Microreactors: Using the Very Small to Make the Very Large
New Technology in Pharmaceutical Development

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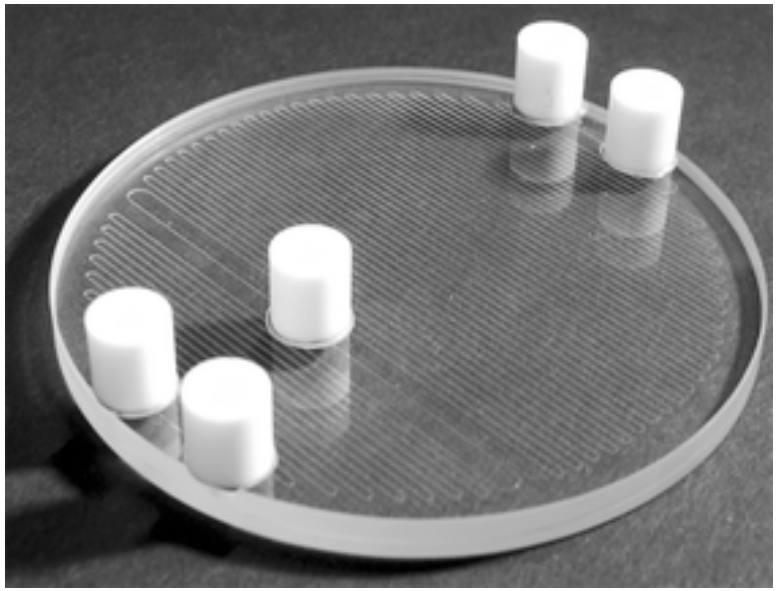
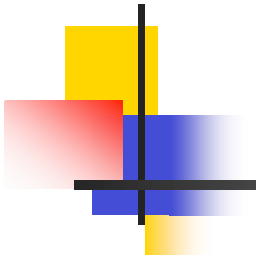
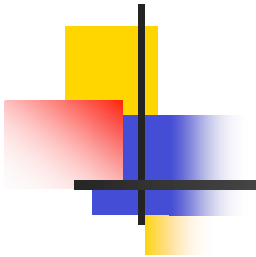
Wipf Group
August 14th, 2004





Outline

- Introduction
- Continuous Flow Reactions
- Lab Style Applications; Yield improvements, ee improvements, time improvements, etc.
- Process Scale Applications; Access to different chemistry, process development improvement, potential cost savings
- Two Real Life Applications
- Conclusions

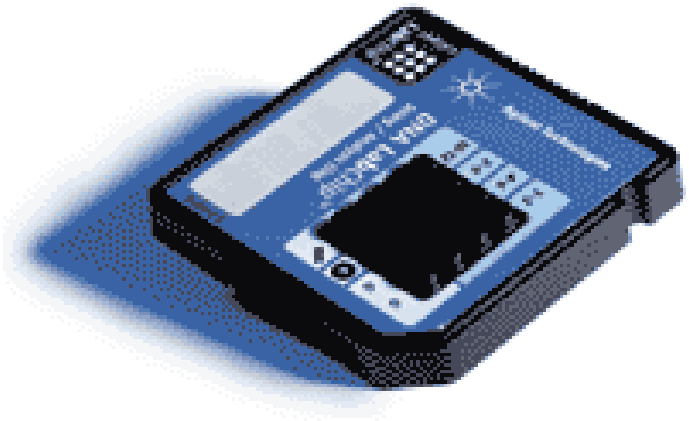


Definitions

- Batch chemistry
  - Basically what we do everyday
  - Add all reactants, stir for x hours, work-up and analyze.
- Combinatorial chemistry
  - What robots do
  - Batch scale chemistry in parallel with automation
- Continuous flow chemistry
  - Less Common
  - Add reactants to pot A; allow to flow into pot B for work-up; never stop flow
- Microreactor chemistry – Continuous flow chemistry using specialized equipment

What is a Microreactor

- An extension of μTotal Analysis (μTAS), i.e., Lab-on-a-Chip
  - 1st example a GC from Stanford
- Recent example
  - DNA Analyzer – Available commercially from Agilent Technologies
  - Can detect 1 ng/L
  - Only need 1 μL of sample



μReactors: Why Should You Care?

- Cleaner reactions
- A wider variety of reactions possible
- Potentially faster scale-up

Definitely has the potential to spend less time on development and scale up and more time selling. i.e. More money for company (and hopefully you)

- Currently a “hot” topic in pharmaceuticals and fine chemicals
- Potential (partial) paradigm shift

Haswell, S. J., Middleton, R. J., O’Sullivan, B., Skelton, V., Watts, P., Styring, P. *Chem. Comm.*, **2001**, 391-398. Tilstam, U.; *Org. Proc. Res. Dev.,* **2004**, *8*, 421.

Advantages of μReactors to "Normal Chemistry"

- Possibility to "number up" instead of scale up reactions
- Reduced reaction time in many cases
- Vastly improved heat transfer
- Ability to perform "dangerous" chemistries

"The technology offers an efficient, safe scale-up, shorter process research times and eventually a reduction in drug development times. Microreactor technology shows promise as an innovative tool to help us fulfill our mission to move new medicines from discovery into patients as quickly as possible." J & J

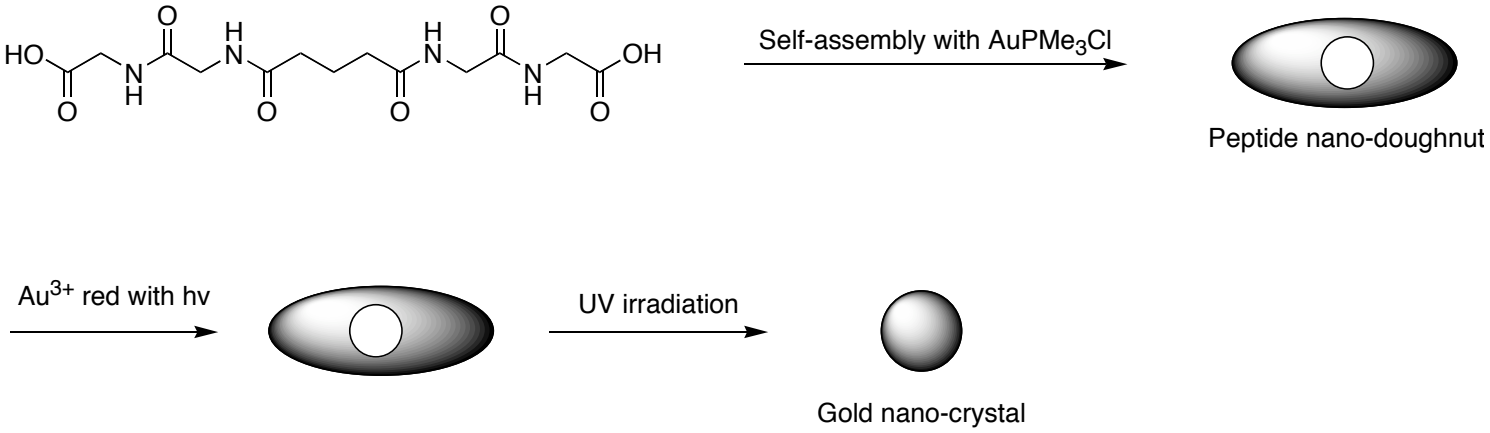
Zhang, X., Stefanick, S., Villani, F. J. *Org. Proc. Res. Dev.*, **2004**, *8*, 455.

What is a μReactor

It is not a nano-reactor

Both reasonable scale and technologies applied

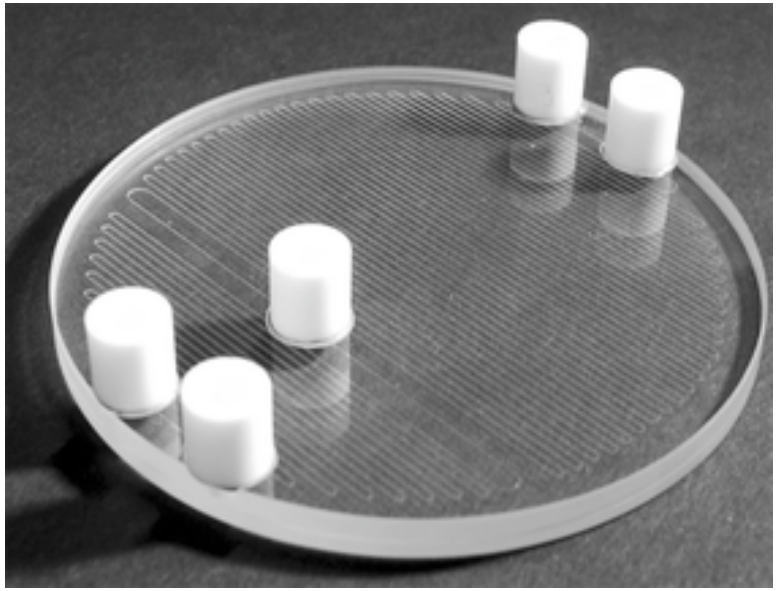
Example of nano-reactor



Djalali, R., Samson, J., Matsui, H. *J. Am. Chem. Soc.,* **2004**, *126*, 7935.

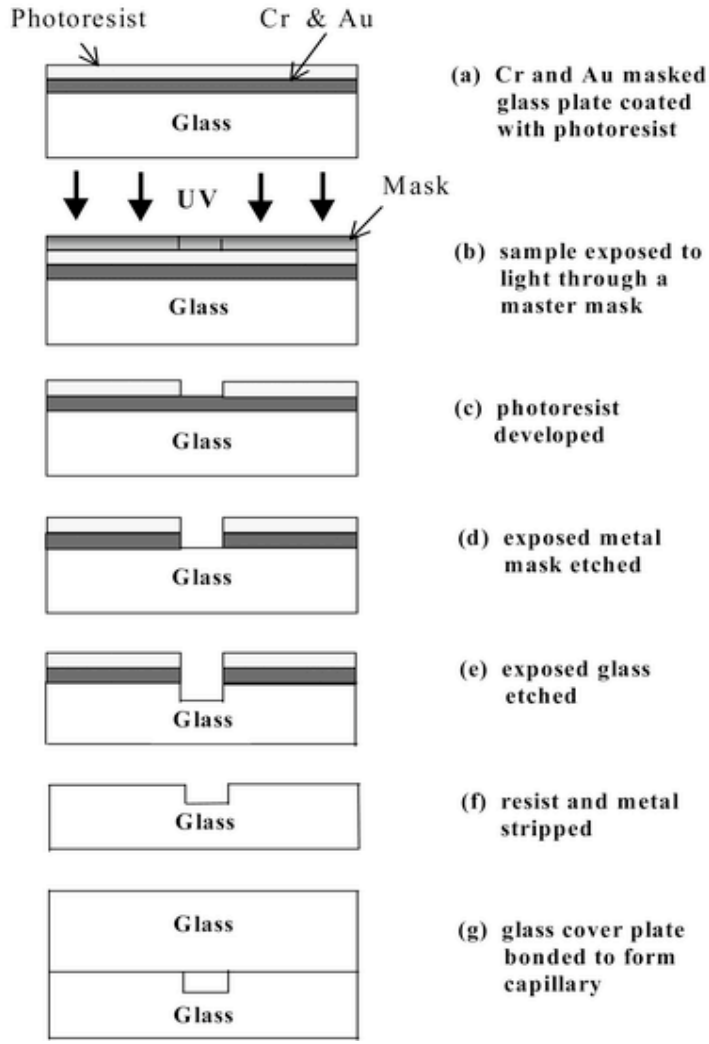
Characteristics of μReactors

- Channels 50 to 500 μm wide
- Wall between reaction and heat exchanger 20 to 50 μm
- Laminar flow, opposed to turbulent mixing



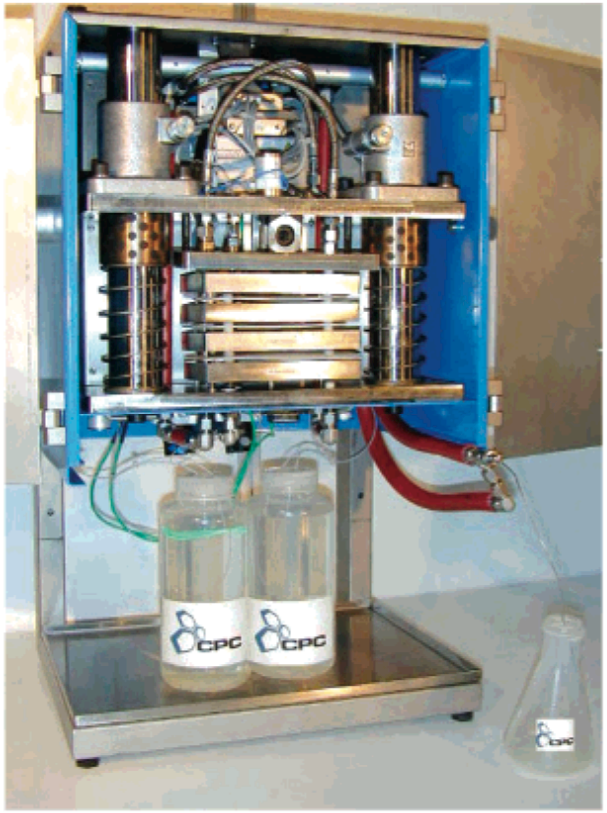
Manufacture of μReactors

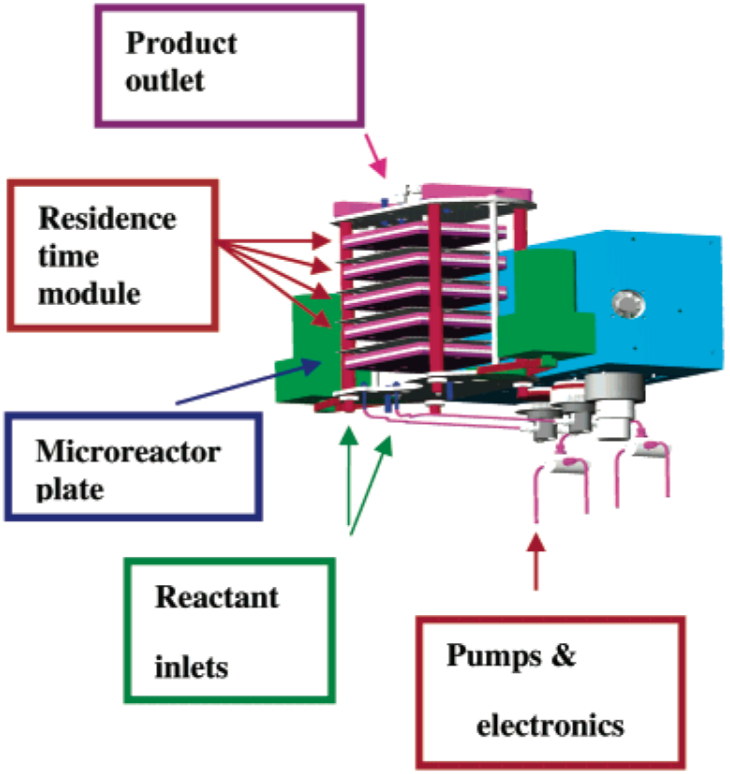
- Bulk machining using wet chemical etching of silicon
- Dry etching using plasma or ion beams
- Micromolding
- Wet chemical etching of glass
- Isotropic wet chemical etching
- Laser abalation
- Buy from commercial sources



Ehrfeld, W., Hessel, V., Lowe, H., *Microreactors: New Technologies for Modern Chemistry* Wiley-VCH, Weinhem, 2004, p. 15

Complete μReactors





Zhang, X., Stefanick, S., Villani, F. J., *Org. Proc. Res. Dev.*, **2004**, *8*, 455. Haswell, S. J., Watts, P. *Green Chemistry*, **2003**, *5*, 240.

Commercially Available

- Cellular Process Chemistry
- Mgt mikroglas
- FZK
- IMM

One drawback is lack of standardized interfaces.

Appears as if academic labs usually make their own system

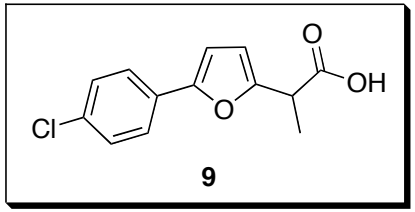
Lowe, H., Hessel, V., Mueller, A. *Pure Appl. Chem.* **2002**, *74, 2271*

Reactions Performed in μReactors

- 1,3 Dipolar cycloadditions
- Suzuki Coupling
- Michaelis-Arbuzov Rearrangement
- $NaBH_4$ Reduction
- Intramolecular Diels-Alder Reaction
- Nef Reaction
- Ketalization
- Aminolysis
- BuLi Add'n to Cyclohexanone
- BuLi Add'n to Benzaldehyde
- Wittig-Horner Reaction
- Wagner-Meerwein Rearrangement
- Beckmann Rearrangement
- Paal-Knorr Pyrrole Synthesis
- Guaresky-Thrope-Pyridone Synthesis
- Red-Al Reduction Synthesis of THP-Ether
- Synthesis of α-Hydroxyacetals
- Synthesis of 2-Amino-Pyrdine-N-Oxide
- Pd-Catalyzed Cross Coupling
- Wittig Reaction
- Favorskii Rearrangment
- Oxidation of Sulfide
- Mitsunobu Reaction
- Nucleophilic Aromatic Substitution

http://www.cpc-net.com/reactions.shtml

An Early Example of Continuous Flow Chemistry



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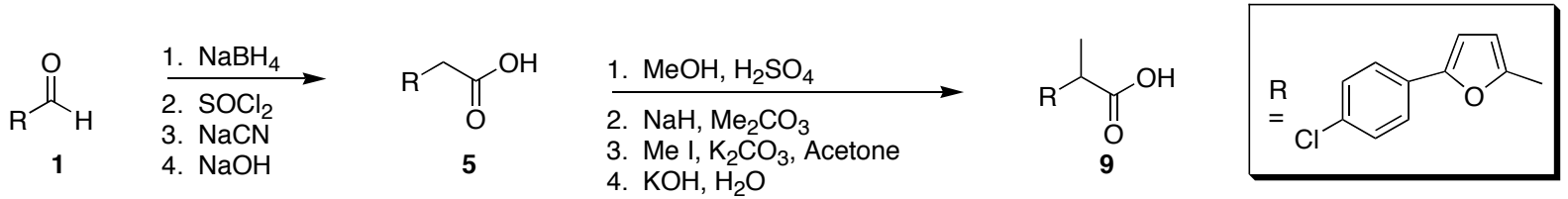
Route A



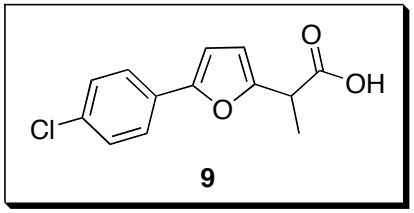
Route A was optimized and proceeded well on scale, however, the overall yield was 12 %

Yields for the eight individual steps were not reported, but avg. yield per step is 77 %

Amount needed not specifed, but eventually 10 kg of intermediate was obtained,

Foulkes, J. A., Hutton, J. *Synthetic Comm.*, **1979**, *9*, 625-630

An Early Example of Continuous Flow Chemistry



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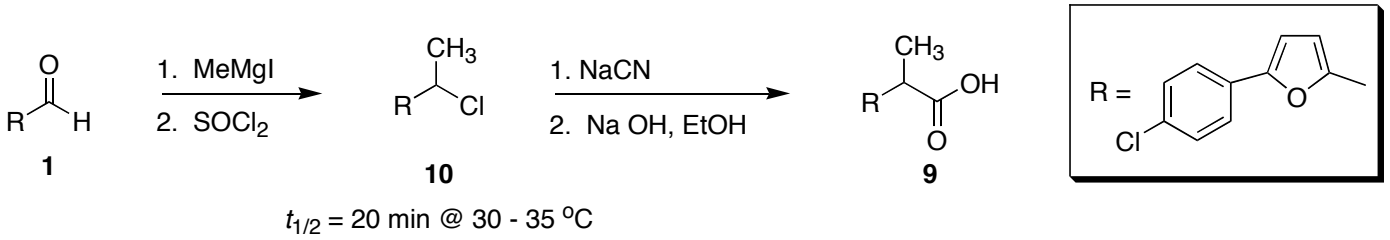
Route B



1 **10** **9**

$t_{1/2}$ = 20 min @ 30 - 35 °C

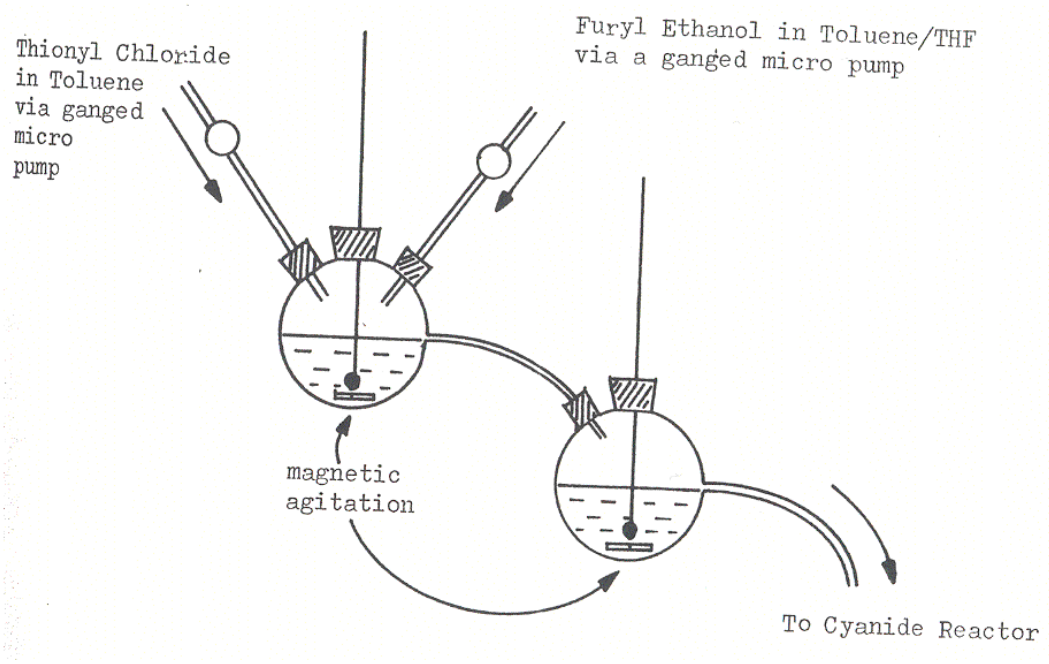
On small scale reaction worked decently, 20-30 % yield over 4 steps

Average yield of 67 % - 74 % per step

Yield on large scale, 100 - 200 g was "unacceptably low"

Foulkes, J. A., Hutton, J. *Synthetic Comm.*, **1979**, *9*, 625-630

An Early Example of Continuous Flow Chemistry



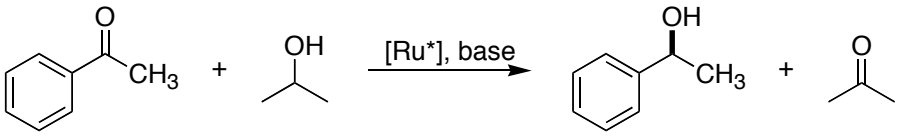
Using above set-up with 10 mL flasks over 10 kg of the nitrile was obtained in one week.

Average lifetime of the chloride was 1 min

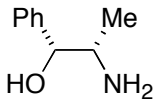
Yield of nitrile was 90 - 92 %, average per step of 97 %

Foulkes, J. A., Hutton, J. *Synthetic Comm.*, **1979**, *9*, 625-630

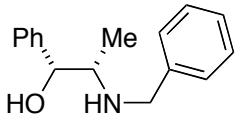
Continuous Flow for Catalyst Stability



Chiral Ligands



1



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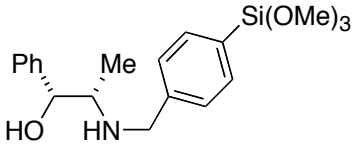

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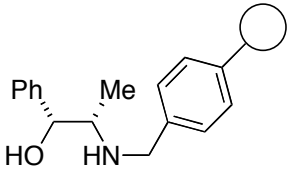
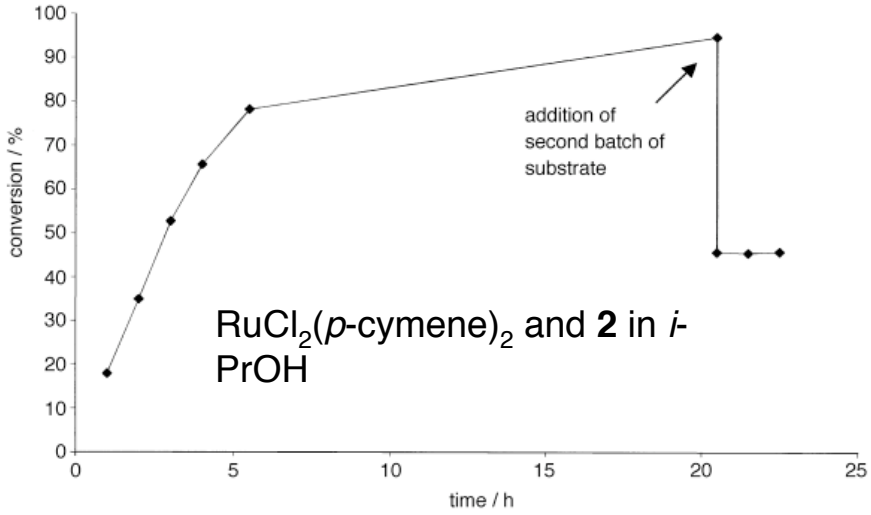
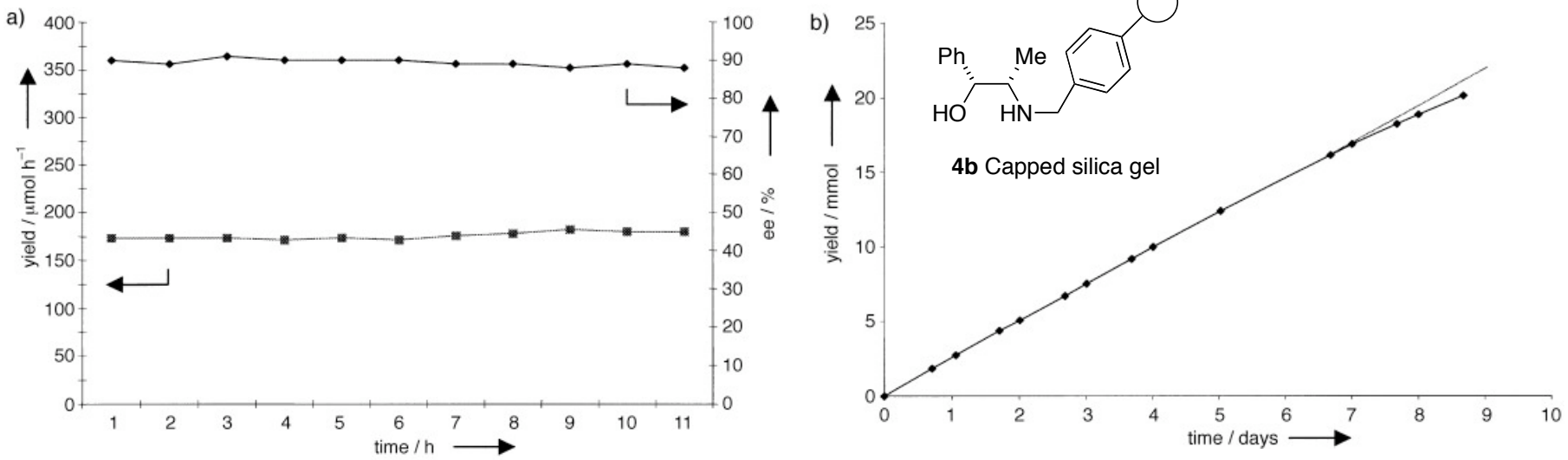


4 Silica gel
4a/4b Capped silica gel



Sandee, A. J., Petra, D. G. I., Reek, J. N. H., Kamer, P. C. J. Leeuwen, P. W. N. M. *Chem. Eur. J.,* **2001**, *7*, 1262.

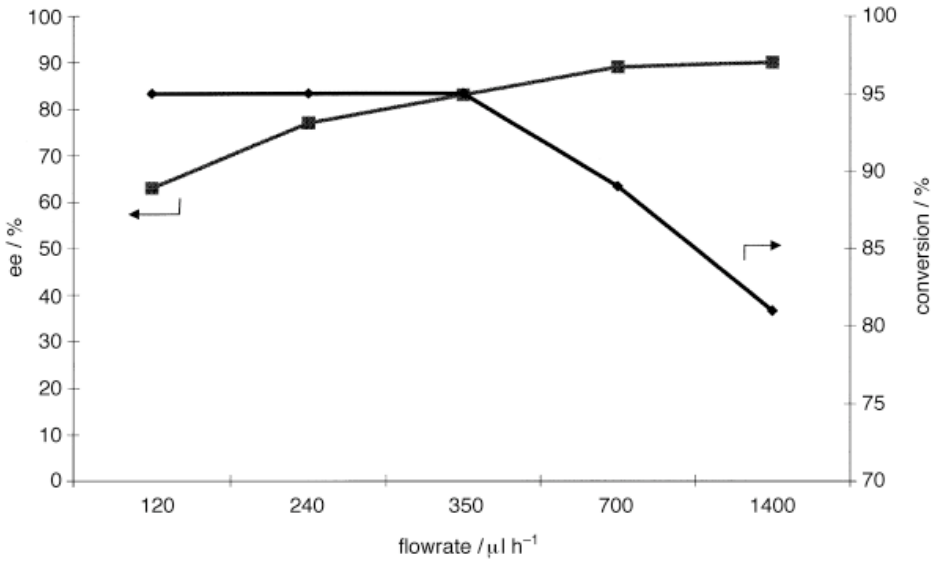
Continuous Flow for Catalyst Stability



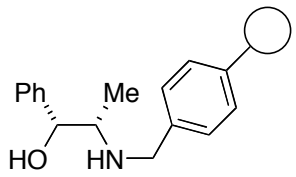
- Both ee and yield are remarkably stable
- Catalytic ability (ee and yield) barely decreases from theoretical over 9 days
- <1 % Ru leaching
- CF yield is 15 g L^{-1} h^{-1}, batch yield is 5.7 g L^{-1} h^{-1}

Sandee, A. J., Petra, D. G. I., Reek, J. N. H., Kamer, P. C. J. Leeuwen, P. W. N. M. *Chem. Eur. J.,* **2001**, *7*, 1262.

Drawback to System, Another Parameter to Optimize



Entry **8** run without base, gave best results

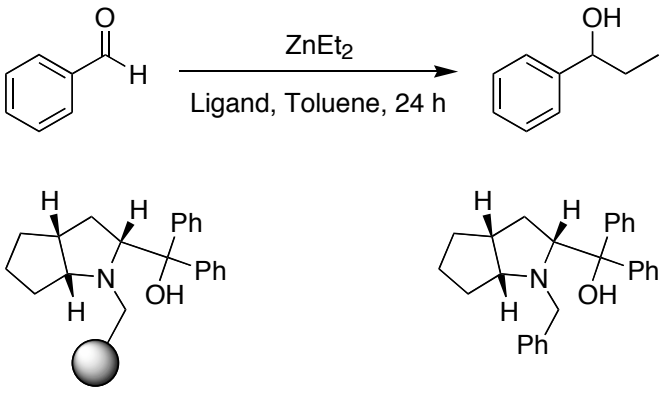


4 Silica gel
4a/4b Capped silica gel

Entry	Flow (µL h^{-1})	Conv %	ee %	Ru leaching
1	120	95	63	n.d.
2	240	95	77	n.d.
3	350	95	83	n.d.
4	700	90	89	<1
5	1400	81	90	<1
6	1400	95	89	<1
7	1400	95	89	<1
8	**1400**	**95**	**90**	**<1**
9	1400	53	88	<1
10	1400	29	88	<1

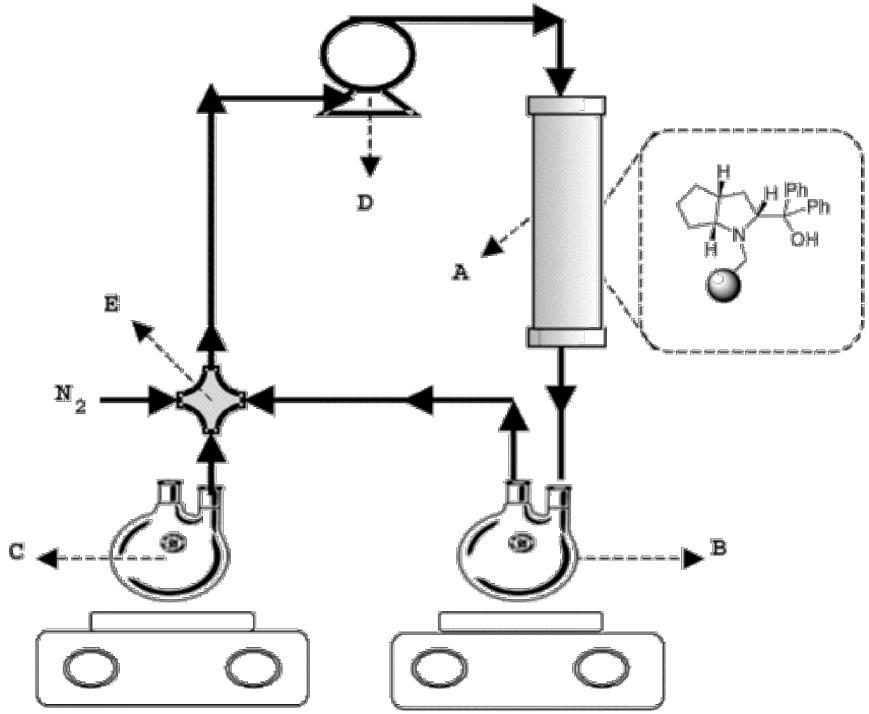
Sandee, A. J., Petra, D. G. I., Reek, J. N. H., Kamer, P. C. J. Leeuwen, P. W. N. M. *Chem. Eur. J.,* **2001**, *7*, 1262.

Continuous Flow: Improvement in ee: A Good Candidate for µReactor Technology



7 (Grafted)
10 (Polymerized)

5

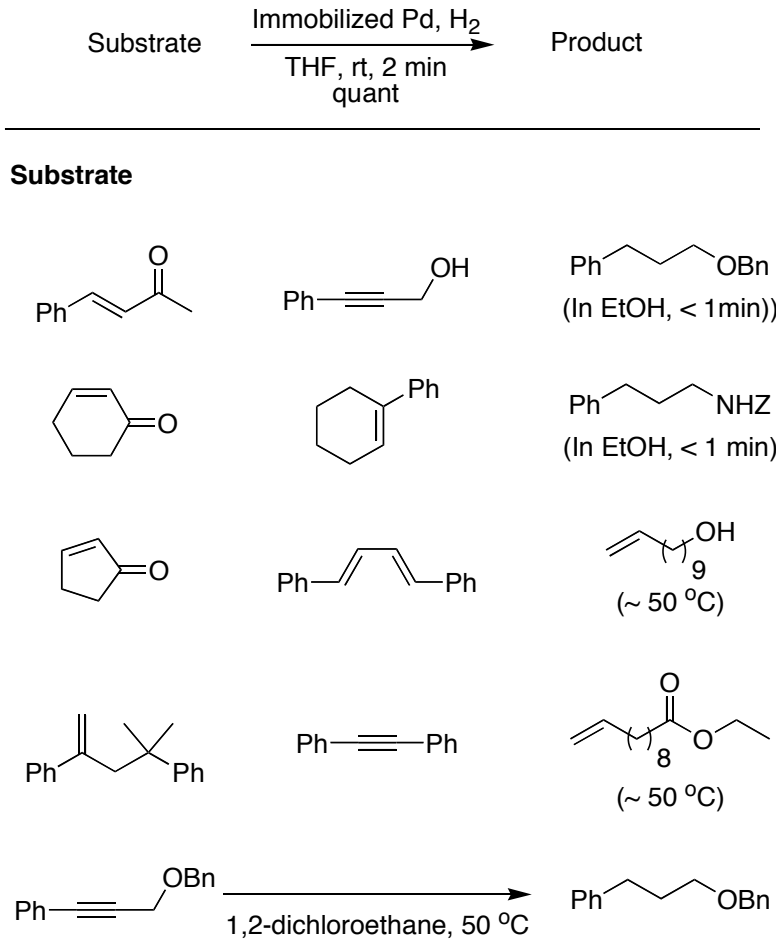


At various ligand concentrations ee's ranged from 74 to 85 % for **5** and **7** in batch-wise operations

10 in a flow-through system gave 99 % ee
Flow through system was re-usable at least 4 times

Burguete, M. I., Garcia-Verdugo, E., Vicent, M. J., Luis, S. V., Penneman, H., von Keyserling, N. G., Martens, J. *Org. Lett.*, **2002**, *4*, 3947

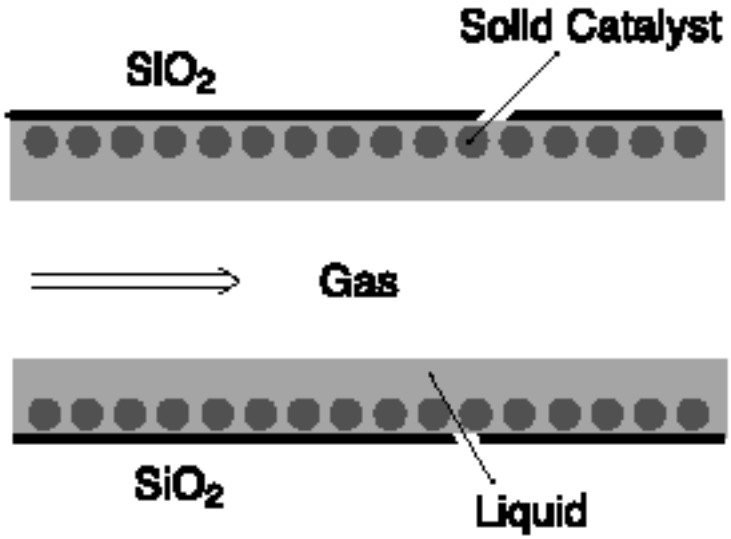
Hydrogenation Reactions

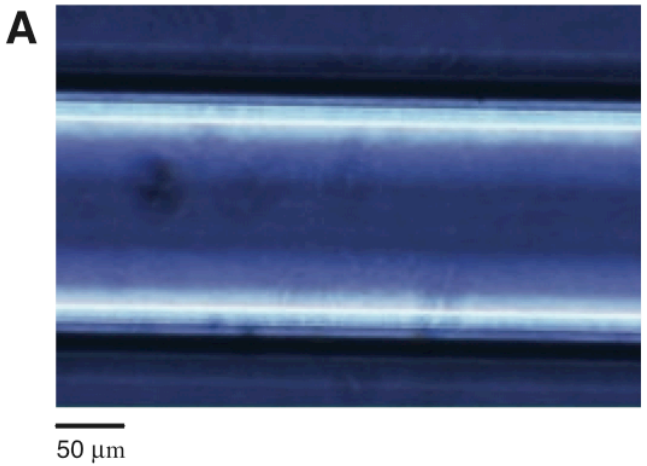


- No Pd leaching
- Product clean after solvent removal
- Scale-up should be easy, just add reactors
- Some yields (benzyl ether deprotection) much higher than batch reactions

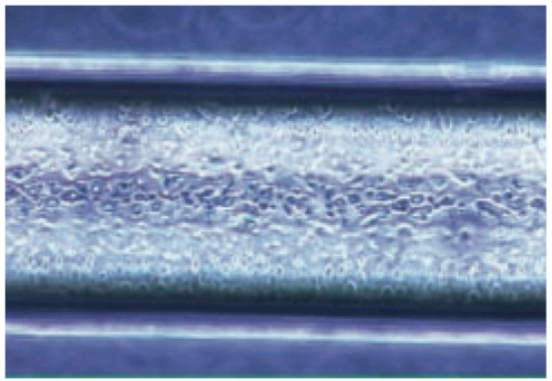
Kobayashi, J., Mori, Y., Okamoto, K., Akiyama, R., Ueno, M., Kitamori, T., Kobayashi, S. *Science* **2004**, *304*, 1305

Hydrogenation Reactions





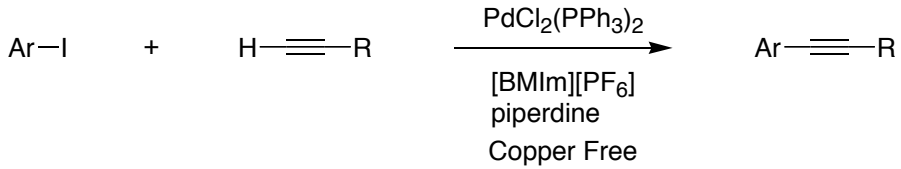
Before immobilization of the catalyst



After immobilization of the catalyst

Kobayashi, J., Mori, Y., Okamoto, K., Akiyama, R., Ueno, M., Kitamori, T., Kobayashi, S. *Science* **2004**, *304*, 1305

Palladium Catalyzed Reactions in μReactors



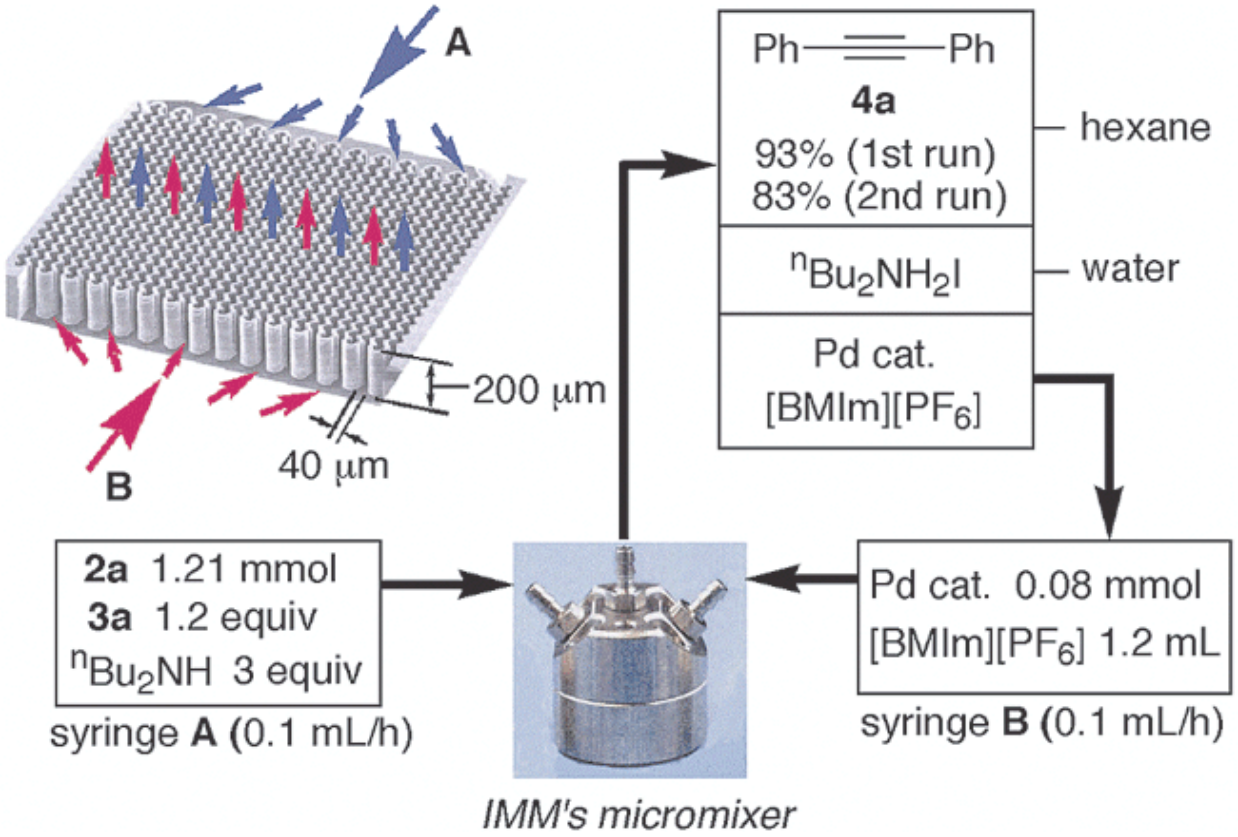
Batch Yields 88 - 97 %; Rxn time 2 h

Micromixer yield was 93 % and 83 %; Residence time 10 min

- Necessary to start with recycled catalysts for solubility issues
- Upon further recycling of the ionic liquid the yield dropped to 83 %
- More proof of concept than an improvement
- At least one Suzuki coupling has been reported as well, but yield was very low.

Fukuyama, T., Shinmen, M., Nishitani, S., Sato, M., Ryu, I. *Org. Lett.,* **2002**, *4* 1691.
Greenway, G. M.; Haswell, S. J.; Morgan, D. O., Skelton, V., Styring, P. *Sens. Actuat. B*, **2000**, *63*, 153.

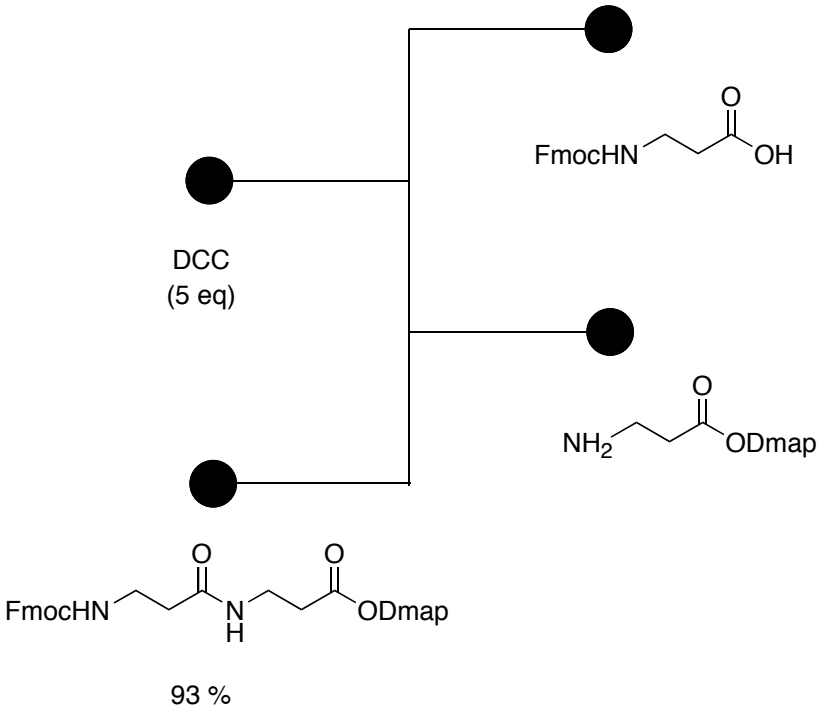
Reactor Used



Fukuyama, T., Shinmen, M., Nishitani, S., Sato, M., Ryu, I. *Org. Lett.,* **2002**, *4* 1691

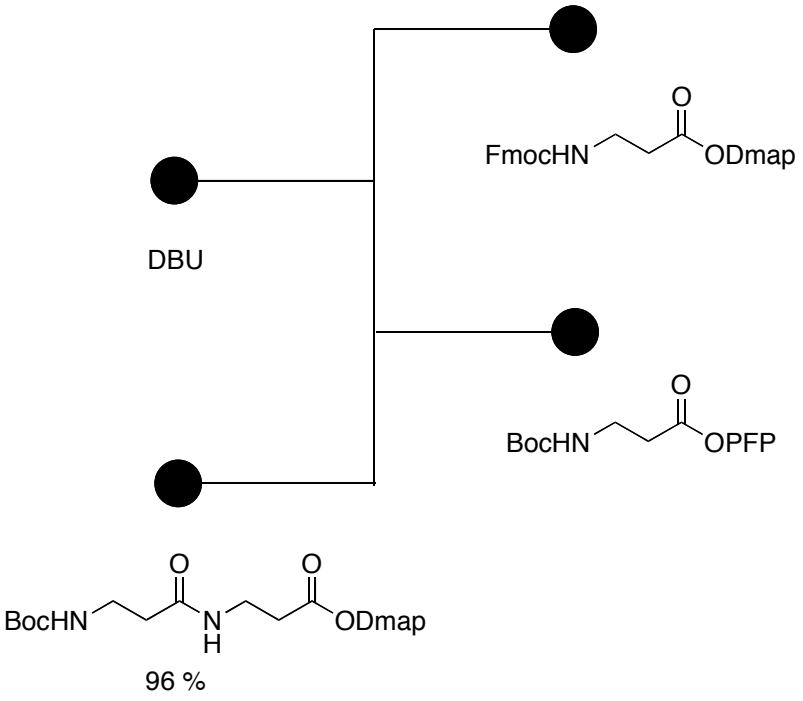
β-peptide Synthesis

Coupling



93 %

Deprotection, then Coupling

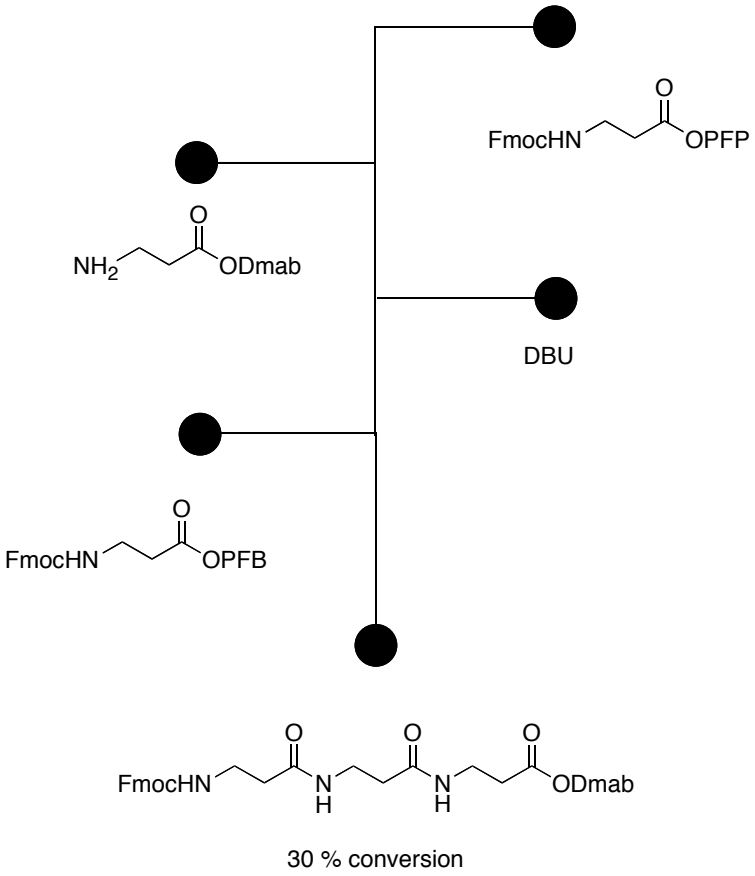


96 %

Watts, P., Wiles, C., Haswell, S. J., Pombo-Villar, E. *Tetrahedron*, **2002**, *58*, 5427.

Tripeptide Synthesis

Coupling

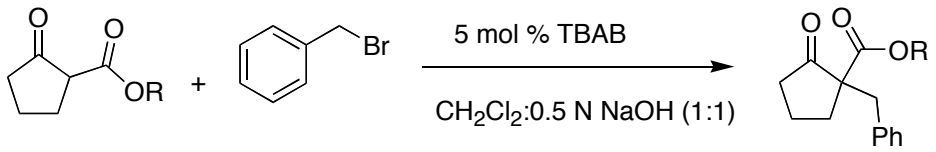


30 % conversion

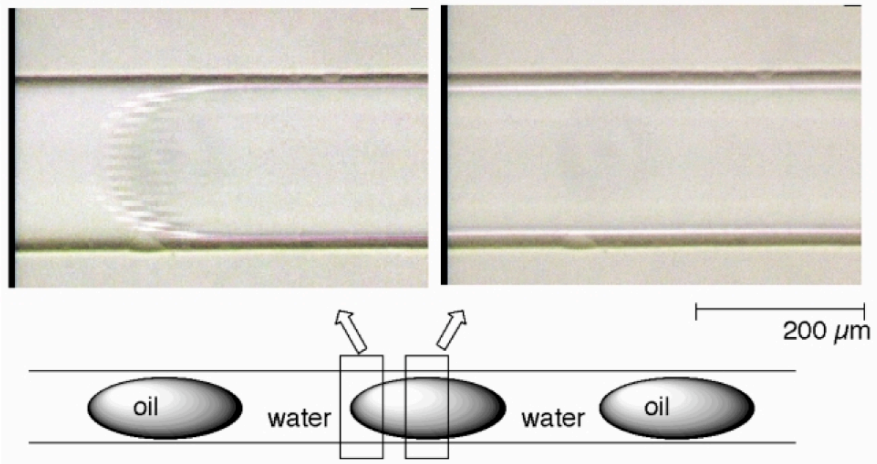
- Reactions faster than batch reactions
- One of only a few examples of two or more reactions in a μreactor

Watts, P., Wiles, C., Haswell, S. J., Pombo-Villar, E. *Tetrahedron*, **2002**, *58*, 5427.

Better Phase Transfer Characteristics



Vessel	Yield
μReactor (60 s)	57 %
μReactor (300 s)	> 90 %
rbf (1350 rpm, 60 s)	37 %
rbf (400 rpm, 60 s)	~ 20 %



Ueno, M.; Hisamoto, H., Kitamori, T., Kobayashi, S. *Chem. Comm.* **2003**, *936.*

Generality of Reaction

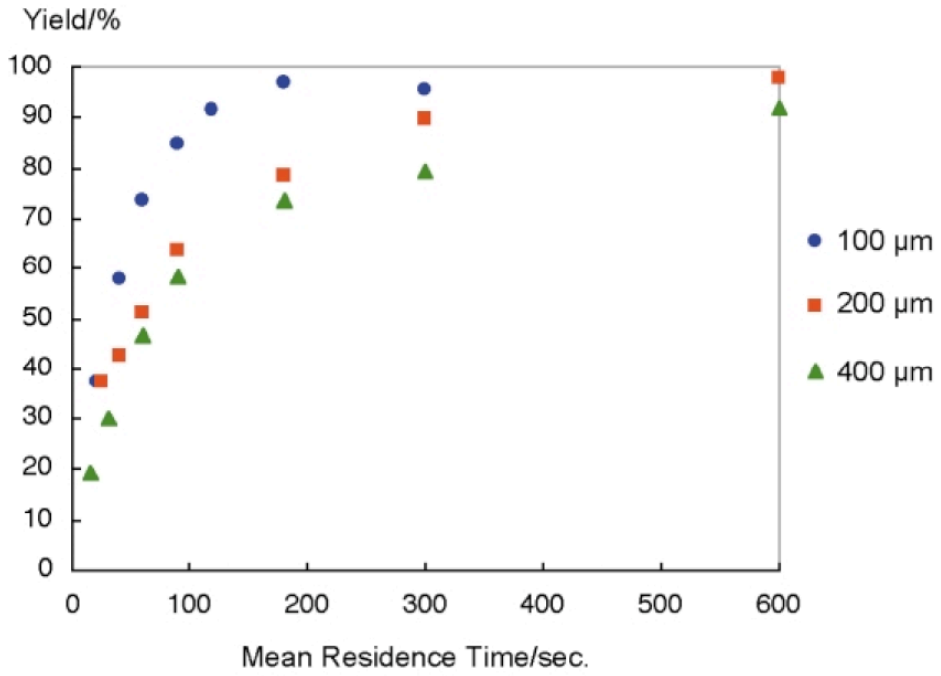
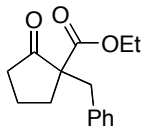
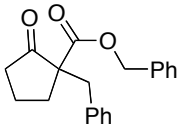
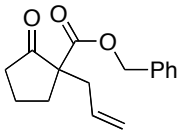
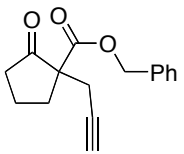
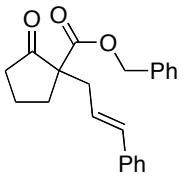
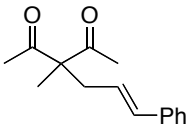


Fig. 3 The effect of the width of the reactors.

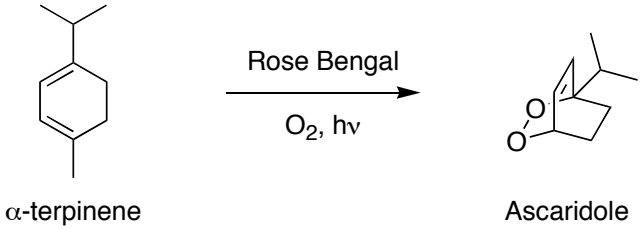
Ueno, M.; Hisamoto, H., Kitamori, T., Kobayashi, S. *Chem. Comm.* **2003**, *936.*

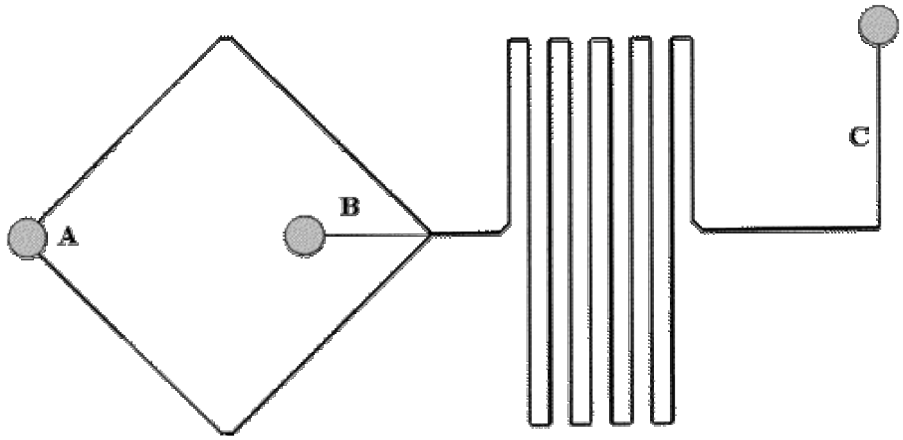
Product	2 min (batch)	10 min
	75 (49)	96 %
	73 (48)	85%
	45 (18)	87 %
	35 (18)	92 %
	91 (87)	97 %
	65 (20)	71 %

Photochemistry on Process Scale

- Problems on large scale
  - Formation of insoluble aggregates
  - Rapid loss of light intensity
  - Explosive nature of O_2 saturated solvents
- Appears that photochemistry is done on scale, but health and safety concerns still exist.
- Ideal case for miniaturization

Proof of Concept





- Chip was 5 cm × 2 cm, channel 50μm deep by 150 μm wide
- ~ 95 % of the light is transmitted
- Light bulb is only 20 W, 6 V.
- Solution is immediately degassed, basically no explosion hazard
- > 80 % conversion in 5 s rxn time

Wooten, R. C. R., Fortt, R., de Mello, A. J. *Org. Proc. Res. Dev.* **2002**, *6,* 187

Heat Control in Reaction Vessels

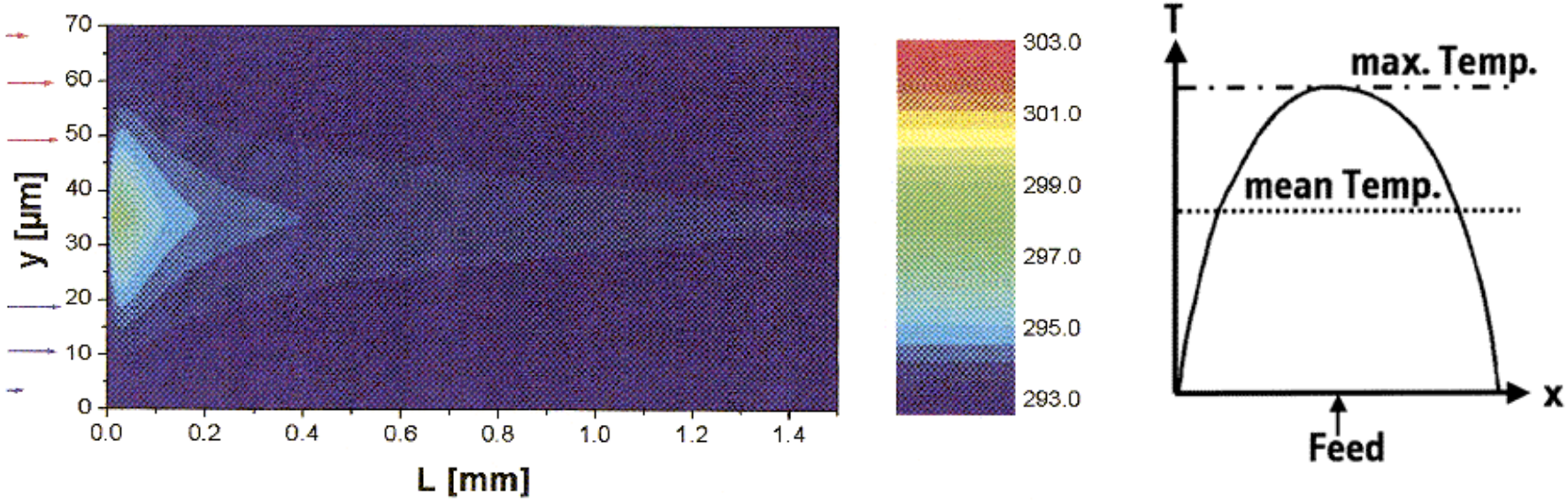
- Heat transfer rate is proportional to surface area of vessel

- Surface to volume ratio thus becomes key

Reaction Vessel	Ratio (cm^2/cm^3)
μReactor	200
100 mL rbf	1
50 gal (190 L)	0.084
1000 L	0.06

Taghavi-Modhadam, S., Kleenman, A., Golbig, K. G., *Org. Proc. Res. Dev.* **2001**, *5*, 652.

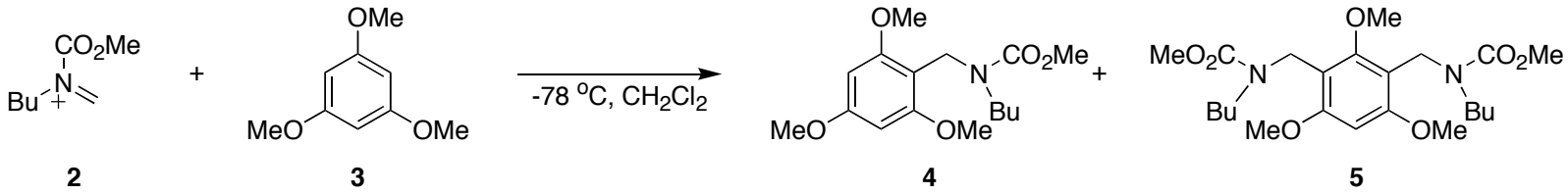
Heat Control in Reaction Vessels



- Hot spots are minimized (eg., 3 K versus 60 K rise)
- Entire rxn mixture can be kept at optimal temperature

Taghavi-Modhadam, S., Kleenman, A., Golbig, K. G., *Org. Proc. Res. Dev.* **2001**, *5*, 652.

Reactions at Low Temperature



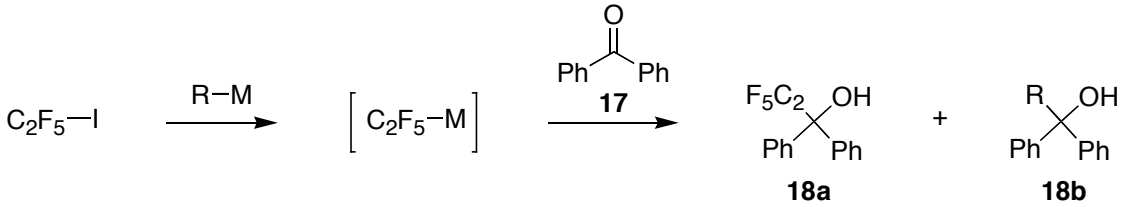
2 **3** **4** **5**

Reactor	**4** (%)	**5** (%)	**4:5**
batch	37	32	54:46
T-shaped tube	36	31	54:46
Micromixer	92	4	96:4

5 increases with temp, improved heat transfer credited with improved selectivity

Suga, S., Nagaki, A., Yoshida, J-I. *Chem. Comm.*, **2003**, 354

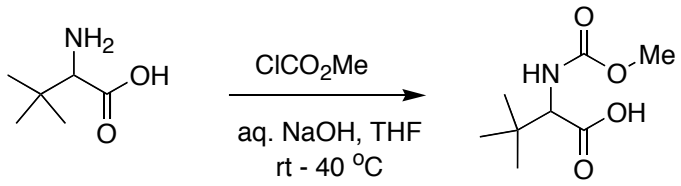
Reactions at Low Temperature: Ability to Raise the Temperature



Entry	Reagent	T, stage 1 (˚C)	T, stage 2, (˚C)	Ratio R–M/C_2F_5I /**17**)	t, Stage 1 (min)	t, Stage 2 (min)	**17** (%)	**18a** (%)	**18b** (%)
3 batch	MeMgCl	-30	0	2.5:2.8:1	10	>60	84	15	1
4	MeMgCl	2	-4	3.9:4.3:1	0.9	<10	65	25	10
5	MeMgCl	1	-4	3.9:2.7:1	0.9	<10	13	80	7
6	MeMgCl	-6	-4	3.9:2.7:1	0.9	8	9	86	5
7	MeMgCl	-8	-6	5.4:2.7:1	0.7	<10	7	82	11
8	MeMgCl	-6	-4	7.8:7.8:1	0.8	<10	28	72	

Schwalbe, T., Autze, V., Hohmann,M., Stirner, W. *Org. Proc. Res. Dev.* **2004**, *8*, 440

Application of μReactor Minimize Addition Concerns



- Heat release upon addition of methyl chloroformate

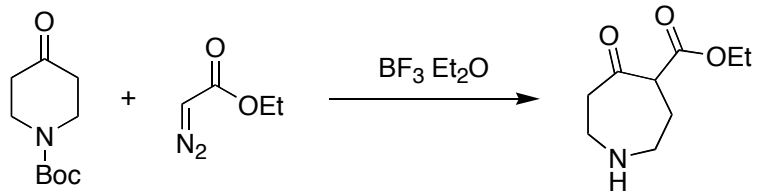
- Slow addition is sufficient to control heat, except in loss of cooling or stirring

- Direct transfer to μReactor at 35 °C provided 91 % yield

- Residence time of 7 min, > 1 kg produced in 1 h

Zhing, Z., Stefanick, S., Villani, F. J. *Org. Proc. Res. Dev.* **2004**, *8*, 455

Application of μReactor to "Unscaleable" Chemistry



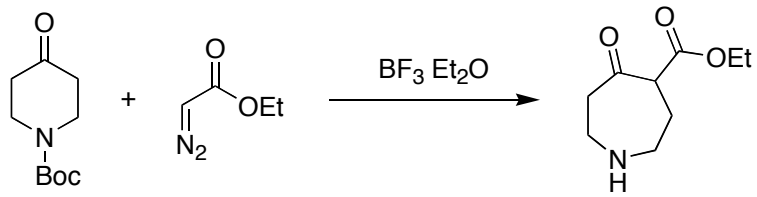
Literature: Et_2O, -25 ^oC, 90 % crude
Process (70 mg scale): CH_2Cl_2/MTBE (1:4), 0.2 eq BF_3Et_2O, < 15 ^0C, 81 %

- Addition of BF_3 Et_2O very exothermic
- Heat release **not** feed controlled, initiation period is observed
- Solvent reflux temperature could be reached with loss of cooling
- Evolution of large amounts of N_2

"Scaling this reaction to kilogram scales *safely* in a conventional reactor is not recommended"

Zhang, X., Stefanick, S., Villani, F. J. *Org. Proc. Res. Dev.,* **2004**, *8*, 455

Application of μReactor to "Unscaleable" Chemistry

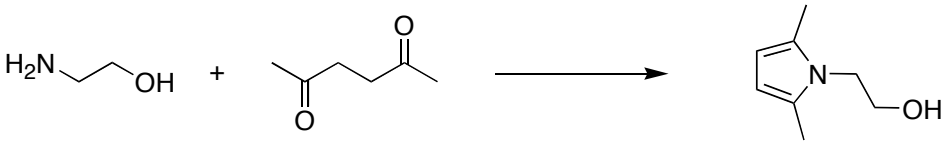


Literature: Et_2O, -25 ^oC, 90 % crude
Process (70 mg scale): CH_2Cl_2/MTBE (1:4), 0.2 eq BF_3Et_2O, < 15 ^0C, 81 %

- 70 mg batch conditions directly transferred to micro-reactor
- Yield increased to 89 % with precise control
- Rxn time of 1.8 min
- 91 g/h obtained, potentially 2.2 kg per day
- "… we were able to reduce the time-consuming process research to find optimal safe conditions."

Zhang, X., Stefanick, S., Villani, F. J. *Org. Proc. Res. Dev.,* **2004**, *8*, 455

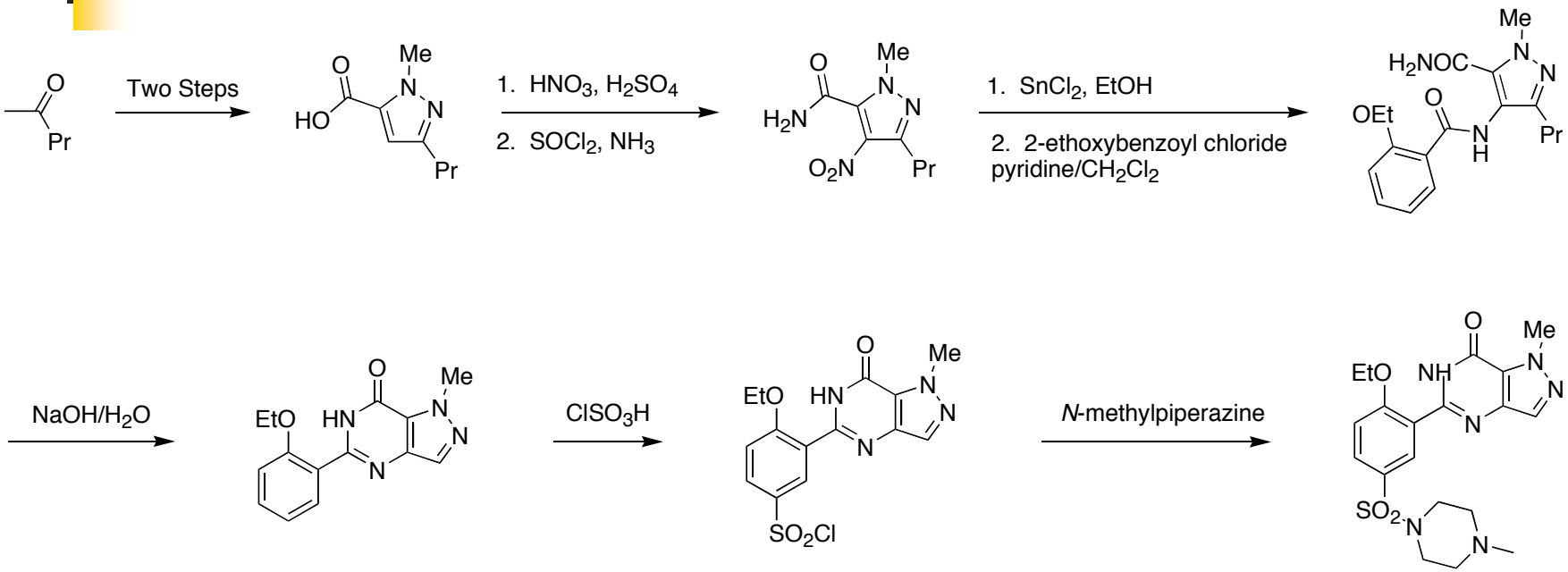
Are μReactors Green?



- Time for addition of reagents quite significant on process scale
- Reaction can be done without solvent in μReactor
- 91 % yield (after distillation)
- 260 g/h (6.2 kg/day)
- 10 min clean-up (flush with EtOH)

Schwalbe, T., Autze, V., Hohmann, M., Stirner, W. *Org. Proc. Res. Dev.* **2004**, *8*, 440.

Application to a Blockbuster Drug: Medicinal Chemistry Route



Sildenafil (Viagra)

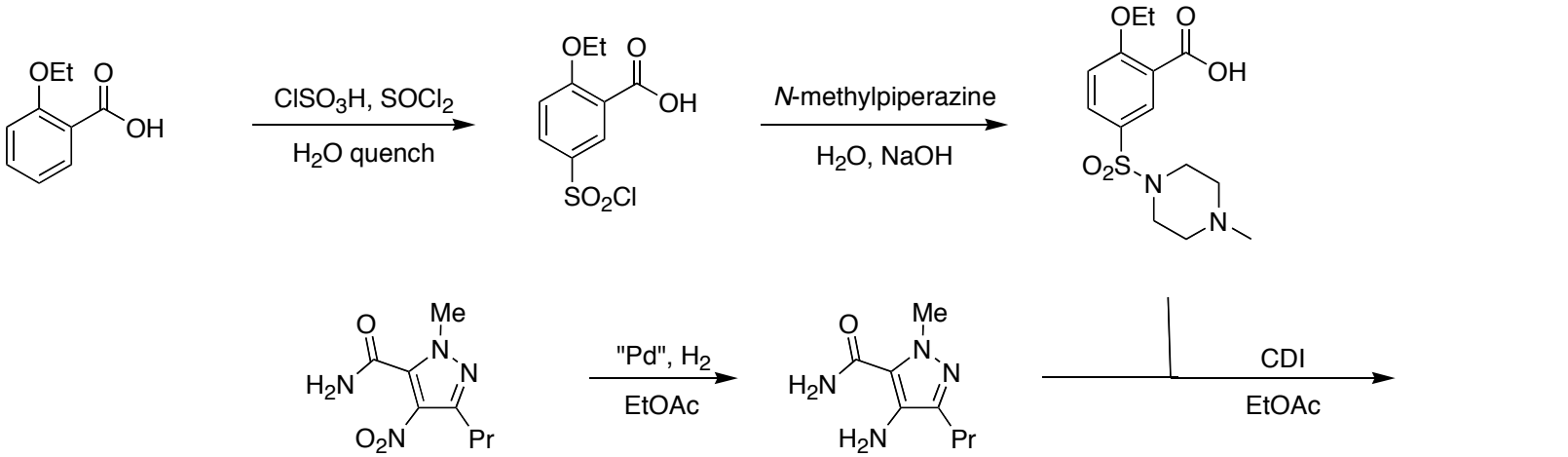
7.5 % over nine linear steps (75 % avg/step)

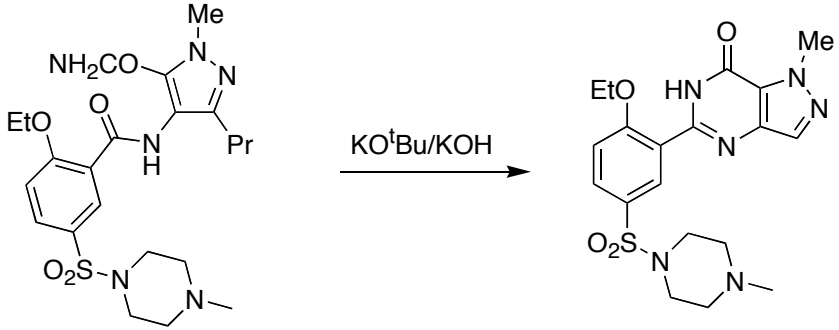
Unsuitable for commercial development

a. Linear
b. Multiple recrystallizations of final product
c. Chlorosulphonation on scale is difficult (quench)

Dale, D. J., Dunn, P. J., Gloightly, C., Hughes, M. L., Levett, P. C., Pearce, A. K., Searle, P. M., Ward., G., Wood, A. S. *Org. Proc. Res. Dev.,* **2000**, *4*, 17-22.

Application to a Blockbuster Drug: Commercial Route





Slidenafil (Viagra)

Yield is vastly improved (75 %)

Synthesis is convergent

Waste is minimized

Dale, D. J., Dunn, P. J., Gloightly, C., Hughes, M. L., Levett, P. C., Pearce, A. K., Searle, P. M., Ward., G., Wood, A. S. *Org. Proc. Res. Dev.,* **2000**, *4*, 17-22.

Application to Commercial Drug: Safety Issues

- Nitropyrazole decarboxylates at 100 °C under reaction conditions
- Mixing of H_2SO_4 and HNO_3 generates 249 kJ/mol (59.5 kcal/mol)
  - Reaction starts at 50 °C and could easily reach 127 °C
- Procedure modified to minimize heat release
  - SM dissolved in H_2SO_4
  - HNO_3 and H_2SO_4 separately mixed
  - SM and 1/3 of nitrating mixture mixed
  - HPLC analysis was performed and another 1/3 added, etc.
- Process is safe and robust, but time consuming and labor intensive

Dale, D. J., Dunn, P. J., Gloightly, C., Hughes, M. L., Levett, P. C., Pearce, A. K., Searle, P. M., Ward., G., Wood, A. S. *Org. Proc. Res. Dev.,* **2000**, *4*, 17-22.

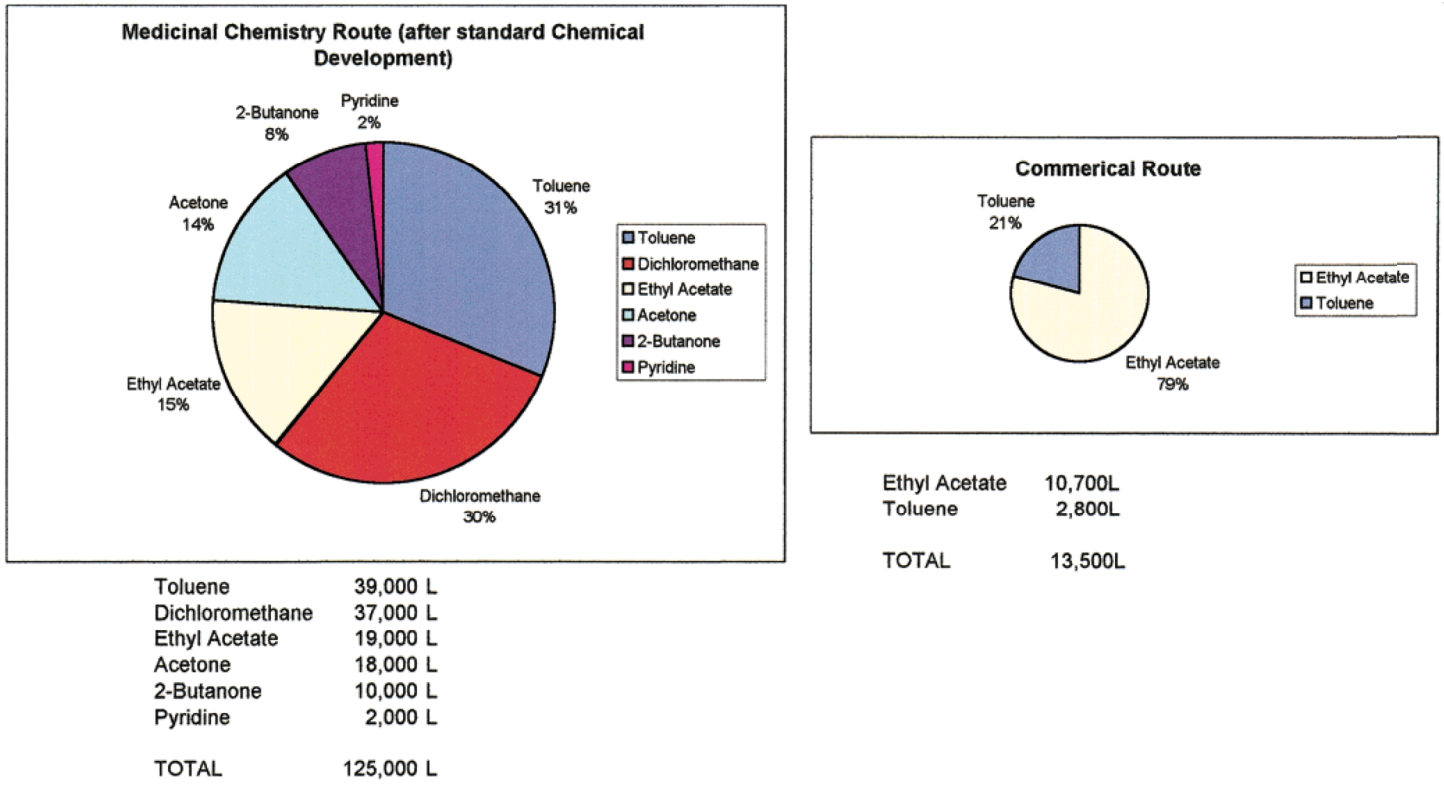
Application to Commercial Drug: An Advertisement

- Interested in proving concept
- Reaction was run at 90 °C – the "ideal" reaction temperature
- Residence time of 35 min
- 5.5 g/h (132 g/day), 46 g/L, 73 % yield
  Commercial scale, 1.93 kg/10h, 2400 g/L
- Direct scale up of medicinal chemistry route (75 %) yield
- *Further optimization of concentration, time and temperature should quickly raise yield.*

Panke, G., Schwalbe, T..; Stirner, W., Taghavi-Moghadam, S., Wille, G. *Synthesis*, **2003**, 2827.

µReactors: Not A Replacement for Process Chemists

Comparison of Organic Waste from Medicinal chemistry and commercial routes

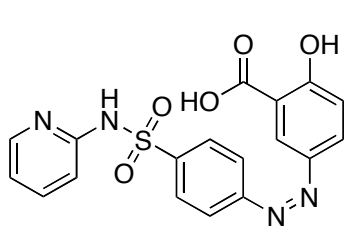


Toluene	39,000 L
Dichloromethane	37,000 L
Ethyl Acetate	19,000 L
Acetone	18,000 L
2-Butanone	10,000 L
Pyridine	2,000 L
TOTAL	125,000 L

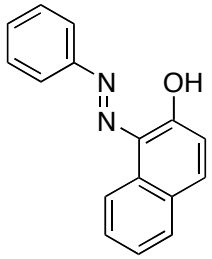
Ethyl Acetate	10,700L
Toluene	2,800L
TOTAL	13,500L

Figure 4. **Comparison of organic waste from medicinal chemistry and commercial routes. The cyclisation solvent, *tert*-butyl alcohol, ends up in the aqueous waste (for treatment) in both medicinal chemistry and commercial routes.**

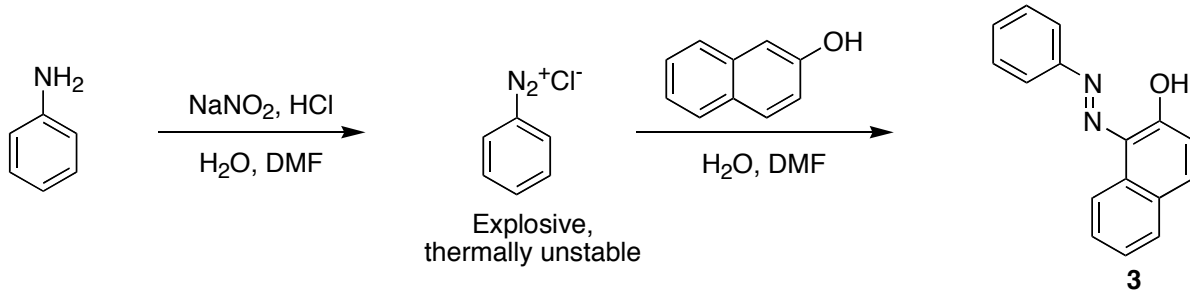
μReactors in series for Hazardous Materials



2



3



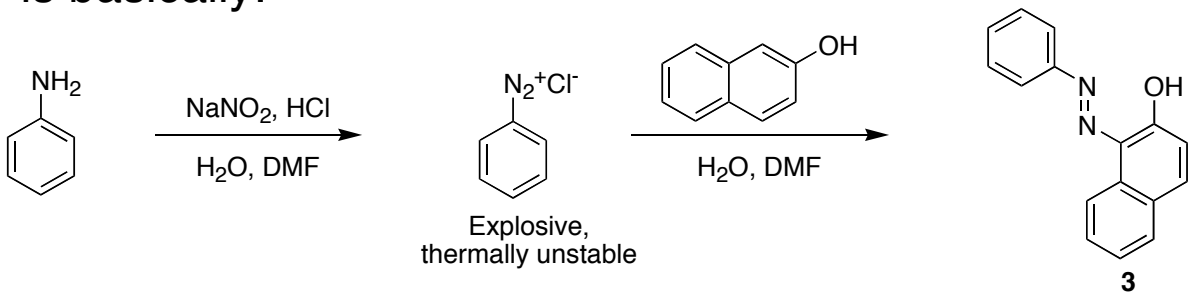
3

- On academic scale reaction proceeded to 52 % conversion

Wooten, R. C. R., Fortt, R., de Mello, A. J. *Lab Chip*, **2002**, *2*, 5.

Azo Coupling on Large Scale

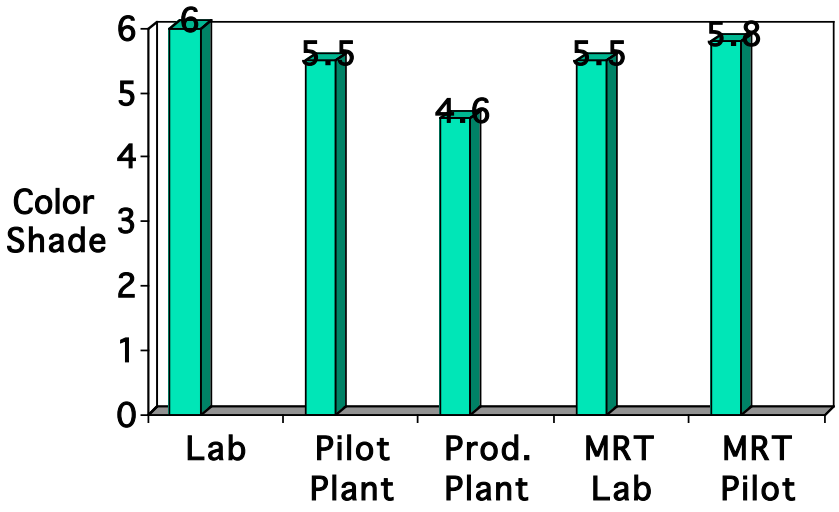
- Application of CPC reactors to dye formation extensively studies by Clariant: Pigments and Additives Division.
- No dye given, no yields
- Explored differences between traditional batch processing for one red and one yellow dye
- Chemistry is basically:

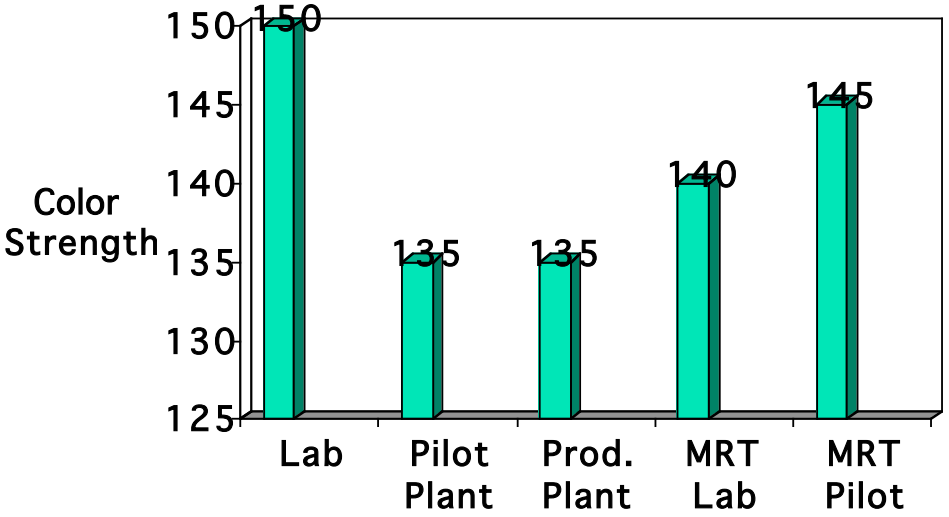


Wille, Ch., Gabski, H.-P., Haller, Th., Kim, H., Unverdorben, R. W., *Chem. Eng. Jour.*, **2004**, *101*, 179.

Results of Study

- Output
  - 80 kg per batch operation and hour
  - 1 kg/h for μReactor
  - Both reproducible to ±3%
- Quality





Wille, Ch., Gabski, H.-P., Haller, Th., Kim, H., Unverdorben, R. W., *Chem. Eng. Jour.*, **2004**, *101*, 179.

μReactor Reproducibility

- Quality improves because of better dosing at strong flow rates
- Particle size and distribution stayed consistent
- Process transfer from lab to plant took 1 week, 2-3 for batch

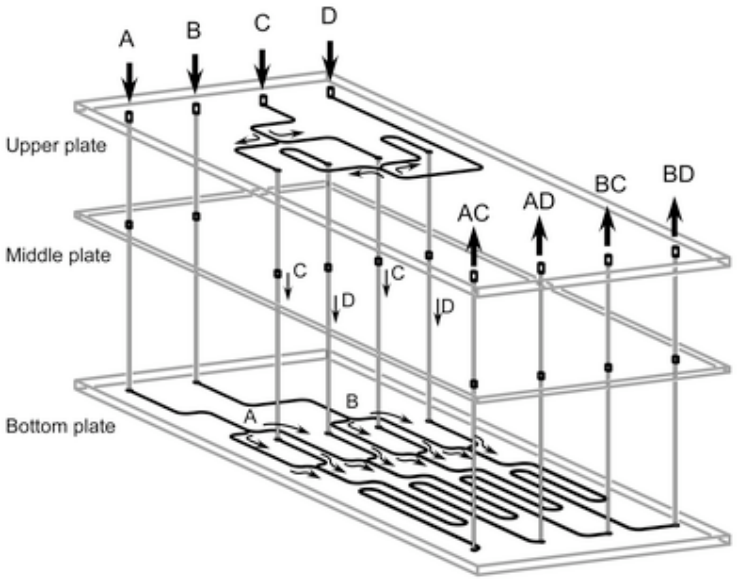
Property	MRT-lab	MRT-pilot
Color dC	1.58	1.52
Color strength (%)	111	118
Color shade dH	0.40	0.38
Color lightness dL	0.42	0.4

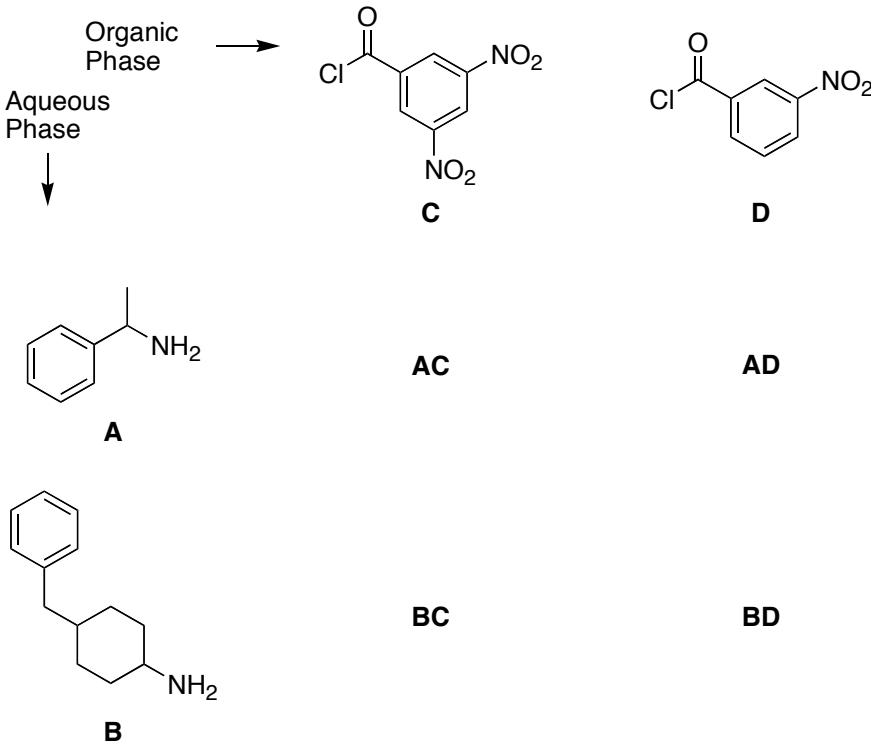
- Only example I could find of a published scale-up
- Pilot plant has been ordered from CPC

Wille, Ch., Gabski, H.-P., Haller, Th., Kim, H., Unverdorben, R. W., *Chem. Eng. Jour.*, **2004**, *101*, 179. Schwakbe, T., Autze, V., Hohmann, M., Stirner, W. *Org. Proc. Res. Dev.* **2004**, *8*, 440.

Combinatorial Chemistry on Chips

- Method A: Parallel Synthesis
  - Complicated chip patterns
  - Multiple pumps and outlets
  - Efficacy demonstrated

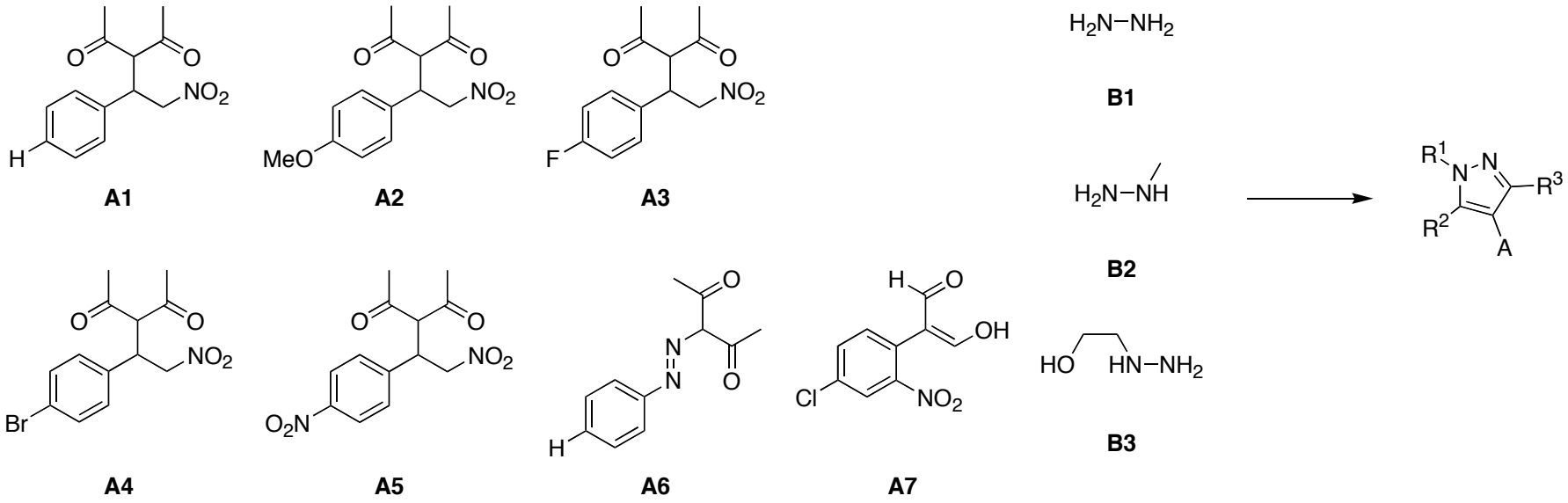




Kikutani, Y., Horiuchi, T., Uchiyama, K., Hisamoto, H, Tokeshi, M., Kitamori, T. *Lab Chip*, **2002**, *2*, 188.

Combinatorial Chemistry on Chips

- "Slug" Injection
  - Less Hardware and complicated chip design needed
  - Possibility of direct analysis of product either with μTAS or conventional methods
  - Amounts obtained are relatively small



Garcia-Edigo, E., Spikmans, V., Wong, S. Y. F., Warrington, B. H. *Lab Chip*, **2003**, *3*, 73-76

Limitations of System

- Will the process be cGMP compliant??
- May not be (is not?) suitable for all reactions.
- NO SOLIDS
- Lack of knowledge about the “art” may hinder and slow usage
- Quality of the commercially available systems has to be improved

Anderson, N., G., *Org. Proc. Res. Dev.,* **2001,** *5,* 613. Wille, Ch., Gabski, H.-P., Haller, Th., Kim, H., Unverdorben, L., Winter, R. *Chem. Eng. Jour.* **2004**, *101*, 179.

Conclusions

- Intriguing way of performing reactions
- Definite possibility for commercial use
- Most likely a medicinal chemist will never see one in his or her lab
- Could be useful first in small scale, on site, manufacture of toxic chemicals in bulk
- Someone needs to use it first:
  - "Nobody wants to take the lead on his own; thus, the situation can be described as wait and see."
  - "Finally, all this information must be used to build plants with μflow devices and to profit from the new technology. Otherwise the technology will stay at a level of an 'innovation,' 'plaything' or whatever."

Quotes from IMM in Penneman, H., Watts, P., Haswell, S. J., Hessle, V., Lowe, H. *Org. Proc. Res. Dev.,* **2004**, *8*, 422

Impact of Chemical Weapon Proliferation

- Small, easily hidden
- Problems of “good” toxic chemicals same as “bad” toxic chemicals
- Microreactors will likely be easily manufactured in the near future
- Could possibly be used for reliable “onsite” generation

Lowe, H., Hessel, V., Mueller, A. *Pure Appl. Chem.* **2002**, *74*, 2271

- Much the same could be said of “batch” chemistry and existing technology
- Should be aware of the problem, but not overly concerned.