FRAUNHOFER INSTITUTE FOR CHEMICAL TECHNOLOGY ICT, BRANCH ICT-IMM

1 *Periodic Table of the Elements: Magnesium*
2 *Mg filled laboratory scale reactor for Grignard reagent formation*

CONTINUOUS GRIGNARD REAGENT FORMATION

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Why Grignard?

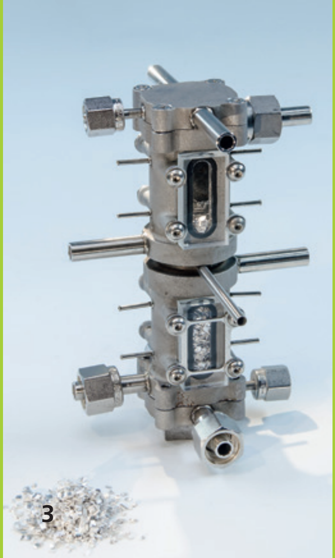
For more than 100 years, Grignard reagents have been invaluable in the chemists' toolbox for efficient C-C bond formation, earning the inventor Victor Grignard the Nobel Prize for Chemistry in 1912. Nowadays, about 10 % of the top 50 API syntheses contain one or more Grignard reactions. However, the reagent formation is plagued by a number of 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, in batch it is dosing controlled to dissipate the heat generated, and often requires long reaction times to drive the reaction to completion.

Advancing Grignard reagent formation through continuous processing

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

- Continuous provision of a large excess of Mg throughout the reaction
- Improved heat management
- Integrated Mg activation
- Fast reaction control allowing temperature jumps as needed for optimal thermal management



- For the case of the pilot-scale set-up: a continuous replenishing of Mg turnings to render the process truly continuous in both reagent feeds

The general considerations made for the case of Grignard reagent formations are also applicable to other solid/liquid processes.

Reactor characteristics and application

In-depth study and control of solid/liquid contacting was done via laboratory and pilot-scale reactor set-ups possessing the following characteristics:

- Viewing windows for optical inspection of reaction progress
- Laboratory-scale throughput: 0.5-5ml/min
- Pilot-scale throughput: 5-50ml/min
- Recording of T, flow rate, and Mg replenishing process

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.

A further goal in establishing continuous Grignard reagent formation is to couple the insitu generation of the reactive intermediate with the Grignard reaction in a second subsequent step to improve overall product quality.

Grignard reagent formation

A number of Grignard reagents (PhMgBr, Allyl MgCl, 2-thienyl MgBr, etc.) have been successfully synthesized in THF at varying concentrations. For the case of 1M PhMgBr, additionally pilot-scale tests over the course of up to 4h were performed in the larger reactor set-up. Product formation and quality were initially observed via inline ATR-IR measurements Grignard concentrations during the course of the reaction and optimization process were determined by titration (methods established via commercially available reference materials). The following results were obtained:

- Full conversion of starting materials is reached after a single passage through the reactor with residence times in the range of minutes
- Yields of Grignard reagents determined by titration range between 89–100%
- For PhMgBr, no coupling side product observed via ATR-IR
- Operation at minimum T
- Insitu Mg activation crucial for fast and successful initiation of the Grignard reagent formation
- On the pilot-scale, refilling of Mg turnings successfully established

In most cases, no auxiliary agents for Mg activation are needed to initiate the Grignard reagent formation. For less reactive Grignard reagents, small amounts of iodine can be added onto the Mg bed prior to the halide addition to successfully initiate the reaction. The product solution containing iodine can be collected and discarded as to not contaminate the main product collected. 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.

Energy efficiency via temperature management

Optimal reaction conditions can be established by increasing liquid flow rate and decreasing temperature to maintain full halide conversion for maximum throughput with minimal energy expenditure.

3 *Full view of laboratory-scale reactor with multiple T zones*
4 *Pilot-scale reactor set-up with Mg replenishing*
5 *Full view of pilot-scale reactor set-up*