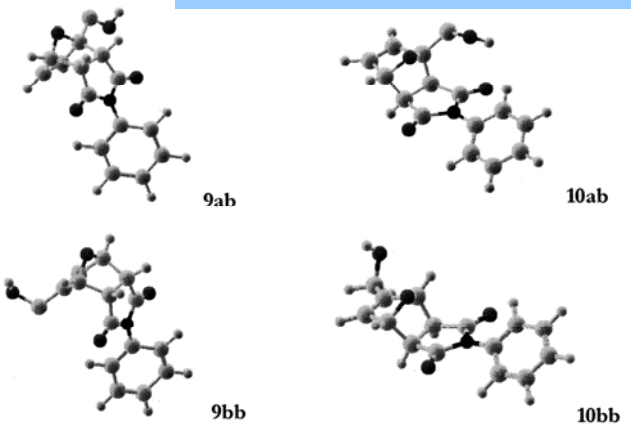
7 8

a 2-furylmethanol
b 3-furylmethanol

a R = CH_3
b R = Ph
c R = CH_2-Ph

→ Volume difference of endo and exo transition states

Elevated pressure



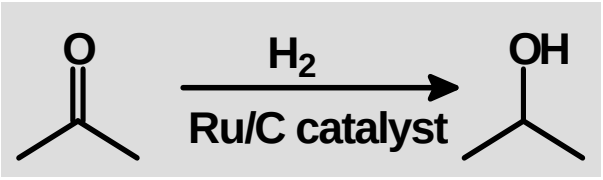
Minimised structures for reaction volumes ΔV

7 + 8	Conversion [%]		endo (9) / exo (10) ratio	
	1 bar	600 bar	1 bar	600 bar
aa	35	66	66:34	59:41
ab	35	55	55:45	52:48
ac	40	62	62:38	57:43
ba	57	57	57:43	57:43
bb	55	54	40:60	39:61
bc	59	58	55:45	54:46

ACETONE HYDROGENATION

Elevated pressure

Catalytic hydrogenation of acetone to isopropanol over Ru/C catalyst



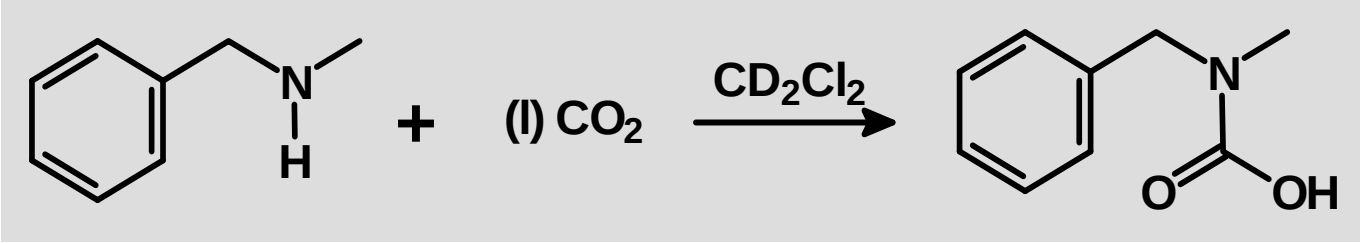
- **Usually, polymeric microreactors cannot easily be operated at high pressure due to lacking mechanical strength**
- **This is overcome by a specialty construction embedding the microreactor in a high-pressure Parr reactor enabling operation up to 725 psi**
- **At 650 psi hydrogen pressure, 20% conversion with no byproduct formation**

K. Pimparkar, R. Lin, R. Y. Ofoli, J. E. Jackson, S. Obare, D. J. Miller, *High Pressure Catalytic Hydrogenation of Acetone in a PDMS Based Recirculating Microreactor System*, Proceedings of the AIChE Annual Meeting 2008, Philadelphia, November 15-21, 2008.

Formation of carbamic acid of N-benzylmethylamine

Elevated pressure

Formation of carbamic acid from N-benzylmethylamine and CO_2



Specialty micro-reactor chip designed for high-pressure chemistry made out of several in-plane fiber-based interface geometries

- **Upper pressure limit of 180–690 bar**

- **Carbamic acid not formed at 10 bar (166 s), but formed up to 300 bar at 8 s**
- **Up to 400 bar no destruction of the chips, no product formed due to too small residence times**

K. Pimparkar, R. Lin, R. Y. Ofoli, J. E. Jackson, S. Obare, D. J. Miller, High Pressure Catalytic Hydrogenation of Acetone in a PDMS Based Recirculating Microreactor System, Proceedings of the AIChE Annual Meeting 2008, Philadelphia, November 15-21, 2008.

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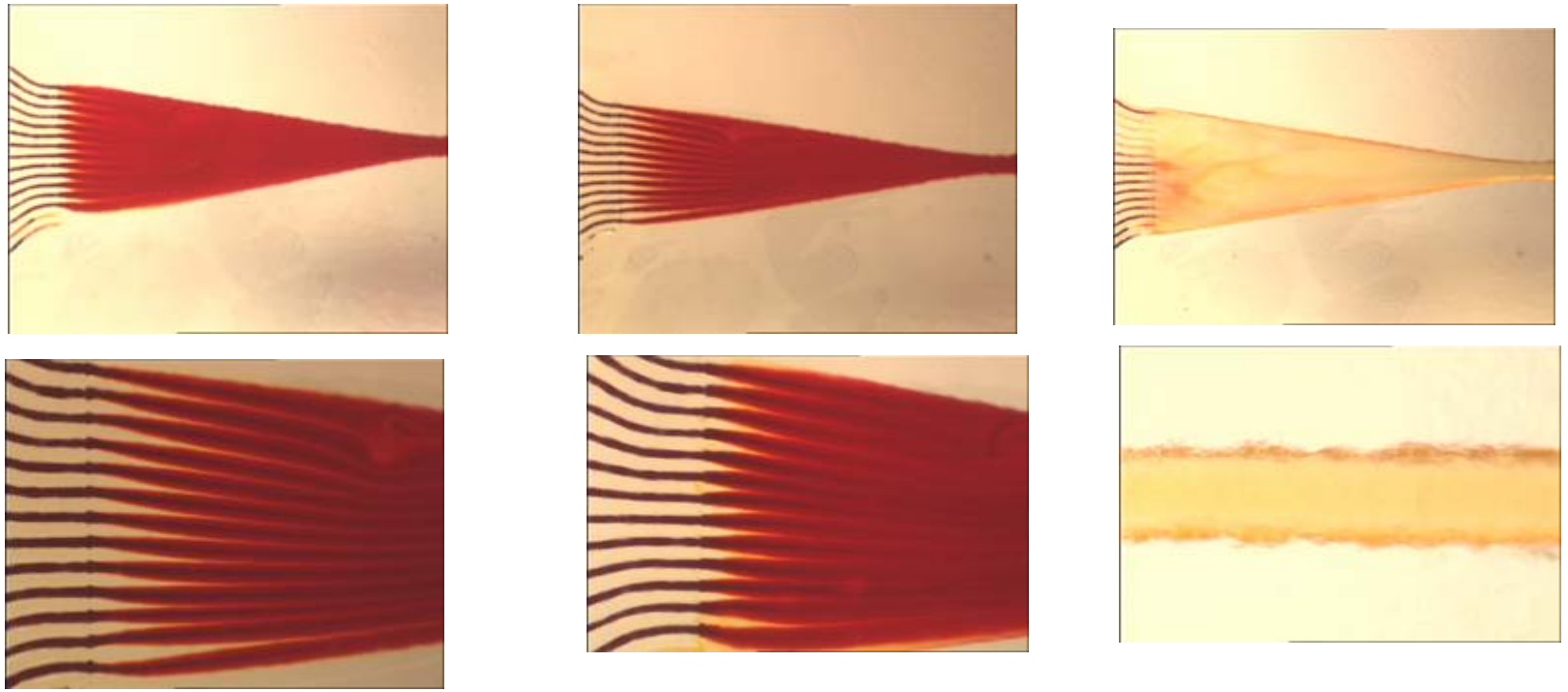
CONTACTING OF THE DIFFERENT EDUCTS WIHT BROMINE (1:1) IN A GLASS MICRO MIXER

meta-nitrotoluene | toluene | thiophene | Solvent-free

reaction speed →

formation of gaseous hydrogen bromide



18.6 / 42.8

Br_2 [ml/h] / Educt [ml/min]:

24.5 / 49.8

18.4 / 28.4

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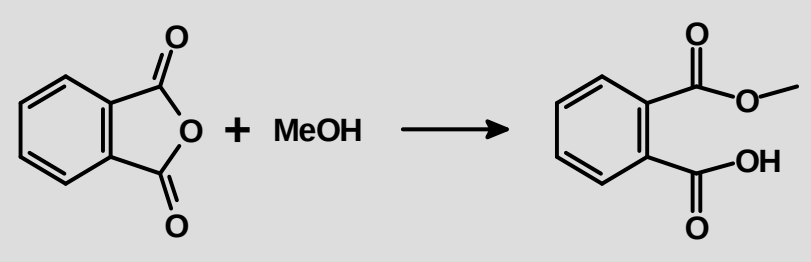
ANHYDRIDE ESTERIFICATION

Alternative solvents

Supercritical processing with CO_2 up to 110 bar

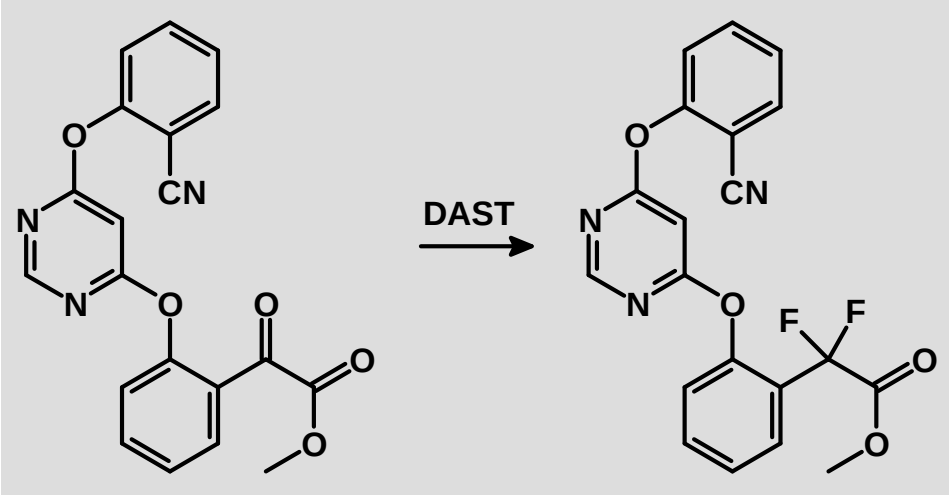


- **Normal high-pressure operation led to 53-fold increase at 110 bar and 60°C as compared to batch experiments at 1 bar and 60°C**
- **Supercritical CO_2 processing led to a 5400-fold increase**
- **Reason: changes in activation energies, possibly due to pressure-induced changes in reaction mechanisms, negative molar activation volume, and surface (catalytic) effects.**

F. Benito-Lopez, R. M. Tiggelaar, K. Salbut, J. Huskens, R. J. M. Egberink, D. N. Reinhoudt, H. J. G. E. Gardeniers, W. Verboom, *Lab Chip* **7** (2007) 1345–1351.

HAZARDOUS REACTIONS
FLUORINATIONS WITH REACTIVE AGENTS

Hazardous reagents



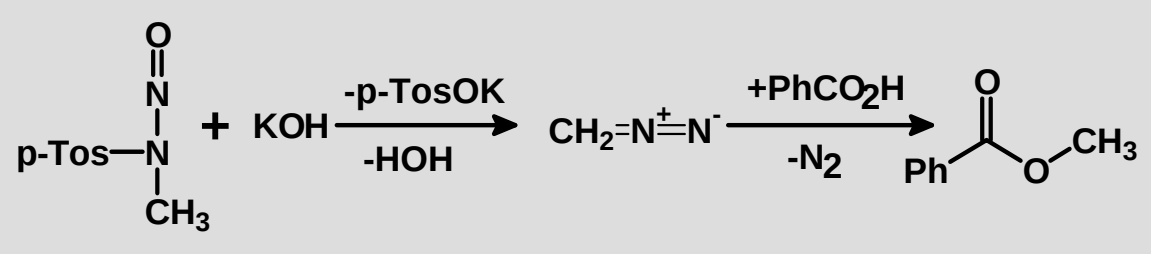
Dedicated fluorinations with diethyl-amino-sulfur trifluoride (DAST), (1-chloro-methyl-4-fluoro-1,4-diazo-niabicyclo-[2.2.2]octane), bis(tetrafluoroborate) (Selectfluor®), and and trimethylsilyl trifluoromethane (TMS-CF3, Ruppert's reagent)

- **DAST, for example, is volatile, reacts violently with water and readily undergoes dismutation to SF_4 and $(Et_2N)_2SF_2$ at temperatures above 90°C**
- **A series of methods including nucleophilic fluorination, electrophilic fluorination and trifluoromethylation in a commercial capillary flow reactor**
- **Products with purities >95% and at yields up to 95%, eliminating purification**
- **Pressurised operation through back-pressure regulators led to superheated processing to accelerate the reactions**

M. Baumann, I.R. Baxendale, L.J. Martin, S.V. Ley, *Tetrahedron* **65** 2009, 6611–6625.

DIAZOMETHANE CONVERSION

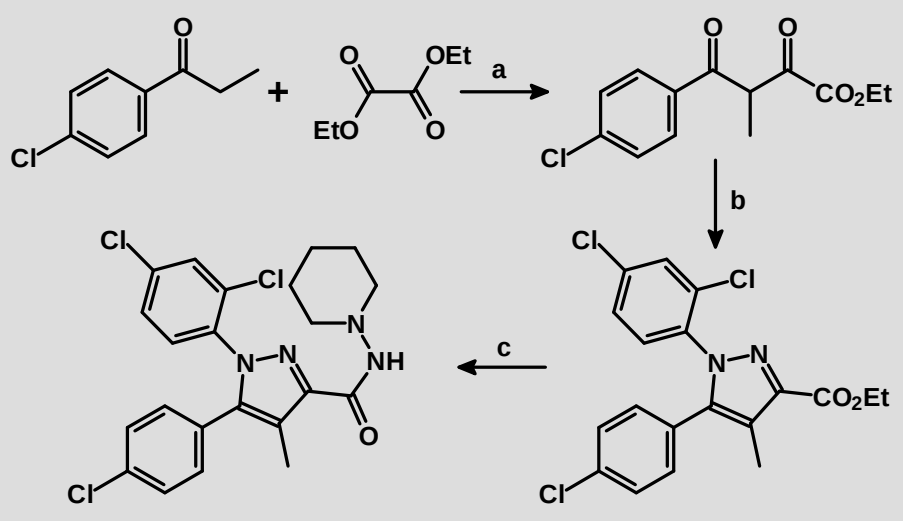
Hazardous reagents



- **Generation of diazomethane from a commercial precursor, Diazald®**
- **Consumed at-site consumed by reaction**
- **Benzoic acid methyl ester at a yield of up to 75% at 0 and 50°C**
- **2.5 mol d^{-1} of diazomethane can be produced with a single microreactor at a total flow rate of 840 ml h^{-1}**

M. Struempel, B. Ondruschka, R. Daute, Annegret Stark, *Green Chem.* **10** (2008) 41–43.

Trimethylaluminium mediated amide bond formation



Hazardous reagents

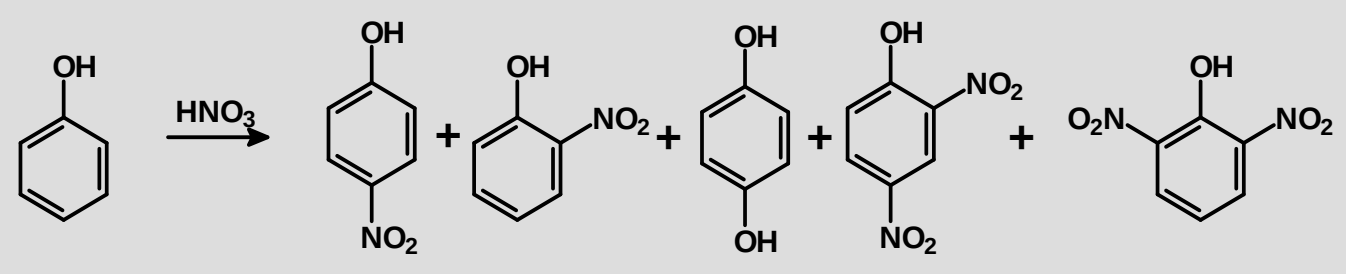
- **Aluminium-mediated amine activation with trimethylaluminium, highly pyrophoric and difficult to handle safely in larger volumes**
- **The aluminium–amide intermediate is unstable at elevated temperatures**
- **Batch reaction at 4 and 16 h**
- **Combined microwave and microreactor operation at 2 min**
- **Applied for the synthesis of rimonabant and efaproxiral at 49% yield**
- **Rimonabant is anti-obesity drug & central cannabinoid receptor antagonist**

T. Gustafsson, F. Pontén, P.H. Seeberger, *Chem. Commun.* 2008, 1100–1102.

AUTOCATALYTIC NITRATION OF PHENOL

Hazardous reagents

- **Nitration of phenol is different from normal nitrations, because it is catalyzed by nitrous acid and not by the nitronium ion**
- **Autocatalytic behaviour**

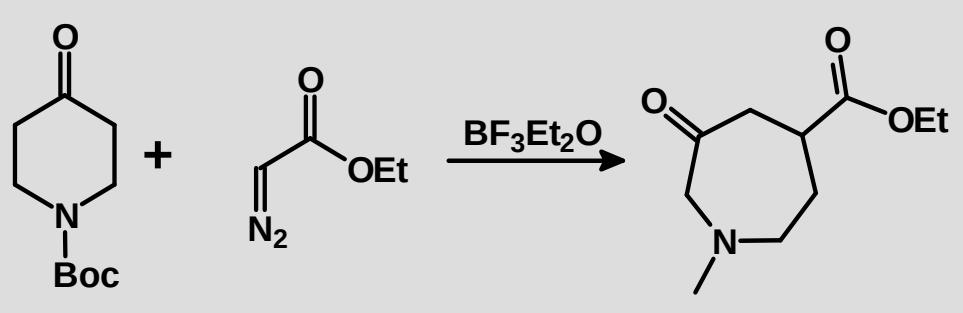


- **Thermal runaway behaviour, even at small scale (1 l) an increase of 55 K**
- **Hot-spot in microreactor was only about 5 K**
- **Micro processing with largely increased purities (batch: up to 25%, micro-flow: up to 79%), and higher yields (batch: up to 32%, micro flow: up to 77%)**
- **Micro processing can use concentrated conditions, almost solvent-free and without H_2SO_4 or CH_3CO_2H**

L. Ducry, D. M. Roberge, *Angew. Chem.* **117** (2005) 8186–8189.

RING EXPANSION WITH DIAZO

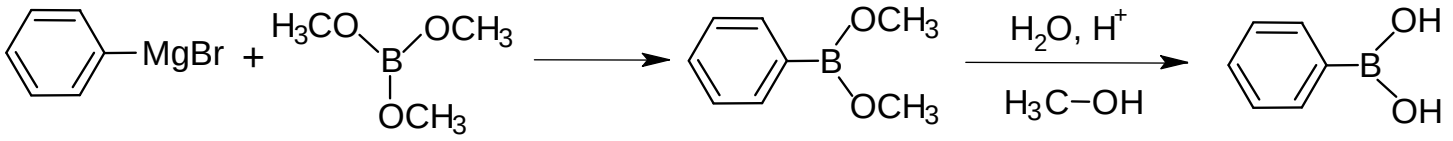
Hazardous reagents



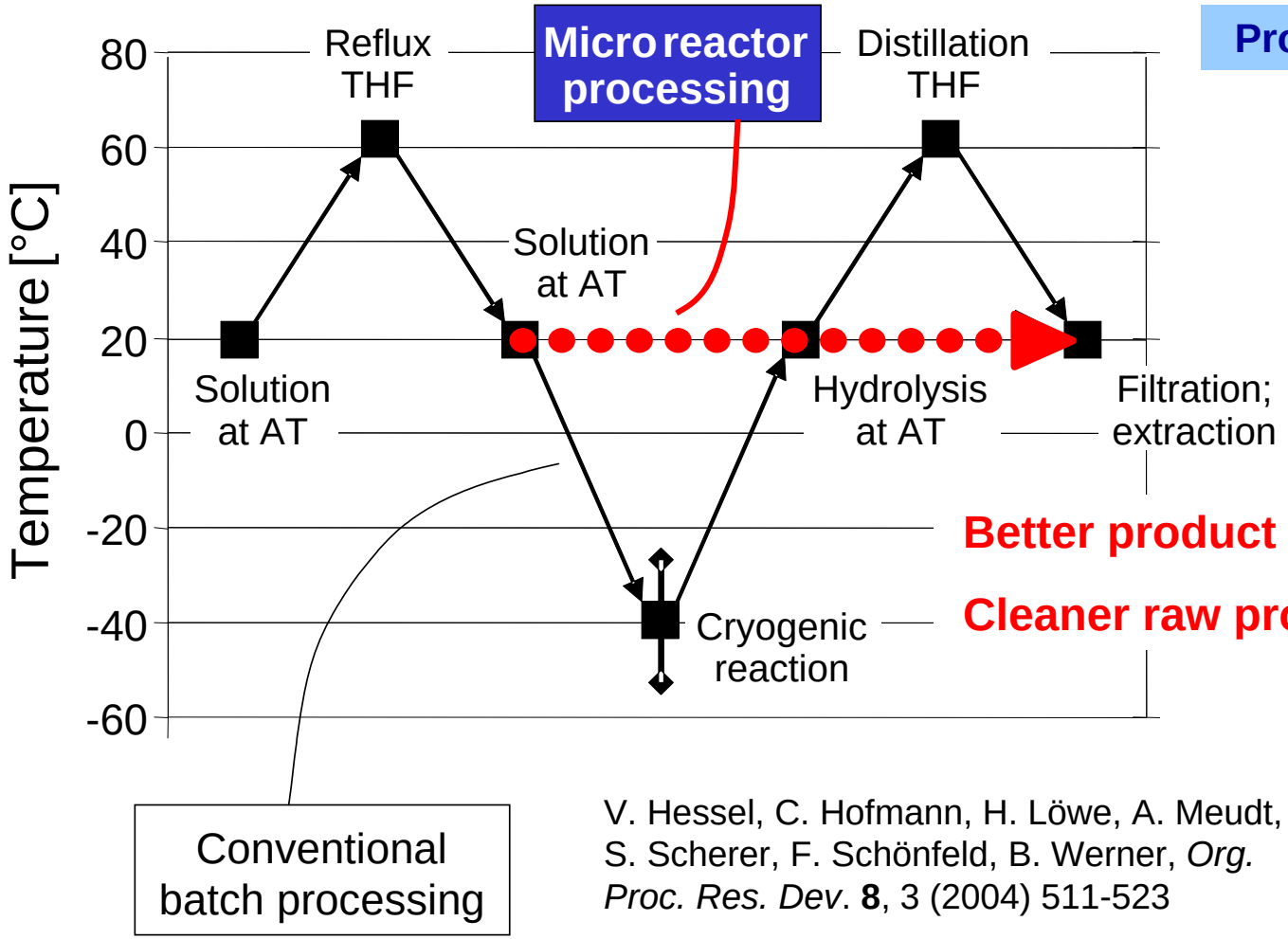
- **Conventional scaling-up of the reaction of *N*-Boc-4-piperidine was not possible despite 90% yield under strongly cooled conditions (-25°C).**
- **Intolerable temperature rises up to 45°C and reactor overpressurisation**
- **Safe micro processing at 89% yield and only 1.8 min**

X. Zhang, S. Stefanick, F.J. Villani, *Org. Process Res. Dev.* **8**, 3 (2004) 455.

ENERGY SAVINGS FOR THE PHENYL BORONIC ACID PROCESS



Process simplification



Better product selectivity by 25%

Cleaner raw product by 10%

V. Hessel, C. Hofmann, H. Löwe, A. Meudt, S. Scherer, F. Schönfeld, B. Werner, *Org. Proc. Res. Dev.* **8**, 3 (2004) 511-523

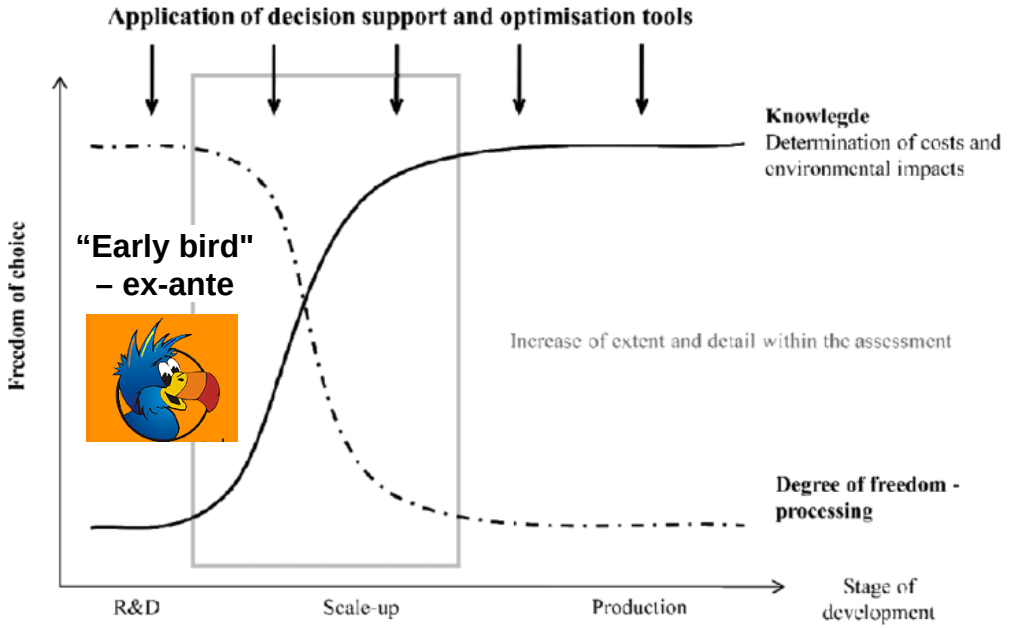
Cost and Environmental Impacts

– Cost and Life-Cycle Analysis

'"EARLY-BIRD MEASURING RODS' AND BE HOLISTIC

(Simplified) Life-Cycle Analysis

"Do not lock the stable door after the horse has bolted"



S. Hübschmann, D. Kralisch, V. Hessel, U. Krtschil, C. Kompter *Chem. Eng. Technol.* **32**, 11 (2009) on-line.

Check for competitiveness

"Be holistic"

INDUSTRY & SOCIETY BOUNDARIES	Market Growth	Sustainability
NEW TECHNOLOGIES	Process Intensification (Green Processing)	Milli and Micro Process Technologies
COMPETITIVENESS CHECK (ex-ante)	Cost Analysis	Life-Cycle Analysis
POTENTIAL & BENEFIT ANALYSIS	Effects of Miniaturization	Benefits of Flow Chemistry
HOLISTIC & SYSTEMIC APPROACH	**Novel Process Windows**	Flash Chemistry
EXPLOITATION	Demonstration Cases	Benefit-Cost Analysis

V. Hessel *Chem. Eng. Technol.* **32**, 11 (2009) on-line.

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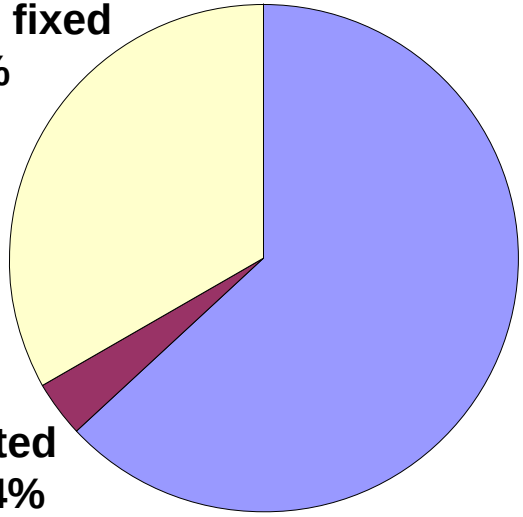
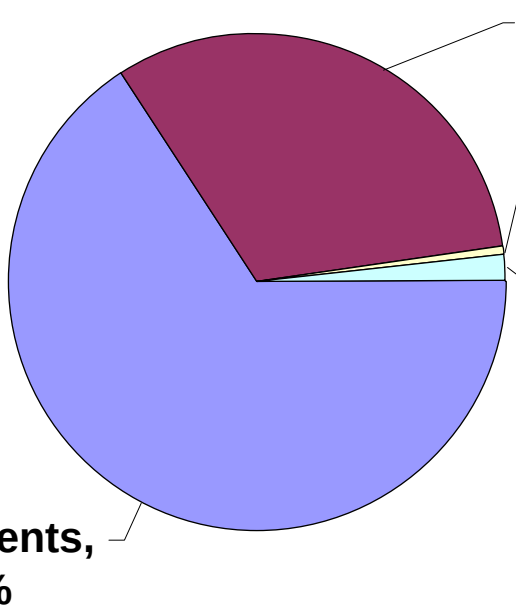
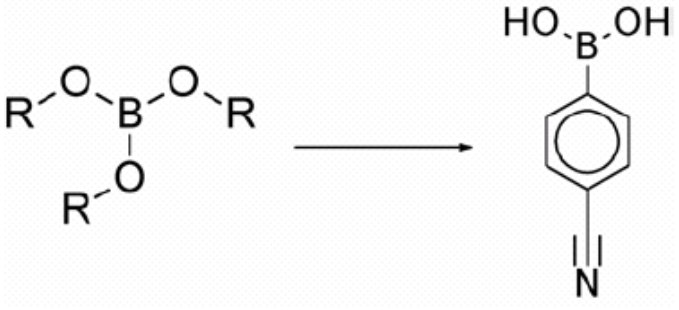
COST ANALYSIS FOR COMMERCIAL MICROREACTOR PROCESS AS IS

Total Costs



Variable Costs





U. Krtschil, V. Hessel, D. Kralisch, G. Kreisel, M. Küpper, R. Schenk *Chimia* **60**, 9 (2006) 611-617.

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COSTING ANALYSIS - 2,4-DIHYDROXY BENZOIC ACID SYNTHESIS

Base case: high-p,T	**µ-REAC PLANT – 1 reactor; 4.4 t/a; 10 l/h** 45% selectivity; 200°C / 40 bar (‚high-p,T')	**92.10 € / kg**
Selectivity	**µ-REAC PLANT – 1 reactor; 4.4 t/a; 10 l/h** 70% selectivity; 200°C / 40 bar (‚high-p,T')	**78.43 € / kg**
External numbering-up	**µ-REAC PLANT – 10 reactors; 44 t/a; 100 l/h** 45% selectivity; 200°C / 40 bar (‚high-p,T')	**57.47 € / kg**
Further PI by high-p,T	**µ-REAC PLANT – 1 reactor; 44 t/a; 100 l/h** 45% selectivity; 200°C / 40 bar (‚high-p,T')	**56.95 € / kg**
Without high-p,T	**µ-REAC PLANT – 1 reactor; 0.01 t/a; 0.025 l/h** 45% selectivity; 100°C / 1 bar	**17,352.52 € / kg**
Bench-marking	**BATCH-REACTOR PLANT – 1 l; 0.27 t/a** 45% selectivity; 100°C / 1 bar (‚Reflux')	**985.18 € / kg**
Bench-marking	**BATCH-REACTOR PLANT – 20 l; 4.3 t/a** 45% selectivity; 100°C / 1 bar (‚Reflux')	**107.05 € / kg**

U. Krtschil, V. Hessel, D. Kralisch, G. Kreisel, P. Löb, H. Löwe *Org. Proc. Res. Dev.* (2006) in preparation.
U. Krtschil, V. Hessel, D. Kralisch, G. Kreisel, M. Küpper, R. Schenk *Chimia* **60**, 9 (2006) 611-617.

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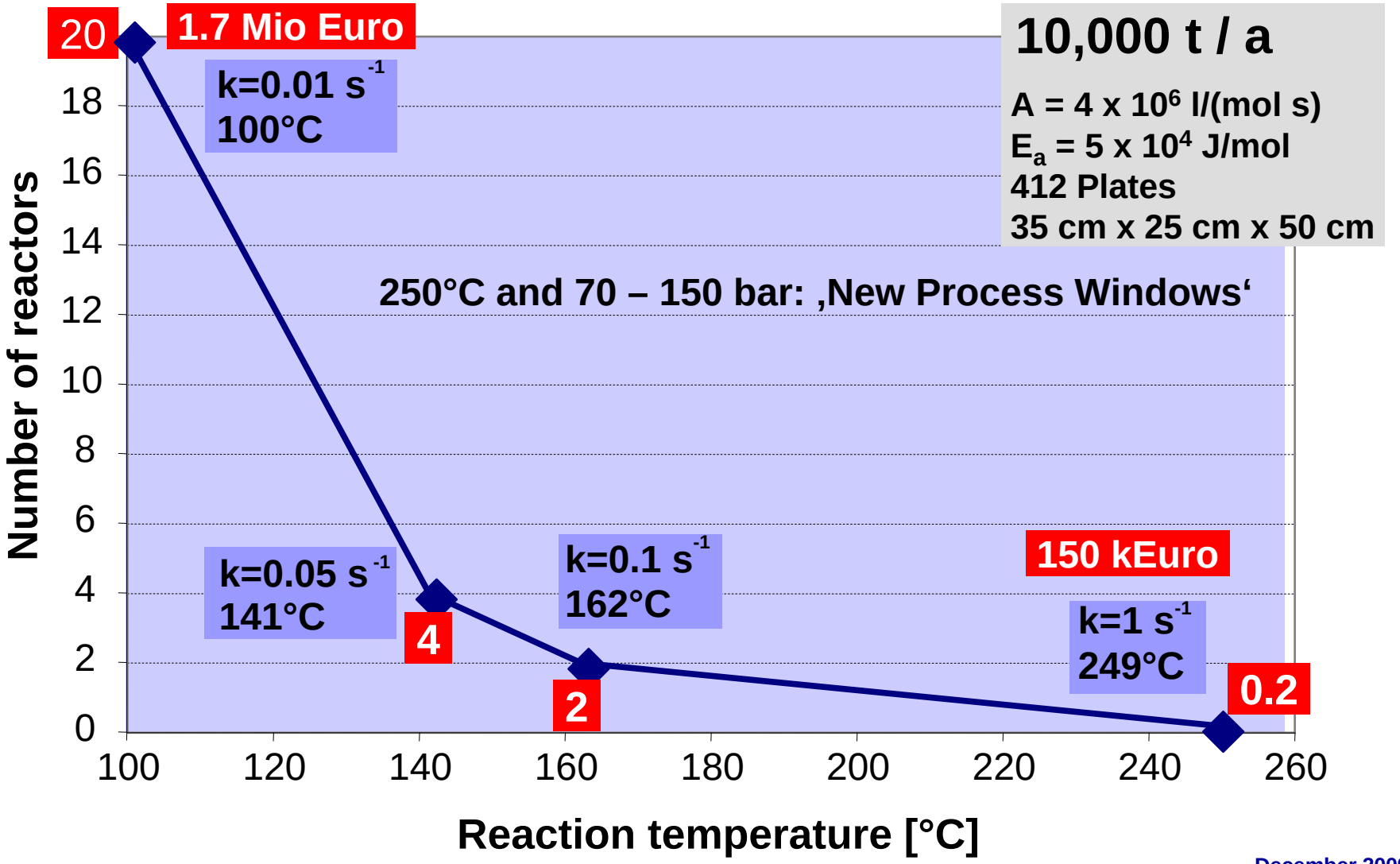
HYPOTHETICAL LIQUID-PHASE REACTION AT THE EDGE TO LARGE-SCALE PRODUCTION



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December 2009

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COMPARISON OF VARIABLE COSTS

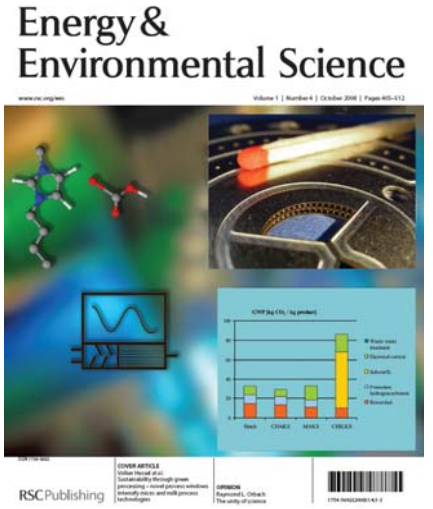
M-A-KS

Raw material	40 € / kg product
Labour	42 € / kg product
Waste	12 € / kg product
Energy	2 € / kg product
Variable costs	96 € / kg product

CH-A-KS

Raw material	54 € / kg product
Labour	41 € / kg product
Waste	16 € / kg product
Energy	2 € / kg product
Variable costs	113 € / kg product

Heating \ Solvent	Aqueous	Ionic liquid
Conventional	CHAKS: 113 € / kg	CHILKS: 258 € / kg CHILKS*: 41 € / kg
Microwave	MAKS: 96 € / kg	not considered



V. Hessel, D. Kralisch, U. Krtschil, Energy Environm. Sci. (2008) in press.

CH-IL-KS

Raw material	202 € / kg product
Labour	40 € / kg product
Waste	15 € / kg product
Energy	1 € / kg product
Variable costs	258 € / kg product

CH-IL-KS *

(20 times lower costs)

Raw material	20 € / kg product
Labour	10 € / kg product
Waste	11 € / kg product
Energy	0.38 € / kg product
Variable costs	41 € / kg product

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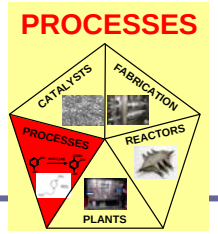
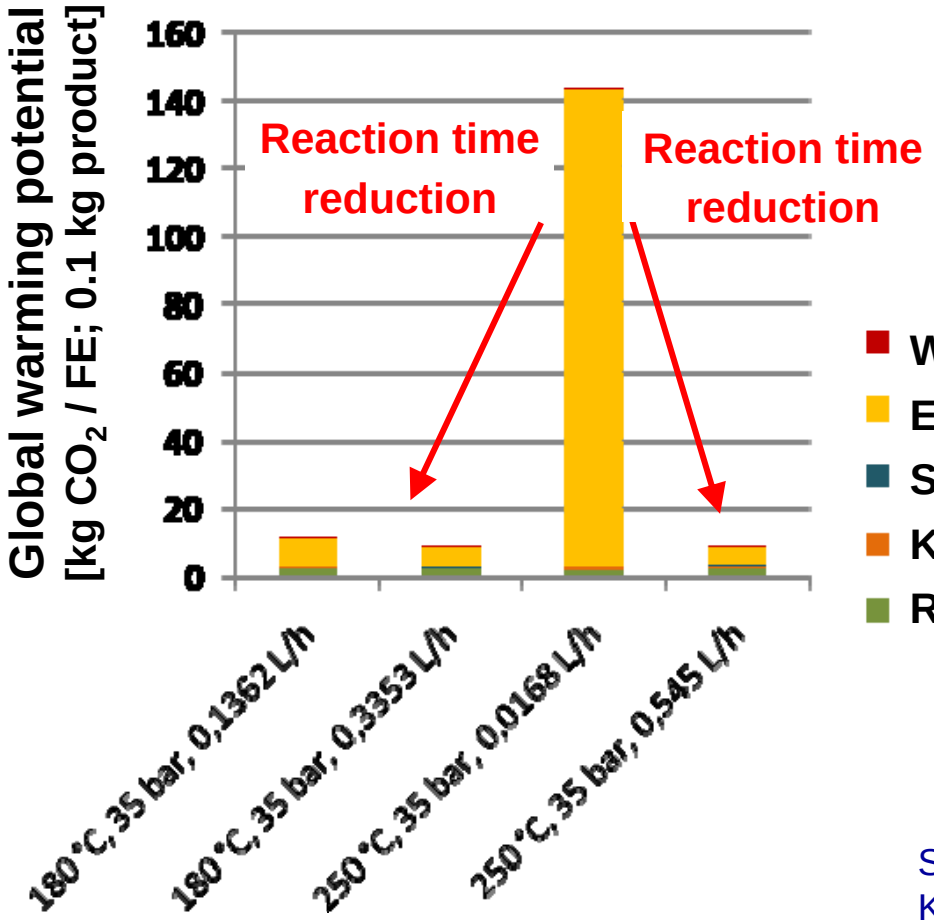
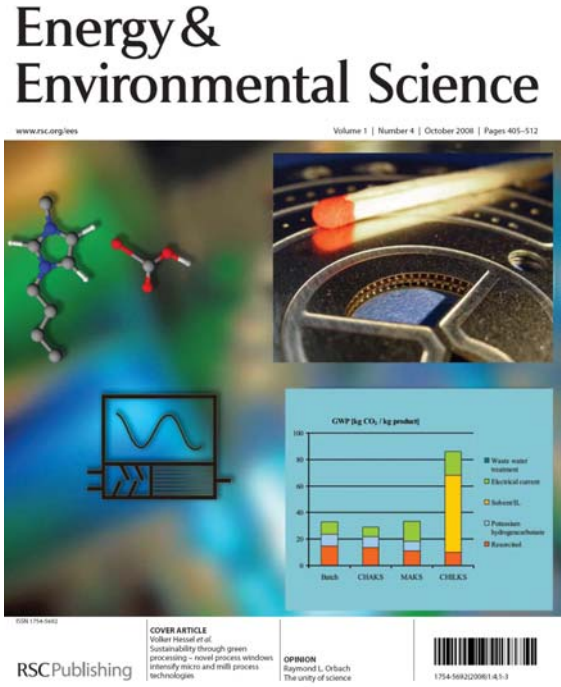


REACTION TIME IS DETERMINING FACTOR NO. 1





V. Hessel, D. Kralisch, U. Krtschil *Energy Environ. Sci.* **1**, 4 (2008) 467- 478.

S. Huebschmann, D. Kralisch, V. Hessel, U. Krtschil, C. Kompter, *Chem. Eng. Technol.* **32**, 11 (2009) 1757-1765.

Fast reaction processing has much better global warming potential

→Efficient use of reactor capacities is prime issue for eco-efficient processing

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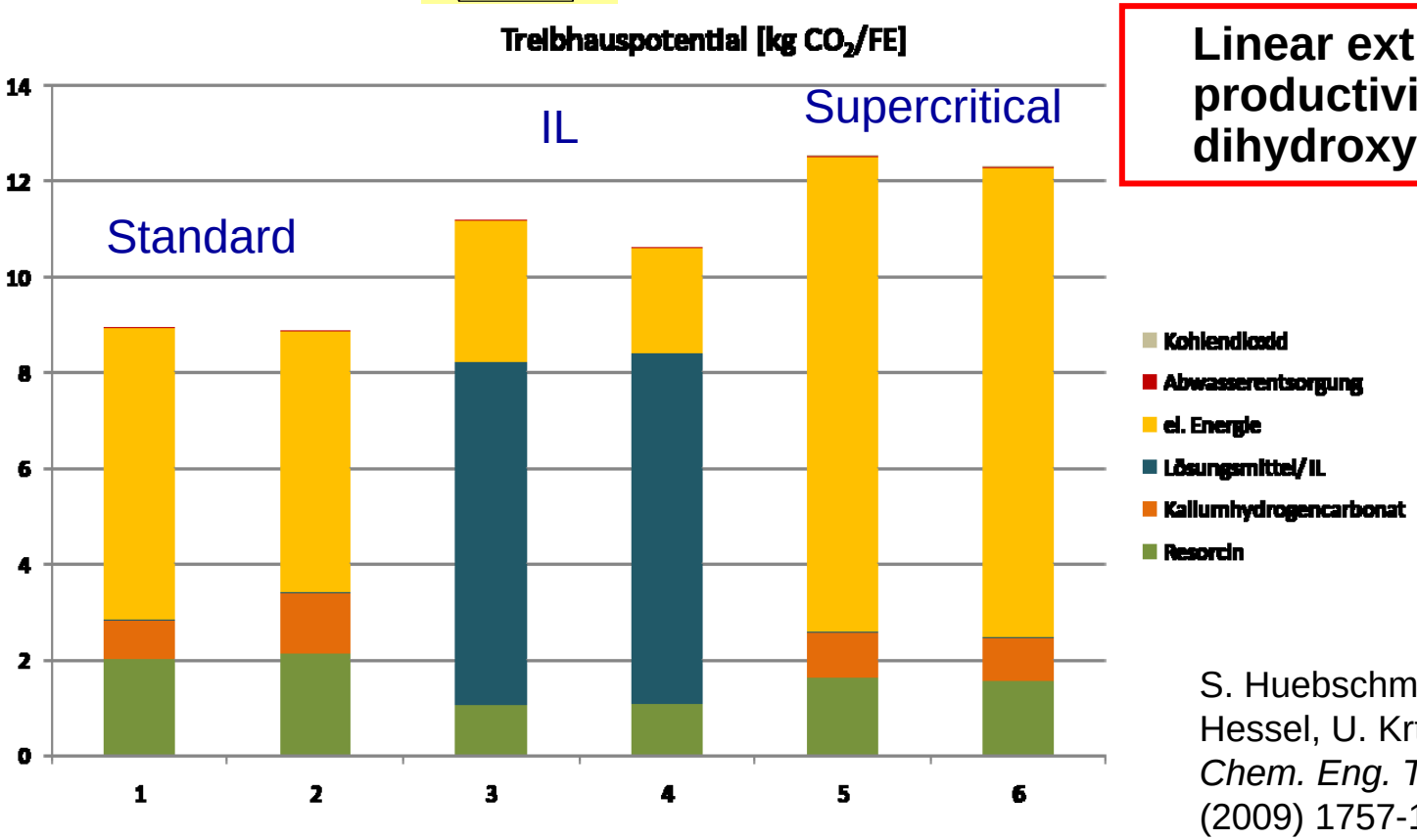
December 2009

GLOBAL WARMING POTENTIAL



Linear extrapolation to productivity 100 g 2,4-dihydroxy benzoic acid

S. Huebschmann, D. Kralisch, V. Hessel, U. Krtschil, C. Kompter, *Chem. Eng. Technol.* **32**, 11 (2009) 1757-1765.

- **Energy and raw materials determining factors**
- **New processing approaches such as use of ionic liquids may provide different, distinct LCA (and costing) patterns – here: overall negative, due to costly manufacture of ionic liquids (recycling)**

- **Dissemination & Exploitation**

  Conferences, Symposia,
  Research Projects, Products

X-CUBE™: NEW COMMERCIAL HIGH-p,T FLOW REACTOR

X-CUBE™

High-temperature, high-pressure bench top flow reactor

200°C and 150 bar

Advantages

- **Completion of many reactions in minutes**
- **Optimization "on the fly"**
- **Low-volume system: conductance of volatile reactions safely and at high pressure**

Suzuki, Sonogashira and Heck couplings, Buchwald reaction, Halogenation, Alkylation Dehydration, Esterification, Azide formation

ThalesNano

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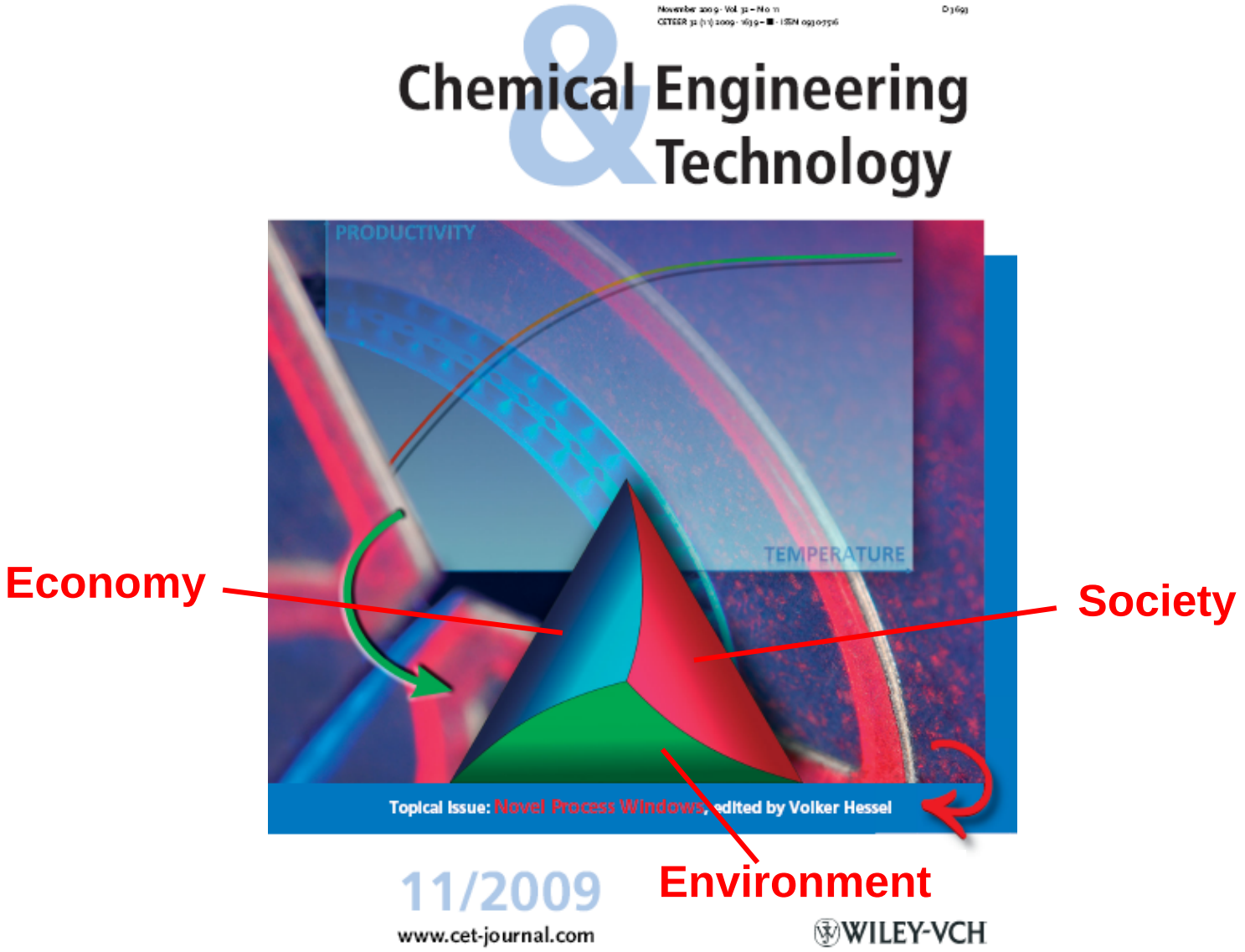
NOVEL PROCESS WINDOWS CET SPECIAL ISSUE

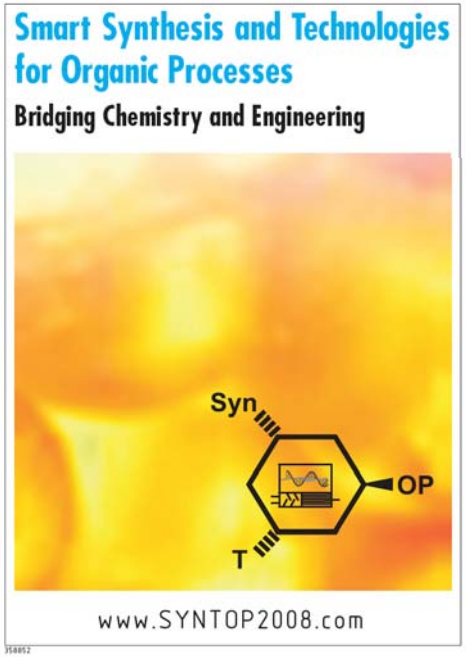


SynTOP CONFERENCE POTSDAM, JUNE 2008: BRIDGING CHEMISTRY AND CHEMICAL ENGINEERING

VDI Wissensforum

Conference Announcement and
Call for Papers
1st SynTOP

June 11-13, 2008
Potsdam, Germany



Main Topics of the Conference

1 **Micro and Milli Continuous Process Technologies**
Microfabricated reactors and other devices (plate-type)
Capillary and tube reactors
Foams, monoliths and other structured media

2 **Alternative Energy Sources**
Microwaves
Ultrasound
Photochemistry
Electrochemistry

3 **Alternative Reaction Media**
Ionic liquids
Supercritical liquids

4 **Intensified Plants and Processes**
Intensified equipment
Modular concepts
Case studies
Process development
Piloting
Scale-out

5 **Advanced Organic Synthesis & Process Chemistry & Automation**
Multi-step synthesis in micro reactors
Challenging reactions in micro reactors
Case studies

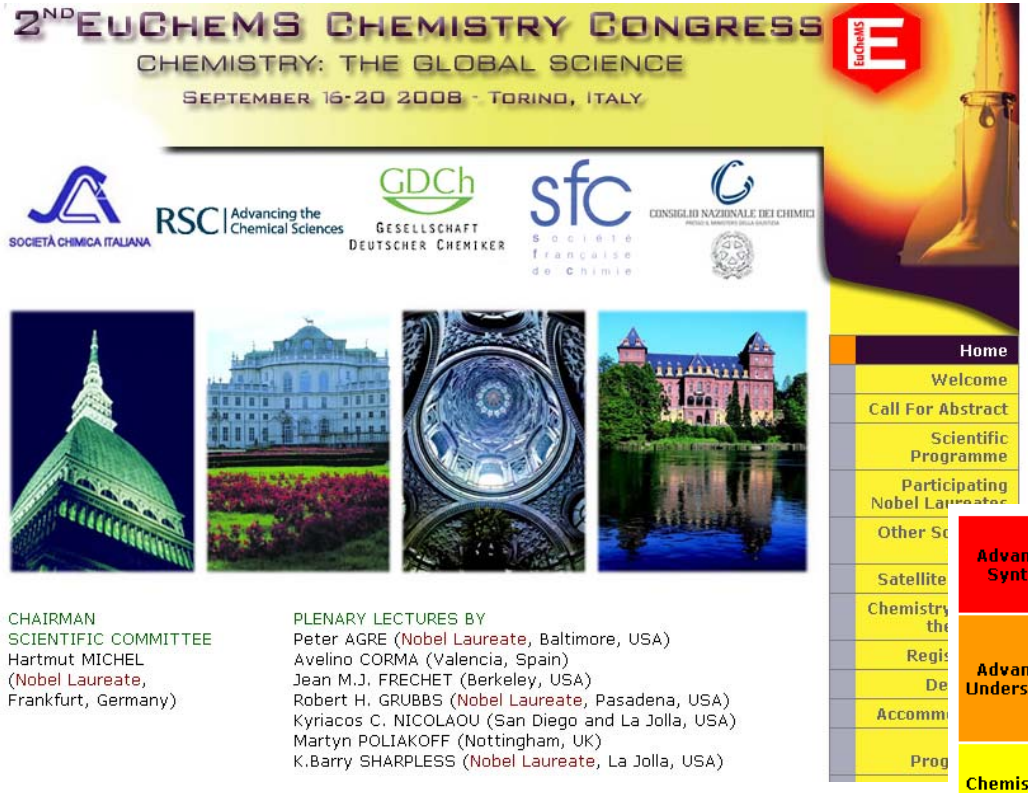
Plenary Lectures

Steven V. Ley, University of Cambridge, United Kingdom
New Tools for Molecule Makers

Michael Matlosz, E.N.S.I.C, Nancy, Fance
Microprocess engineering, process intensification and multiscale design

Syntop (Ökologie): Lebewesen, die in einem bestimmten Biotop gemeinsam vorkommen

CONGRESS OF THE EUROPEAN ASSOCIATION FOR CHEMICAL AND MOLECULAR SCIENCES (EuCheMS), TURINO, SEPTEMBER 2008



Reactions under Novel Conditions

Convener: V. Hessel (NL/DE)

Keynote:

J.-i. Yoshida (Uni Kyoto)

Topic Lectures:

N. Kockmann (Lonza)
L. Magna (IFP)
H. Lehmann (Novartis)
W. Verboom (Uni Twente)
D. Kralisch (Uni Jena)

Advances in Synthesis	Organic Catalysis Convener: J.S. Siegel (CH)	Radical Reactivity in Transition Metal Chemistry Convener: R. Poli (FR)	Reactions under Novel Conditions Convener: V. Hessel (NL/DE)
Advances in Understanding	Chemical Measurement Quality: Societal Impact Conveners: B. Magnusson (SE) E. Ferrara (IT)	Cutting Edge Chemistry with Computers Conveners: M. Yáñez (ES) T. Brinck (SE)	Food [illegible] Pushing Detection Limits down to Nothing Conveners: R. Battaglia (CH) R. Marchelli (IT)
Chemistry and Life Sciences	Biomolecular Interactions and Mechanisms Convener: J. Jiménez Barbero (ES)	Drug Targeting and Delivery Convener: K. Dawson (IE)	Metal Homeostasis Convener: H. Kozlowski (PL)
Energy and Industry	Biorefineries and Biotechnologies Convener: M. Penttilä (FI)	Energy Production & Storage Convener: C. Buess-Herman (BE)	New Trends for Agrochemicals Convener: C. Lamberth (CH)
Environment	Greening Chemistry Convener: G. Centi (IT)	Greenhouse Gases Convener: A.A. Jensen (DK)	Water Pollutants Conveners: S. Facchetti (IT) S. Herve (FI)
Materials and Devices	Branched Polymers - Smart Functional Materials Convener: D.K. Smith (UK)	Nanomaterials Convener: N. Champness (UK)	Porous Materials Convener: U. Müller (DE)

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TU/e technische universiteit eindhoven

FIVE COMING AND STARTED EU PROJECTS ON FUTURE CHEMICAL FACTORIES

F3 Factory
flexible • fast • future

Bayer Technology Services
BASF
Evonik-Degussa
Arkema
Rhodia …

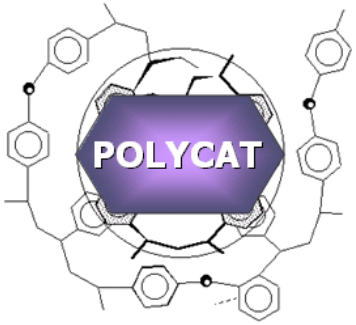
CoPIRIDE

Evonik-Degussa
Chemtex
Mythen
ITI Energy …

PILLS
Process Intensification of Liquid Liquid Systems

Huntsman
Givaudan
CUF

‘SYNFLOW’



Sanofi-Aventis
Bayer Technology Services
Evonik-Degussa
Picosun …

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December 2009