

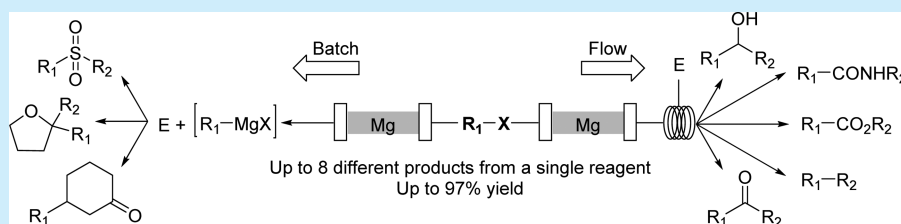
# Grignard Reagents on a Tab: Direct Magnesium Insertion under Flow Conditions

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**S** Supporting Information



**ABSTRACT:** An on-demand preparation of organomagnesium reagents is presented using a new flow protocol. The risks associated with the activation of magnesium are circumvented by a new on-column initiation procedure. Required amounts of solutions with a precise titration were obtained. Telescoped flow or batch reactions allow access to a diverse set of functional groups.

The Grignard reaction was discovered in 1900 by Victor Grignard. It is one of the most significant organometallic reactions because diverse C–C bonds can be formed by reaction with different electrophiles.<sup>1,2</sup> Organomagnesium reagents have been widely used to make numerous intermediates and final products in the pharmaceutical, food, and related chemical industries.<sup>3</sup>

Different methodologies have been used to prepare Grignard reagents.<sup>4</sup> Among them, halogen/magnesium insertion is one of the preferred alternatives as it is an atom economical, cheap, and low toxicity process.<sup>5</sup> However, several drawbacks limit the application of this approach. For instance, activation can be an issue due to its exothermic nature, and the compounds obtained are air-sensitive, which makes handling and storage more difficult.<sup>6</sup>

Recently, flow chemistry has shown potential as an enabling technology that allows very efficient heat transfer, good control of reaction temperature, and enhanced mass transfer.<sup>7</sup> This approach could circumvent the problems associated with highly exothermic reactions and dangerous or air- and moisture-sensitive compounds, such as organomagnesium reagents.

Despite the potential applicability of flow to these transformations, only two studies have been described to date in the literature.<sup>8</sup> The first example was described in 2012, and it involved the use of a stirred column-type apparatus filled with granulated magnesium.<sup>8a,b</sup> The second approach concerned the synthesis of phenylmagnesium bromide and its subsequent reaction with CO<sub>2</sub>.<sup>8c</sup> However, considering these two precedents, only five examples were described, and these were nonfunctionalized alkyl and aryl reagents, which means that the full potential of the approach remains unexplored. For

production purposes, the use of continuous stirred tank reactors has been described.<sup>6a,c</sup>

As a continuation of our previous work on organozinc preparation in flow using a zinc column,<sup>9</sup> we present here a new methodology for the synthesis of Grignard reagents using a packed magnesium column. The methodology is very functional-group-tolerant, and it can be extended to bromo-, chloro-, and iodoalkyl and aryl derivatives.

We initially explored magnesium activation and the type of magnesium to be used (Table 1). Considering our previous experience, a magnesium particle size of 20–230 mesh was selected. This size is ideal for flow protocols as it is large enough to prevent an increase in the pressure of the system but also provides a high surface area to maximize the contact between the metal and the halogenated derivative. Magnesium activation and

**Table 1. Optimization of Activation and Reaction Conditions**

entry	solvent (activation)	temp (°C)	solvent (reaction)	t <sub>R</sub> (min)	[2a] (M)
1	LiCl in THF	rt	THF	7.5	0.24
2	LiCl in THF	40	THF	7.5	0.23
3	LiCl in THF	40	LiCl in THF	7.5	0.35
4	1:1 THF/tol	50	LiCl in THF	7.5	0.38
5	1:1 THF/tol	50	LiCl in THF	3.8	0.2
6	1:1 THF/tol	50	LiCl in THF	15	0.12

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Table 2. Synthesis of Compounds 7–10 by Magnesium Insertion and Subsequent Treatment with Electrophiles<sup>a</sup>

$R_1-X$  (1a-q)  $\xrightarrow{Mg}$   $\xrightarrow{E}$  Products (7-10 a-q)

entry	R <sub>1</sub> -X	E	product	entry	R <sub>1</sub> -X	E	product
1				11		3a	
2	1a			12		5	
3	1a			13		3a	
4	1a			14		3a	
5				15		3a	
6		4		16		3a	
7		3a		17		3b	
8	1d	4		18		3b	
9		3a		19		3a	
10		3a		20		6	

<sup>a</sup>Reaction conditions: **1** (0.5 M)  $t_R = 7.5$  min, 50 °C, then electrophile (0.4 M),  $t_R = 20$  min, room temperature; <sup>a</sup>electrophile (0.45 M),  $t_R = 1$  min; <sup>b</sup>**1** (0.5 M),  $t_R = 15$  min, 60 °C.

metal insertion were performed, one after the other, without any intermediate washing step. Concentration of the corresponding organomagnesium reagent was determined by two colorimetric titration procedures: reaction with salicylaldehyde phenyl hydrazone<sup>9</sup> or menthol with phenanthroline<sup>10</sup> to obtain a more precise value.

First, a 1 M solution of DIBAL-H in toluene was flowed through the column to remove the oxide layer on the metal surface.<sup>6b</sup> As metal was not fully activated by this procedure, we reproduced the protocol optimized for zinc,<sup>11</sup> passing a preprepared solution of TMSCl and 1-bromo-2-chloroethane in THF. To our surprise, a precipitate was observed at the end of the column and the exit tubing, which led to clogging of the system. That solid was soluble in toluene and 0.5 M LiCl in THF. However, due to the limited solubility of Grignard reagents in toluene, we decided to use LiCl solution as the reaction media, as it has been reported to accelerate the metal insertion (entries 1–3).<sup>5,12</sup> When both steps were done using this salt, a 0.35 M solution of the Grignard reagent was obtained (entry 3). This interesting result was further improved using a 1:1 mixture of THF/toluene (entry 4). Reducing or increasing the residence time did not provide better outcomes (entries 5 and 6).

One of the key advantages of the flow protocol is the ability to prepare the appropriate amount of organometallic solution on demand. In this way, a 0.5 M of bromobenzene solution in 0.5 M LiCl in THF was pumped through a 10 mm × 100 mm (diameter × length) column filled with 4 g of metal for 3 h. Magnesium was previously activated following the conditions shown in entry 4. As a result, 90 mL of 0.38 M phenylmagnesium bromide solution was obtained (estimated yield 76%). During the course of the reaction, titration of the outcome solution was performed every 30 min to check the reproducibility of the system. The concentration of the outcome solution was sustained throughout the whole process (see [Supporting Information](#)). Around one-fourth of the initial magnesium was consumed. Once the reaction had finished, the column was manually refilled, reactivated, and used for subsequent reactions, thus minimizing the amount of metal waste. Larger runs could also be done as outcome concentration did not drop until 60–70% of the initial amount of metal was consumed.<sup>11</sup>

Once the preparation of the Grignard reagents had been optimized, the scope and limitations of this methodology were studied. The outcoming organomagnesium solutions were mixed in line with the corresponding electrophile in flow to obtain the final compounds in high yields in less than 30 min total reaction time ([Table 2](#)).<sup>13</sup> For example, alcohol **7a**, ester **8a**, ketone **9a**, and amide **10a** were obtained in good to excellent yields (entries 1–4). Alcohol **7a** was also reported in batch using the same approach with a comparable yield (97%).<sup>14</sup>

The tolerance of different functional groups at the aromatic ring was subsequently studied. Bromo-3-chlorobenzene **1b** underwent selective insertion at the bromine atom to give compound **7b** after quenching with 3-pyridinecarboxaldehyde **3b** in 74% isolated yield.

It is well-known that the synthesis of Grignard reagents starting from benzotrifluorides is dangerous because of the potential for runaway reactions.<sup>15</sup> In our case, the use of mild conditions and flow led to a safe magnesium insertion into 3-bromobenzotrifluoride **1d**. Subsequent reactions with benzaldehyde **3a** or *tert*-butoxycarbonyl anhydride **4** afforded the corresponding alcohol **7d** and ester **8d**, respectively, in excellent yields.

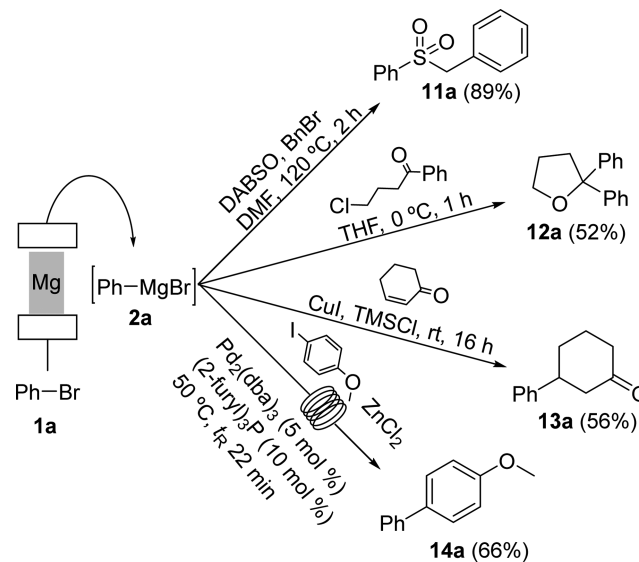
The effect of the substituent position was explored in *ortho*-, *meta*-, and *para*-methoxybromobenzenes **1e**, **1f**, and **1g**. In all cases, the reaction products expected after treatment with benzaldehyde were obtained in high yields (entries 9–11). Alcohol **7f** was reported in batch using the same approach in lower yield (75%).<sup>16</sup> Dimethoxybromobenzene **1h** was also employed, and this provided ketone **9h** in high yield after reaction with the Weinreb amide **5**. However, the magnesium insertion reaction required a temperature of 60 °C and a residence time of 15 min to obtain a 0.4 M concentration of the organomagnesium reagent.

Compatibility with potentially reactive groups was explored with benzonitrile **1i**, which produced alcohol **7i** in very good yield. In an effort to extend the methodology to heterocycles, pyridyl bromide **1j** and iodide **1k** were also tested. The magnesium insertion took place in an efficient way in 15 min at 60 °C, and the subsequent reaction gave the final products **7j** and **7k**, respectively.

The use of aliphatic bromides, iodides, and chlorides was explored. The magnesium insertion at primary carbons gave the final alcohols **7l**, **7m**, and **7n** in good yields. In the case of secondary alkyl halide **1p**, the final amide **10p** was obtained in 55% yield. Piperidines were evaluated as they are important intermediates in medicinal chemistry. The magnesium insertion in chloropiperidine **1o** took place under standard conditions, and subsequent quenching with benzaldehyde provided alcohol **7o** in high yield.

All of the above examples were prepared by direct quenching of the Grignard reagent in flow. Likewise, this methodology provides solutions of organomagnesium reagents with a precise titration that can be used in batch protocols to provide other types of compounds ([Scheme 1](#)). These batch approaches are

Scheme 1. Extended Scope in Batch and Flow



more suitable when insoluble reagents or intermediates are required or when long reaction times are needed to obtain the corresponding product. Thus, a one-pot procedure was used to evaluate different reactions by collecting the outcome of the column over different reagents. When 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO) was used as the electrophile,<sup>17</sup> the corresponding sulfone was obtained, and this yielded sulfone **11a** in an efficient manner after addition of

benzyl bromide. Similarly, as reported previously for organozinc reagents,<sup>11b</sup> reaction with 4-chloro-1-phenylbutanone yielded tetrahydrofuran **12a**. 1,4-Addition compounds on cyclohexanone were also obtained using copper iodide as catalyst to give **13a**.<sup>18</sup> Finally, flow Negishi coupling was attempted by mixing the outcome with zinc chloride, iodoarene, and the corresponding palladium catalyst following the procedure described by Knochel and co-workers.<sup>19</sup> In all examples mentioned above, good to excellent yields of the corresponding products were obtained.

In summary, we have shown that insertion of magnesium into various aryl and heteroaryl bromides and iodides, as well as alkyl halides, takes place when the reactants flow through a magnesium column. The approach can be easily scaled up by simply flowing the solution through the column for a longer period. Precise titration solutions were obtained and used in either batch or flow protocols to yield a diverse set of compounds with a wide range of functional groups. Alcohols, ketones, esters, amides, ethers, and sulfones were all obtained in good to excellent yields. Additionally, new C(sp<sup>2</sup>)-C(sp<sup>3</sup>) and C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bonds were formed in a single step from the Grignard reagents. A wide range of functional groups at the aromatic ring were well-tolerated, and the methodology is also applicable for heterocyclic systems as well as different functionalized alkyl groups. Taking all of the results into consideration, the methodology can be considered as an interesting tool for diversity oriented synthesis<sup>20</sup> of compounds with different functional groups as well as for the diverse preparation of intermediates for the synthesis of compounds with potential biological activity, including new scaffolds like 2,2-disubstituted tetrahydrofurans. The further applicability of this technology in the field of drug discovery will be described in future publications.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.7b01590](https://doi.org/10.1021/acs.orglett.7b01590).

Experimental procedures, spectral data, and NMR spectra of the compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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