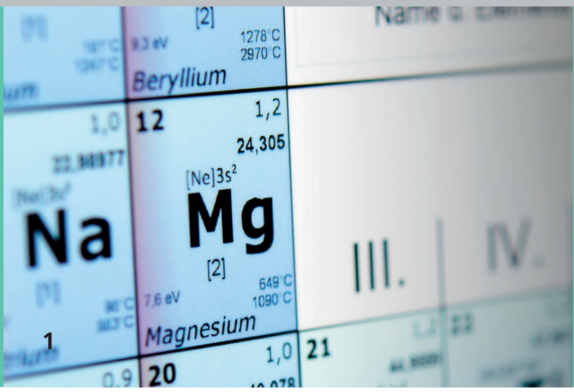
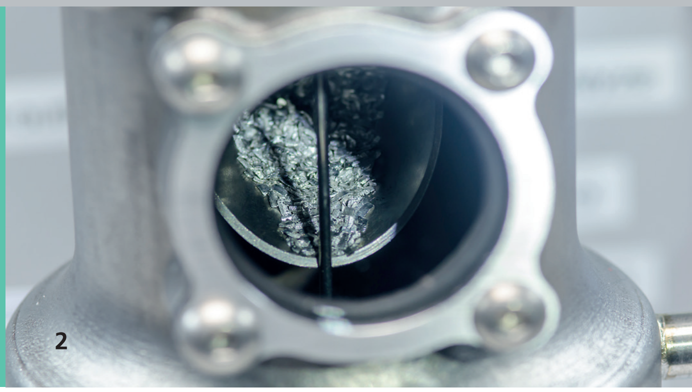
Fraunhofer

IMM

FRAUNHOFER INSTITUTE FOR MICROENGINEERING AND MICROSYSTEMS IMM





1 *Periodic Table of the Elements: Magnesium*

2 *Mg replenishing in the small scale pilot reactor*

SCALABLE CONTINUOUS GRIGNARD REAGENT FORMATION

Fraunhofer Institute for Microengineering and Microsystems IMM

Carl-Zeiss-Strasse 18-20
55129 Mainz | Germany

Contact

Dr. G. Menges-Flanagan
Phone: +49 6131 990-425
gabriele.menges-flanagan@imm.fraunhofer.de

www.imm.fraunhofer.de

Why Grignard?

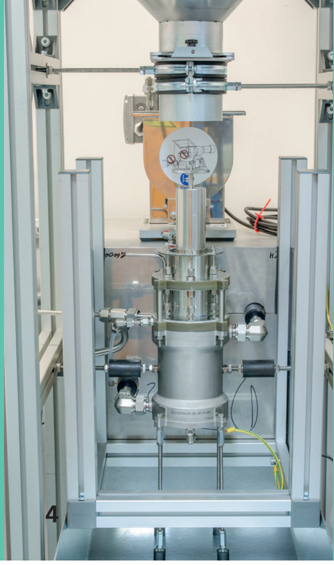
For more than 100 years, Grignard reagents have been invaluable in process chemists' toolboxes for efficient C-C bond formation, earning their inventor Victor Grignard the Nobel Prize for Chemistry in 1912. Nowadays, about 10 % of the top 50 API syntheses contain one or more Grignard reactions. However, the Grignard reagent formation is plagued by various drawbacks: depending on the halide used, variable-length incubation periods are observed and activating agents for the Mg such as iodine or an additional active halide may be needed to aid the start up.

Furthermore, once started, the Grignard reagent formation is an exothermic reaction, side product formation diminishes yields e.g. through coupling of starting material and product (Wurtz coupling). In batch, it is dosing controlled to dissipate the heat generated, and often requires long reaction times to drive the reaction to completion.

Scalable Grignard reagent formation via continuous processing

Considering these drawbacks, the Grignard reagent formation is an ideal candidate to benefit from continuous processing. Fraunhofer IMM has developed a laboratory as well as a pilot-scale continuous set-up for Grignard reagent formation that in either case allows for:

- Continuous provision of a large Mg excess throughout the reaction
- Integrated mechanical Mg activation
- Improved heat management
- Mg replenishing to render the process truly continuous in both reagent feeds



- Fast reaction control allowing temperature jumps as needed for optimal thermal management

The general considerations made for the case of Grignard reagent formations are also applicable to other solid/liquid processes, e.g. the formation of Zn organometallic reagents.

Reactor features

In-depth study and control of solid/liquid contacting was done in the laboratory as well as the pilot-scale reactor set-up possessing the following characteristics:

- Laboratory-scale throughput: 0.5-5 mL/min (0.03-0.3 L/h)
- Pilot-scale throughput: approx. 8-80 mL/min (0.5-5 L/h) in single reactor module approx. 30-300 mL/min (2-20 L/h) in four reactor modules

Furthermore, to enable a cost efficient reactor manufacturing, 3D laser melting was used for the reactor fabrication. It is envisioned that for scale-up of the solid/liquid reactor, 3D laser melting will play a crucial role in establishing sufficiently effective heat exchange structures.

Grignard reagent formation

A number of Grignard reagents (PhMgBr, Allyl MgCl, Ethyl MgBr, etc.) have been successfully synthesized in THF at varying concentrations. For the case of 1M PhMgBr, pilot-scale tests were successfully performed with a single pilot reactor module at the envisioned 15-fold throughput establishing the same product quality and yield as achieved on the laboratory scale. Product formation and quality were investigated via manual titration (methods established via commercially available reference materials). For more in-depth analysis of side product formation and conversion, samples were quenched and analyzed by gas chromatography (GC).
The following results were obtained:

- Full conversion of starting materials after a single passage through the reactor
- Residence times in the range of minutes
- Yields of Grignard reagents: 89–100 %
- Operation at minimal energy expenditure (heating/cooling)
- In-situ Mg activation (crucial for fast and successful initiation of the Grignard reagent formation)
- Refilling of Mg turnings established

Therewith, optimal reaction conditions can be rapidly established by increasing liquid flow rate and decreasing/increasing heating/cooling temperature to maintain full halide conversion for maximum throughput with minimal energy expenditure.

Reaction control is achieved by appropriate temperature management, rapid parameter optimization can be conducted, and fast start-up in case of less reactive Grignard reagents can be achieved via pre-tempering the reactor.

Overall, the continuous scalable formation of Grignard reagents yields the three dominant advantages of:

- Flexibility in production of reactive intermediates
- Improvement in product quality by suppression of side product formation
- Safety of formation of reactive intermediates

A further goal in establishing continuous Grignard reagent formation is the coupling on in-situ generated reactive intermediates with the Grignard reaction in a second subsequent step to improve overall product quality. This has been demonstrated on the laboratory scale and pilot scale reactor modules are avaialable for testing.

Applications

A focus of developments lies in establishing industrially relevant throughputs for the synthesis of Active Pharmaceutical Ingredients (API) but application areas also are e.g. agrochemicals as well as fragrances.

3 *Laboratory scale reactor with Mg replenishing unit*
4 *Pilot scale set-up with single module (full view)*
5 *Pilot scale view: Grignard reagent formation*