Frontiers in Chemistry:
Microfluidics and Microreactors in Organic Synthesis

John Goodell

7/23/11

Flow of Presentation

- Promise of microfluidics
- Trends in literature
- Reactor materials and fabrication
- Flow regimes
- Benefits of using microreactors
- Developing applications and advancements

The Promise of Microfluidics/Microreactors

- **Frontier:** a new field for explorative or developmental activity

  — *Merriam-Webster Dictionary*

- "Reactions performed within a microreactor invariably generate **relatively pure** products in **high yield**, in comparison to batch reactions, in much **shorter times** and in **sufficient quantities** to perform full structural characterization of the product(s) using spectroscopic techniques."

  — *Watts and Haswell* (*Chem. Soc. Rev.* **2005**, *34*, 235)

- "Will **microreactors** replace the round-bottomed flask to perform chemical reactions in the near future?"

  — *Seeberger* (*Chem. Eur. J.* **2006**, *12*, 8434)

Batch Chemistry vs. Microfluidics

Batch

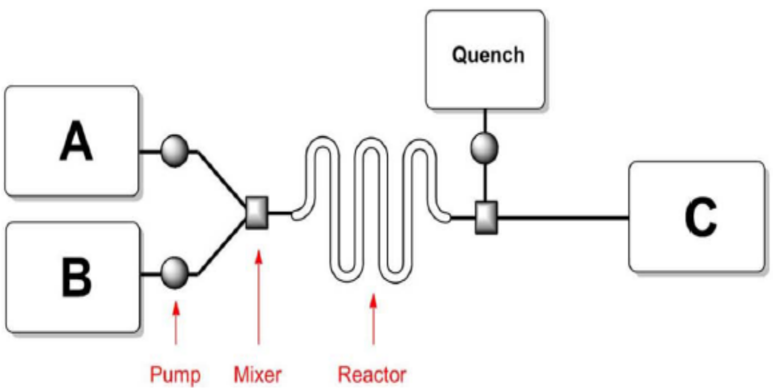
Scale-up

Pilot

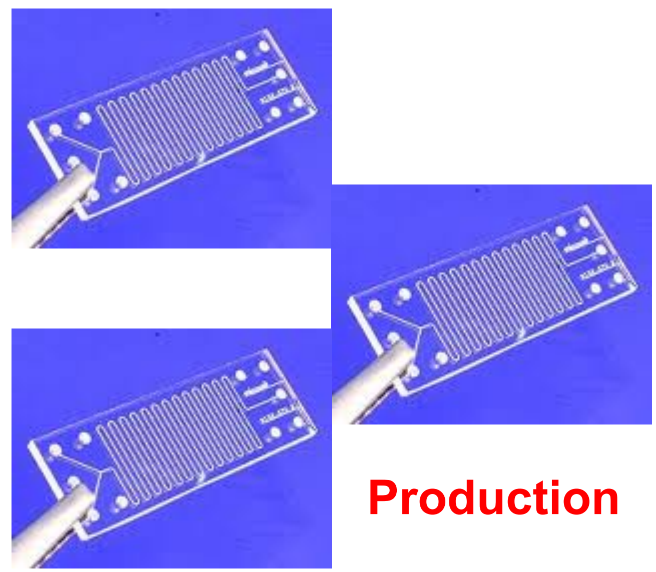
Scale-up

Production

- Scale-up from batch often posses new challenges requiring re-opimization of reaction conditions.



Scale-out

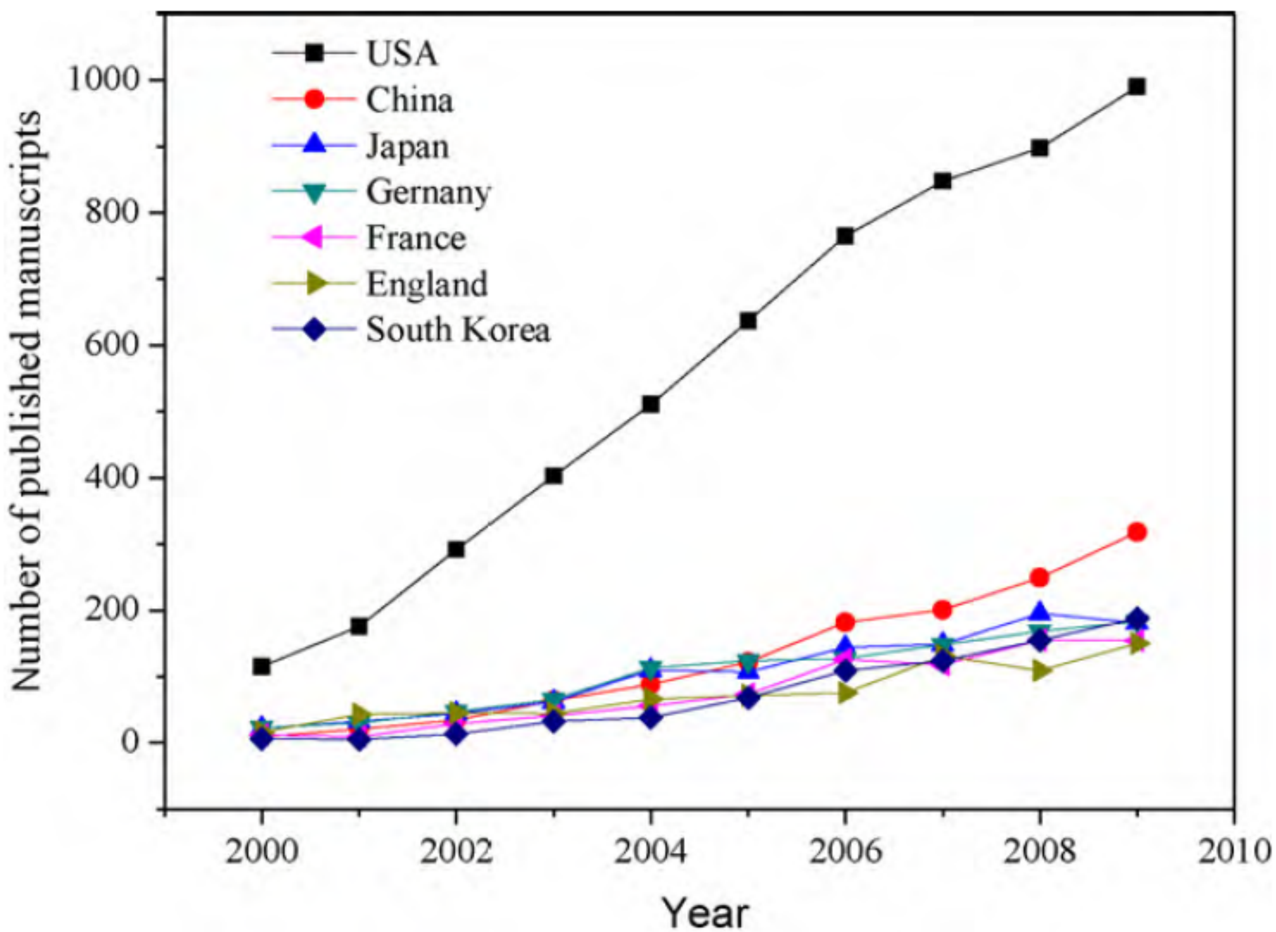


Production

- Scale-up by numbering up…reaction conditions remain the same.

http://www.princeton.edu/chemistry/macmillan/group-meetings/JEC_microreactors.pdf

Development Trends of Microfluidics in Different Countries (2000-2009)



Web of Science (Thomson Reuters) literature search. Keywords: micro react*, microfluid*, microstructured reactor*, micro chemical, micro thermal, micro heat, micro pump, micro valve.

Chemical Engineering Journal **2010**, *163*, 165.

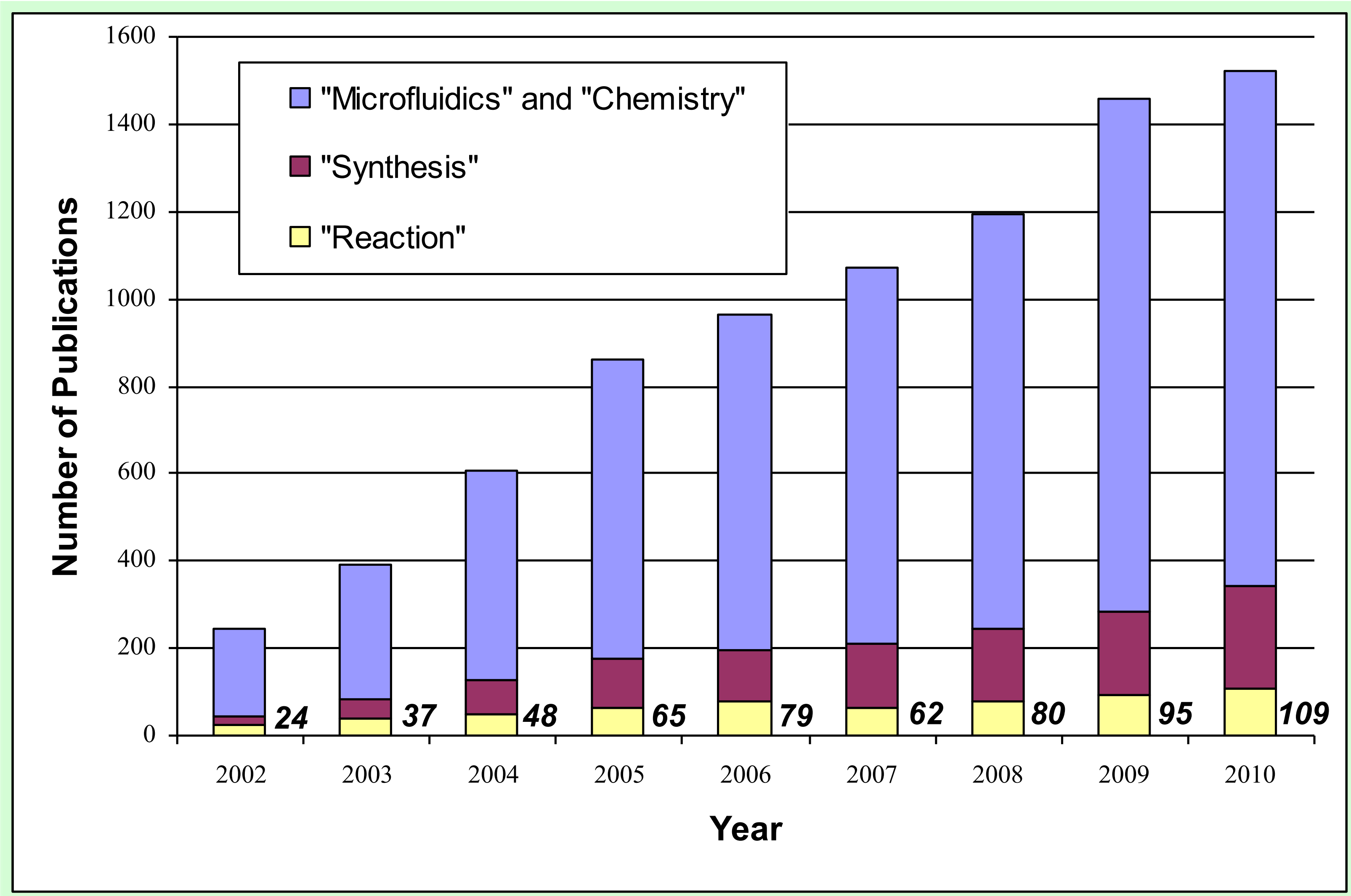
Distribution of Microfluidics Literature by Subject Area (2000-2009)

Subject	World records	% of 13,942
Analytical chemistry	3149	22.52%
Nanoscience & nanotechnology	3078	22.08%
Multidisciplinary chemistry	2562	18.38%
Biochemical research methods	2382	17.09%
Material science, multidisciplinary	1797	12.89%
Instruments & instrumentation	1539	11.04%
Electrical & electronic engineering	1459	10.46%
Applied physics	1429	10.25%
Physical chemistry	1124	8.06%
Mechanics	853	6.12%
Electrochemistry	676	4.85%
Mechanical engineering	588	4.22%
Chemical engineering	584	4.19%
Fluid & Plasmas physics	553	3.97%
Optics	474	3.40%

Web of Science (Thomson Reuters) literature search. Keywords: micro react*, microfluid*, microstructured reactor*, micro chemical, micro thermal, micro heat, micro pump, micro valve.

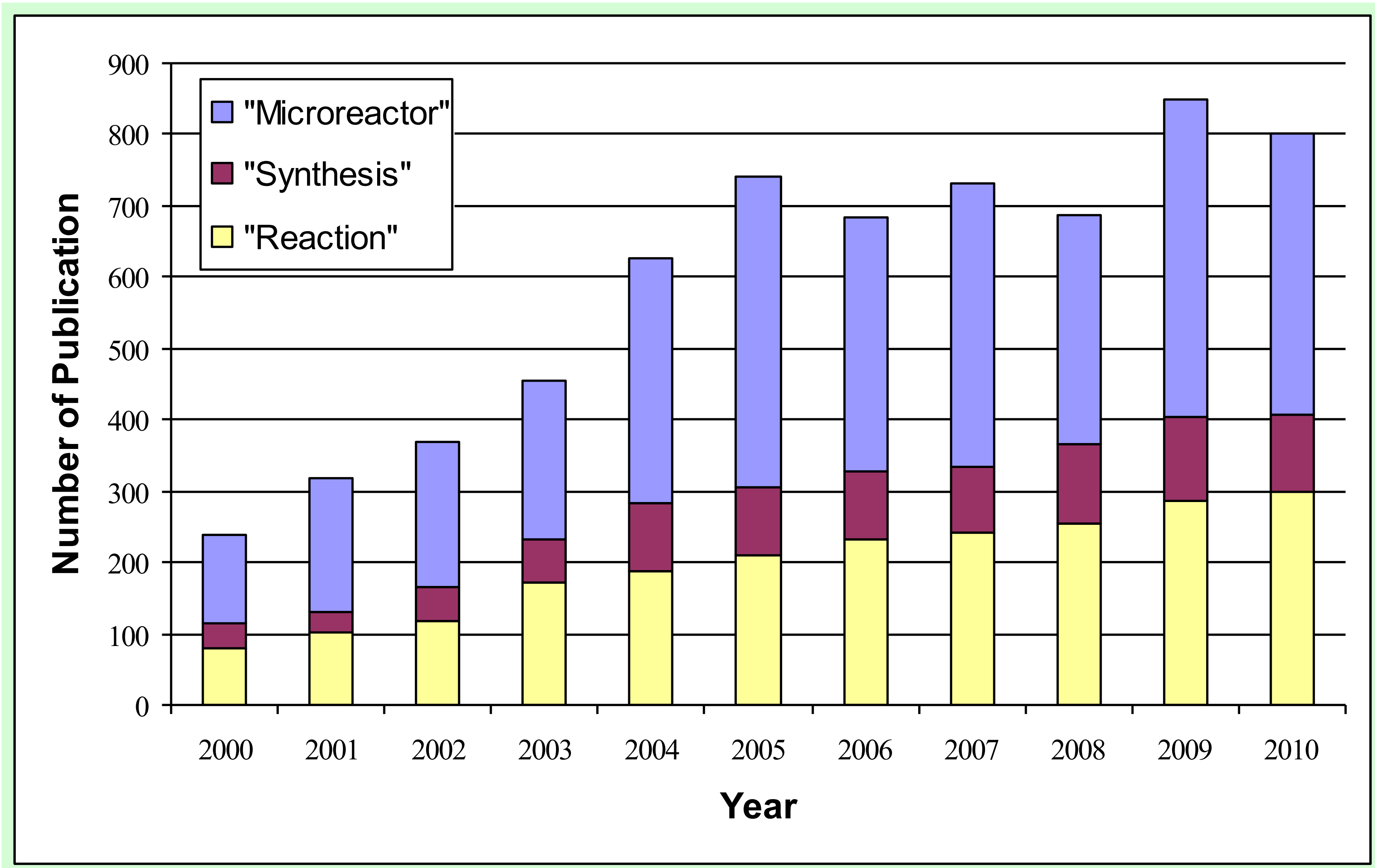
Chemical Engineering Journal **2010**, *163*, 165.

Search for Organic Chemistry Related Literature (2002-2010)



Scifinder Scholar 2007 keyword search.

Search for Organic Chemistry Related Literature (2000-2010)



Scifinder Scholar 2007 keyword search.

Examples of Reactions: Batch vs. Flow

- http://www.princeton.edu/chemistry/macmillan/group-meetings/JEC_microreactors.pdf

- Fletcher, P. D.; et al. *Tetrahedron* **2002**, *58*, 4735-4757.

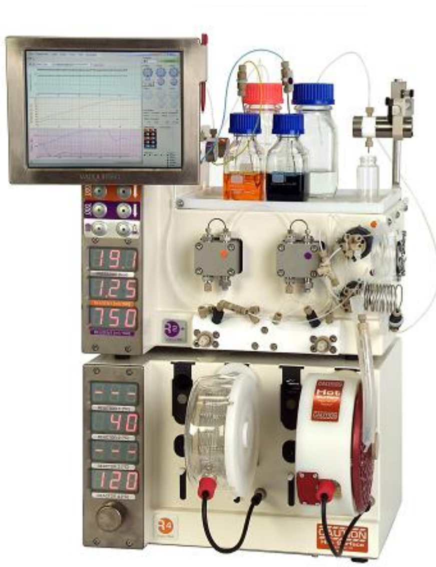
- Watts, P.; Wiles, C.; *Chem. Commun*. **2002**, 443-467.

- Hessel, V.; Lowe, H. *Chem. Eng. Technol*. **2005**, *28*, 267-284.

- Watts, P.; Hasewell, S. J. *Chem Soc. Rev*. **2005**, *34*, 235-246.

- Seeberger, P. H.; et al. *Synlett*, **2009**, *15*, 2382-2391.

Commercial Microfluidics and Flow Systems



Vapourtec
$45,000-130,000

Syrris (Asia System) $34,000-150,000

Accendo (Conjure)
$100,000-200,000

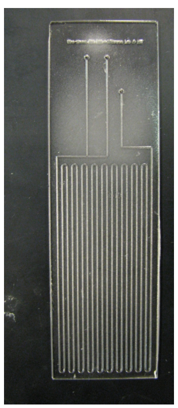
Chemtrix

ThalesNano (H-Cube)

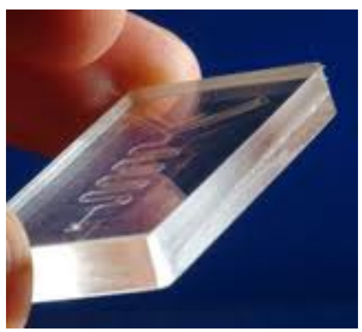
Fabrication and Feature of Microreactor Materials

Material	Fabrication techniques	Advantages	Disadvantages
Ceramic	Stereolithography; powder molding; electrodischarge machining; laser machining	Stable at high tmperatures with low heat loss; chemically resistant	High development costs; shrinkage after sintering
Glass	Photolithography; powder blasting; wet etching, ultrasonic machining	High chemical resistance; direct visualization of reaction	Deep, anisotropic etch is difficult, incompatible with strong aqueous bases at moderate temperature
Plastic	Soft lithography; injection molding, hot embossing	Fast fabrication; inexpensive development costs	Incompatible with organic solvents; not suitable for high temperature and pressure
Silicon	Photolithography; wet and dry etching	Operation at high pressure and temperature; superior heat conductivity; high aspect ratio designs	Incompatible with strong aqueous bases at moderate temperture
Stainless steel	Lithography, electroplating, and molding; stamping; micromachining	Operation at high pressure and temperature	Incompatible with acidic media except for expensive, specialized steels

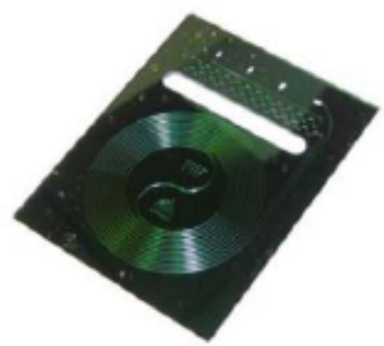
Ceramic



Glass



Plastic



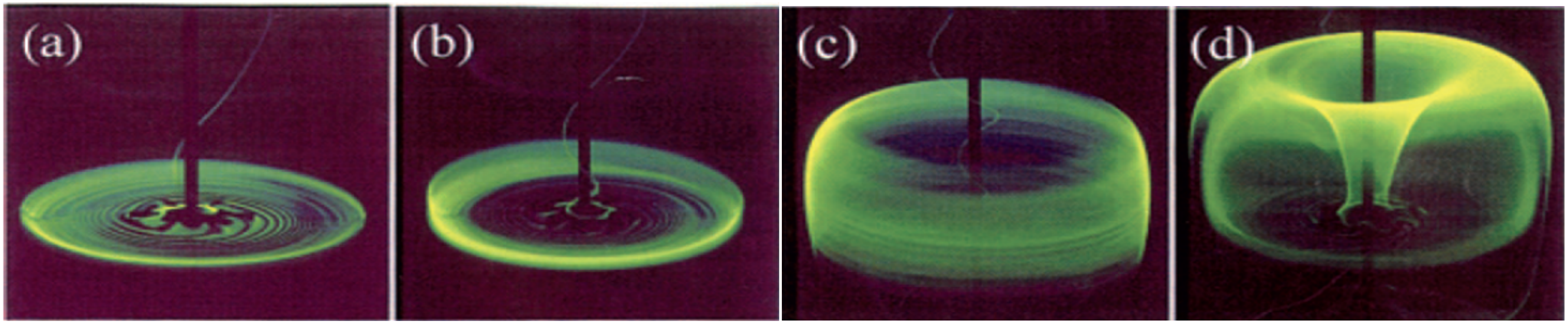
Silicon

Stainless steel

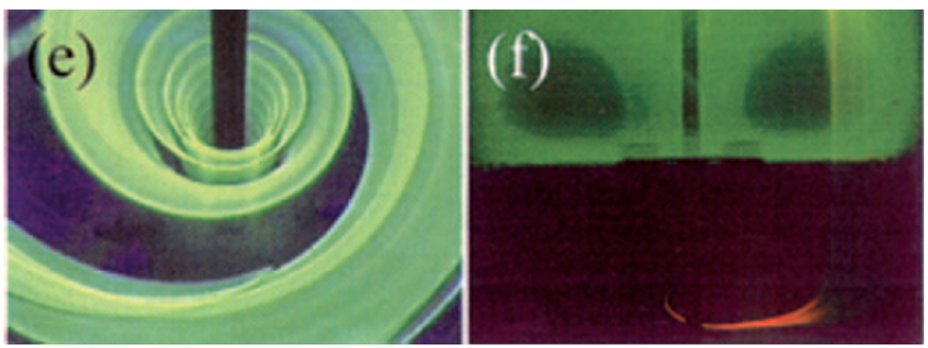
Annu. Rev. Anal. Chem. **2010**, *3*, 19-42.

Mixing in Batch vs. Flow

- Fluorescent dye in glycerin (20 L reactor, impeller mixing)



3 s | **5 s** | **10 s** | **50 s**



3 min

Mixing in a 250 mL cylinder
- magnetic stirrer, 500 rpm
- 95% mixed, ~ 8 s

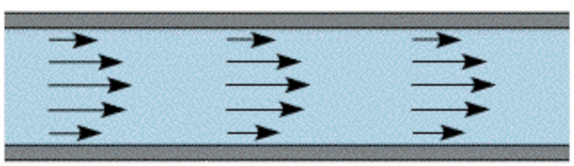
Factors effecting batch mixing
- reaction size vs. stirrer size
- stir rate, type, and shape

Angew. Chem. Int. Ed. **2011**, *Early View*

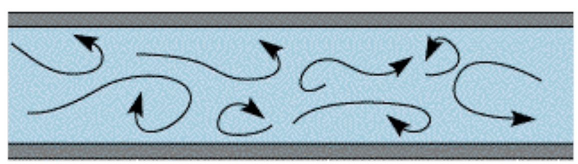
Mixing in Batch vs. Flow

Kaskawulsh Glacier
Kluane National Park, Canada

Laminar Flow

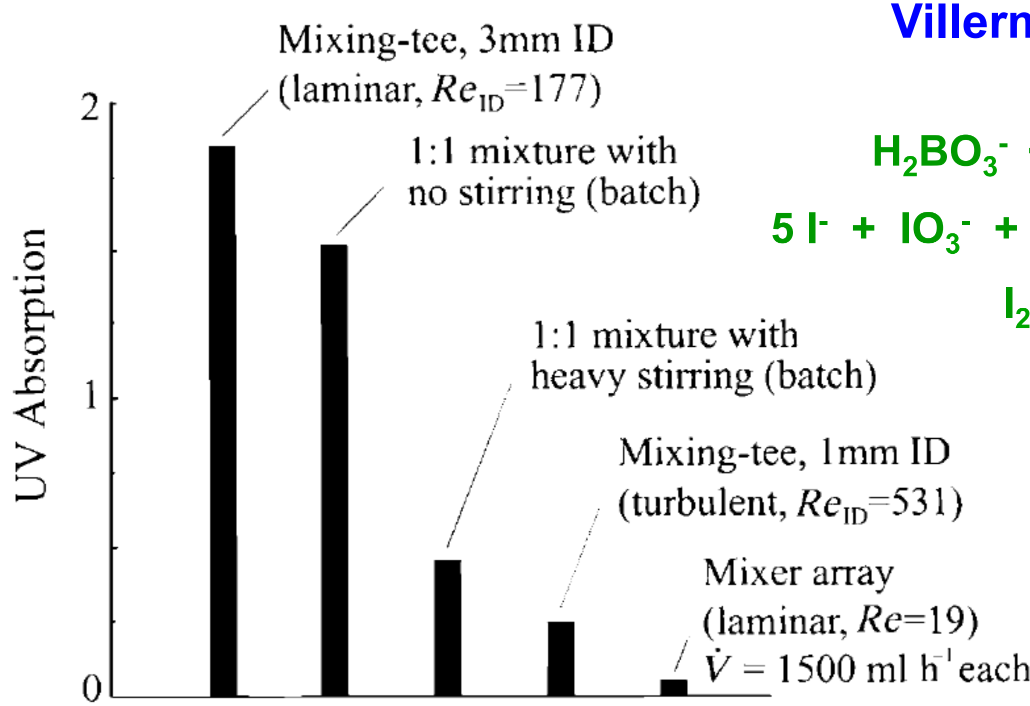


Turbulent Flow



Meso Flow

Mixing in Batch vs. Flow



40 μm channels

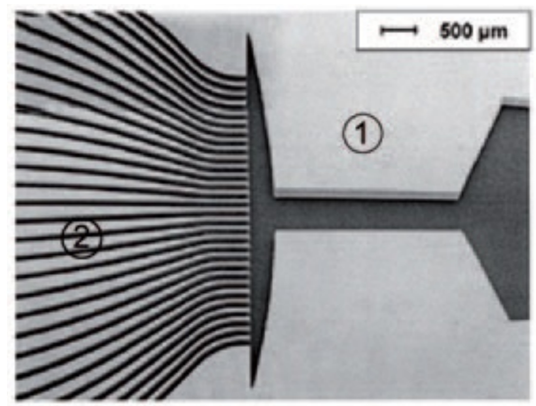
Villermaux-Dushman Reaction

(iodide-iodate test)

$H_2BO_3^- + H^+ \rightleftharpoons H_3BO_3$ ***quasi-instantaneous***

$5\ I^- + IO_3^- + 6\ H^+ \rightleftharpoons 3\ I_2 + 3\ H_2O$ ***very fast***

$I_2 + I^- \rightleftharpoons I_3^-$ ***quasi-instantaneous***



Efficiency of mass transport is related to interfacial contact

Greater specific area translates to better mixing

Reactor type	Specific area (m^2m^{-3})
Microreactor (140 μL)	10000
Microreactor (gas-liquid)(50:50)	5000
250 mL Round bottom flask	80
Round bottom flask (half full)	20

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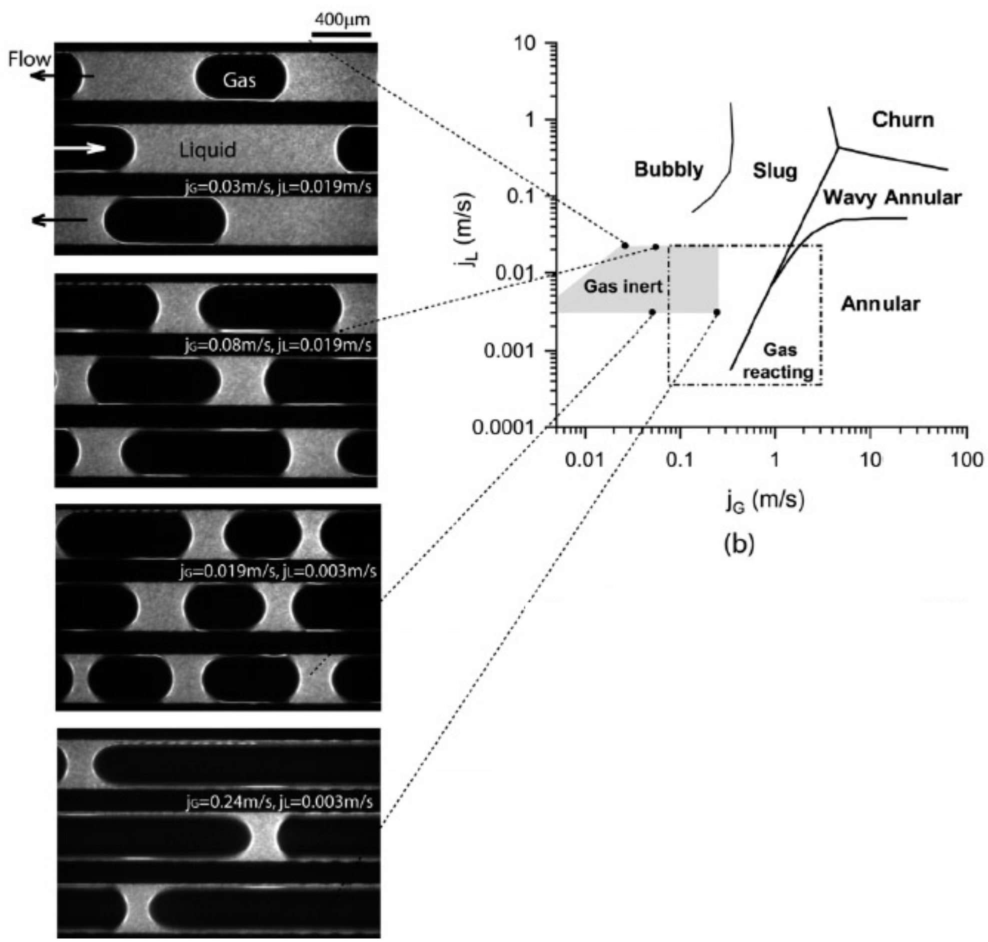
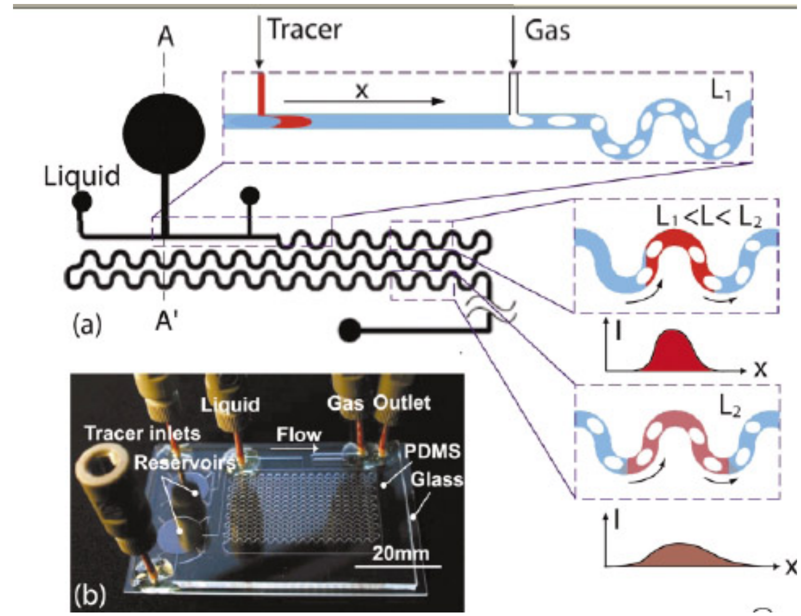
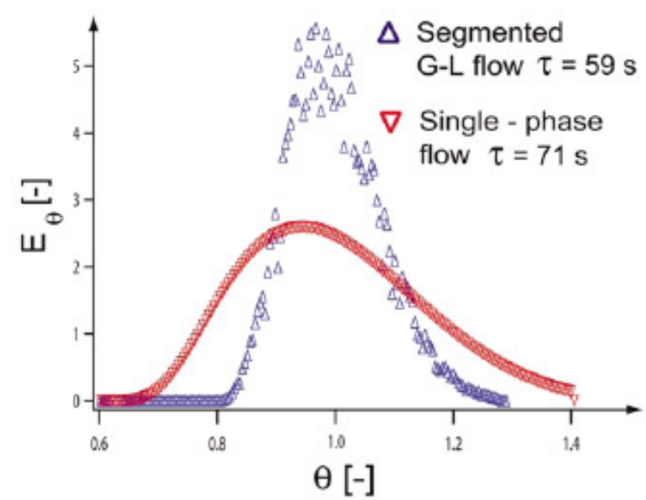
Gas-Liquid Segmented Flow

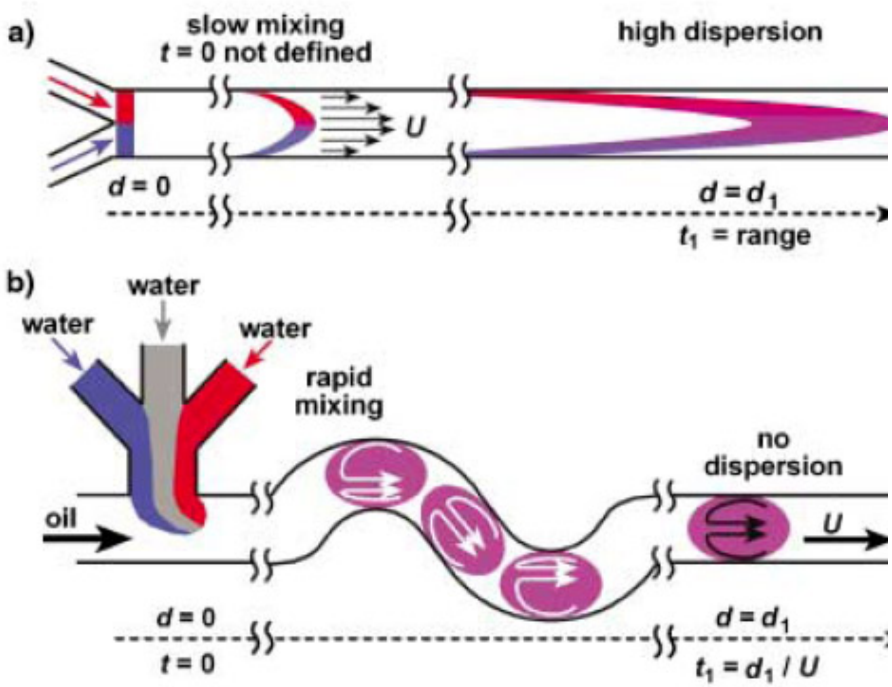




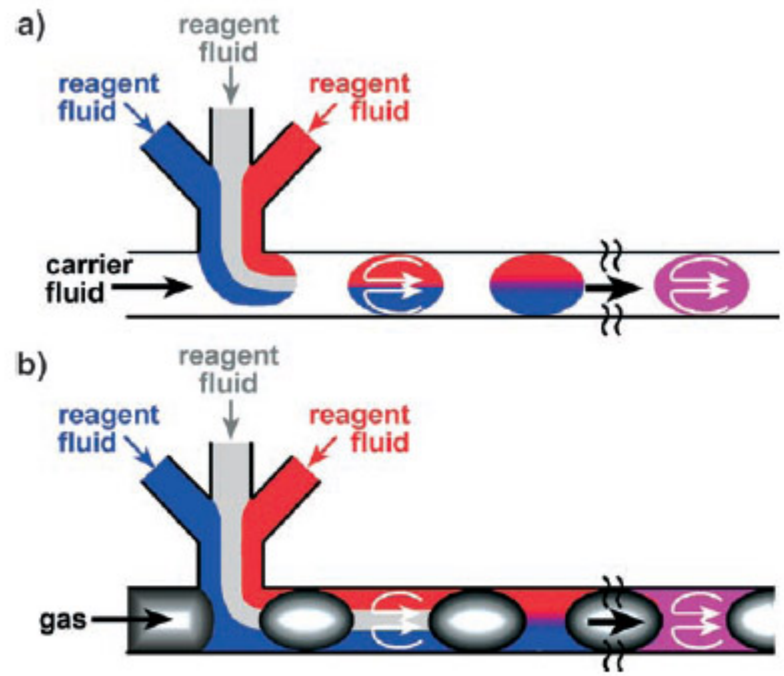


Jensen's Group: *Lab Chip*, **2004**, *4*, 278-286.

Fluorous-Liquid Segmented Flow



Angew. Chem. Int. Ed., **2003**, *42*, 767-772.



Angew. Chem. Int. Ed., **2006**, *45*, 7336-7356.

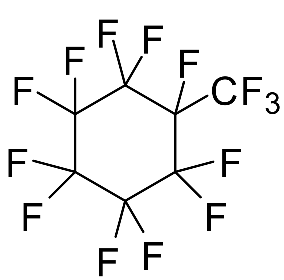
Ismagilov's Group

Fluorous Phase Properties/Limitations

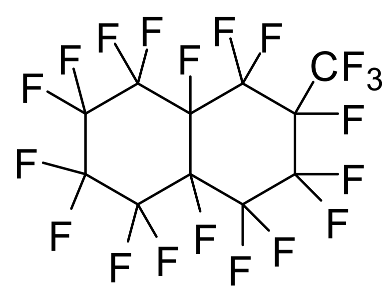
Miscibility Table for 1:1 mixture of fluorous and organic phase

Fluorous	Organic	Two Phase at (^oC)	One Phase at (^oC)
$CF_3C_6F_{11}$	CCl_4	RT	≥ 26.7
$CF_3C_6F_{11}$	$CHCl_3$	RT	≥ 50.1
$CF_3C_6F_{11}$	C_6H_6	RT	≥ 84.9
$CF_3C_6F_{11}$	$CH_3C_6H_5$	RT	≥ 88.6
$CF_3C_6F_{11}$	ClC_6H_5	RT	≥ 126.7
$CF_3C_6F_{11}$	hexane	0	RT
$CF_3C_6F_{11}$	pentene	-16	RT
$CF_3C_6F_{11}$	ether	0	RT
$C_{10}F_{18}$	$CH_3C_6H_5$	RT	64

Handbook of Fluorous Chemistry, **2004**, Gladysz, Curran, and Horvath

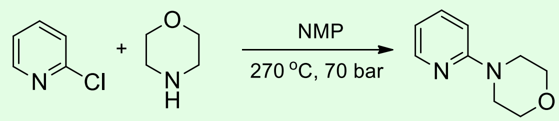
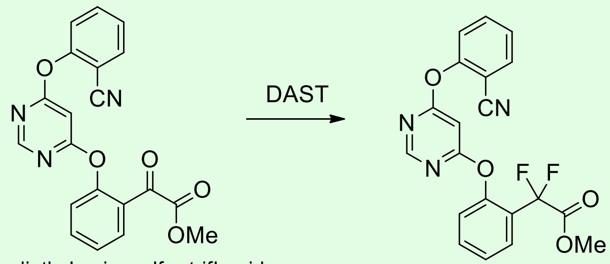
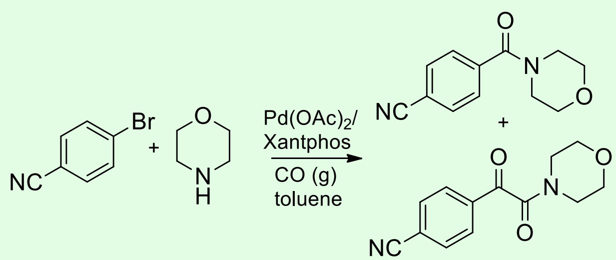
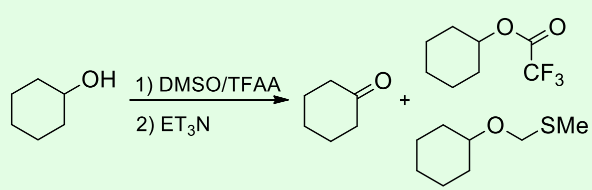


Perfluoro(methylcyclohexane)
F.W. = 350.06
Bp = 75-76 Mp = -37
d = 1.800
Alfa Aesar
100g $63.50
500g $296.00



Perfluoro(methyldecaline)
F.W. = 512.09
Bp = 137-160   Mp = -40
d = 1.95
Aldrich
25g $22.40
100g $65.00

Reaction Benefiting from Enhanced Mixing in Flow

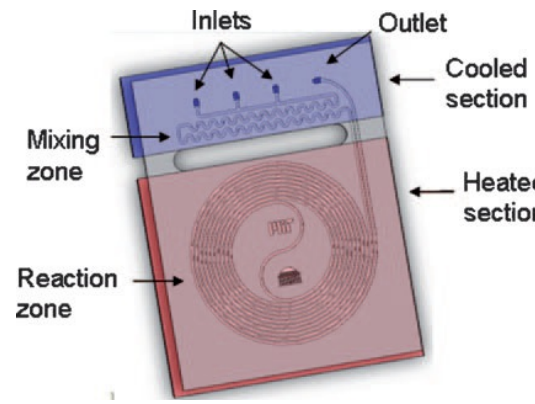
Reaction type	Examples of reactions	Benefit from microflow reactor	Highlights
C-N Bond formation		Faster at elevated temp and pressure	82% yield in 8 min batch: requires days for unactivated substrates
Electrophilic substitution	 DAST = diethylaminosulfur trifluoride	Use of DAST which is highly reactive with water , is volatile, undergoes dismutation above 90 ^{o}C	94% Yield without aformentioned hazards/challenges
Organometallic		Selectivity controlled by temp and pressure, enhanced mass transport via gas-liguid segmentation	Amide favored at high temp; Ketoamide favored at low telp
Oxidation		Fast micromixing prevents by-product formation	88% Yield of ketone at 20 ^{o}C in 10 ms batch: 19% yield at -20 ^{o}C

Angew. Chem. Int. Ed. **2011**, *Early View*

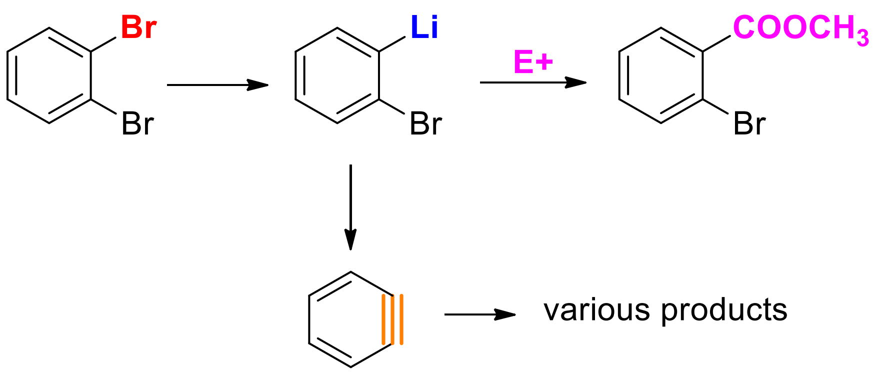
Temperature Control in Flow: Material Matters

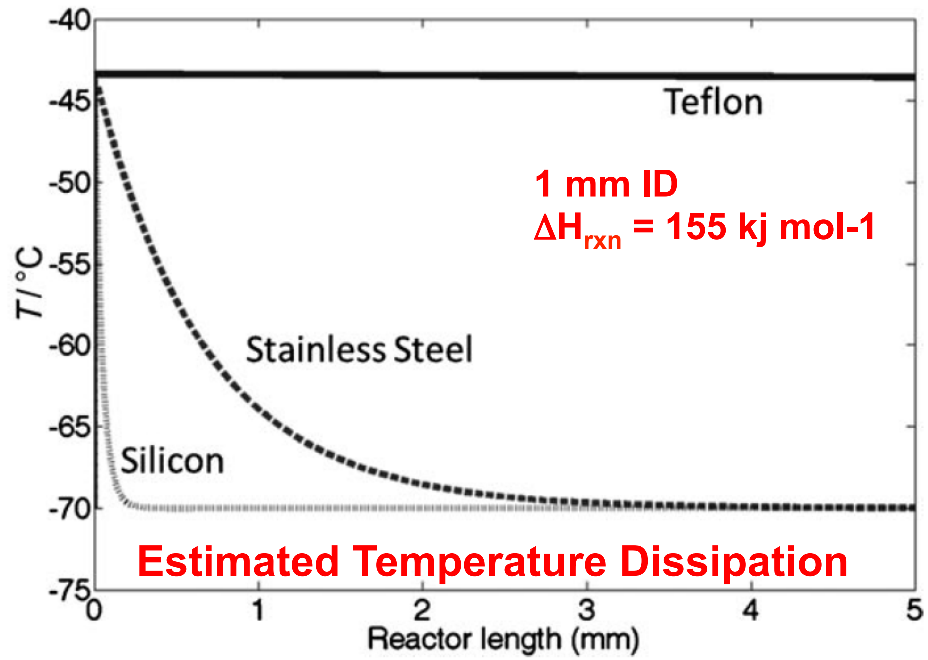
Thermal Conductivity

Microflow reactor type	Conductivity (W mK^{-1})
Teflon	0.1
Stainless steel	10
Silicon	150



Lithiation Example (*exothemic*)





- ➢ Ability to run reactions at desired temperature with desired stoiciometry in flow
- ➢ Batch reaction require portion-wise addition of reagents (*not ideal*)

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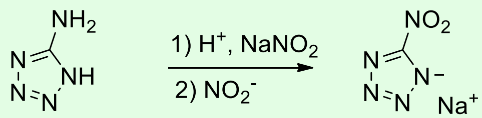
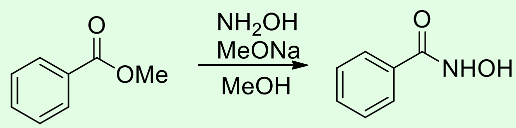
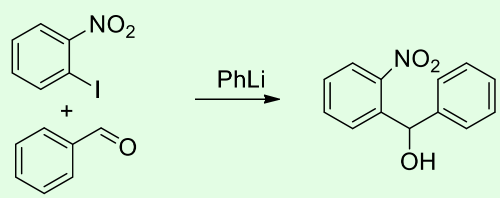
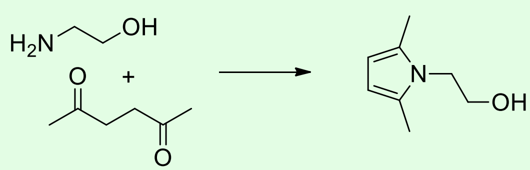
Reaction Benefiting from Enhanced Heat Transfer in Flow

Reaction type	Examples of reactions	Benefit from microflow reactor	Highlights
Diazotization of aromatic amines		Removal of exothermal heat prevented product degradation	Kinetic investigation: scaled up to 2.8 gh^{-1}
Electrophilic substitution		Prevension of exothermal heat provides safer use of hydroxylamine	Improved synthesis hydroxamic acids
Organometallic		Selectivity controlled by temp and pressure, enhanced mass transport via gas-liguid segmentation	Screened kinetic and thermal properties of *o*-, *m*-, and *p*-nitrophenyl lithium reagents
Paal-Knorr		Faster heat transfer allow the reaction to run neat	Production rate of 136 gh^{-1}

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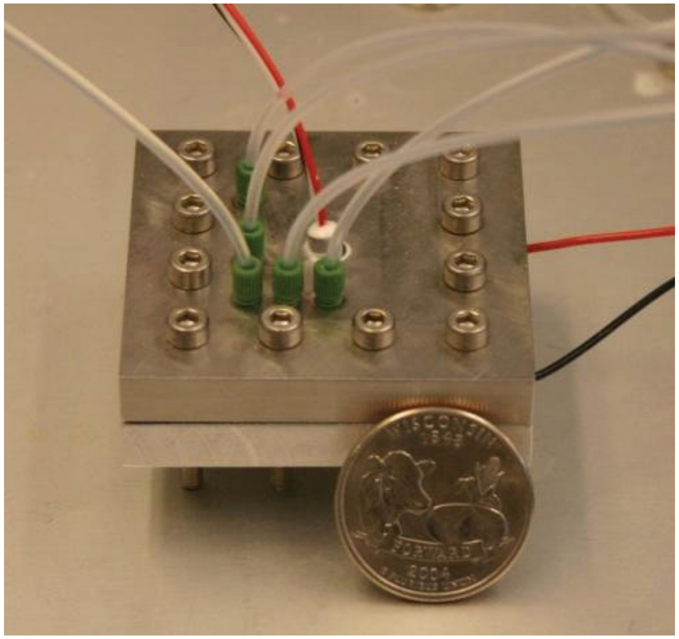
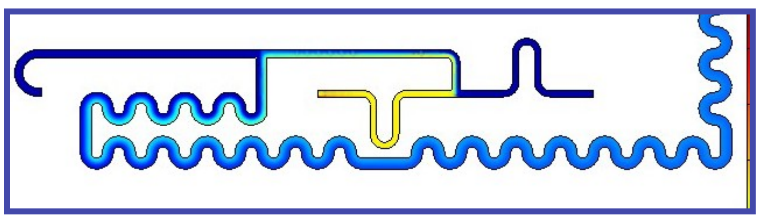
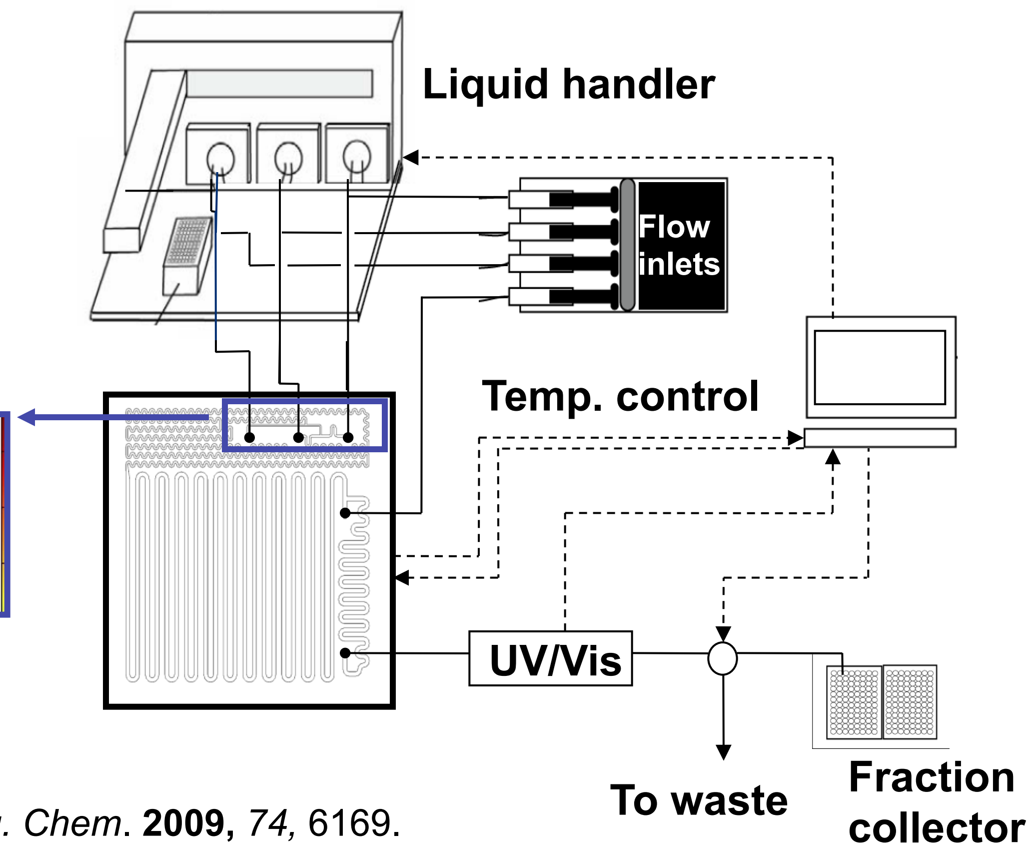
Combining Microreactors with Reaction Screening



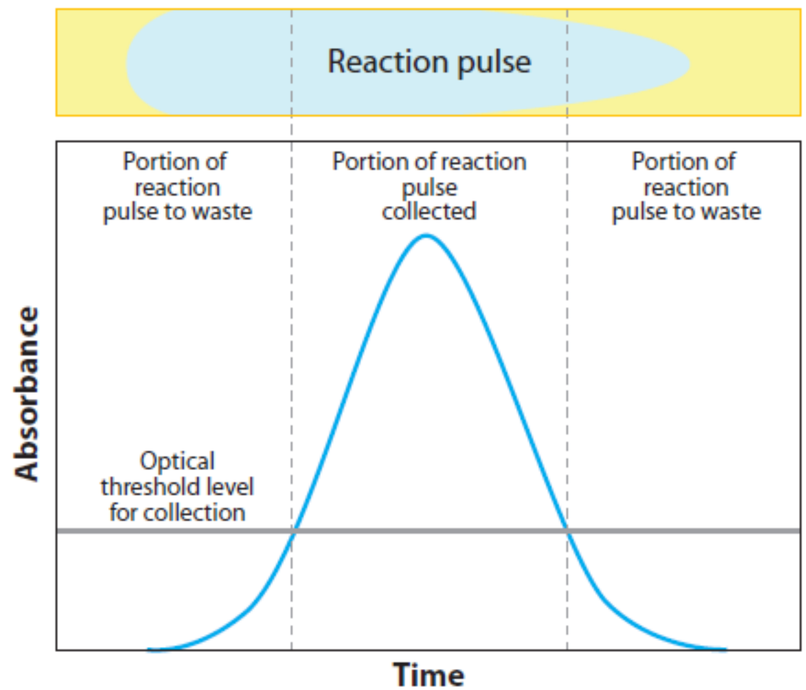


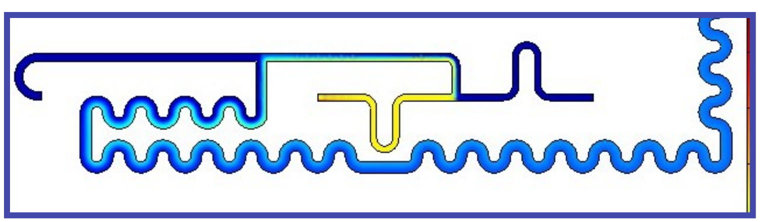
Simulations show uniform concentration profile at reactor inlets



J. Org. Chem. **2009,** *74,* 6169.
J. Org. Chem. **2010,** *75,* 2028.

Combining Microreactors with Reaction Screening





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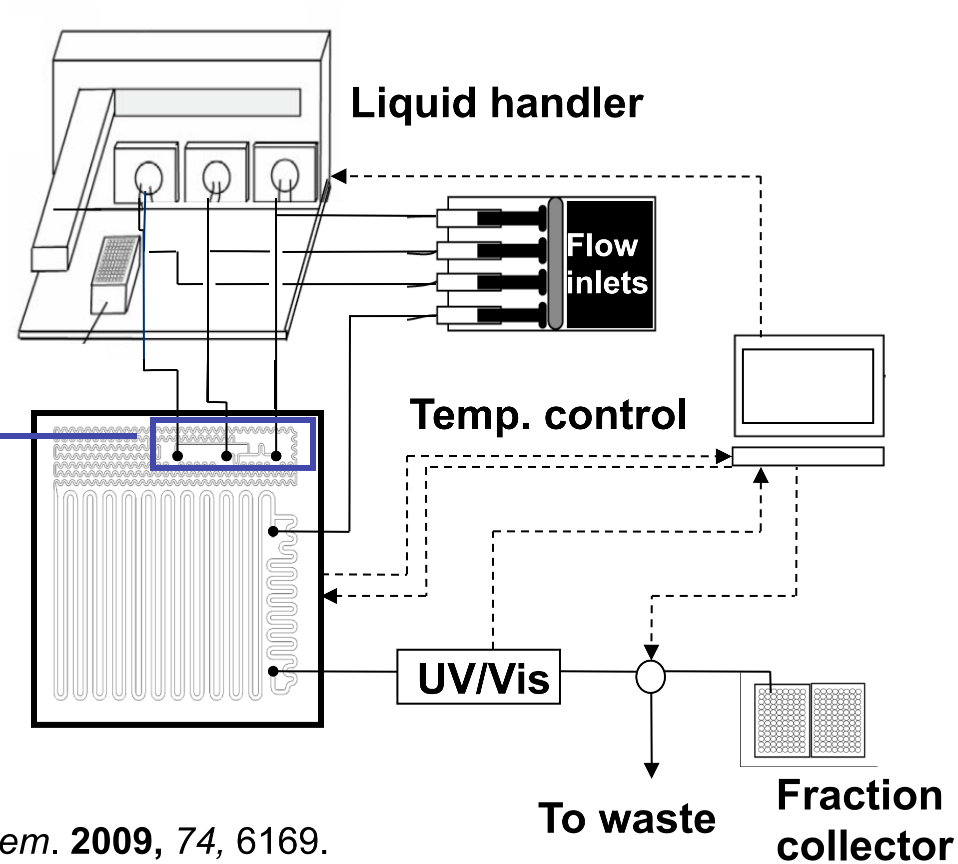

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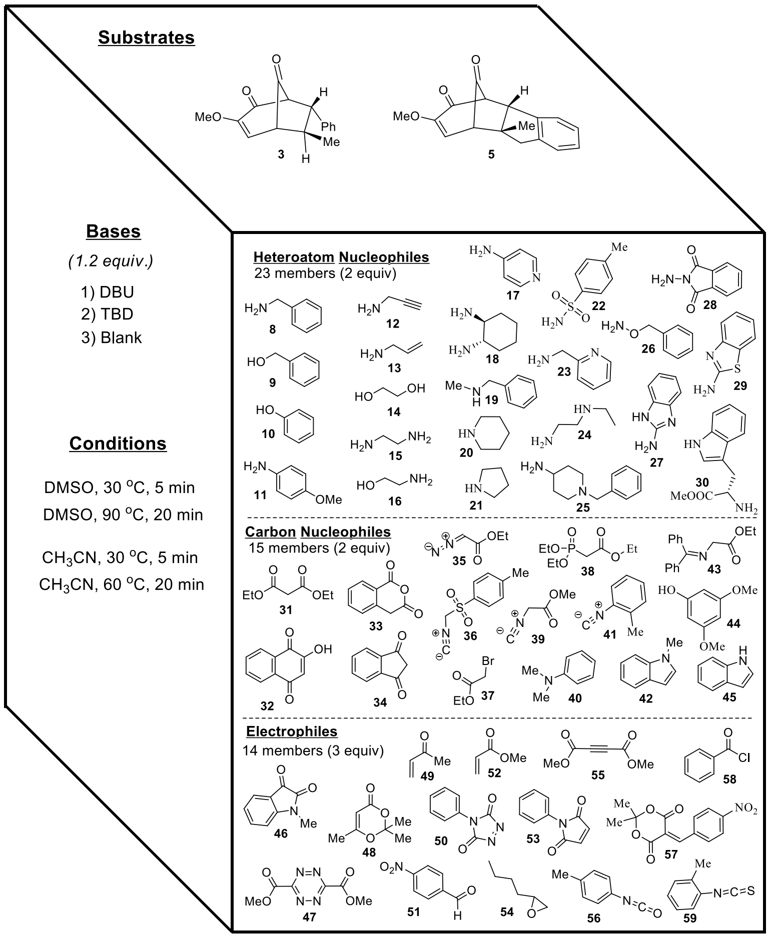
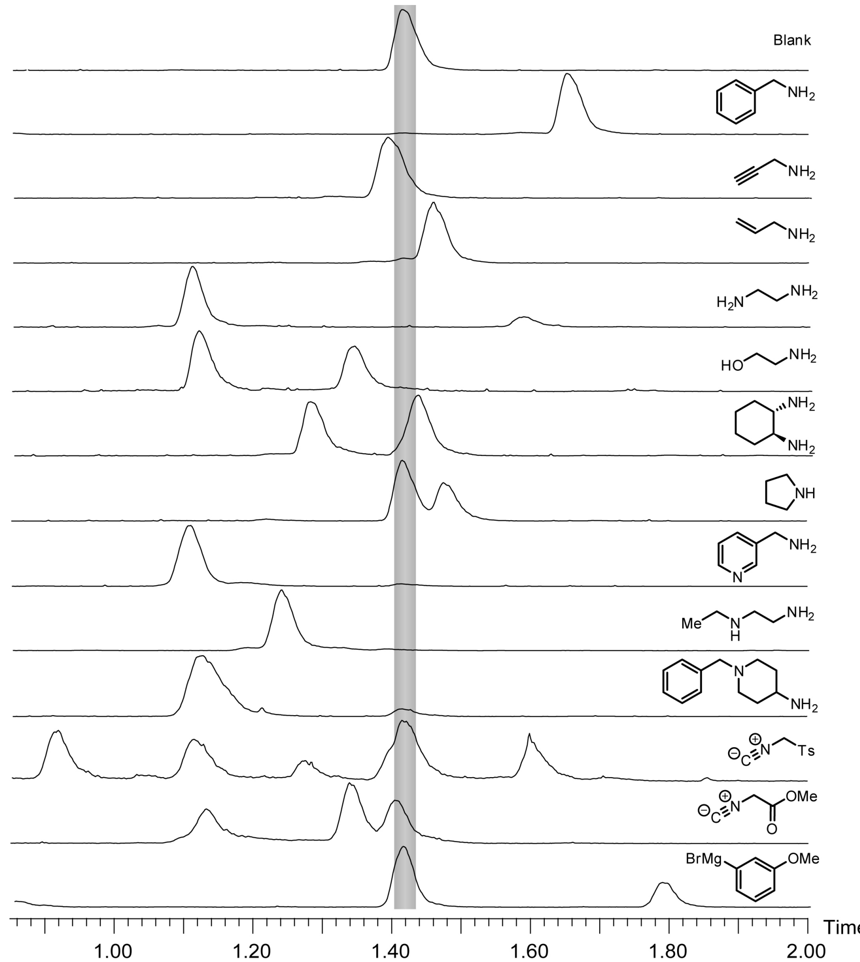




- ➢ **Enabled screening of 1296 reactions**
- ➢ **UPLC reaction profiling: *ELS/MS***

J. Org. Chem. **2009,** *74,* 6169.

Fluorosilane Modification of Silicon Microreactor

- Surface treatment of silicon reactor affords reduced dispersion
  - **Plugs can be inserted closer together: increased throughput**

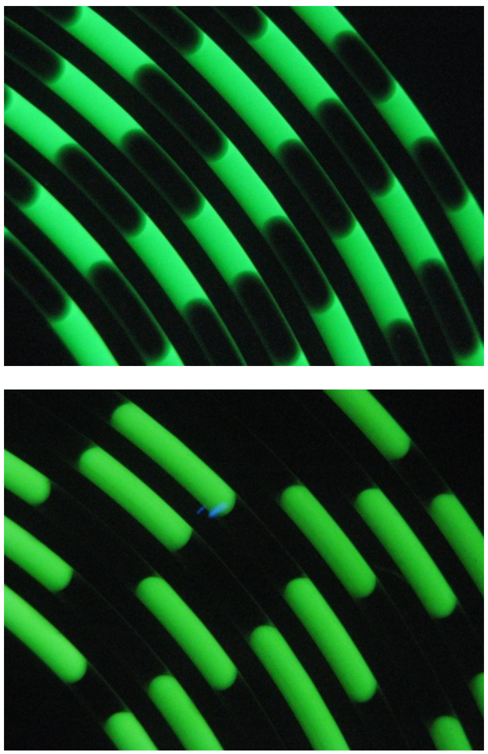
Water/hexane

Silicon oxide

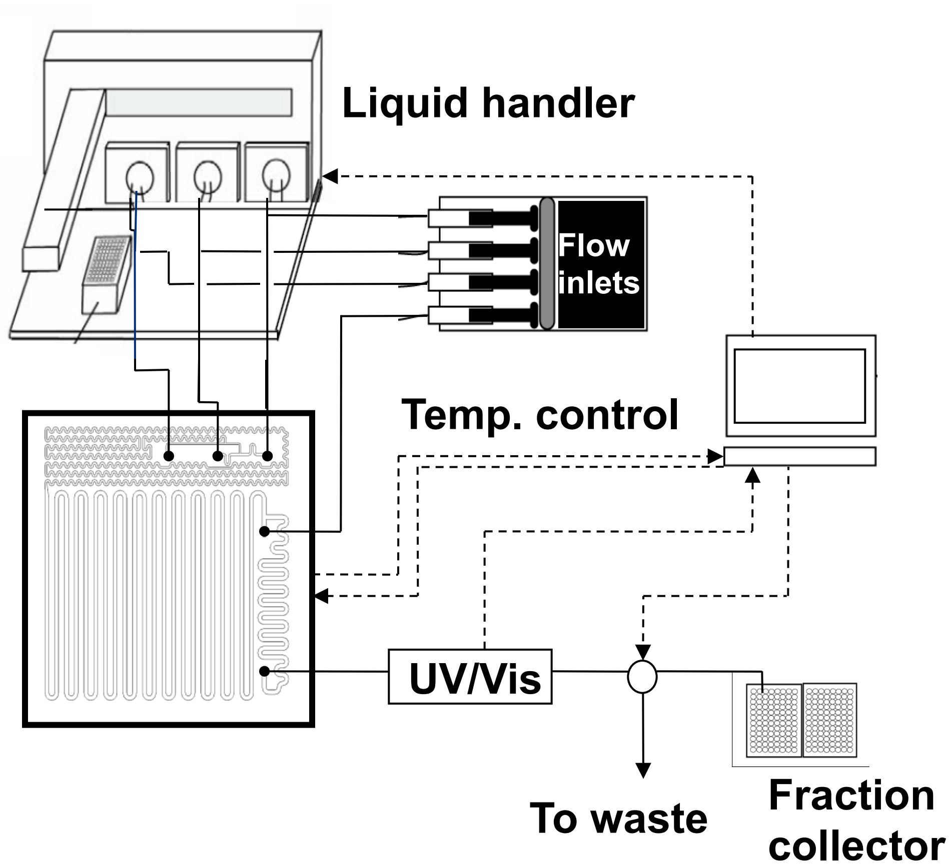
wetting surface

PTFE (Teflon)

non-wetting surface

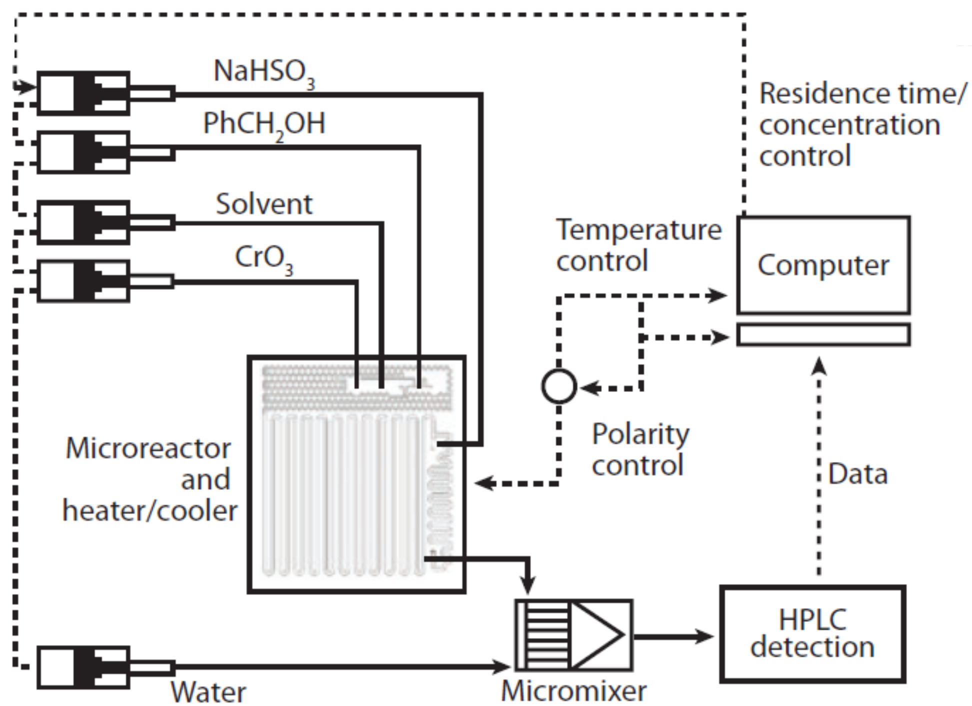


Langmuir **2011,** *27,* 6519.



Combining Microreactors with Reaction Optimization

- Fully automated system for rapid identification of optimal reaction conditions
  - **Complex and multi-step reactions**
  - **Minimal use of reagents**

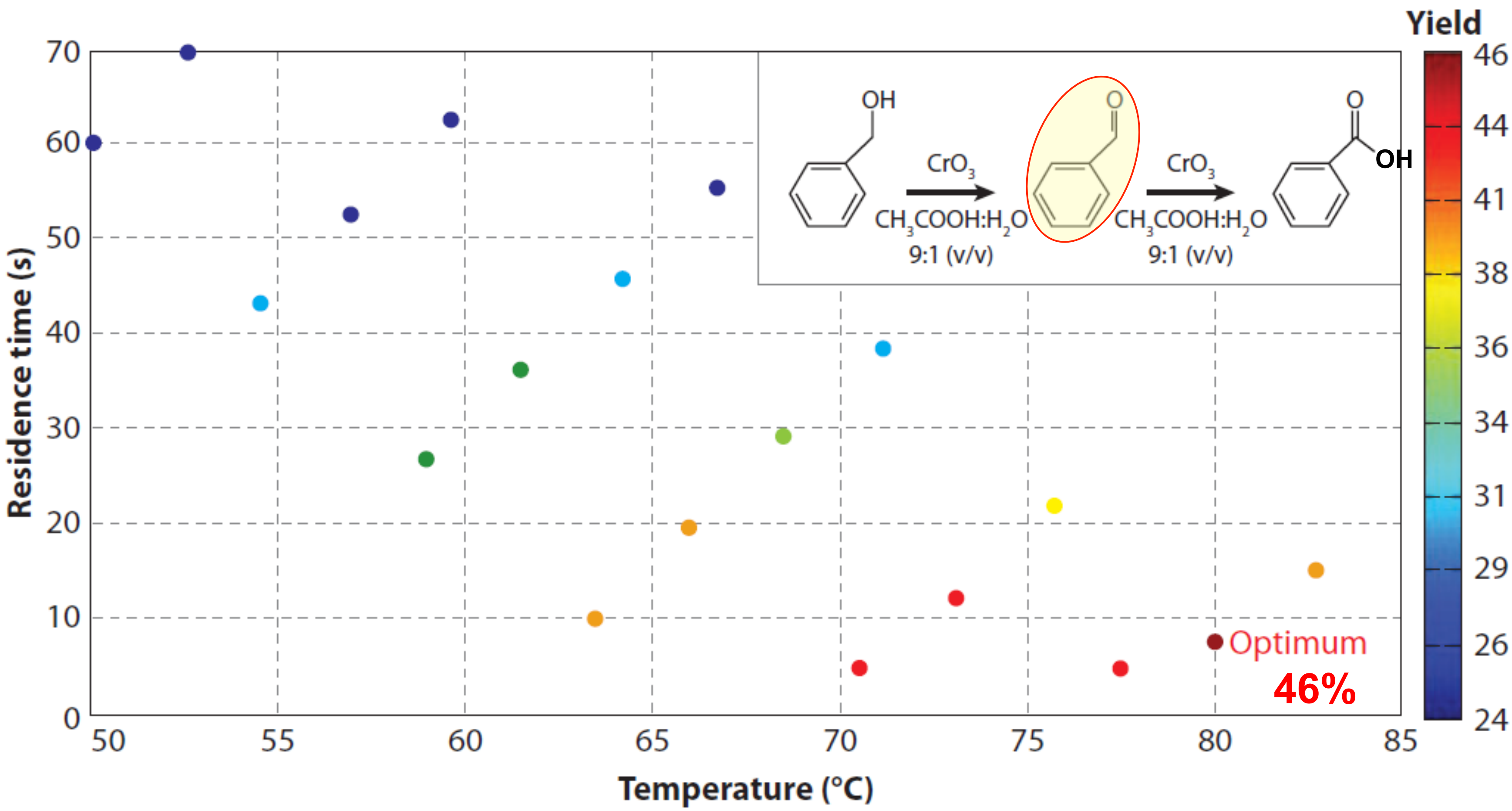


- Platform addresses typical process questions:
  - **What is the maximum achievable yield?**
  - **What are the kinetics?**

Maximize yield by varying reaction time, reaction temperature, stoichiometry, catalyst loading, ligand amount

Annu. Rev. Anal. Chem. **2010**, *3*, 19–42.
Org. Process. Res. Dev. **2010**, *14*, 1169-1176.

Combining Microreactors with Reaction Optimization

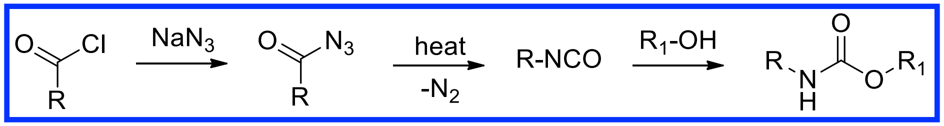


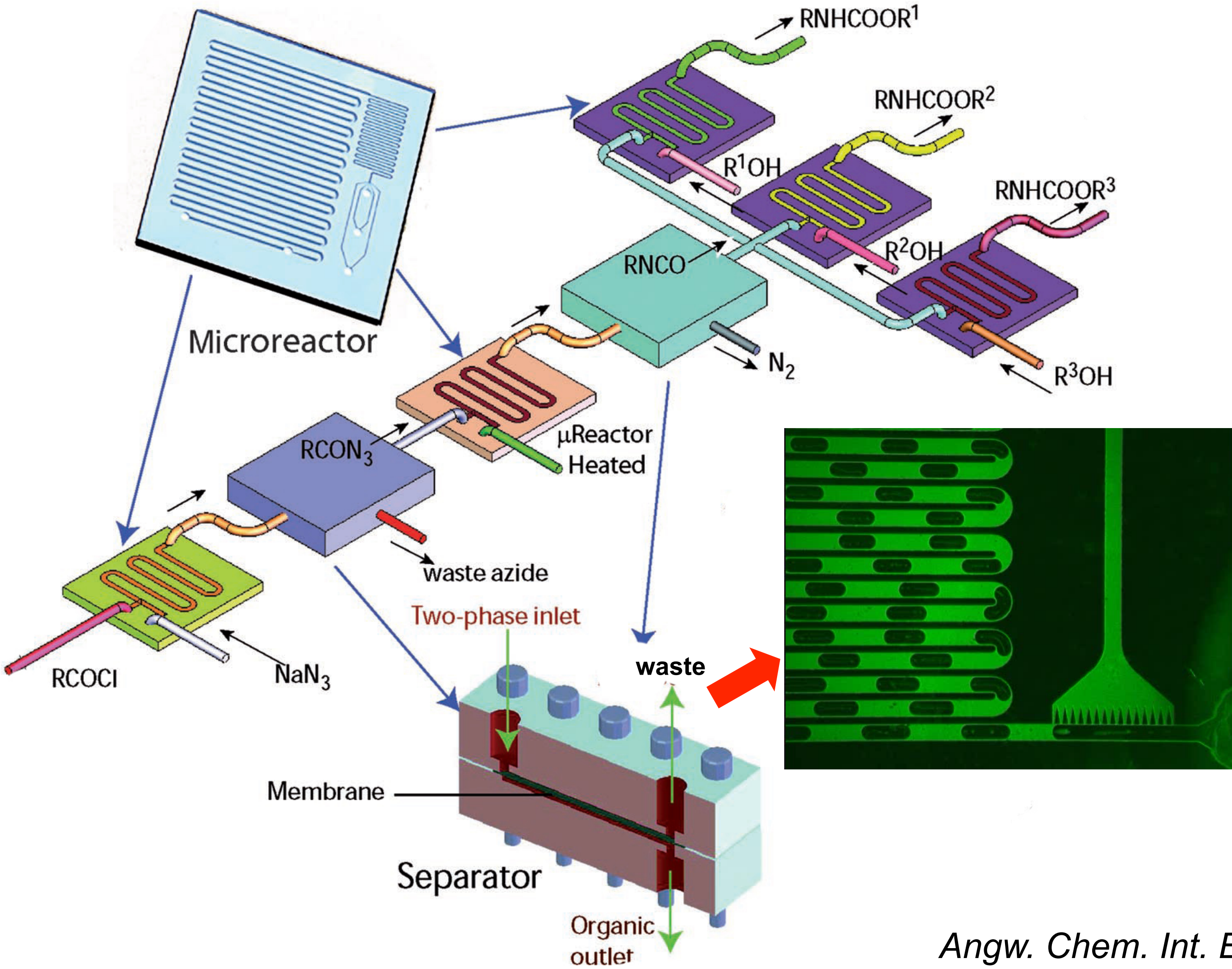
- Nelder-Mead simplex algorithm: 2D when from 21% to 46%
- 4D optimization (added concentrations of SM): 21% to 80%
  - Starting: 50 °C, 60 s, 1.0 equiv CrO_3, 8 mM alcohol
  - Optimized: 88 °C, 48 s, 0.65 equiv CrO_3, 8.24 mM alcohol

Annu. Rev. Anal. Chem. **2010**, *3*, 19–42.

Combining Microreactors with Multistep Synthesis

Integration of Separation Techniques

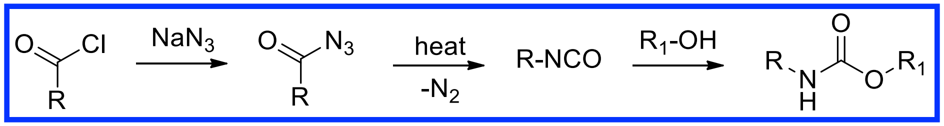


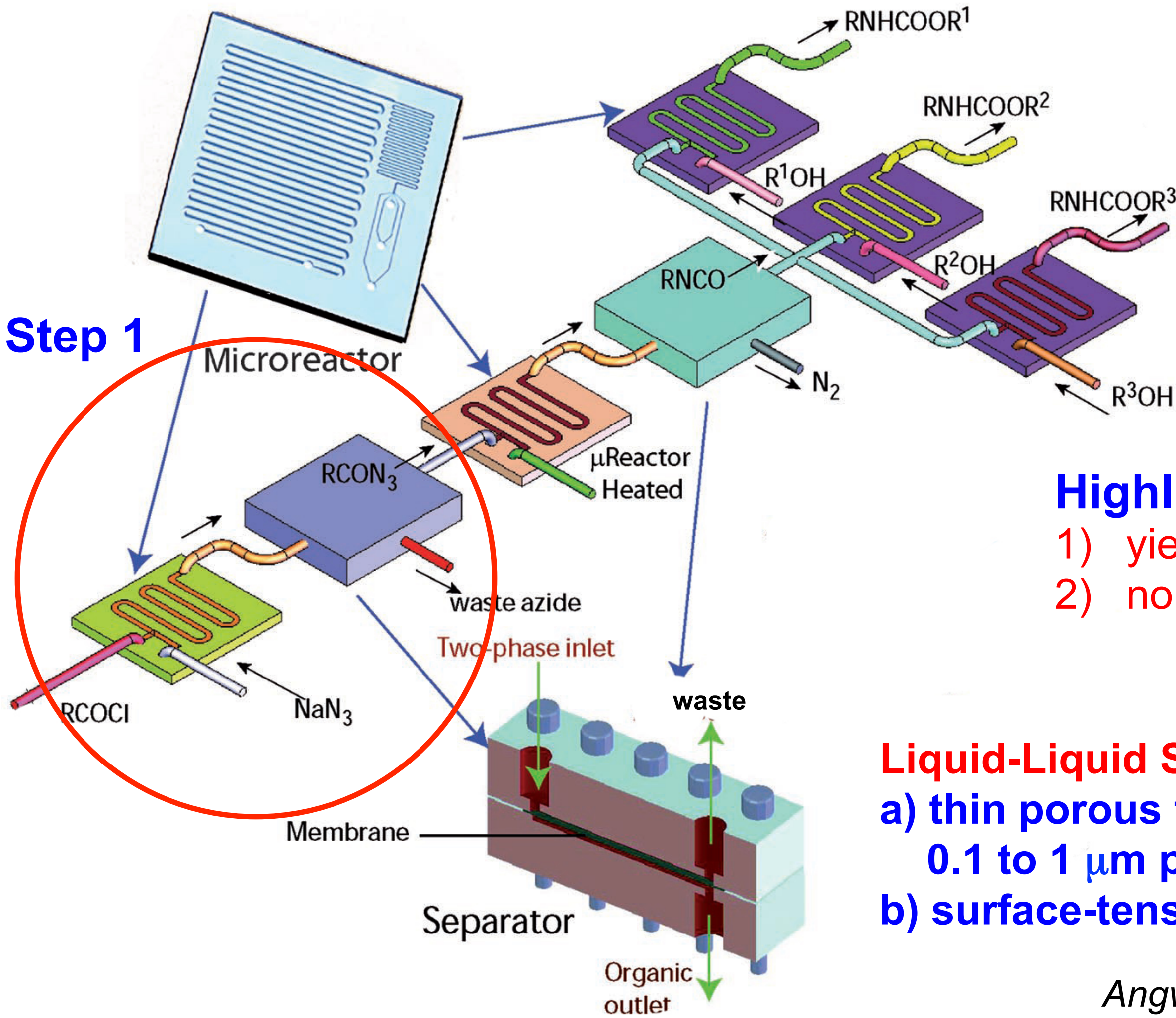


Angw. Chem. Int. Ed., **2007**, *46*, 5704

Combining Microreactors with Multistep Synthesis

Integration of Separation Techniques





Step 1

1) 65%, 90 min
2) 98%, 200 min

Highlights

1) yield function of residence time
2) no phase-transfer agent

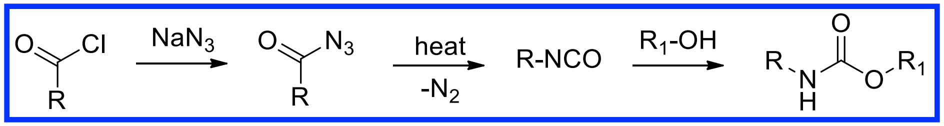
Liquid-Liquid Separation

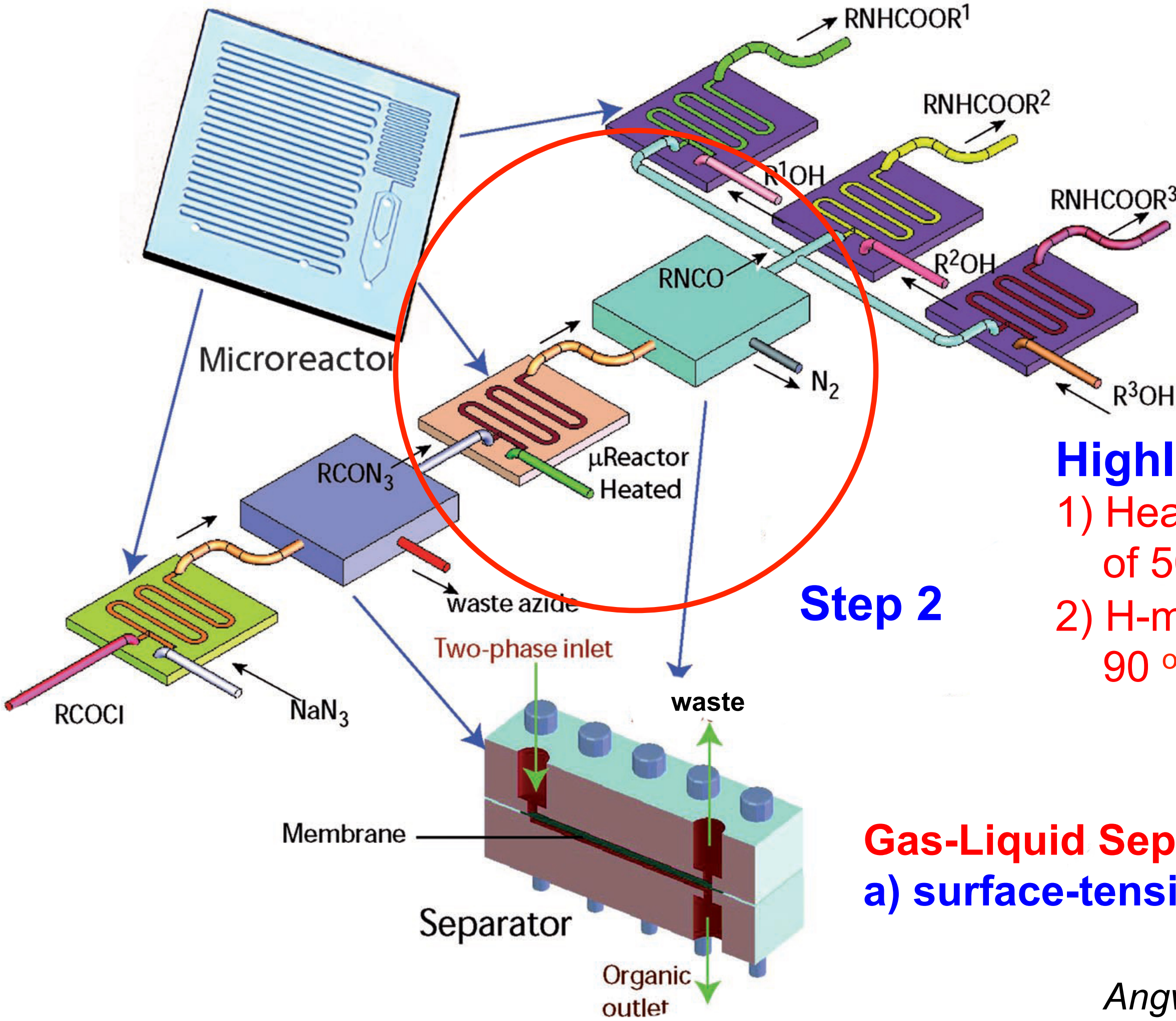
a) thin porous fluoropolymer membrane
0.1 to 1 μm pore size
b) surface-tension forces vs. gravity

Angw. Chem. Int. Ed., **2007**, *46*, 5704

Combining Microreactors with Multistep Synthesis

Integration of Separation Techniques





Step 2 (% conv.)

1) 60 °C, 60 min, 7%
2) 90 °C, 60 min, 91%
3) 105 °C, 60 min, 99%

Highlights

1) Heat above decomposition temp of 50-80 °C
2) H-mordenite solid acid catalyst 90 °C, 60 min, 99.9% conv.

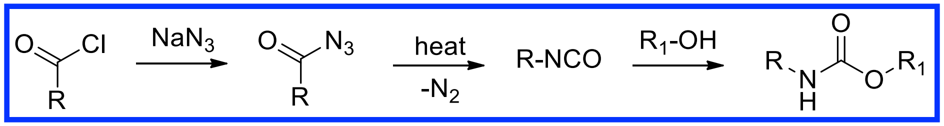
Gas-Liquid Separation

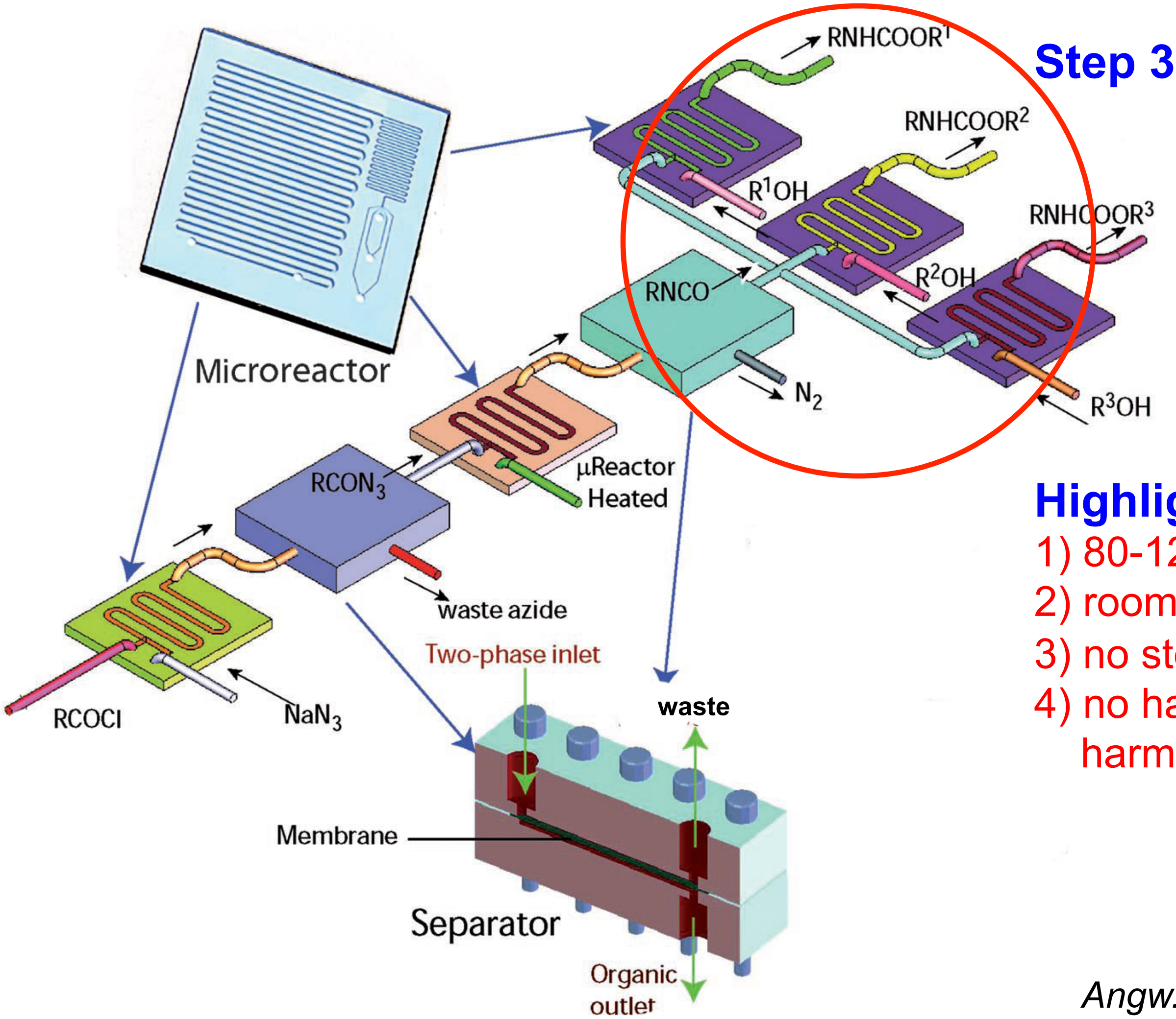
a) surface-tension forces vs. gravity

Angw. Chem. Int. Ed., **2007**, *46*, 5704

Combining Microreactors with Multistep Synthesis

Integration of Separation Techniques





Step 3

Step 3 (fast)

Yields 96-99% of product

Highlights

1) 80-120 mg/day
2) room for improvement
3) no stored sensitive intermediate
4) no handling of potentially
   harmful intermediates

Angw. Chem. Int. Ed., **2007**, *46*, 5704

Combining Microreactors with Multistep Synthesis

Integration of Distillation Techniques

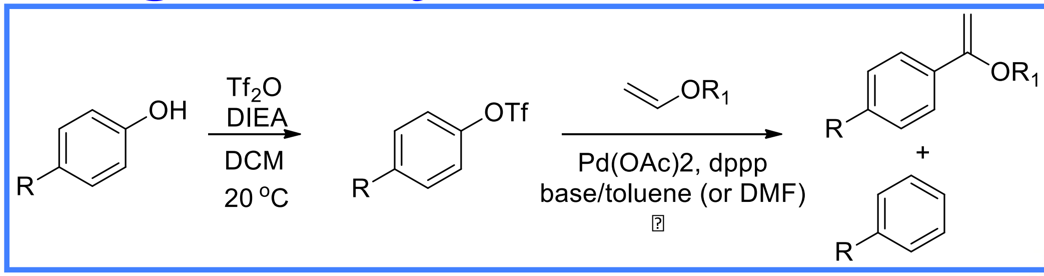
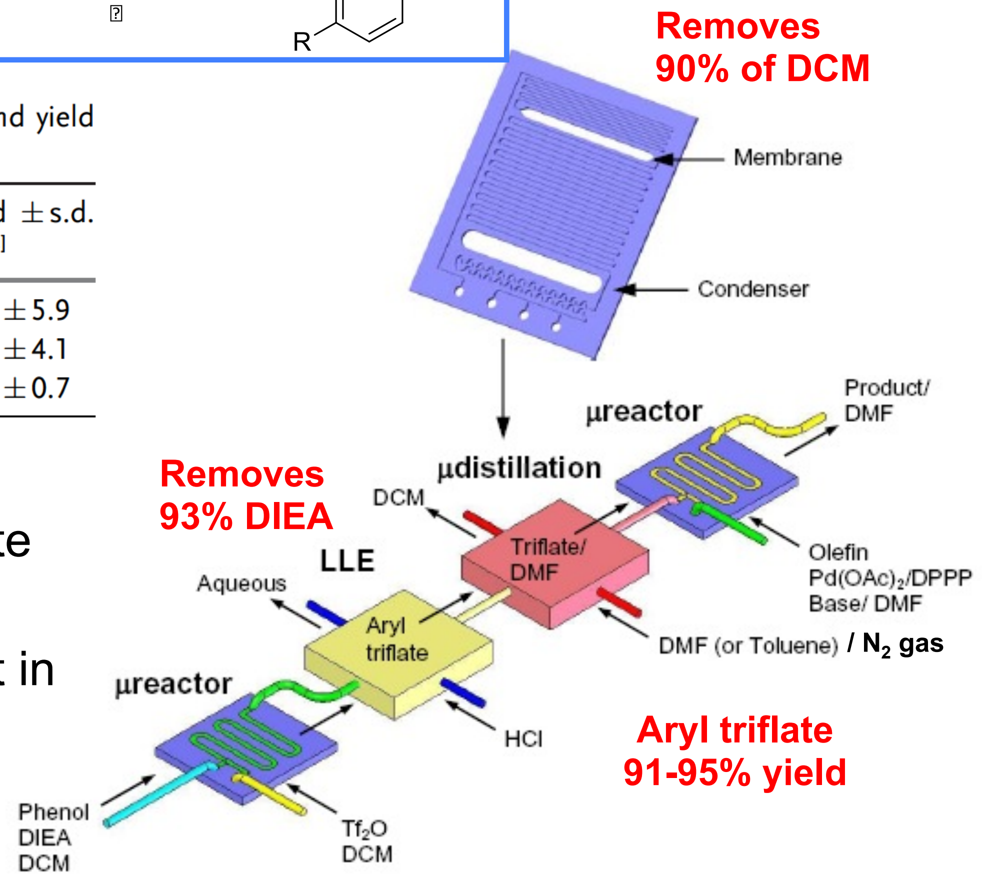


Table 1: Residence time (t), CH_2Cl_2 composition, conversion, and yield as a function of distillation temperature.

T [°C]	t [min]	CH_2Cl_2 [vol%]	Conv. ± s.d. [%][a]	Yield ± s.d. [%][a]
110	5.1	9.6	47.1 ± 8.7	42.8 ± 5.9
120	5.5	7.1	67.6 ± 4.5	57.5 ± 4.1
125	8.1	6.0	96.3 ± 0.4	76.8 ± 0.7

[a] s.d. = standard deviation for three samples.



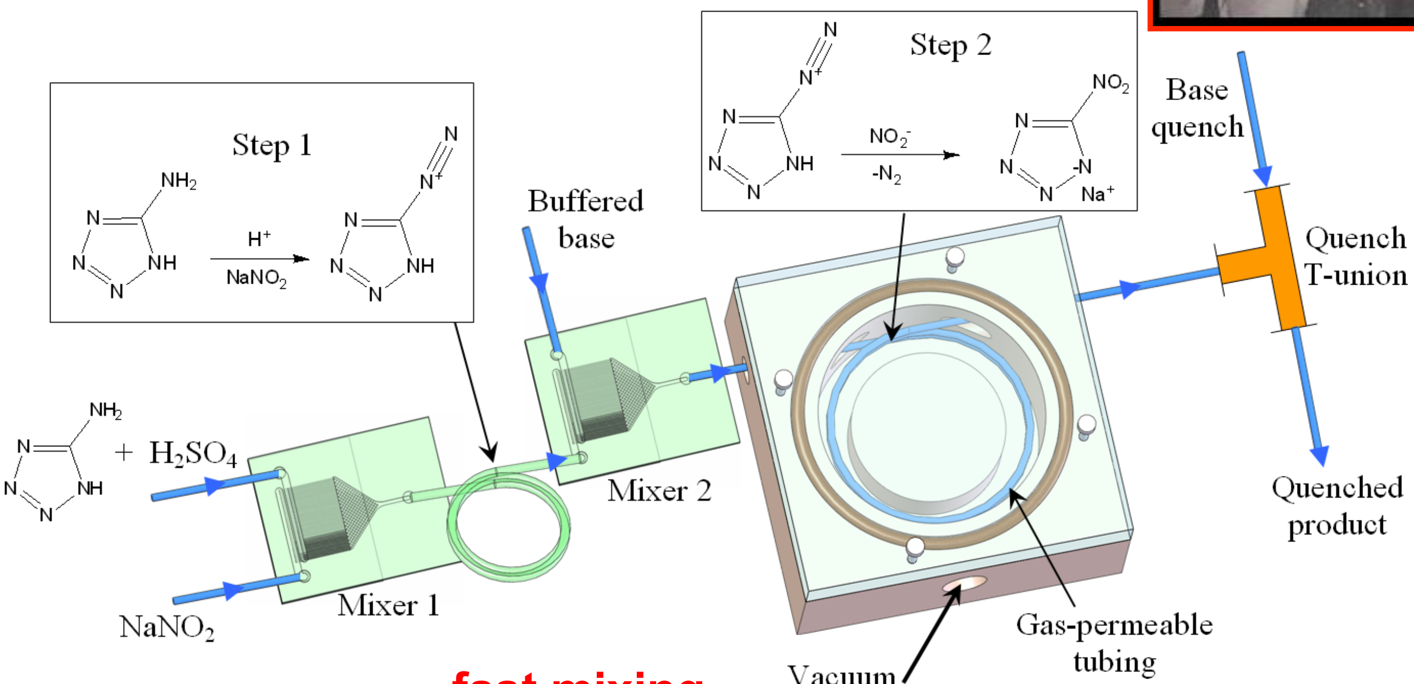
- Challenging: surface forces dominate over gravitational forces
- Vaporization of lower boiling solvent in gas-liquid segmentation
  - removed solvent vapors with N_2 gas
- Reduced product minor (15:1)
  - similar to batch

Angew. Chem. Int. Ed., **2010**, *49*, 899.

Combining Microreactors with Highly Energetic Reactions

Handling of Energetic Materials

- **Continuous flow allows for safer and simpler synthesis**
- **Silicon reactor dissipates reaction exotherm**
- **In flow removal of evolved gas**

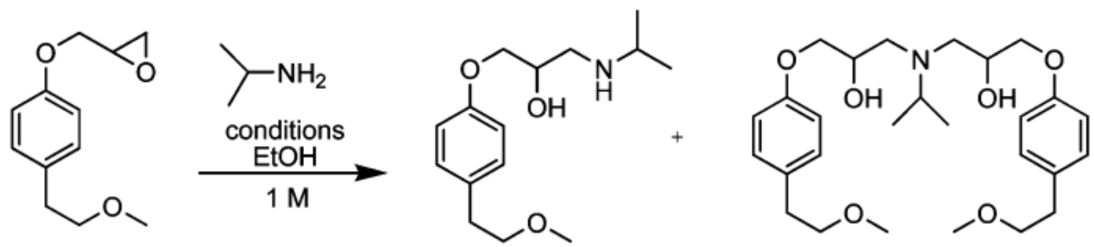


fast mixing

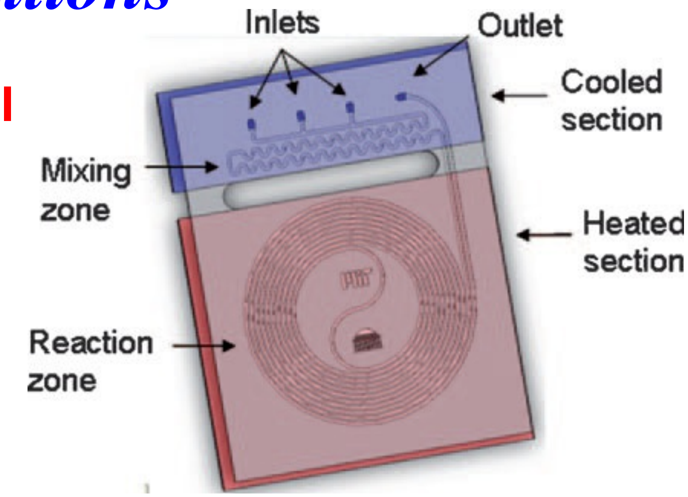
Ind. Eng. Chem. Res. **2010**, *49*, 4132.

Combining Microreactors with Super Heating
Microwave-Type Conditions

Aminolysis of Epoxides: Formation of Metoprolol



20 | metoprolol (19) | 21



entry	conditions (psi)	amine (equiv)	temp (°C)	flow rate[a] (μL/min)	time	yield **19**[b,c] (%)	yield **21** (%)	conversion (%)
1	batch μw[d] (~100)	1.2	150	–	30 min	65	31	100
2	batch μw[e] (~100)	1.2	150	–	30 min	69	28	100
3	μreactor (500)[f]	1.2	240	480	15 s	61	14	76
4	μreactor (500)[f]	1.2	240	240	30 s	69	21	92
5	μreactor (500)[f]	1.2	240	120	1 min	72	24	99
6	μreactor (500)[f]	2.0	240	480	15 s	80	8	89
7	μreactor (500)[f]	2.0	240	240	30 s	86	12	99
8	μreactor (500)[f]	4.0	240	480	15 s	91	6	98

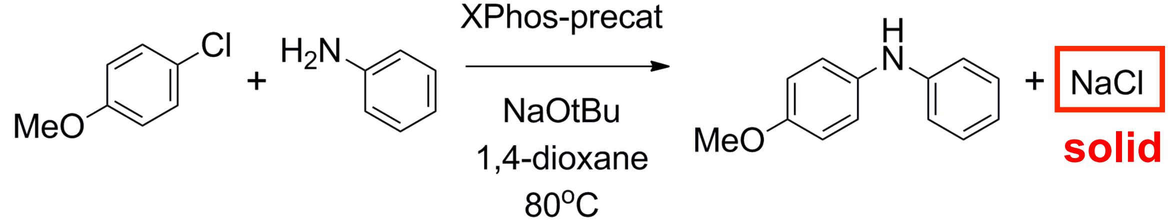
[a] Combined flow rate of both reagents. [b] All yields and conversions are calculated on the basis of HPLC analysis with an internal standard. [c] ~1% of the regioisomer can be isolated but was not quantified. [d] 1 mL in a 5 mL vial. [e] 2 mL in a 5 mL vial. [f] Backpressure regulator.

- Comparable to microwave reactions: shorter and cleaner reactions
- Reactions are scalable whereas microwave reactions are not

Org. Proc. Res. Dev. **2010**, *14*, 432-440.

Combining Microreactors with Solids

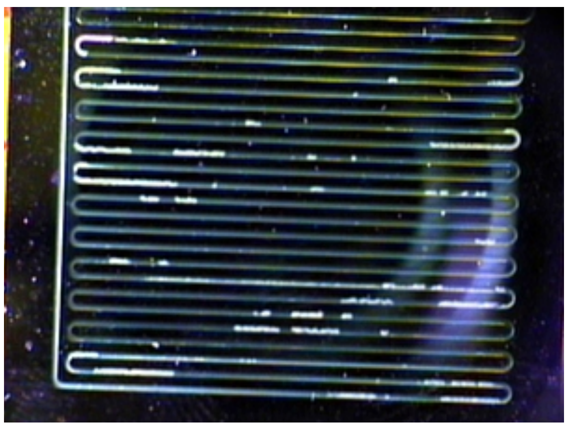
Limiting Clogging with Acoustics



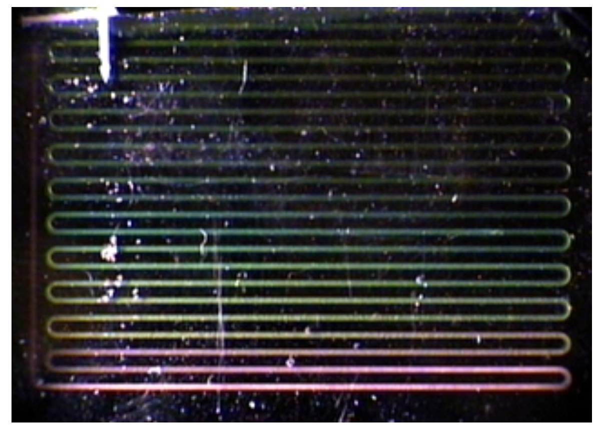
1 min reaction
28 g/day

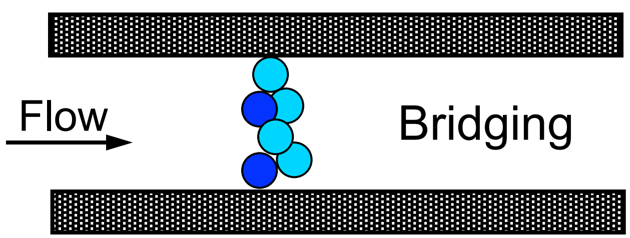
- Teflon and Silicon/glass both experience clogging problems
- Sonication produces smaller particle sizes and reduces/delays clogging

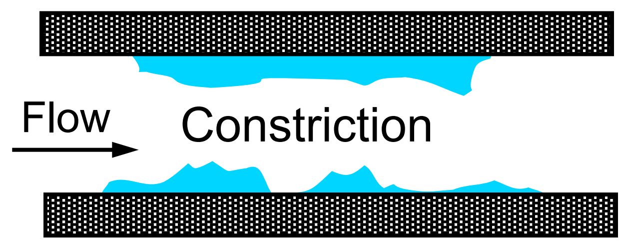
Flow:
20 μL/min



Flow:
70 μL/min

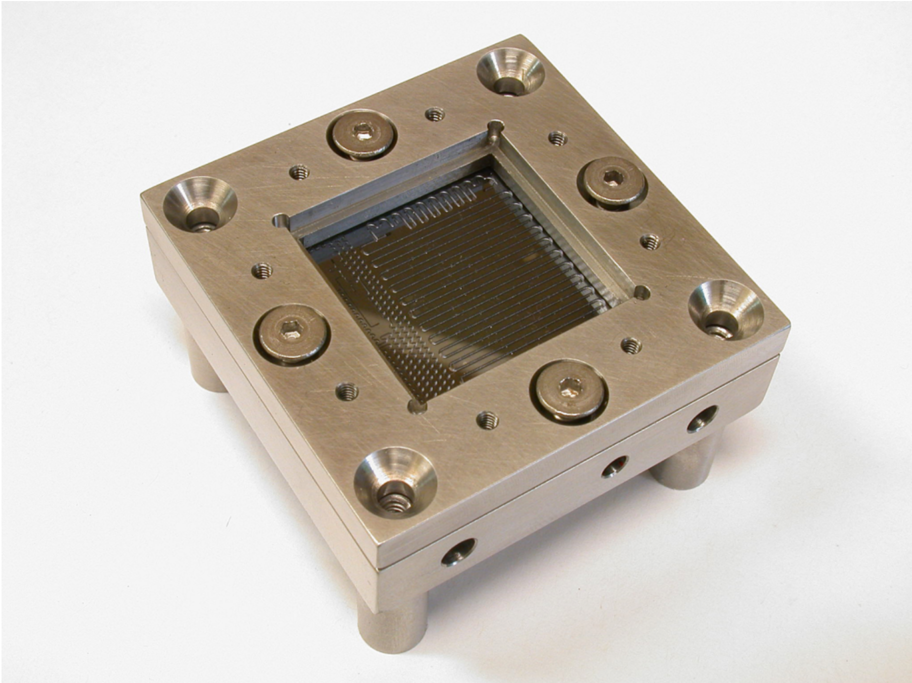






Org. Proc. Res. Dev. **2010**, *14*, 1347.

Combining Microreactors with Photochemistry



- Poor UV penetration
- Long diffusion lengths
- Potential degradation of product
- Poor control of temperature
- Difficult to use filters

- Excellent UV penetration
- Short diffusion lengths
- Reduced chance for degradation
- Good control of temperature
- Easy wavelength filtering
- Integrated UV capillary lamps

Combining Microreactors with Photochemistry

Glass available for making reactors

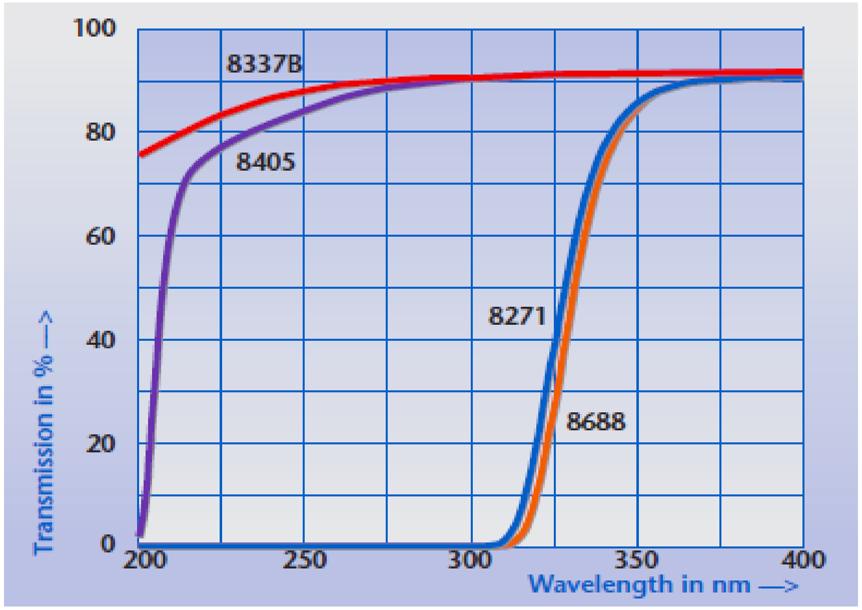
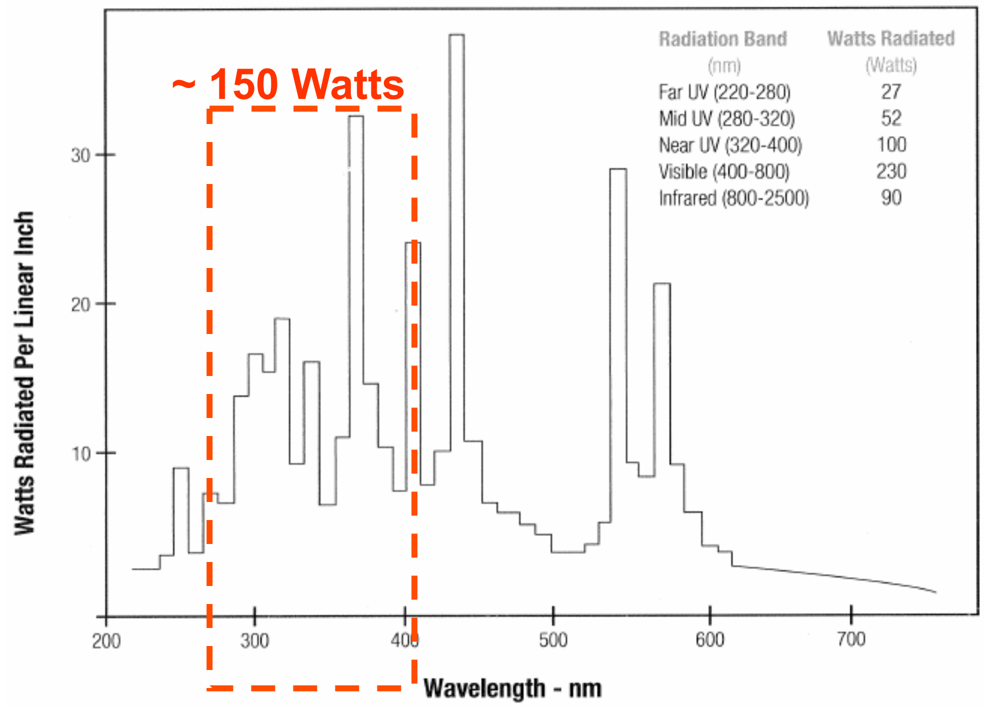
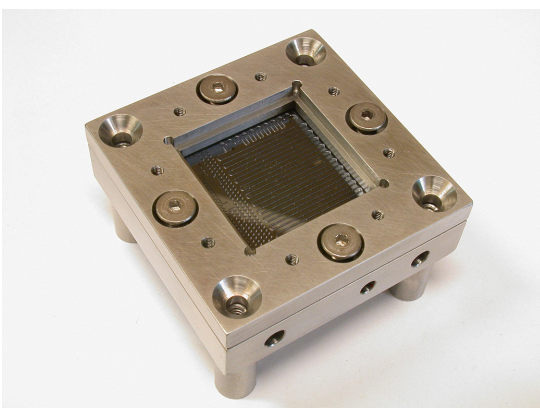


Fig. 28. *UV-transmission of highly UV-transparent technical glass types 8271, 8337B, 8405 and 8688 at 0,5 mm glass thickness*

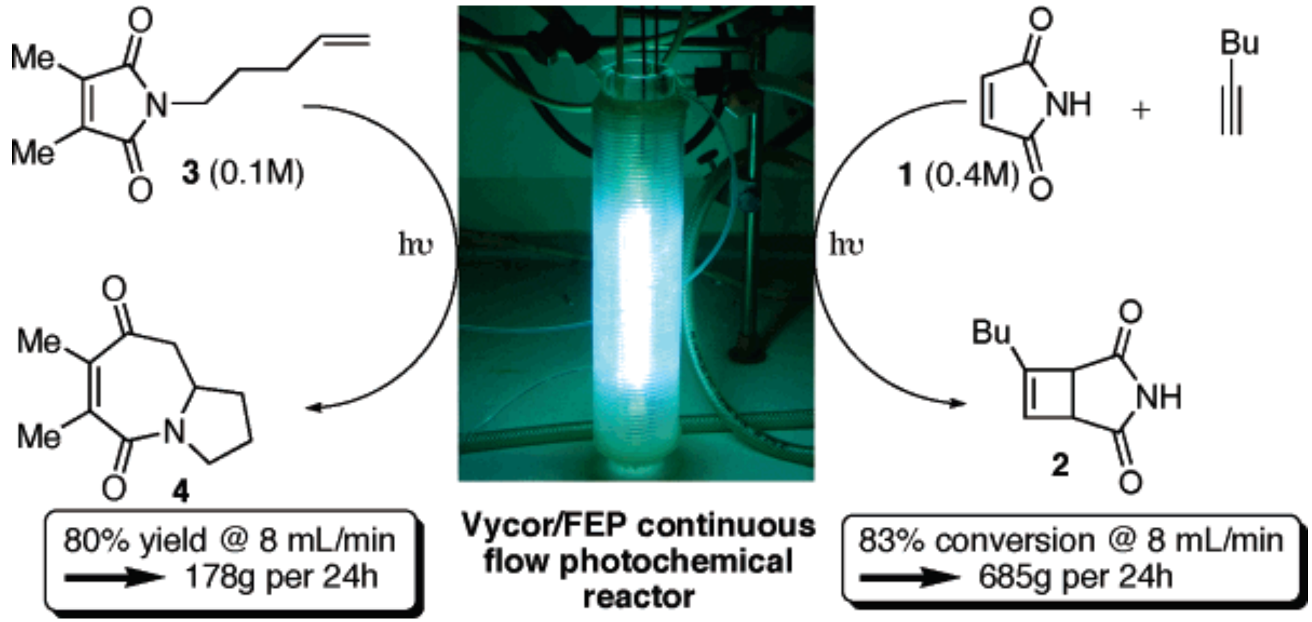
1000 W High Pressure Mercury Lamp

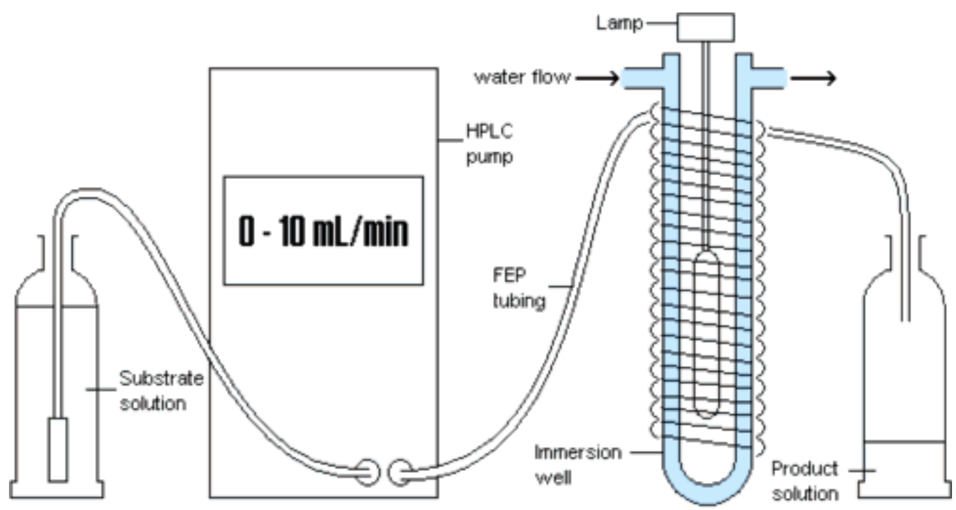




- Excellent UV penetration
- Short diffusion lengths
- Reduced chance for degradation
- Good control of temperature
- Easy wavelength filtering
- Integrated UV capillary lamps

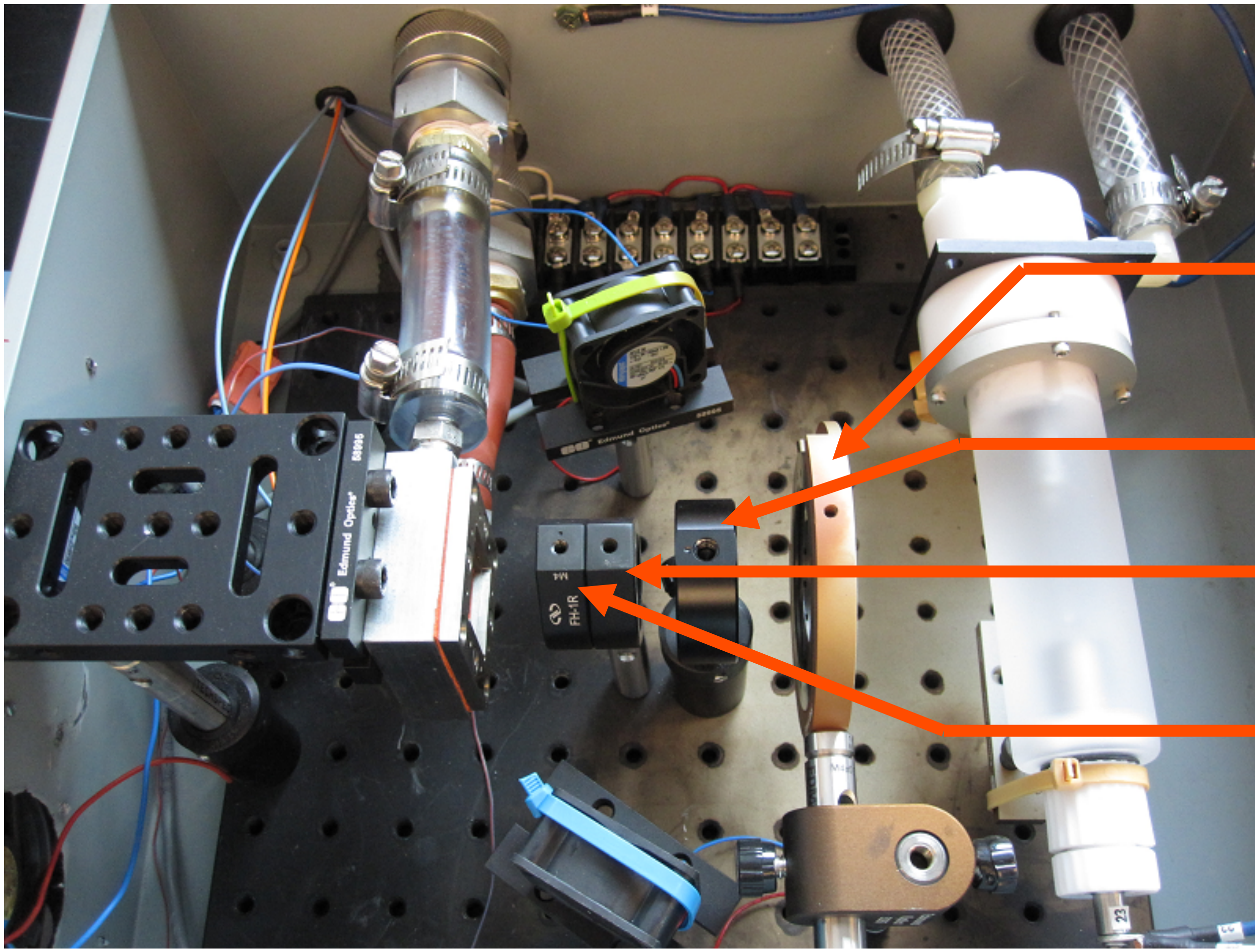
Combining Microreactors with Photochemistry





J. Org. Chem. **2005**, *70*, 7558.

CMLD BU Micro-photochemistry Platform



Adjustable Iris
(blocks incidental light)

Plano Concave Lens
(focuses/collimates light)

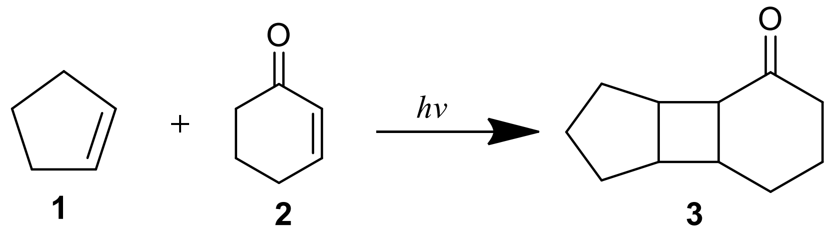
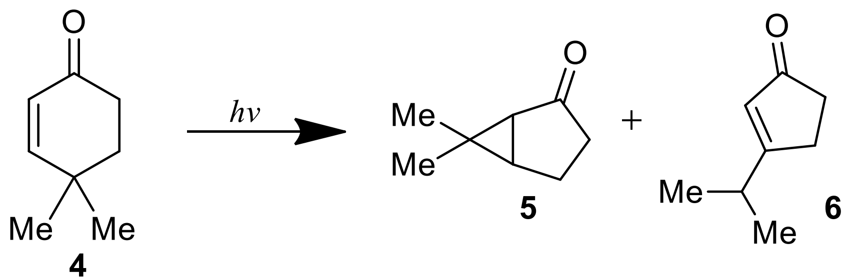
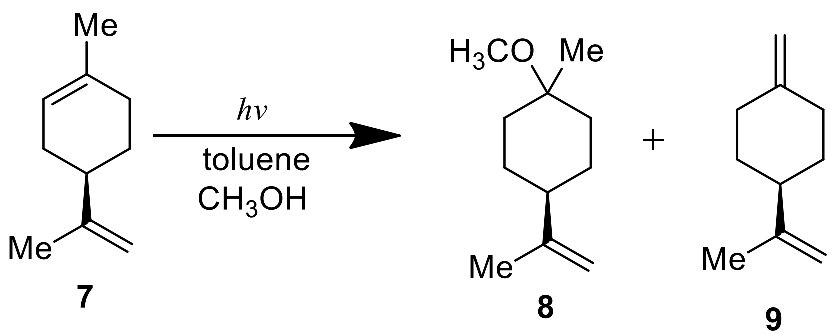
IR Heat Mirror
(blocks IR wavelengths)

Optical Filter
(blocks unwanted UV)

<u>Current Filter Section</u>
Longpass (50% cutoff): 280, 295, 305, 320, 370 nm
Bandpass (30% cutoff): 255-375, 305-365, 330-380, 340-405 nm

Combining Microreactors with Photochemistry

Benchmark Photochemical Reactions

		Low Pressure Lamp		High Pressure Lamp	
entry	reaction	time (min)	conv	time (min)	conv
1)		50	30%	1	100%
2)		50	40%	1	100%
3)		50	14%	1	44%

K. Pimparkar et al. 2010

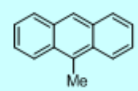
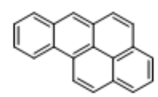
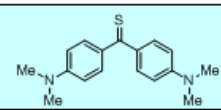
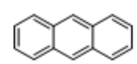
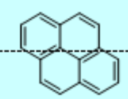
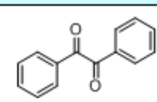
Combining Microreactors with Photochemistry

Photosensitizer Selection

- Fast ISC to triplet state (ϕ_{ST} ~1.0)
- Adequate triplet energy (E_T) to allow energy transfer to acceptor
- Long triplet lifetime (τ) to maximize efficiency of energy-transfer
- Substantial absorption in region that acceptor does not
- Low chemical reactivity and can be easily removed
- Ideal concentration of 10^{-3}M

Microsoft Excel - sensitizer_table2.xls

Filters and Lamp	code	280long	295long	305long	320long	370long	U-330	U-340	UG-1	B-370
	range (nm)						255-375	305-365	330-380	340-405
Click here for lamp info.	Click on specific filter code to see absoption spectrum.									

entry	sensitizer	excitation: solvent	λ_{max} Abs	ε	E_S (kJ/mol)	E_S (kcal/mol)	λ_S^{0-0}(nm)	nonpolar: E_T (kJ/mol)	E_T (kcal/mol)	τ_T (µs)	Φ_T
1		DCE	387	21168	310(n) 306(p)	73.2(p)	387(n) 391(p)	173	41.3		0.48
		MeOH									
		ACN	385	6902							
2		DCE	403	26736	295(n) 297(p)		405(n) 403(p)	175	41.8	8700	
		DCE	385	4480							
		ACN	383	21248							
		ACN	402	1590							
3		DCE						176	42.1	1.3	1
		MeOH									
		ACN									
4		DCE	377	17670	318(n) 319(p)		376(n) 375(p)	178	42.5	670	0.71
		MeOH									
		ACN	374	4912							
5		DCE	371	205	322(n) 321(p)	76.8(p)	372(n) 373(p)	293	48.5	180	0.37
		DCE	333	35680							
		ACN	370	218							
		ACN	333	32928							
6		DCE	385	63	247(n)	59.1(n)	485(n)	223	53.3	150	0.92
		MeOH									
		ACN	375	60							
		DCE	440	9							

Sheet1 / Sheet2 / Sheet3 / Sheet4

Summary: Questions before Answers

- **Understand the benefits of microfluidics and the use of microreactors**
  - **Better mixing**
  - **Better temperature control**
  - **Better control of reaction time**
  - **Contained devise allows handle/use of hazardous material**
  - **Use less material and scaleable optimization**

- **Understand the reaction in question**
  - **Can microfluidics improve reaction yield/selectivity**
  - **How much material is required**
  - **Do you have a question about reaction kinetics (accuracy?)**

Acknowledgments

- **CMLD-BU:**
  - **Aaron Beeler**
  - **John Porco**

- **MIT:**
  - **Klavs Jensen**
  - **Jonathan McMullen**
  - **Nikolai Zaborenko**
  - **Hemantkumar Sahoo**
  - **Ketan Pimparkar**