

Safe Industrial-Scale Production of Grignard Reagents in Continuous Mode, A Successful Paradigm Shift



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Executive Summary

CHEMIUM is reshaping Grignard reagent manufacturing for the fine chemical, pharmaceutical, agrochemical and specialty chemicals industries. Based in Louvain-la-Neuve, Belgium, this innovative company with its proprietary continuous flow Mg^{Flow}® technology, is taking this chemistry a huge step towards safer, more sustainable, and economically advantageous Grignard production at industrial scale. Supported by a strategic collaboration with Swiss CDMO partner Valsynthese, CHEMIUM's approach marks a paradigm shift in overcoming the traditional limitations of batch processing, setting new standards in process reliability.

Grignard reagents, these organometallic intermediates widely used to produce pharmaceuticals, agrochemicals, flavors and fragrances, opto-electronics and specialty chemicals, have become an integral part of countless synthetic routes. Since their initial discovery by Victor Grignard in the early 1900's, their industrial production relied on batch processes.

This reaction is challenging by nature, (a) first because of its high exothermicity: the heat of reaction released during the synthesis is very high (on average 340 kJ/mol). (b) second, the kinetic profile is nonlinear with an (often unpredictable) induction period, (c) Finally, some Grignard reagents can decompose under certain conditions and cause uncontrolled run-away reactions.

In spite of all those hazards, and a lack of safe alternatives, industry still relies on batch processes for large scale syntheses, sometimes using up to 500 kg of magnesium per batch². Still the number of accidents and casualties is sufficient to state that this reaction is hazardous (see Table 1).

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² Prativa B.S. *Molecules* **2010**, 15 - <https://pmc.ncbi.nlm.nih.gov/articles/PMC6257204/pdf/molecules-15-01825.pdf>

Table 1. A few incidents related to Grignard production (focus on self-degradation).

Chemical / Reason	Location	Damage/casualty	Scale	Year
Vinyl-MgCl in THF, thermal run-away and decomposition	Germany ³	“parts of the equipment were significantly damaged”	Pilot plant	1993
(unsp.) uninitiated reaction in the induction period, with large heat accumulation	China ⁴	1 fatality 2 injured	Unsp.	2014
2-(F₃C)Ph-MgBr	USA ⁵	ND	“small amount”	-
3-(F₃C)Ph-MgBr	USA ⁵	ND	1.5 kg	-
	UK ⁶	Extensive laboratory damage	2 kg	1971
4-(F₃C)Ph-MgBr	_7	“... minor damage was done to the laboratory area.”	< 250 ml	1997
	USA ⁸	“Destruction of a factory and loss of life. 1 killed, 6 injured.	Plant-scale	1981
(5-F-2-MePh)-MgBr	_9	“Lab reaction explodes”	20 L	1995

In the last decade, flow chemistry has emerged as a safe alternative to the most hazardous reactions and has been successfully implemented on an industrial scale for highly energetic transformations such as nitration or fluorination.¹⁰ By contrast, despite research attempts documented in numerous patents, already from the 1950s¹¹, Grignard chemistry—characterized by exothermicity and hazards comparable to those of typical nitrations—lacks industrially proven safe continuous solutions to our knowledge.

The reasons for this gap are summarized in Table 2 and lie predominantly at the interface between chemistry and process development.

Table 2. Main difficulties found in the implementation of Grignard reactions in a continuous setup.

Heat management	Design for proper heat removal Automated thermal control
Safety management	Direct magnesium activation (no induction) Work under strictly controlled conditions Fully autonomous safety response – no human intervention required Wetted parts compatibility Material abrasion
Multiphase management	Proper dosing of solids (magnesium) Handling of gaseous halides Sustaining inert gas blanketing
Quality management	Steady product quality Full conversion with minimal residence time Grignard free of any contamination (no solids) Process Analytical Tool and reliability over long productions
Solid management	Sustain flowability over time (no clogging, no crystallization) Inorganic salts sequestration

³ Rittmeyer P., *Z. Naturforsch.* **1993** 48 b, 1223-1226.

⁴ (a) Wang W, *Int J. Chem. Eng.* **2022**; Thermal Hazards of Synthesizing a Grignard Reagent under Different Dosing Rates.

(b) Wei P., Lu J., Li X., *China Occupational Safety and Health.* 9 (2014) 56-57, CNKI:SUN:ZGAQ.0.2014-09-034

⁵ Bretherick's Handbook of Reactive Chemical Hazards, Vol. 1, 7th ed. (Ed.: P. G. Urben), **2007**.

⁶ Appleby, I. C. *Chem. Ind.* **1971**, 120.

⁷ *Chem. Eng. News*, **1997**, 75(11), 6

⁸ Ashby, E. C.; Al-Fekri, D. M. *J. Organomet. Chem.* **1990**, 390, 275 Post Tribune; Gary, Indiana; November 6th, 1981

⁹ Jasiewicz, M., *Chem. Ind.* **1995**, 246-246.

¹⁰ Xing D. *RSC Adv.*, **2025**, 15, 3474–3479 - Development of a scalable and sustainable continuous-flow microreaction process for mononitration of aromatic compounds with high selectivity and yield

¹¹ US2414505A (priority date: **1943**, inventor: C.E. Arntzen, Continuous grignard reaction process); US2464685A (priority date: **1946**, inventor: A. Hirsch, Continuous grignard method).

CHEMIUM started the development of a continuous Flow system for Grignard reactions in 2016 with a highly skilled team of professionals at the interface of chemistry and process development (see **Figure 1**).

The first small scale continuous prototype initially tested was fully manual (**L-Flow**, laboratory). It has gradually evolved in design, to solve operational issues and be able to work with gaseous halides such as methyl chloride. In 2021, the process design including automation was patented and registered as the **Mg^{Flow}**® technology thanks to the pilot scale unit (**P-Flow**, Pilot) in which the production of a dozen of Grignard reagents has been validated.

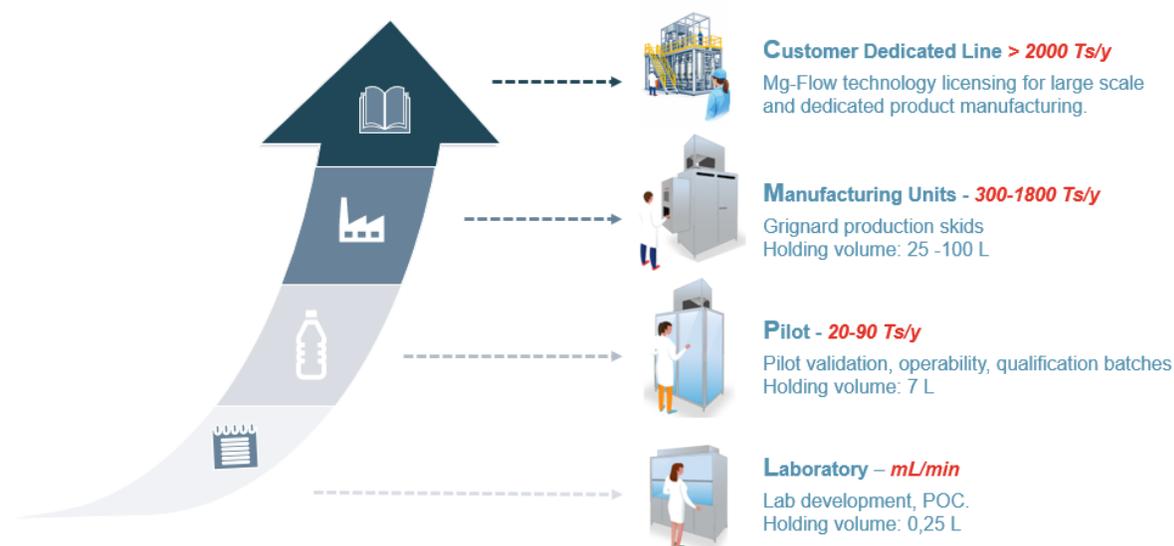


Figure 1. Continuous production units developed by CHEMIUM.

In 2023, the manufacturing unit was built (**M-Flow**, see Figure 2); it is operated at Valsynthese in Switzerland and remotely controlled and monitored from Belgium. With a Grignard production unit integrated in the certified and qualified infrastructure of Valsynthese (ISO, GMP), CHEMIUM benefits from the Swiss CDMOs deep knowledge and established expertise and culture of handling and supervising hazardous chemistries on large scale. The site in Brig is perfectly fitted to allow the shipment of large volumes, from drums to pressure tanks (portable or isotanks).



Figure 2. From raw materials to Grignard reagents – **Mg^{Flow}**® is a proven and demonstrated technology for the continuous production of Mg-based organometallics. CHEMIUM technology hosted at Valsynthese (Switzerland).

CHEMIUM is producing and selling Grignard reagents on commercial scale using its novel **Mg^{Flow}**® Technology,¹² and is also licensing the same. Companies having such a skid in their portfolio will enjoy additional means of fine tuning their reaction conditions, overcoming safety, viscosity, solubility and selectivity challenges. Furthermore, producing these intermediates on site and using them right after paves the way for higher concentrations than the standards traditionally offered on the market, reducing the amount of solvent used and minimizing recycling volumes.

Key benefits of continuous Grignard production

Moving production from standard batch to continuous with **Mg^{Flow}**® offers significant advantages:

- **Process Safety** - The reaction takes place in a small, confined volume with high heat removal capacity and a high degree of automation. The production is stable and smooth with no risks of a run-away reaction. This is key when dealing with hazardous reagents or heat-sensitive intermediates, also significantly reducing the risks while handling fluorinated intermediates.
- **Seamless Operational Control** - In-process monitoring by PLC and sensors is constantly available, and the campaigns can be operated remotely. Production can be paused and restarted at any time with no impact on product quality and no need for reinitiation. Handling operations are reduced to a strict minimum.
- **Product Quality** - is monitored continuously online using Process Analytical Tools (PAT). Out-of-specification material is automatically detected and diverted before collection, ensuring downstream quality and reliable automated operations. Impurity profiles are improved through higher Grignard selectivity—particularly sharp reduction of Wurtz coupling byproducts—while maximizing yields.
- **Beyond Standard Conversions** - By design, the unit allows total conversion of the halide precursor. In several cases, this new process allows the use of chlorides, where batch processes only work with the bromides, paving the way for cost reduction and higher efficiency.
- **Cost savings** – This technology comes with an excellent heat exchange that allows a constant but reduced cooling requirement, as a result, cooling infrastructures are downsized by a factor of 5. The footprint of the unit - requiring just a few m² - and the cost structure are set to remain unrivaled for some time.

¹² for details, please visit https://www.chemium.com/grignard_reagents/

After 2 years of successful and safe manufacturing, the technical challenge is met for CHEMIUM. Industrial large scale Grignard manufacturing is now possible with high reliability with the **Mg^{Flow}**® continuous technology. Capacities can be scaled up seamlessly due to the technology's continuous nature; an additional large-scale manufacturing skid was commissioned in early 2026.

Beyond standalone Grignard production, CHEMIUM is developing integrated downstream chemistry systems that enable direct utilization of freshly generated Grignard reagents in subsequent reactions. This continuous integration maximizes yields, improves impurity profiles - especially for unstable Grignard reagents - and significantly reduces solvent consumption by eliminating intermediary storage and recycling steps. This approach delivers superior economics and operational safety for industrial partners seeking seamless, thermally-optimized production chains.

Large-scale manufacturing extends far beyond catalog Grignard reagents: our agile R&D team accelerates custom solutions from development to industrial production in just a few weeks, enabling partners to rapidly scale tailored intermediates and capture competitive advantages in pharma, agrochem, and specialty applications.



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EFFICIENCY BY DESIGN