Immiscible, or Thermomorphous Phases in Double Emulsions
-
Application of Droplet-based Microfluidics with Unusual Solvents

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Outline

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- **Introduction – continuous flow - vs. droplet flow**
- **Heck- C-C coupling in thermomorphous double emulsions**

  (fluorous triphasic catalysis)
- **Carbene chemistry (if some time will be left)**
- **Summary**

Microfluidics – choice of flow

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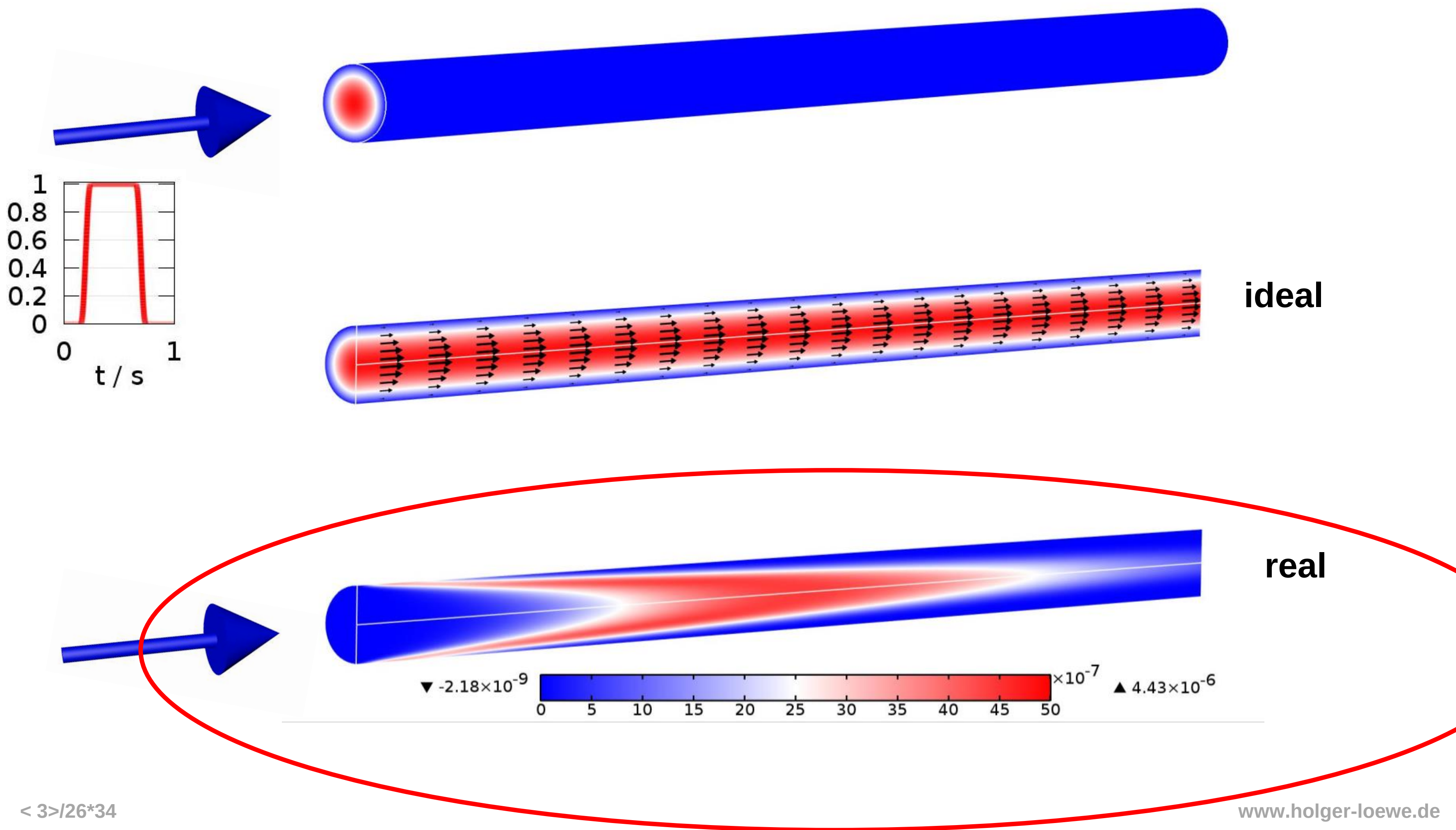
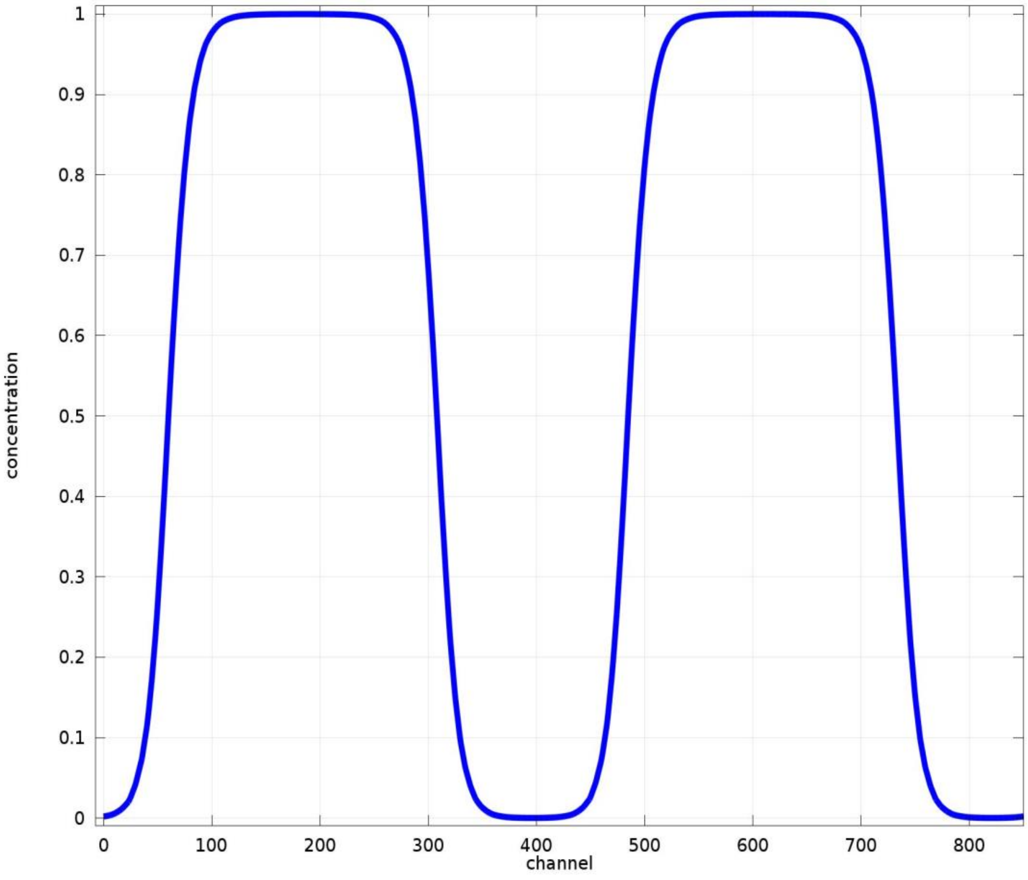
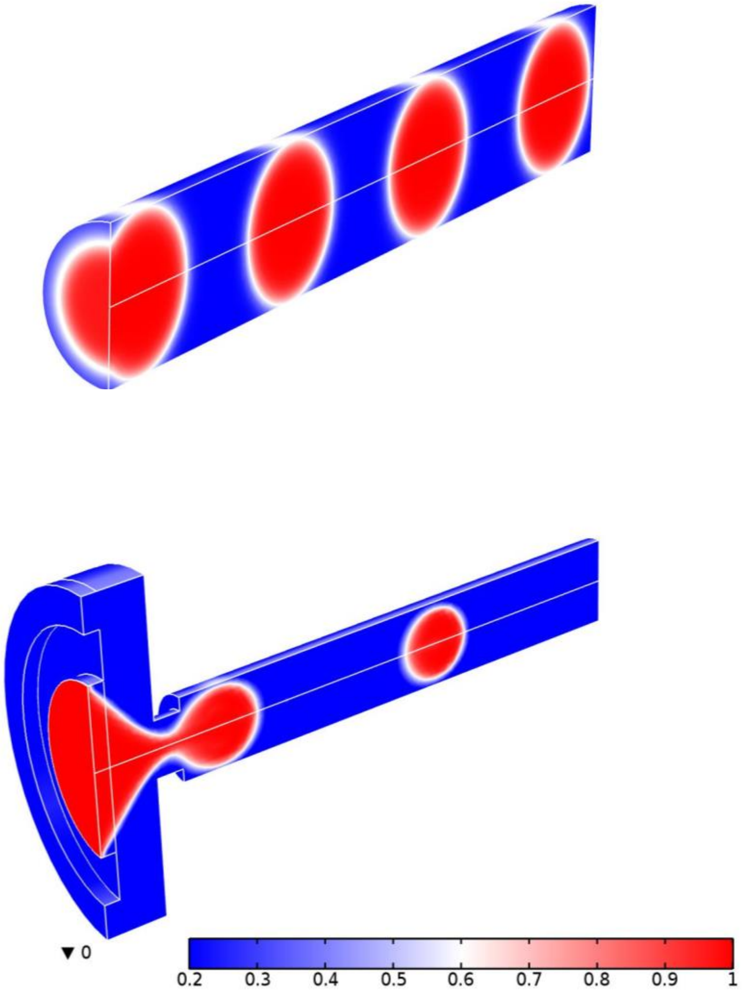
Laminar flow with broad residence time distribution



Droplet flow – residence time distribution





Droplet generation and flow behavior

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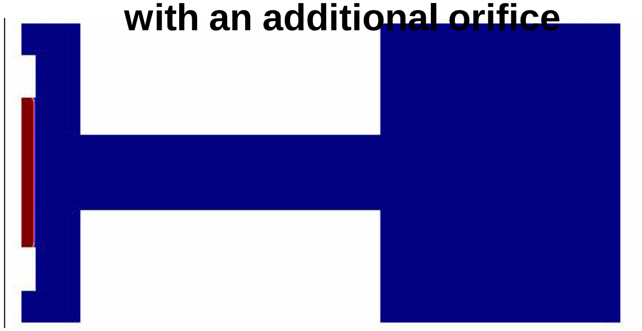
Coaxial tube-in-tube ( ) droplet generation

3-D simulation with openFOAM™ software

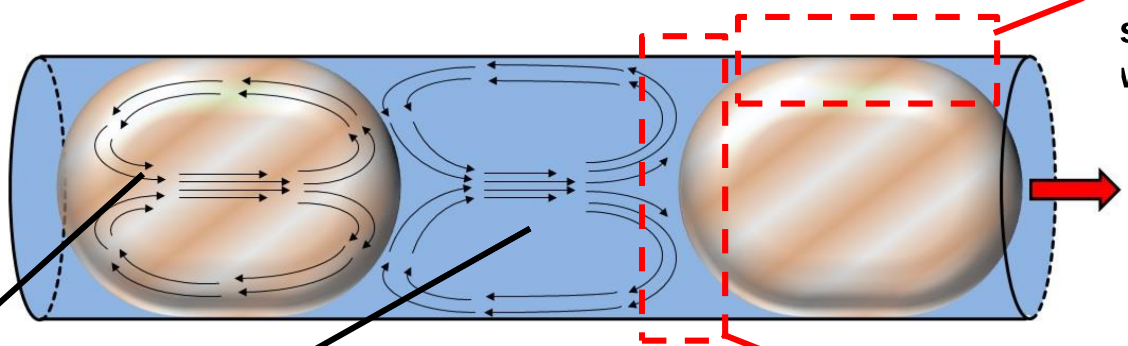
Mogon-Cluster University Mainz
34240 CPUs, 2,1,Ghz each

Cross junction droplet generation (2-D) with an additional orifice



2-D simulation with COMSOL™ software

Reaction/mass transfer at the surface of the wetting film



Circulation inside the plug

External circulation in the continuous phase

Reaction/mass transfer at the interphase

See: Jovanovic, J., Rebrov, E. V., Nijhuis, T. A., Hessel, V., Schouten, J. C.; *Ind. Eng. Chem. Res. 49 (2010) 2681-2687.*

Droplet generation - coaxial configuration

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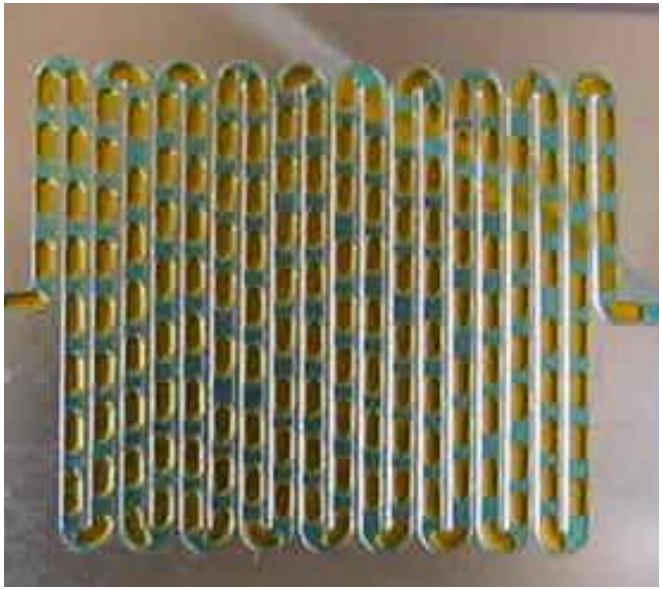
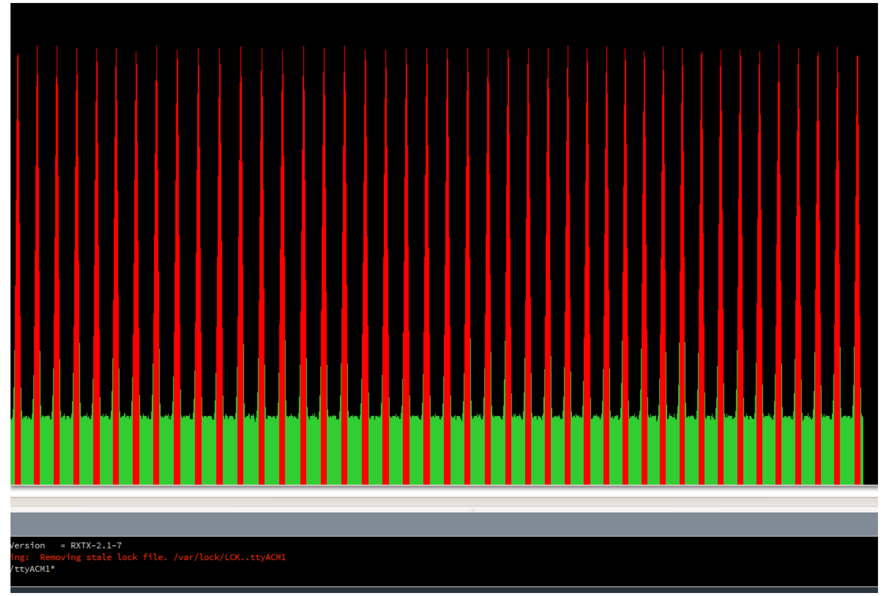




3-phase double emulsion droplet in flow:

Droplet: FC40 / toluene

Continuous phase: water

Optical monitoring of droplet flow by a light barrier sensor:

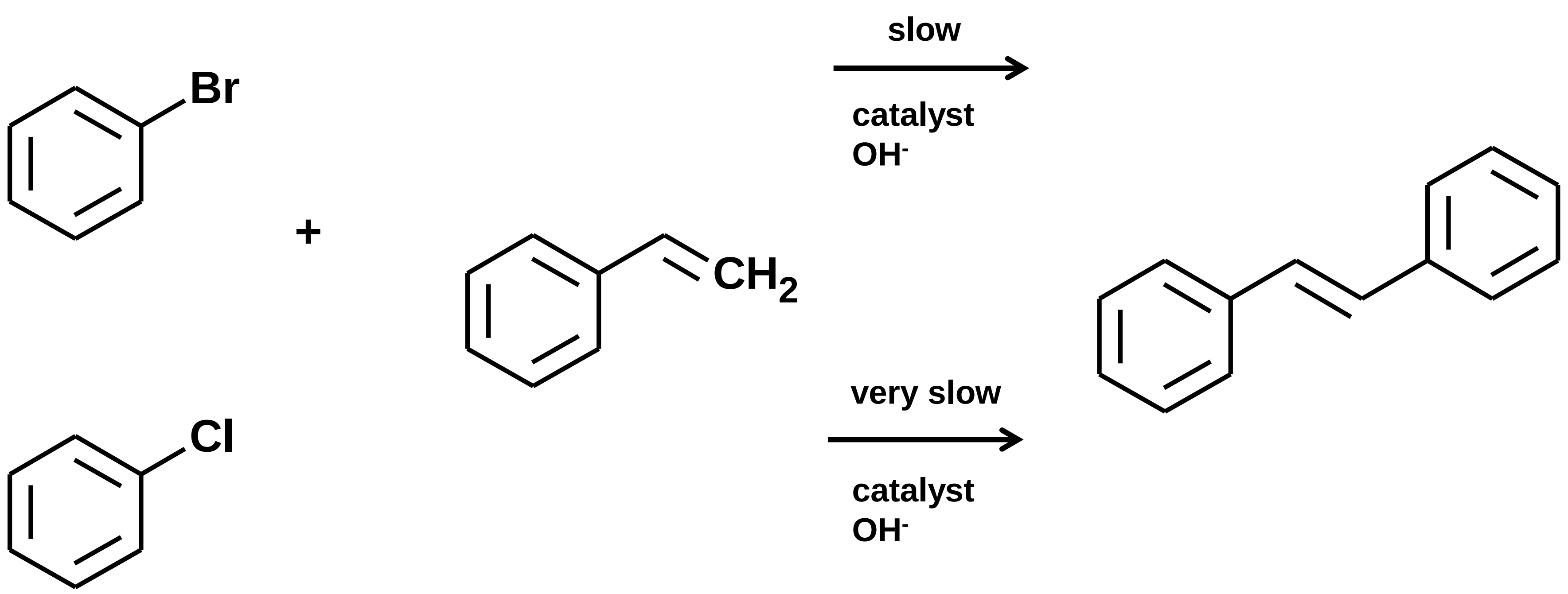
- **red peaks indicate droplets**
- **frequency < 0.5 Hz**

control of flow behavior, residence time and droplet size

- **manipulation of droplets**

Palladium catalyzed C-C cross coupling reactions in thermomorphous double emulsion droplets – Fluorous Triphasic Catalysis (FTC)

Similar to Horvath, I. T., Rabai, J.;*Science 266, 5182 (1994) 72-75.*
(Fluorous Biphasic Catalysis in batch)



Heck C – C coupling: reaction mechanism

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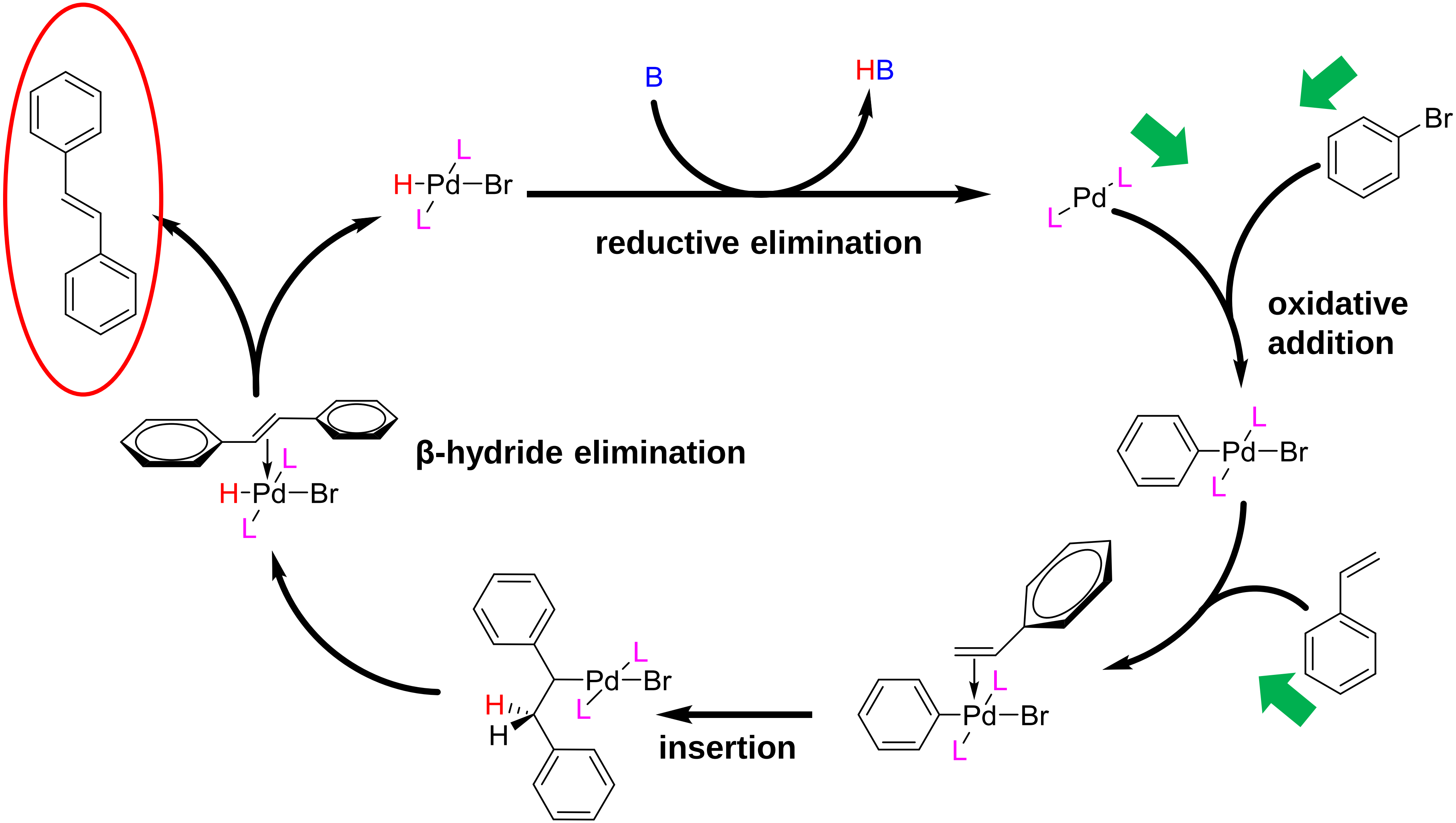
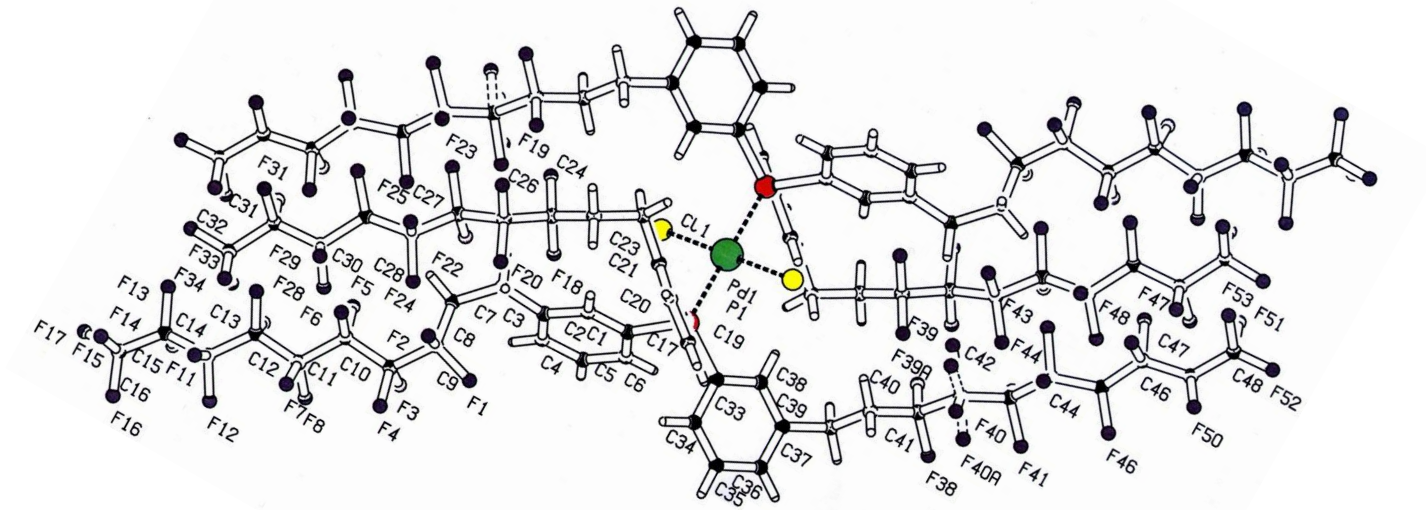


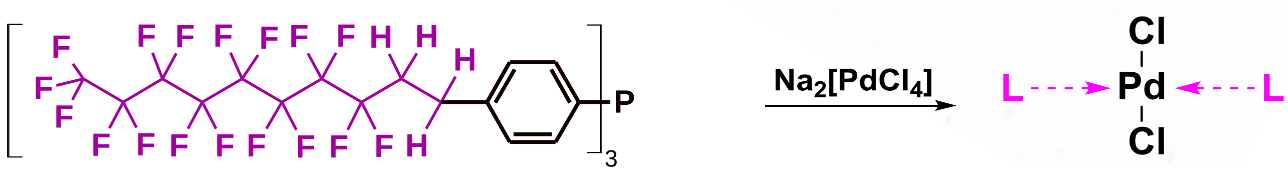
Richard Fred Heck, John Paul Nolley jr. : *J. Org. Chem*. 37, Nr. 14, **1972**

Palladium catalyzed C-C cross coupling reactions in thermomorphous double emulsion droplets

Catalyzed by Pd containing Ionic Liquid dissolved in Fluorinert® FC-40



Catalyst



Setup: double emulsion droplet generator- coaxial configuration - fluid connection

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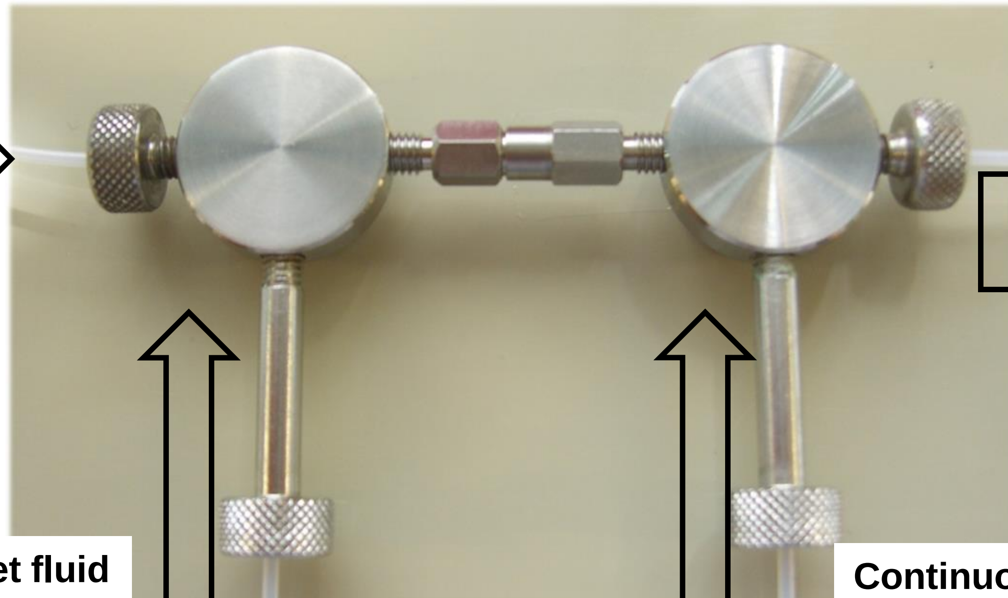
Core droplet fluid



Double emulsion droplets

Shell droplet fluid

Continuous phase fluid

Modular capillary tube-in-tube-in-tube setup:

2 x Stainless steel T-junctions 1000 µm ID

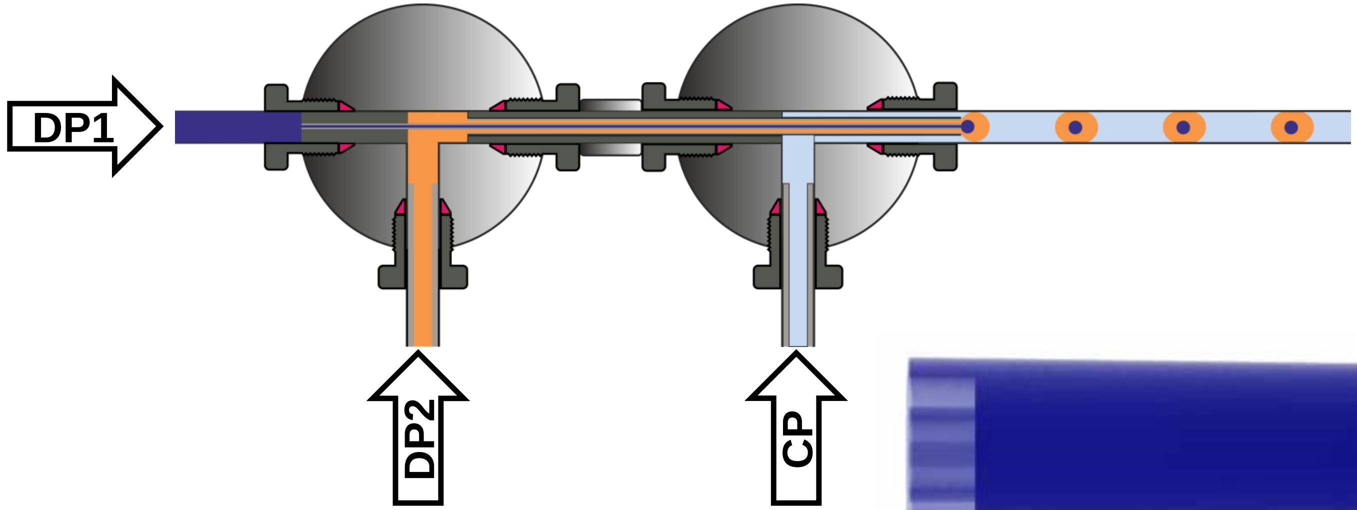
Core capillary, PEEK, OD = 360 µm and = 150 µm.

Middle capillary, FEP, OD = 1/32´´, ID = 500 µm.

Outer capillary, PTFE, OD = 1/16´´, ID = 1,000 µm.

Flow rates from nl h^{-1} to ml min^{-1} possible

Setup I: double emulsion droplet generator-coaxial configuration: openFOAM®-simulation



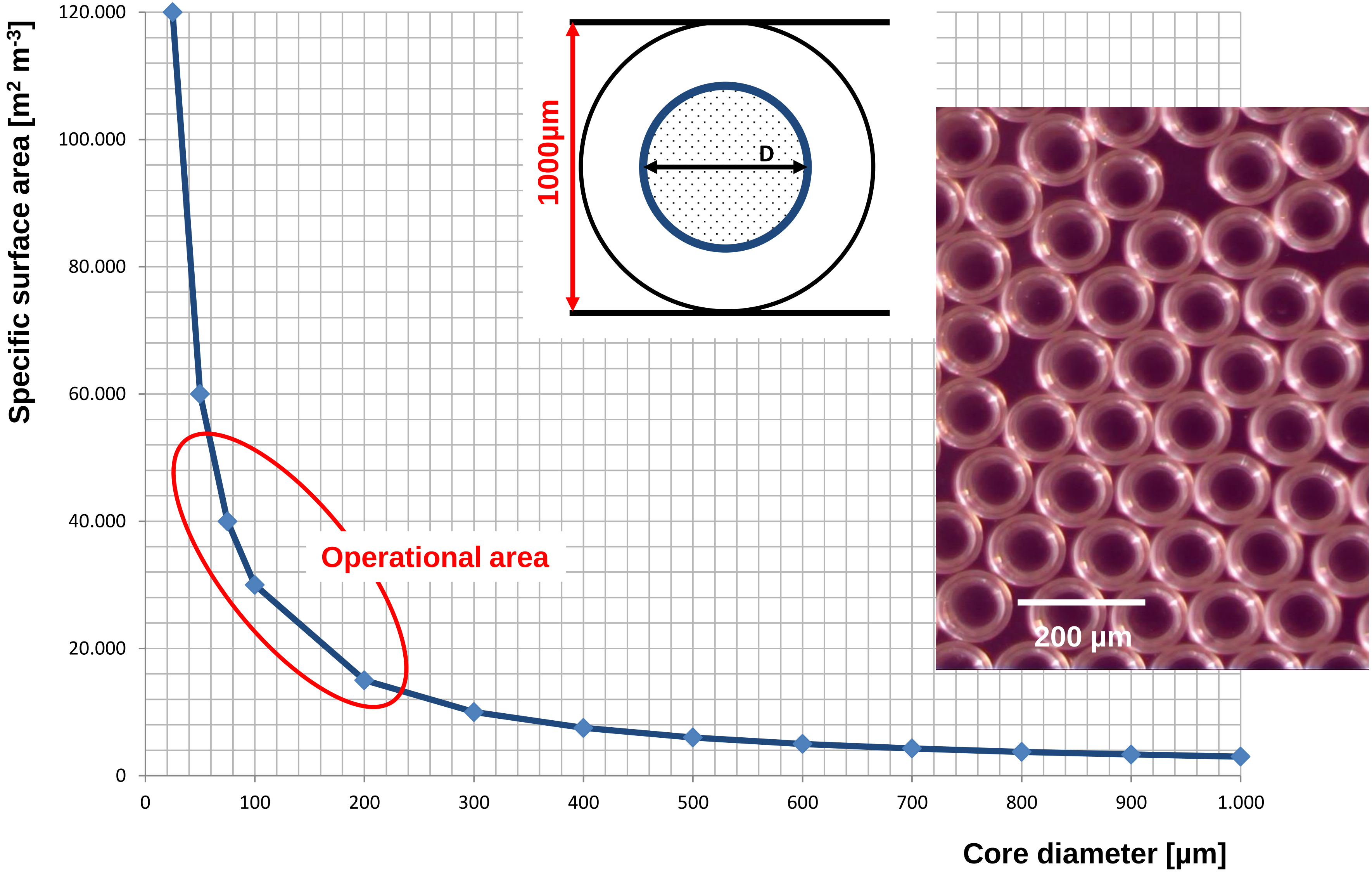
CP: continuous phase (aqueous phase)

DP1: core droplet phase perfluorinated phase

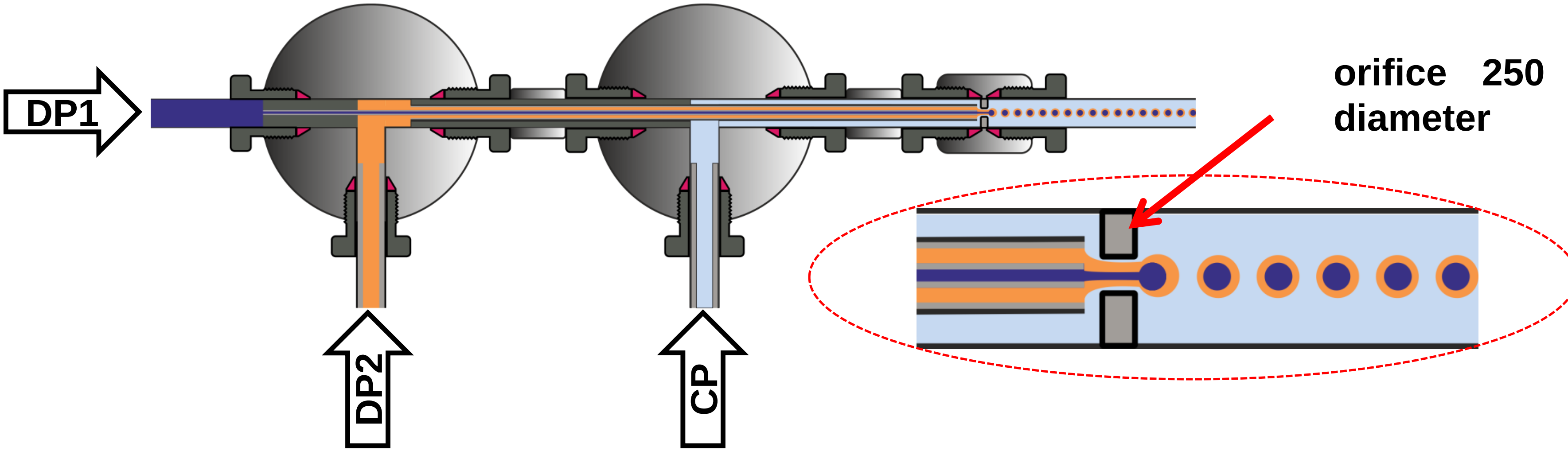
DP2: shell droplet phase organic phase

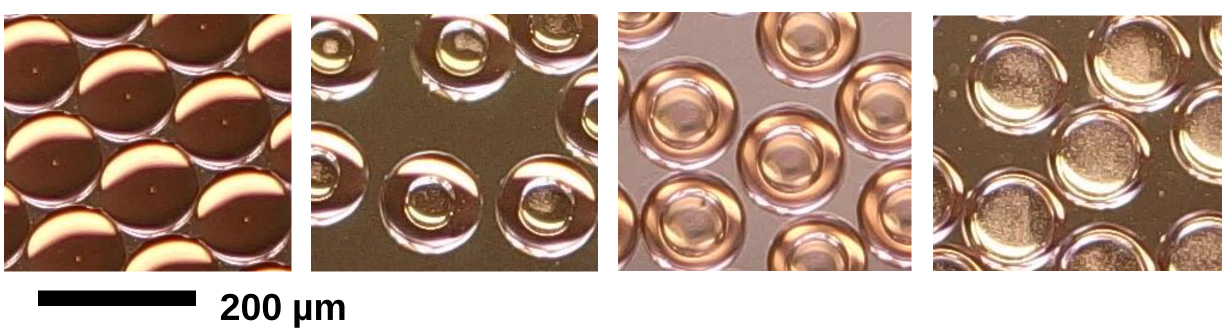
- slug flow
- without surfactants
- slug dimension depends on channel diameter and flow of continuous phase

Achievable specific surface area



Setup II: double emulsion droplet generator- coaxial configuration with flow focusing





$$\dot{V}_{DP1} + \dot{V}_{DP2} = const.$$

$$\frac{\dot{V}_{DP2}}{\dot{V}_{DP1}} \rightarrow increase$$

- bubbly flow
- coaxial flow with flow focusing by an orifice
- surfactants necessary
- monodispers

Temperature controlled mixing – phase separation by a thermomorphous solvent

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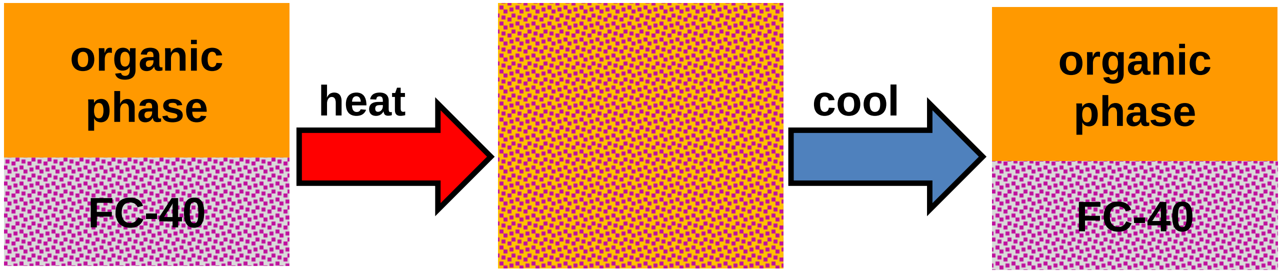
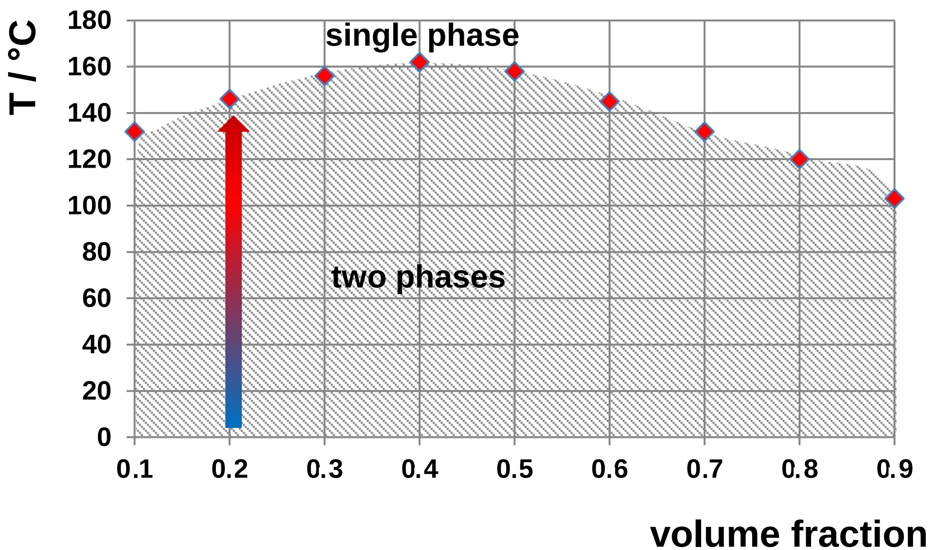
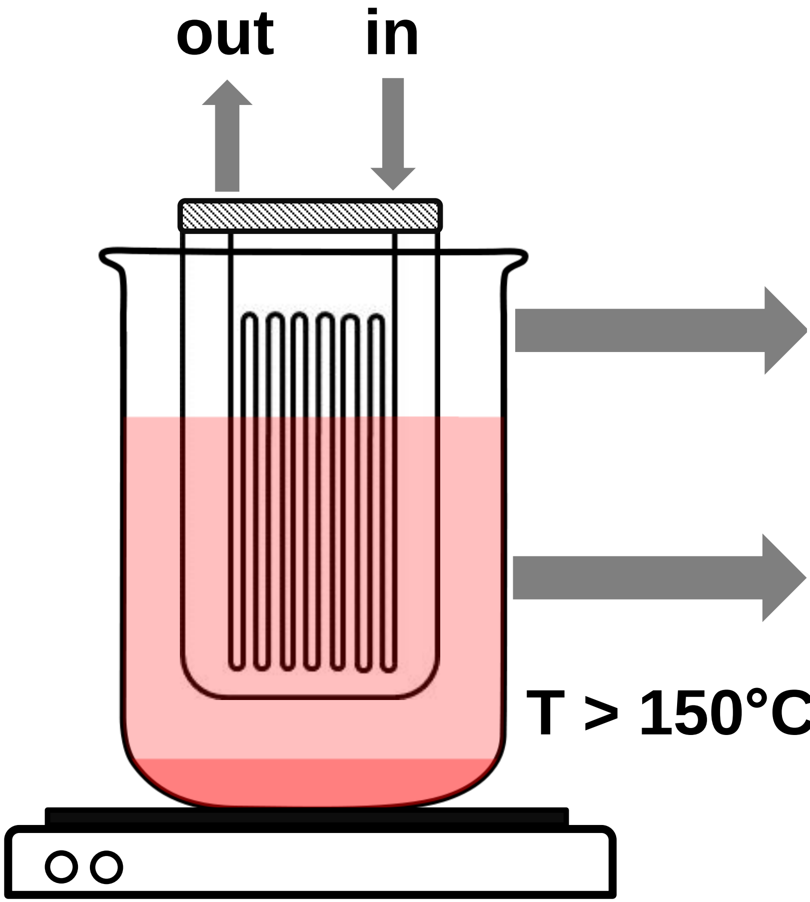
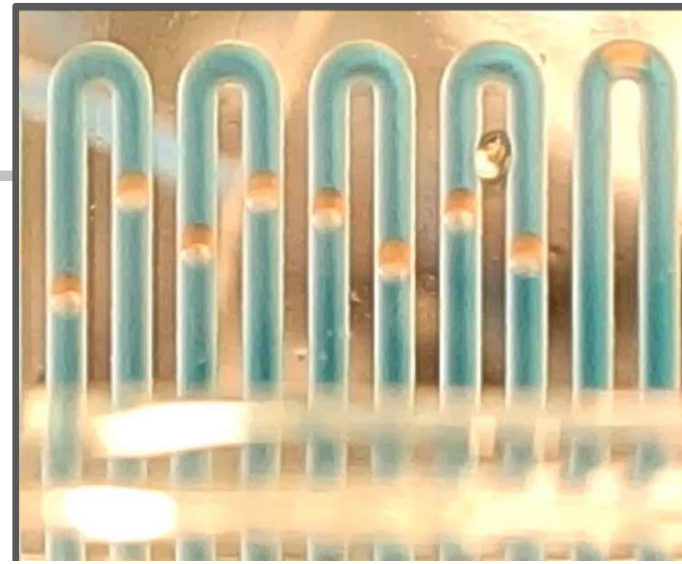
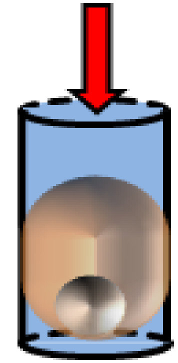




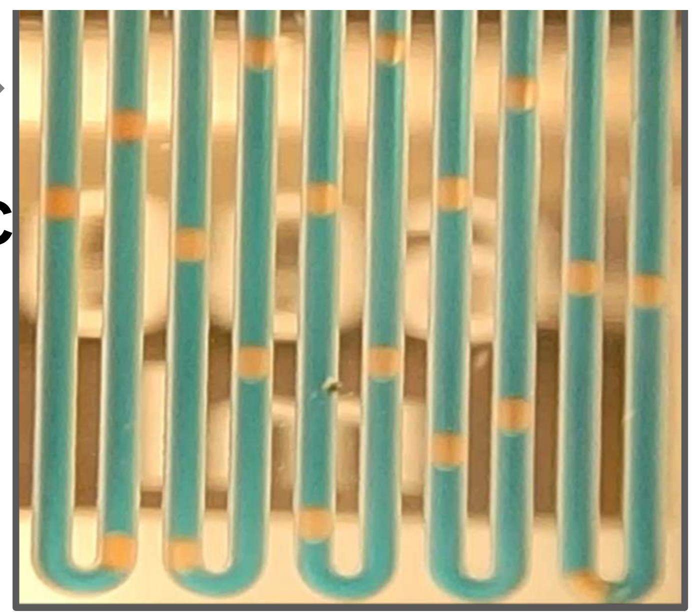
- binary mixture of FC-40 / toluene
- mixing above 142°C
- below 142°C → phase separation

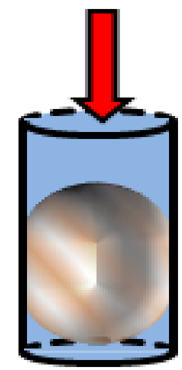






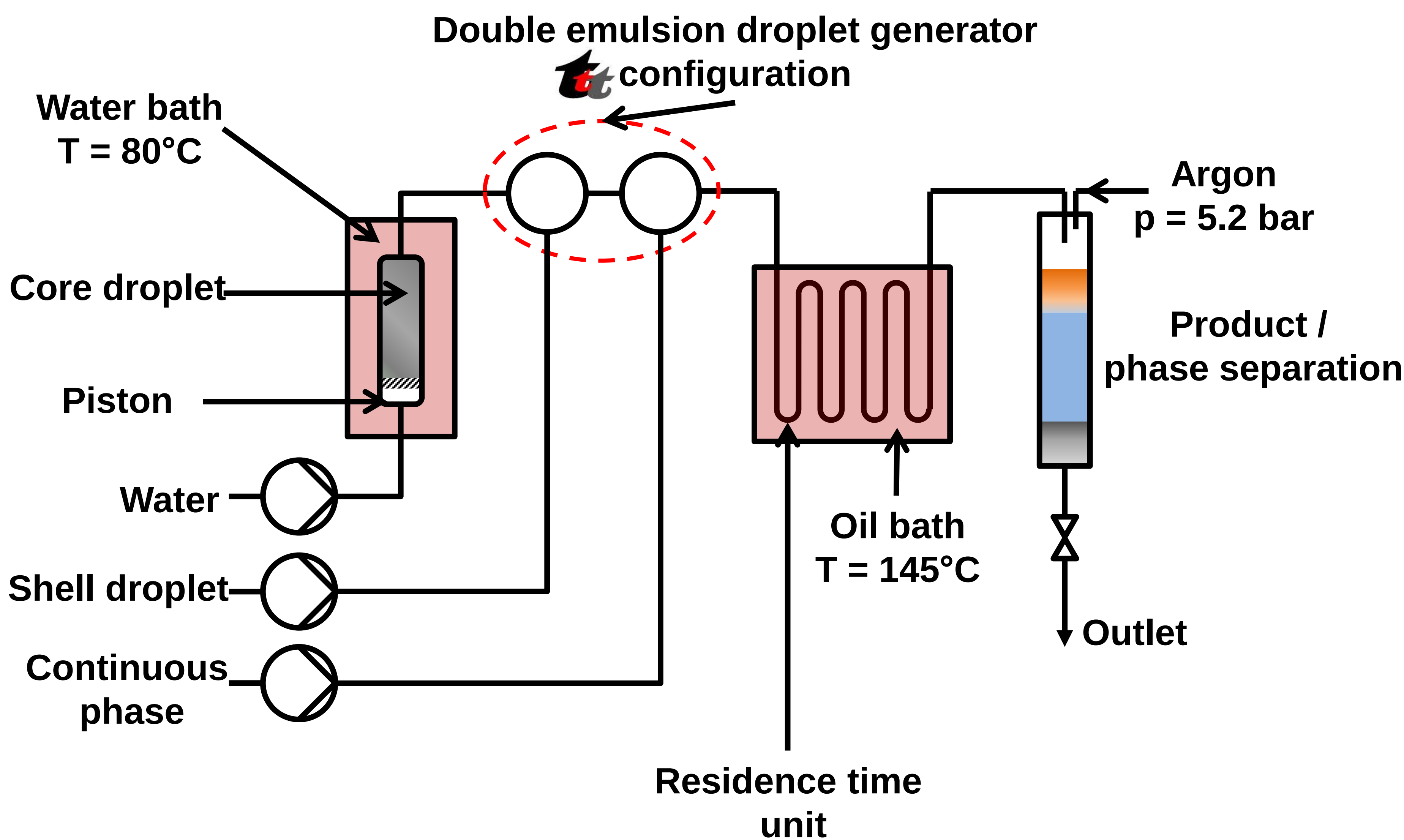
two phases



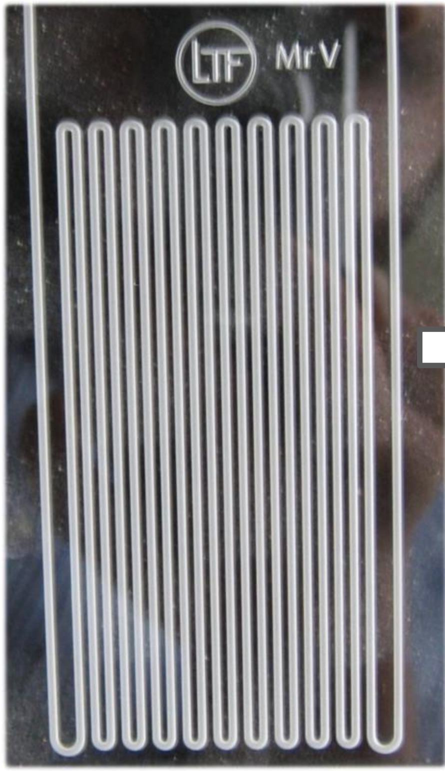


one phase

Experimental setup - overview

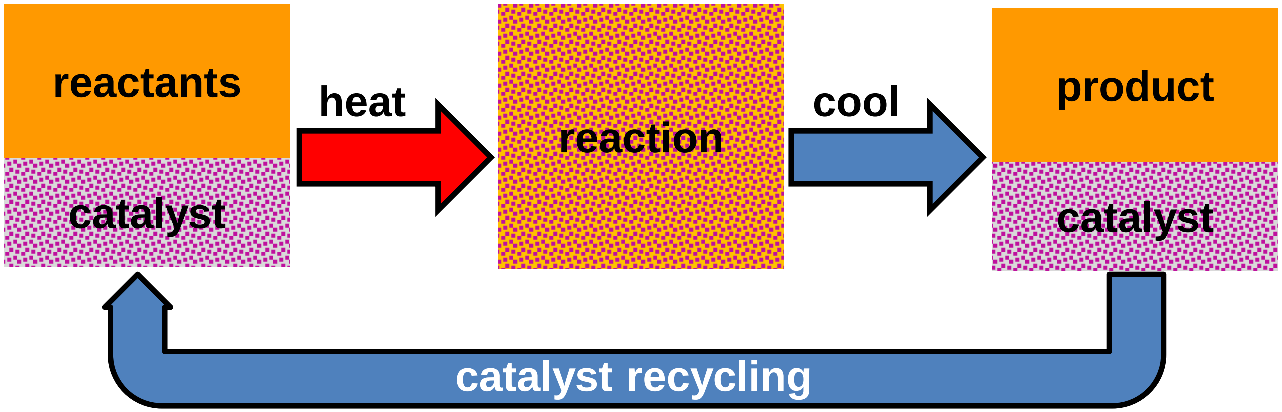


Setup: residence time unit

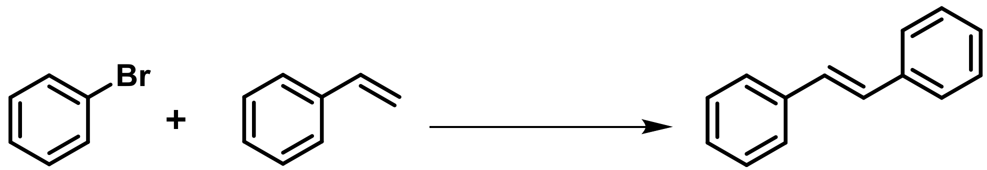


- Little Things Factory GmbH
- volume 1.7 mL
- channel diameter 1000 µm
- pressure resistance up to 15 bar

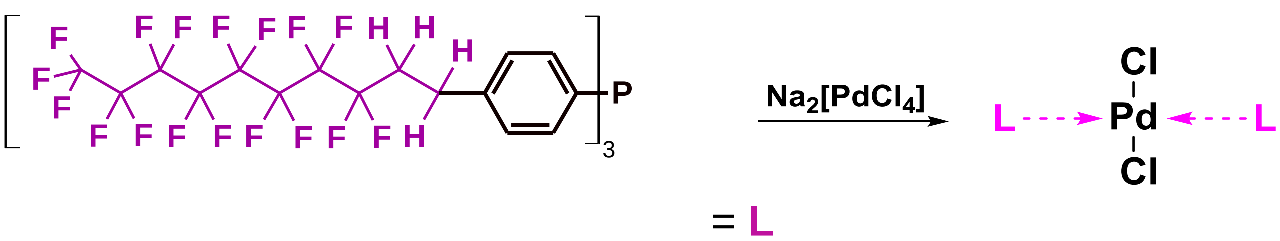
HECK C–C coupling reaction



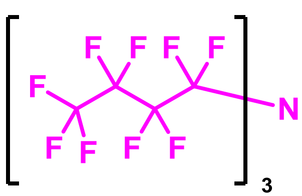
Reaction scheme:



Ligand:



Solvent:
Fluorinert® FC-40



S. Schneider, W. Bannwarth: *Angew. Chem. Int. Ed*. 39. **2000**. Nr.22 4142

Fluorous Triphasic Catalysis (FTC) in double emulsion droplets

(Similar to
Horvath, I. T., Rabai, J.; *Science 266, 5182 (1994) 72-75)*

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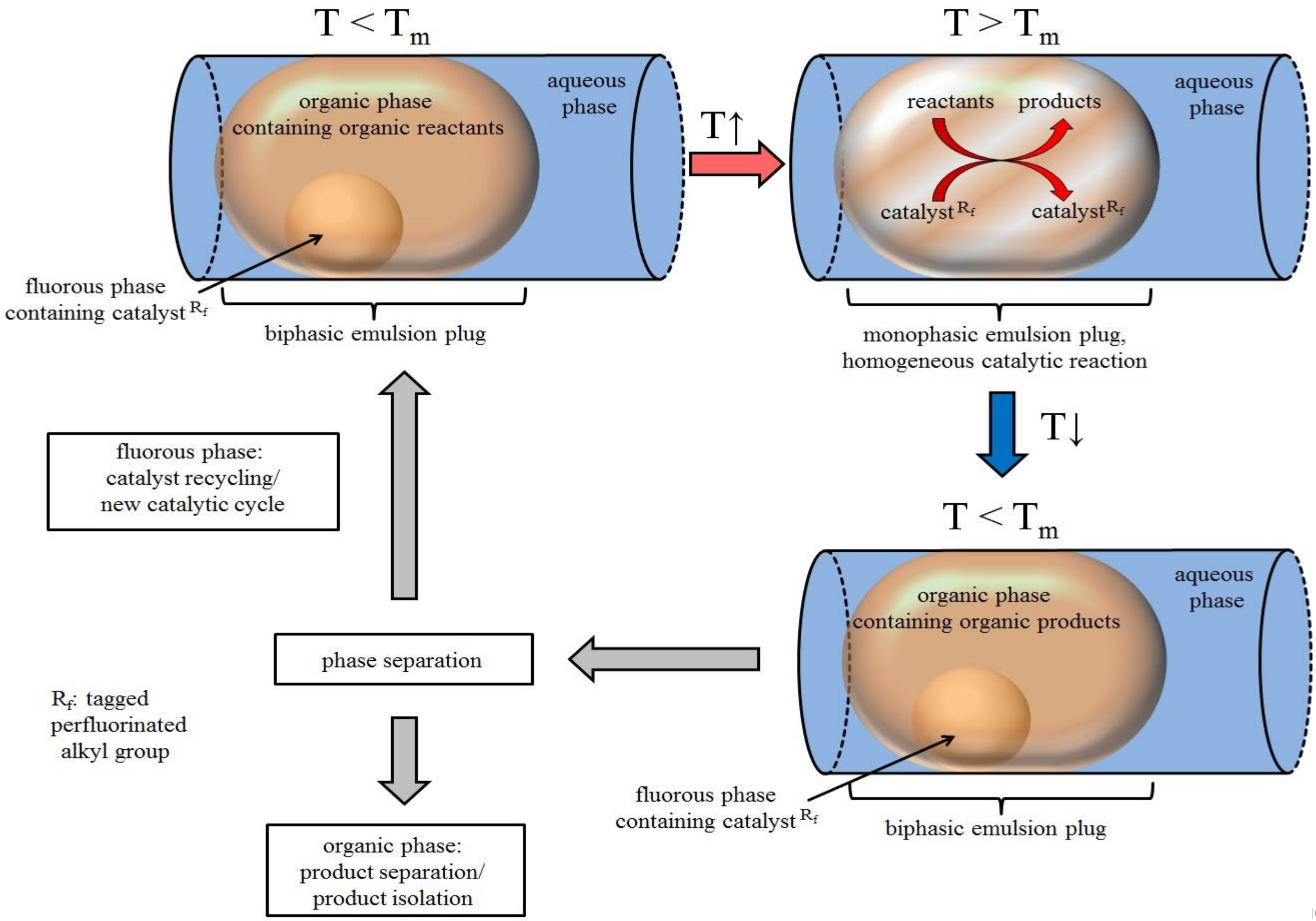

Heck C – C coupling: reaction mechanism

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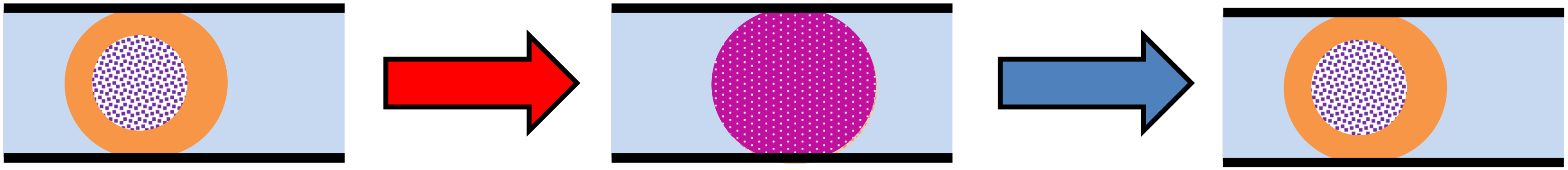
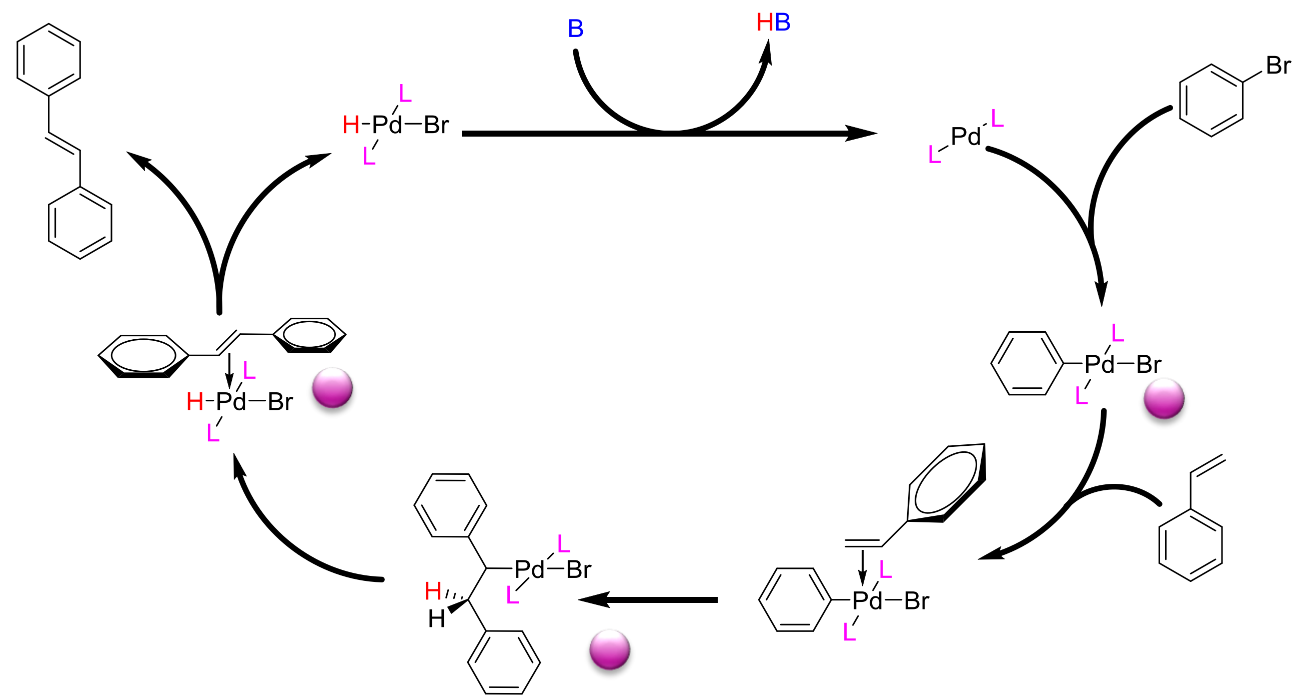


- oxidative addition
- insertion
- β-hydride elimination

reductive elimination

inside the droplet



Heck C – C coupling: reaction mechanism

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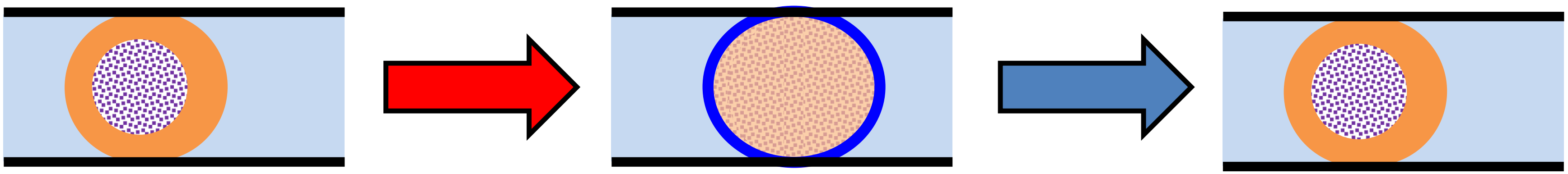
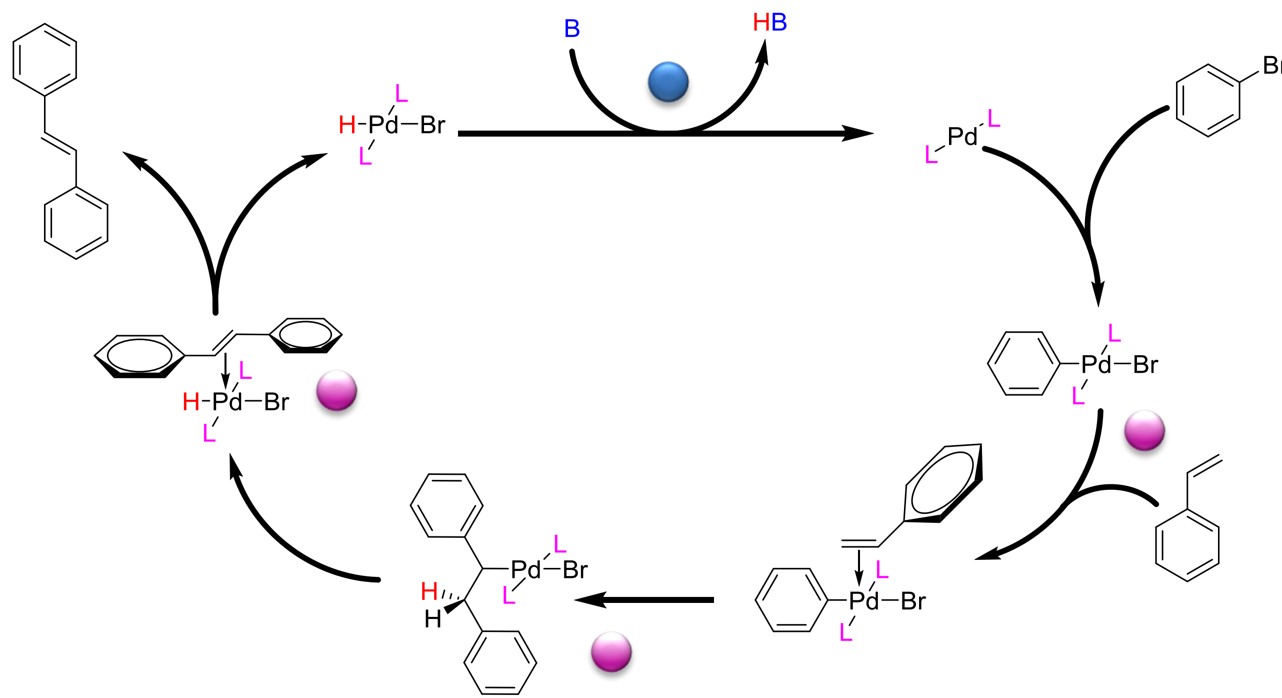


- oxidative addition
- insertion
- β-hydride elimination

} inside the droplet

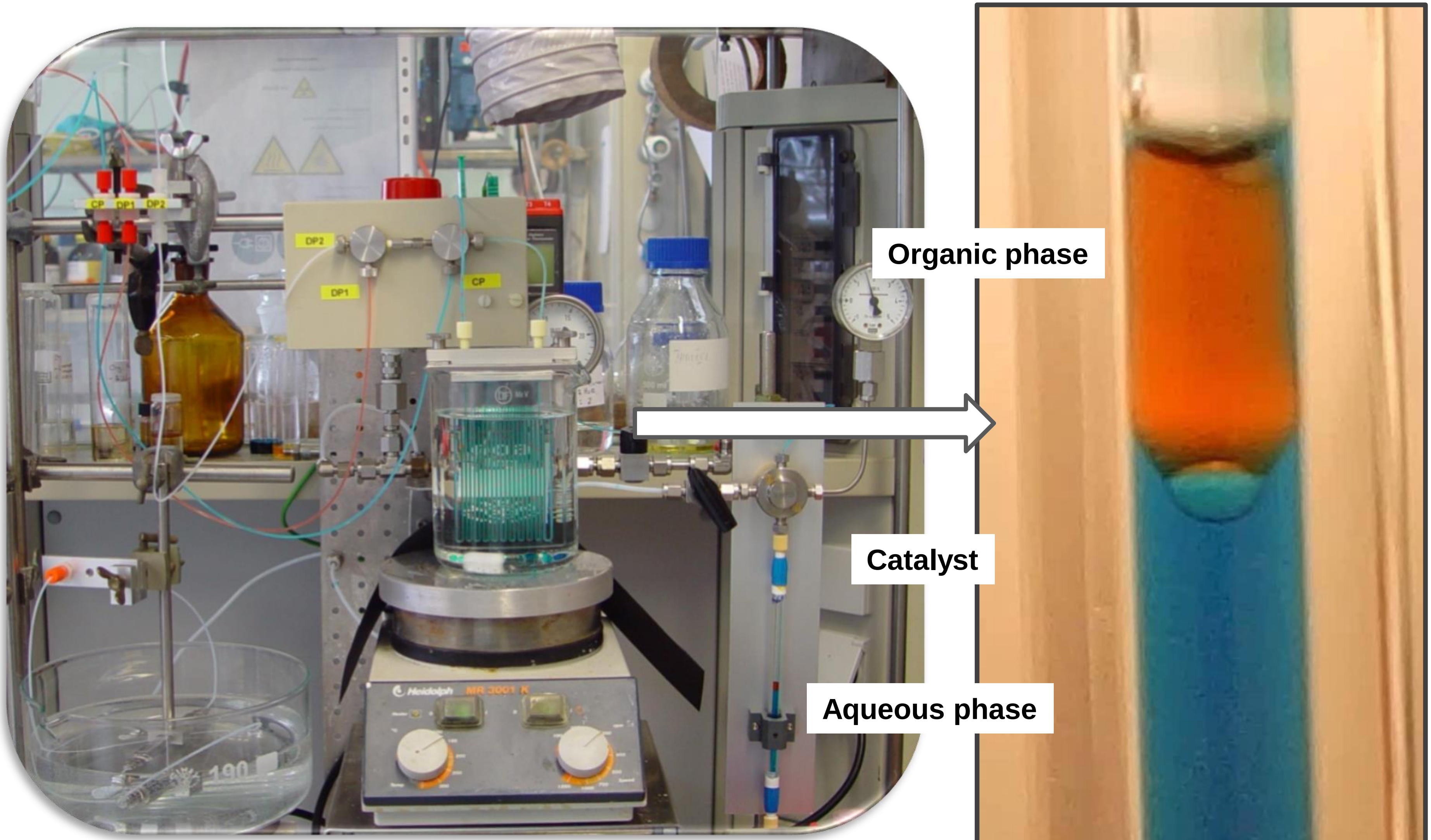
- reductive elimination

→ at the surface



- $V = 1.76 \cdot 10^{-12} m^3 = 1.76 µl$
- $A = 7.0 \cdot 10^{-8} m^2$
- $A_s = 40{,}000 m^2 m^{-3}$

Phase separation and catalyst recycling



Heck - coupling of bromobenzene: results

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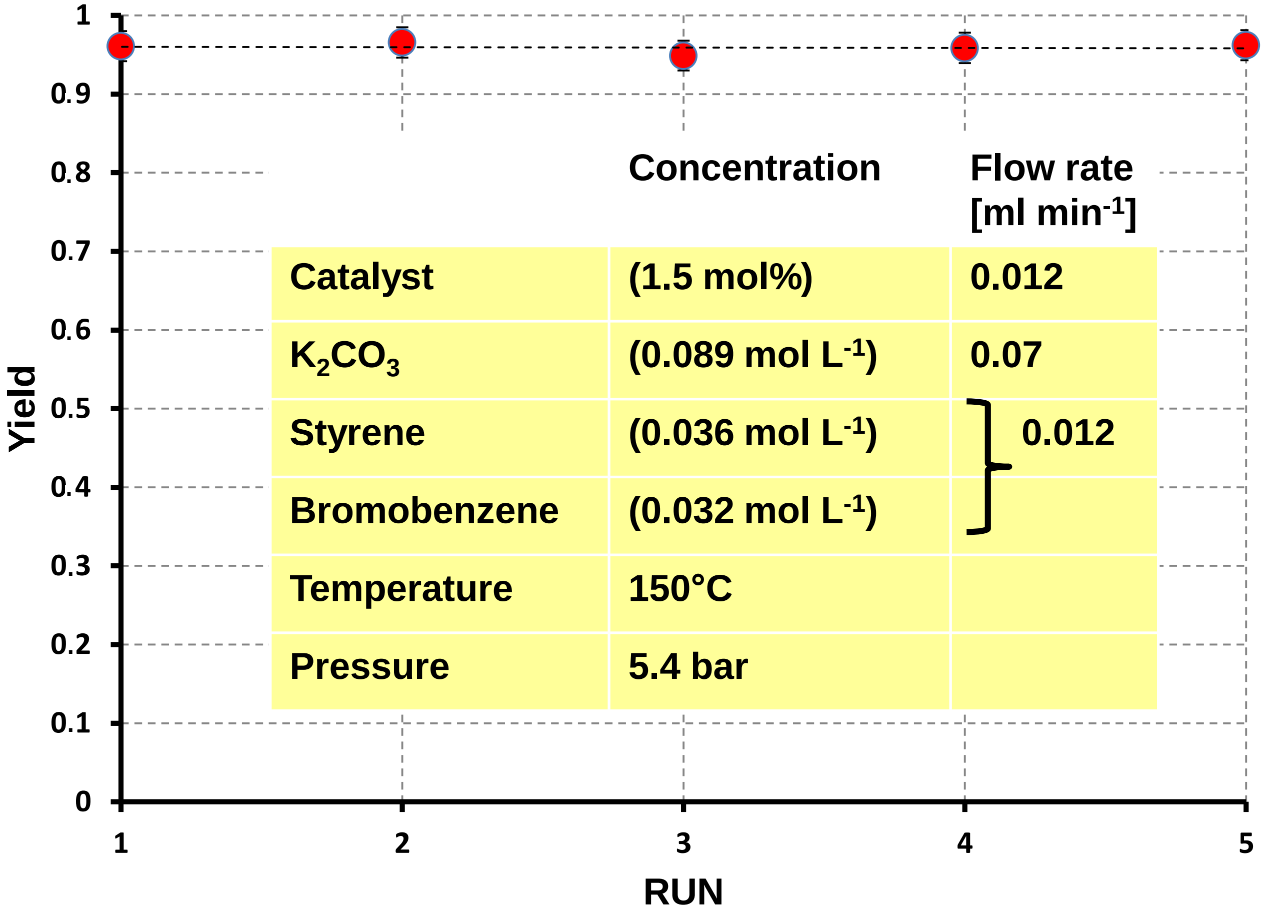


	Concentration	Flow rate [ml min^{-1}]
Catalyst	(1.5 mol%)	0.012
K_2CO_3	(0.089 mol L^{-1})	0.07
Styrene	(0.036 mol L^{-1})	} 0.012
Bromobenzene	(0.032 mol L^{-1})	
Temperature	150°C	
Pressure	5.4 bar	

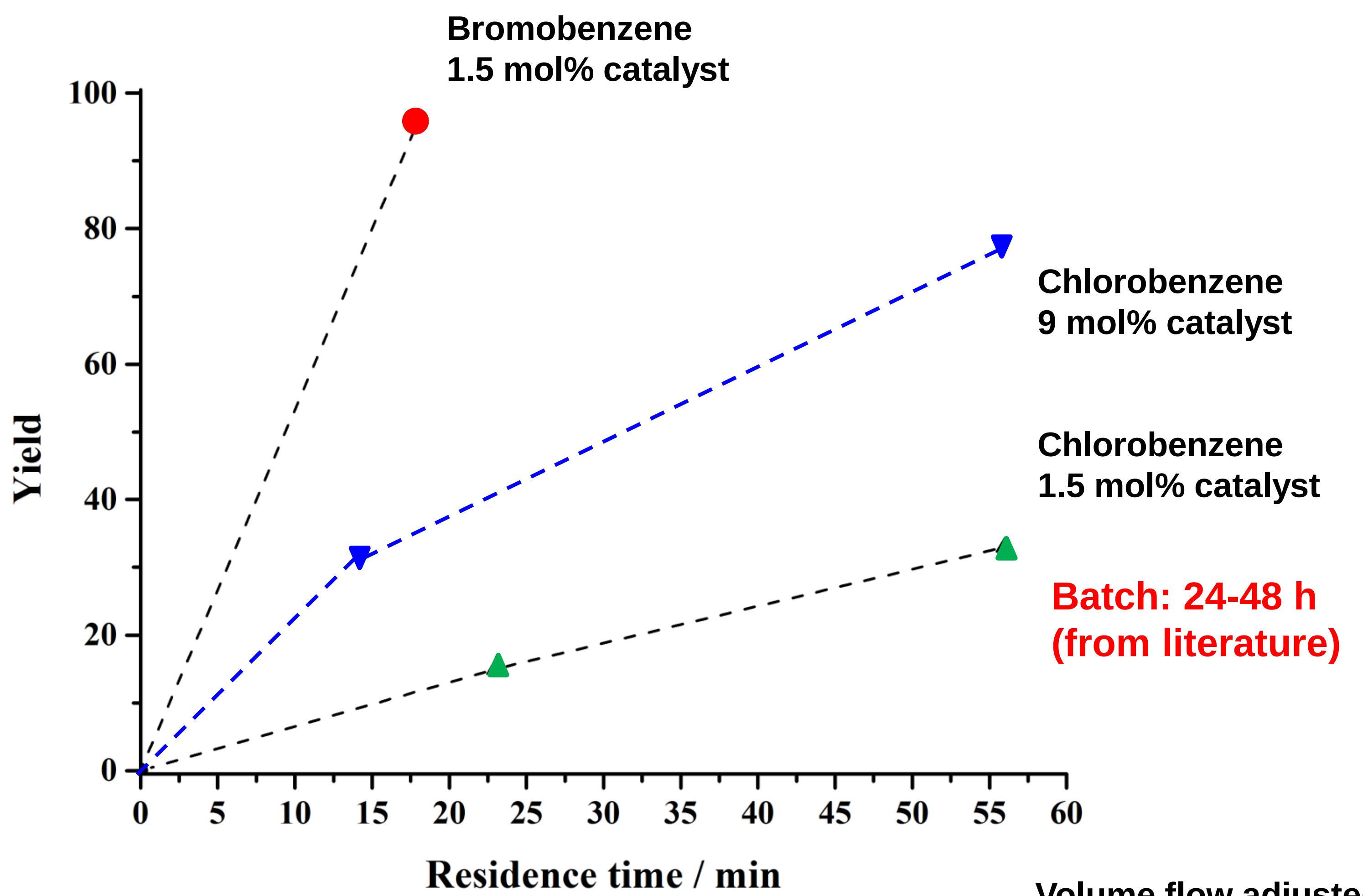
τ = 18 min

Batch: 6.5 h (from literature)

>96% yield / run

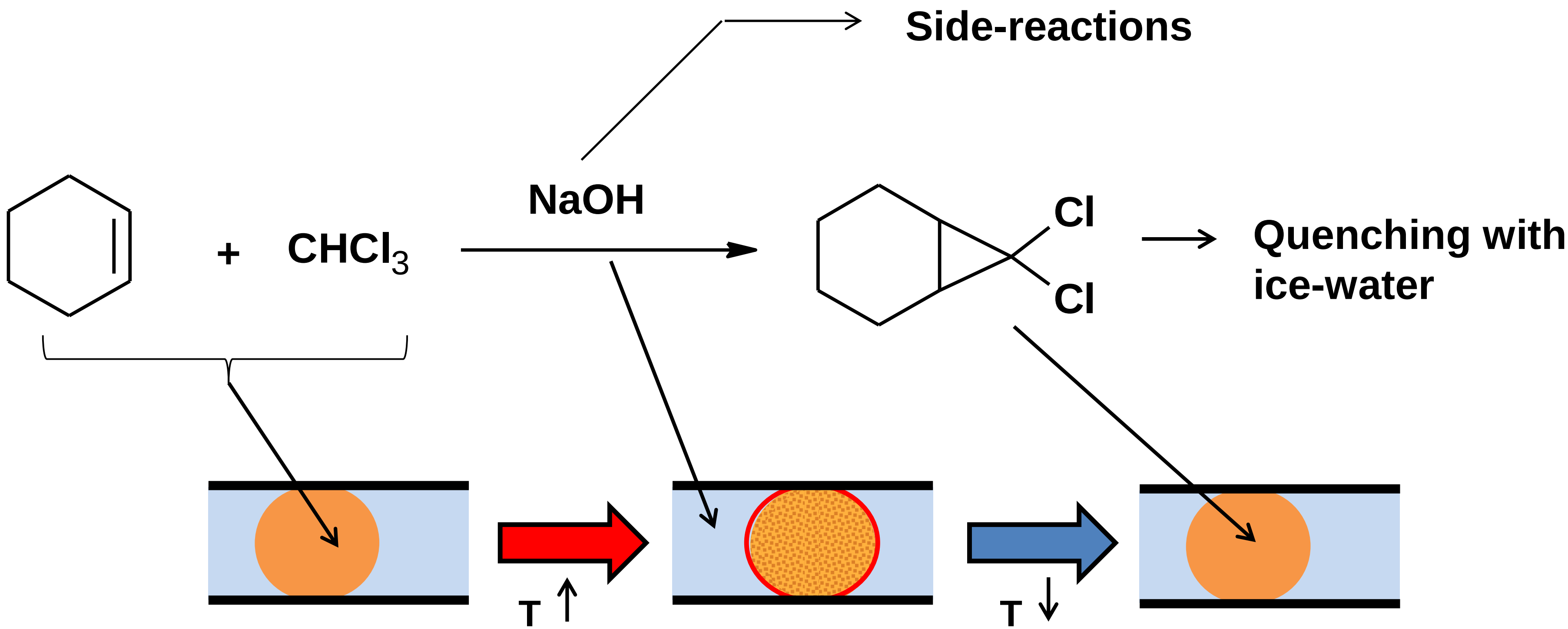
same catalyst solution was reused several times without loss of catalytic activity !

Heck - coupling of bromo- and chlorobenzene: results



Volume flow adjusted to achieve residence time – fixed length of capillary

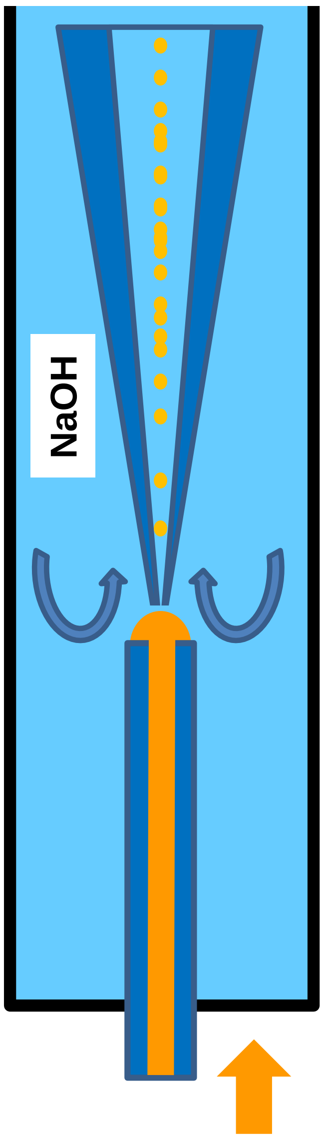
Synthesis of cyclopropanes with highly reactive carbenes as intermediates – single droplets

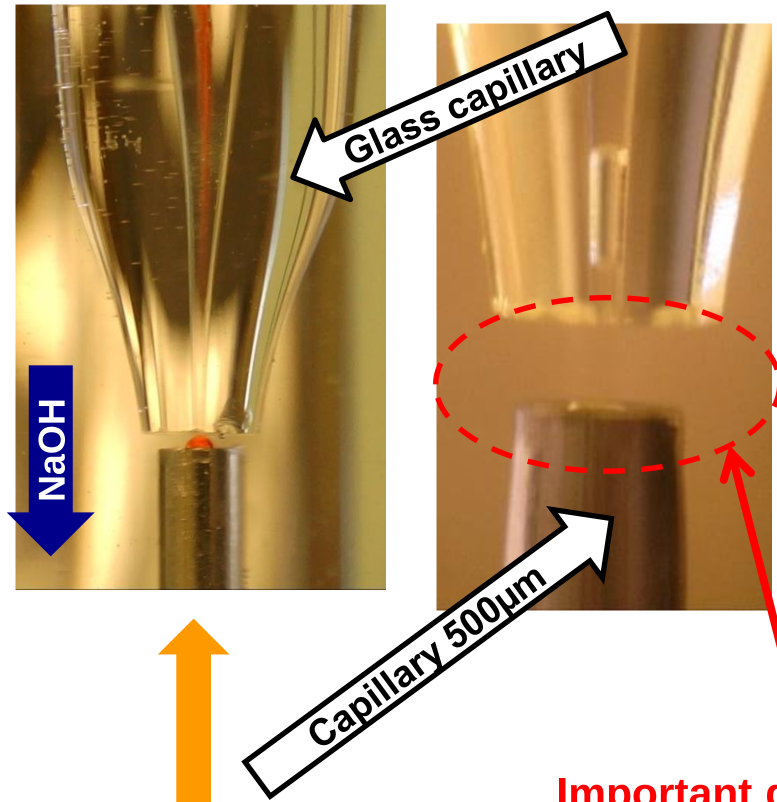


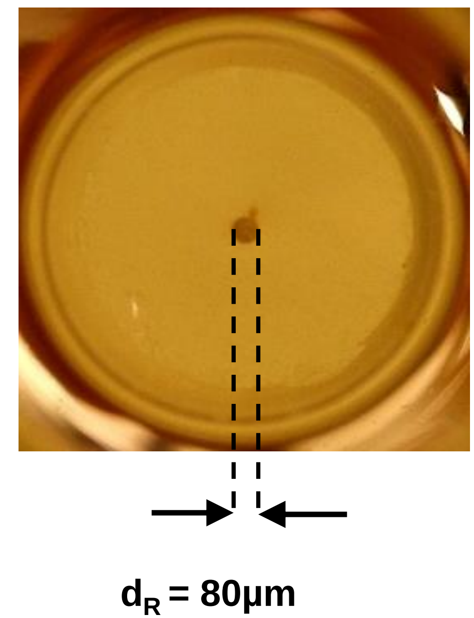
PTC-reaction
at phase boundary

Formation of carbenes
$Cl_2C|$

Droplet generator



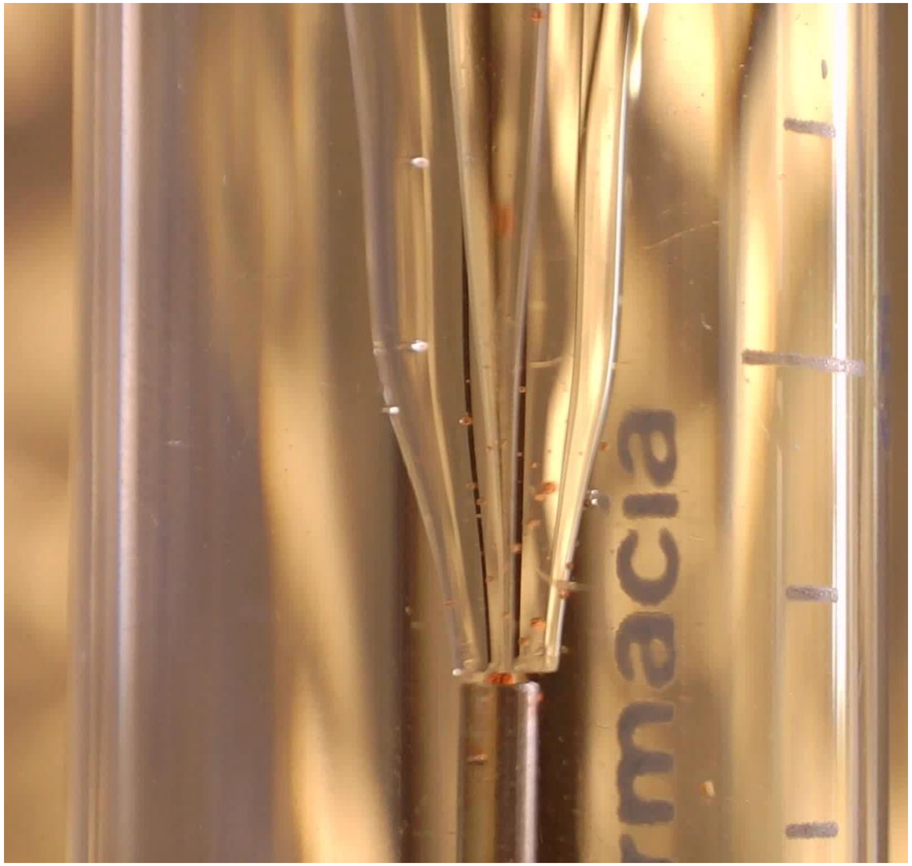


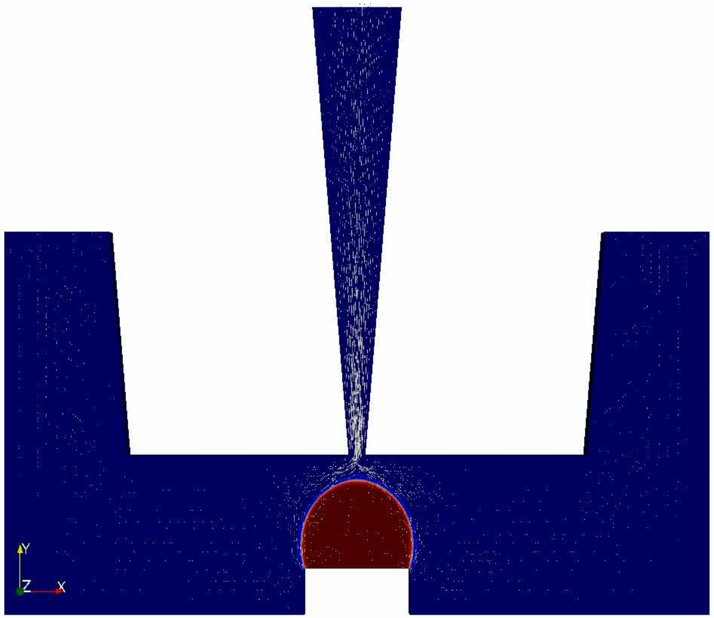


$CHCl_3$ / cyclohexene mixture

Important gap to adjust droplet size

Fluid-fluid interface in μ–channels



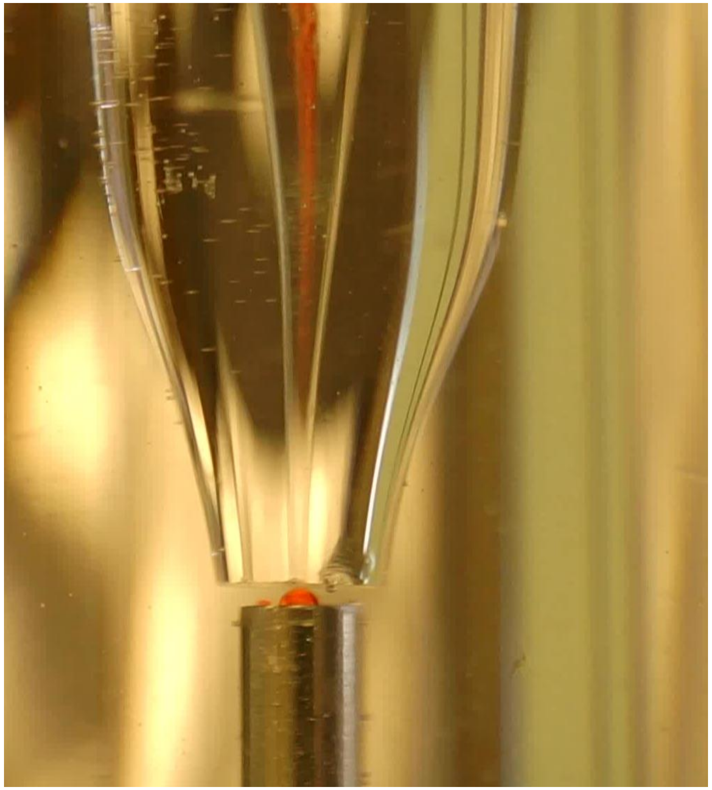


Slow performing system

Continuous phase 0.05 m s^{-1}
Dispersed phase 0.0025 m s^{-1}

Oscillation droplet generation due to slow flow rates. Simulation with openFoam™

Carbene formation – batch vs. droplet based processing: Comparison of interfacial areas

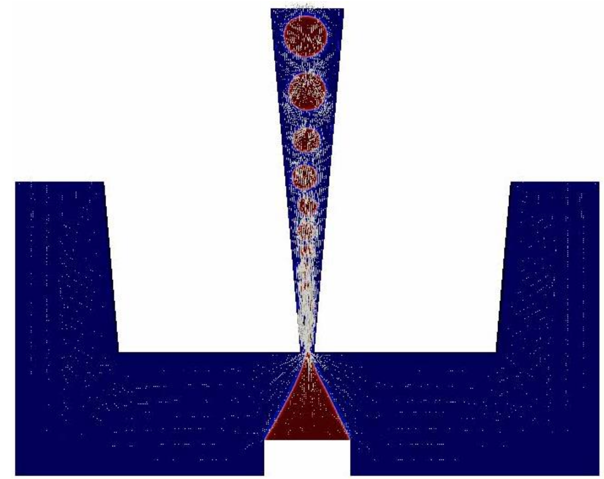


d_D = approx. 80 µm

$A = 2*10^{-8} m^2 - 7.85*10^{-9} m^2$

$V = 2.6 *10^{-13} m^3 - 6.5*10^{-14} m^3$

$A_S = 75000 m^2/m^3 - 120000 m^2/m^3$

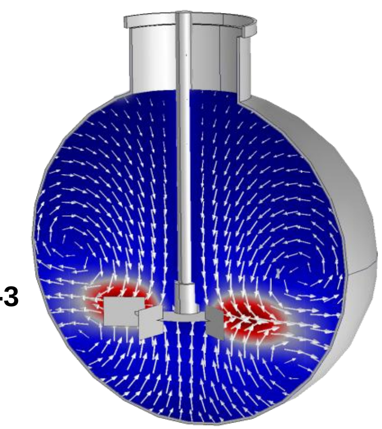


Fast performing system

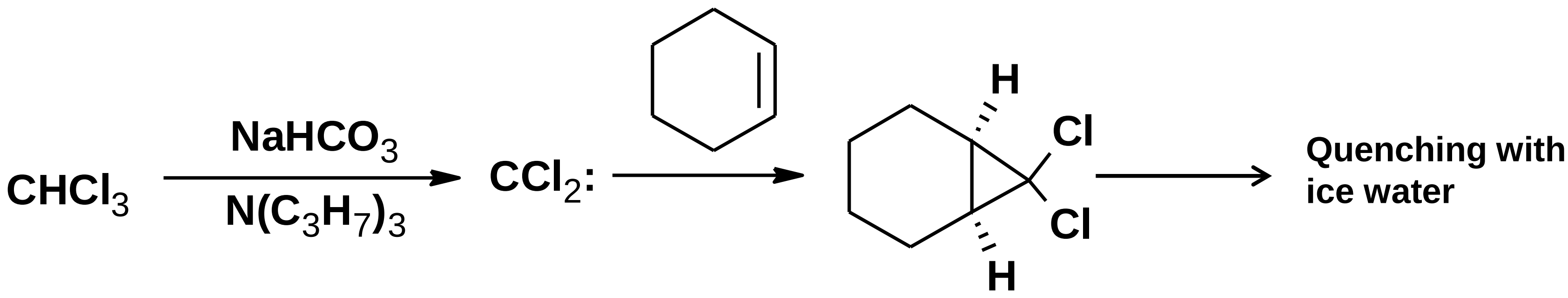
Continuous phase 0.05 m s^{-1}
Dispersed phase 0.0025 m s^{-1}

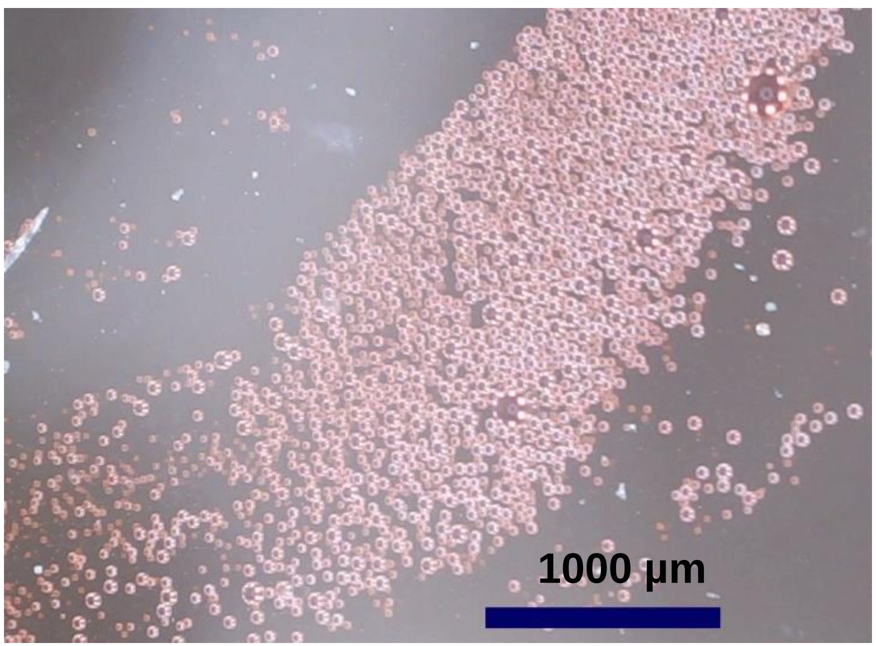
Stirred batch tank

$A_s = 100 m^2 m^{-3} – 1000 m^2 m^{-3}$



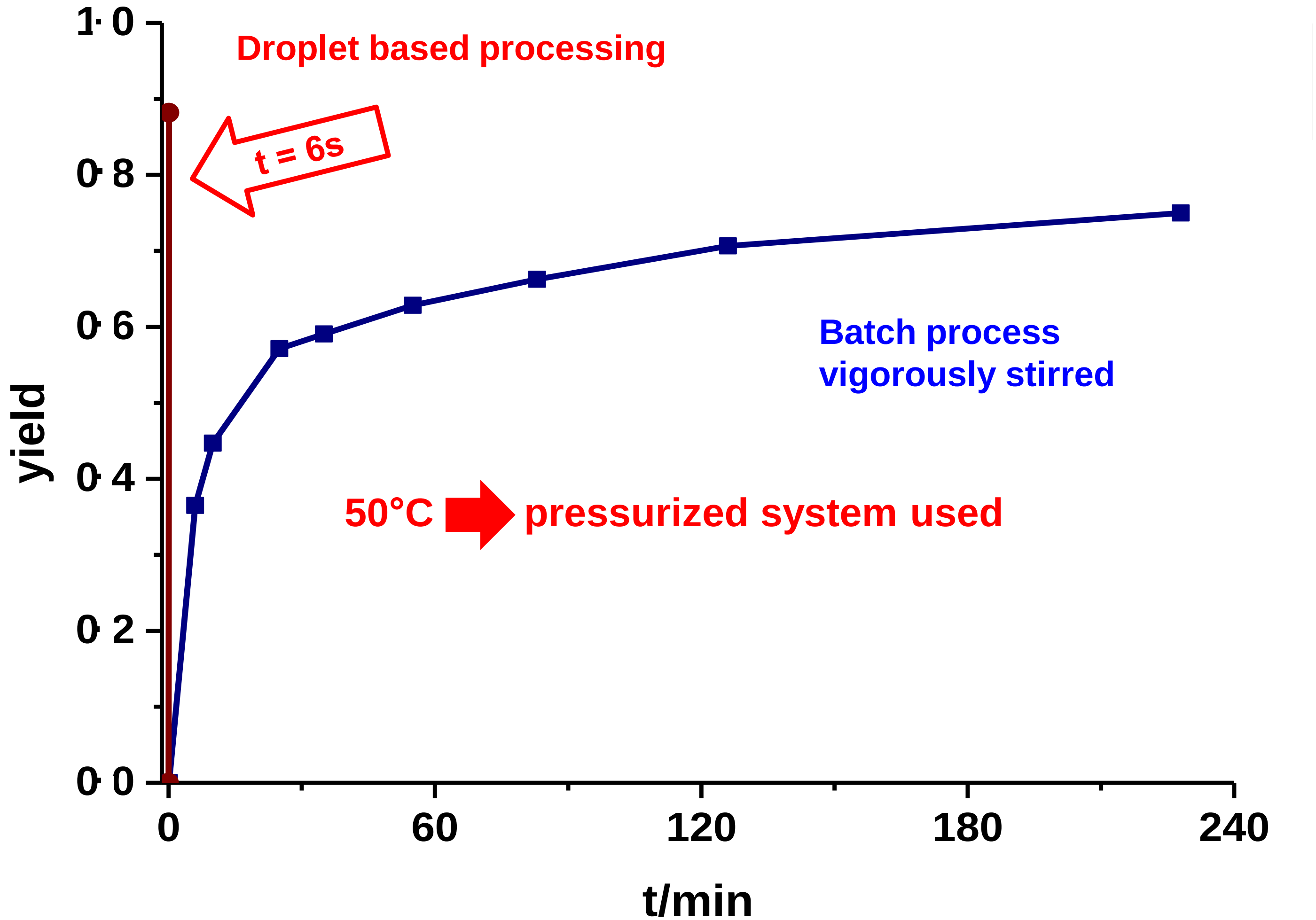
Synthesis of 7,7-dichlorobicyclo[4.1.0]heptane (7,7-dichloronorcaran) in droplet-based continuous flow





	Concentration	Volume flow
NaOH	50% (water)	5 mL h^{-1}
Cyclohexene	0.5 mol L^{-1}	
Tri-n-propylamine	0.01 mol L^{-1}	1 mL h^{-1}
$CHCl_3$		
Temperature	50°C	
Pressure	~1 bar	

Synthesis of *7,7*-dichloronorcaran – comparison of droplet-based and batch processing



Summary

- Heck –reaction can be performed in a 3-phase continuous droplet flow process.
  Thermomorphous solvents shift to a 2-phase process at elevated temperatures
  Coupling reaction and catalyst reactivation are performed at the same time

- Stilbene yields of 96% could be achived with bromobenzene within 18 minutes
  The catalyst could be separated and reused many times without loss of activity
  At the same conditions chlorobenzene gives approx. 36% yield within 60 minutes,
  with 10-times higher catalyst concentration the yield could be increased up to 75%

- *7*,*7*-dichloronorcaran (cyclopropanes) were synthesized from carbenes by a continuous droplet-flow mode
  High yields (89%) could be achieved within a few seconds residence time
  Vigorously stirred batch gave approximately 75% within 3 hours