

A LiCl-Mediated Br/Mg Exchange Reaction for the Preparation of Functionalized Aryl- and Heteroarylmagnesium Compounds from Organic Bromides**

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Dedicated to Professor Friedrich Bickelhaupt

Polyfunctionalized organometallic reagents are ubiquitous intermediates in modern organic chemistry.^[1] One of the best methods for preparing these reagents is the halogen–metal exchange reaction.^[1,2] Whereas Br/Li exchange is fast and occurs at low temperatures, the corresponding Br/Mg exchange^[3] is considerably slower, which limits its synthetic application for several reasons: 1) The exchange requires higher reaction temperatures and is therefore not compatible with many functional groups; 2) The slow Br/Mg exchange especially for electron-rich aromatic bromides is in competition with the elimination of HBr from the alkyl bromide also produced during the reaction (usually isopropyl bromide) and therefore results in low yields. A catalyzed version of the Br/Mg exchange reaction would be a highly desirable process.

Recently we found that I/Zn exchange can be converted into a catalytic reaction by the addition of [Li(acac)] (10 mol %, acac = acetylacetonato) to an aryl iodide and *i*Pr₂Zn.^[4] Encouraged by these results, we have examined the effect of salt additives on the rate of Br/Mg exchange.^[3] We chose the electron-rich and therefore unreactive 4-bromoanisole (**1a**) and treated it with *i*PrMgCl (1.05 equiv; 1 M in THF) in the presence of several lithium salts. A slow Br/Mg exchange occurred in the absence of additives, leading to only 18% conversion after 68 h at room temperature (entry 1, Table 1). Whereas the addition of LiBF₄ resulted in several products (entry 2), the addition of LiBr, LiI, and LiClO₄ gave minor improvements (38–40% conversion; entries 3–5). On the other hand, the addition of LiCl (1 equiv) led to a spectacular rate increase and 70% conversion (entry 6). The addition of smaller amounts of LiCl resulted in lower conversion (entries 7 and 8), whereas larger quantities did not lead to further rate increases (entries 9 and 10). When a

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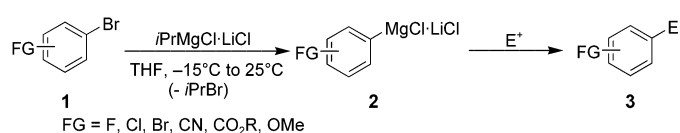
Table 1: Effect of the addition of lithium salts on the formation of 4-methoxyphenylmagnesium chloride at 25 °C after a reaction time of 68 h (1 M solution in THF).

Entry	Additive	Equiv.	Conv. [%] ^[a]
1	–	–	18
2	LiBF ₄	1.0	5
3	LiBr	1.0	40
4	LiI	1.0	38
5	LiClO ₄	1.0	38
6	LiCl	1.0	70
7	LiCl	0.25	22
8	LiCl	0.5	43
9	LiCl	1.5	73
10	LiCl	2.0	74
11	LiCl	1.0	84 ^[b]

[a] The conversion of the reaction was determined by GC analysis of reaction aliquots; precision ± 2%. [b] The concentration of *i*PrMgCl·LiCl was 2.22 M.

more concentrated solution of *i*PrMgCl·LiCl (2.22 M) was used, 84 % conversion was achieved (entry 11).^[5] Trapping of **2a** with benzaldehyde furnished the benzhydryl alcohol **3a** in 70 % yield (entry 1 of Table 2). Analogous results were obtained with other aryl- and heteroarylmagnesium derivatives (Scheme 1).

Herein we describe the preparation of functionalized arylmagnesium compounds of type **2** using the new reagent



Scheme 1. Preparation of functionalized arylmagnesium reagents.

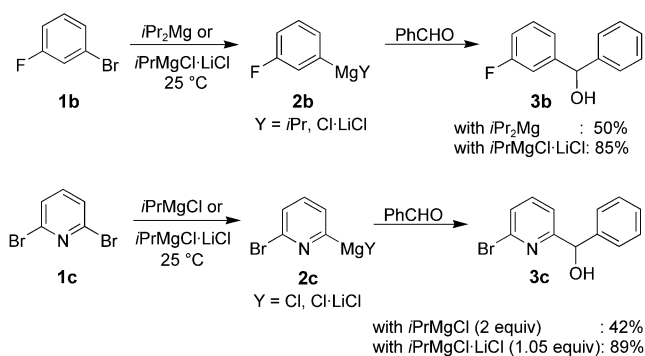
*i*PrMgCl·LiCl, which was made by adding *i*PrCl to Mg turnings and LiCl (*i*PrCl/Mg/LiCl = 1:1.1:1) in THF. Alternatively, the reagent can be prepared by addition of a solution of *i*PrMgCl in THF to LiCl. This reagent was used for the preparation of a range of aryl- and heteroarylmagnesium derivatives (**2a–p**) starting from the corresponding bromides. After the reaction with electrophiles (E⁺), the expected products (**3a–p**) were isolated in good to excellent yields (Scheme 1 and Table 2).

Thus, the previously reported reaction of 1-bromo-3-fluorobenzene (**1b**)^[6a] with *i*Pr₂Mg (1.1 equiv, RT, 3 h) provided the corresponding Grignard reagent **2b** with moderate conversion, and after the subsequent reaction with PhCHO the alcohol **3b** was obtained in only 50 % yield (Scheme 2). When we conducted the reaction with *i*PrMgCl·LiCl, the alcohol **3b** was obtained in 85 % yield. Similarly, the reaction of 2,6-dibromopyridine (**1c**) with *i*PrMgCl (2 equiv) was reported to afford the alcohol **3c** in 42 % yield.^[6f] By using *i*PrMgCl·LiCl (1.05 equiv), we have now obtained **3c** in 89 % yield (Scheme 2).

Table 2: Preparation and reaction of functionalized Grignard reagents of type **2** using *i*PrMgCl·LiCl.

Entry	Grignard reagent ^[a]	Electrophile	Product	Yield ^[b]	Entry	Grignard reagent ^[a]	Electrophile	Product	Yield ^[b]
1		PhCHO		70	8		ClPPh ₂		85 ^[d]
2		PhCHO		81	9		PhCHO		83
3		PhCOCl		87 ^[c]	10		PhCHO		90
4		PhCOCl		88 ^[c]	11		I(CH ₂) ₃ CO ₂ Et		81 ^[c]
5		allyl bromide		93 ^[c]	12		allyl bromide		82 ^[c]
6		PhCHO		90	13		allyl bromide		88 ^[c]
7		PhCHO		87	14		PhCHO		80 ^[e]

[a] Y = Cl·LiCl. [b] Yield of isolated analytically pure product. [c] The Grignard reagent was transmetalated with CuCN·2LiCl before reaction with an electrophile. [d] The reaction mixture was worked up oxidatively with aq. H₂O₂. [e] The exchange reaction was conducted in THF/DMPU (1:3).



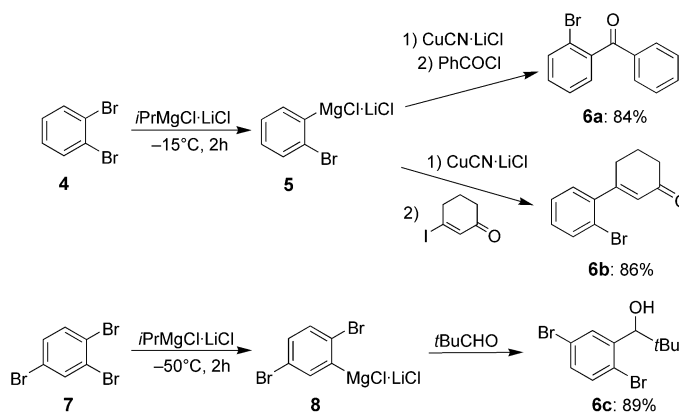
Scheme 2. Br/Mg exchange reactions with various magnesium reagents.

The presence of an electron-withdrawing group considerably increases the exchange rate, and 4-cyanophenylmagnesium chloride (**2d**) was formed within 2 h at 0 °C (> 95% conversion) when *iPrMgCl*-LiCl was employed. In contrast, with *iPrMgCl* a conversion of only 50% was reached. The addition of PhCHO led to the alcohol **3d** in 81% yield (entry 2). The position of the substituent on the aromatic ring is not important, and both 2-cyano- and 3-cyanophenylmagnesium chloride **2e,f** were readily prepared and benzoylated in the presence of CuCN·2 LiCl (0.2 equiv; entries 3 and 4). The inductive effect of the cyano group accelerates further the formation of **2e** (1 h, 0 °C) relative to that of **2f** (3 h, 0 °C). Similar reactivity was observed for 5-bromo-3-pyridylmagnesium chloride (**2g**; prepared at -10 °C within 15 min, > 95% conversion). The copper-catalyzed allylation of **2g** led to pyridine **3g** in 93% yield. Other heterocyclic systems such as 3-bromothiophene and 2-bromothiazole reacted smoothly with *iPrMgCl*-LiCl at room temperature furnishing **2h** and **2i**, respectively.^[7] After reaction with PhCHO the corresponding alcohols **3h** and **3i**^[8] were obtained in yields of 87% and 90%, respectively (Table 2, entries 6 and 7). Aryl bromides bearing electron-donating substituents undergo the Br/Mg exchange only slowly with *iPrMgCl*. The *iPrMgCl*-LiCl reagent was used in an expeditive preparation of the methoxy-substituted Grignard compound **2j**. Reaction with Ph₂PdCl provided, after oxidative workup, the phosphane oxide **3j** in 85% yield (entry 8). Similarly, sterically hindered 2,6-dichlorophenylmagnesium chloride (**2k**) was prepared from the corresponding bromide (25 °C, 1 h), and its reaction with PhCHO furnished the alcohol **3k** in 83% yield (entry 9). Various unfunctionalized aromatic Grignard compounds such as **2l** and **2m** can be prepared in high yields as well. Interestingly, the copper derivative of **2m** underwent a smooth cross-coupling with I(CH₂)₃CO₂Et furnishing phenanthrene **3m** in 81% yield (entry 11).^[9]

We have also examined the formation of a Grignard reagent bearing an ester functionality. Preliminary results have shown that the presence of LiCl enhances the reactivity of *iPrMgCl*, making the competitive addition to the ester carbonyl group a serious side reaction. However, a *tert*-butyl ester is compatible with the Br/Mg exchange reaction. The copper-catalyzed allylation gave the desired esters **3n** and **3o** in 82% and 88% yields, respectively (entries 12 and 13).

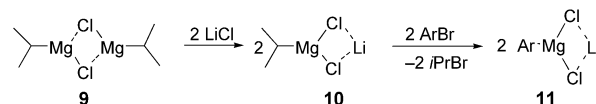
Moreover, when a THF/DMPU (1:3; DMPU = 1,3-dimethyltetrahydro-2(1*H*)-pyrimidinone) mixture was used, 2-isopropyl bromobenzoate could serve as a substrate. The resulting Grignard reagent **2p** (-10 °C, 3 h) then reacted with PhCHO leading to lactone **3p** in 80% yield (entry 14).

Only a few reports are available on the preparation of *ortho*-bromophenylmagnesium halides from 1,2-dibromobenzene (**4**).^[10] Oshima et al. have reported that lithium tributylmagnesiolate (Bu₃MgLi) leads to the formation of benzyne by means of 1,2-elimination and not to *ortho*-bromophenylmagnesium halide (**5**).^[6c] The generation of this Grignard reagent can be achieved conveniently with *iPrMgCl*-LiCl. Thus, the reaction of **4** with *iPrMgCl*-LiCl was complete within 2 h at -15 °C and led to the Grignard reagent **5**.^[11] After transmetalation with CuCN·2 LiCl,^[9] reactions with PhCOCl and 3-iodo-2-cyclohexen-1-one furnished the products **6a** and **6b** in yields of 84% and 86%, respectively. Also unsymmetrical 1,2,4-tribromobenzene (**7**) reacted with *iPrMgCl*-LiCl by means of a highly regioselective Br/Mg exchange to provide exclusively the Grignard reagent **8**,^[11] which after reaction with pivalaldehyde gave alcohol **6c**^[12] in 89% yield (Scheme 3).



Scheme 3. Selective Br/Mg exchanges of polybromides.

The necessity of using the stoichiometric complex *iPrMgCl*-LiCl leads us to postulate that the addition of LiCl breaks the polymeric aggregates **9** of *iPrMgCl*, producing the reactive complex **10** (Scheme 4).^[13] The magnesiate character



Scheme 4. Catalysis of the Br/Mg exchange reaction with LiCl.

of **10** [*iPrMgCl*₂⁻Li⁺] may be responsible for the enhanced reactivity of this reagent. Interestingly, the magnesiate character of the resulting organometallic complexes **11** is similar to that of a dimeric or oligomeric magnesium reagent prepared in the absence of LiCl (standard Grignard reagent) but the former display higher reactivity towards electrophiles.

In conclusion, we have shown that *i*PrMgCl·LiCl can be used for the simple, high-yielding preparation of a broad range of functionalized aryl- and heteroarylmagnesium reagents starting from cheap and readily available aryl bromides.^[14] All reactions proceed within a convenient range of temperatures (−15°C–RT) and can be extended to the large-scale preparation of Grignard reagents. We have demonstrated for the first time the promoter effect of LiCl in the Br/Mg exchange reaction. Extensions of this work are currently underway in our laboratories.

Experimental Section

1) Preparation of the reagent *i*PrMgCl·LiCl: Magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol) were placed in an Ar-flushed flask, and THF (50 mL) was added. A solution of *i*PrCl (100 mmol) in THF (50 mL) was slowly added at room temperature. The reaction started within a few minutes. After the addition, the reaction mixture was stirred for 12 h at room temperature. The gray solution of *i*PrMgCl·LiCl was cannulated into another Ar-filled flask and removed in this way from excess magnesium. *i*PrMgCl·LiCl was obtained in a yield of ca. 95–98%.

2) Typical procedure (**3g**): A dry and argon-flushed 10-mL flask equipped with a magnetic stirrer and a septum was charged with *i*PrMgCl·LiCl (1 mL, 1.05 M in THF, 1.05 mmol). The reaction mixture was cooled to −15°C, and 3,5-dibromopyridine (237 mg, 1.0 mmol) was added in one portion. The reaction temperature was increased to −10°C, and the Br/Mg exchange was complete after 15 min (checked by GC analysis of reaction aliquots, the conversion was more than 98%). Allyl bromide (133 mg, 1.1 mmol) was added, followed by addition of one drop of CuCN·2 LiCl (a 1.0 M solution in THF was used, ca. 0.02 mmol, 0.02 equiv). The reaction mixture was stirred for 1 h at 0°C and was then quenched with saturated aqueous NH₄Cl solution (2 mL). The aqueous phase was extracted with ether (3 × 4 mL), dried with Na₂SO₄, and concentrated in vacuo. The crude residue was purified by flash chromatography (CH₂Cl₂) yielding 3-allyl-5-bromopyridine (**3g**; 184 mg, 93%) as a colorless oil.

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