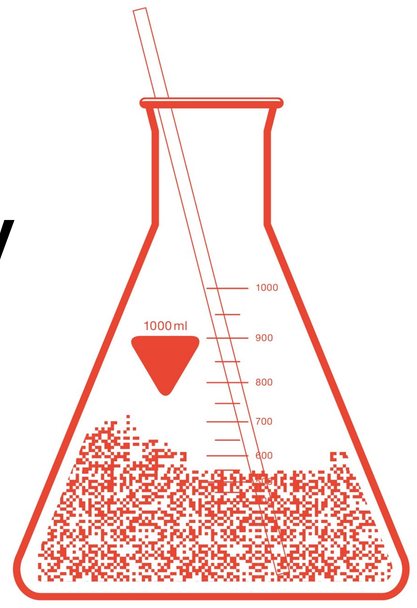
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Synthesis of Grignard Reagents Using Mechanochemistry

Marcel Marti

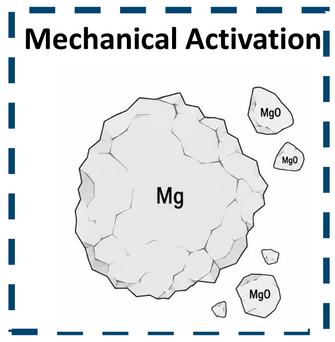
Bachelor-Thesis, Chemistry

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Introduction The Grignard reaction remains widely used in industry for C–C coupling but carries inherent safety concerns. Delayed initiation and stalled reactions, both caused by the passivating oxide layer on the magnesium, can release the accumulated reaction heat rapidly and destabilize the reaction mixture thermally [1]. Several technologies address these concerns. Flow processes such as packed magnesium bed reactors lower the reactive inventory compared to classical semi-batch operation [2]. Mechanochemistry instead facilitates Grignard formation by mechanical activation of the magnesium [3]. Bead milling, closely related to ball milling, uses microbeads that enhance the reaction properties at high rotational speeds and has recently been applied to a more sustainable amide bond formation [4].

Objective This work aims to develop a bead mill Grignard process that improves safety through mechanical magnesium activation and continuous processing. Benzyl chloride was chosen as an exemplary substrate, as it is known for its pronounced tendency towards side product formation. The process is transferred from Semi-batch operation to, ultimately, a Single-pass mode, accompanied throughout by a safety assessment. Selectivity serves as the key indicator for comparing the operating modes.



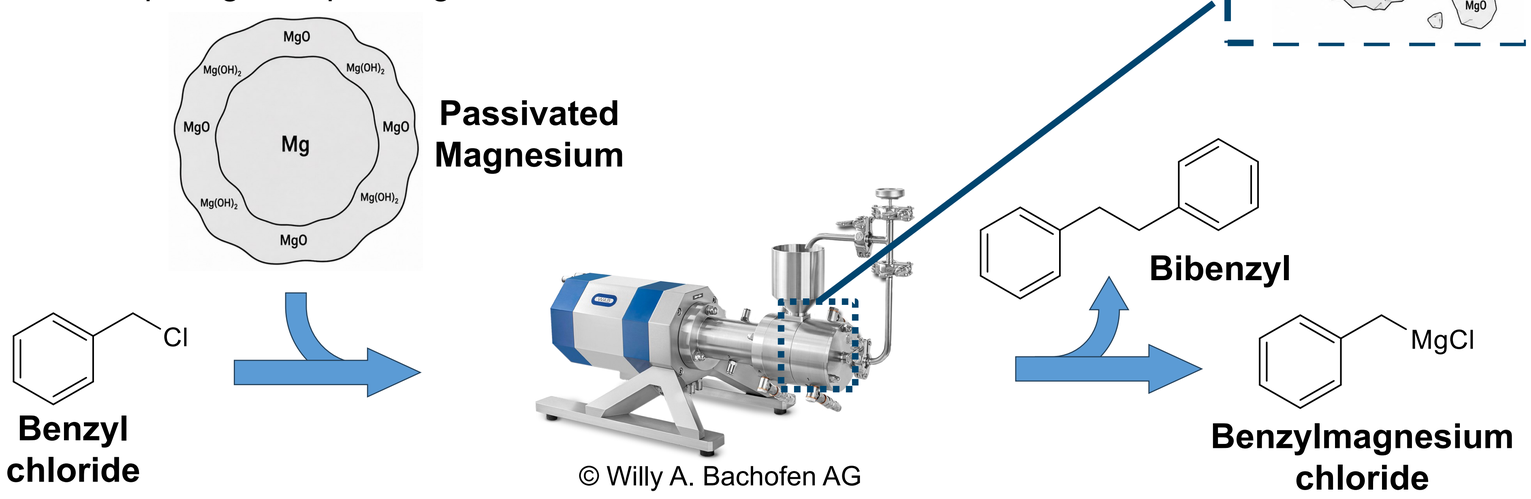
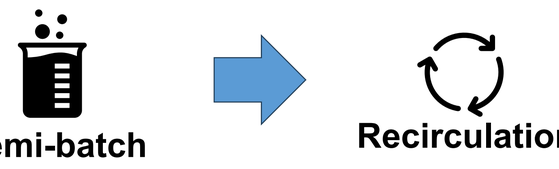


Figure 1 Grignard formation from benzyl chloride in the DYNO®-MILL RESEARCH LAB (RL), bibenzyl side product from Wurtz coupling.

Reaction Performance At higher concentration, the modes differed clearly in selectivity. Recirculation performed best, but Single-pass was rated superior because it possibly decouples throughput from reactor volume.



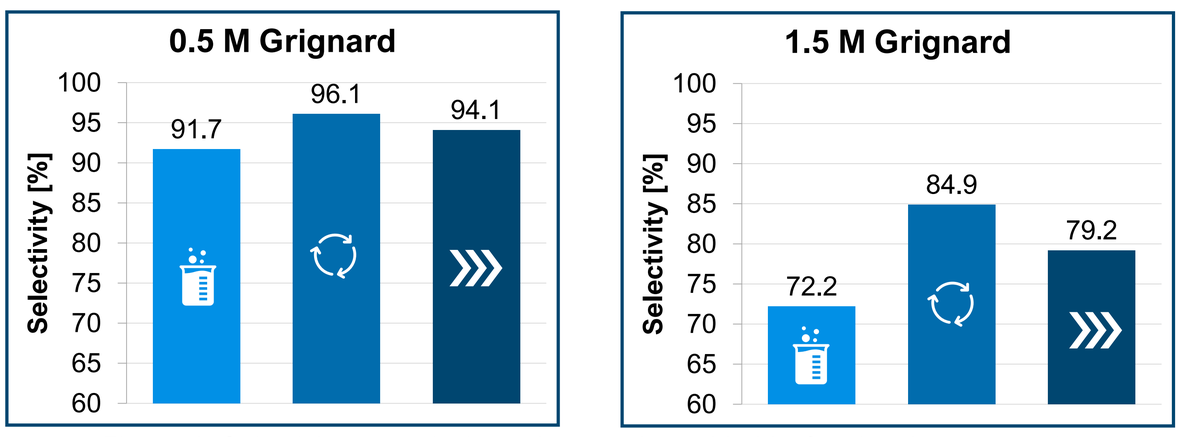


Figure 2 Selectivity towards benzylmagnesium chloride for the three operating modes at 0.5 M and 1.5 M target concentration. Single experiments, GC analysis.

Process candidate Single-pass enabled semi-continuous Grignard synthesis with up to 96.8 % selectivity at 96.6 % conversion, competitive with modern Grignard processes [2]. A larger magnesium excess was crucial for a stable operating window with steady conversion. Increasing the halide flow rate shifted the balance by +2.7 % selectivity and −1.3 % conversion, indicating further potential for optimization.

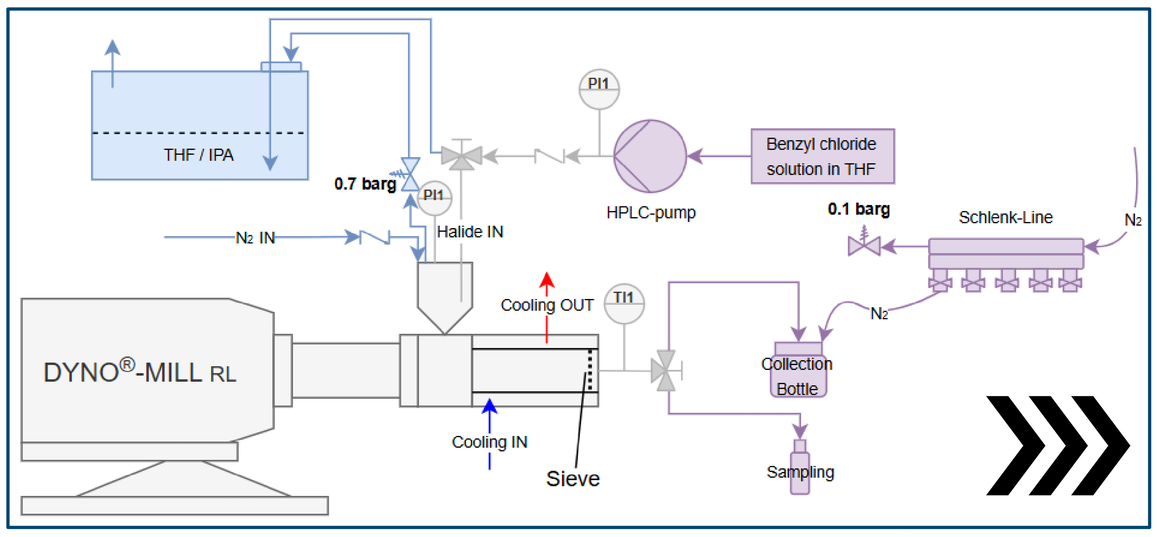
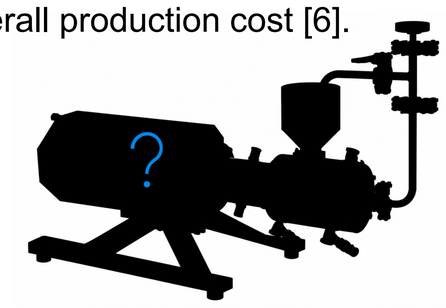


Figure 3 Process flow diagram of the single-pass setup with DYNO®-MILL RL.

Outlook The developed Single-pass process is only semi-continuous with respect to magnesium. Optimizing the milling chamber to enable continuous magnesium feeding is therefore crucial for achieving competitiveness with modern Grignard process technologies. Multiple halide feeds could further improve the selectivity of the Single-pass mode at higher bulk Grignard concentrations.

Benzyl chloride proved to be a suitable probe for evaluating the achievable product selectivity of the process. However, the main strength of mechanical activation lies in its ability to facilitate reaction initiation. Substrates such as 3-chloroanisole are reported to be difficult to initiate with conventional magnesium turnings and are therefore typically used as the corresponding bromide [5]. Demonstrating the synthesis of this widely used building block with mechanically activated magnesium could give access to the less expensive chloride and reduce the overall production cost [6].



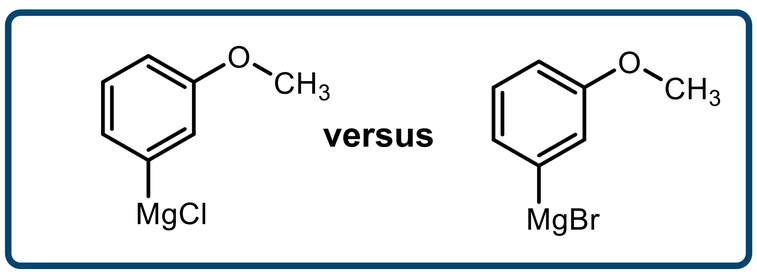


Figure 4 Target of a future substrate extension

Conclusion The Grignard synthesis in a bead mill was demonstrated in different operating modes, with Single-pass emerging as the most viable candidate. It combines the reduced inventory of continuous processing with the vigorous mechanical activation provided by the beads.

The reliable initiation is the main safety advantage of the process. At the same time, a new hazard was identified, as the reduced particle size of the reactive metal showed pyrophoric properties. This was controlled by design, but an intrinsic risk remains. The process is still at an early stage, but its potential field of application has been defined and provides a basis for future studies.

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