Selectivity of Grignard reagent formation – from semi-batch to continuous lab and pilot scale

Eva Deitmann [1,2], Kai Dahms [1], Michael Maskos [1], Dirk Ziegenbalg [2,], Gabriele Menges-Flanagan [1,*]*

1 Fraunhofer IMM, Carl-Zeiss-Strasse 18-20, 55129 Mainz/Germany

2 Ulm University, Institute of Chemical Engineering, Albert-Einstein-Allee 11, 89081 Ulm/Germany

KEYWORDS Grignard reagent formation, scale-up, organometallic synthesis, flow chemistry, selectivity.

ABSTRACT The formation of Grignard reagents from metallic magnesium and a halide is often accompanied by the formation of the Wurtz coupling product, an undesired side product formed by the reaction of a Grignard reagent molecule and a halide molecule. By using a scale-up approach from semi-batch type synthesis to continuous lab and pilot scale for various Grignard reagents, it is demonstrated that a continuous production process can improve Grignard reagent selectivity and reduce Wurtz coupling.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

INTRODUCTION

Grignard reagents are organomagnesium halides and known for roughly about 100 years since Victor Grignard was awarded the Nobel Prize for Chemistry in 1912. The most common used production procedure for Grignard reagents is the direct synthesis, which is an exothermic surface reaction between the metallic magnesium and the halide in a water-free and mostly ethereal solvent (figure 1)[1]. Grignard reagents are known for their potential to be used as intermediates in C-C-coupling reactions, forming a new carbon-carbon bond. They are used as intermediates in numerous production processes, e.g. in the production of agrochemicals, flavors and fragrances and active pharmaceutical ingredients[2–9]. On an industrial level, a dosing-controlled semi-batch process for direct Grignard reagent synthesis is the established production method to manage the heat generated in the exothermic reaction[1], although within process development research there have been studies to develop a continuous Grignard reagent formation process either based on a flow tube reactor[10–16] or a stirred tank reactor[8,17–21]. Furthermore, scale-up of the Grignard reagent formation to continuous or discontinuous pilot or production scale are also reported, in some cases accompanied by integrated online or inline infrared spectroscopy to monitor the feed and consumption of the halide educt or the formation of the Grignard reagent[22–26]. Compared to a batch reactor, a continuous production process for Grignard reagent synthesis has some advantages, which are mostly based on the novel process window employing a large magnesium excess and the smaller reactor volume required for the continuous synthesis. Oftentimes, solvents and halides for Grignard reagent formation are noxious or even dangerous for humans and the environment. In case of leakage of continuous reactors, less chemicals are released due to the smaller reactive volume. Furthermore, using a continuously operated and potentially automatized production process reduces risks due to

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

exposure to the chemicals. Halide accumulation in combination with boiling retardation can result in a sudden start of the reaction and vigorous boiling[26]. Such an event is less problematic for a continuous production process in which the halide is constantly pumped through a reactor filled with magnesium and in which reactants cannot accumulate. Beside this, additional chemicals, potentially required to facilitate reaction initiation, are more easily removed from a continuously operated reactor.

Nevertheless, Grignard reagent formation remains challenging for the following reasons[1,27,28]:

- varying induction periods due to a passivating oxide layer on the magnesium surface or due to traces of moisture,
- high exothermicity with the risk of a potential run-away reaction,
- side-product formation such as the Wurtz coupling product by reaction of a halide molecule and a Grignard reagent molecule (figure 1) or decomposition of the Grignard reagent upon contact with air or moisture.

While varying induction periods and high exothermicity are potential production safety hazards that must be addressed through efficient heat management and magnesium activation, side-product formation diminishes Grignard reagent quantity and product quality.

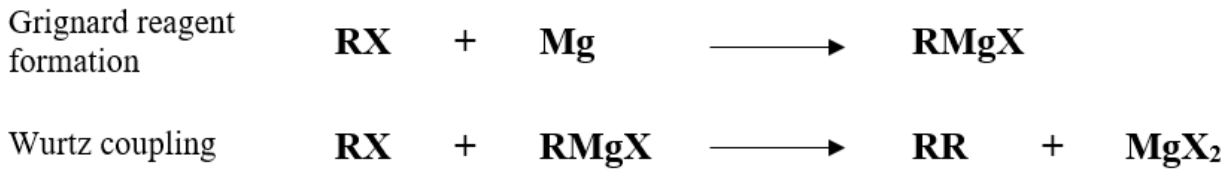


Figure 1: Grignard reagent (RMgX) formation from a halide RX and metallic magnesium Mg and undesired Wurtz coupling of a halide molecule RX and a Grignard reagent molecule RMgX.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

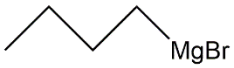
It was previously shown for the benzylmagnesium bromide synthesis, that the selectivity of the Wurtz-affine Grignard reagent strongly depends on the residence time distribution as well as the degree of backmixing and that the reaction can benefit from continuous processing in terms of improved product quality[29,30]. Within literature, only few comparisons of batch type processes and continuous production processes for the formation of Grignard reagents can be found[10,12,17,19], but studying the impact of a continuous process on the selectivity of a Grignard reagent was not the main aspect of these publications.

Encouraged by the results achieved with the benchmark benzylmagnesium bromide synthesis, it is intended to investigate the suitability of a continuous production process to Grignard reagent formation in general. This publication analyses selectivities of semi-batch type and continuous lab scale processes for various Grignard reagents with varying susceptibilities to Wurtz coupling (chart 1). Five benchmark syntheses are then transferred from a lab scale to a pilot scale production process, to show feasibility of large-scale syntheses.

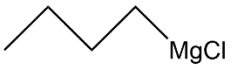
https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

Chart 1: Scope of Grignard reagents for semi-batch type and continuous production process.

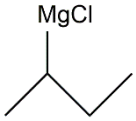
1



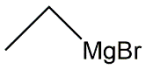
2



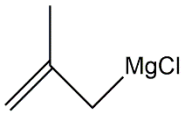
3



4



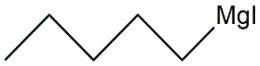
5



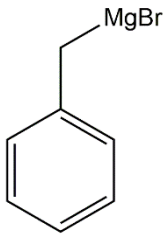
6

7

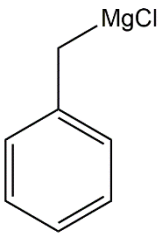
8



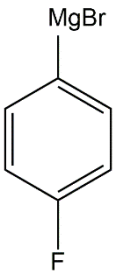
9



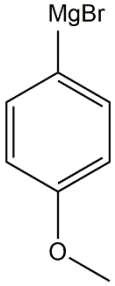
10



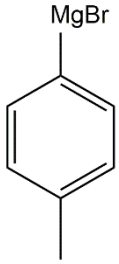
11



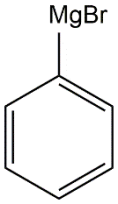
12



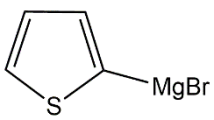
13



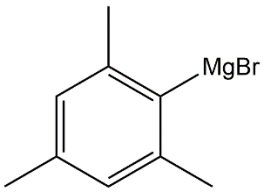
14



15



16



17

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

EXPERIMENTAL SECTION

Materials

Chemicals and reagents are listed in table 1 and were used without further purification.

Table 1: Chemicals and reagents used.

substance	**purity**	**supplier**
1-bromo-4-fluorobenzene	99 %	Thermo Fisher Scientific Inc.
1-bromo-4-methoxybenzene	99 %	Thermo Fisher Scientific Inc.
1-bromo-4-methylbenzene	98 %	abcr GmbH
1,2-xylene	99 %	Thermo Fisher Scientific Inc.
2-bromo-1,3,5-trimethylbenzene	99 %	Thermo Fisher Scientific Inc.
2-bromothiophene	98 %	Thermo Fisher Scientific Inc.
2-chlorobutane	≥ 99 %	Merck KGaA
3-chloro-2-methylpropene	98 %	Thermo Fisher Scientific Inc.
3-chloroprop-1-ene	98 %	Merck KGaA
bromobenzene	≥ 99 %	Merck KGaA
bromobutane	≥ 98 %	Merck KGaA
bromoethane	98 %	Merck KGaA
bromopentane	98 %	Merck KGaA
(bromomethyl)benzene	99 %	Thermo Fisher Scientific Inc.
butan-1-ol	≥ 99.5 %	Merck KGaA
butan-2-ol	99 %	Thermo Fisher Scientific Inc.
chlorobutane	≥ 99.5 %	Merck KGaA
chloropentane	99 %	Merck KGaA

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

(chloromethyl)benzene	≥ 99 %	Merck KGaA
diethyl ether	≥ 99.8 %, puriss p.a.	Honeywell International Inc.
iodine	≥ 99.8 %	Merck KGaA
iodopentane	98 %	Thermo Fisher Scientific Inc.
magnesium turnings	≥ 99 %	coarse: Merck KGaA fine: Almamet GmbH
methanol	≥ 99.9 %	Honeywell International Inc.
tetrahydrofuran	> 99.9 % p.a.	Th. Geyer GmbH & Co. KG
	≥ 99 %	Avantor Inc.
toluene	≥ 99.7 %	Honeywell International Inc.

Solvents used on lab scale (semi-batch and continuous) are tetrahydrofuran (THF, Th. Geyer GmbH & Co. KG, boiling point 66°C) and diethyl ether (DEE, Honeywell International Inc., boiling point 35°C). On pilot scale, THF (Avantor Inc.) is used as well. Particle size distributions for the magnesium turnings used (coarse and fine) can be found in a previous publication[29].

Thermocouples (type K, RS Components GmbH) are used to measure temperatures within the magnesium bed. Temperatures are logged by a data logger (Expert Key 200L, Delphin Technology AG).

The following pumps are used: PN1610 syringe dosing system (Postnova Analytics GmbH), mzr-7205 micro annular gear pump (for continuous lab scale, HNP Mikrosysteme GmbH), mzr-11540 micro annular gear pump (for pilot scale, HNP Mikrosysteme GmbH).

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

The reactor cartridges are tempered by using thermostatic baths from Julabo GmbH (F31-C on lab scale, FP55-SL and PRESTO A45 on pilot scale).

The following equipment is used for semi-batch experiments: 250 mL 4-neck flask, reflux condenser, Postnova syringe pump (PN1610 syringe dosing system), cannula, magnetic stirrer with hot plate and stirring bar, thermocouple (type K), septa, thermostatic bath and stainless-steel tempering coil, oil bath.

Laboratory and pilot scale reactor systems

The reactor used for continuous laboratory scale syntheses of Grignard reagents has been described previously in detail including residence time distributions within a non-reacting magnesium packing as well as during Grignard reagent formation[29,30]. It is designed by Fraunhofer IMM, manufactured by 3D laser melting, and generally used for the formation of organometallic halide reagents. The reactor consists of a reactor cartridge filled with magnesium turnings, and a magnesium replenishment unit for replenishing magnesium turnings during Grignard reagent synthesis. When using coarse magnesium turnings, the void fraction of the magnesium packing is 0.58, whereas for the finer magnesium turnings it is 0.51. Compared to a 1-molare halide educt solution, there is an approximately 53-fold (coarse turnings) or 69-fold (fine turnings) molar excess of magnesium turnings in the reactor.

As on the lab scale, the stainless-steel reactor used for pilot scale Grignard reagent synthesis is designed by Fraunhofer IMM, manufactured by 3D laser melting and consists of a reactor cartridge filled with magnesium turnings and a magnesium replenishment unit. The reactor

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

system can be enlarged to up to four reactor modules, depending on necessary residence time and throughput. The pilot scale reactor is used with coarse magnesium turnings and the void fraction of the magnesium packing is 0.57, comparable to lab scale. The molar excess of magnesium turnings is 54, when processing a 1-molare halide educt solution. In terms of reactor volume, one pilot scale module provides an 18.5-fold scale-up compared to the continuous lab scale.

Semi-batch procedure for Grignard reagent synthesis

Prior to the semi-batch experiments, all glassware used is placed in a drying oven at 115°C for at least 12 hours, cooled down in a desiccator and flushed with argon to avoid contamination with air and moisture. A stoichiometric amount of magnesium turnings under argon atmosphere is activated (removing passivating oxide layer) for 30 min in an ultrasonic bath. Batch experiments are performed by using an overall liquid volume of 100 mL.

The stoichiometric amount of magnesium turnings is introduced into the 250 mL 4-neck-flask while already tempering the flask (hot plate and/or thermostat bath depending on required temperature). Then, 1/20 of the overall halide mass and about 30 % of the overall solvent mass are added manually (magnetic stirrer at 150 RPM). After an incubation period of ten minutes, the remaining halide in the solvent is added by means of a Postnova syringe pump and a specific volumetric flow rate comparable to the continuous laboratory scale synthesis (magnetic stirrer at 300 RPM). After complete addition of the halide solution, 30 minutes post-stirring time is applied. Afterwards the reaction mixture is heated up until gentle boiling for another 30 minutes. A sample is taken and analyzed by gas chromatography and thermometric titration.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

The set-up for the semi-batch synthesis is shown in figure 2. Specific reaction conditions for each Grignard reagent can be found within the ESI.

Flow procedure for Grignard reagent synthesis

Continuous lab scale Grignard reagent synthesis

The reactor is charged with magnesium turnings (23 g for coarse magnesium turnings, 27 g for fine turnings) while the jogging motor at the bottom of the reactor is running. An inert atmosphere in the reactor is realized with argon. Four thermocouples are placed along the magnesium bed for temperature monitoring. Before starting the synthesis, the reactor is purged for 30 minutes by an argon flow, while the magnesium bed is compacted due to vibrations generated by the jogging motor and the reactor cartridge is already tempered. Recording of measured temperatures is started. Subsequently, the reactor is filled with a solution of educt halide in the solvent (Postnova PN1610 syringe pump for coarse Mg turnings and mzr-7205 micro annular gear pump for fine Mg turnings unless otherwise specified). This leads to a temperature increase resulting from the initiation of the exothermic reaction. As soon as the reactor is entirely filled with educt solution, the pump is turned off and the reactor content is allowed to rest for ten minutes for initial formation of Grignard reagent and further activation of the magnesium turnings. Afterwards, the pump is turned on again. To accelerate the start of the reaction, elevated temperatures and flow rates can be applied. After waiting for about three residence times, samples from the outlet solution are taken for analysis. Magnesium turnings are replenished manually during synthesis by using the replenishing unit (1-2 g per replenishment).

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

Residence times for the applied flow rate range of 1-4 mL min^{-1} are 5-18 min (coarse turnings) or 4-16 min (fine turnings). The lab scale set-up for Grignard reagent formation is shown in figure 2. Specific reaction conditions for each Grignard reagent can be found within the ESI.

Continuous pilot scale Grignard reagent synthesis

For the pilot scale Grignard reagent formation, two reactor modules are used, unless stated otherwise. The procedure of performing a pilot scale Grignard reagent synthesis is mostly comparable to the continuous lab scale synthesis. The reactor is charged with coarse magnesium turnings (around 460 g per module) while the jogging motor is running. Argon is used to realize an inert atmosphere during Grignard reagent synthesis. The reactor cartridge is filled with the halide educt solution (mzr-11540 micro annular gear pump) while the reactor is already tempered, and temperatures are being recorded. As on the lab scale, the pump is turned off for ten minutes after filling the cartridge with the halide educt solution is completed. Afterwards, the pump is turned on again for the production of the Grignard reagent. Samples from the outlet solution are taken and analyzed. Magnesium turnings are replenished manually during synthesis (15-30 g per replenishment). To increase sustainability of the production procedure, leftover magnesium turnings can be re-used if flushed thoroughly with the solvent and stored under argon atmosphere.

Residence times for the applied flow rate range of 74-148 mL min^{-1} (two reactor modules) are 5-10 min. Under consideration of the scale-up-factor and the specific flow rates, residence times are comparable for lab and pilot scale. The set-up for pilot scale synthesis is depicted in figure 2. Specific reaction conditions for each Grignard reagent can be found within the ESI.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

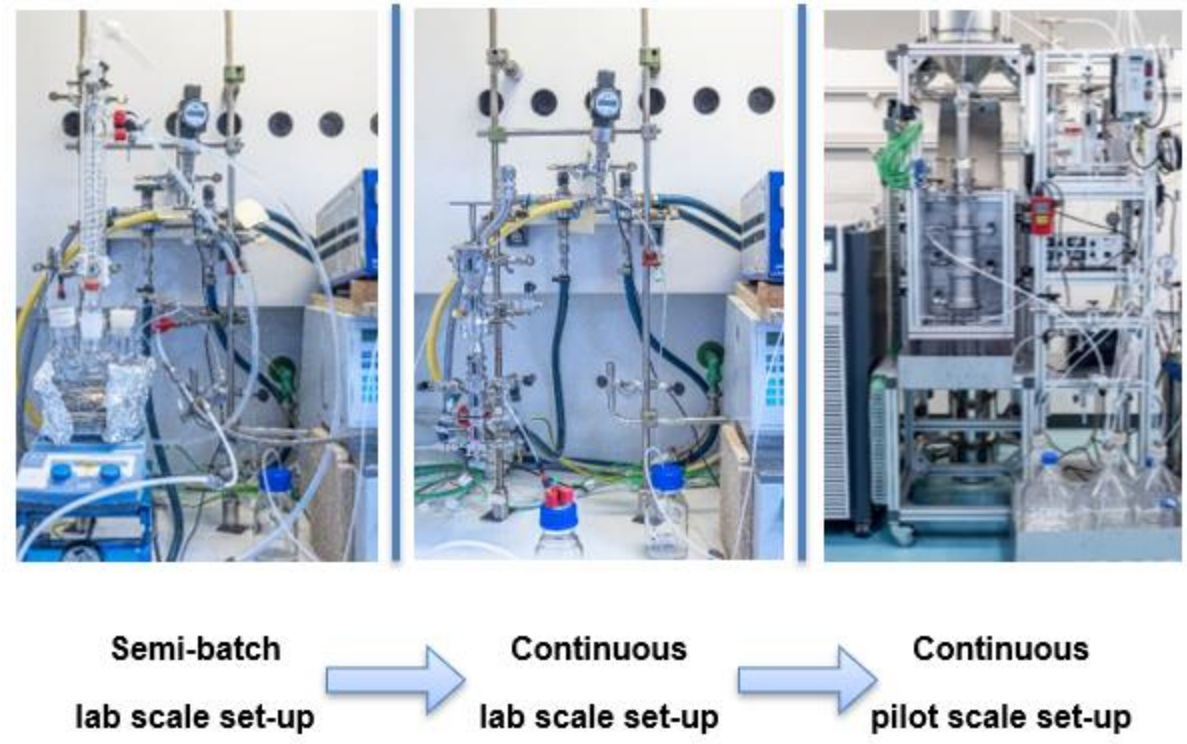


Figure 2: Set-ups for semi-batch, continuous lab scale and continuous pilot scale synthesis of Grignard reagents.

Sample analysis

Thermometric titration is performed to determine the active Grignard reagent concentration by using a thermometric titration setup from Metrohm AG (Titrotherm). Analysis is done by adding 0.5 mL to 2.0 mL of the product solution to 30 mL toluene by means of a syringe and under nitrogen atmosphere. Sample weight is determined by back weighing of the syringe. Titration is done using a solution of 1 mol L^{-1} butan-2-ol in 1,2-xylene. To determine the titration endpoint, the heat released by the exothermic reaction of the Grignard reagent and butan-2-ol is detected by a thermoprobe. The endpoint is reached if no further heat is released. Concentration determination is done by using the titrator software *tiamo* (Metrohm AG).

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

Gas chromatography is performed to determine side product concentration and residual halide educt concentration. To prepare the samples, 0.5 mL sample solution are quenched in a 5 mL graduated flask with methanol (for synthesis of **8** 1-butanol is used as the quenching agent due to peak overlapping when using methanol). The quenched solution is filtered using a syringe filter (0.45 µm pore size) and filled in a gas chromatography vial. Gas chromatography is performed using a calibrated Varian GC 3900 system with Varian GC 8400 GC-autosampler. Infrared spectra (Bruker Matrix-MF with diamond ATR-probe, Bruker Optics GmbH) of the Grignard reagent solution and the halide educt solution can be found within the ESI.

RESULTS AND DISCUSSION

Semi-batch to continuous lab scale Grignard reagent formation

On an industrial level, Grignard reagents are produced in a semi-batch type procedure. Consequently, semi-batch type syntheses on a 100 mL scale are performed as a comparative case to continuous Grignard reagent formation. Direct comparability is enabled by maintaining the same solvent, halide concentration, halide/solvent flow rate and temperature for batch and continuous lab scale synthesis. Commercially available coarse magnesium turnings are used. The Postnova syringe pump PN1610 is utilized, since it was previously shown that the pump system has an impact on the residence time distribution in a non-homogeneous and randomly packed-bed of non-uniform, non-spherical magnesium turnings and that the Postnova syringe pump in combination with the coarse magnesium turnings yields the narrowest residence time distribution on continuous lab scale[29]. Results for conversion and selectivity of the Grignard reagents displayed in chart 1 and synthesized in a semi-batch type procedure and on continuous lab scale

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

are listed in table 2. It was previously shown for the benchmark benzylmagnesium bromide **10** synthesis, that the side product benzyl alcohol is formed after the actual Grignard reagent has left the reactor cartridge and that for evaluation of the Grignard reagent selectivity, the alcohol can be added to the Grignard reagent. Therefore, the selectivities listed contain the alcohol fraction, if available. Details on the selectivity of the specific alcohol and the Wurtz product can be found within the ESI.

Table 2: Conversion and selectivity of Grignard reagents in THF, synthesized by using a Postnova syringe pump and coarse magnesium turnings.

Grignard reagent	**halide concentration / (mol L^{-1})**	**semi-batch lab scale**		**continuous lab scale**	
		conversion / %	selectivity / %	conversion / %	selectivity / %
allylmagnesium chloride **1**	1.0	100	75	100	98
butylmagnesium bromide **2**	1.0	100	94	100	98
butylmagnesium chloride **3**	1.0	97	100[a]	100	100[a]
2-butylmagnesium chloride **4**	2.0	100	94	97	98
ethylmagnesium bromide **5**	1.0	100	95	100	98
2-methylallylmagnesium chloride **6**	0.5	100	62	100	94
pentylmagnesium bromide **7**	1.0	100	92	100	96
pentylmagnesium chloride **8**	1.0	100	97[b]	100	100[c]

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

pentylmagnesium iodide **9**	1.0	30	90	-[d]	-[d]
benzylmagnesium bromide **10**	0.7	100	46	100	83
benzylmagnesium chloride **11**	1.0	100	73	100	90
4-fluorophenylmagnesium bromide **12**	1.0	100	95	100	94
4-methoxyphenylmagnesium bromide **13**	0.5	100	74	100	82
4-methylphenylmagnesium bromide **14**	1.0	100	95	100	99
phenylmagnesium bromide **15**	1.0	100	99	100	96
2-thienylmagnesium bromide **16**	1.0	100	97	100	96
2,4,6-trimethylphenylmagnesium bromide **17**	1.0	100	91	100	96

[a] Initiation of reaction by use of the Grignard reagent.

[b] Initiation of reaction by use of iodine.

[c] Initiation of reaction by synthesis of **7**.

[d] Failure of synthesis due to immediate clogging of reactor.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

In most cases full conversion of the halide educt is reached in the semi-batch and the continuous lab scale set-up. Using the batch procedure, selectivities above 45 % and up to 100 % are possible, although for Grignard reagents known to be prone to Wurtz coupling (e.g., allylmagnesium chloride **1**, 2-methylallylmagnesium chloride **6**, benzylmagnesium bromide **10** and benzylmagnesium chloride **11**) the lowest selectivities are obtained. Instead, on continuous lab scale selectivities above 80 % are possible and besides **10** and **13** the selectivities are even above 90 %. Except for a few cases in which selectivities on semi-batch and continuous lab scale are similar or equal, the selectivity of the Grignard reagent formation is enhanced by using the continuously operated packed-bed reactor instead of the semi-batch type reactor. This improvement is especially important for those Grignard reagents that are known to easily form the Wurtz coupling product, because the continuous process provides higher product qualities and reduced post-reaction processing. The continuous set-up enables a narrow residence time distribution and reduced backmixing, through which the contact time between the halide molecule and the Grignard reagent molecule is reduced. Due to the continuous provision of a halide educt and a magnesium excess, the reaction rate remains high, whereas in the semi-batch process with overall stoichiometric amounts of halide and magnesium metal the reaction rate decreases with increasing magnesium conversion. The increasing Grignard reagent concentration and the decreasing magnesium mass in combination with complete backmixing lead to an increase of the contact between the added halide and the Grignard reagent, which can increase the probability of Wurtz product formation. After complete addition of the halide to the batch flask and 30 min post-stirring, the reaction mixture was heated until gentle boiling to increase the reaction rate and potentially reach full conversion. Only then, conversions are comparable for the batch and continuous lab scale procedure. Without this procedure, the average halide conversion

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

is only 95 % for the batch synthesis (synthesis of **7** not considered). Due to the same addition or flow rate for batch syntheses and continuous lab scale syntheses, the addition of the halide educt lasts the same time for both cases. But due to the additionally required post-stirring and boiling time, the batch syntheses need more time than the continuous syntheses (not considering set-up time for preparing the flask or reactor). This results in a lower productivity for the Grignard reagent formation in the semi-batch lab flask compared to the continuous lab scale synthesis (e.g., 0.00091 mol min^{-1} instead of 0.002 mol min^{-1} for a 1-molar halide solution and an addition rate of 2 mL min^{-1}).

The syntheses of **3** and **8** have only been possible through an additional initiation procedure by using either iodine or pre-made Grignard reagent. Within a batch process, these additional chemicals remain within the reaction solution and therefore are to be avoided if possible. On the contrary, within a continuous production process, additional chemicals to facilitate the reaction start are easier to handle, since they are easily discharged from the reactor and cannot affect the further course of the reaction.

For the pentylmagnesium iodide **9** synthesis, the halide conversion on semi-batch lab scale is only 30 % and on continuous lab scale the synthesis was not possible due to clogging of the reactor and an increase in pressure. In both cases, excessive precipitation of a white solid was observed, which covered the magnesium turnings (pictures within ESI). This resulted in low halide conversion in the batch flask and immediate clogging in the continuous lab scale reactor, making it impossible to run the synthesis or analyze a product sample. The formation of solids shows the limits and challenges of the continuous production in a flow reactor. In general, less byproduct and side product formation are observed on the continuous lab scale, but as soon as the byproduct or side product precipitates due to insufficient solubility, clogging becomes a

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

serious problem resulting in unsuccessful Grignard reagent production. To enable synthesis of **9** in the continuous packed-bed reactor, the solvent was switched to diethyl ether and the results were compared (table 3). In general, the syntheses in DEE are performed at lower temperatures than in THF due to the lower boiling point of DEE and to avoid boiling in the reactor cartridge.

Table 3: Conversion and selectivity of pentylmagnesium bromide **7**, pentylmagnesium chloride **8** and pentylmagnesium iodide **9** synthesis in diethyl ether on semi-batch and continuous lab scale.

Grignard reagent	**semi-batch lab scale**		**continuous lab scale**	
	conversion / %	selectivity / %	conversion / %	selectivity / %
pentylmagnesium bromide **7**	100	88	100	86
pentylmagnesium chloride **8**	85	100[e]	98	99[f]
pentylmagnesium iodide **9**	100	66	98	73

[e] Initiation of reaction by use of iodine.

[f] Initiation of reaction by synthesis of **7**.

Slightly lower selectivities are obtained for **7** when using the solvent diethyl ether instead of THF. Grachev et al. also obtained higher Grignard reagent selectivities in THF than in DEE for some Grignard reagents and stated that this is because THF has a higher stabilizing potential in the formation of the Grignard reagent[10]. The conversion of chloropentane is reduced due to the lower temperature and the reduced reaction rate, whereas the selectivities are similar to the ones obtained for the syntheses in THF. Synthesis of **9** is possible in the batch flask and on continuous lab scale without any precipitation. Since for the results in table 2 and 3 only the highest yielding reaction parameters (temperature, flow rate) are applied, reaction conditions for the pentyl-

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

Grignard reagents slightly differ. **7** and **9** have equal parameters, while **8** is prepared at a slightly higher temperature to reach high conversion on continuous lab scale. Full comparability is achieved by performing the continuous lab scale synthesis of **8** at the same temperature and flow rate as **7** and **9**. By doing so, conversion on continuous lab scale decreases from 100 % to 90 % in THF and from 98 % to 80 % in DEE due to the reduced reaction rate while the Grignard reagent selectivity remains at about 100 % in both solvents. Within table 3 it can be noticed that the selectivity decreases significantly with increasing reactivity of the Grignard reagent and that the decrease in selectivity is more pronounced for the batch results. This again underlines the benefits of a continuously operated flow reactor for the synthesis of Wurtz affine Grignard reagents, independent of the solvent used.

Lab scale Grignard reagent formation – Comparison of fine and coarse Mg turnings

Narrow residence time distributions and therefore high Bodenstein numbers can be obtained by using a compact and homogeneous magnesium packing[29]. Therefore, narrow particle size distributions are favorable. Grignard reagents were chosen, that showed significant side product formation and therefore likely a distinct difference in selectivity is visible. For the Grignard reagents presented in table 4, full conversion of the halide educt is achieved on semi-batch and continuous lab scale.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

Table 4: Comparison of selectivity for the use of fine and coarse Mg turnings in THF on semi-batch and continuous lab scale.

Grignard reagent	**halide concentration / (mol L^{-1})**	**selectivity / %**			
		fine Mg turnings		coarse Mg turnings	
		semi-batch	continuous lab scale	semi-batch	continuous lab scale
2-methylallylmagnesium chloride **6**	0.5	71	94	62	94
	2.0	42	73	34	58
benzylmagnesium bromide **10**	0.7	55	92	46	83
benzylmagnesium chloride **11**	1.0	80	94	73	90
4-methoxyphenylmagnesium bromide **13**	0.5	83	89	74	82

On the basis of the selectivities obtained by using coarse or fine magnesium turnings, it can be seen for all syntheses that higher selectivities of Grignard reagent can be achieved with the use of fine magnesium turnings. This is in particular due to the more compact magnesium bed, the more narrow particle size distribution and the higher surface area of the fine magnesium turnings[30]. Based on the synthesis of **6** at two different halide concentrations, it can be seen that an increased halide concentration leads to an increased side product formation independent of the magnesium turning size and the synthesis procedure. Higher concentrations increase the likelihood that halide and Grignard reagent will meet and form the corresponding Wurtz product. In addition, Grignard reagent formation cannot be operated under isothermal conditions and the released heat of reaction is not dissipated instantaneously (see exemplary temperature profiles of **10** in the ESI), the reaction temperatures are higher at higher halide concentrations. The higher reaction

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

temperatures favor the formation of the Wurtz coupling product. For the production on continuous lab scale the difference between the fine and coarse magnesium turnings is more pronounced at the higher halide concentration than at the lower concentration.

The influence of the reactivity of the Grignard reagent on the affinity for the Wurtz coupling is also clear from the syntheses carried out. The reactivity of halides decreases from the iodine atom to the fluorine atom due to the increasing electronegativity and the strength of the carbon-halogen bond. Bromides thus exhibit weaker bonds and higher reactivity than chlorides. Compared with the bromine-containing **10**, the synthesis of the chlorine-containing **11** achieves higher yields and selectivities, the synthesis is possible at a higher halide concentration and the difference between the fine and coarse magnesium turnings is less pronounced. This shows that the reactivity of the halide cannot only exert a positive influence on the synthesis of the Grignard reagent with respect to facilitated formation, but also has a negative aspect in terms of enhanced Wurtz coupling. For this reason, higher yields and selectivities are achieved with the chlorine-containing **11** despite the higher halide concentration and lower reactivity.

Fine magnesium turnings not only provide a larger magnesium surface area, but also allow for a more compact magnesium bed. When a suitable pump is used, narrower residence time distributions and higher Bodenstein numbers can also be achieved in the reactive magnesium bed of fine turnings than in a packed bed of coarse magnesium turnings. Therefore, further improvement of the residence time distribution within the magnesium bed might improve the yield and selectivity in various Grignard reagent syntheses.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

Lab to pilot scale Grignard reagent formation

To scale up Grignard reagent formation from lab scale to pilot scale, five different Grignard reagents serve as exemplary syntheses. To allow for comparison, only bromides are used. The selection was made based on the different properties of the Grignard reagents and on their usability for the synthesis of active pharmaceutical ingredients (API). The benzylmagnesium bromide **10** synthesis suffers from severe side-product formation (Wurtz coupling) but it was already possible to achieve increased yield and selectivity by transferring the reaction from semi-batch type processing to continuous processing on lab scale. Ethylmagnesium bromide **5** is a Grignard reagent with a very short carbon rest. Phenylmagnesium bromide **15** is widely used within research and industry and contains an aryl group. 4-Fluorophenylmagnesium bromide **12** has another halogen atom attached to the benzene ring. 4-Methoxyphenylmagnesium bromide **13** does have an oxygen atom, being rare for Grignard reagents. Except for the Wurtz-affine **10**, the selected Grignard reagents are among the 20 most cited Grignard reagents on the platform SciFinder[31]. All Grignard reagents chosen for pilot scale synthesis are potentially used in API syntheses: **5** for *bupropion*[32] (antidepressant) or *eletriptan*[33] (treatment of migraine), **10** for *clomiphene*[34] (treatment of infertility in women) or *englitazone*[34] (anti-diabetic treatment), **12** for *paroxetine*[35] (antidepressant) or *citalopram*[35] (antidepressant), **13** for *raloxifene*[36] (treatment of osteoporosis) and **15** for *tamoxifene*[32] (treatment of breast cancer) or *terfenadine*[33] (antihistamine).

As it was shown previously, the pump system and the pump-induced flow behavior can have an impact on the selectivity of Grignard reagent formation and especially on the formation of Wurtz affine Grignard reagents[30]. Therefore, contrary to the results displayed in table 2 and to allow comparison with the pilot scale results, for the lab scale syntheses presented in table 5 the micro

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

annular gear pump instead of the syringe pump was used. That way, the same pump type is used on lab and pilot scale and influences of the pump system on selectivity are similar. A 37-fold higher productivity in terms of amount of substance per minute (mol min^{-1}) is achieved on pilot scale when two reactor modules are used. The flow rate scales linearly according to the volume-dependent scale-up factor of 18.5 per module. The yields for the syntheses on lab and pilot scale are displayed in table 5. Within every synthesis, full conversion of the halide educt was achieved, therefore selectivity equals yield.

Table 5: Selectivity for lab and pilot scale syntheses of exemplary Grignard reagents in THF and by using micro annular gear pumps and coarse magnesium turnings.

Grignard reagent	**halide concentration / (mol L^{-1})**	**selectivity / %**	
		continuous lab scale	continuous pilot scale
ethylmagnesium bromide **5**	1.0	91	98
benzylmagnesium bromide **10**	0.7	77	97
4-fluorophenylmagnesium bromide **12**	1.0	93	99
4-methoxyphenylmagnesium bromide **13**	0.5	80	93
phenylmagnesium bromide **15**	1.0	93	99

Comparing the lab scale results from table 5 (HNP micro annular gear pump) to the corresponding results from table 2 (Postnova syringe pump), it is noticed, that by using the pulsation-free micro annular gear pump slightly lower selectivities (less than 10 % difference)

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

are obtained. This is due to the impact of the pump system on the residence time distribution within the magnesium bed and these findings correlate well to the results obtained previously[30]. Although the same pump type and similar process parameters (halide concentration in THF, thermostat temperature, residence time, void fraction of magnesium packing) are used for lab and pilot scale syntheses, higher yields and selectivities could be obtained on pilot scale, also exceeding syringe pump lab scale selectivities. Even for the Wurtz affine synthesis of **10,** the selectivity is increased by 20 %. For the pilot scale syntheses partly higher reaction temperatures were registered (exemplary temperature profiles for lab and pilot scale synthesis of **10** can be found within the ESI). On the contrary, in the literature it is reported, especially for the batch synthesis of the benzylic Grignard reagent, that the Wurtz product can be minimized by decreasing the temperature[1]. High temperatures lead to an increase in reaction rates both for the Grignard reagent formation and the Wurtz coupling reaction. Due to the large magnesium excess in the continuous production process and therefore almost constant high magnesium concentration, the reaction rate for the Grignard reagent formation is high. Since the magnesium concentration can be considered constant, the Grignard reagent formation kinetics can be considered as pseudo-first order in terms of the magnesium. Thus, the reaction rate is mostly influenced by the halide concentration and the temperature (as part of the Arrhenius equation) during the reaction. For the packed-bed reactor, halide concentration at the reactor inlet is high, constant, and equal for continuous lab and pilot scale synthesis. Wong et al. studied the formation of a benzylmagnesium bromide derivative and found, that the kinetics of the undesired Wurtz coupling were three orders of magnitude slower than the reaction rate of the Grignard reagent formation in a continuous stirred tank reactor operating at a temperature of 0 °C[20]. Kinetic data especially for the Grignard-Wurtz coupling are rarely published and kinetic studies

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

of the Grignard reagent formation and the Wurtz coupling reaction are out of scope for this publication. Narrowing residence time distributions in a packed-bed reactor already increases Grignard reagent selectivity, but the results obtained indicate, that high temperatures in combination with a narrow residence time distribution can increase the selectivity even further. Achieving almost ideal plug flow behavior in a poured, non-homogeneous magnesium bed of non-uniform, non-spherical magnesium turnings is difficult, and targeted high reaction temperatures could eventually solve the remaining selectivity issue. An additional continuous lab scale synthesis of **10** at a targeted higher temperature at the reactor inlet resulted in a Grignard reagent selectivity of 94 % (data within ESI). This value is close to the selectivity achieved on pilot scale and 17 % higher than the selectivity achieved before on lab scale. Thus, the continuous lab scale synthesis of **10** underlines what was concluded from the pilot scale synthesis: high temperatures combined with the benefits of a continuous packed-bed reactor can lead to high selectivities even for highly Wurtz-affine Grignard reagents.

Scalability of pilot scale synthesis of 15

Phenylmagnesium bromide **15** is a widely used Grignard reagent and the 2nd most cited Grignard reagent on the platform SciFinder[31]. Industrially, the Grignard reagent is used as an intermediate in the production of *tamoxifen*, one of the best-selling breast cancer drugs in the world[32,37]. Since **15** is industrially required in large quantities, the synthesis of **15** was used to demonstrate the scalability of pilot scale production. As mentioned before, the pilot scale reactor system can be adapted to required throughputs and necessary residence times by using multiple reactor modules. The modularity of the reactor concept is expected to allow for flexibility in production

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

quantities. Up to four modules are utilized and the requirements for the scale-up aim to increase the throughput while keeping the selectivity constant. The throughput is supposed to scale linearly according to the number of modules used.

Table 6 displays the results for the synthesis of **15** by using up to four reactor modules. The throughput can be doubled by using twice the number of reactor modules while still maintaining 100 % conversion and a constant selectivity. Even with a fourfold increase in the number of modules and the throughput, high conversion and selectivity can be maintained, emphasizing the scalability of the continuous pilot scale Grignard reagent synthesis of **15**. In this study, a complete scale-up from a small semi-batch lab scale to a continuous lab scale to a scalable continuous pilot scale synthesis is demonstrated. Comparing the pilot scale syntheses to the semi-batch lab scale synthesis, the productivity is increased by a factor of up to 220 (0.0009 mol min^{-1} for semi-batch to 0.2 mol min^{-1} for a pilot scale reactor of four modules).

Table 6: Conversions and selectivities for the continuous pilot scale synthesis of phenylmagnesium bromide **15** in THF by using multiple reactor modules.

Grignard reagent	**halide concentration / (mol L^{-1})**	**number of modules**	**throughput / (mL min^{-1})**	**conversion / %**	**selectivity / %**
phenylmagnesium bromide **15**	1.0	1	45	100	99
		2	100	100	99
		4	200	100	99

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

CONCLUSIONS

Continuous on-demand production of Grignard reagents eliminates the need to store the reactive intermediate, as the reagents can be used right away. The Grignard reagent formation benefits from the continuous production process also in terms of an increased selectivity, as demonstrated by comparing semi-batch type syntheses of several Grignard reagents to continuous lab and pilot scale syntheses while maintaining similar reaction conditions. In general, the continuous flow reactor provides higher selectivity and consequently higher product quality than the semi-batch process. Although changing the solvent from THF to the more sustainable 2-methyltetrahydrofuran is known to potentially reduce Wurtz coupling, changing the solvent only to suppress Wurtz coupling is not necessarily required when using a continuous approach. The continuous production processes proved particularly advantageous for Wurtz-affine Grignard reagents, although less reactive reagents still benefit to some extent from the narrower residence time distributions achieved in the packed-bed reactor. The transfer of Grignard reagent formations from a small lab scale (semi-batch and continuous) to a larger pilot scale is feasible even for Wurtz-affine Grignard reagents and does not adversely affect selectivity when using a continuously operated packed-bed reactor. In addition, the combination of the beneficial residence time distribution in a packed-bed reactor with an elevated temperature has the potential to increase the selectivity even further. Therefore, optimization by fine-tuning the process parameters for the reacting magnesium bed could further improve selectivity and control the undesired Wurtz coupling reaction.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

ASSOCIATED CONTENT

Supporting Information: Reaction conditions, analytical data, and infrared spectra specific for each Grignard reagent, temperature profiles for benzylmagnesium bromide synthesis (PDF).

AUTHOR INFORMATION

Corresponding Author

*Corresponding author.

Gabriele Menges-Flanagan; Tel: +49 6131 990425; Fax: +49 6131 990205; E-mail address: gabriele.menges-flanagan@imm.fraunhofer.de

Dirk Ziegenbalg; Tel: +49 731 5025703; Fax: +49 731 501225700; E-mail address: dirk.ziegenbalg@uni-ulm.de

Author Contributions

Conceptualization: E. D. (lead), **Data curation**: E. D. (lead), K. D. (supporting), **Formal analysis**: E. D. (lead), K. D. (supporting), **Funding acquisition**: M. M. (lead), E. D. (supporting), G. M.-F. (supporting), **Investigation**: E. D. (lead), K. D. (supporting), **Methodology**: E. D. (lead), D. Z. (supporting), **Project administration**: E. D. (lead), **Resources**: E. D. (supporting), M. M. (supporting), G. M.-F. (supporting), **Supervision**: D. Z. (equal), G. M.-F. (equal), M. M. (supporting), **Validation**: E. D. (lead), K. D. (supporting), **Visualization**: E. D. (lead), **Writing – original draft**: E. D. (lead), **Writing – review & editing**: E. D. (equal), G. M.-F. (equal), D. Z. (supporting)

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

The authors acknowledge the Fraunhofer IMM and the Fraunhofer-Gesellschaft for internal funding including the funding *via* the Fraunhofer development and career program TALENTA. The authors also acknowledge Lisa Pokropp (Fraunhofer IMM) for the creation of the Table of Content graphic.

ABBREVIATIONS

API, active pharmaceutical ingredient; DEE, diethyl ether; ESI, electronic supplementary information; Mg, magnesium; RPM, revolutions per minute; THF, tetrahydrofuran.

REFERENCES

(1) Silverman, G. S., Ed. *Handbook of grignard reagents*; Chemical industries, Vol. 64; Dekker, 1996.

(2) Kadam, A.; Nguyen, M.; Kopach, M.; Richardson, P.; Gallou, F.; Wan, Z.-K.; Zhang, W. Comparative performance evaluation and systematic screening of solvents in a range of Grignard reactions. *Green Chem.* **2013**, *15* (7), 1880. DOI: 10.1039/c3gc40702k.

(3) Samineni, R.; Eda, V.; Rao, P.; Sen, S.; Oruganti, S. Grignard Reagents as Niche Bases in the Synthesis of Pharmaceutically Relevant Molecules. *ChemistrySelect* **2022**, *7* (5). DOI: 10.1002/slct.202102853.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

(4) Baumann, M.; Baxendale, I. R. The synthesis of active pharmaceutical ingredients (APIs) using continuous flow chemistry. *Beilstein journal of organic chemistry* **2015**, *11*, 1194–1219. DOI: 10.3762/bjoc.11.134.

(5) Porta, R.; Benaglia, M.; Puglisi, A. Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products. *Org. Process Res. Dev.* **2016**, *20* (1), 2–25. DOI: 10.1021/acs.oprd.5b00325.

(6) Gambacorta, G.; Sharley, J. S.; Baxendale, I. R. A comprehensive review of flow chemistry techniques tailored to the flavours and fragrances industries. *Beilstein journal of organic chemistry* **2021**, *17*, 1181–1312. DOI: 10.3762/bjoc.17.90.

(7) Banno, T.; Hayakawa, Y.; Umeno, M. Some applications of the Grignard cross-coupling reaction in the industrial field. *Journal of Organometallic Chemistry* **2002**, *653* (1-2), 288–291. DOI: 10.1016/S0022-328X(02)01165-8.

(8) Johnson, M. D.; Braden, T.; Calvin, J. R.; Campbell Brewer, A.; Cole, K. P.; Frank, S.; Kerr, M.; Kjell, D.; Kopach, M. E.; Martinelli, J. R.; May, S. A.; Rincon, J.; White, T. D.; Yates, M. H. The History of Flow Chemistry at Eli Lilly and Company. *Chimia* **2023**, *77* (5), 319. DOI: 10.2533/chimia.2023.319.

(9) Keutz, T. von; Williams, J. D.; Kappe, C. O. Continuous Flow C -Glycosylation via Metal–Halogen Exchange: Process Understanding and Improvements toward Efficient Manufacturing of Remdesivir. *Org. Process Res. Dev.* **2020**, *24* (10), 2362–2368. DOI: 10.1021/acs.oprd.0c00370.

(10) Grachev, A. A.; Klochkov, A. O.; Shiryaev, V. I. Continuous synthesis of organomagnesium compounds. *Russ J Appl Chem* **2012**, *85* (4), 629–638. DOI: 10.1134/S1070427212040167.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

(11) Klokov, B. A. Continuous Single-Stage Organomagnesium Synthesis of a Mixture of Ethylethoxysilanes and Dimethylethylethoxysilane. *Org. Process Res. Dev.* **2000**, *4* (2), 122–128. DOI: 10.1021/op990011g.

(12) Jennings, J. R. A novel, continuous high-yield synthesis of Grignard reagents. *Journal of Organometallic Chemistry* **1987**, *325* (1-2), 25–29. DOI: 10.1016/0022-328X(87)80384-4.

(13) Reimschuessel, H. Notes: On the Continuous Preparation of Vinyl Grignard Reagents. *J. Org. Chem.* **1960**, *25* (12), 2256–2257. DOI: 10.1021/jo01082a628.

(14) Storozhenko, P. A.; Grachev, A. A.; Klochkov, A. O.; Shiryaev, V. I. Continuous organomagnesium synthesis of organometallic compounds. *Russ J Appl Chem* **2013**, *86* (3), 387–393. DOI: 10.1134/S1070427213030166.

(15) Goldbach, M.; Danieli, E.; Perlo, J.; Kaptein, B.; Litvinov, V. M.; Blümich, B.; Casanova, F.; Duchateau, A. L. Preparation of Grignard reagents from magnesium metal under continuous flow conditions and on-line monitoring by NMR spectroscopy. *Tetrahedron Letters* **2016**, *57* (1), 122–125. DOI: 10.1016/j.tetlet.2015.11.077.

(16) Huck, L.; La Hoz, A. de; Díaz-Ortiz, A.; Alcázar, J. Grignard Reagents on a Tab: Direct Magnesium Insertion under Flow Conditions. *Organic letters* **2017**, *19* (14), 3747–3750. DOI: 10.1021/acs.orglett.7b01590.

(17) Changi, S. M.; Wong, S.-W. Kinetics Model for Designing Grignard Reactions in Batch or Flow Operations. *Org. Process Res. Dev.* **2016**, *20* (2), 525–539. DOI: 10.1021/acs.oprd.5b00281.

(18) Kopach, M. E.; Cole, K. P.; Pollock, P. M.; Johnson, M. D.; Braden, T. M.; Webster, L. P.; McClary Groh, J.; McFarland, A. D.; Schafer, J. P.; Adler, J. J.; Rosemeyer, M. Flow Grignard and Lithiation: Screening Tools and Development of Continuous Processes for a Benzyl Alcohol

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

Starting Material. *Org. Process Res. Dev.* **2016**, *20* (9), 1581–1592. DOI: 10.1021/acs.oprd.6b00131.

(19) Kopach, M. E.; Roberts, D. J.; Johnson, M. D.; McClary Groh, J.; Adler, J. J.; Schafer, J. P.; Kobierski, M. E.; Trankle, W. G. The continuous flow Barbier reaction: an improved environmental alternative to the Grignard reaction? *Green Chem.* **2012**, *14* (5), 1524. DOI: 10.1039/c2gc35050e.

(20) Wong, S.-W.; Changi, S. M.; Shields, R.; Bell, W.; McGarvey, B.; Johnson, M. D.; Sun, W.-M.; Braden, T. M.; Kopach, M. E.; Spencer, R. D.; Flanagan, G.; Murray, M. Operation Strategy Development for Grignard Reaction in a Continuous Stirred Tank Reactor. *Org. Process Res. Dev.* **2016**, *20* (2), 540–550. DOI: 10.1021/acs.oprd.5b00268.

(21) Braden, T. M.; Johnson, M. D.; Kopach, M. E.; McClary Groh, J.; Spencer, R. D.; Lewis, J.; Heller, M. R.; Schafer, J. P.; Adler, J. J. Development of a Commercial Flow Barbier Process for a Pharmaceutical Intermediate. *Org. Process Res. Dev.* **2017**, *21* (3), 317–326. DOI: 10.1021/acs.oprd.6b00373.

(22) Ende, D. J. am; Clifford, P. J.; DeAntonis, D. M.; SantaMaria, C.; Brenek, S. J. Preparation of Grignard Reagents: FTIR and Calorimetric Investigation for Safe Scale-Up. *Org. Process Res. Dev.* **1999**, *3* (5), 319–329. DOI: 10.1021/op9901801.

(23) Menges-Flanagan, G.; Deitmann, E.; Gössl, L.; Hofmann, C.; Löb, P. Scalable Continuous Synthesis of Grignard Reagents from in Situ-Activated Magnesium Metal. *Org. Process Res. Dev.* **2020**, *24* (2), 315–321. DOI: 10.1021/acs.oprd.9b00493.

(24) Pesti, J.; Chen, C.-K.; Spangler, L.; DelMonte, A. J.; Benoit, S.; Berglund, D.; Bien, J.; Brodfuehrer, P.; Chan, Y.; Corbett, E.; Costello, C.; DeMena, P.; Discordia, R. P.; Doubleday, W.; Gao, Z.; Gingras, S.; Grosso, J.; Haas, O.; Kacsur, D.; Lai, C.; Leung, S.; Miller, M.;

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

Muslehiddinoglu, J.; Nguyen, N.; Qiu, J.; Olzog, M.; Reiff, E.; Thoraval, D.; Totleben, M.; Vanyo, D.; Vemishetti, P.; Wasylak, J.; Wei, C. The Process Development of Ravuconazole: An Efficient Multikilogram Scale Preparation of an Antifungal Agent. *Org. Process Res. Dev.* **2009**, *13* (4), 716–728. DOI: 10.1021/op900065c.

(25) Wiss, J.; Ermini, G. Safety Improvements of a Grignard Reaction by Controlling the Reactant Feed Rate by On-line Concentration Monitoring Using NIR. *Org. Process Res. Dev.* **2006**, *10* (6), 1282–1286. DOI: 10.1021/op0601159.

(26) Wiss, J.; Länzlinger, M.; Wermuth, M. Safety Improvement of a Grignard Reaction Using On-Line NIR Monitoring. *Org. Process Res. Dev.* **2005**, *9* (3), 365–371. DOI: 10.1021/op049784h.

(27) Tanaka, K.; Kumasaki, M.; Miyake, A. Influence of Mg surface layer for induction period of Grignard reagent formation. *J Therm Anal Calorim* **2013**, *113* (3), 1395–1401. DOI: 10.1007/s10973-013-2995-5.

(28) Kryk, H.; Hessel, G.; Schmitt, W.; Tefera, N. Safety aspects of the process control of Grignard reactions. *Chemical Engineering Science* **2007**, *62* (18-20), 5198–5200. DOI: 10.1016/j.ces.2007.01.013.

(29) Deitmann, E.; Maskos, M.; Menges-Flanagan, M. G.; Ziegenbalg, D. Impact of residence time distributions in reacting magnesium packed-beds on Grignard reagent formation – Pump-induced flow behaviour in non-reacting magnesium beds (part 1). *React. Chem. Eng.* **2023**, Advance Article. DOI: 10.1039/D3RE00190C.

(30) Deitmann, E.; Maskos, M.; Menges-Flanagan, M. G.; Ziegenbalg, D. Impact of residence time distributions in reacting magnesium packed-beds on Grignard reagent formation –

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0

Selectivity of Grignard reagent formation (part 2). *React. Chem. Eng.* **2023**, Advance Article. DOI: 10.1039/D3RE00191A.

(31) Berton, M.; Sheehan, K.; Adamo, A.; McQuade, D. T. Disposable cartridge concept for the on-demand synthesis of turbo Grignards, Knochel-Hauser amides, and magnesium alkoxides. *Beilstein journal of organic chemistry* **2020**, *16*, 1343–1356. DOI: 10.3762/bjoc.16.115.

(32) Vardanyan, R.; Hruby, V. J. *Synthesis of essential drugs*; Elsevier, 2006.

(33) Lednicer, D.; Mitscher, L. A. *The organic chemistry of drug synthesis*; Wiley, 1999.

(34) Lednicer, D. *Strategies for Organic Drug Synthesis and Design*, 2., Auflage; John Wiley & Sons, 2009.

(35) Vardanyan, R.; Hruby, V. *Synthesis of best-seller drugs*; Academic Press, 2016.

(36) Vardanyan, R. *Piperidine-based drug discovery*; Heterocyclic drug discovery series; Elsevier, 2017.

(37) Quirke, V. M. Tamoxifen from Failed Contraceptive Pill to Best-Selling Breast Cancer Medicine: A Case-Study in Pharmaceutical Innovation. *Frontiers in pharmacology* **2017**, *8*, 620. DOI: 10.3389/fphar.2017.00620.

https://doi.org/10.26434/chemrxiv-2023-qdvdk **ORCID:** https://orcid.org/0000-0002-8769-7247 Content not peer-reviewed by ChemRxiv. **License:** CC BY-NC-ND 4.0