Azide Synthesis in Microstructured Flow Systems

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Sigma-Aldrich – The company

- Headquarter in St. Louis, Missouri
- Revenues (2009) > 2.1 bln. $
- ~ 8'000 Employees world wide
- > 1 Million customers
- Custom synthesis executed by SAFC

St. Louis (USA)

Buchs (CH)
Center of Excellence,
Organic Technologies & Synthesis

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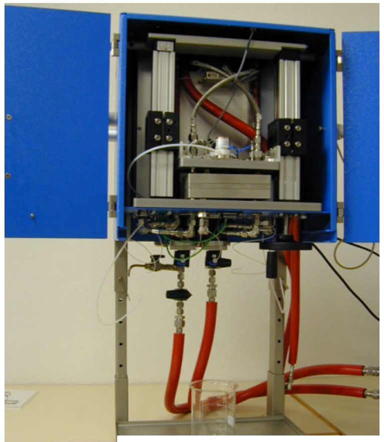
Flow Chem history at Sigma-Aldrich

2004

- Purchase of an integrated MRT-system

  Idea: Product profile improvement by better heat management
- Corporate production of retinol (vitamin A alcohol, sales 230 k$/a)
- Enabling technology for exo-methylene cyclopentane



CPC-Systems

- Further technology development (glass reactors) with LTF company (Germany).
- 2007: Microreactor Explorer Kit (19979) launched

MRE kit 19979

today

- Production of > 65 catalogue products
- Several SAFC custom synthesis projects done

- Personal situation:
- Two labs in Buchs for Flow Chem R&D (3 FTE)
- Technology established in small scale dept., (CH), SAFC (CH) and kg-scale lab (USA)

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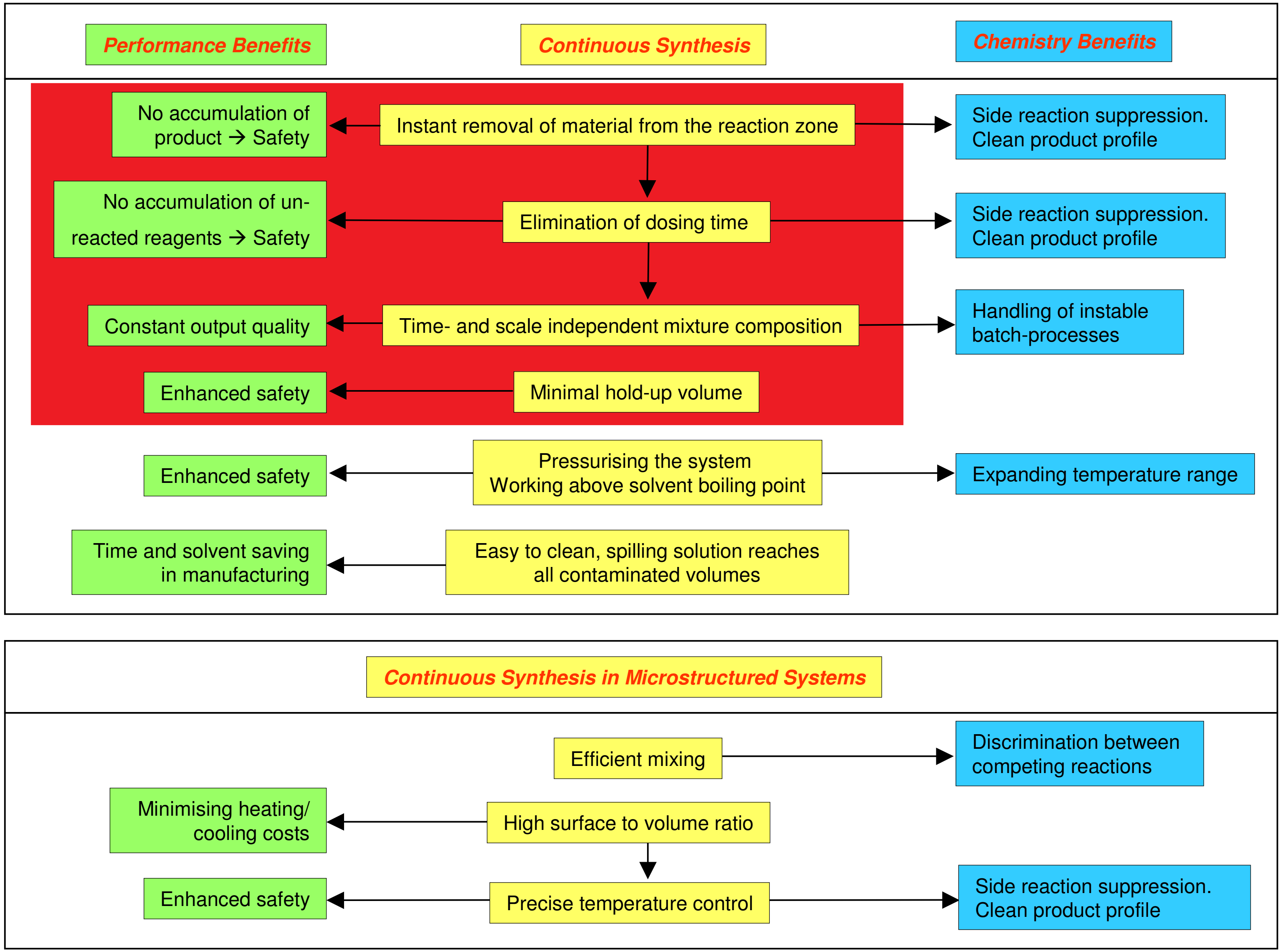
Learning curve, MR technology benefits



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Cornerstones

- Pragmatic approach
- 1st Batch campaign typically 100 – 500 g (later up to kg-scale)
- Focus on synthesis in liquid/liquid systems
- Reaction mixture must stay into solution

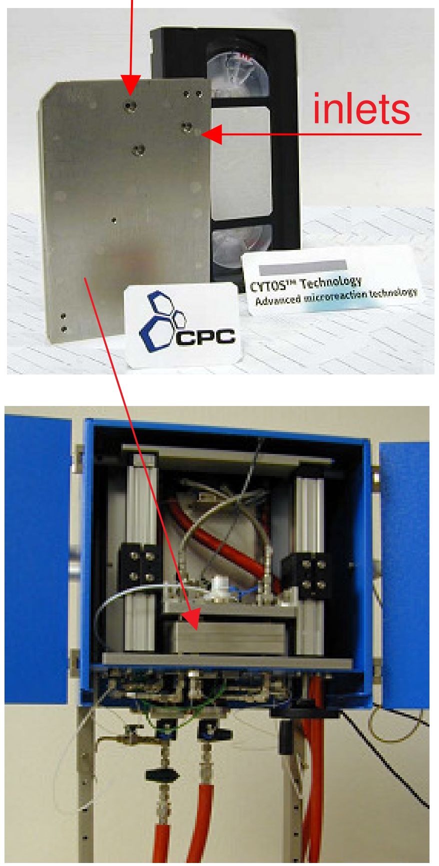
- Heat management & safety play important roles
- Multi purpose equipment for synthesis ***and work-up***

- Choice of executed reactions

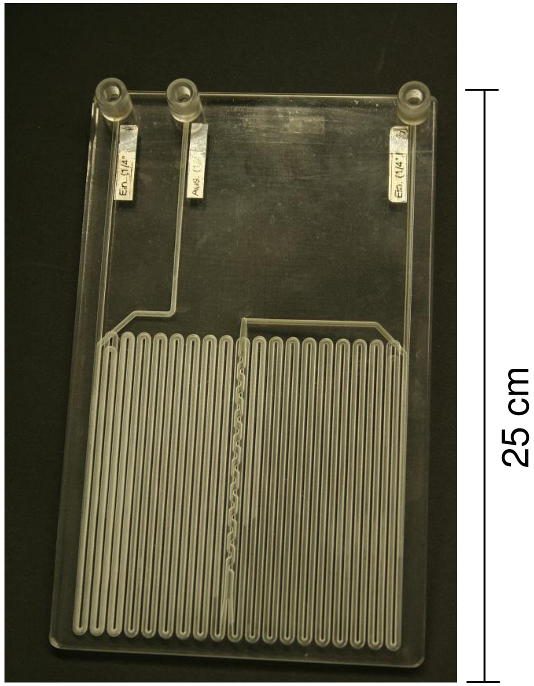
Grignard	Carbocyclisation
DAST synthesis	BuLi handling
Epoxidations	Bromine handling
Diazo acetate synthesis & handling	Azide synthesis
Selective Boc introduction	

MR systems at Sigma-Aldrich (Swiss site)

Stainless Microreactor
Type CYTOS
Channel width ca. 0.2 mm
Active temperature control

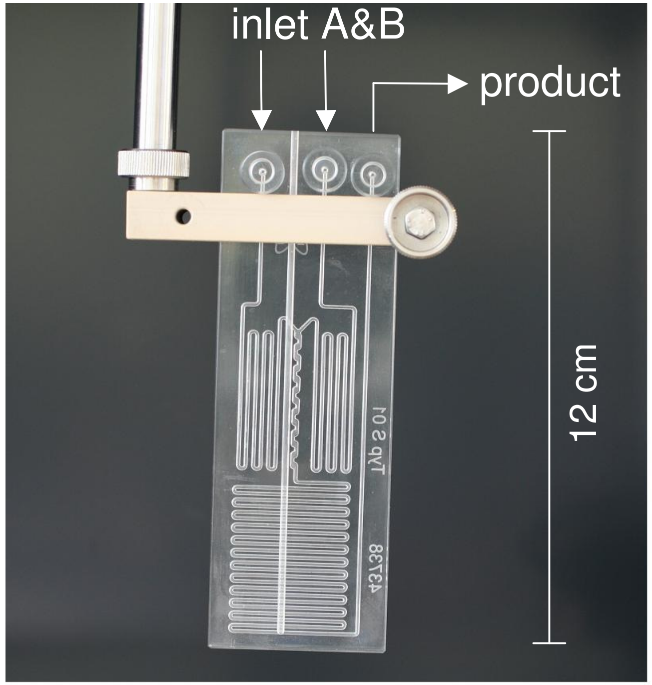


Glass Mesoreactor
Type XXL
Channel width 2 mm
15 mL RTU



Little Things Factory

Glass Microreactor
Type S02
Channel width 0.5 – 1 mm
Inner volume ca. 1 mL



Little Things Factory

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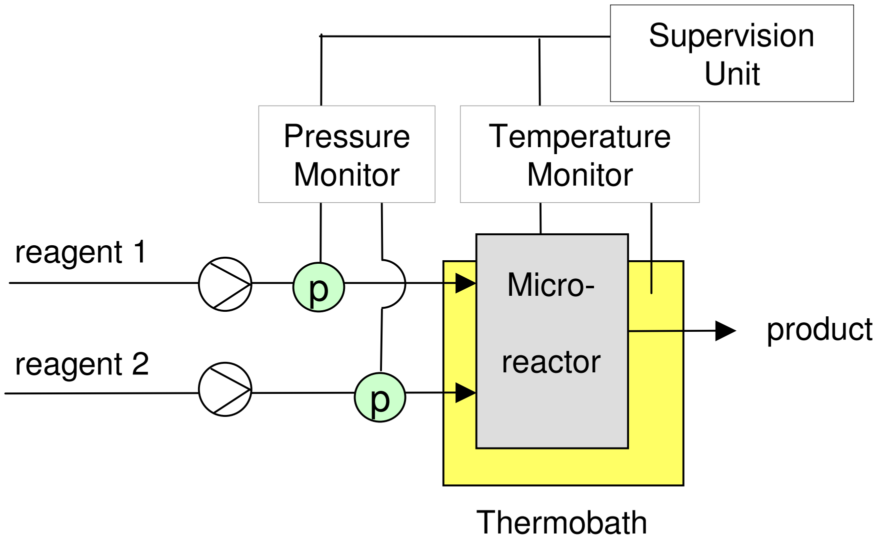
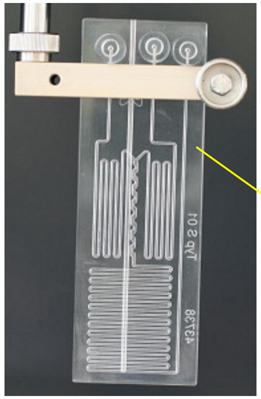
Microreactor Explorer Kit – product 19979





- All-in-one solution*
- Built from commercially available elements
- Microreactor type S02 & rotary piston pumps
- Suitable for kg-campaigns
- In house use at Sigma-Aldrich

*) Thermobath not included

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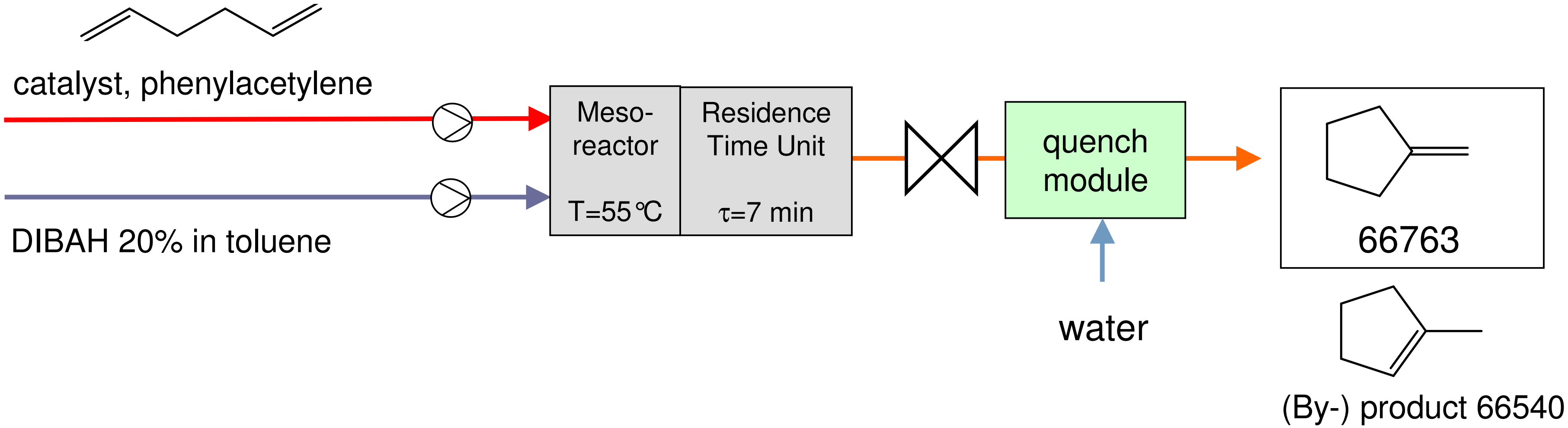
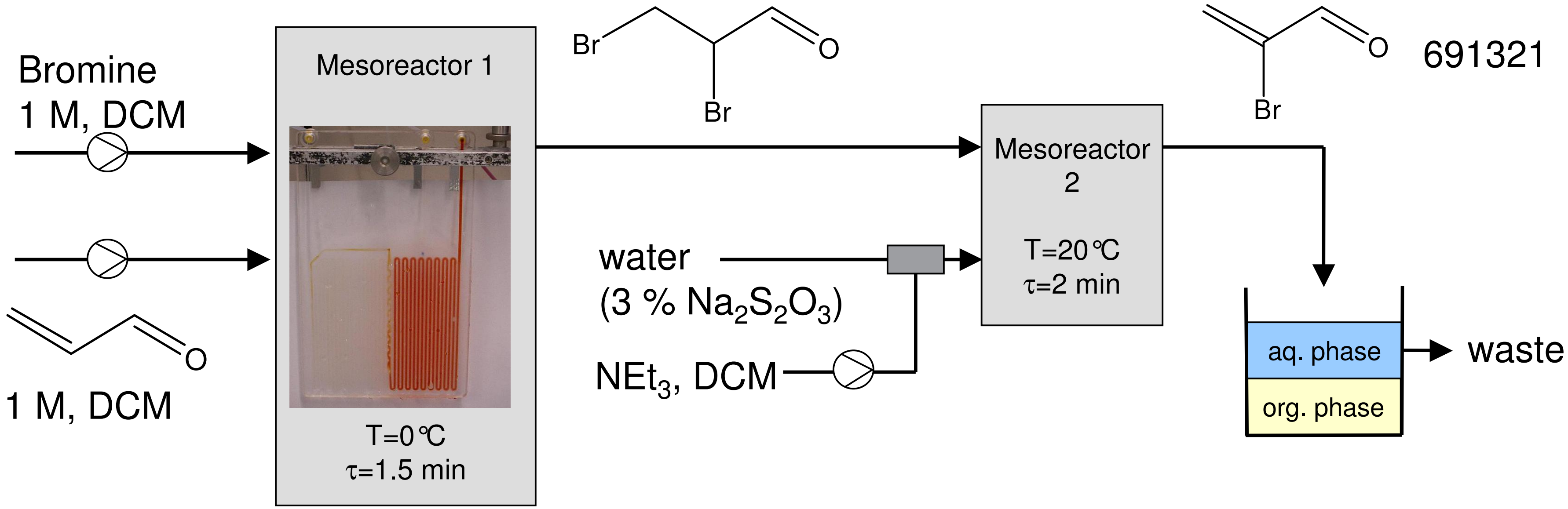
Early example I, Methylene cyclopentane



- Product **66763** isomerises on extended contact time product/catalyst
  → Instant catalyst quench essential
- Specification of product **66763**: Purity > 99%
- By-product has very similar b.p. (distillation problem)
  → Raw material must be pure
- Output > 4 kg/24h
- Importance of instant quench & continuous extraction

Early example II, Handling of bromine



- Complete conversion
- Yield ca. 50%, output 350 g/24h
- DSC analysis intermediate **691321** (1:1 DCM mixture) 641 J/g, left limit 88° C
- Elimination time with aq. KOH (heterogen.) >20 min (to long)

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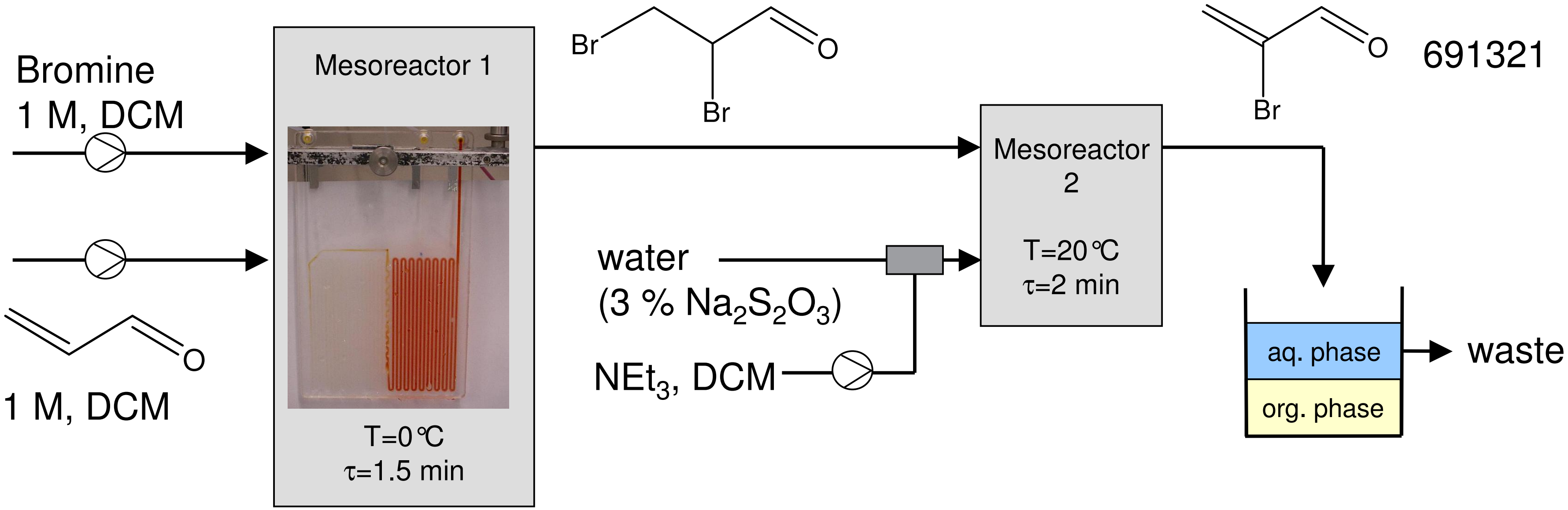
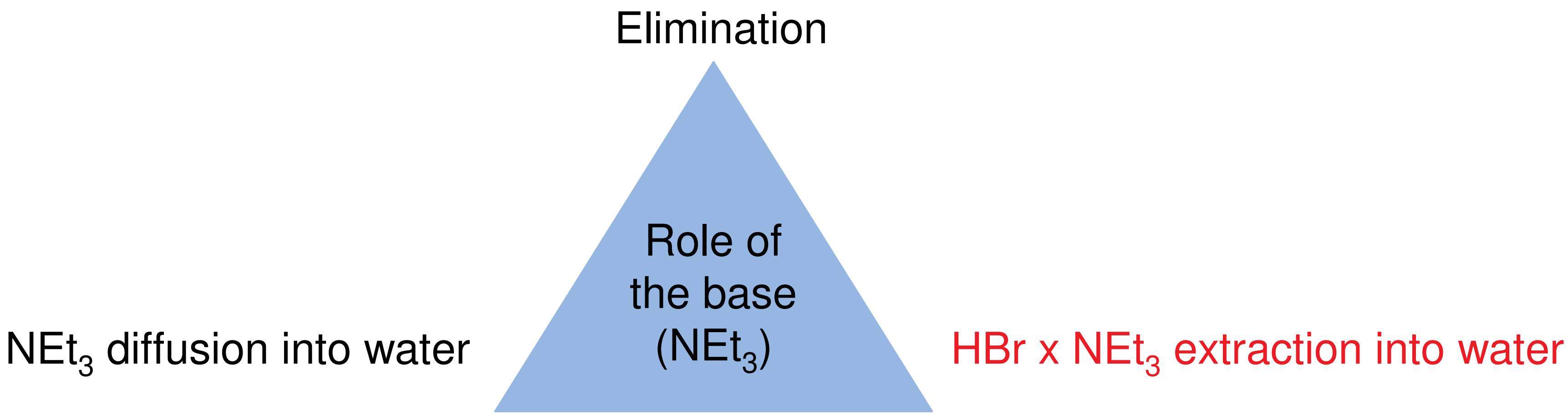
Early example II, Handling of bromine





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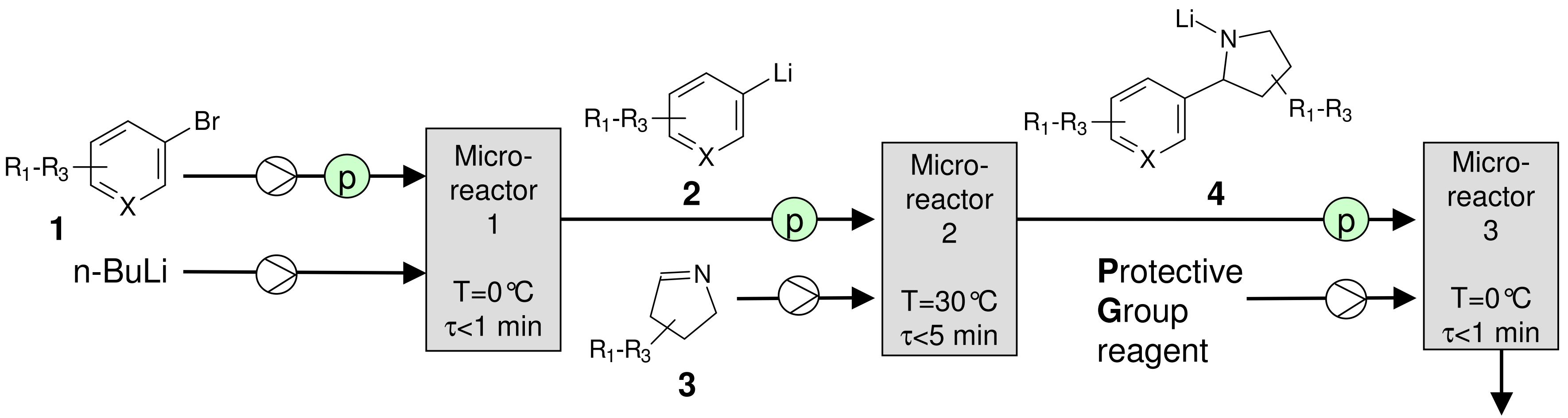
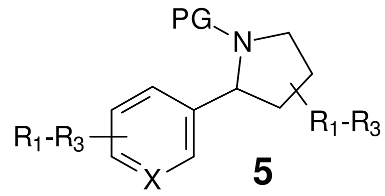
Early example III, Li-R interception





- Yield 55%, output > 3 kg/24h
- Campaign in a Corning G1 3-stage system, tests in S02 MR
- Impurity profile improved

  → Elimination of dosing time suppresses side reactions
- Batch yields changing

  → Mixture from MR comes in constant quality
- Work-up needed before running stage 4

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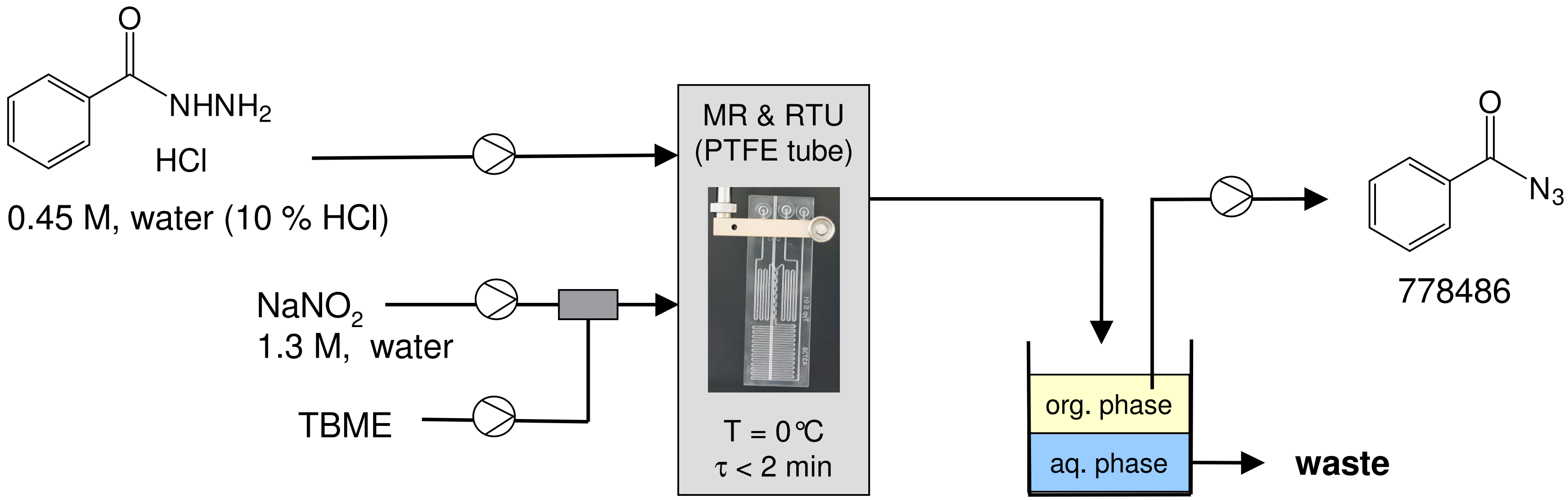
Curtius reaction II, benzoyl azide

Product idea: Lowering the potential of the azide by making it a solution



- Yield 77% → Output 730 g/24h
- Concentration estimation by NMR → fine tuning by TBME flow modification
- All inorganic compounds extracted (purity > 96%, LC)
- Final sln. 0.5 M, stable up to 75° C (Radex), energy 250 J/g (DSC)

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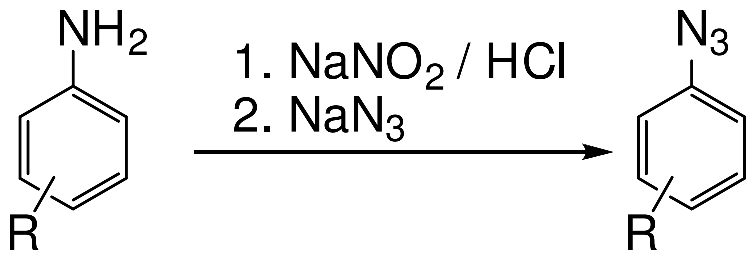
BAP – Buchs Azide Process

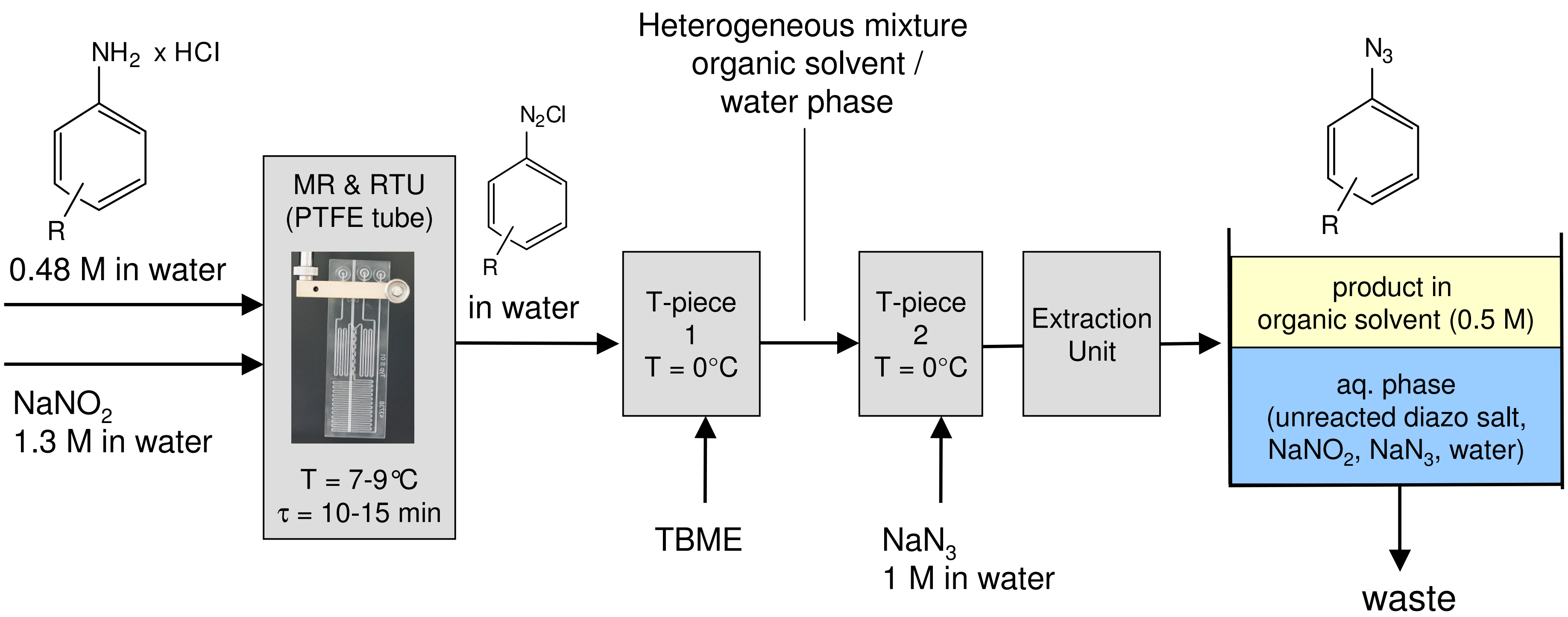


Project target

- Product: 0.5 M in sln. in organic solvent
- Only extraction accepted for post processing
  → Product must be the only extricable compound (org. solvent)
- Process and product safety (United Nation criteria)

Also see: T. Tsuritani et al. *OPRD* **2009**, *13*, 1407.

BAP – Buchs Azide Process



- Major problem: Solid formation
  → Adding alcohols or higher dilution
- Standard flow rates: 5.3 mL/min (aniline), 2.5 mL/min (TBME)
- Intensive gas formation on stage 2
- Aq. phase may be contaminated with HN_3

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Buchs Azide Process - Results

Halides					
	Yield (%)	Purity (min. %)	Additive	Output (g/24 h)	SIAL no.
o-F	40	96	No, but ISQ	270	778842
m-F	32	95	No, but ISQ	250	779814
p-F	70	99	No	415	779253
o-Cl	72	99	No	480	778958
m-Cl	71	99	Yes	505	779938
p-Cl	71	99	No	475	727482
o-Br	96	99	Yes	780	779318
m-Br	81	98	Yes	780	779083
p-Br	81	98	Yes	675	779377
o-I	17	97	Yes	255	779059
m-I	55	99	Yes	740	778516
p-I	68	95	Yes	960	779482

- No incorporation of chloride or OR into the product

Buchs Azide Process - Results

Rest					
	Yield (%)	Purity (min. %)	Additive	Output (g/24 h)	SIAL no.
o-CH3	48	91	No	300	779164
m-CH3	47	97	No	285	778613
p-CH3	47	99	No	630	772466
o-OCH3	72	95	Yes	590	779261
m-OCH3	60	97	Yes	480	778729
p-OCH3	32	91	No	210	727431
o-CF3	82	97	No	570	779520
m-CF3	94	99	No	570	779415
p-CF3	67	95	Yes	395	779199
o-CO2Me	47	99	No	300	779741
m-CO2Me	71	98	No	335	779644
p-CO2Me	50	96	No	525	779598

- Flow rates doubled for 772466 → Stage 1 temp. jumped to 9-11℃

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Buchs Azide Process - Results

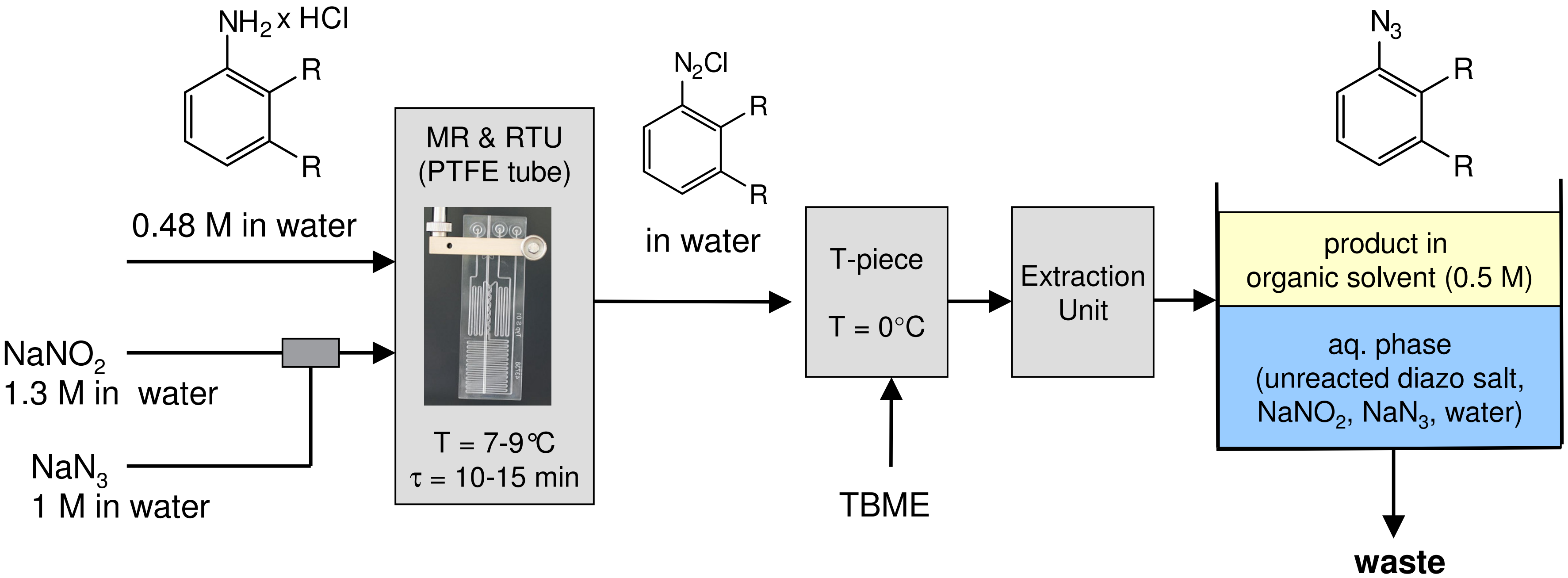
	Yield (%)	Purity (mind. %)	Additive	Output (g/24 h)	SIAL no.
Phenyl, TBME	**59**	**98**	**No**	**230**	**727490**
Phenyl, 2-Me-THF	**72**	**98**	**No**	**355**	**778583**

	Yield (%)	Purity (mind. %)	Additive	Output (g/24 h)	SIAL no.
o-CO2H	**24**	**97**	**No**	**175**	**727458**

Final concentration was set to 0.15 M because of limited solubility

→ General problem for acids

BAP – Buchs Azide Process, ISQ variation



- Solid formation problem solved
- Low yields

	Yield (%)	Purity (mind. %)	Additive	Output (g/24 h)	SIAL no.
o-F	**40**	**96**	**No, but ISQ**	**270**	**778842**
m-F	**32**	**95**	**No, but ISQ**	**250**	**779814**

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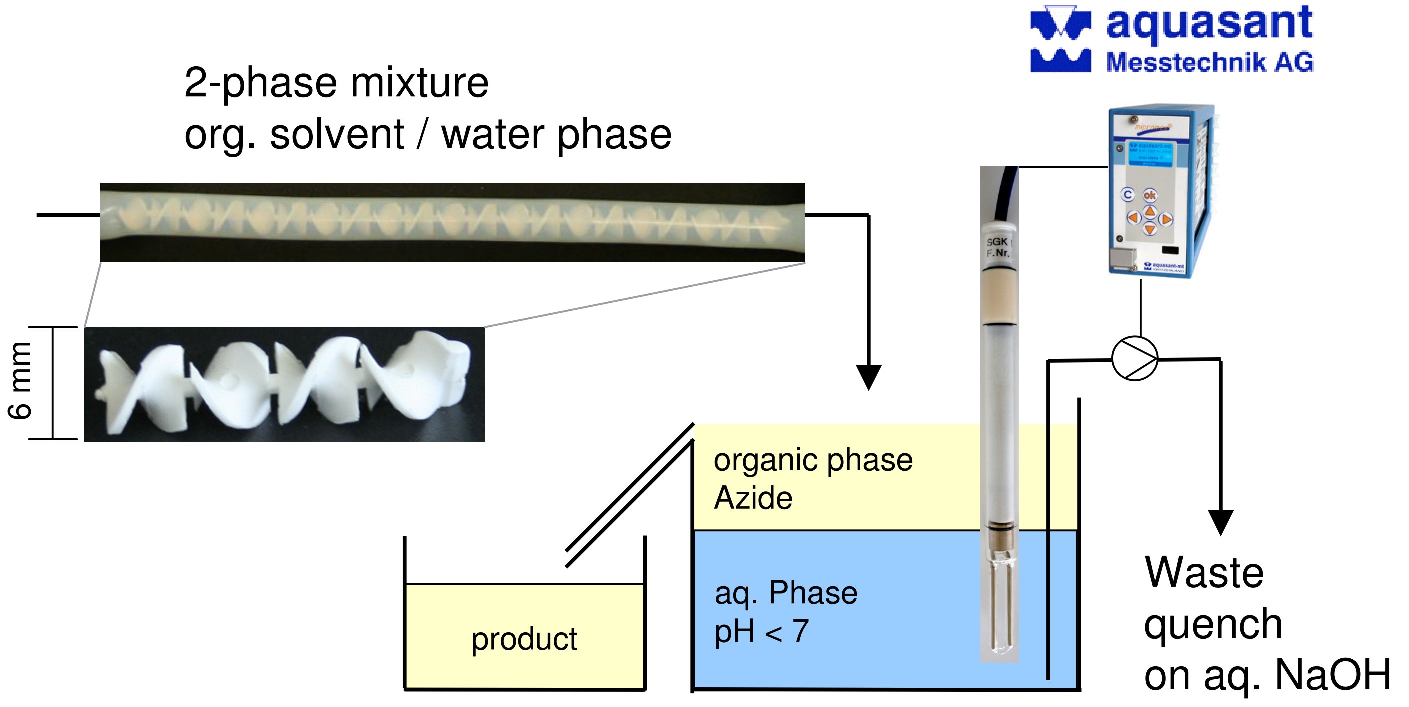
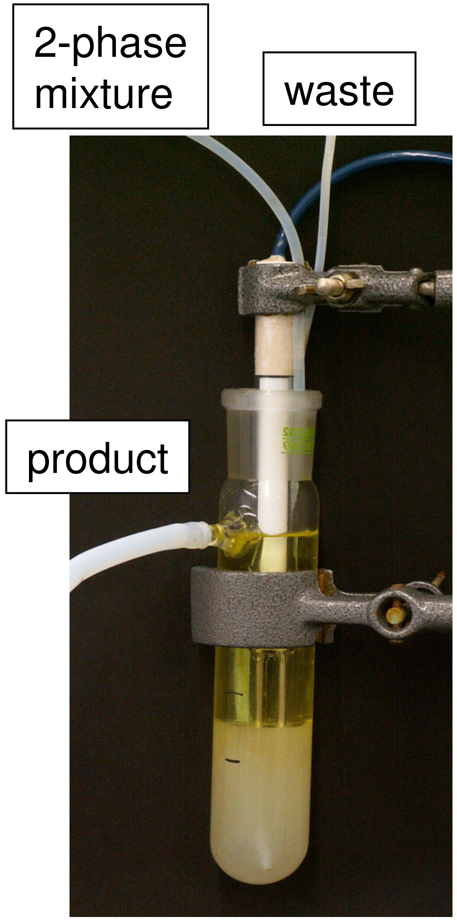
BAP – Buchs Azide Process, work-up





- Aq. phase max. volume 100 mL
- Phase interface detection by impedance measurement
- Mixer built from commercially available elements (problem: cleaning)

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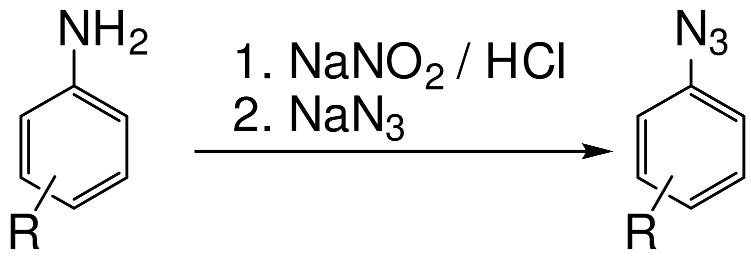
Buchs Azide Process - Summary



- 26 derivatives synthesised
- Yields 17 – 96 %
- Most products came in > 95 % purity (only one extraction)
- Solutions stable up to 80°C (Radex), energy < 500 J/g (DSC)

- Robust process (also tolerant towards pulsation)
- Output (sln.) 3.5 – 4.0 L / 24 h → max. 5 mol / 24 h
- Potential for output improvement given
- Product sln. suitable for further processing

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Flow Chem at Sigma-Aldrich - Summary

- Flow chemistry in MR systems used to make commercial products
- Enabling technology
  → Rapid access to the safety-critical processes
- Development time shortened by elimination of interim thermo analysis
- Instant conversion of intermediates & small hold-up volumes are strong points

- Trend to two- or more stage systems
- Future focus on continuous work-up (product volume minimisation)

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Thanks to the colleagues

- Gökcen Yilmaz
- Sascha Bollhalder (DSC and Safety analysis)

Literature

M. Weber, G. Yilmaz, G. Wille *Chemistry Today*, **2011** (in press)

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