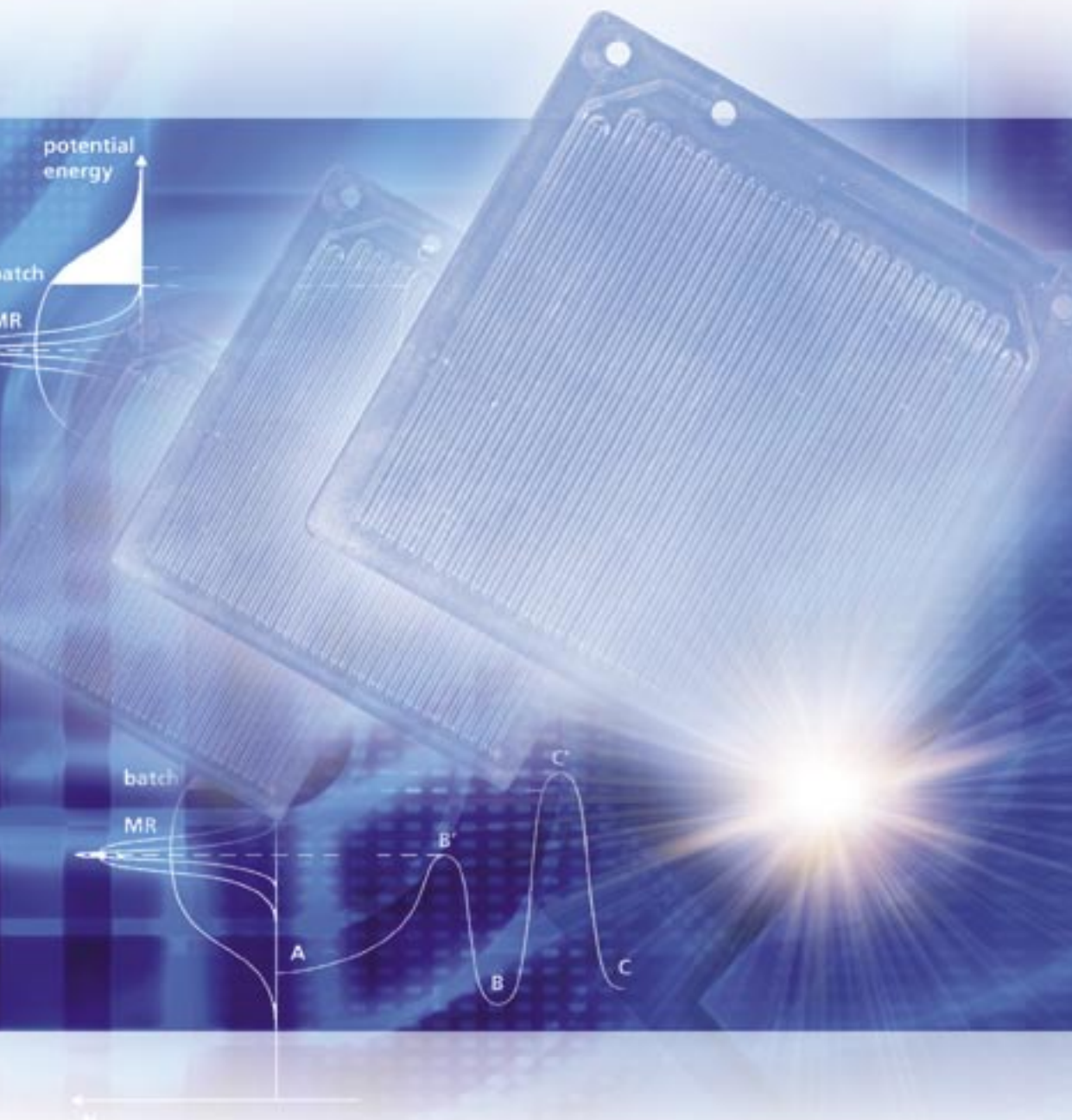


Enabling Technologies

Microreactor Technology



Advantages of Microreactor Technology

Diazomethane Chemistry

Epoxidation

Lithiation

Optimizing the BOC — protection of diamines

Custom Syntheses in the Microreactor

SAFC Pharma Special: Simulated Moving Bed (SMB) Technology

Preface

Microreactor Technology — The Chemist's Round Bottom Flasks of the 21st Century



*Prof. Dr. Peter H. Seeberger
Swiss Federal Institute
of Technology (ETH)
Zurich, Switzerland*

Synthetic chemists rely on an innumerable variety of organic reactions to construct a diverse range of molecular targets. Many organic transformations depend on multiple factors that determine the outcome of the reaction. Much of the effort spent by organic chemists is consumed searching for optimal reaction conditions to achieve a particular transformation. Method optimization frequently requires the commitment of time and large quantities of valuable starting materials. The ability to find ideal reaction conditions quickly and efficiently would have a major impact on the practice and pace of research and development in organic chemistry.

Once these optimal reaction conditions have been found, another challenge presents itself. Sufficient amounts of compound have to be prepared as intermediates for further transformations, as active pharmaceutical compounds or for use by chemical, fragrance, flavor, polymer, and materials manufacturers. Particularly, the highly complex molecules used by chemists working for pharmaceutical companies often require a complete redesign of the synthesis to allow for scale-up.

Microfluidic-based devices are capable of performing a wide range of single and multi-phase organic reactions. In addition to requiring small quantities of reagent, sub-millimeter reaction channels allow for the precise control of reaction variables, such as reagent mixing, flow rates, reaction time, and heat

and mass transfer. Microfluidic devices are also amenable to integrated reaction monitoring using UV/VIS, IR, NMR, Mass Spectrometry (MS), and LC/MS. Unlike conventional bench-top batch reactions, microreactors are easily scalable, rendering a device capable of both analytical and semi-preparative scales of production. Finally, the microreactor format is amenable to automation of reaction optimization.

Microreactors made from a series of different materials have been described: stainless steel, etched silicon, glass, and others. Each material has advantages and disadvantages, but inexpensive reactors created from etched silicon hold the potential to become the chemists round bottom flasks of the future as they are inert to almost all reagents, stable under a wide range of temperatures and pressures, and can be customized to every specific task at hand. It has been already demonstrated that such microreactors can be loaded with catalysts to carry out heterogenous reactions. In the near future, preloaded microreactors ready to conduct a specific transformation will become available.

In addition to reaction optimization and ready reaction scale-up, microreactors present the opportunity to synthesize libraries of compounds in a serial rather than a parallel fashion. Separation of different reactions in a single reactor is accomplished by addition of immiscible solvents. Thus, microreactors hold the potential to be used at all stages of chemical product development.

Currently, efforts to extend past simple model reactions to the synthesis of complex molecules of interest to the practitioners of organic synthesis are underway. Soon we will see fully integrated microchemical systems for reaction optimization that include the capability to work up reactions and to carry out multi-step transformations in series. Initially, few specialists will be drawn to the new technology, but with the commercial availability of the devices and reactors such systems will eventually be available in all laboratories, in academia and industry, and will revolutionize how we chemists will ply our trade.

Trademark Index

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Introduction

Microreactor Technology — The Revolution in the Lab



Fabian Wahl
Manager of R&D
Sigma-Aldrich
fwahl@sial.com

Micro- and nanotechnology are currently areas of rapid growth with a huge field of applications. In the last decade, Microreactor Technology (MRT) as a new concept in chemical engineering has demonstrated the advantages of microstructured devices for chemical reactions impressively.^{1,2}

Even if the two graphs in **Figure 1** appear to be similar, a closer view of the x-axis shows the difference: We are leaving time resolved chemical processes! On a microstructured surface, the process is space resolved!

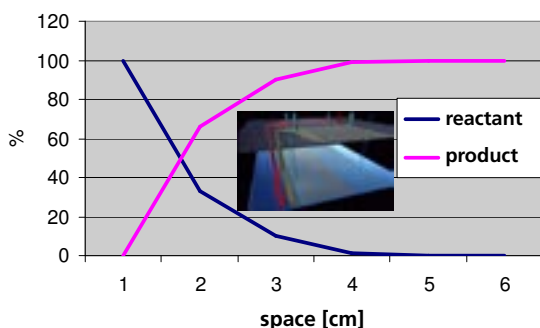
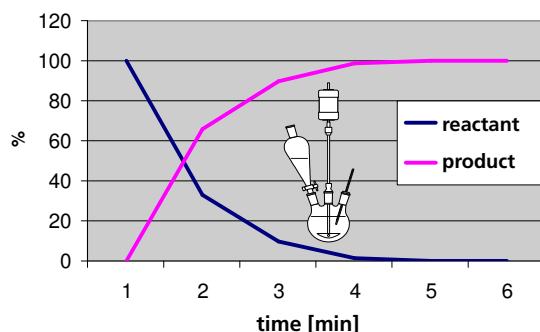


Figure 1: Chemical processes in round-bottom flasks and microreactors.

The intrinsic advantage of the small dimensions is the unprecedented control of the reaction parameters through:

Improved surface-area-to-volume ratio

On a typical microreactor surface, this ratio is about $200 \text{ cm}^2 \text{ cm}^{-3}$, compared with $1 \text{ cm}^2 \text{ cm}^{-3}$ for a 100 mL glass flask and $0.06 \text{ cm}^2 \text{ cm}^{-3}$ for a 1 m^3 batch reactor.

This advantage of microreactor systems in regard to temperature control (**Figure 2**) and progression of concentrations (**Figure 3** next page) is demonstrated by comparing a simulated neutralization reaction (HCl and NaOH)³ in a 5 m^3 vessel (stirring 500 rpm) versus in a microstructured surface.

This high heat exchanging efficiency permits highly exothermic reactions to be performed under isothermal conditions. The development of hot spots and the accumulation of reaction heat within the microreactor are suppressed so that undesirable side reactions and fragmentation are hindered.

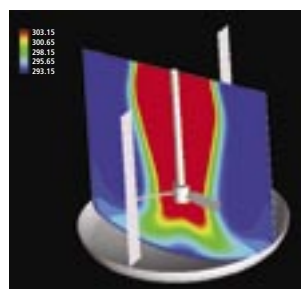


Figure 2 (a): Batch Synthesis: Levels of temperature ranging from 293.15 K (blue) to 303.15 K (red) according to the color scale top left.

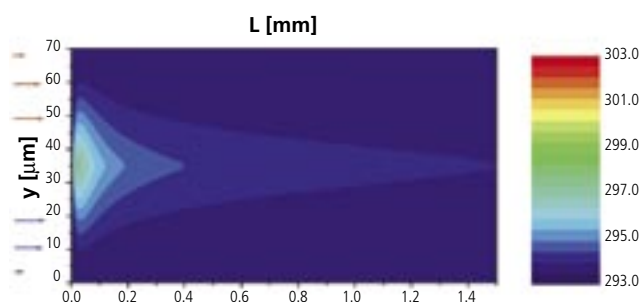


Figure 2 (b): Microreactor Technology: HCl (red arrows on the left); NaOH (blue arrows on the left). Local temperatures are given according to the scale (right) in K (y represents the cell thickness; L represents the channel length).



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Introduction (Continued)

Efficient mixing

In addition to the above mentioned heat transfer, mass transport is also considerably improved in microreactors. Mixing in microreactors can occur through diffusion between laminar flow layers. This is visualized in **Figure 3** for the same neutralization reaction as in **Figure 2**.

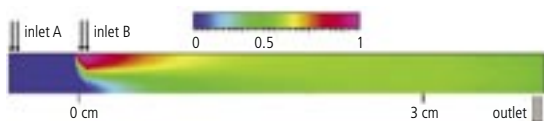
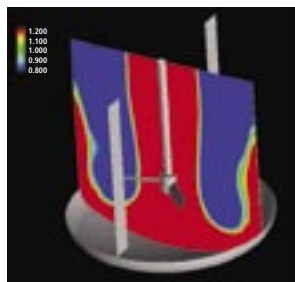


Figure 3 (a): Batch Synthesis: Concentration equivalents (ranging from 0.8 (blue) to 1.2 (red) according to the color scale top left).

Figure 3 (b): Microreactor Technology: Compound B is injected (inlet) to a flow of compound A (blue). The green color indicates the 1:1 mixture.

Small reaction volumes

Process parameters such as pressure, temperature, residence time, and flow rate are more easily controlled in reactions that take place in small volumes. The hazard potential of strongly exothermic or explosive reactions can also be drastically reduced.^{4,5} Higher safety can also be achieved with toxic substances or higher operating pressures. All of these advantages can be used most favorably in kinetically controlled reactions.

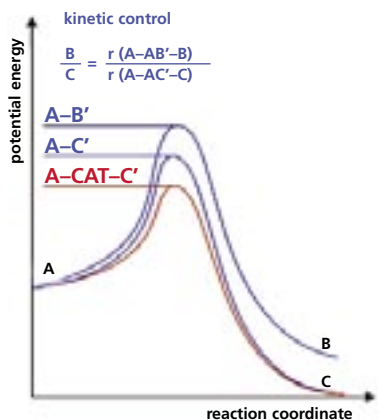


Figure 4: Chemical process diagram.

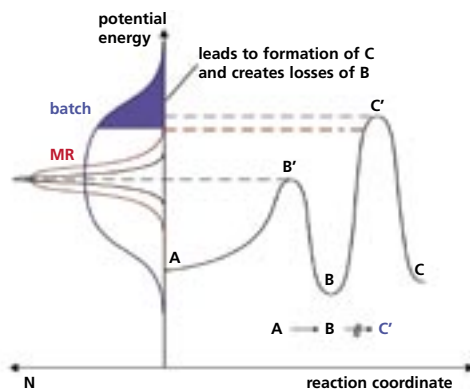


Figure 5: Chemical processes in round-bottom flasks and microreactors.

Figure 4 shows the classical textbook graph. This diagram meets the most common thinking of organic chemists when discussing product distributions. In this example, product C is favored if the activation energy provided to the reaction is limited. **Figure 5** demonstrates the importance of temperature control for selective, kinetically controlled transformations.

Due to all of these advantages described above, Microreactor Technology is a perfect tool for fast process engineering to acquire information, which allows a safe and fast transfer to pilot or production scale.

But, the “big picture” of this fascinating technology is a new thinking for production concepts, which supersedes this transfer. MRT means continuous processing (24 hours per day, 7 days a week). Depending on the demand, microreactors as modular subunits could be running in parallel (“numbering-up” concept) and therefore no further scale-up development is necessary for a process which is performed in a microreactor once.

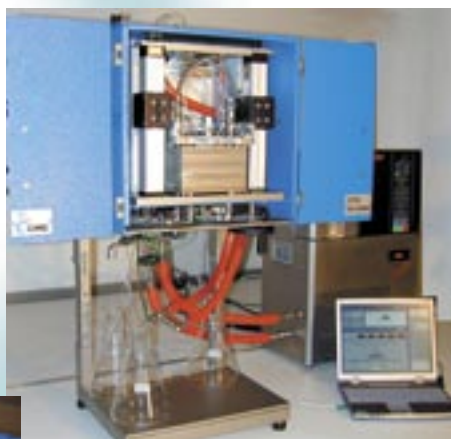
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CYTOS[®] Lab System is the result of a core technology development at CPC-Systems, a standard microreaction system designed by chemists for chemists. CYTOS[®] Lab System offers internal & external modularity for high flexibility in running different chemical reactions, even with unstable intermediates. The internal modularity provides a variable reacting time up to 135 min. by using several residence time units. The external modularity enables a system configuration for multi-step synthesis. CYTOS[®] Lab System allows the production of chemicals from gram to higher kilogram quantities, all in one system and with reproducible results.



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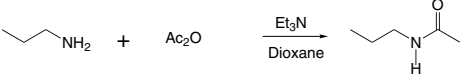



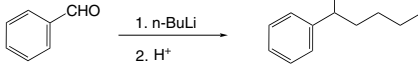

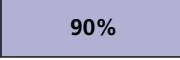

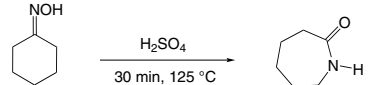

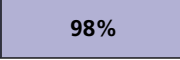

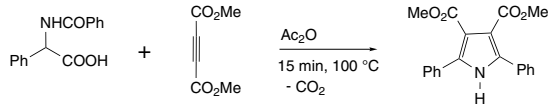
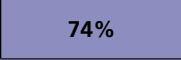
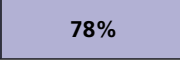

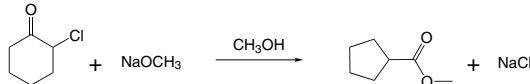



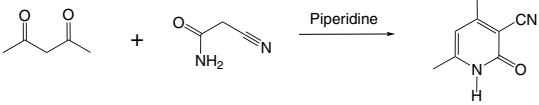



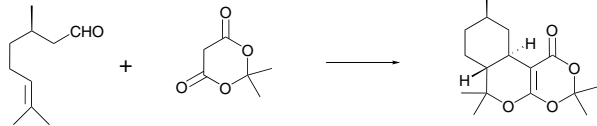



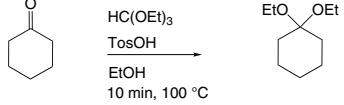
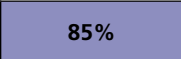
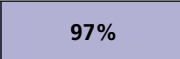

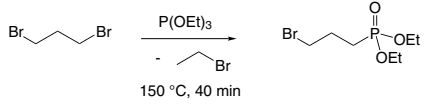
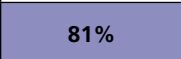
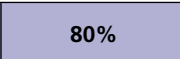

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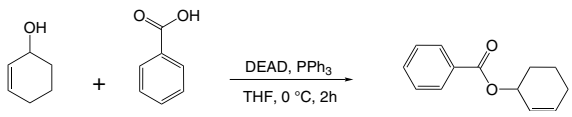
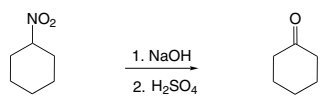
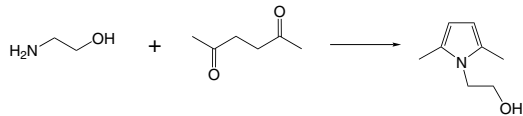
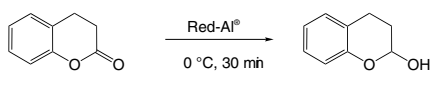
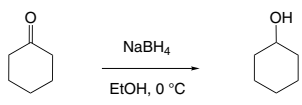
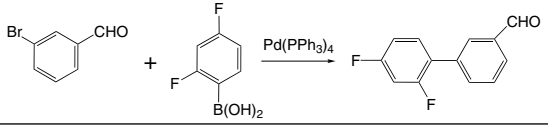
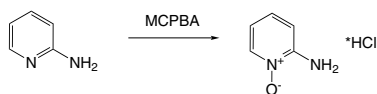
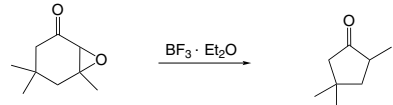
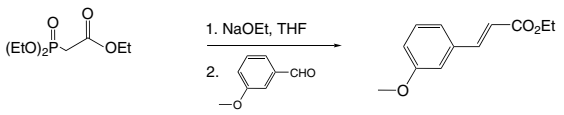
Organic Reactions Performed in a CYTOS® Lab System Microreactor

Numerous organic reactions, including many industrially relevant transformations, have been performed successfully in microreactors. Below is a list of prominent reactions, demonstrating the breadth of chemistry achievable in microreactors.

Definitions:  Yield of the reaction under batch condition
 Yield of the reaction performed in a CYTOS® Lab System Microreactor
 Productivity of the continuous process performed

Aminolysis			
 82%	 80%	 24 g/h	
Addition of BuLi to Benzaldehyde			
 76%	 90%	 50 g/h	
Beckmann Rearrangement			
 80%	 98%	 46 g/h	
1,3-Dipolar Cycloaddition			
 74%	 78%	 29 g/h	
Favorsky Rearrangement			
 56%	 76%	 17 g/h	
Guaresky-Thorpe Pyridone Synthesis			
 63%	 71%	 51 g/h	
Intramolecular Diels-Alder Reaction			
 78%	 85%	 19 g/h	
Ketalization			
 85%	 97%	 130 g/h	
Michaelis-Arbuzov Rearrangement			
 81%	 80%	 34 g/h	

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Mitsunobu Reaction			
82%	98%	10 g/h	
Nef Reaction			
67%	85%	32 g/h	
Paal-Knorr Pyrrole Synthesis			
87%	98%	260 g/h	
Red-Al® Reduction			
43%	61%	9 g/h	
Sodium Borohydride Reduction			
80%	86%	75 g/h	
Suzuki Coupling			
63%	88%	14 g/h	
Synthesis of 2-Amino-pyridine-N-oxide			
71%	82%	46 g/h	
Wagner-Meerwein Rearrangement			
58%	57%	5 g/h	
Wittig-Horner Reaction			
N/A	85%	116 g/h	



Continuous Diazomethane Chemistry



Gernot Mueller
Senior Scientist R&D MRT
gmuller@sial.com

Theo Gaup
R&D Scientist

Diazomethane^{1,2} is a highly reactive gas, useful in a wide range of chemical reactions (Figure 1). It reacts readily with carboxylic acids, yielding the corresponding methyl esters in excellent yields. Reactions with alcohols lead to methyl ethers. The reaction rates are dependent upon the acidity of the substrates. While phenols generally react very fast, ordinary aliphatic alcohols remain unreactive, unless the reaction is catalyzed by addition of acids like HBF_4 ³ or silica⁴. The only side product following transfer of a methyl group is gaseous nitrogen. Further common and extremely useful reactions employing diazomethane are A) methylation of aldehydes to methylketones, B) cyclopropanation of olefins, and C) diazoketone formation starting from acid halides.

In contrast to its very useful chemical properties, diazomethane is physiologically hazardous. It is known to be a powerful carcinogen, allergen, and it is also highly toxic, with a permissible exposure limit of 0.2 ppm. The major drawback of diazomethane is the explosive nature^{5,6} of the substance. As the use of standard ground glass joints can lead to an explosion, the application of specially designed fire-polished glassware is highly recommended! Such glassware devices are available from Aldrich in different sizes. All glassware dedicated for diazomethane generation in amounts from 1–300 mmol per batch incorporates special Clear-Seal® joints.

Nevertheless, any precautions performed during the preparation of diazomethane cannot eliminate the potential hazard of an explosion, which is inherent in the substance itself. To overcome this problem, we developed a less hazardous continuous process, where no dangerous amounts of diazomethane are present in the system at a time. An additional advantage of the new process is the fact that the chemist does not have to move around any flasks or containers with larger amounts of dangerous gas.

The continuous process is based on the procedure which is outlined in the technical bulletin delivered with the Aldrich Diazald® Kits (technical bulletin AL-180). Diazomethane is formed by the reaction of Diazald® (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) in ether with an emulsion of 2-(2-ethoxyethoxy)ethanol and potassium hydroxide in water at 65 °C (Figure 2).

For the continuous generation of diazomethane, the reaction flask of the Diazald® Kit No. Z100250 (Figure 3) has two inlet tubes for the addition of the diazomethane precursor and the KOH and one outlet tube for the removal of side products such as toluenesulfonic acid potassium salt. The outlet tube transports the waste into a container with acetic acid to destroy traces of diazomethane. When the ether solution of Diazald® gets into contact with KOH at 65 °C, diethyl ether and diazomethane evaporate instantly and condense at –5 °C. The diazomethane

solution drops into a receiving flask which is also cooled down to –5 °C and which, for example, may contain a carboxylic acid, consuming the diazomethane in methyl ester formation. In order to run this methyl ester formation continuously, the acid solution is circulated until the conversion inside the storage container is nearly complete.

This continuous system allowed an easy and safe synthesis of 0.6 mol of pentenoic acid methyl ester (Figure 2) within one day. After separation from the diethyl ether by distillation, the purity of the final product is 99.9% as measured by gas chromatography.

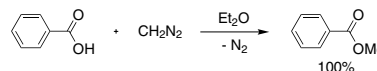
Solutions and Feeds

Feed A:	5.0 mL/min	0.47 M Diazald® in diethyl ether
Feed B:	2.4 mL/min	3.9 M KOH in water: 2-(2-ethoxyethoxy)ethanol 0.8:1 (v/v)
Waste:	3.0 mL/min	

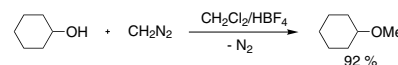
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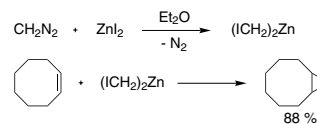
A) Methyl esters from carboxylic acids⁷



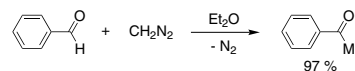
B) Methyl ethers from alcohols³



C) Cyclopropanes from olefins⁸

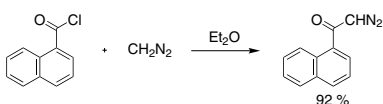


D) Ketones from aldehydes⁹



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E) Diazo ketones from carboxylic acid halides¹⁰



Such diazo ketones can be further converted into carboxylic acids with one additional carbon compared to the original carboxylic acid halides (**Arndt-Eistert Synthesis**), or give the corresponding α -haloketones after treatment with HBr or HCl.

Figure 1: Selected organic reactions applying diazomethane.

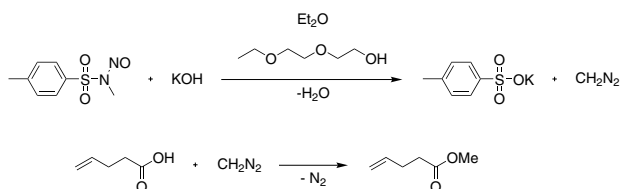


Figure 2: Generation of diazomethane in a Aldrich Diazald® glassware kit Z100250 and synthesis of pentenoic acid methylester.

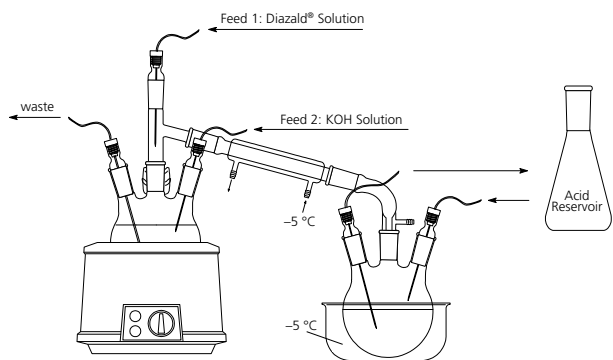


Figure 3: Apparatus for continuous generation and reaction of diazomethane.

Aldrich Diazomethane Generators

Cat. No.	Description	Amount of diazomethane (mmol)
Z108898	Mini Diazald® Apparatus with 19/22 Clear-Seal® joints	1–50
Z202509	Mini Diazald® Apparatus with 19/26 Clear-Seal® joints	1–50
Z419761	Diazald® Set with System 45® compatible connections	1–100
Z100250	Diazald® Kit with 19/22 Clear-Seal® joints	~100
Z108510	Macro Diazald® Kit with 24/40 Clear-Seal® joints	200–300
Z203076	Macro Diazald® Kit with 29/32 Clear-Seal® joints	200–300

Aldrich Diazomethane Precursor

Diazald® (N-methyl-N-nitroso-p-toluenesulfonamide), 99%

CH₃C₆H₄SO₂N(CH₃)NO

MW: 214.24

[80-11-5]

Sales restrictions may apply

D28000-25G	25 g
D28000-100G	100 g



SAFETYBARB™ GLASS

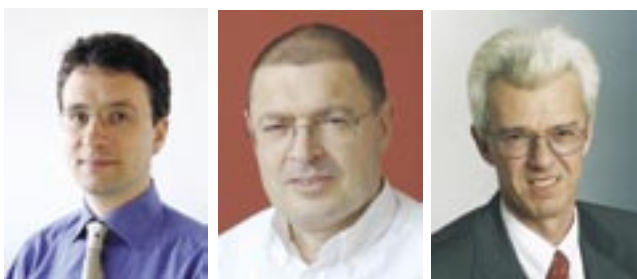
- Virtually eliminates breakage when installing or removing hoses.
- Reduces the incidence of personal injury.
- Costs no more than standard glassware.

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Safe Oxidation Reactions with Peracetic Acid in a CYTOS® Lab System



Gregor Wille, Gerhard Jas, Synthacon GmbH, Frankfurt, Germany; Volker Auze, CPC-Systems GmbH, Mainz, Germany



The synthesis of epoxides from olefins is one of the mainly used synthetic transformations on laboratory and production scale. Usually, this oxidation reaction can be carried out using peracids in a classical stoichiometric approach or hydroperoxides along with a variety of catalysts. On laboratory scale, the reagent of choice is *m*-chloroperbenzoic acid (MCPBA). Although MCPBA generally allows safe and clean reaction, its commercial use is limited because of its high costs. Furthermore, the application of MCPBA results in the formation of stoichiometric amounts of chlorobenzoic acid as undesired by-product that needs to be separated from the reaction mixture by complex work-up procedures. From a commercial point of view, peracetic acid is much more attractive since the only by-product, acetic acid, can be easily distilled off. Commercially available peracetic acid (40% solution in acetic acid) is a cheap technical product. Unfortunately, there are some limitations regarding the use of peracetic acid. First, for safety reasons the reaction temperature should not exceed 60 °C, since peracetic acid is known to be explosive.¹ Second, the reaction times are usually long even with reactive olefins. Last but not least, the product yields are often insufficient since the by-product acetic acid induces a variety of degradation reactions, such as ring opening reactions of the epoxide. In order to overcome these restrictions and to utilize the entire potential of this epoxidation reagent, several protocols for synthesis in microreactors, have been elaborated. Because of the small hold-up volumes and the excellent heat exchange capacities of microreactors, hazardous reagents can be handled in a very safe manner. The first results using peracetic acid as oxidizing reagent are shown below.

One of several performed examples started from 4-vinyl-cyclohexene which has a moderate reactivity in epoxidation reactions. It was converted smoothly to 4-vinyl-cyclohexene oxide by reaction with peracetic acid at 50 °C in a microreactor (Figure 1). However, the non-optimized work-up conditions result in slightly lower isolated yield than reported for a corresponding experiment,² while the GC in our In-Process-Control reveals the formation of the desired product with

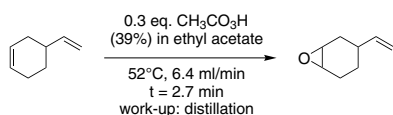
higher than 90%. Due to its inherent safety, including the total consumption of explosive peracetic acid, we have found a base for a technical production process, particularly if continuous distillation or extraction is considered for work up. Thus, the epoxidation of vinyl cyclohexene is a representative example for the epoxidation of other olefinic systems. In order to test the limits of the system, we examined allyl acetate which has a very low reactivity towards standard epoxidation conditions and tends to cause significant side reactions such as polymerization. Even this challenging epoxidation reaction could be performed successfully using a standard microreactor (Figure 2). Once again, the excellent safety features of this technology enable the performance, especially since temperatures of at least 70 °C were required to induce significant conversion. Actually, temperatures of 80–90 °C were tested and do not cause any problems in handling this critical reagent.

Peracetic acid is also known as a useful reagent for Baeyer-Villiger oxidation reactions. One of the most important examples is the preparation of a synthetic intermediate used in various synthetic approaches to prostaglandins.³ The commercially available bicyclo[3.2.0] hept-5-en-2-one can be smoothly converted to the corresponding lactone by stirring the starting material in a mixture of acetic acid/hydrogen peroxide. Usually, the reaction is carried out at 0 °C with reaction times of several hours. We succeeded in transferring the reaction to our CYTOS® Lab System (Figure 3). When using the technical solution of peracetic acid in acetic acid, the reaction temperature could be increased up to 58 °C without any problem. The main advantage was that at the chosen conditions the reaction time was impressively reduced to 4 min. The use of ethyl acetate as co-solvent was advantageous, too. Despite a rather tricky work-up, which in the batch performance, is worse due to more impurities, a throughput of 14 g/h could be realized. It can be expected that by further fine tuning of flow and residence time using additional residence time units and higher flow rates, respectively, the throughput may be increased again by a factor of 5–10.

In general, we have shown that peracetic acid is an attractive alternative for epoxidation and Baeyer-Villiger lactonization reactions. Either lab or production scale at high temperatures, the conversion of peracetic acids by applying microreaction technology can be realized.

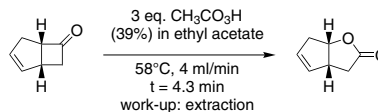
References

1. Explosion point for peracetic acid is 110 °C. In order to retain a temperature buffer (for exothermic reactions in particular), this limit of 60 °C is applied in many companies dealing with peracetic acid.
2. This special experiment is reported to be performed in a continuous manner: Frostick, F. C.; Phillips, B.; Stracher, P. S. *J. Am. Chem. Soc.* **1959**, *81*, 3350.
3. Akermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729. Grieco, P. A. *J. Org. Chem.* **1972**, *37*, 2363.



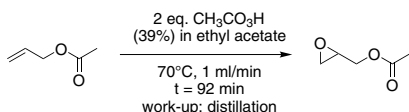
Yield, batch conditions ²	82%
Yield from CYTOS [®] LabSystem	65%
Productivity, CYTOS [®] LabSystem	12.8 g/h

Figure 1: Epoxidation of 4-vinylcyclohexene.



Yield, batch conditions ³	85%
Yield from CYTOS [®] LabSystem	90%
Productivity, CYTOS [®] LabSystem	13.6 g/h

Figure 3: Baeyer-Villiger Oxidation of bicyclo[3.2.0]hept-5-en-2-one.



Yield from CYTOS [®] Lab System	34%
Productivity, CYTOS [®] Lab System	1.2 g/h

Figure 2: Epoxidation of allyl acetate.

Peracids and Peroxides-Oxidizing Reagents from Sigma-Aldrich

3-Chloroperbenzoic acid, MCPBA ≤77%

[937-14-4]

273031-25G	25 g
273031-100G	100 g
273031-500G	500 g

3-Chloroperbenzoic acid, MCPBA technical, ~70% RT

[937-14-4]

25800-25G	25 g
25800-100G	100 g
25800-500G	500 g

Peracetic acid solution purum, ~39% acetic acid RT

[79-21-0]

77240-100ML	100 mL
77240-500ML	500 mL

Peracetic acid solution 32 wt. % dilute acetic acid

[79-21-0]

269336-5ML	5 mL
269336-100ML	100 mL
269336-500ML	500 mL

tert-Butyl peroxide 98%

[110-05-4]

168521-5ML	5 mL
168521-250ML	250 mL
168521-1L	1 L

Di-tert-butyl peroxide technical, ≥95% GC

[110-05-4]

34790-50ML-F	50 mL
34790-250ML-F	250 mL
34790-1L-F	1 L

OXONE[®], monopersulfate compound

[70693-62-8]

228036-5G	5 g
228036-100G	100 g
228036-1KG	1 kg

Hydrogen peroxide solution 35 wt. % water

[7722-84-1]

349887-500ML	500 mL
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Hydrogen peroxide solution puriss. p.a., ACS reagent, not stabilized, ≥30% RT

[7722-84-1]

95313-500ML	500 mL
95313-1L	1 L

PERDROGEN[®], hydrogen peroxide solution puriss. p.a., reagent, ISO, reagent, Ph. Eur., ≥30%

[7722-84-1]

31642-500ML	500 mL
31642-1L	1 L
31642-6X1L	6X1 L
31642-5L	5 L
31642-4X5L	4X5 L

Hydrogen peroxide solution ACS reagent, 30 wt. % water

[7722-84-1]

216763-100ML	100 mL
216763-500ML	500 mL
216763-4L	4 L

Hydrogen peroxide solution 3 wt. % water

[7722-84-1]

323381-25ML	25 mL
323381-500ML	500 mL
323381-4L	4 L



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Synthesis of Aryllithium Compounds in a CYTOS® Lab System



Joachim Sommer, Wolfgang Stirner, Gerhard Jas,
Synthacon GmbH, Frankfurt, Germany



In recent years, Microreaction Technology (MRT) has evolved as a beneficial, innovative tool for the improvement and optimization of reactions. Based on its unique miniaturization approach, MRT allows you to carry out reactions under flow-through conditions. Thus, MRT enables excellent control of reaction parameters such as temperature and concentration equipartition. In many cases, higher yields, fewer by-products, and higher selectivity can be achieved. Sometimes MRT is the only accessible approach toward particular reactions, e.g., the direct fluorination of organic compounds. Meanwhile, there is a broad consensus that MRT can be applied to organic synthesis in general. Consequently, it has been shown that a considerable number of organic reactions can be advantageously carried out in microreactors.¹ Not surprisingly, synthesis in microreactors has become increasingly interesting for small-scale production in the pharmaceutical and fine chemical industry, particularly as standardized microreaction systems have become commercially available. The flow-through approach opens the door to shorten dramatically the timelines needed for chemical development simply by running the reactions continuously. Moreover, when thinking of large-scale production, the numbering-up concept leads to significant minimization of scale-up risks, namely for cryogenic reactions (e.g., organometallic reactions) or when using hazardous reagents.

Lithiation reactions of aromatic compounds are of high synthetic value since a variety of substitution patterns can be released by reacting aryllithium compounds with electrophiles in cases where electrophilic aromatic substitution reactions lead to different substitution patterns or the reactivity of electrophiles is insufficient. Generally, the aryllithium species can be gained by lithium-halogen exchange reactions or by directed metallation reactions of the aromatic core system. We have recently shown that bromo-lithium exchange is easily applicable to microreaction technology. Generally, because of the excellent heat exchange capacities of microreactors, the crucial lithiation step can be carried out at significantly higher temperatures.^{1,2} Additionally, the precise control of reaction conditions significantly reduces side reactions like Wurtz-coupling reactions. This will expand the range of applicability of the convenient *in situ* quench protocol,^{3a} whose latent potential seems to be not fully exploited yet, especially for haloarene synthesis.^{3b} In terms of microreaction technology, the *in situ* quench protocol means that the starting aromatic compound and the electrophile can be premixed, and the lithium reagent (e.g., butyllithium) needed for generation of the aryllithium species is added to the mixture.^{3c} Depending on

scale, in batch experiments addition of the lithium reagent to the electrophile (e.g., a carbonyl compound) is a serious side reaction or even the main reaction. Using the MRT approach, these side reactions can almost be suppressed nearly completely. An interesting example is illustrated in **Figure 1**.

Arylboronic acids are versatile building blocks in a variety of Pd-catalysed cross-coupling reactions. Usually, these building blocks can be synthesised by lithiation reactions (e.g., through bromo-lithium exchange reactions and subsequent reaction with alkyl borates). Generally, the reactions are carried out at $-78\text{ }^{\circ}\text{C}$. Although it has been shown that particularly *N*-Boc-indoles can be lithiated with LDA at $0\text{ }^{\circ}\text{C}$ under non-cryogenic conditions⁴, the scale-up of this reaction may be cumbersome. For that reason, the transformation was examined in a CYTOS® microreactor using the same *in situ* quench approach as in the batch experiment. In a clean reaction, the 2-Indolyl borate could be prepared in high yield and purity on a multigram scale after acidic work-up and recrystallization (**Figure 1**).

Ortho metallation of aromatic compounds is a versatile approach for regioselective lithiation of aromatic compounds.⁵ Often an amide group is used as a directing moiety.⁶ The use of bulky amide substituents suppresses the addition of the lithium base to the amide functionality.⁷ Depending on individual requirements, the *in situ* quench approach is a powerful procedure to further minimize side reactions. However, in some cases this procedure fails. Then another advantage of our continuous approach using Microreaction Technology comes into operation, particularly when unstable intermediates are involved, as often happens in organometallic chemistry: a two-stage performance is the solution. In a first stage, the intermediate is built which, after a very short reaction time, almost instantaneously is converted in the second stage, where the electrophile is added. Using this approach, the methylation or silylation reaction of the herein investigated benzamides (**Figure 2**) can be carried out even at $0\text{ }^{\circ}\text{C}$ in high yields. The short contact times even enable high flow rates and, thus, the corresponding products could be obtained in reasonable production rates without extensive optimization efforts.

Fluoroanisole is an interesting starting compound for lithiation reactions. It has been reported that the regioselectivity of the lithiation step strongly depends on the specific reaction conditions.⁸ Performing this reaction with PMDTA (pentamethyl-diethylenetriamine) as additive, which requires a temperature below $-50\text{ }^{\circ}\text{C}$, we found only one regioisomer formed using our microreaction approach. Using DMF or boronic esters as electrophile, we could prepare the corresponding aldehyde and boronic acid in good yields with a reasonable throughput rate (**Figure 3**).

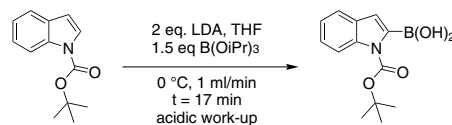
Regioselective lithiation can be achieved also when using 2,5-dibromopyridine as starting material. It is known from the literature⁹ that the regioselectivity is strongly influenced by reaction temperature and solvent. As shown by Hawkins,¹⁰ a performance in toluene using Microreaction Technology delivers — depending on the ketone — ratios of up to 18:1 (2, 5-substituted isomer), while THF leads to an opposite ratio of higher than 1:87. The yields were relatively high, around 60%. Using a two-stage CYTOS® Lab System, we were able to confirm these data of obtaining only 5-isomer even when applying MTBE as solvent whose complexing properties are significantly lower compared to THF (**Figure 4**).

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call 1-800-325-3010 (USA), or visit sigma-aldrich.com.

In summary, we have shown that lithiation of aromatic species and subsequent reaction with electrophiles can be generally performed in microreactors under non-cryogenic conditions. Yields and selectivities are generally high. Moreover, high throughput rates can be achieved allowing instantaneous small-scale production (of up to several kilograms).

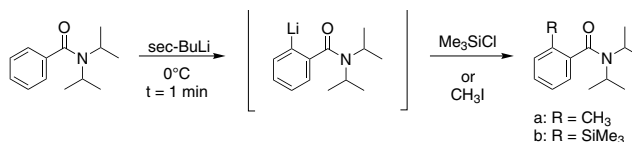
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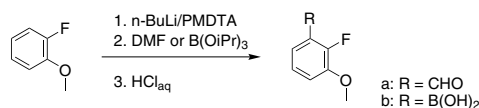
Yield, batch conditions, 2 g scale [4]	96%
Yield from CYTOS® Lab System	89%
Productivity, CYTOS® Lab System	18,4 g/h

Figure 1: Synthesis of 2-indolyl borate.



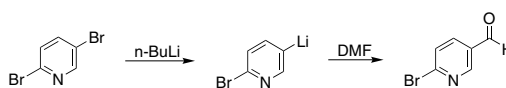
Yield (a,b), batch condition [7]	76%/86%
Yield (a,b) from CYTOS® Lab System	85%/98%
Productivity (a,b), CYTOS® Lab System	12,2/16,8 g/h

Figure 2: Ortho-metallation of benzamide.



Yield (a,b), batch condition (20 mmol scale) [8]	99%/N/A
Yield (a,b) from CYTOS® Lab System	85%/78%
Productivity (a,b), CYTOS® Lab System	6,8/15,6 g/h

Figure 3: Lithiation of 2-fluoroanisole.



Yield, batch condition [9]	60–80%
Yield from CYTOS® Lab System	94%
Productivity, CYTOS® Lab System	21 g/h

Figure 4: Synthesis of 2-bromopyridine carbaldehyde.



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Synthesis of Aryllithium Compounds in a CYTOS® Lab System (Continued)

Organolithium Reagents from Sigma-Aldrich

Lithium diisopropylamide solution 2.0 M in heptane/ tetrahydrofuran/ethylbenzene

C ₆ H ₁₄ LiN [4111-54-0]	
361798-100ML	100 mL
361798-800ML	800 mL

Butyllithium solution 1.6 M in hexanes

C ₄ H ₉ Li [109-72-8]	
186171-100ML	100 mL
186171-1L	1 L

Butyllithium solution 2.0 M in pentane

C ₄ H ₉ Li [109-72-8]	
302104-100ML	100 mL
302104-800ML	800 mL
302104-1L	1 L

Butyllithium solution 2.5 M in hexanes

C ₄ H ₉ Li [109-72-8]	
230707-100ML	100 mL

Butyllithium solution techn. ~2.5 M in toluene

C ₄ H ₉ Li [109-72-8]	
20164-100ML-F	100 mL
20164-500ML-F	500 mL

Butyllithium solution purum ~2.7 M in heptane

C ₄ H ₉ Li [109-72-8]	
20159-500ML-F	100 mL
20164-500ML-F	500 mL

Butyllithium solution 10.0 M in hexanes

C ₄ H ₉ Li [109-72-8]	
230715-100ML	100 mL
230715-800ML	800 mL

Isobutyllithium solution techn. ~15% in heptane (~1.6 M)

C ₄ H ₉ Li [920-36-5]	
58565-100ML	100 mL

sec-Butyllithium solution 1.4 M in cyclohexane

C ₄ H ₉ Li [598-30-1]	
195596-100ML	100 mL
195596-800ML	800 mL

tert-Butyllithium solution 1.7 M in pentane

C ₄ H ₉ Li [594-19-4]	
186198-100ML	100 mL

tert-Butyllithium solution purum 1.6-3.2 M in heptane

C ₄ H ₉ Li [594-19-4]	
94439-100ML-F	100 mL

Ethyllithium solution 0.5 M in benzene/cyclohexane (90/10)

C ₂ H ₅ Li [811-49-4]	
561452-25ML	25 mL
561452-100ML	100 mL

Hexyllithium solution 2.3 M in hexane

C ₆ H ₁₃ Li [21369-64-2]	
468568-100ML	100 mL
468568-1L	1 L

Hexyllithium solution purum ~2.5 M in hexane

C ₆ H ₁₃ Li [21369-64-2]	
53200-100ML	100 mL
53200-500ML	500 mL

Isopropyllithium solution 0.7 M in pentane

C ₃ H ₇ Li [1888-75-1]	
529745-100ML	100 mL
529745-1L	1 L

Methylithium solution 1.0 M in diethyl ether

CH ₃ Li [917-54-4]	
316768-100ML	100 mL

Methylithium solution purum ~1 M in cumene/THF

CH ₃ Li [917-54-4]	
67737-50ML	50 mL
67737-250ML	250 mL

Methylithium solution 1.6 M in diethyl ether

CH ₃ Li [917-54-4]	
197343-100ML	100 mL
197343-800ML	800 mL

Methylithium lithium bromide complex solution 1.5 M in diethyl ether

CH ₃ Li • BrLi [917-54-4]	
186201-100ML	100 mL
186201-800ML	800 mL
186201-1L	1 L

Continuous Mono-Boc-protection of Diamines in the Microreactor



Genrot Mueller
Senior Scientist R&D MRT
gmuller@sial.com

Theo Gaup, R&D Scientist

Microreactors are expected to have a significant impact on chemical synthesis and production in the near future. The speed in optimizing processes in these continuous systems is one of their major advantages, and should be demonstrated in the following example.

The *tert*-butyloxycarbonyl (Boc) group^{1,2} is probably the most widely used protecting group for amines, especially in peptide synthesis. It is inert to catalytic hydrogenation and stable to basic conditions or attack of other nucleophiles: thus, orthogonal to other amine protecting groups like the fluorenylmethyloxycarbonyl (Fmoc) group. Deprotection is easily performed with acids like HCl in ethyl acetate³ or trifluoroacetic acid (TFA) in methylene chloride (CH₂Cl₂).⁴

Mono-Boc-protected diamines are important building blocks used as spacer moieties, linkers, or polyamine monomers. A broad range of mono-protected diamines offered by Sigma-Aldrich is listed below.

For the synthesis of mono-protected diamines, usually (Boc)₂O is added to the diamine, resulting in a crude mixture of mono- and di-protected products together with unreacted starting material (Figure 1). The optimization of such a reaction with respect to yield and productivity is easily performed using Microreactor Technology. The ability to run many experiments in a short time provides information and enables the optimization for the mono-protection of piperazine within two days as shown below.

The experiments were run with a CYTOS[®] Lab System from CPC equipped with a 75 mL residence unit. In a first series of experiments, several solvents were tested at different temperatures (Table 1). In all experiments with no blockings, the conversion was complete [no unreacted (Boc)₂O in the crude product mixture]. In consideration of the later optimization of the production, methanol turned out to be the preferred solvent with good solubility of reactants over a range of temperatures. In the second series of experiments, we optimized at T=30 °C in methanol, the best molar equivalent of (Boc)₂O to be added in order to receive the best yields of mono-protected piperazine (Figure 2).

After identification of the ideal molar equivalents of (Boc)₂O, the productivity had to be optimized in a third series of experiments (Table 2).

Productivity [g/h] in a microreactor system can be improved either by increasing the concentration of the reactants or by increasing the flow rate in the system. In a microreactor, the evolution of CO₂ gas during reaction of the amine with (Boc)₂O becomes an important factor. With a higher throughput of reactants, more residence space is filled with CO₂ gas. This leads to a reduction of the residence time just like an increase of the flow rate. Based on these considerations, concentration was the first parameter to optimize. The concentration of piperazine in Feed A was therefore increased from 0.2 M to 1.6 M with a simultaneous increase of the concentration of (Boc)₂O in Feed B according to the optimal molar equivalents, as determined before. At a concentration of 1.6 M piperazine in Feed A, *N,N'*-di-Boc-piperazine starts to precipitate in the microreactor.

As a consequence, the residence time was reduced by increasing the flow rate to an optimum value of 4 mL/min. Higher flow rates showed an incomplete conversion of (Boc)₂O.

Overall, this process was optimized within 20 experiments yielding about 600 g/day of mono-protected *N*-Boc-piperazine. With the knowledge accumulated during this process optimization, similar reactions can now be developed within one day.

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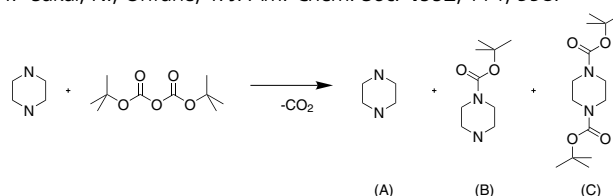


Figure 1: Mono-Boc-protection of piperazine. (A) = piperazine, (B) *N*-Boc-piperazine, (C) *N,N'*-di-Boc-piperazine.

Experiment No.	Solvent	Temp. (°C)	Composition of the crude product		
			piperazine (%)	mono-Boc-piperazine (%)	di-Boc-piperazine (%)
1	THF	60	MR blocked		
2	Toluene	60	26	47	27
3	Toluene	40	MR blocked		
4	MeOH	60	29	43	28
5	MeOH	40	31	38	31
6	MeOH	20	29	41	29
7	CH ₂ Cl ₂	20	MR blocked		

Table 1: Optimization of Solvent and Temperature for the mono-Boc-protection of piperazine. Experimental details: 1 eq. (Boc)₂O, Feed A: 0.2 M piperazine 2 mL/min, Feed B: 0.2 M (Boc)₂O; 2 mL/min, 1.5 mL MR, 75 mL residence unit.

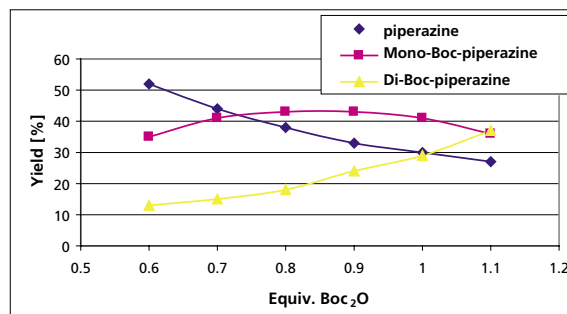


Figure 2: Optimization of the molar equivalents of (Boc)₂O for the mono-Boc-protection of piperazine. Experimental details: Feed A (0.2 M piperazine in methanol): 2 mL/min, Feed B (Boc)₂O in methanol): 2 mL/min, 1.5 mL MR, 75 mL residence unit, 30 °C.



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Continuous Mono-BOC-protection of Diamines in the Microreactor (Continued)

(A)

Optimization of Concentration		
Experiment No.	$C_{(\text{Feed A})}$ [M]	Production [g/day]
1	0.5	115
2	1.3	299
3	1.6	MR blocked

(B)

(B) Optimization of Residence Time		
Experiment No.	Flow (Feed A, B) [mL/min]	Production [g/day]
1	2	299
2	2.7	404
3	4	597
4	6	90% conversion

Table 2 (A) and (B): Optimization of concentration (A) and residence time (B) for the mono-Boc-protection of piperazine. Experimental details (A): 0.8 eq. Boc_2O , Feed A (piperazine in methanol): 2 mL/min, Feed B (Boc_2O in methanol): 2 mL/min, 1.5 mL MR, 75 mL residence unit, 30 °C. Experimental details (B): 0.8 eq. $(\text{Boc})_2\text{O}$, Feed A (1.3 M piperazine in methanol); Feed B (1.04 M $(\text{Boc})_2\text{O}$), 1.5 mL MR, 75 mL residence unit, 30 °C.

Mono-Boc-protected Diamines from Sigma-Aldrich

N-Boc-ethylenediamine purum, $\geq 98.0\%$ NT

[57260-73-8]

15369-1G	1 g
15369-5G	5 g
15369-25G	25 g

N-Boc-1,3-propanediamine purum, $\geq 97.0\%$ GC NT

[75178-96-0]

15408-1ML	1 mL
15408-5ML	5 mL

N-Boc-1,4-butanediamine purum, $\geq 97.0\%$ GC/NT

[68076-36-8]

15404-1ML	1 mL
15404-5ML	5 mL

N-Boc-cadaverine purum, $\geq 97.0\%$ NT

[51644-96-3]

15406-1ML	1 mL
15406-5ML	5 mL

N-Boc-1,6-hexanediamine purum, $\geq 98.0\%$ GC

[51857-17-1]

79229-1G	1 g
79229-5G	5 g

N-Boc-1,6-hexanediamine hydrochloride purum, $\geq 98.0\%$ AT

[65915-94-8]

15392-1G	1 g
15392-5G	5 g

N-Boc-*N*-methylethylenediamine purum, $\geq 98.0\%$ GC

[121492-06-6]

15567-1ML	1 mL
15567-5ML	5 mL

*N*1-Boc-2,2'-iminodiethylamine purum, $\geq 97.0\%$ NT

[193206-49-4]

17752-1ML	1 mL
17752-5ML	5 mL

*N*1-Boc-3,3'-iminodipropylamine purum, $\geq 97.0\%$ NT

[82409-04-9]

17756-1ML	1 mL
17756-5ML	5 mL

O-(2-Aminoethyl)-*O'*-[2-(Boc-amino)ethyl]octaethylene glycol $\geq 90\%$ oligomer purity

79141-500MG-F	500 mg
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O-(2-Aminoethyl)-*O'*-[2-(Boc-amino)ethyl]decaethylene glycol $\geq 90\%$ oligomer purity

77090-500MG-F	500 mg
---------------	--------

O-(2-Aminoethyl)-*O'*-[2-(Boc-amino)ethyl]hexaethylene glycol $\geq 90\%$ oligomer purity

[206265-98-7]

70023-500MG-F	500 mg
---------------	--------

N-Boc-*p*-phenylenediamine purum, $\geq 97.0\%$ NT

[71026-66-9]

15485-1G	1 g
15485-5G	5 g
15485-25G	25 g

(*S*)-3-(Boc-amino)pyrrolidine purum, $\geq 98.0\%$ TLC

[122536-76-9]

52927-1G-F	1 g
52927-5G-F	5 g

(*R*)-3-(Boc-amino)pyrrolidine purum, $\geq 98.0\%$ TLC

[122536-77-0]

56308-1G-F	1 g
56308-5G-F	5 g

4-Amino-1-Boc-piperidine hydrochloride purum, $\geq 97.0\%$ N

[179110-74-8]

75578-500MG-F	500 mg
---------------	--------

4-(Aminomethyl)-Boc-piperidine purum, $\geq 98.0\%$ TLC

[144222-22-0]

50206-1G-F	1 g
50206-5G-F	5 g

(\pm)-3-(Boc-aminomethyl)piperidine purum, $\geq 98.0\%$ TLC

[142643-29-6]

55787-500MG-F	500 mg
---------------	--------

1-Boc-piperazine purum, $\geq 98.0\%$ GC

[57260-71-6]

15502-5G	5 g
15502-25G	25 g

1-Boc-hexahydro-1,4-diazepine purum, $\geq 98.0\%$ GC

[112275-50-0]

17759-5ML	5 mL
17759-25ML	25 mL

Microreactor Technology for Custom Synthesis at Sigma-Aldrich

Microreactor Technology has demonstrated its broad applicability in numerous chemical syntheses in recent years. A large number of projects showed that microreactors can support fine chemical synthesis by improving selectivity, speeding-up process development, and substituting scale-up by simple numbering-up.

Does your process suffer from...

	Never	Sometimes	Often
1. Low selectivity?	A	B	C
2. Low yields?	A	B	C
3. High exotherme?	A	B	C
4. High endotherme?	A	B	C
5. Unstable intermediates?	A	B	C
6. Dangerous production processes?	A	B	C
7. Multiple parameters that need screening?	A	B	C
8. Unsatisfactory scale-up?	A	B	C

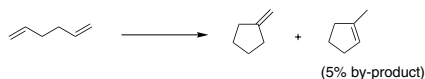
If your answer is not always A, you should think about MRT-Systems to support your process development, scale-up, and production. Please contact our world-class SAFC project management team to learn how MRT-Systems can add real value to your development process.

MRT — It really makes a difference to classical batch reactions!

- Continuous processing enables rapid screening of reaction parameters resulting in fast process optimization.
- Diffusion in small microchannels leads to perfect mixing.
- High surface-to-volume ratio enables perfect temperature control.
- The presence of only small amounts of hazardous materials at a time eliminates safety issues.
- Numbering-up instead of scaling-up provides fast process transfer to production scale without further optimizations.

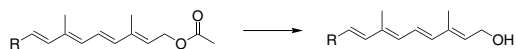
Selected continuous processes performed in a microreactor at Sigma-Aldrich:

A) Synthesis of methylenecyclopentane (Fluka No. 66763)



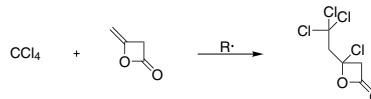
When applying a standard batch process, the very exothermic reaction leads to 5% of 1-methyl-1-cyclopentene, which is not separable. Our continuous process yielded methylenecyclopentane without any by-product at a 4 kg/day scale.

B) Synthesis of vitamin A alcohols (e.g., Fluka No. 95144)



Vitamin A alcohols are extremely air-, temperature-, and light-sensitive. They are also difficult to isolate in excellent purities from a batch process. The continuous process performed under cGMP conditions delivered 0.7 kg of vitamin A alcohol per day.

C) Transformation of diketene (Aldrich No. 422363)



Diketene is explosive. By performing the radical addition process in a continuous manner, we were able to consume about 10 kg of diketene safely within 10 days.

Our facilities at Sigma-Aldrich:

- Fully equipped Microreactor Technology laboratory with experienced staff
- CPC-CYTOS® based microreactor
- Glass-based microreactor for extreme temperatures and corrosive reagents (Figure 1)

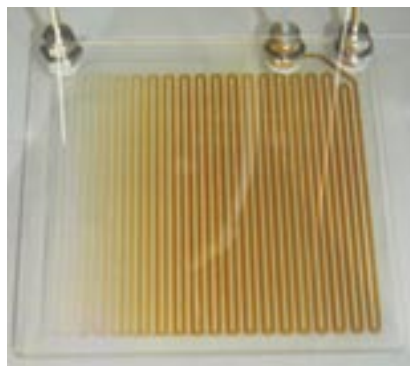


Figure 1: Reaction in a glass microreactor at $-100\text{ }^{\circ}\text{C}$.

Contact us...

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Figure 2: Our Process Development Team for SAFC Pharma in Buchs, Switzerland



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Simulated Moving Bed (SMB) Technology at SAFC Pharma

In late 2004, **SAFC Pharma**, a member of the Sigma-Aldrich group, implemented a CSEP 916 simulated moving bed (**SMB**) instrument from Knauer (**Figure 1**). The application of this state-of-the-art chromatographic technique expands our expertise in separation services. We offer method development and custom separation up to kg scale, also conforming to cGMP regulations, if requested.

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The Simulated Moving Bed Principle

The characteristic feature of the SMB technology is the simulation of a counter-current between the liquid and solid phases in a loop of chromatographic columns (beds). The loop is divided into four sections (**Figure 2**), two separation sections (II, III), and two desorbing sections (I, IV). The substrate mixture, or feed, is introduced continuously between sections II and III. The components are then separated in sections II and III and are withdrawn by the raffinate and the extract streams. Due to differences in the net flow between sections I and II, and sections III and IV, respectively, the components are desorbed totally from the solid phase material between sections I and IV. The solvent loss is compensated by an eluant inlet between sections I and IV. The positions of the inlet and outlet valves are switched periodically to match the advancing concentration profiles.



Figure 1: Knauer CSEP 916 Pilot SMB installed at Sigma-Aldrich.

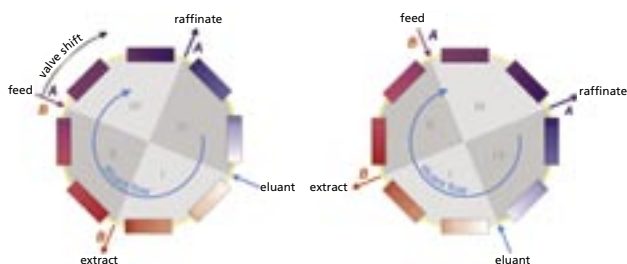


Figure 2: Simulated Moving Bed Principle

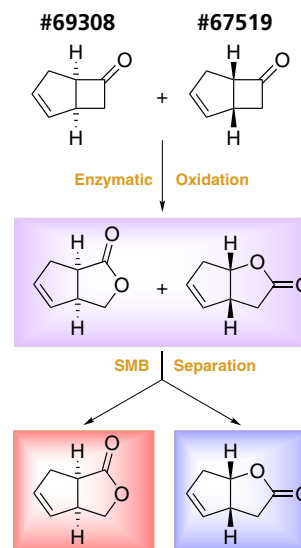
Scope and Advantages of the SMB Technology

SMB has many advantages over conventional batch column chromatography (e.g., HPLC), often making it an obvious choice to solve separation problems:

- Continuous separation of two compounds or fractions
- Significant lower solvent consumption
- High feed concentration and high overloading lead to high productivity
- High recovery rates
- High product purities
- Easy scalability of separation process

Please note that our SMB instrument is equipped with conventional preparative HPLC columns up to 4 cm in diameter. A wide choice of solid phase materials is available for the separation of chiral and non-chiral compounds.

Application of the SMB Methodology



Scheme 1: SMB Separation of Chiral Lactones

A recent application at **SAFC Pharma** was the separation of chiral, diastereomeric lactones (**Scheme 1**). The 1:1 mixture of the enantiopure lactones was derived by an enzymatic enantioselective oxidation of racemic bicyclo[3.2.0]hept-2-en-6-one. The products ($\alpha = 1.21$) were separated on our SMB equipped with 12 silica columns (2 x 25 cm, 10 mm). The lactones could be isolated in 99% purity, each using only 300 mL solvent per gram product.



Contact us...

For more detailed information or to receive a quote for your separation problem, please contact **SAFC Pharma** or visit us at www.safcpharma.com.

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