PIN-NL

Dutch Process Intensification Network

Process Intensification Research and Development

One of our PIN-NL objectives:
dissiminate and exchange PI knowledge and experience

PIN-NL meeting 19 October 2016

“Novel Process Windows for Enabling, Accelerating, and Uplifting Flow Chemistry”

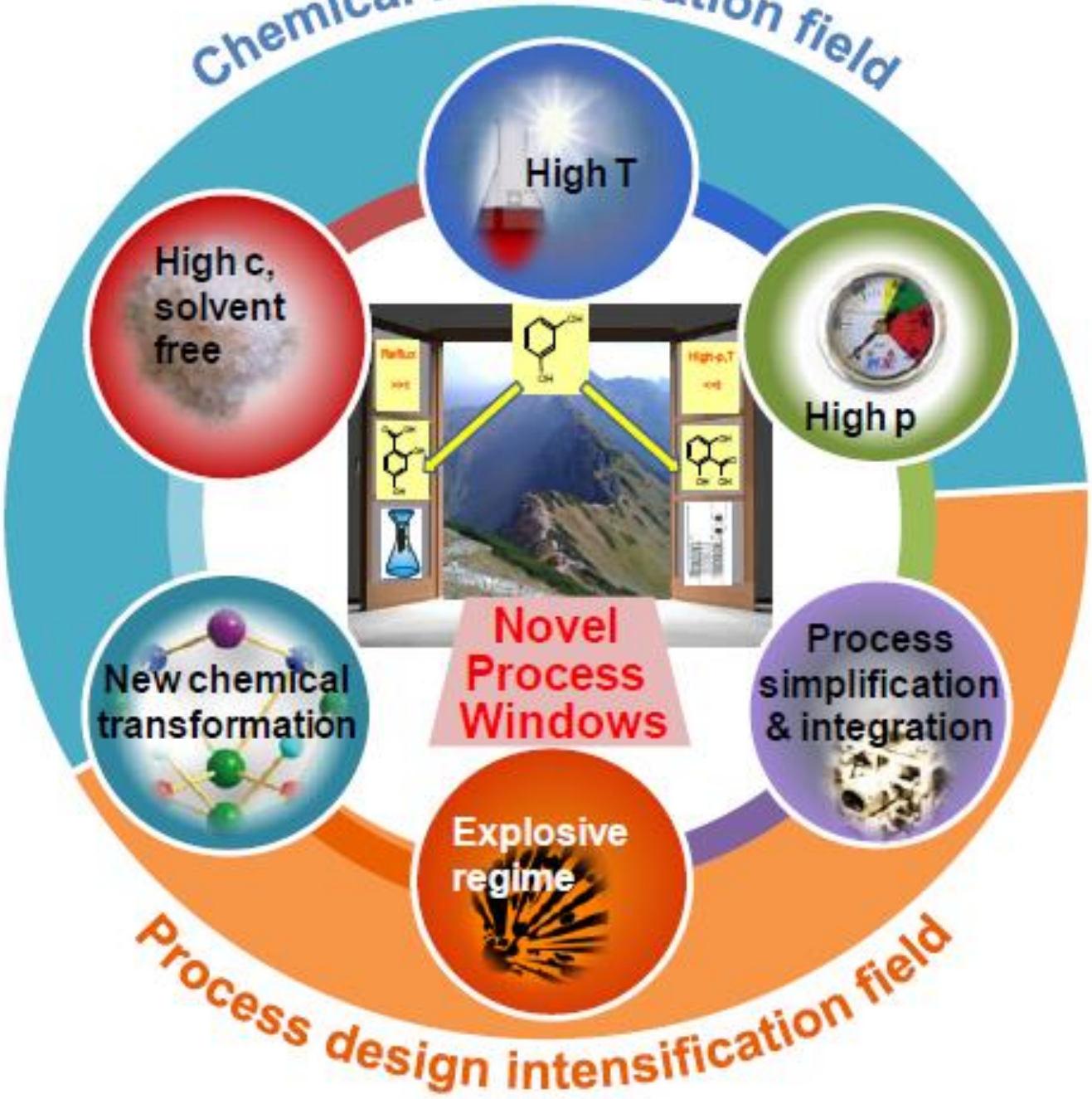
Volker Hessel, Dana Kralisch, Norbert Kockmann, Timothy Noël, and Qi Wang

ChemSusChem 2013, 6, 746 – 789 *a review*

Novel Process Windows = process conditions far from conventional practices:

- high temperatures, high pressures, high concentrations (solvent-free) / green solvents, new chemical transformations, explosive conditions
- process simplification and integration to boost synthetic chemistry on both the laboratory and production scale.

→ **microstructured** flow reactors due to their excellent transport intensification properties.


Chemical intensification field
High T
High c, solvent free
High p
Novel Process Windows
New chemical transformation
Process simplification & integration
Explosive regime
Process design intensification field

Introduction

Microreactor technology (see also spinning disk etc.)

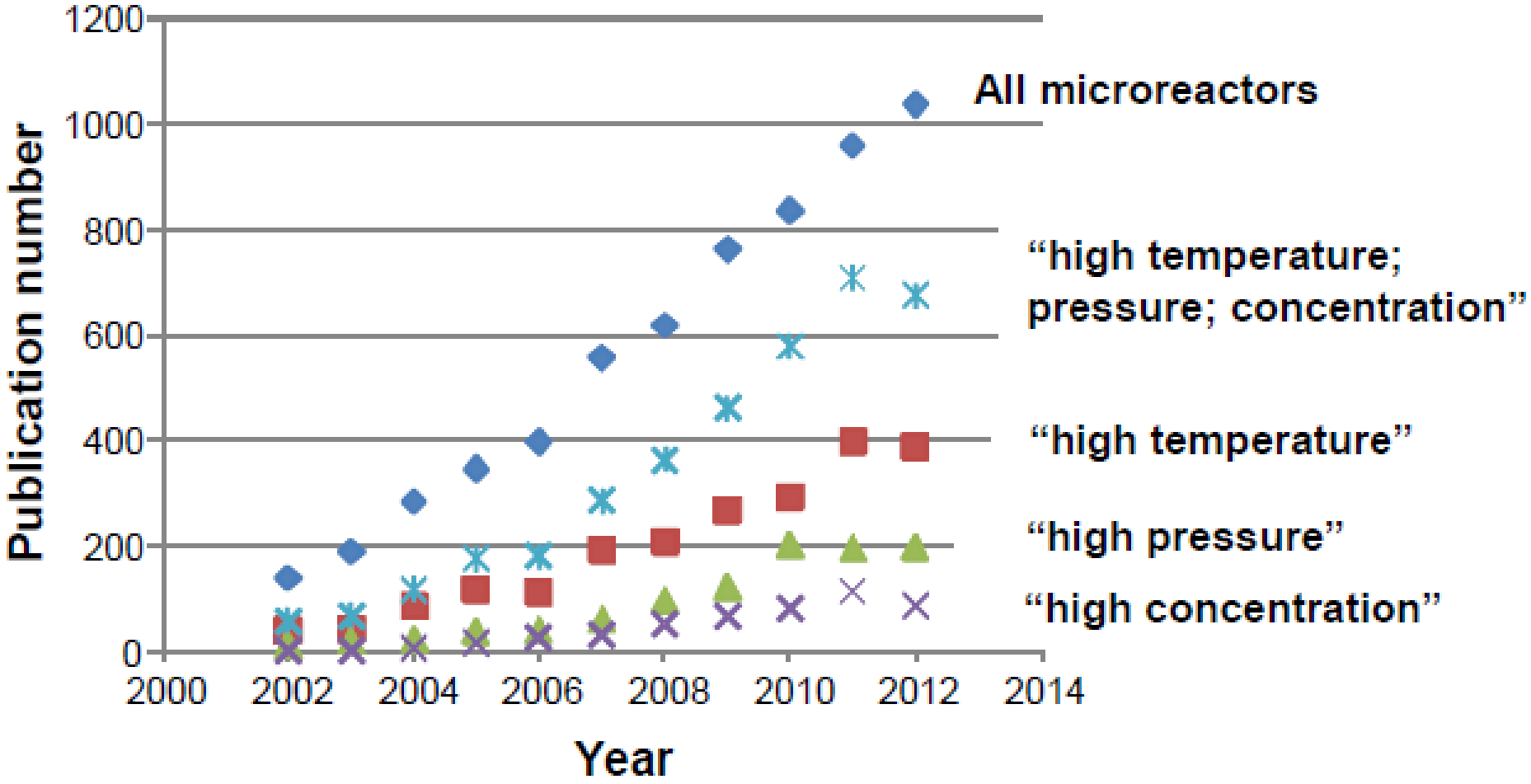
- Unique flow: laminar flow for single flows or defined multiphase flow patterns
- Short diffusion paths for heat and mass transfer
- High surface-to volume ratios for phase contact areas
- High share of solid wall material →a short path to the catalyst.

Leading to:

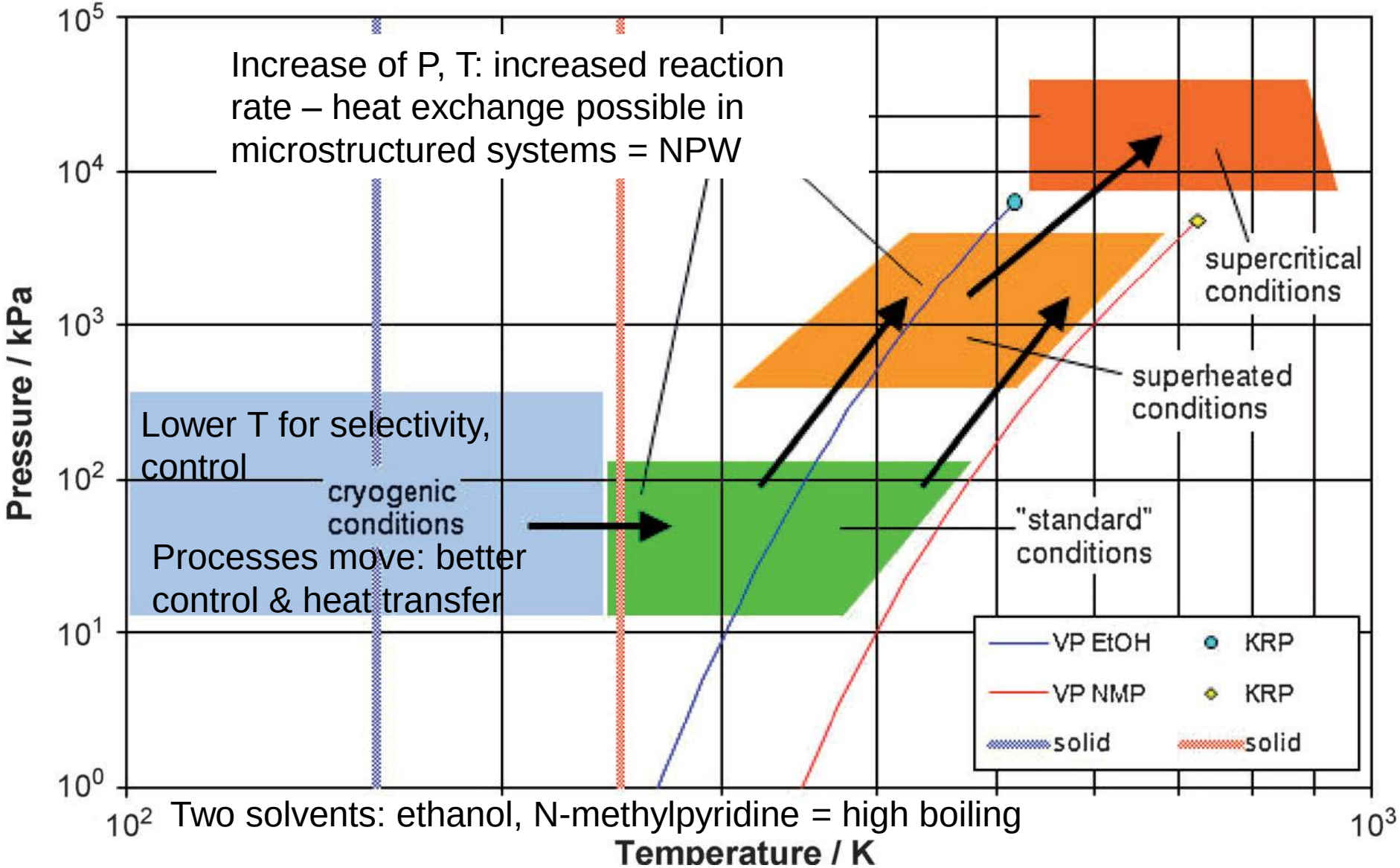
- Short residence times, narrow residence time distribution
- Faster mixing of miscible phases → to higher dispersion of immiscible phases
- Improved heat transport
- Improved safety.

New Process Windows

Chemical intensification = apply harsh – often unusual – conditions → change of chemistry



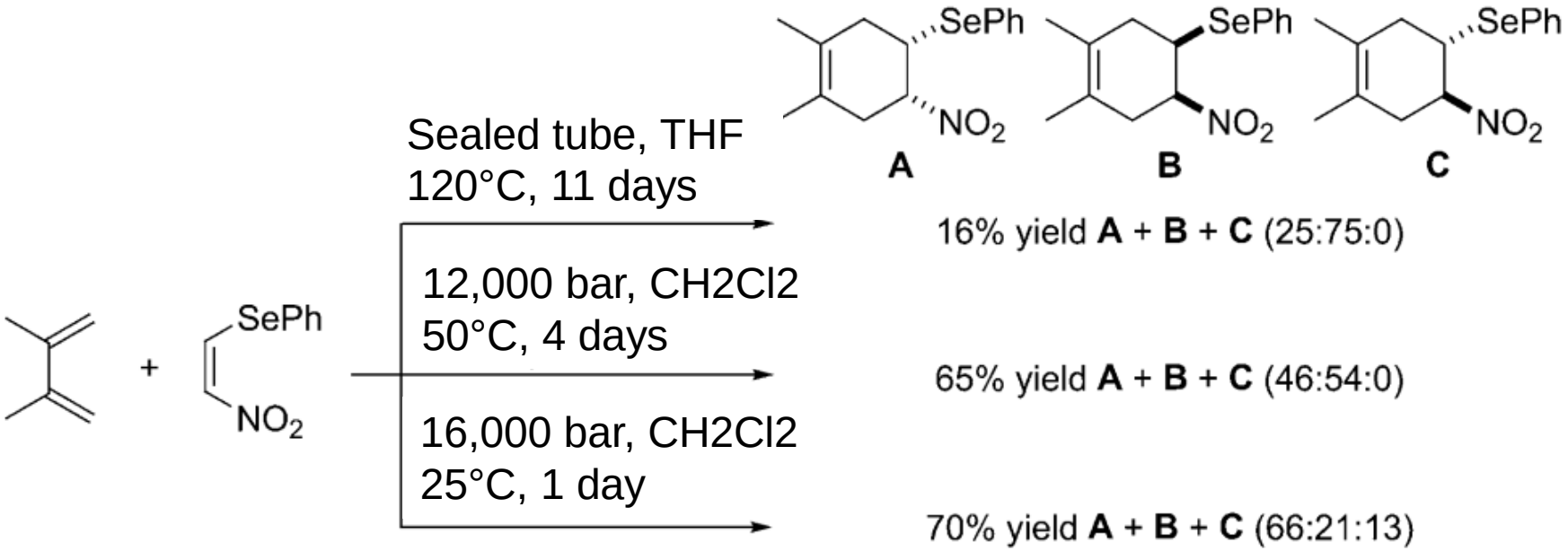
Chemical Intensification - Fundamentals



Two solvents: ethanol, N-methylpyridine = high boiling

Chemical Intensification – Pressure intensification

Cycloaddition between 2,3-dimethylbuta-1,4-diene and (E)-2-nitroethenyl]seleno}benzene →adducts endo-A and exo-B in only 16% yield in a ratio of 25:75 under low-pressure conditions. Under higher pressure (16 kbar), 70% yield and an endo/exo ratio of 66:21 were achieved

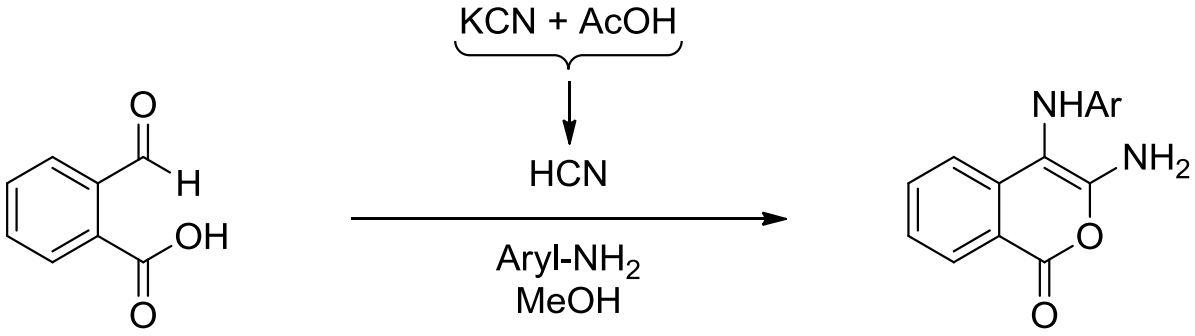


Use “Forbidden” regimes

Strecker synthesis - use of highly toxic HCN → hazardous on a batch scale.

Microreactor - generate small quantities of HCN in situ from

KCN and HOAc, HCN is immediately consumed in the reaction to yield 3,4-diamino-1H-isochromen-1-ones



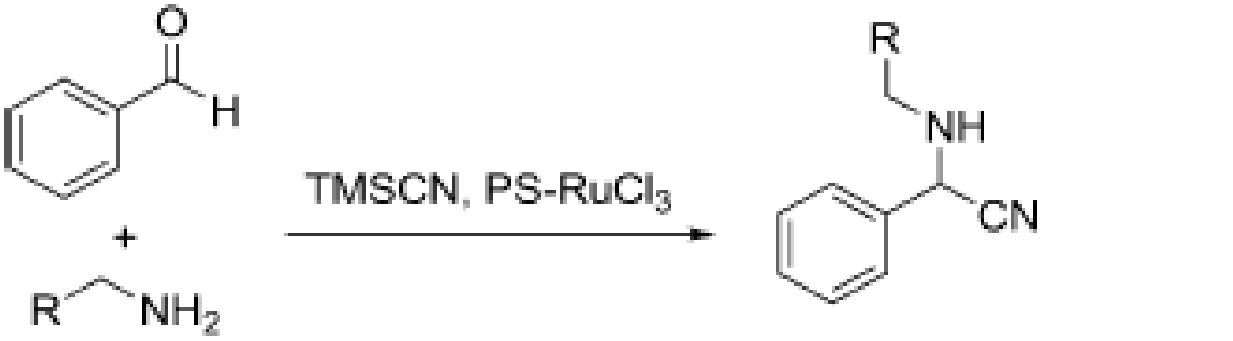
- 49-75 % yield
- T = 50 °C
- *p* = 1 bar
- *t* = 39 min
- tubular microreactor (CYTOS)

New Paths—New Chemical Transformations

Strecker: first mix carbonyl-containing compound + amine,

2nd introduce cyanide source (trimethylsilyl cyanide) – solid supported Lewis acid catalyst → aminonitrile, hydrolysis →amino acid

Conventional one pot: process P/T, cat losses, side reactions



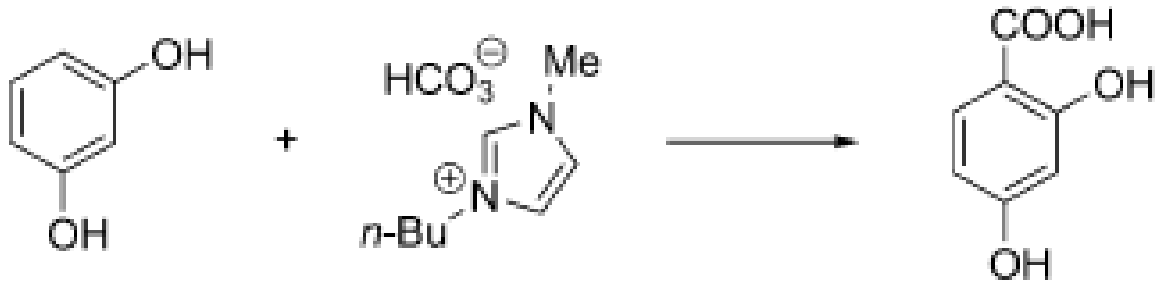
- >99.5% yield
- T = RT
- p = 1 bar
- t = 1.1-2.2 s
- glass microreactor

In glass chip 3x3x0.6 cm,
150x50 µm microchannels
PS - polystyrene

High-Temperature processing

Kolbe-Schmidt reaction: resorcinol + weak base KHCO3 → 2,4-dihydroxybenzoic acid

operation	time	Yield	Space time yield
Batch, 1 L flask	2 hrs	45%	0.02 ton/hr.m3
Micro channel, “superheated”	4 sec	40%	18
Micro + ionic liquid, no solvent			64
Micro channel, microwave heating	130 sec	59%	



Hessel et. al. review: 15 publications related to high temperature conversions, and 4 related to high T + P

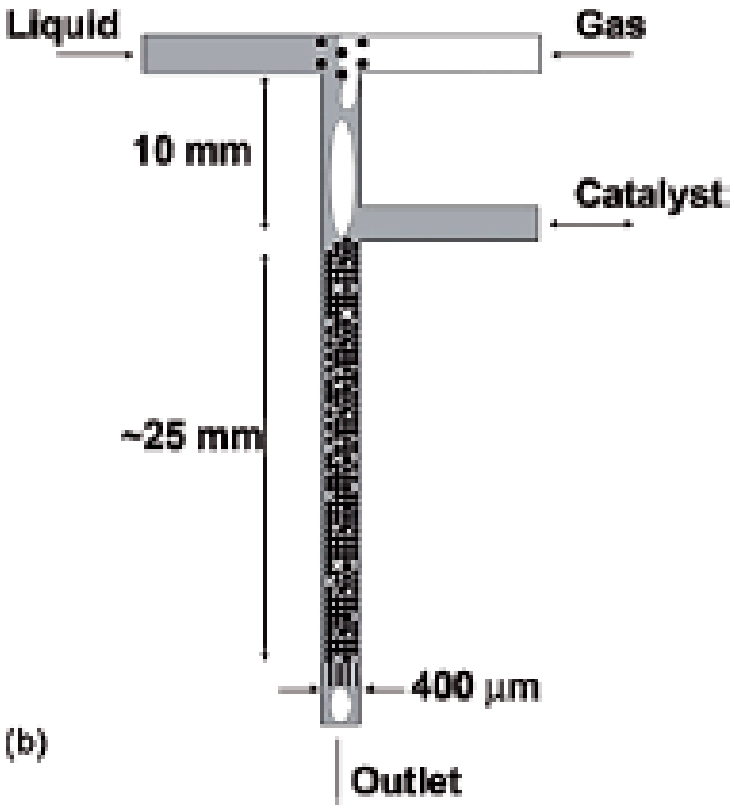
- 59 % yield
- T = 180 °C
- p = 35 bar
- t = 130 s
- tubular microreactor

High-Pressure processing

High pressure to intensify interfacial transport in G/L reactions.

Exothermic G/L/S hydrogenation of cyclohexane over a Pd catalyst is mass-transfer-limited.

Micro packed bed at high P:
increase reaction rate from
0.004 mol/gramcatmin(ambient)
to
0.046 mol/gramcatmin at 51 bar and 71°C

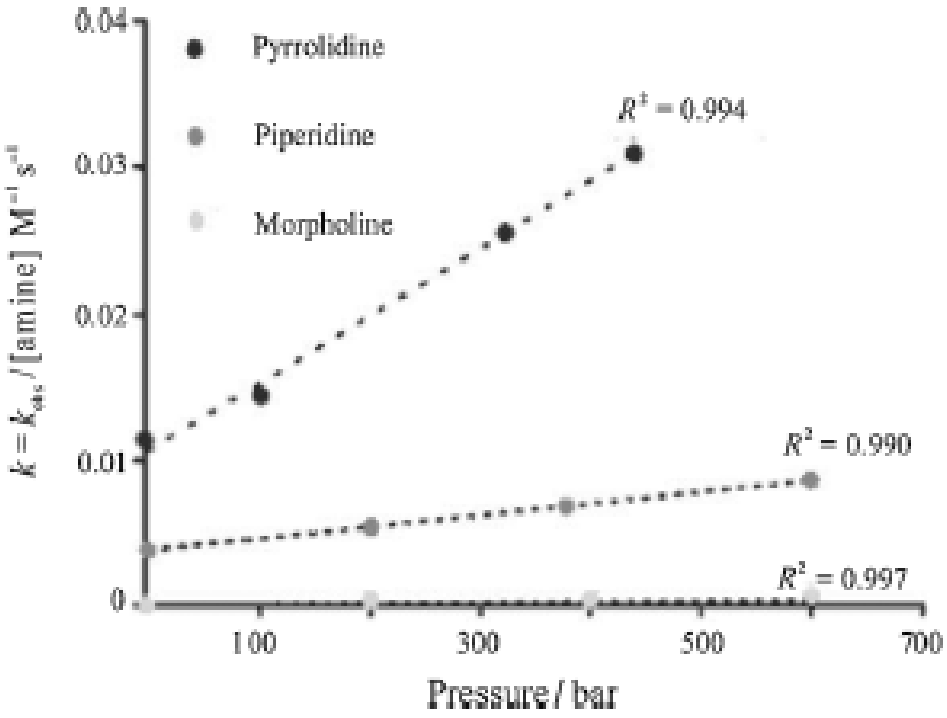


High-Pressure processing – effect on chemistry

Nucleophilic aromatic substitution of p-halonitrobenzenes

$n = 0$: pyrrolidine
$n = 1$, X = CH_2 : piperidine
$n = 1$, X = O : morpholine

Morpholine – small P effect
Pyrrolidine k x 2.7 for P to 450 bar

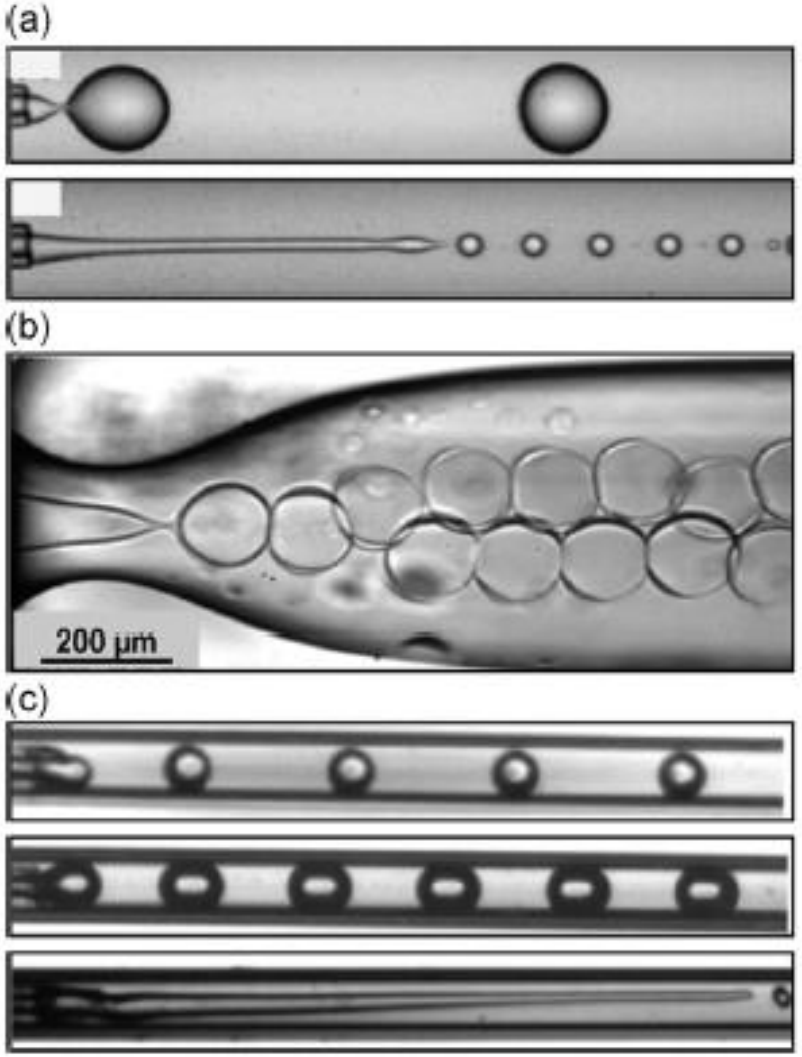


High-Pressure processing – $scCO_2$ in water

High-pressure devices based on co-flow arrangements of small silica tubing with millimeter internals (“millifluidics”) scCO2 droplets or jets were formed in liquid water without the need for stabilization by surfactants

a. droplets/emulsions
b. at low pressure
c. high P in super critical fluids

Application?



High Concentration and Tailored Solvent Processing

Opportunities: in pharma/fine batch chemical operation 80-90% of mass utilization is devoted to solvent.

Green flow processing-without solvent or workup-to synthesize allyl para-substituted phenyl phenols (R=Me, tBu, Ph, MeO, CN) through a Claisen rearrangement was developed in a capillary microreactor.

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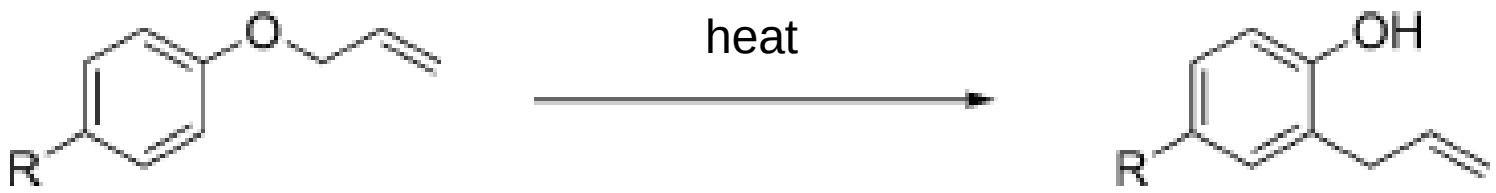
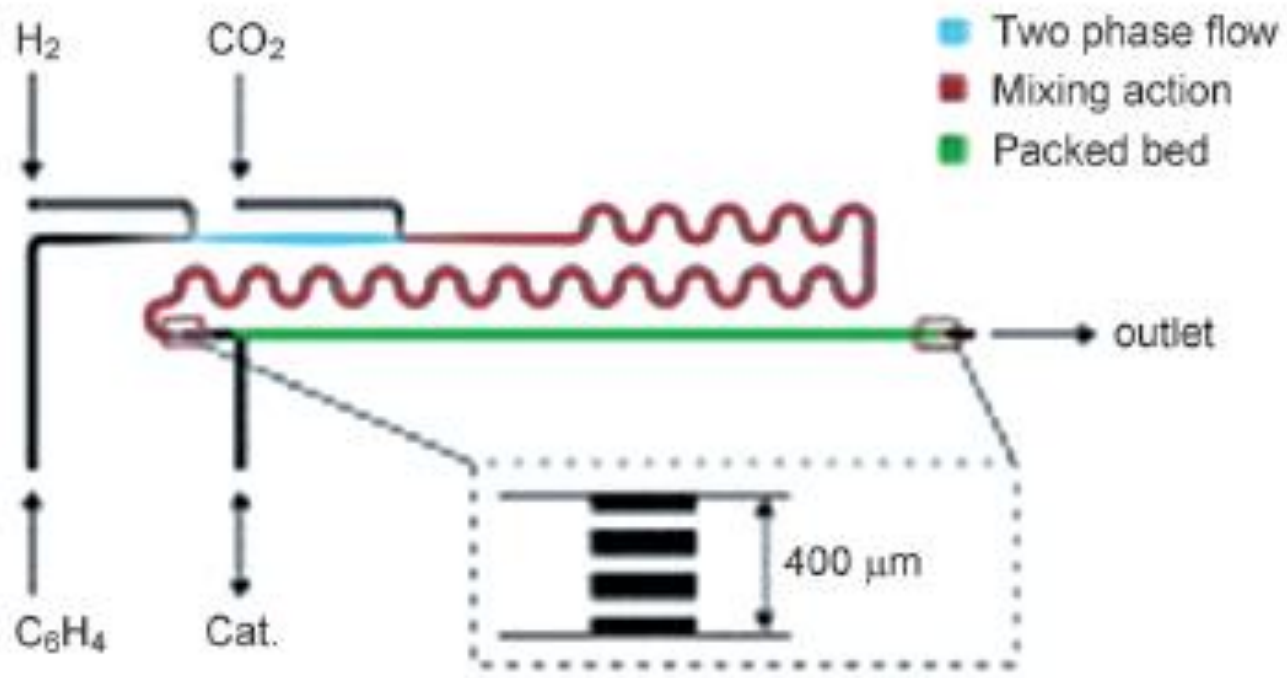


Compared with conventional batch processing under reflux, considerably higher yields and purities could be achieved in much shorter reaction time.

- 73-99 % yield
- T = 200-245 °C
- t = 24-36 min
- tubular microreactor

High Concentration and Tailored Solvent Processing

scCO2 as a reaction solvent for the hydrogenation of cyclohexene in a packed-bed silicon/glass microreactor. The mass-transfer limitations of conventional multiphase processing (1 bar, 25°C) are overcome through single-phase flow processing (136 bar, 25°C). The space–time yield is increased by one order of magnitude.



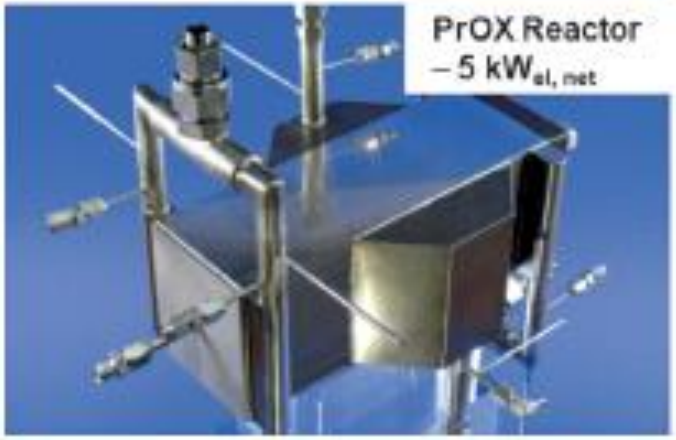
Combination mass/heat – Process Integration

Thermally coupled: a microstructured steam reformer for methane-based hydrogen generation + coupling to a catalytic combustor. The latter delivers the heat needed for the endothermic steam reforming reaction in co-flow.

WGS Reactor
– 5 $kW_{el, net}$

CH_4 conversion ~70%.

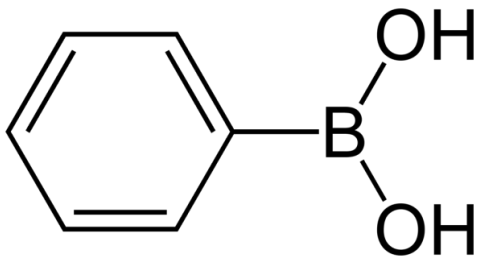
Total: 6.5 kW_{el}; >10 kW_{th}
Diesel STR/AFB -
5 $kW_{el, net}$



PrOX Reactor
– 5 $kW_{el, net}$

The same with less – Process Simplification

Synthesis of phenyl boronic acid
from phenyl magnesium bromide
and trimethyl boronic acid ester:



$PhMgBr + B(OMe)3 \rightarrow PhB(OMe)2 + MeOMgBr$

very fast reaction, needs to be cooled to cryogenic conditions to avoid mixing masking, which leads to severe losses in yield (>10–20%).

Industrial batch synthesis at the Clariant Company (Frankfurt, Germany) operated at -40 to -50°C, even then with only 65% yield of the product phenyl boronic acid.

Even slight temperature increases are sufficient to reduce the yield by some 10%.

The same with less – Process Simplification

Synthesis of phenyl boronic acid – continued:

Cooperation Clariant and IMM in Mainz: a microprocessing route was developed, → >20% higher yields at much increased temperatures, with a maximum yield of 89% at 20°C.

Moreover, higher purity of the raw product is achieved (99%) compared with the conventional process (82 %).

Separation simplification: better mixing and higher purity of the raw product eliminated the need for a capital- and energy-intensive distillation step.

Energy and cooling equipment was saved because microreactor chemistry could be conducted at ambient temperature instead of under cryogenic conditions.

Scale-up in Modular Flow Reactors

- More channels or devices
- Longer operational times
- Higher flow rates
  limited by increased pressure drop

Invite - F^3-Factory - fast, flexible, future 2009-2013

The F^3 Factory project has two key aims:

- to deliver radically new ‘plug and play’ modular chemical production technology, capable of widespread implementation throughout the chemical industry
- to deliver holistic process design methodology applying process intensification concepts and innovative decision tools

Objective of this contribution: show participants examples of new developments in PI related R&D

Method applied:
Selection of PI R&D sources – literature and contacts

This time a 40 pages review was selected

Open: next topic to be discussed

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