Cruciform Precursor Synthesis Pathways – From Batch to Flow Processes

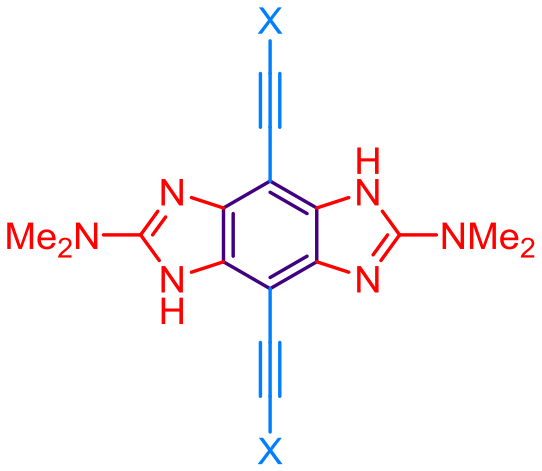
IMRET14, Beijing 2016

Dominik Karl[1], Pia Börner[2], Holger Löwe[1]

[1] Fraunhofer ICT-IMM, Center for Applied Fluidics and Engineering, Duesbergweg 10-14, 55128 Mainz
[2] Johannes Gutenberg University, Duesbergweg 10-14, 55128 Mainz

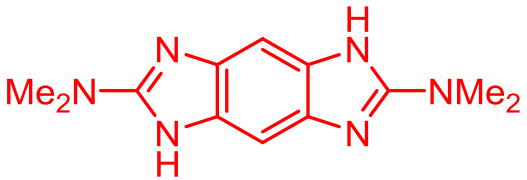
Cruziforms

So-called “cruciforms” consist of two conjugated p-systems (blue and red), which form a cross-like structure.



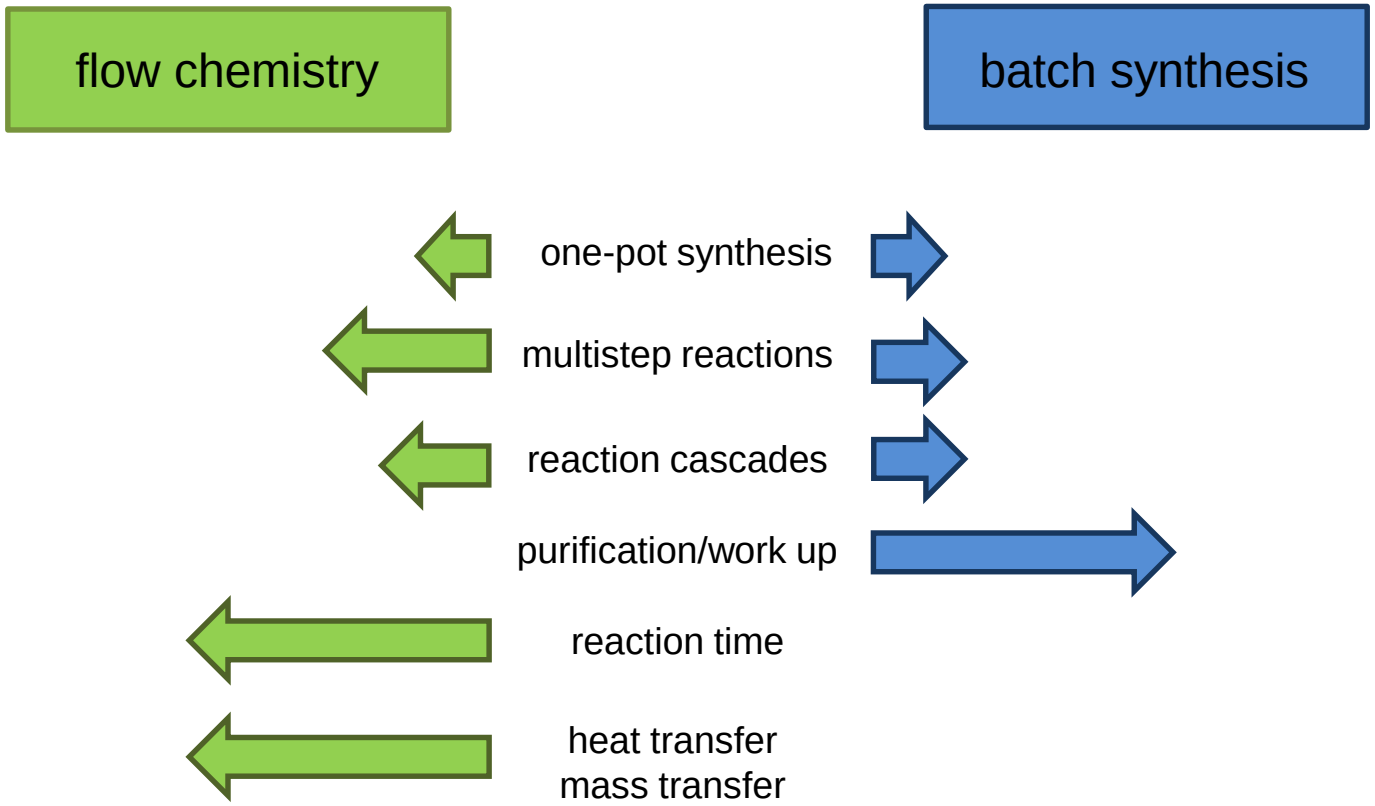
They are commonly used as fluorescent materials for optoelectronics. The central **aromatic core** of theses substances often consists of condensed heteroaromatics, such as benzobisimidazoles.

Only obtainable as a byproduct with 12-30% yield!



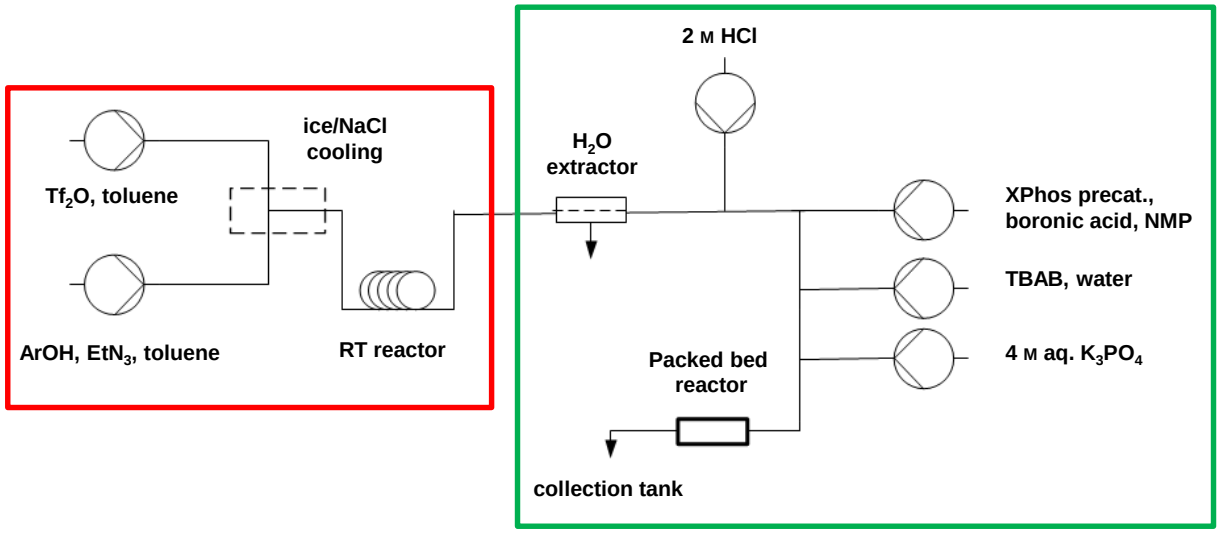
Microfluidics as a solution?

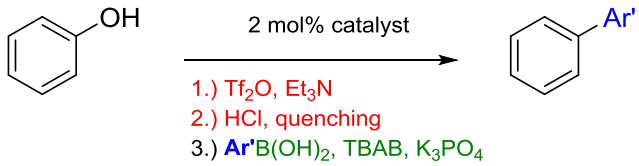
What Can Flow Chemistry Offer?



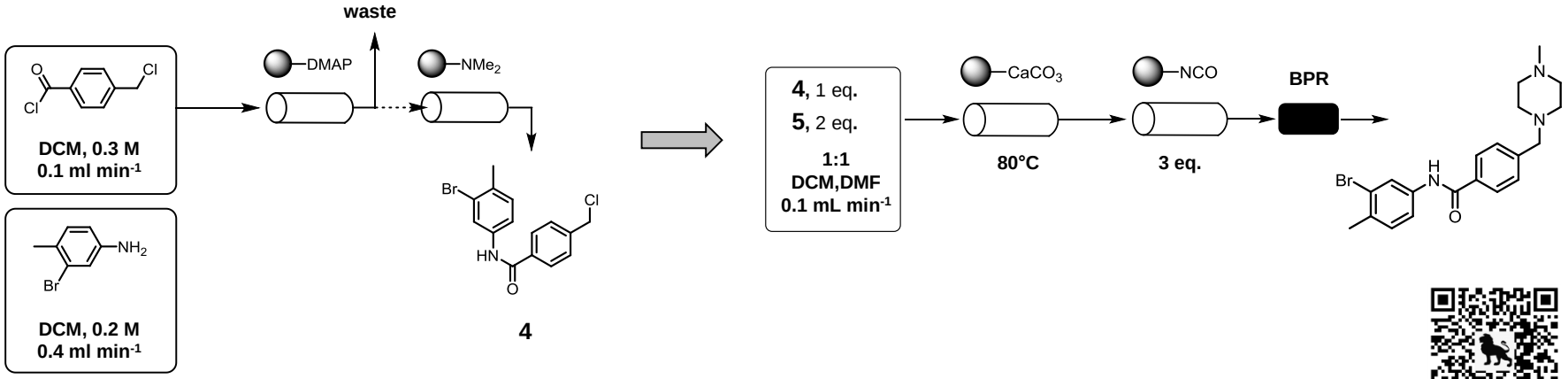
Flow chemistry should be a solution to problems in batch chemistry and aim to improve the „problem childs“

What Can Flow Chemistry Offer?



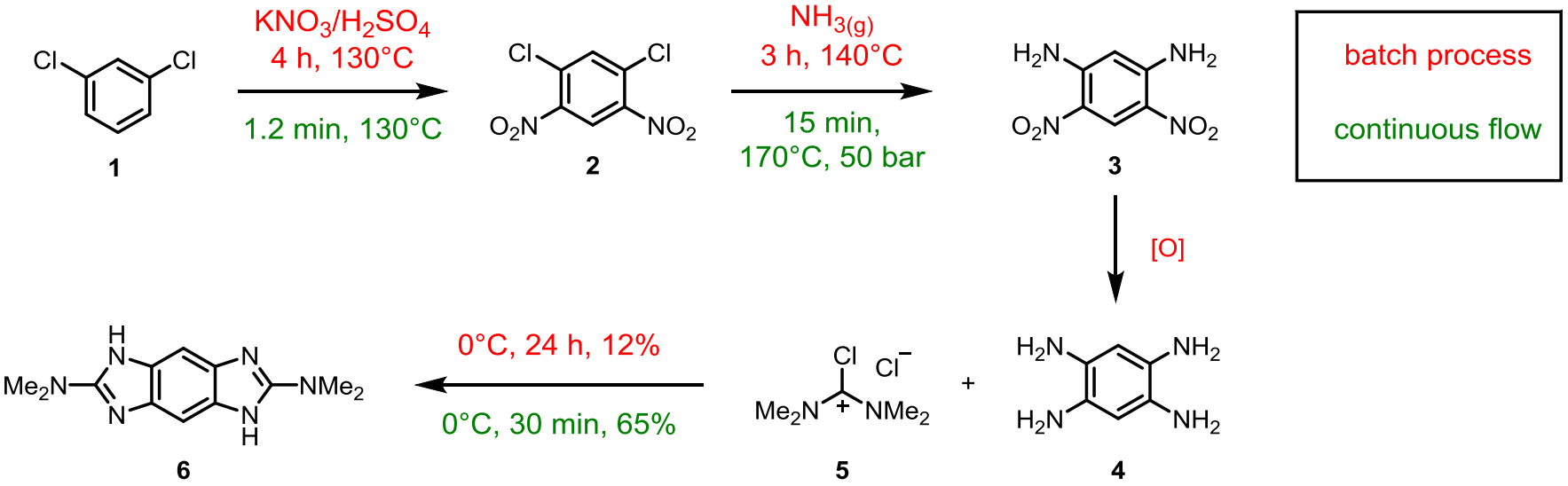


T. Noël, S. Kuhn, A. Musacchio, K. Jensen, S. Buchwald, *Angewandte Chemie Int Ed* **2011**, *50*, 5943–5946.

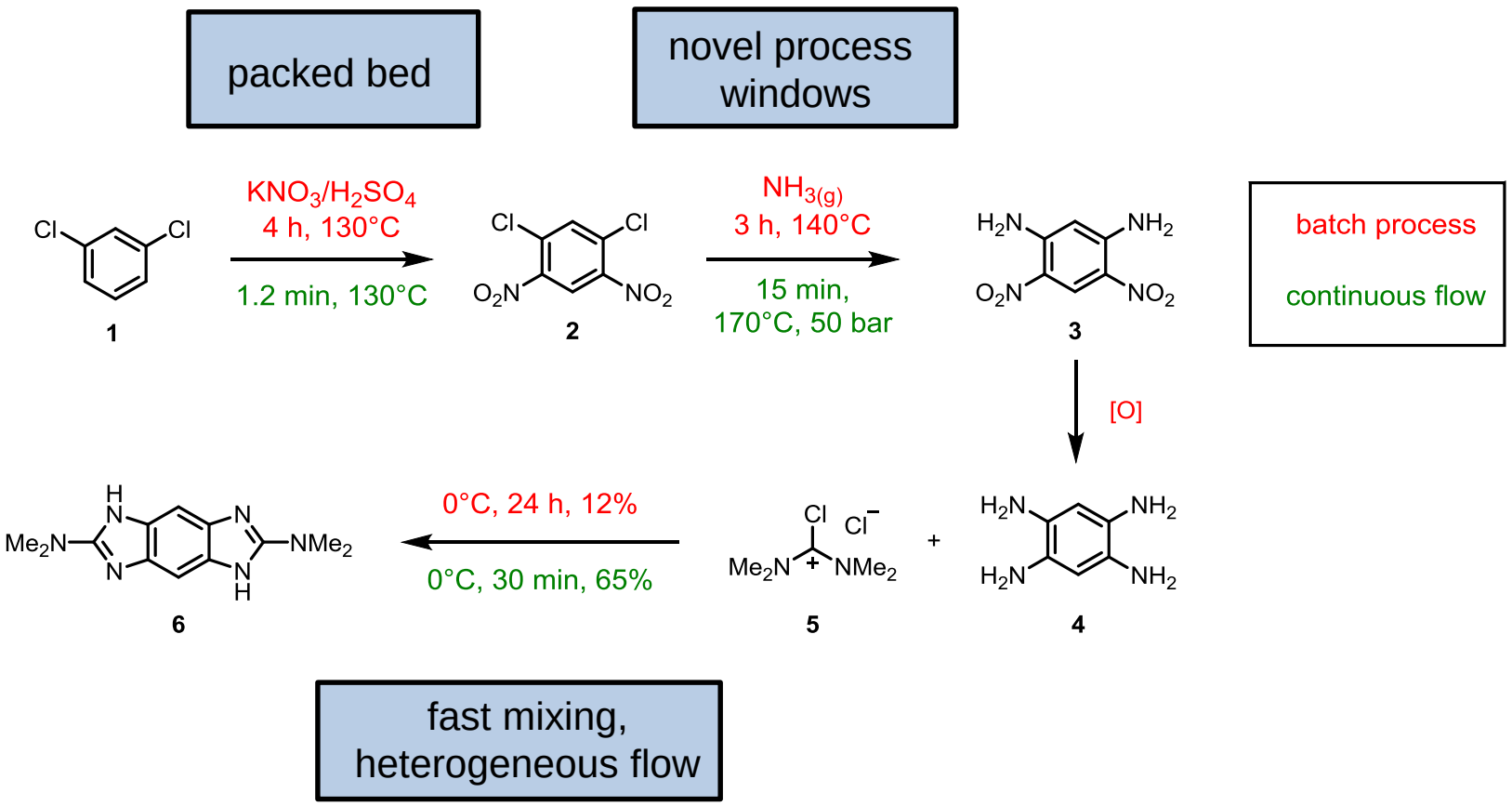


M. Hopkin, I. Baxendale, S. Ley, *Chem. Commun.* **2010**, *46*, 2450–2452.

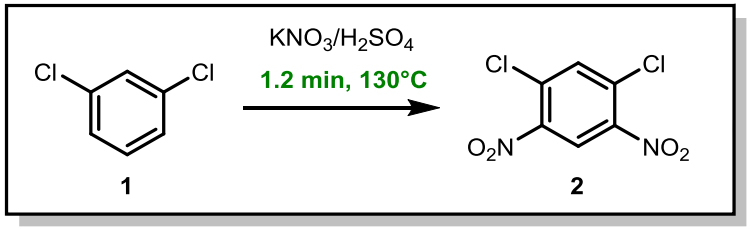
Synthesis Pathway



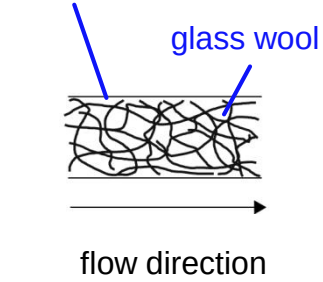
Synthesis Pathway



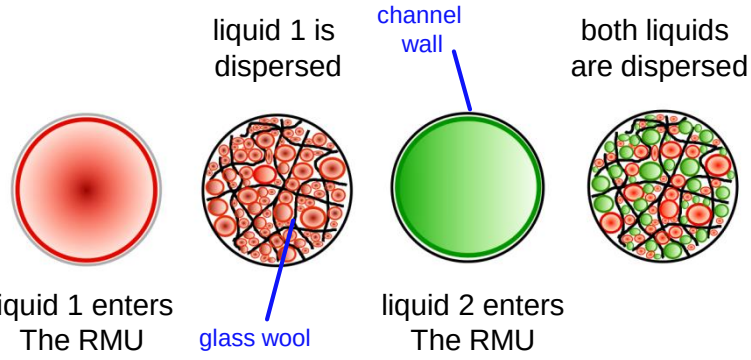
Nitration of 1,3-Dichlorobenzene

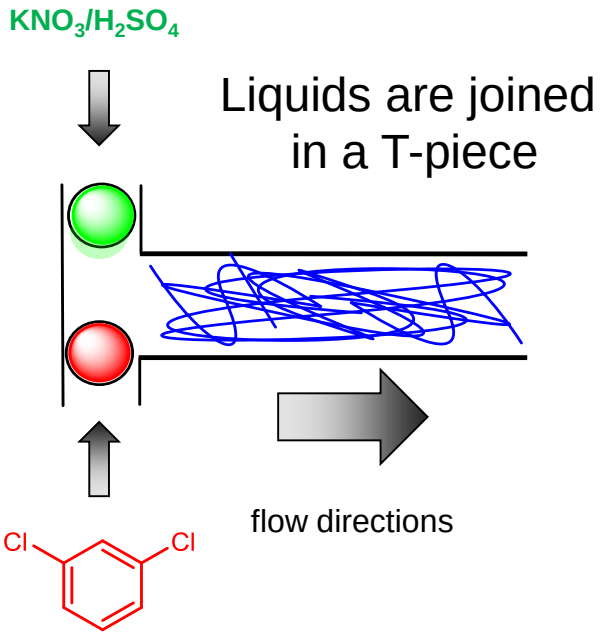


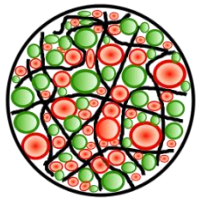
longitudinal cut



cross section of the channel



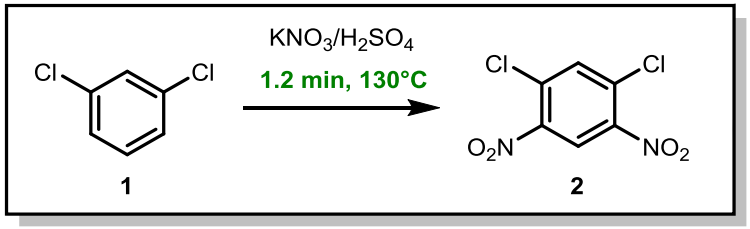




Enhanced mass transfer

- chaotic dispersed flow
- perpetually changing surface areas
- shear forces induce intra-droplet mixing

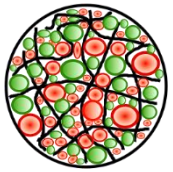
Nitration of 1,3-Dichlorobenzene

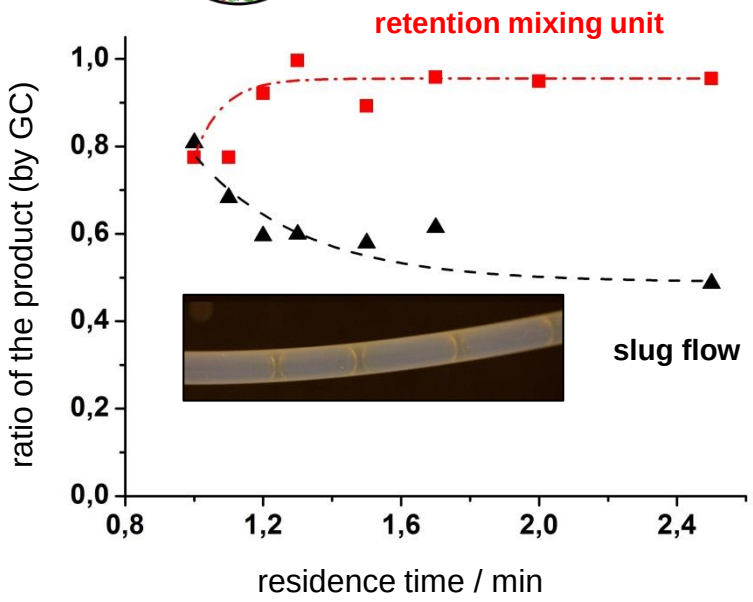


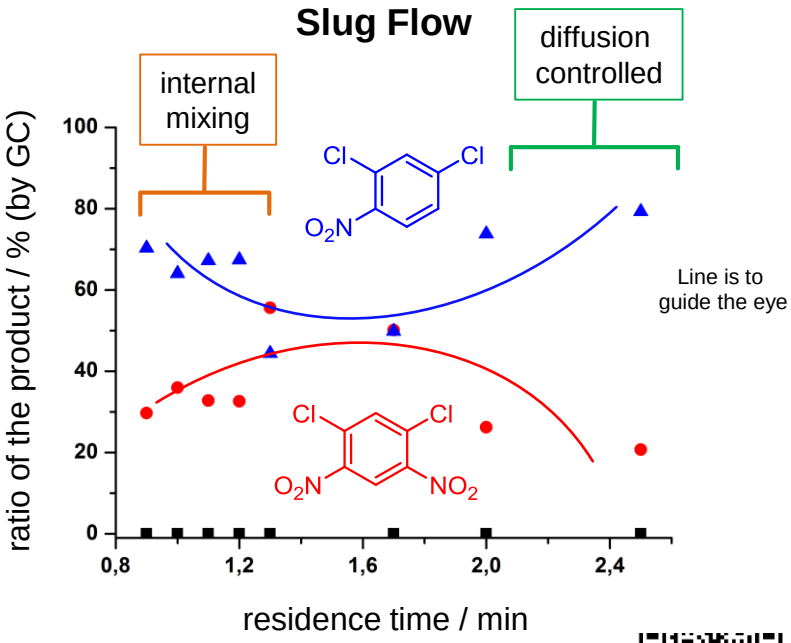
chaotic dispersed flow

perpetually changing surface areas

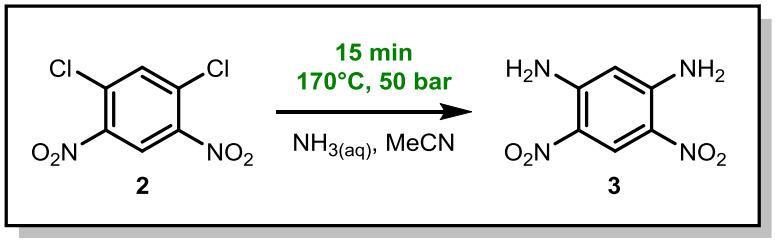
shear forces induce intra-droplet mixing

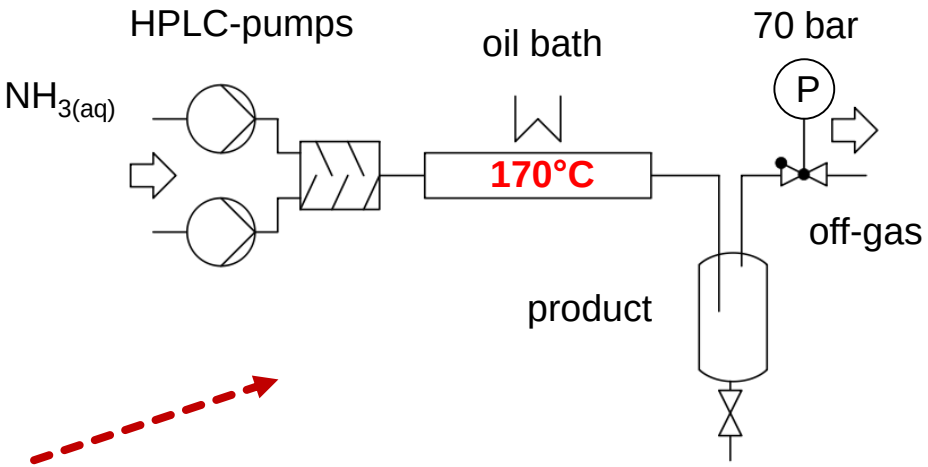


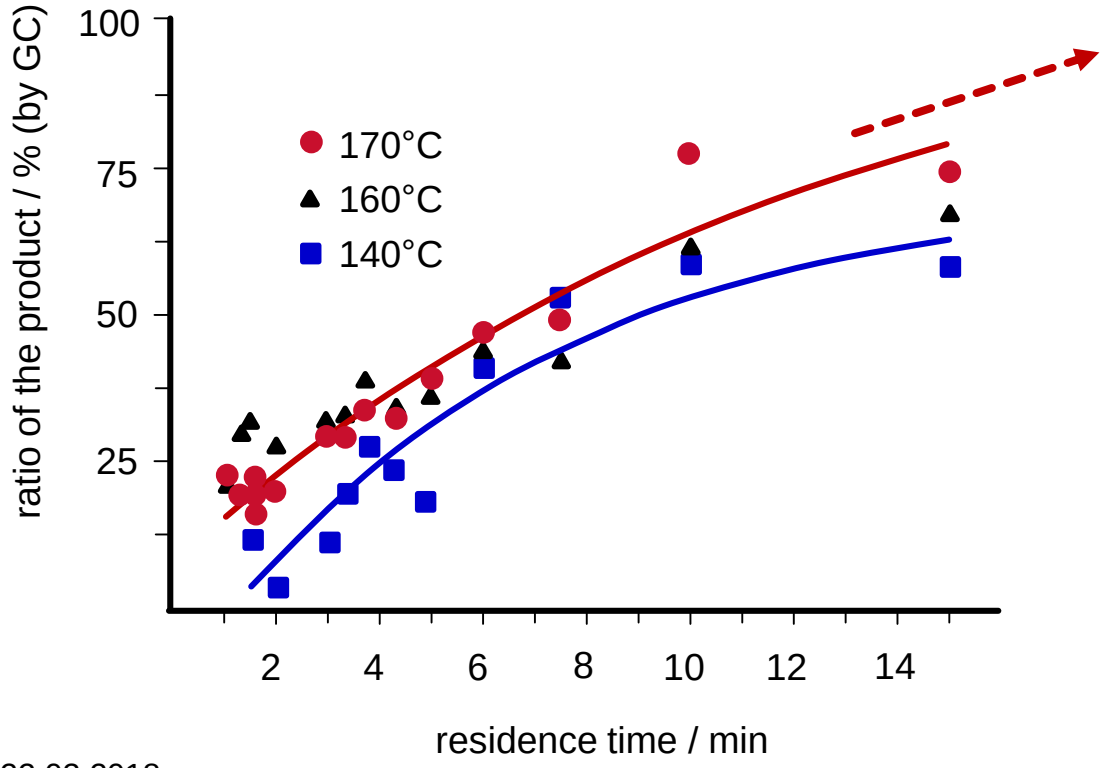




Novel Process Windows

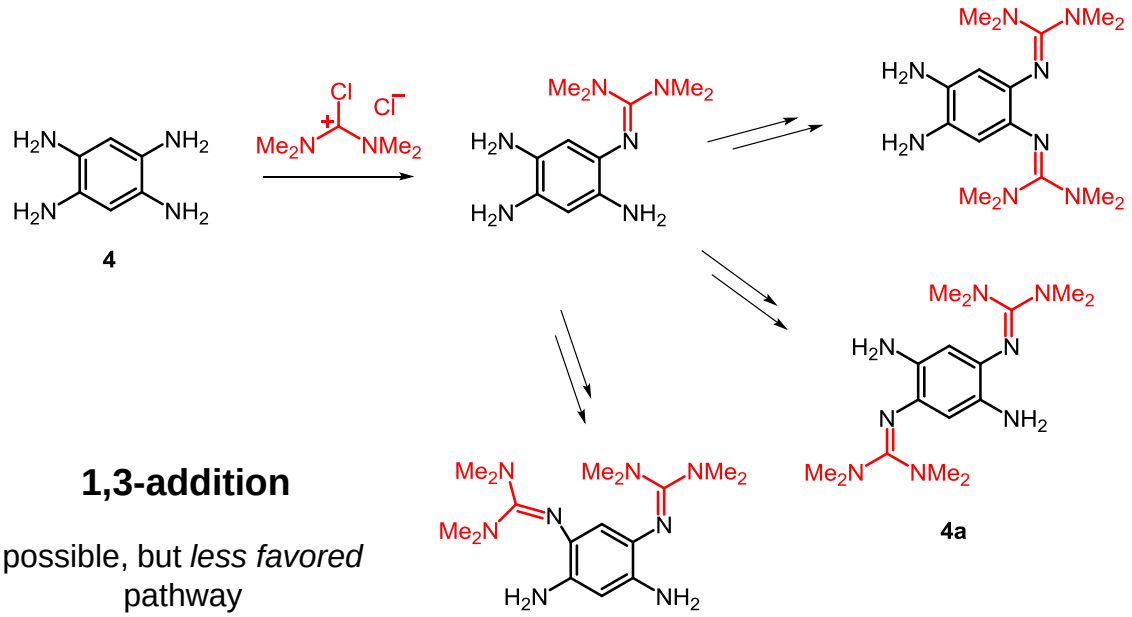


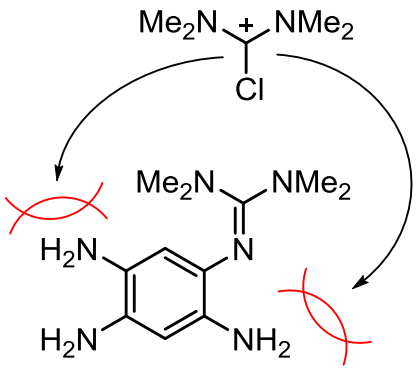




- temperatures over the boiling point of the solvent
- vastly shortened reaction time
- safer reagent handling

Kinetically Controlled Reactions

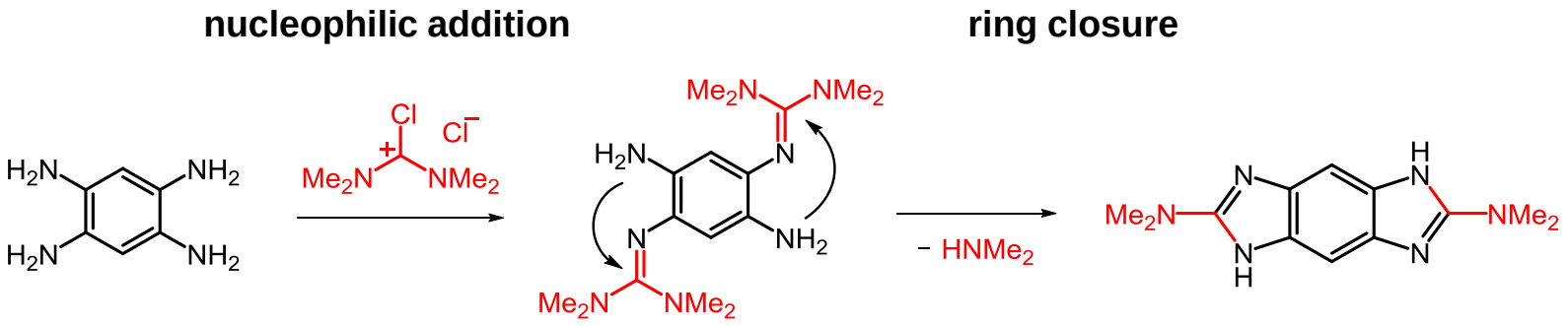




Steric hindrance leads to higher energy barriers

1,4-addition is kinetically favored

Kinetically Controlled Reactions



4 **4a** **6**

very fast

multiple side reactions possible

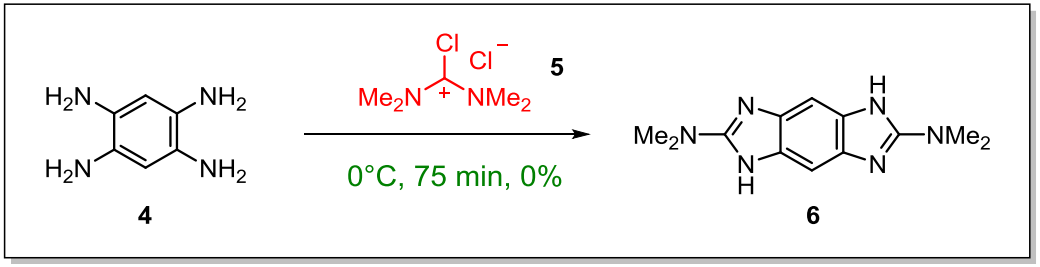
microtechnology necessary

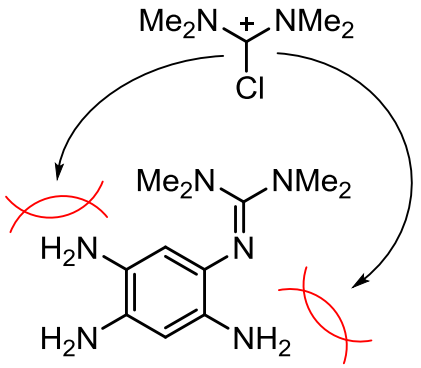
"slow"

aromatization occurs readily

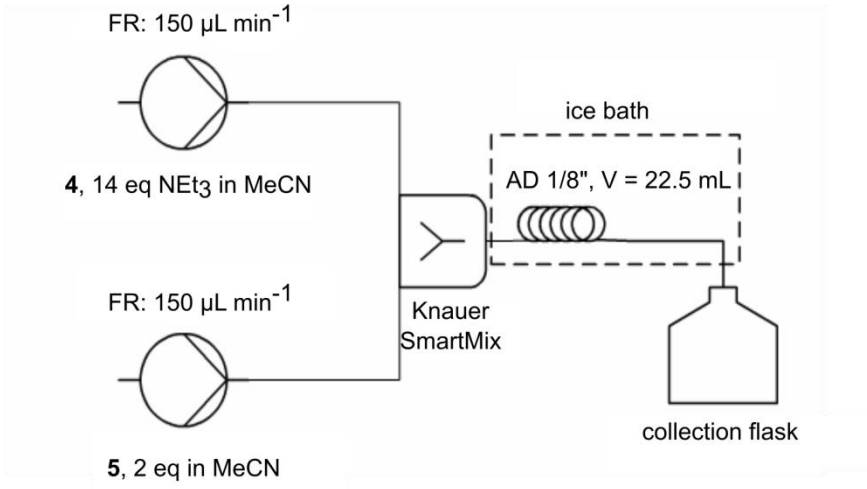
microtechnology not "necessary"

Evolution of a Reaction Setup



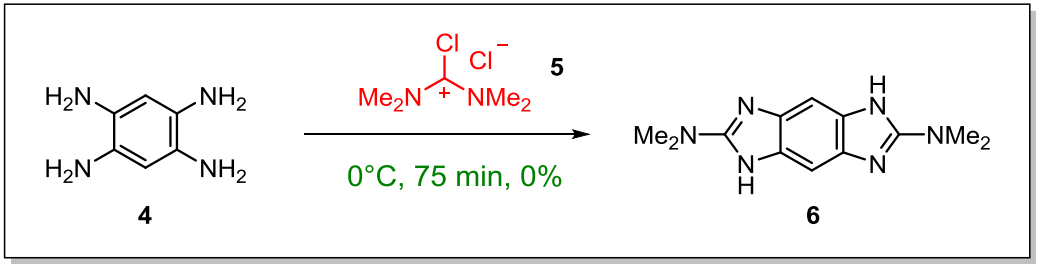


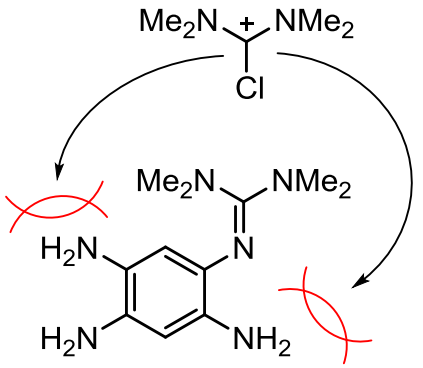
?



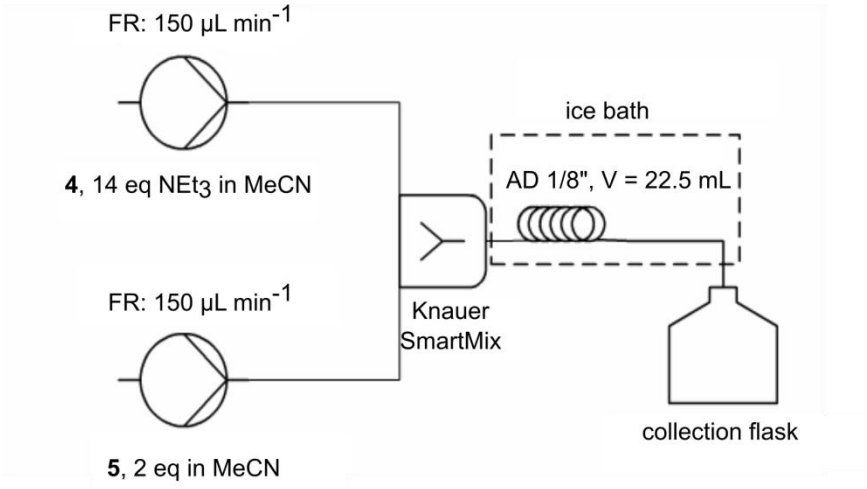
low temperatures
fast mixing

Evolution of a Reaction Setup





?

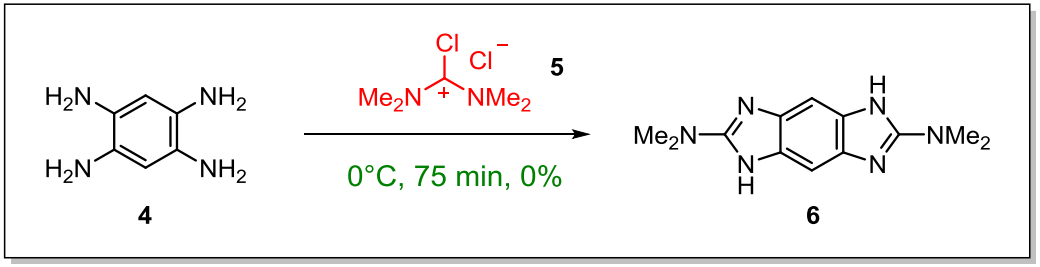


low temperatures
fast mixing

clogging inside the *reaction coil*

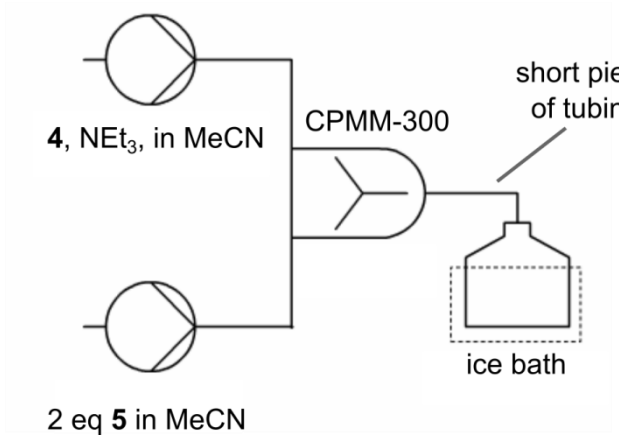
solvent changes led to side reactions

Evolution of a Reaction Setup



solubility is the main problem

?



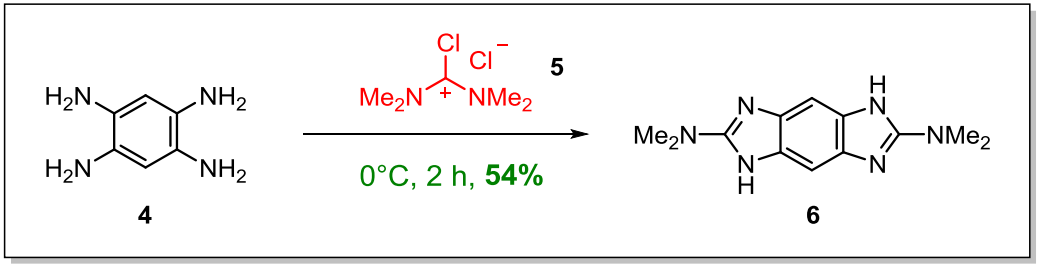
the solution is stirred after exiting the reactor

clogging inside *the mixer*

higher flow rates showed no improvement (300-1200 µL min^{-1})

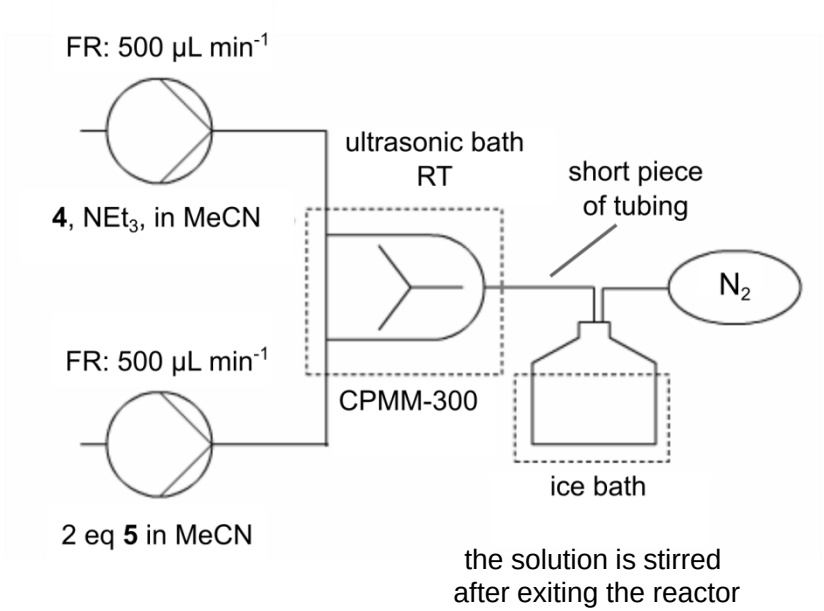
low temperatures
fast mixing
short tubing

Evolution of a Reaction Setup



is the mixing speed too slow?

?



the solution is stirred
after exiting the reactor

low temperatures
fast mixing
short tubing

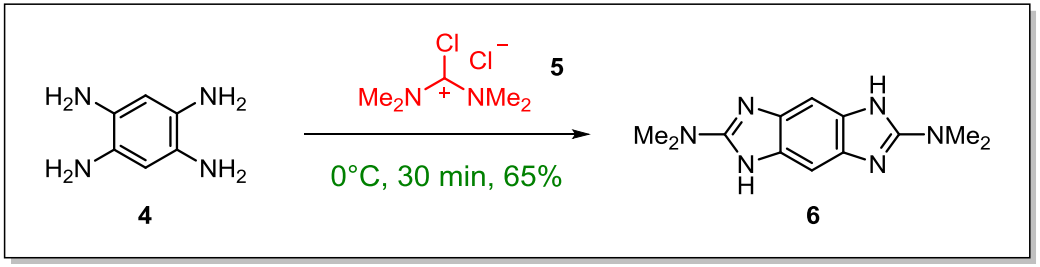
high flow rates
inert atmosphere

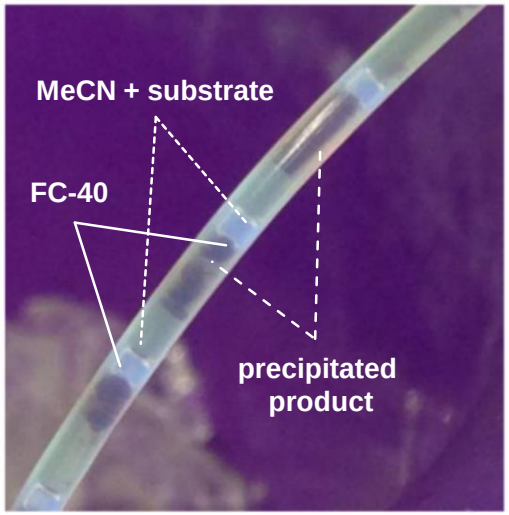
54% yield (4 times the batch yield)

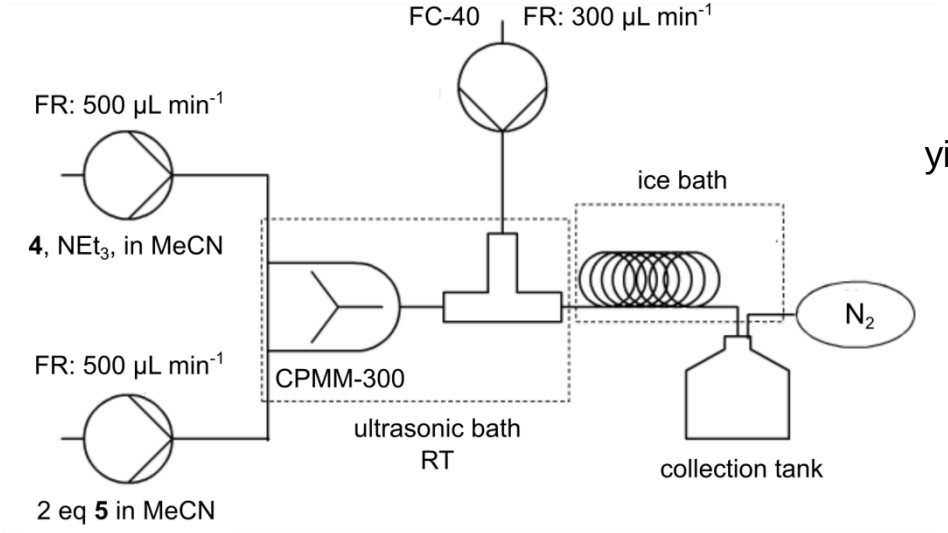
higher mixing efficiency

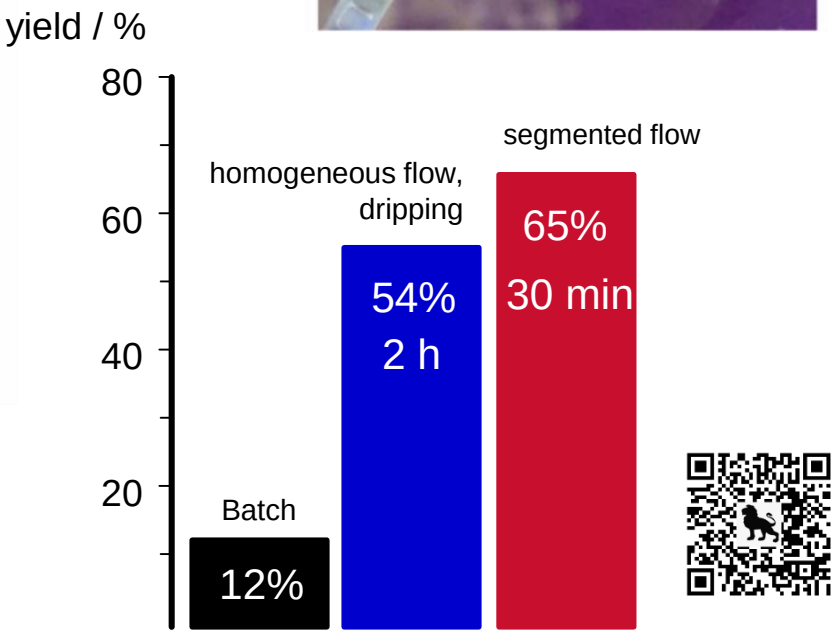
no clogging

Evolution of a Reaction Setup

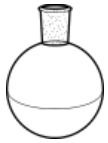


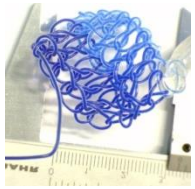






Summary





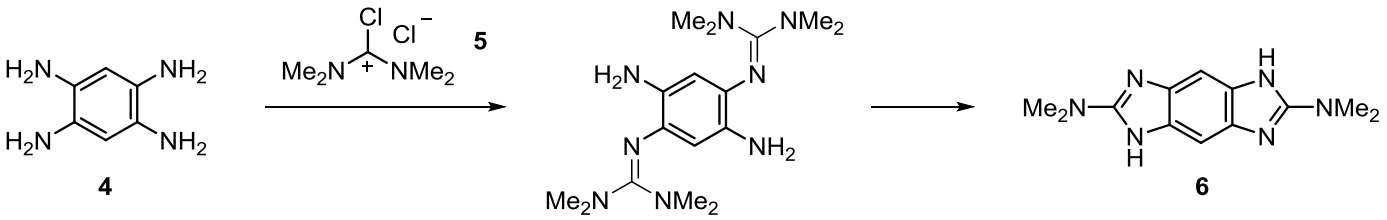
Step	Reaction	time	yield	time	yield	
1	electroph. subst.	4 h	70%	1.2 min	72%	
2	nucleoph. subst.	3 h	80%	15 min	**50%**	------ Not optimized
3	hydrogenation	//	//	//	//	
4	nucleoph. addition ring closure	24 h	12%	30 min	65%	
		∑ 31 h	7%	47 min	23%	

Switching to flow systems resulted in vastly improved reaction parameters!

Summary

A four step batch synthesis was transferred to a flow system.

Each step could have consisted of standard operations, but a specifically tailored approach generated bigger payoffs.



The reaction to 1,4-bis-[*N*,*N*,*N*',*N*'-tetramethylguanidino]-2,5-diaminobenzene was not controllable in batch. Only fast mixing and heterogeneous flow in micro flow made the reaction feasible.

Thank you!

Pia Börner, M.Sc

Pia single handedly developed and improved the process and setups for the key step.

(and is looking for a PhD position starting early 2017)