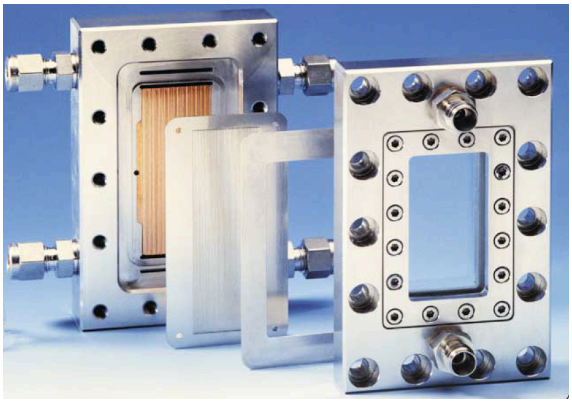
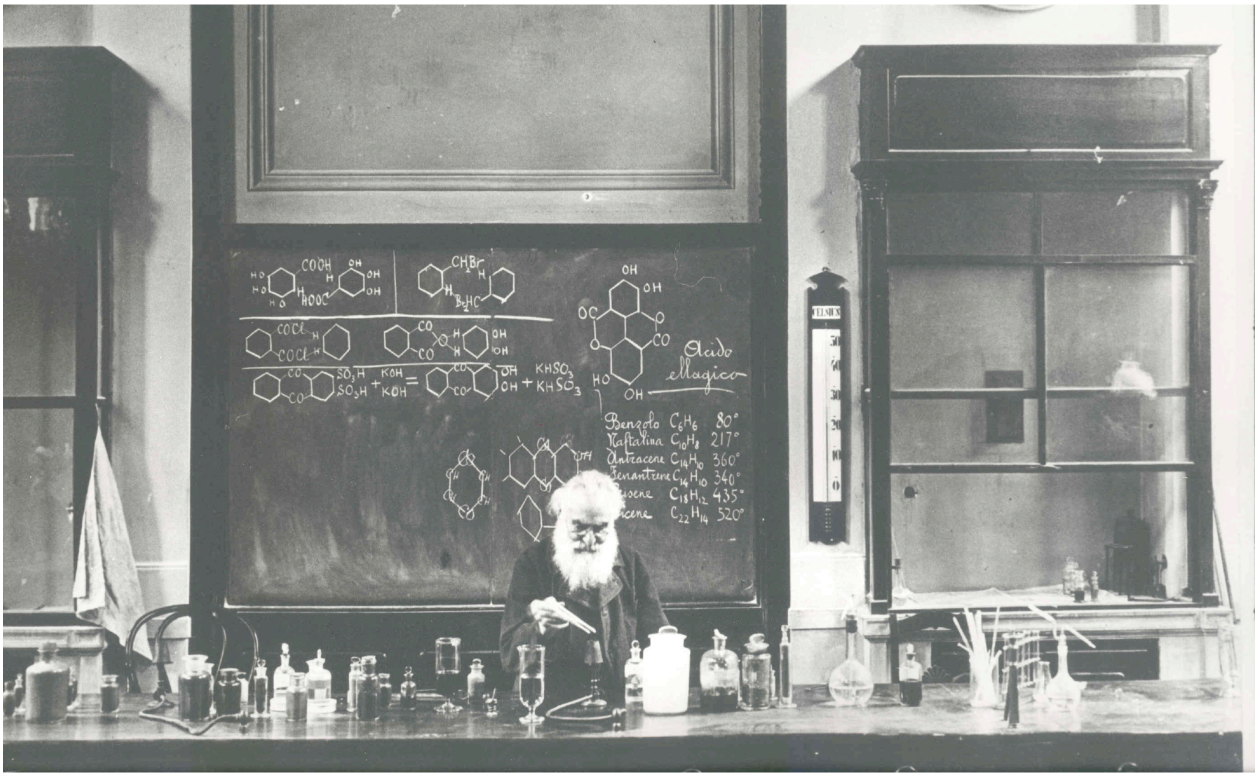
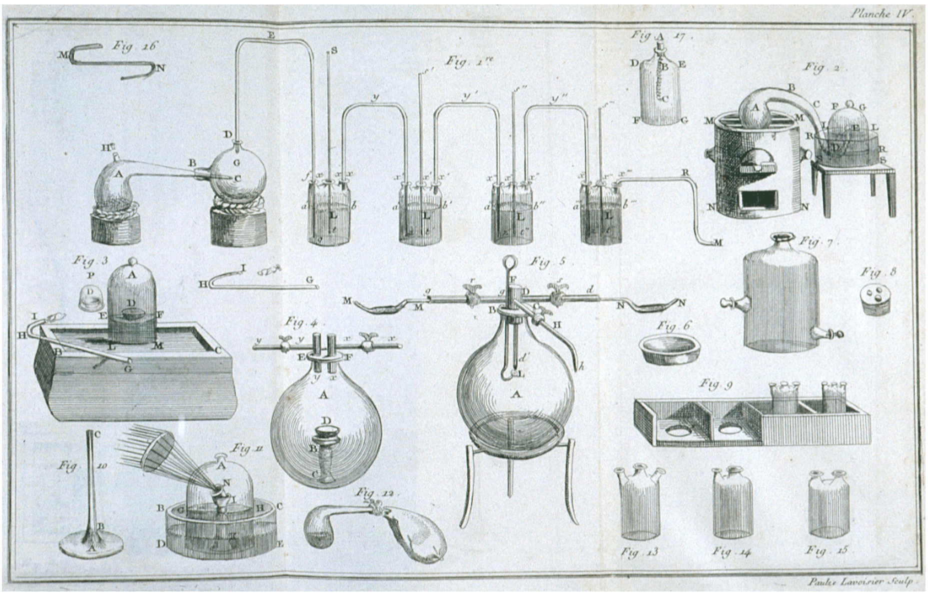
Microreactors in Chemistry

Christina Moberg

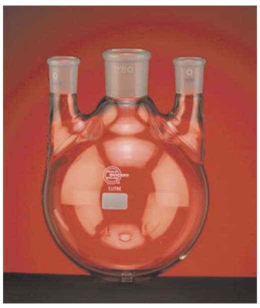


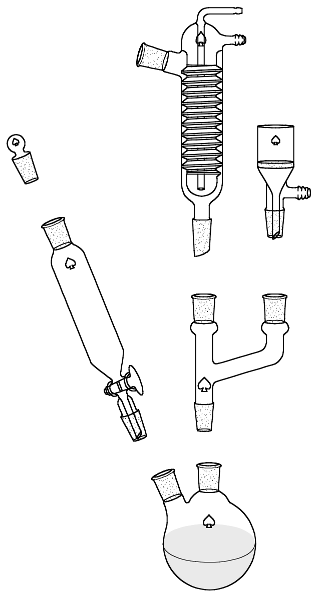


19th century equipment for synthesis

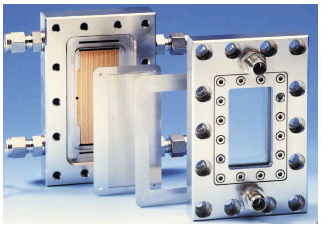


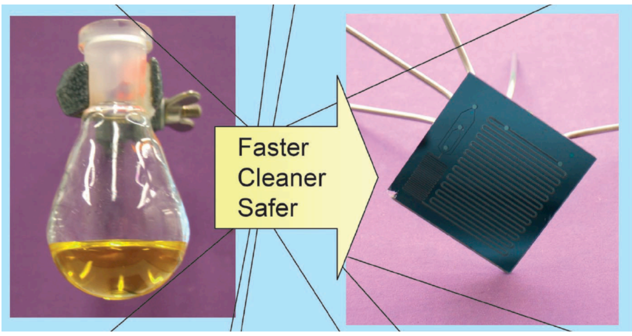
20th centrury equipment for synthesis





Today: high throughput and downsizing





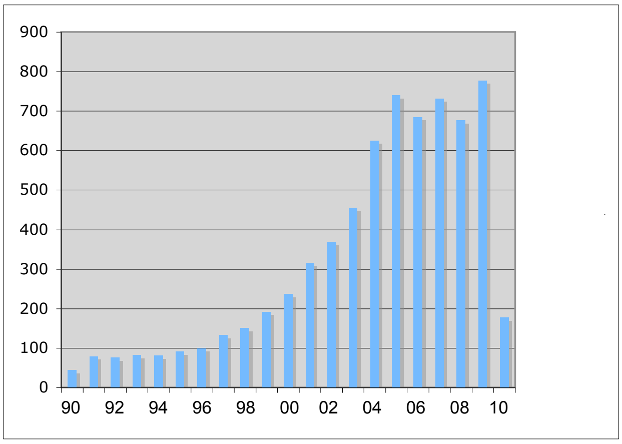
Karolin Geyer, Jeroen D. C. Codée, and Peter H. Seeberger*

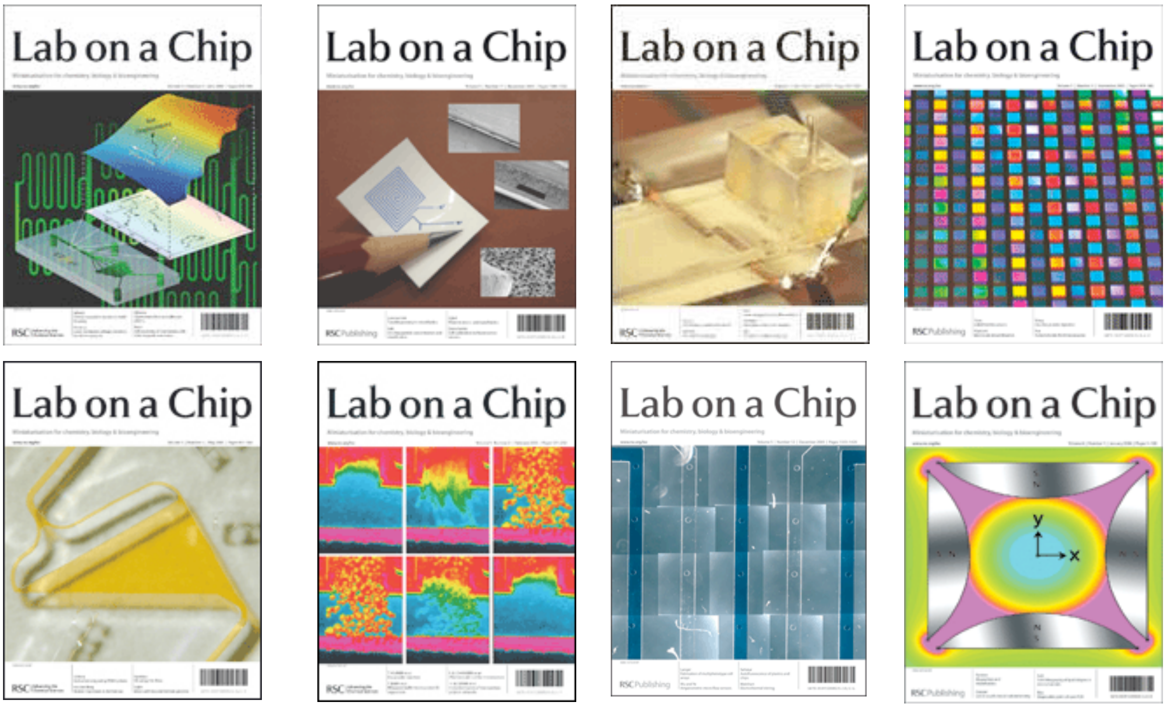
Chem. Eur. J. **2006**, *12*, 8434–8442

Microreactors

- *Threedimensional structures with inner dimensions under 1 mm*
- *High surface-to-volume area: 10 000-50 000 m^2m^{-3} (compared to about 100 m^2m^{-3} for a traditional reactor)*
- *Efficient heat transfer - suitable for exothermic and endothermic reactions*
- *Temperature induced side reactions suppressed*
- *Higher safety (toxic compounds, high temperatures/pressures, explosions)*

Number of publications 1990-2010





Reviews

T. Fukuyama, M. T. Rahman, M. Sato, I. Ruy, "*Adventures in Inner Space: Microflow Systems for Practical Organic Synthesis", Synlett,* **2008**, 151-163.

B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, "*Greener Approaches to Organic Synthesis Using Microreactor Technology", Chem. Rev*. **2007**, *107*, 2300-2318.

B. Ahmed-Omer, J. C. Brandt, T. Wirth, "*Advanced organic synthesis using microreactor technology", Org. Biomol. Chem*. **2007**, *5*, 733-740.

P. Watts, C. Wiles, "Micro reactors, a new tool for the synthetic chemist, *Org. Biomol. Chem*. **2007**, *5*, 727-732.

C. Wiles, P. Watts, *"Continous Flow Reactors, a Tool for the Modern Synthetic Chemist", Eur. J. Chem.* **2007***,*

P. Watts, C. Wiles, *"Recent advances in synthetic micro reactions technology", Chem.Commun.* **2007***,* 443-467.

K. Geyer, J. D. C. Codée, P. H. Seeberger*, "Microreactors as Tools for Synthetic Chemists - The Chemists' Round-Bottomed Flask of the 21st Century?, Chem. Eur. J.* **2006**, *12,* 8434-8442*.*

M. Brivio, W. Verboom, D. N. Reinhoudt, *"Minituarized continous flow reaction vessels: Influence on chemical reactions", Lab Chip* **2006**, *6,* 329-344.

P. Watts, S. J. Haswell, *"The application of micro reactors for organic synthesis", Chem. Soc. Rev.* **2005**, *34,* 235-246.

K. Jänisch, V. Hessel, H. Löwe, M. Baerns, *"Chemistry in Microstructured Reactors", Angew. Chem. Int. Ed.* **2004**, *43,* 406-446.

B. H. Weigl, R. L. Bardell, C. R. Cabrera, *"Lab-on-a-chip for drug development", Adv. Drug Deliv. Rev.* **2003**, *55,* 349-377.

P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong, X. Zhang, *"Micro reactors: principles and applications in organic synthesis", Tetrahedron* **2002***, 58,* 4735-4757.

Downsizing

- *Production of chemical compounds*
- *Synthesis of new compounds to be evaluated for specific applications*
- *Optimization of reactions*
- *Biotechnology (e g DNA sequencing)*

SIGMA-ALDRICH®

When can MRT be useful?

- Improved mixing & heat transfer compared to batch process
    - Improved Yields
    - Improved product profiles, higher purity
    - Topmost reproducibility
- Safe & reliable handling of highly exothermic or hazardous reactions.
- Easy scale-up from mg to kg scale
- Easier handling of instable products & intermediates
- Minimise time frame for process development

Scaling up vs Numbering up

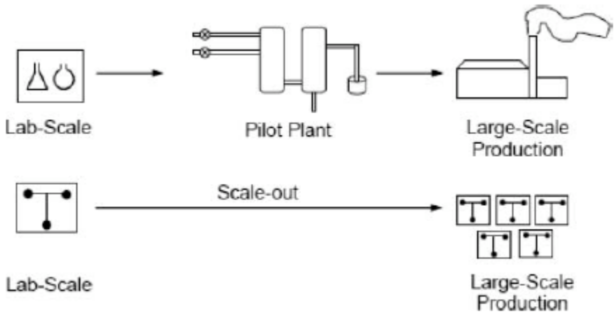


Fig. 1 Schematic comparing the traditional and continuous flow approaches to large-scale production.

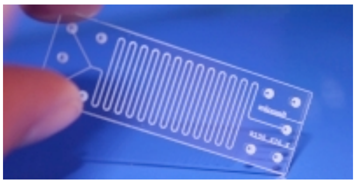
P. Watts, C. Wiles, "Micro reactors, a new tool for the synthetic chemist, *Org. Biomol. Chem*. **2007**, *5*, 727-732.

SYNTHACON

Capacity: 25-30 tons/year

SIGMA-ALDRICH®

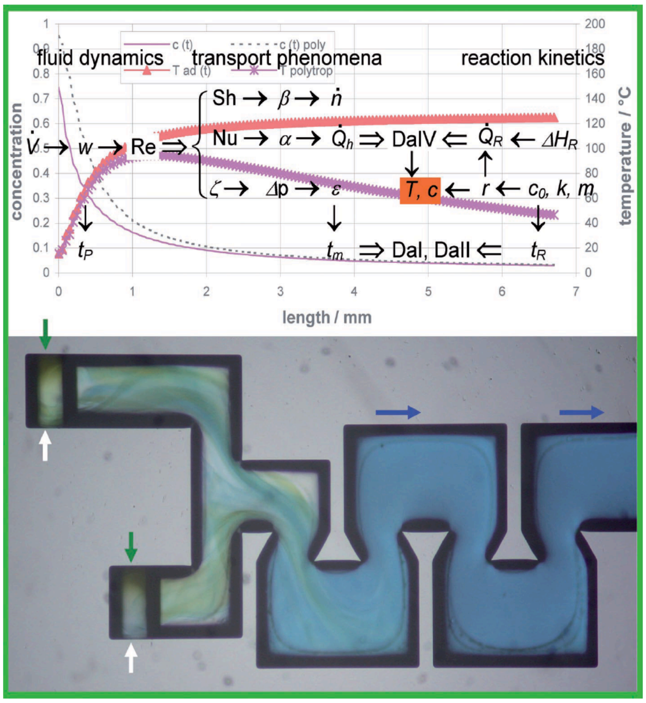
Commercial microreactors



Made of
silicon, quartz, metal,
polymer, ceramics, glass

Enabling Continuous-Flow Chemistry in Microstructured Devices for Pharmaceutical and Fine-Chemical Production

Norbert Kockmann,*[a] Michael Gottsponer,[a] Bertin Zimmermann,[a] and Dominique M. Roberge[b]



7470 InterScience © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim Chem. Eur. J. 2008, 14, 7470–7477

Fig. 1. A glacier illustrates laminar flow. No mixing occurs between the two side-by-side streams of ice.

B. H. Weigl, R. L. Bardell, C. R. Cabrera, *"Lab-on-a-chip for drug development"*, *Adv. Drug Deliv. Rev.* **2003**, *55,* 349-377.

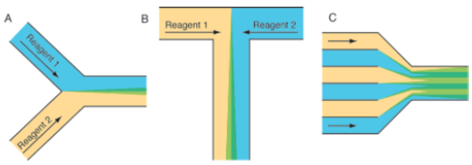


Figure 2. Various channel geometries: (A) Y-junction, (B) T-junction, and (C) interdigitated multilamellar mixer.

Efficient mixing

B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, "*Greener Approaches to Organic Synthesis Using Microreactor Technology", Chem. Rev.* **2007**, *107*, 2300-2318

Control of fluids

Hydrodynamic flow

(pressure-driven flow)

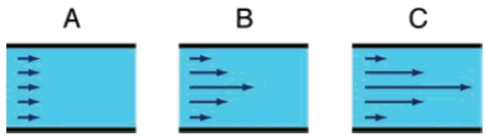


Figure 5. Parabolic flow profile of hydrodynamic flow. (A) At the beginning of the channel, the velocity vectors are equal across the channel, but further down the channel (B, C), fluid flows faster in the center of the channel than near the sides.

Electrokinetic flow

(electroosmotic flow)

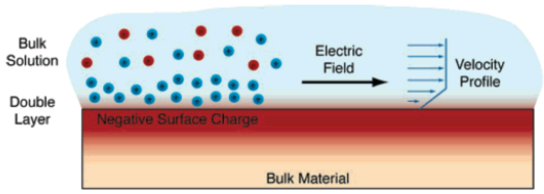
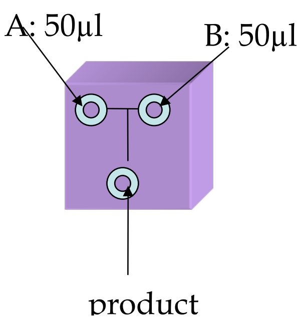
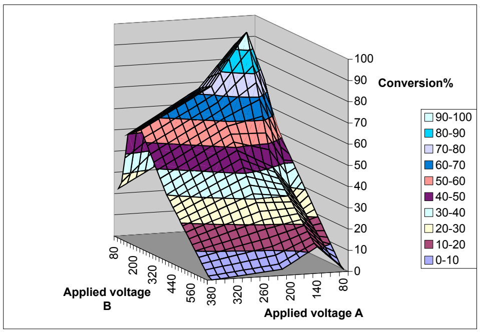
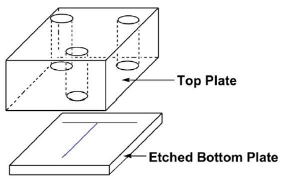


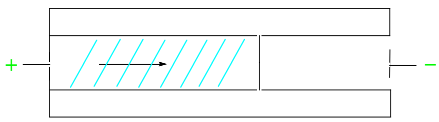
Figure 6. Principles of electroosmotic flow. At appropriate pH, a negative surface charge is present on the microreactor walls, which attracts positive ions from solution and forms an electrical double layer. When an electric field is applied along a microreactor's channel, the mobile cations move toward the negative electrode, dragging along the rest of the solution. The flow velocity profile is nearly flat across the channel except for a thin (few nanometer) diffusive layer immediately adjacent to the channel wall.

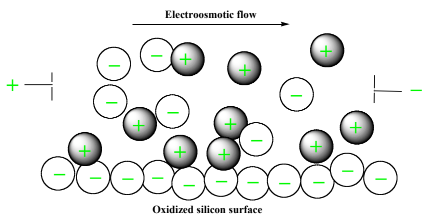
B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade,
"*Greener Approaches to Organic Synthesis Using Microreactor Technology", Chem. Rev.* **2007**, *107*, 2300-2318.

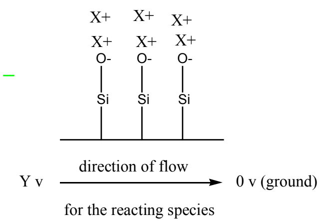












S Haswell, Hull

Synthesis of new compounds

There are about 10^{60} stable compounds with mw ≤ 500 (a size of molecules suitable for pharmaceuticals).

Around 2-3x10^{6} compounds are known today.

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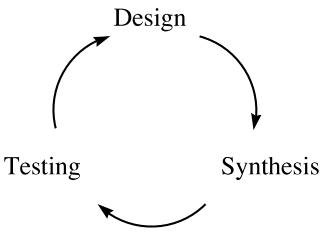
New compounds are needed for applications in

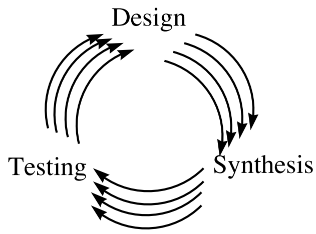
- *Life sciences* — *There is a need for synthesis of new small organic molecules needed for test against targets*
- *Material sciences*

Downsizing why?

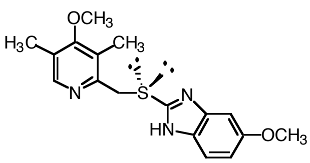
- *Availibility of material: 10^{63} stable compounds with up to 30 atoms of the elements C, O, N and S. If 1 mg of each is synthesized, the total mass of the products is 10^{60} g, to be compared to the mass of the universe, 10^{63} g.*
- *Safety*
- *Environmental aspects*
- *Economy*

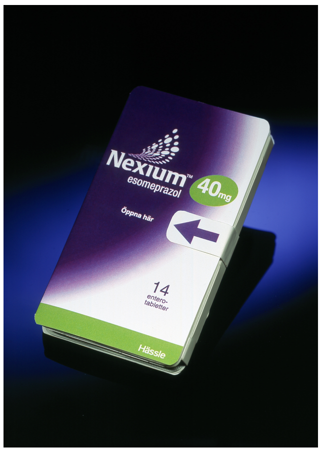
High throughput strategies to identify effective organometallic chiral catalysts

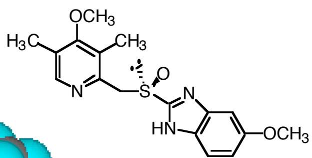


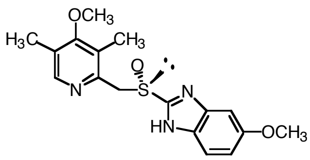


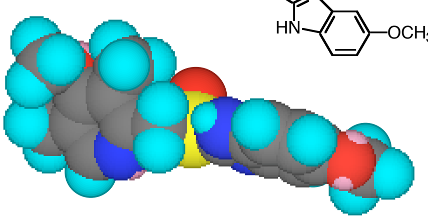
Rational design and high throughput evaluation

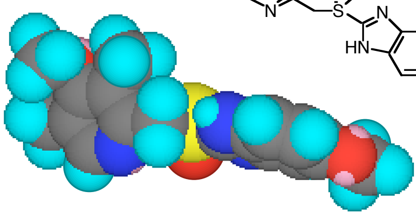












Optimization of reactions

Reaction conditions:
- *solvent*
- *temperature*
- *stoichiometry*

Catalyst structure:
- *ligand*
- *metal ion*
- *activator*

Variation of substrate - scope and limitations

Importance of temperature control for chemical selectivity

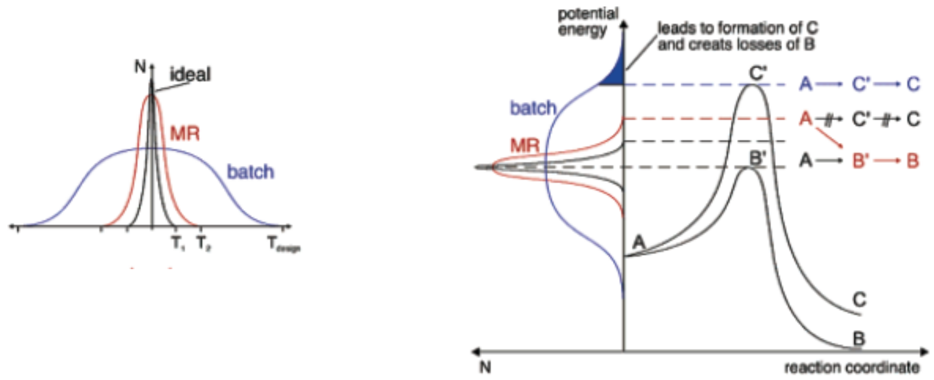
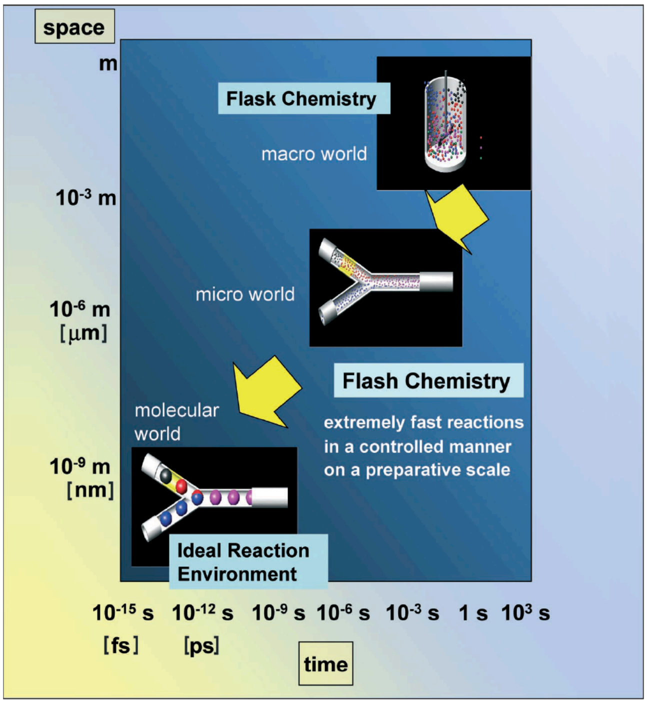


Figure 7. (left) Comparison between ideal temperature distributions for a hypothetical reaction (black) and actual temperature distributions in a batch reactor (blue) and a microreactor (red). (right) Schematic comparison of these temperature distributions to two product-forming pathways. The batch reactor's broad temperature distribution allows the production of the undesired product C, but the narrow temperature distribution in the microreactor restricts the reaction to the target product B. Reprinted with permission from ref 91. Copyright 2004 American Chemical Society.

B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300-2318.

Flash Chemistry: Fast Chemical Synthesis by Using Microreactors

Jun-ichi Yoshida, Aiichiro Nagaki, and Takeshi Yamada[a]



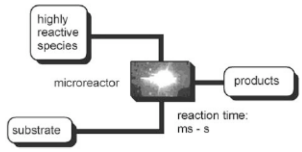


Figure 1. General concept of flash chemistry using a microreactor.

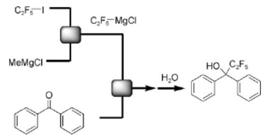


Figure 5. Grignard exchange reaction of C_2F_5I with MeMgCl followed by reaction with benzophenone in a microreactor system.

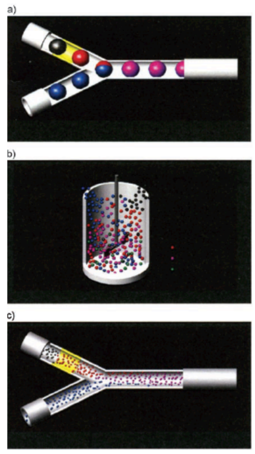


Figure 3. Reactors for chemical reactions: a) ideal reactor in molecular size, b) conventional macrobatch reactor, c) microreactor.

Reactive intermediates:

lifetime shorter than generation time

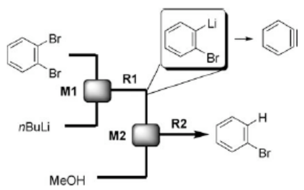


Figure 7. Microreactor system for the Br-Li exchange reaction of *o*-dibromobenzene. **M1**, **M2**: micromixers. **R1**, **R2**: microtube reactors.

Twostep/multistep reactions

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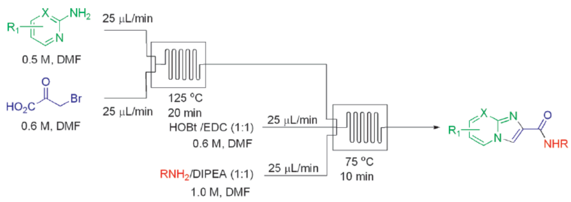
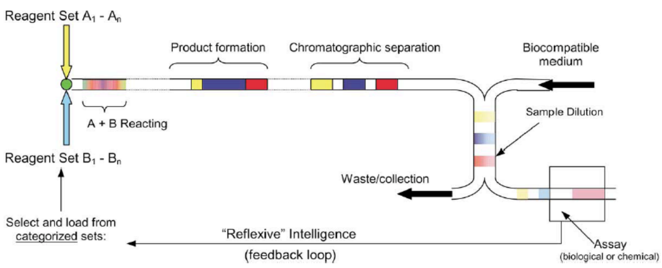
Fully Automated Continuous Flow Synthesis of Highly Functionalized Imidazo[1,2-a] Heterocycles

Ananda Herath, Russell Dahl, and Nicholas D. P. Cosford*

Program in Apoptosis and Cell Death Research and Conrad Prebys Center for Chemical Genomics, Burnham Institute for Medical Research, 10901 North Torrey Pines Road, La Jolla, California 92037

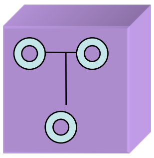


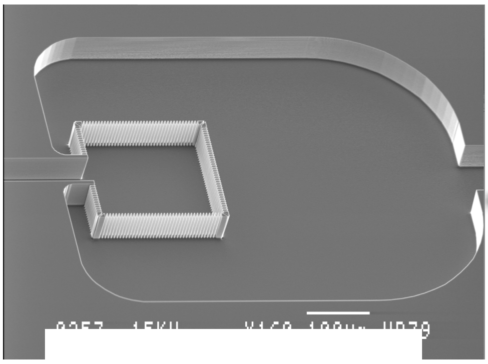
Synthesis - purification, separation



Integration of a micro reactor with a biological assay system.

Synthesis - analysis





High throughput strategies to analyze yield and selectivity in catalytic reactions

Enantioselective Catalysis and Analysis on a Chip**

Detlev Belder, Martin Ludwig, Li-Wen Wang, and Manfred T. Reetz**

Angew. Chem. Int. Ed. **2006**, *45*, 2463–2466

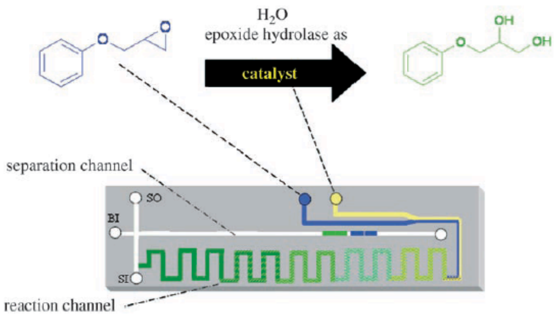


Figure 1. Schematic drawing of the working principle of the integrated catalysis/analysis chip. SO: sample outlet, SI: alternative sample inlet, BI: buffer outlet.