Fraunhofer IMM

Fraunhofer Institute for Micro-engineering and Microsystems IMM

Organometallic reactive intermediates

Scalable continuous organometallic reagent formation and consumption

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, a large number 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.

Considering these drawbacks, the Grignard reagent formation is an ideal candidate to benefit from continuous processing that will allow for:

- continuous provision of 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
- applicability to other solid/liquid processes, e.g. the formation of Zn organometallic reagents

Organometallics in flow

Laboratory scale

A large number of Grignard reagents (PhMgBr, Allyl MgCl, Ethyl MgBr, etc.) as well as Zn reagents have been successfully synthesized in THF and other solvents at varying concentrations. Optimal reaction conditions were rapidly established by varying liquid flow rate and decreasing/increasing heating/cooling temperature to maintain full halide conversion for maximum throughput with minimal energy expenditure. Yields ranged from 80-100 % depending on reagent.

Pilot scale

Again, a number of Grignard as well as Zn reagents were successfully synthesized on pilot scale throughputs of up to 20 l/h. Ease and speed of scale-up were successfully proven in the patented modular Fraunhofer IMM developed set-up consisting of 3D laser-melted reactor modules and again including a mechanical integrated in-situ metal activation.

Conversion of organometallics in flow

Laboratory scale

A number of follow-up reactions have been investigated for both, Grignard and Zn, reagents including the following:

- Grignard reaction
- Reformatsky reaction
- Saytzeff reaction
- Negishi coupling

Throughputs on the laboratory scale varied from 1-10 ml/min depending on reactivity and nature of the second step.

Pilot scale
Exemplary, the synthesis of diphenylmethanol from phenylmagnesium bromide and benzaldehyde was successfully piloted at a total throughput of 5 l/h again using a modular Fraunhofer IMM developed set-up.

Applications and beyond

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 flavors and fragrances as well as other fine chemical synthesis employing organometallic reagents.

Available equipment
At present, three laboratory scale set-ups and two-pilot scale set-ups with 2 and 4 reactor modules are available for organometallic synthesis testing. Additionally, 2nd step set-ups on the laboratory as well as pilot scale are available for testing.

The configuration of these test rigs allow the investigation of organometallic reagent formation reactions followed immediately by catalyzed or non-catalyzed consumption reactions with integrated quality control ensuring the reactive intermediate quality e.g. by online IR. Additionally, existing set-ups can be adapted or new set-ups can be equipped according to the specifications of your application.

Experimental conditions
- temperatures from 0 °C up to 100 °C depending on solvents used
- laboratory scale throughput: 0.5-10 ml/min (0.03-0.6 l/h) for organometallic reagent formation
- pilot-scale throughput: approx. 10-100 ml/min (0.6-6 l/h) in single reactor module, approx. 30-300 ml/min (2-20 l/h) in four reactor modules for organometallic reagent formation
- throughputs doubled for follow-up reactions
- adaptations towards higher temperatures and pressures or other requirements can be carried out according to the specifications defined by our clients

Analytical instruments
All organometallic reagents are quality controlled and analyzed via the appropriate analytical equipment. Available are the following analytical tools:

- GC/FID
- GC/MS
- online FTIR
- titration
- thermometric titration

Services and benefits

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 flavors and fragrances and fine chemicals.

Our services in the field of organometallics in flow
- process development for novel Grignard and Zn organometallic reagents
- investigations on the laboratory and pilot scale for formation and consumption of organometallics
- optimization of reaction conditions for maximum throughput with minimal energy expenditure

Your benefits
Employing our technology in the synthesis and consumption of organometallic reactive intermediates, you gain:

- safer production through small reactor hold-up
- cost and time savings through improved product quality
- faster time-to-market through a scalable and modular approach
- access to the entire range of Grignard and Zn reagents in one set-up through intelligent temperature management
- maximum in quality/yield
- minimum in side product formation (e.g. Wurtz coupling)
- innovation head start through our longstanding experience in the field

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G. Menges-Flanagan et al., Org. Process Res. Dev. 2020, 24, 2, 315-321 | G. Menges-Flanagan et al., Org. Process Res. Dev. 2021, 25, 427-433 | Patent: DE102016206211