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Chemium & Valsynthese

Partner for safe & efficient supply of grignard reagents and more

First discovered at the start of the twentieth century, Grignard reagents are a powerful tool in organic chemistry. Formed by the reaction of magnesium metal with halide derivatives, these highly reactive organomagnesium halides, which are still an active area of research, have found application in industry segments as diverse as pharmaceuticals, agrochemicals, materials science, and energy storage. Grignard reagents are mostly used for carbon-carbon bonds forming reactions, leading to a variety of chemical functions including alcohols, carboxylic acids, and other organic compounds.

Yet the way Grignard reagents are industrially synthesized has not evolved until recently. Produced from the heated combination of organic halides and magnesium in the presence of ethereal solvents (diethyl ether (Et²O), tetrahydrofuran (THF), methyl tetrahydrofuran (MeTHF), etc.), their synthesis has historically been plagued by quality and safety issues. Because they are highly reactive, they react violently with water to produce heat and possibly flammable gases. And as they are often supplied in flammable solvents, and are required in large volumes, preparation, handling and storage can be challenging.

An alliance to bring Grignard reagent supply into the future

To provide safe and reliable development, scale-up and supply of Grignard reagents, Belgium based Chemium srl and Swiss Fine Chemicals manufacturer Valsynthese SA have combined the benefits of Chemium's cutting-edge Mg^{FLOW}® technology with Valsynthese vast experience of working with hazardous and high-energy chemicals, and upstream and downstream expertise, and its multi-purpose plant configuration. Valsynthese's cGMP and ISO production facility has grown over the last 40 years to become a highly versatile site with complementary capabilities and scale, including a Kilo-Lab and pilot plant (1 to ca. 100 kg), two multipurpose plants (> 100 kg to multi-tons), phosgenation plant (> 50 kg to multi tons), and a brand new hydrogenation plant (> 50 Kg to multi-tons), plus full research and development and quality control for any kind of CDMO development projects.

Mg^{FLOW}® Technology

As its name suggests, Chemium's patented Mg^{FLOW}® technology relies on continuous flow chemistry principles to tackle many of the safety and efficiency challenges associated with the synthesis of Grignard

reagents. Mg^{FLOW}® units are comprised of a reactor column that is continuously fed with magnesium, organohalide and a solvent under inert atmosphere. The product is continuously withdrawn from the unit and directed to the next processing step's reactor or to a storage container. Mg^{FLOW}® is a true continuous process that can operate on a 24/7 basis.

The process is continuously monitored by probes gathering temperature, pressure, flow rate data and others. In addition, the technology is equipped with a process analytical tool, used to closely examine chemical information and the instantaneous products quality as the Grignard solution exits the Mg^{FLOW}® unit.

These data support exceptional process stability and are valuable tools to prevent any safety issue or out-of-specification production.

Compared with traditional batch production, Mg^{FLOW}® provides advantages in:

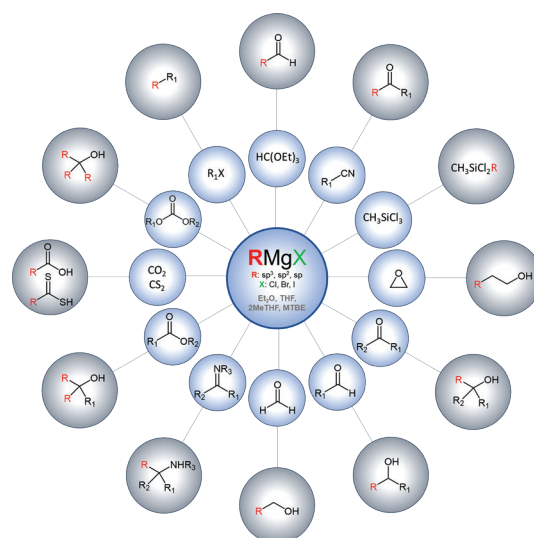
Safety

- Limited reactor volume - regardless of production scale, which effectively caps the potential for runaway reactions.
- Self-initiated reaction, which does not require additional activation compounds.
- Automatic triggering of safe mode should any failure occur.

Efficiency

Thanks to optimized chemistry including favorable magnesium stoichiometry, extensive working range of temperatures (0 - 110 - °C), and reduced residence time, formation of Grignard reagents is promoted, and the presence of impurities is minimized.

Quality is optimized further through the precise control of temperature and flow rate within a homogenous reactor. With inline PAT for continuous



quality control, Mg^{FLOW}® technology yields products of consistently high quality, contributing to significantly reduced wastes.

Scalability

The Mg^{FLOW}® Technology removes any scalability concern typically observed in a batch production. The seamless scale-up allows the technology to produce kilograms of solution up to hundreds of tons without impacting the quality, nor the safety.

The two companies' partnership brings many advantages to clients.

For example, in the case of synthesis sequences, where halide derivatives are not commercially available, they can be produced by Valsynthese and converted to meet a customer's needs using Mg^{FLOW}® technology, reducing handling and transportation of dangerous Grignard reagents as intermediates.

Easy access to custom Grignard reagents

As established supplier and manufacturer, Chemium provides a wide range of ready-to-use Grignard solutions for further processing.

	Batch Process	Mg ^{FLOW} ®
Reactor Volume (l)	3'000 - 12'000	Less than 30 liters
Energy Potential (J)	600'000 - 2'400'000	Ca. 4'000
Temperature Control	Fluctuates	Highly stable
Residence Time	Hours	Minutes
Initiation	Tricky	Easy
Waste	5 - 10%	0.5 - 3%
Footprint	Workshop	A few m ²
Quality Control	One per batch	Every minute
Operations	Largely manual	Fully automated
Energy Consumption	Pre-heating + heat removal + cooling	No Pre-heating, no cooling

Product	Wt%*	[RMgX]*	Solvent
iso-Propylmagnesium chloride	20%	2.0 M	THF
Ethylmagnesium bromide	40%	3.4 M	2MeTHF
Phenylmagnesium bromide	18%	1.0 M	THF
Phenylmagnesium chloride	25%	1.9 M	THF
4-Tolylmagnesium chloride	15%	1.0 M	THF
4-(N,N-Dimethylaniline) magnesium bromide	12%	0.5 M	THF
Cyclopropylmagnesium bromide	8%	0.7 M	THF
n-Butylmagnesium chloride	24% (17%)	2.0 M (1.7 M)	THF (DBE)
Cyclohexylmagnesium chloride	20%	1.3 M	THF/Toluene
4-Methoxyphenylmagnesium bromide	11%	1.0 M	THF
tert-Butylmagnesium chloride	20% (13%)	1.7 M (0.9 M)	THF (DBE)
sec-Butylmagnesium chloride	25%	2.1 M	THF
Cyclopentylmagnesium bromide	18%	1.0 M	THF
n-Propylmagnesium bromide	27%	2.0 M	THF
3-Methoxyphenylmagnesium bromide	21%	1.0 M	THF
n-Amylmagnesium chloride	27%	2.0 M	THF
Methyl Magnesium Bromide	35%	3.4 M	2-MeTHF
Methyl Magnesium Chloride	22%	3.0 M	THF

Should custom-made Grignard reagents or downstream products be required, Chemium and Valsynthese collaborate closely with clients from project definition to feasibility, methods development, pilot production and a scalable commercial supply, ensuring high-quality services and tailored solutions.

In the research stage, Valsynthese collaborates with the client to define the research and production process strategy. This includes identifying the most efficient synthetic routes and process optimization. Valsynthese focuses on the chemistry, manufacturing, and controls (CMC) aspects, ensuring robust and reproducible processes. If required, kilo-lab-scale or pilot-scale quantities are produced for customers' trials and scale-up processes are defined to identify any challenges, and further optimize the process. During scale-up to production, Valsynthese assesses tech transfer readiness to commercial manufacturing.

This step ensures that the process is robust and suitable for large-scale production.

For new reagents, Chemium will conduct a flowability assessment through its laboratories and pilot-scale equipment, culminating in a quick go/no go decision with the client for commercial/ industrial production, typically in only a few weeks.

Conclusion

The cooperation of Valsynthese and Chemium will provide customers with integrated solutions around Grignard chemistry, making a comprehensive package of 'off-the-shelf' and custom Grignard reagents available for various chemical processes. At the core of the partnership is the innovative Mg^{FLOW}® Technology, a ground-breaking continuous flow process designed especially for the safe and efficient manufacturing of Grignard reagents.

This technology offers exceptional temperature control and innovative mixing, which reduces wasteful impurities and eliminates infamous reaction runaway risks, requires minimum human monitoring or intervention, and further reduces the process safety concerns inherent to Grignard batch production.

Both companies bring a wealth of knowledge and experience to the table to provide custom synthesis and contract manufacturing for the chemical and pharmaceutical industries in combination with the latest advances in flow technologies.

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