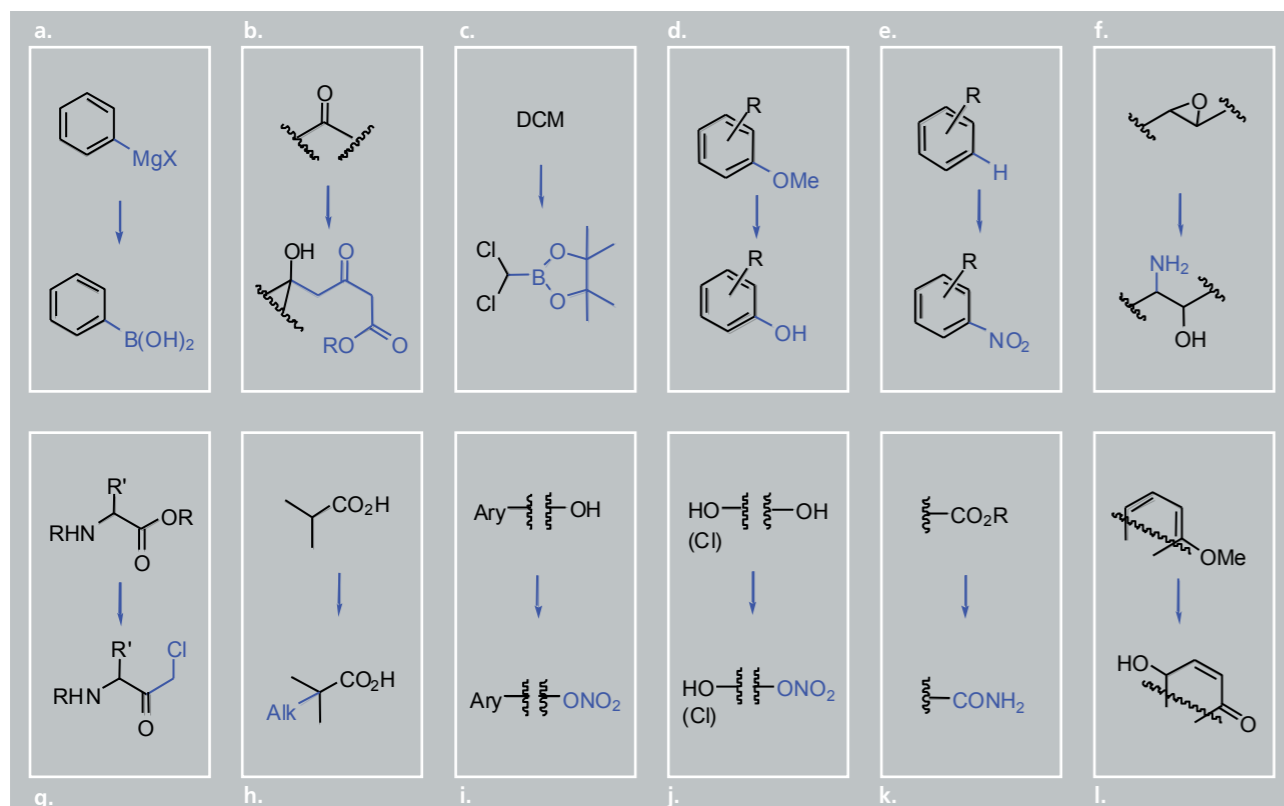


## Siegfried Examples



- a. Aromatic boronic acid  
 b. Metalorganic reaction (double de-protonation)  
 c. Pinacolato-dichloromethylborane formation  
 d. Demethylation or MeO-Aryl

- e. Nitration of an aromatic system  
 f. Epoxide opening with ammonia  
 g. Multi-step sequence; deprotonation, silylation, alkylation, hydrolysis  
 h.  $\alpha$ -Alkylation of a carboxylic acid

- i. O-Nitration of an aromatic alcohol  
 j. Mono-nitration of an aliphatic alcohol  
 k. Ammonolysis of an ester  
 l. Oxidation with hydrogen peroxide

### Further Applications

Siegfried has explored more than a dozen chemical transformations for MRT application. We focussed on reactions which either need improved selectivity or use hazardous reagents and/or reaction mixtures. For these applications the majority of the tested reactions benefit from the MRT application.

Based on the experience gained during the last years we can draw the following conclusions:

- Metalorganic reactions can be run at higher temperature in MRT equipment with equal or better yields than their batch counterparts.
- Improved functional group selectivity is found for metalorganic reactions and nitrations.

- Control of hazardous mixtures is straightforward due to the small reaction inventories involved.
- Reactions above the boiling point of solvents become easily accessible.

The reactions explored so far are summarized in the figure above. Additional examples are being continuously added. We are fully aware that these examples represent only a limited selection of what can be done or explored. However, when facing demanding transformations these examples have already shown us the value of always keeping MRT in mind. ■

**Beat Weber**  
 Head Process Research

### Summary and Outlook

We have demonstrated the utility of micro reactor technology for chemical synthesis in API (active pharmaceutical ingredient) production. For transformations suited to this technology fast process transfer from lab to kilo-lab and beyond can be expected. Furthermore, scale-up effects are eliminated to a large extent. In some cases yield improvements are easily achieved, as demonstrated by the reaction just presented. We believe that this technology will increasingly appear in the chemical and pharmaceutical industry, adding its benefits, and become as common as stirred tanks. ■

# behind the scenes

Siegfried

## Microreactor Technology Becomes Part of Siegfried's API Manufacturing

In our Newsletter 2/2007 we described the history and the set-up of our Microreactor Laboratory. There it was described which reactions are suitable, and which are not. The improvised installations of those early days looked somewhat like child's play with pipes, tubes and drums.

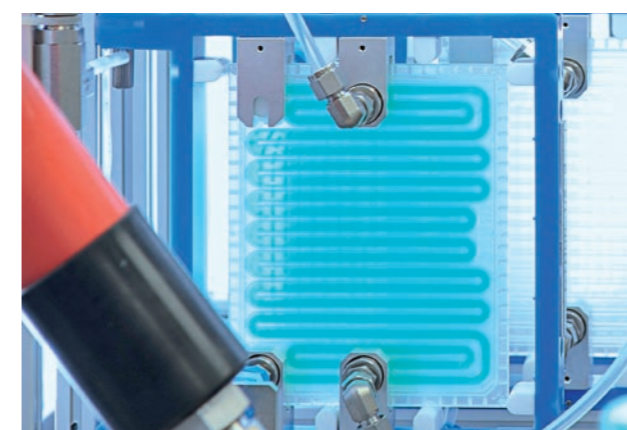
It has, however, now matured into an efficient operation. The experience gained during these past years covers the types of chemistries suited for MRT conversion and, as important as the chemistry, the necessary infrastructure. No more dripping joints, failing seals or clogged pipe connections.

Depending on the demands of the reaction being checked, we are now able to quickly assemble the necessary reactor and infrastructure configuration. A new candidate can quickly be checked for feasibility. Moreover, if the feasibility proves positive one of the major strengths of the MRT concept

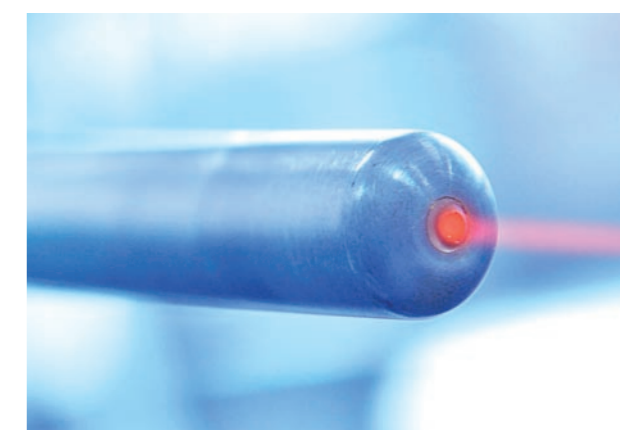
comes into play: there is no scale-up delay. The installation is moved to our kilo-lab and the reactor is run for just the required time to produce the first kilos. This can be done without having to change anything besides the size of the feed tanks and the receiver for the product solution. ■



Beat Weber, Ph.D., Head Process Research, has been working for Siegfried for 15 years. He received his Ph.D. at the ETH Zürich under the supervision of Prof. Dieter Seebach. He gained industry experience in the fields of vitamins, detergents and API chemistry. ■

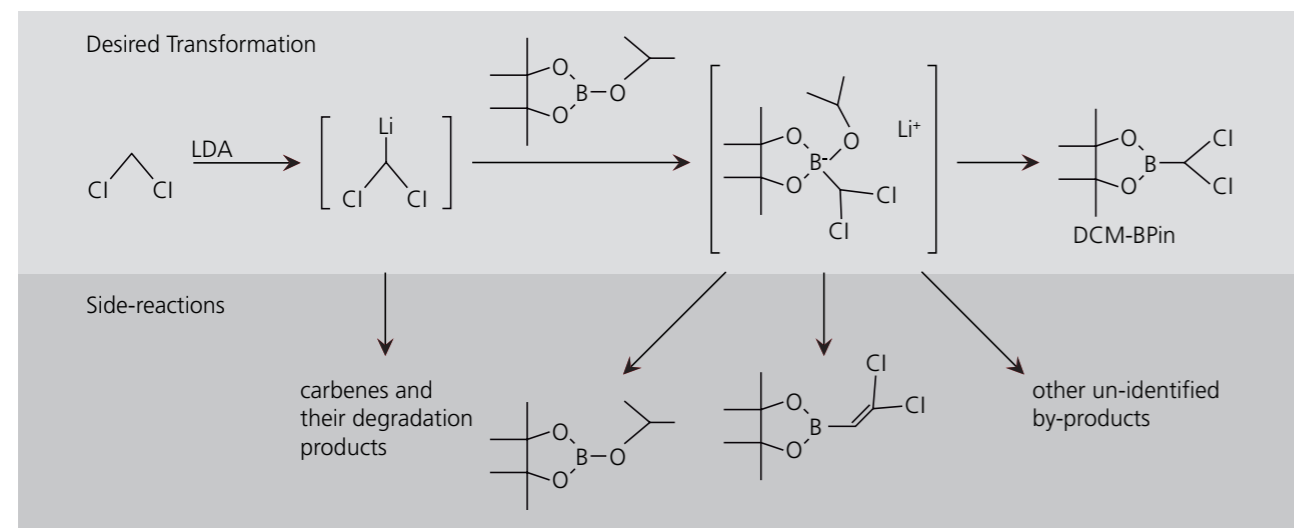


The behavior of the reaction media in the glass MRT can be visually inspected



The Raman probe can be added to the MRT units as in-line analytical tool

## Reaction scheme including paths to side products



### A Typical Reaction

The formation of DCM-BPin (2-dichloromethyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane) is well suited for MRT since the synthesis of this compound combines prerequisites for MRT reactions and the types of problems that can be solved by this technology:

- The reaction sequence is fast
- The metal-organic reaction is homogeneous
- There are instable intermediates involved
- Side reactions occur within or close to the reaction temperatures.
- The strongly exothermic reaction will ask for prolonged addition times if scaled-up batch wise.

A typical literature process<sup>1</sup> de-protonates dichloromethane at -100°C by slow addition of LDA, after an aging period boronic ester is added and a next aging is done. Eventually, an aqueous quench finalized the procedure. Attempts to transform this protocol into a user-friendly batch reaction have been made, however, with the drawback of a reduced yield<sup>2</sup>.

### The Chemistry Involved

The reaction is known to proceed via tetra-coordinated boron species. These species can form either the desired product, or react back to the starting material or they may form olefins by the Matteson reaction.

<sup>1</sup> J. Am. Chem. Soc. 2004, 706-707,

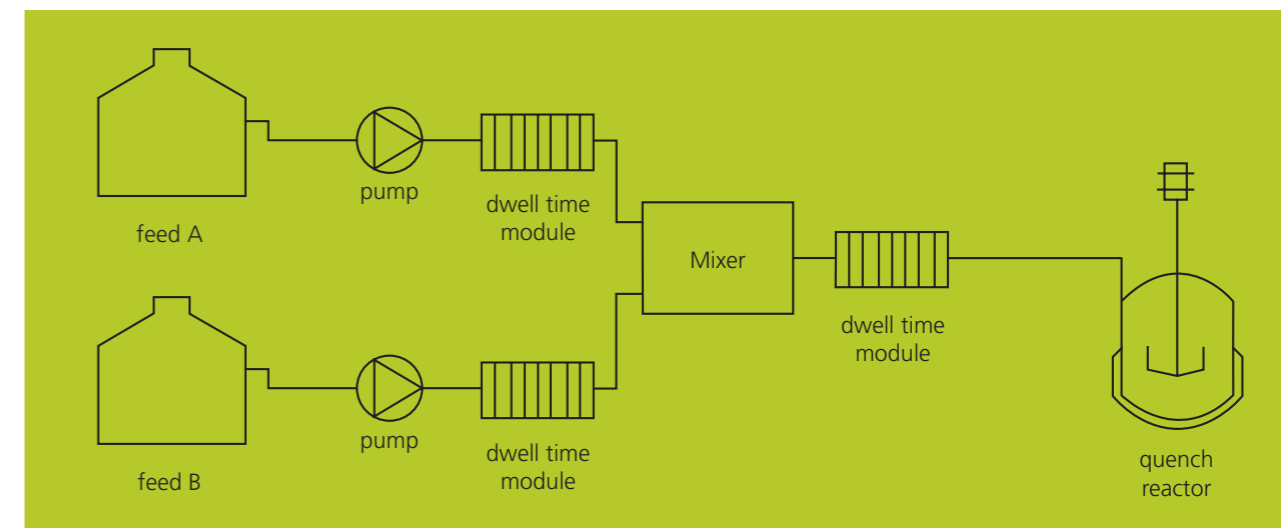
<sup>2</sup> Patent US 4,701,545

Furthermore, the de-protonated dichloromethane is known to form carbenes easily, which result in a multitude of by-products. The target for the MRT process can be enunciated in a nutshell: Run the reaction at moderate temperature but keep the low temperature selectivity and yield.

### MRT Solution

Our MRT setup for the reaction encompasses a mixer, dwell-time modules, tanks holding the reagents and a quench reactor where the product is collected for classical work-up. The development phase was started with a reference reaction run in a round bottom flask at a reaction temperature of -55°C for both the de-protonation and conversion with boronic ester, followed by a quench at room temperature. This resulted in 56% isolated yield of

## MRT-set-up for the lab and kilo-lab trials



**feed A:** dichloromethane + pinacolato-isopropylborane

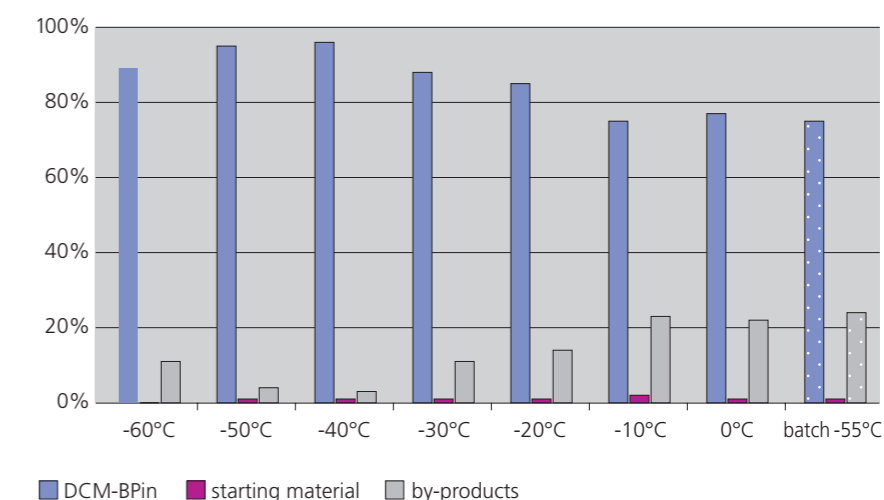
**feed B:** LDA in THF

**quench reactor:** holds the quench mixture (THF + HCl)

**note:** T-probes, flow-control units, secondary flows, and check-valves are not shown.

DCM-BPin (75% in the crude mixture). The MRT trials were run at different temperatures, while fixing the quench temperature at 20°C. A wide temperature range was found for the MRT reaction where high yield is possible. The eye-catching result is that the 0°C MRT trial already equals the -55°C batch reaction and a -40°C MRT run forms significantly more product.

### Results of the MRT trials and the reference (batch) reaction at -55°C



### Kilo-lab Quantities

The reaction was then executed on a kg-basis in order to provide material for R&D. The equipment was left unchanged besides the size of the feed tanks and

the quench reactor. Hence, no scale-up effects (prolonged reaction times, unexpected side reactions, etc.) were to be expected or had actually been seen. The MRT equipment was maintained at -40°C to -30°C. A three-mole run taking half a day resulted in 90% isolated yield.

### MRT and cGMP Conditions

We do not share the concerns we hear about MRT and cGMP conditions. If properly adjusted and instrumented, the control of a reaction performed in a continuous device is easier than a batch

reaction. If a batch reaction is out of the predetermined range hundreds of kilos of valuable material may be lost. In a micro-device the in-line analytical tool will be able to stop the process immediately if deviations are detected. PAT tools allowing this monitoring and controlling are optical sensors such as our newly installed Raman probe or the NIR probe. During early development, just to keep analytical expenditures low, we can also do it the classical way and analyze the bulk collected in the quench reactor as typically done for IPC.



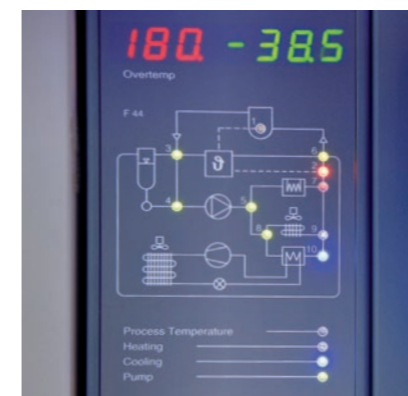
Operator supervising the control panel



Mass flow controller, a prerequisite for well defined mixtures



Pressure release valves are installed as safety precautions



Temperature control of the reaction media and the heat exchange liquid is assured