Further Applications
Siegfried has explored more than a dozen chemical transformations for MRT application. We focused 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 nitration.
- 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.

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.

It has, however, now matured into an efficient operation. The experience gained during these past years covers the types of chemicals 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.

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.
A Typical Reaction
The formation of DCM-BPin (2-dichloro-dimethyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane) is well suited for MRT since the synthesis of this compound combines the 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.

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.

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 DCM-BPin (75% in the crude mixture).

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.