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Scalable continuous synthesis of Grignard reagents from *in situ* activated magnesium metal

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ABSTRACT

The continuous synthesis of Grignard reagents has been investigated under continuous processing conditions using Mg turnings at variable liquid throughputs and concentrations. A novel process window easily accessible through continuous processing was employed, namely using a large molar access of Mg turnings within the reactor and achieving Mg activation by mechanical means. A laboratory as well as a tenfold increased pilot-scale reactor set-up was built and evaluated including integrated inline analytics via ATR-IR measurements. The main goal of this work was to explore the full potential of classic Grignard reagent formation through the use of scalable flow chemistry and to allow for fast and safe process optimization. It was found that on the laboratory as well as the pilot scale full conversion of the employed halides could be achieved with a single passage through the reactor. Furthermore, yields of 89-100 % of Grignard reagent were reached on the laboratory scale.

KEYWORDS Grignard reagent formation, solid processing, flow chemistry, organomagnesium compound, continuous processing, scale-up.

INTRODUCTION

Organomagnesium reagents, also known as Grignard reagents, constitute one of the most important intermediates in C-C bond formation reactions.[1,2] Their formation and reaction with e.g. carbonyl compounds was discovered by Victor Grignard in 1900, earning him the Nobel prize for chemistry in 1912.[3] In an industrial setting they are prepared in batch mode by charging the reaction vessel with solid magnesium in the form of powder or turnings and a small amount of appropriate solvent, and slowly adding the organic halide while maintaining tight control over the

reaction temperature. Key challenges are controlling the Grignard reagent formation initiation and not overcharging the vessel with halide and risking a runaway reaction.[4]

Given the above, the classic reagent formation via elemental magnesium is obviously plagued by a number of drawbacks: depending on the halide used, variable-length incubation periods are observed and activating agents for the Mg such as previously prepared Grignard reagent, iodine, bromine, or an additional active halide may be needed to aid the start up. Furthermore, once started, the Grignard reagent formation is an exothermic reaction, side product formation diminishes yields e.g. through Wurtz coupling of starting material and product, in batch it is dosing controlled to dissipate the heat generated, and often requires long reaction times to drive the reaction to completion.

Therefore, in the past decade a growing number of efforts have been undertaken to gain access to Grignard reagents with the most important one being the approach through means of halogen-metal exchange. Here, through the use of an auxiliary agent such as ethyl magnesium bromide or *iso*-propyl magnesium chloride (often in conjunction with LiCl) a large number of organomagnesium compounds with excellent tolerance to sensitive functional groups can be obtained.[5-8] This approach has also been taken up for continuous processing[9] and has even been scaled-up recently.[10]

In addition to that, with the field of flow chemistry gaining more and more interest not only academically but also industrially, a growing number of publications have used Grignard reagents in flow applications to synthesize a large number of molecules, mainly for the production of active pharmaceutical ingredients (APIs).[11-19] Notable examples here are the use of (3-methoxyphenyl)magnesium bromide in the synthesis of Tramadol used to treat pain[12], allylmagnesium chloride (Allyl MgCl) in the synthesis of the antipsychotic Clopixol[14], and

phenylmagnesium bromide (PhMgBr) in the synthesis of Tamoxifen used for treating breast cancer.[16] For such seemingly simple Grignard reagents, carrying no potentially sensitive functional groups, an easily accessible continuous approach to them directly from metallic magnesium would be desirable. This could then easily be included in the above described continuous flow synthesis, freshly preparing the reactive intermediate Grignard reagents and omitting the need for storage of such reagents over time diminishing their quality, and thereby potentially improving the product quality through purer intermediates.

The direct Grignard reagent formation from Mg in the form of turnings as described here is an ideal candidate for continuous processing since it can benefit tremendously from improved heat management and fast reaction control, allowing temperature jumps as needed for optimal thermal management. Furthermore, through flow chemistry a continuous provision of a large excess of Mg throughout the reaction can be achieved, Mg activation can be integrated, and Mg can be continuously replenished throughout the course of the reaction. The general considerations made for the case of Grignard reagent formations are also applicable to other solid/liquid processes. Therefore, the developed set-up dedicated to continuous solid/liquid processing is applicable to a variety of other processes. The proof-of-concept for the set-up however has been performed *via* a Grignard reagent formation.

A number of patents have been concerned with the preparation of Grignard reagents from metallic Mg[20-22], and recently two papers have been published detailing the laboratory scale synthesis of PhMgBr as well as other Grignard reagents continuously without Mg replenishing.[23,24]

Furthermore, Eli Lilly has performed Barbier as well as Grignard reactions in a series of continuous stirred tank reactors mapping the operational space for continuous Grignard reagent formation and consumption combining a modeling approach with experimental runs at scale.[25-27]

In this paper, the Fraunhofer IMM approach to Grignard reagent formation on the laboratory scale as well as the pilot scale is shown. The developed set-ups use Mg turnings activated *in situ* throughout the reaction. The set-ups allow access to a novel process window, namely a large excess of Mg (5-25 molar excess) to suppress unwanted side reactions and to allow the reaction to proceed within only a few minutes residence time while yielding 100% conversion within a single passage through the reactor. Analysis of the reaction progress was performed using inline IR monitoring and verified *via* titration. A tenfold scale-up is described and particular care given to the thermal management of the reaction.

RESULTS AND DISCUSSION

A laboratory scale reactor was designed and manufactured by 3D laser melting. This technology was used for the reactor fabrication to enable cost efficient manufacturing of the hardware and plays a crucial role in establishing sufficiently effective heat exchange structures for the scale-up. Heating/cooling therewith can be achieved efficiently according to the reaction's needs and progression. Figure 1 shows the flow chart of the Grignard reagent formation with the reactor at its midst, Figure 2 details the reactor constructed and patented[28] detailing fluid inlet and outlet, temperature measuring points along the reactor, as well as showing integrated viewing windows for visual inspection of reaction progress. Four temperature measuring points are included with T1 being situated at the entrance of the fluid into the reactor, and T4 placed at the top of the reaction zone. The reactor is manufactured from two identical halves, allowing two different temperature zones to be used within the reactor since it was found that the lower half of the reactor exhibited significantly more heat release than the upper part.

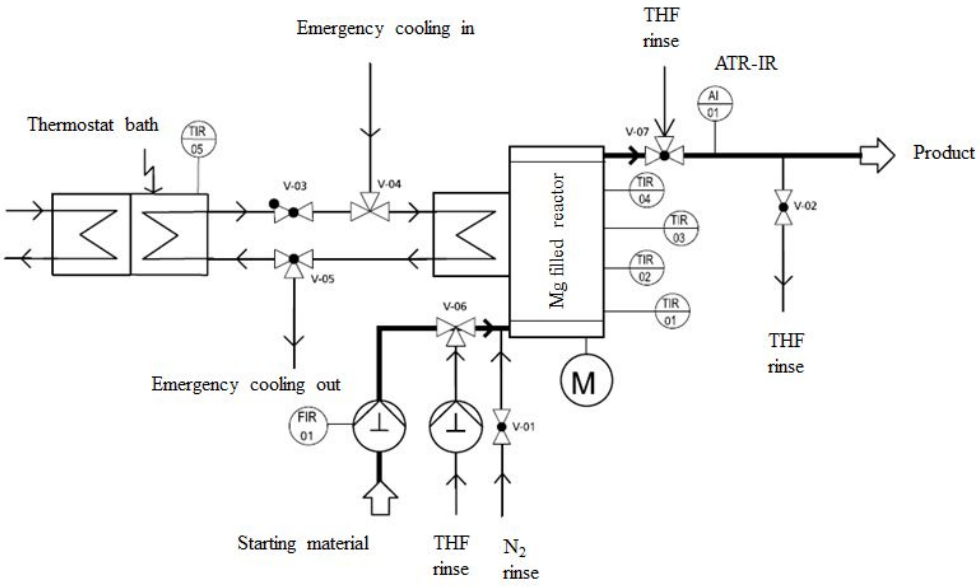

Figure 1: Flow chart detailing the components for Grignard reagent formation.

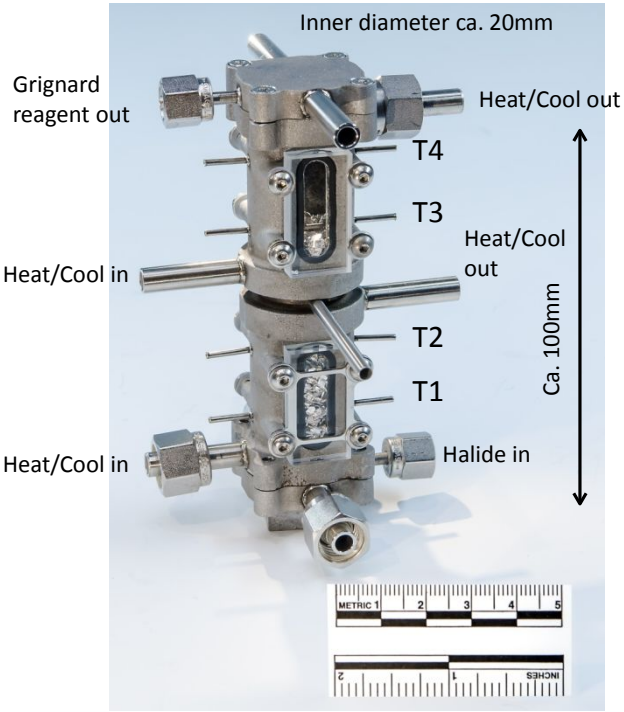

Figure 2: Laboratory-scale Grignard reagent formation reactor.

As an instantaneous inline analysis tool, an ATR-IR spectrometer was incorporated. Additionally, titration either with menthol and 1,10-phenanthroline[29] or *via* iodine/LiCl[30] was used. In the case of benzylmagnesium chloride, samples were quenched with methanol and analysed *via* GC. The operating conditions were chosen as follows: The magnesium turnings had an average size of 0.5-3 mm. Activation of the Mg was performed mechanically through a jogging motor, which provides abrasion on the surface of the magnesium by mutual rubbing of the turnings. In most cases, no other activation such as auxiliary chemicals or pretreatment with Grignard reagent was necessary. Water-free THF was used but other appropriate solvents can also be employed. Temperature can be rapidly varied *via* a thermostatic bath, and very sensitive Grignard reagents can be formed by employing a chiller. Alkyl or aryl halides can be used in concentrations from about 0.5-3.0 molar with the upper limit given by the solubility of the formed Grignard reagent. Residence times in the reactor ranged from 5.0-30.0 minutes (residence time distribution measurements show a behavior close to a PFR with Bodenstein Numbers up to about 90 at flow rates between 1-4 ml/min under Mg activation) given by the flow rate used and dependent on the Grignard reagent's reaction time needed to reach full conversion of the used halide within one passage through the reactor. In terms of safety considerations, it was estimated from available reaction enthalpies that a heat being released within the reactor of up to only a few tens of Watts can be expected, so the integrated heat exchanger is able to handle the temperature rise within the reactor and remove the heat efficiently.

For each investigated Grignard reagent, multiple runs were performed varying temperature of the thermostat bath employed for heating/cooling the reactor as well as flow rate in order to achieve complete halide conversion within one reactor passage with the goal of achieving maximum flow rate at minimal energy expenditure in terms of excessive heating/cooling necessary. Initial Grignard reagent formation reactions were investigated with the reactor as given above. Later on

an Mg replenishing unit was established to render the reaction truly continuous in both, liquid and solid, feed. Figure 3 shows an example of typical temperature profiles obtained along the reactor, here shown for processing of a 1M ethyl bromide solution in THF.

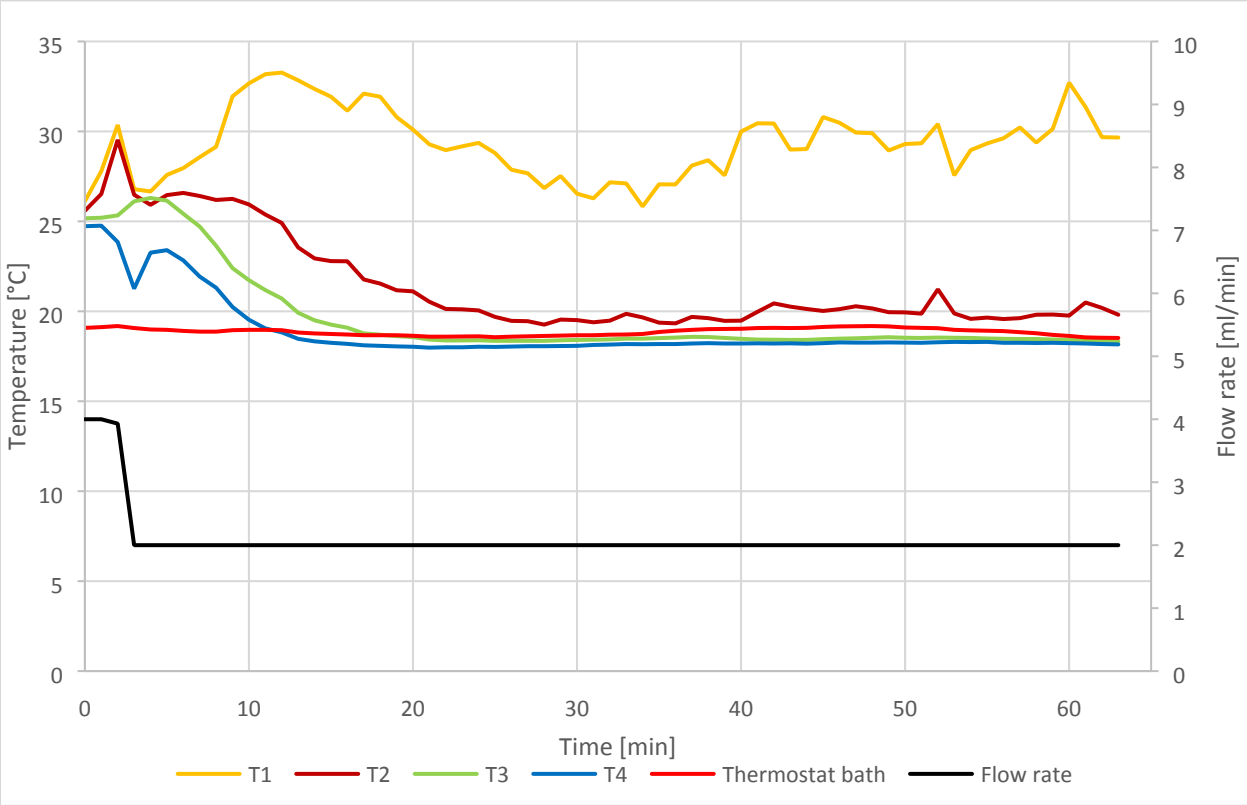

Figure 3: Temperature progression along the reactor: Flow rate: 2 ml/min (Filling: 4 ml/min), 1M EtBr in THF, Thermostat bath setting: 18°C.

For this Grignard reagent care had to be taken to not exceed the boiling point of the starting material ethyl bromide (38°C) during processing. More halide starting materials of common Grignard reagents on the market were explored and their synthesis optimized in flow aiming at maximum flow rate for full halide conversion within a single passage through the reactor while using minimal energy input namely thermostat bath settings with minimal heating/cooling possible. Table 1 summarizes the Grignard reagent synthesis investigated detailing halide

concentrations employed, maximum flow rate possible for full conversion, temperature setting of the thermostat bath, and yields of Grignard reagents achieved (determined by manual titration). For comparison, concentration ranges for commercially available reference materials are also given.

Table 1: Reaction conditions and yields for investigated standard Grignard reagents.

Grignard-Reagent	Concentration starting material [mol/l]	Flow Rate [ml/min]	Residence Time [min]	Temperature TT [°C]	Concentration (achieved in flow) [mol/l]	Yield [%]	Concentration (reference material) [mol/l]
AllylMgCl	2	Filling: 4 Run:1.5	10	15	1.96 – 2.00	98-100	1.90 – 2.20 (2.08)
EtMgBr	1	Filling: 4 Run: 2	7.5	18	0.94 – 0.98	94-98	0.95 – 1.10 (0,96)
PhMgBr	1	Filling: 8 Run: 2	7.5	Start: 50 Run: 35	0.98 – 1.00	98-100	0.95 – 1.15 (0.78)
	2	Filling: 8 Run: 1	15	40	ca. 2.00	Ca. 100	-
i-PrMgCl	2	Filling: 2 Run: 0.5	30	Start: 29 Run: 21	1.85 – 1.89	92.5-94.5	1.80 – 2.20 (1.89)
2-Thienyl-MgBr	1	Filling: 6 Run: 1.5	10	20	0.89 – 0.93	89-93	0.95 – 1.10 (0.95)

It is noteworthy that with the exception of the 2-thienylmagnesium bromide all results achieved lay within the range of the reference materials but are narrower than the commercial products. Additionally it should be mentioned that the given flow rates correspond to residence times of the halide over the Mg bed of about 7.5-30 minutes. As mentioned above, the Mg turnings are mechanically activated through vibration within the reactor. In order to verify that this *in situ* activation really had a significant influence on the Grignard reagent formation, the optimized reaction conditions for a number of the reagents were tested without Mg activation. Table 2

summarizes the differences in time of start of reaction after halide is being introduced into the reactor.

Table 2: Comparison of Grignard reagent formation with and without Mg mechanical activation.

Grignard-Reagent (all in THF)	Reaction starts	Time of start of reaction [min]		Complete conversion of starting material	Remaining starting material [mol/l]
		Without Activation	With Activation	Without Activation	
2M AllylMgCl	Yes	14	3	No (35.5 %)	1.29
1M EtMgBr	Yes	6	0	No (62 %)	0.38
1M PhMgBr	Yes	12	3	No (88.5 %)	0.26
2M PhMgBr	Yes	4	2	No (74 %)	0.23

It was found that without Mg activation the Grignard reagent formation does still start without the need for auxiliary chemicals for initiation; however, the time is much higher and no more full conversion of halides is achieved on the previously optimized reaction conditions.

It had been found that the reactor was performing so well that Mg was consumed very fast and that a Mg replenishing unit was needed to be able to run reactions over an extended period of time and to render the set-up truly continuous. A manual portion-wise Mg refilling unit was constructed and attached to the reactor as depicted in Figure 4.

Figure 4: Laboratory-scale Grignard reagent formation reactor including the Mg refilling unit.

The replenishing unit and two temperatures zones were then used in the synthesis of benzylmagnesium chloride. Figure 5 shows the temperature profiles within the reactor over time. It has to be noted that 2-Me THF instead of THF was used to suppress side product formation. Furthermore, the Mg turnings were pre-activated through ultrasound to decrease the incubation period observed in the reactor when only using the mechanical activation through vibration as implemented in the reactor.

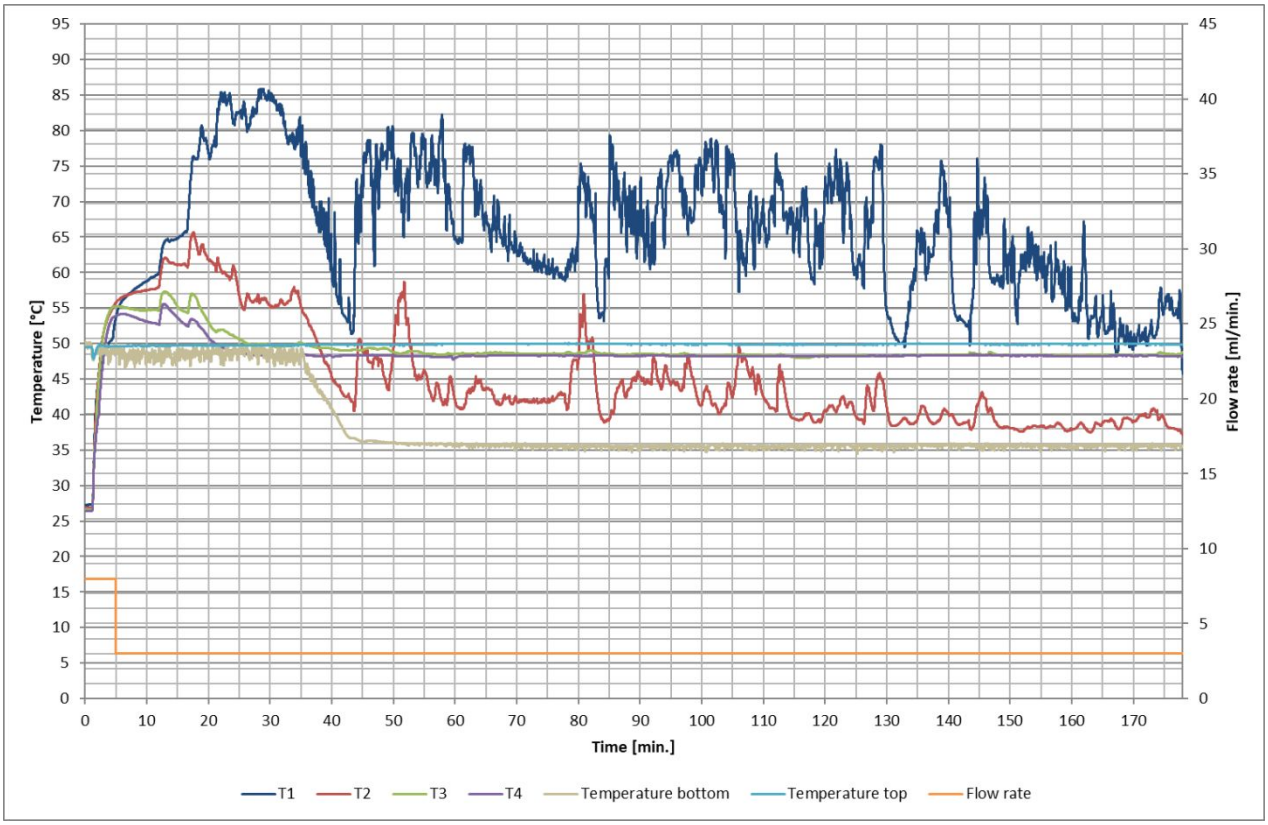

Figure 5: Temperature progression along the reactor: Flow rate: 3ml/min (Filling: 8ml/min), 1M BenzylCl in 2-Me THF, Thermostat bath setting: 50°C (top), 35°C (bottom).

It was found that full conversion of halide and steady-state operation with full chloride conversion could be reached after only about 30 minutes of run time. Yield of Grignard reagent as determined by GC analysis was found to be 97% with the main by-product being benzyl alcohol (2%) and very little Wurtz coupling product and no remaining starting material benzyl chloride being observed. In addition, the reaction could be conducted for about 3 hours with Mg being replenished six times (each time about 5-10% of total Mg amount in the reactor is added from the top, refilling is initiated, when a gap in the top viewing window can be observed) so about half of the initial Mg amount was consumed and refilled within one single experiment without loss in product quality.

In terms of scalability of the process to industrially relevant throughputs, a pilot reactor allowing a tenfold increased flow through has been built and tested and is depicted in Figure 6.

Figure 6: Pilot-scale Grignard reagent formation reactor with implemented automated Mg refilling.

It includes an automated Mg replenishing unit however only has one accessible temperature zone within the reactor. It has been successfully tested with 1M phenylmagnesium bromide and efforts are under way to build a pilot plant at Fraunhofer IMM that will ultimately allow flow rates of up to 15 l/h halide throughput.

EXPERIMENTAL SECTION

FLOW PROCEDURE FOR GRIGNARD SYNTHESIS

The reactor was charged with about 20 g of Mg turnings, inerted with Argon and four thermocouples were placed along the Magnesium bed for temperature monitoring. Activation of the magnesium turnings was started using a jogging motor placed at the bottom of the reactor (3V, 150 mA). Then the reactor was filled with a solution of starting material halide in dry THF at an elevated flow rate using a Postnova syringe pump resulting in a temperature increase as a hint for initiation of the exothermic reaction (filling with educt was carried out without additional heating/cooling for most Grignards). As soon as the reactor was completely filled with educt solution, temperature control was started using a thermostat bath and the flow rate was reduced to keep temperatures below the solvent's (here THF) boiling point. The course of the reaction was observed by means of an ATR-IR fiber probe placed in the reactor outlet. Samples of the outlet solution were titrated to determine the Grignard concentration. Specific reaction conditions for investigated Grignard reagents are shown in Table 1.

MATERIALS AND METHODS

All solvents and reagents were purchased from commercial suppliers and were used without further purification. Namely the chemicals used and their suppliers were: allyl chloride (Sigma-Aldrich, 99%), 2M allylmagnesium chloride in THF (Sigma-Aldrich), benzyl chloride (Thermo Fischer Kandel, 99%, stabilized), bromobenzene (Merck KGaA, 99%), bromoethane (Sigma-Aldrich, 98%), 2-bromothiophene (Fluorochem Ltd., 98%), chlorobenzene (Sigma-Aldrich, >99.5%), chloropropane (Sigma-Aldrich, >99%), 1M ethylmagnesium bromide in THF (Sigma-

Aldrich), iodine (Fluka Chemie AG, >99.5%), 2M isopropylmagnesium chloride (Sigma-Aldrich), lithium chloride (Sigma-Aldrich, >98%, waterfree), Mg turnings (Merck KGaA, >99%), menthol (Sigma-Aldrich, 99%), methanol (T H Geyer, 99.95%), 1,10-phenanthroline (Sigma-Aldrich, >99%), 1M phenylmagnesium chloride in THF (Sigma-Aldrich), THF (T H Geyer, 99.9%, waterfree), 1M 2-thienylmagnesium bromide (Sigma-Aldrich), toluene (Carl Roth, 99.5%).

Pumps used were Postnova syringe pumps (PN 1610 Syringe Dosing System). For tempering of the reactors, thermostatic baths from Lauda (C6CS), Julabo (F31-C), and Peter Huber Kältemaschinenbau (CC-405, CC-3) were used. The temperatures were measured using miniature thermocouples (type K from RS Components), recorded by a data logger (either Siemens PCS7 Lab or Type Expert Key 200L, from Delphin Technology) and for evaluation transferred to a notebook. Inline ATR-IR monitoring was performed using a Bruker Matrix-MF spectrometer and a self-constructed flow through cell. Titration of the Grignard reagent was done following the method of Lin and Paquette for the titration with 1,10-phenanthroline[29] and following the method of Krasovskiy and Knochel when using the titration with iodine.[30] Analysis for the benzylmagnesium chloride was done via quenching Grignard reagent samples in methanol and analyzing via calibrated GC measurements. Here, a Varian GC 3900 system with Varian 8400 GC-autosampler was used.

CONCLUSIONS

In conclusion, a continuously operating laboratory set-up for Grignard reagent formation was established including inline process monitoring and a process control unit, allowing for the optimization of process parameters for scalable continuous Grignard reagent formation. Reaction conditions for full halide conversion in one single reactor passage were found aiming for maximum

throughput with minimal energy input. The reactor allows processing in a novel process window of large Mg access also allowing for *in situ* Mg activation. An Mg replenishing unit as add-on to the reactor was built and tested allowing for truly continuous halide processing without loss of product quality. Furthermore, the scale-up to pilot-scale throughput (scale-up factor of 10) including a continuous mechanical Mg replenishing unit and sensors for Mg level filling was established and investigated. Efforts to increase its throughput to halide solution flow rates of up to 15 l/h are underway.

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