#### **Grignard Reagents**

## **Convenient Preparation of Polyfunctional Aryl Magnesium Reagents** by a Direct Magnesium Insertion in the Presence of LiCl\*\*

Fabian M. Piller, Prasad Appukkuttan, Andrei Gavryushin, Matthew Helm, and Paul Knochel\*

Dedicated to Professor Gernot Boche on the occasion of his 70th Birthday

The preparation of complex polyfunctional organometallic reagents is of pivotal interest in organic synthesis.<sup>[1]</sup> Recently, functionalized organomagnesium reagents have become accessible through a halogen/magnesium exchange<sup>[2]</sup> or a directed metalation.<sup>[3]</sup> During these studies it became apparent that aryl magnesium halides are compatible with important functional groups, such as cyano, nitro, ester, or even keto groups.<sup>[4]</sup> This observation prompted us to reinvestigate the direct insertion of magnesium metal into aromatic and heterocyclic halides pioneered by Grignard.<sup>[5]</sup> Such a direct insertion reaction has several advantages: 1) It is atom economical,<sup>[6]</sup> 2) magnesium turnings are one of the cheapest reagents for the formation of organometallic species,<sup>[7]</sup> and 3) the low toxicity of magnesium makes organomagnesium compounds particularly environmentally friendly. A significant drawback of this well-known reaction is that the insertion of magnesium metal into an aryl halide requires harsh conditions: This transformation usually only takes place at 30-60°C,<sup>[8]</sup> which is a serious limitation if functionalized substrates are used. In pioneering studies, Rieke<sup>[9]</sup> prepared highly activated magnesium powder by the treatment of MgCl<sub>2</sub> with lithium in the presence of naphthalene (20 mol%); this highly activated magnesium powder was used for the preparation of some functionalized aryl magnesium reagents at -78 °C.<sup>[10]</sup> Recently, we found that aryl zinc halides can be obtained readily from aryl halides by using zinc powder in the presence of LiCl.<sup>[11]</sup> LiCl serves several purposes: 1) It solubilizes the resulting organozinc compound and thus provides a constantly clean metal surface, 2) it promotes the initial electron transfer by the electrophilic activation of the aromatic ring through complexation,<sup>[11b]</sup> and 3) the high ionic strength of LiCl solutions facilitates charge separation and accelerates the metal insertion.<sup>[12]</sup>

 [\*] F. M. Piller, Dr. P. Appukkuttan, Dr. A. Gavryushin, Dr. M. Helm, Prof. Dr. P. Knochel Ludwig-Maximilians-Universität München Department Chemie und Biochemie Butenandtstrasse 5–13, Haus F, 81377 München (Germany) Fax: (+49) 892-1807-7680 E-mail: paul.knochel@cup.uni-muenchen.de

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author. Herein, we report the direct preparation of a range of new functionalized aryl and heteroaryl magnesium species **2** from the corresponding chlorides and bromides **1** with commercial magnesium turnings or powder (1.5-2.5 equiv) in the presence of LiCl  $(1.25 \text{ equiv})^{[13]}$  under mild conditions (Scheme 1).<sup>[14]</sup>



**Scheme 1.** LiCl-promoted insertion of magnesium into aryl and heteroaryl chlorides and bromides. FG = functional group.

Thus, the addition of 2-chloro- or 2-bromobenzonitrile (1.0 equiv) to magnesium turnings (2.5 equiv)<sup>[15]</sup> and LiCl (1.25 equiv) in THF at 25 °C led to 2-cyanophenylmagnesium chloride or bromide (2a) within 30-45 min, as indicated by an iodometric titration. In the absence of LiCl, a reaction time of approximately 5 h was required for the insertion, and considerable decomposition was observed. A palladiumcatalyzed Negishi cross-coupling reaction<sup>[16]</sup> with 4-iodoanisole then furnished the arylated benzonitrile **3a** in 73-85% yield (Table 1, entry 1). This remarkable compatibility of a cyano group with a  $C(sp^2)$ -Mg bond at 25 °C was not limited to this substitution pattern. The magnesium insertion into various chloro- and bromobenzonitriles proceeded similarly (25°C, 45 min-3 h) and led, after palladium-catalyzed crosscoupling,<sup>[16]</sup> to the expected substituted benzonitriles **3b** and **3c** in 69–83% yield (Table 1, entries 2 and 3).

Benzotrifluorides react violently with magnesium dust (no reaction occurs with magnesium turnings). Therefore, the synthesis of such magnesium reagents is dangerous owing to possible runaway reactions.<sup>[17]</sup> However, the use of magnesium turnings in the presence of LiCl led to a safe magnesium insertion into 4-bromobenzotrifluoride at 0 °C to produce the magnesium reagent **2d** within 30 min. Palladium-catalyzed Negishi cross-coupling<sup>[16]</sup> with ethyl 4-iodobenzoate then furnished the biphenyl derivative **3d** in 97 % yield (Table 1, entry 4). Even a sensitive pivalate group was tolerated: The



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Entry	Magnesium reagent <sup>[b]</sup>	T [°C], t [min]	Electrophile	Product	Yield [%] <sup>[c]</sup>
1	MgX CN	25, 30 25, 45 <sup>[f]</sup>	OMe	OMe	85 <sup>[d]</sup> 73 <sup>[d,f]</sup>
2	2 a F MgBr CN	25, 45	MeO	3a F CN	81 <sup>[d]</sup>
3	2b NC	25, 120 25, 180 <sup>[f]</sup>	CO <sub>2</sub> Me	3 b NC	83 <sup>[d]</sup> 69 <sup>[d,f]</sup>
4	2c F <sub>3</sub> C	0, 30	CO <sub>2</sub> Et	3c F <sub>3</sub> C	97 <sup>[d]</sup>
5	2d Br MgBr Pivo	-20, 60	PhCHO	3d OH PivO	86
6	MgBr OBoc	—10, 60	CI CI		95 <sup>[e]</sup>
7	2 f MgBr BocO	-10, 20	MeSO <sub>2</sub> SMe	3 f SMe BocO	92
8	2g MgBr OTs	0, 120	DMF	3g CHO OTs	77
9	MgBr Cl	25, 10	CO <sub>2</sub> Et	CO <sub>2</sub> Et	94 <sup>[d]</sup>
10	2i CI MgBr	25, 10	PhCHO	3i OH CI	89
11	2j	25, 30	MeCOCI	3j Me	90 <sup>[e]</sup>
12	2k CI N MgBr	0, 30	OMe	3 k CI N	84 <sup>[d]</sup>

**Table 1:** Synthesis of products **3** by magnesium insertion into aryl and heteroaryl bromides and chlorides in the presence of LiCl and subsequent treatment with electrophiles.<sup>[a]</sup>

[a] Reaction conditions: aryl halide (1.0 equiv), electrophile (0.7 equiv). [b] Complexed LiCl is omitted for clarity. [c] Yield of the analytically pure product. [d] The product was synthesized by transmetalation with ZnCl<sub>2</sub> and Pd-catalyzed cross-coupling.<sup>[16]</sup> [e] The magnesium reagent was transmetalated with CuCN-2 LiCl (20 mol%).<sup>[18]</sup> [f] The chloro compound was used to form the magnesium reagent (X = Cl). X = Br, Cl; Boc = tert-butylcarbonyloxy, DMF = N,N-dimethylformamide, Piv = pivaloyl, Ts = paratoluenesulfonyl.

magnesium reagent 2e<sup>[10]</sup> was prepared regioselectively from the corresponding dibromide within 1 h at -20°C and underwent addition to benzaldehyde to give the alcohol 3e in 86% yield (Table 1, entry 5). An O-Boc protecting group is not compatible with lithium reagents; however, the O-Boc-protected magnesiated phenols 2f and 2g were prepared from the corresponding bromides at -10°C within 20-60 minutes. After acylation<sup>[18]</sup> or thiolation with MeSO<sub>2</sub>SMe, the expected products 3f and 3g were obtained in 95 and 92% yield, respectively (Table 1, entries 6 and 7). Similarly, a tosylate functionality was compatible with the LiCl-mediated Mg insertion (0°C, 2 h): After treatment of the magnesium reagent 2h with DMF, the benzaldehyde 3h was obtained in 77%yield (Table 1, entry 8). A remarkable chemoselectivity was observed with bromochlorobenzene derivatives. Magnesium inserted only into the C-Br bond; the aryl magnesium derivatives 2i and 2j were obtained within 10 min at 25 °C. Negishi cross-coupling<sup>[16]</sup> or treatment with benzaldehyde led to the desired products 3i and 3j in 94 and 89% yield, respectively (Table 1, entries 9 and 10).

The expeditious preparation of heterocyclic organometallic reagents is of central importance in modern pharmaceutical and research.[19] agrochemical The LiCl-promoted insertion of magnesium is suitable for the preparation of a variety of polyfunctional heteroaryl organomagnesium reagents. Thus, 3-bromopyridine reacted smoothly with magnesium turnings at 25°C to give the corresponding pyridylmagnesium species 2 k within 30 min. Cu<sup>I</sup>-catalyzed acylation<sup>[18]</sup> of  $2\mathbf{k}$  gave the ketone  $3\mathbf{k}$  in 90% yield (Table 1, entry 11). In the case of 5-bromo-2-chloropyridine, complete chemoselectivity was observed in favor of insertion into the C-Br bond, and the magnesium reagent 21 was obtained after 30 min at 0 °C. Palladium-catalyzed cross-coupling<sup>[16]</sup> with 4-

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iodoanisole led to the biaryl compound **31** in 84% yield (Table 1, entry 12).

When a more sensitive ester functionality was present, the experimental procedure had to be modified. Bromo-substituted aromatic esters also underwent a magnesium insertion in the presence of LiCl, but the resulting aryl magnesium compounds decomposed rapidly. In the presence of  $ZnCl_2$  (1.1 equiv), however, the initially formed aryl magnesium species was transmetalated in situ to give the corresponding stable organozinc reagent. Thus, ethyl 2-bromobenzoate (4a) was converted readily into the aryl zinc reagent 5a with magnesium powder<sup>[20]</sup> (1.6 equiv), LiCl (1.5 equiv), and  $ZnCl_2$  (1.1 equiv) within 3 h at 25 °C. After a Cu<sup>1</sup>-catalyzed reaction with allyl bromide,<sup>[18]</sup> the expected product 6a was isolated in 88 % yield (Scheme 2).

This method proved to be general; the *meta*- and *para*substituted ethyl esters **4b** and **4c** reacted similarly (25 °C, 3 h) to provide the expected products **6b** and **6c** in 78 and 76% yield, respectively, after quenching with electrophiles (Table 2, entries 1 and 2). Heterocyclic ethyl esters were also functionalized easily by this method: The addition of the bromofuran **4d** to magnesium powder in the presence of LiCl and ZnCl<sub>2</sub>, and subsequent Cu<sup>1</sup>-catalyzed allylation,<sup>[18]</sup> furnished the functionalized furan **6d** in 79% yield (Table 2, entry 3). Methyl esters are sensitive substrates and can usually only be metalated at low temperatures. Remarkably, the

methyl bromobenzoates **4e–g** could be converted into the corresponding zinc species within 2.5–3 h at 25 °C. After Negishi cross-coupling reactions<sup>[16]</sup> or Cu<sup>1</sup>-catalyzed acylation,<sup>[18]</sup> the expected products **6e–g** were obtained in 79–89% yield (Table 2, entries 4–6).

A remarkable reactivity was observed with 2,5-dichlorothiophenes.<sup>[21]</sup> Magnesium insertion into the C–Cl bond of thiophene **7** was completed after 3 h at -50 °C. After a Pd-catalyzed cross-coupling reaction<sup>[16]</sup> with iodobenzene, the 2phenylthiophene derivative **8** was obtained in 82% yield. A further magnesium insertion into compound **8** was also possible, and the highly functionalized thiophene **9** was isolated in 88% yield after a Cu<sup>1</sup>-catalyzed allylation reaction<sup>[18]</sup> (Scheme 3).

Only few dimagnesiated species are known. They usually have to be prepared by using highly active magnesium,<sup>[22]</sup> strong alkali-metal bases,<sup>[23]</sup> toxic organomercury compounds,<sup>[24]</sup> or very-electron-poor aryl halides.<sup>[25]</sup> The dimagnesiated compounds **10** and **11** were obtained from the corresponding dibromides or diiodides with mag-



**Scheme 2.** LiCl-promoted insertion of magnesium into ethyl 2-bromobenzoate (4a) and direct transmetalation with  $ZnCl_2$ .

nesium turnings (10 equiv) and LiCl (5 equiv) and could be functionalized sequentially with two different electrophiles. Thus, after transmetalation of **10** with CuCN·2LiCl (1.0 equiv), the dimetallic species reacted selectively with benzaldehyde (0.7 equiv). The subsequent addition of ethyl 2-(bromomethyl)acrylate furnished compound **12** in 89% overall yield. The magnesium reagent **11** reacted analogously: After transmetalation with CuCN·2LiCl (1.0 equiv) and a selective reaction with isobutyraldehyde, the intermediate was acylated with an acid chloride to give the ketone **13** in 77% overall yield (Scheme 4).

**Table 2:** Synthesis of products **6** by magnesium insertion into aryl or heteroaryl bromides **4** in the presence of LiCl and  $ZnCl_2$  and subsequent treatment with electrophiles.<sup>[a]</sup>



[a] Reaction conditions: aryl halide (1.0 equiv), electrophile (0.7 equiv). [b] Yield of the analytically pure product. [c] The product was synthesized by Pd-catalyzed cross-coupling.<sup>[16]</sup> [d] The zinc reagent was transmetalated with CuCN-2 LiCl (20 mol%).<sup>[18]</sup>



**Scheme 3.** Synthesis of the highly functionalized thiophene derivative **9**. dba = *trans*,*trans*-dibenzylideneacetone, tfp = tris(o-furyl)phosphine.



**Scheme 4.** Synthesis of the dimagnesiated species **10** and **11**, and their stepwise reaction with electrophiles: a) 1. PhCHO (0.7 equiv), 2. ethyl (2-bromomethyl)acrylate (1.4 equiv); b) 1. isobutyraldehyde (0.7 equiv), 2. 4-bromobenzoyl chloride (1.4 equiv).

In summary, we have shown that magnesium in the presence of LiCl can be used for the practical synthesis of functionalized aryl and heteroaryl magnesium reagents, many of which were previously inaccessible. Sensitive substrates, such as methyl and ethyl esters, can also be converted by transmetalation with  $ZnCl_2$  in situ into the corresponding organozinc reagents, which then undergo reaction with various electrophiles. Studies to extend this synthetic methodology to further applications are in progress.

#### Experimental Section

Typical procedure: Magnesium turnings (122 mg, 5 mmol) were placed in a dry Schlenk flask equipped with a magnetic stirrer and a septum under argon. LiCl (5.0 mL, 0.5 M in THF, 2.5 mmol) was added, and the magnesium was activated with diisobutylaluminum hydride<sup>[14]</sup> (0.2 mL, 0.1M in THF, 0.02 mmol). The resulting mixture was stirred for 5 min and then cooled to 0°C. 5-Bromo-2-chloropyridine (11, 385 mg, 2 mmol) was then added in one portion, and the reaction mixture was stirred for 30 min, then transferred with a cannula into a solution of ZnCl<sub>2</sub> (2 mL, 1M in THF, 2.0 mmol) at 0 °C. This mixture was stirred at 0°C for 15 min, and then [Pd(dba)<sub>2</sub>] (23 mg, 2 mol%), tfp (19 mg, 4 mol%), and 4-iodoanisole (328 mg, 1.4 mmol) were added, and the mixture was warmed to 25°C and stirred at this temperature for 6 h. The reaction mixture was then quenched with a saturated solution of NH<sub>4</sub>Cl (10 mL) and extracted with Et<sub>2</sub>O ( $3 \times 10$  mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Flash column chromatography of the residue on silica gel with CH<sub>2</sub>Cl<sub>2</sub> gave **31** (258 mg, 84%) as a colorless solid.

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