

# Convenient magnesiation of aromatic and heterocyclic rings bearing a hydroxy group in presence of LiCl†

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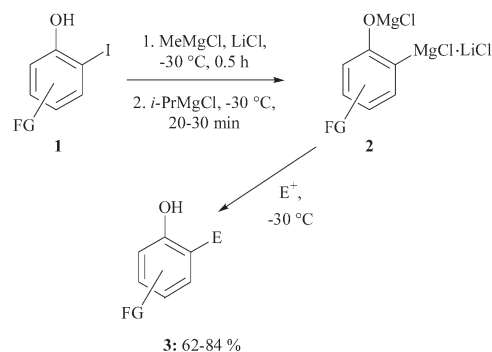
The reaction of various iodophenols with MeMgCl in presence of LiCl followed by the addition of *i*-PrMgCl provides the corresponding magnesiated magnesium phenolates as THF soluble reagents; this approach can be extended to heterocyclic compounds bearing a hydroxy group like pyridines and quinolines.

The preparation of polyfunctional Grignard reagents is an important task since these organometallics undergo readily bond formation with a broad range of electrophiles.<sup>1</sup> Functionalized aryl- and heteroaryl-magnesium compounds are best prepared *via* an I/Mg-exchange reaction using *i*-PrMgCl. The reaction is very general and applies to a wide range of aromatic and heteroaromatic iodides.<sup>2</sup> Unfortunately, the corresponding aryl bromides are much less prone to undergo the exchange reaction and require often higher reaction temperatures which are not compatible with the presence of functional groups.<sup>3</sup> Recently, we have found that the mixed organometallic *i*-PrMgCl·LiCl allows the performance of a Br/Mg-exchange with numerous aromatic and heteroaromatic bromides under exceedingly mild conditions.<sup>4</sup> The addition of LiCl to *i*-PrMgCl gives an ate-character to the mixed organometallic (*i*-PrMgCl<sub>2</sub><sup>-</sup>Li<sup>+</sup>). Furthermore, we noticed that also the resulting arylmagnesium species are generally both more soluble and more reactive due to the presence of LiCl. Herein, we wish to report that various polyfunctional iodophenols and related heterocyclic iodides of type **1** are readily protected *in situ* as soluble magnesium alcoholates and smoothly converted to the dimagnesiated species of type **2** by addition of *i*-PrMgCl.<sup>5</sup> These bimetallics react with standard electrophiles leading to products of type **3** in good yields (Scheme 1 and Table 1). Thus, the reaction of 4-bromo-2,6-diiodophenol (**1a**) with MeMgCl (1.0 equiv.) in a THF solution of LiCl (1 equiv.) at -30 °C followed by the addition of *i*-PrMgCl (1.1 equiv.) produced the Grignard reagent **2a** as a slightly opalescent solution within 20 min reaction time. After addition of benzaldehyde (1.2 equiv.), the desired alcohol **3a** was isolated in 84% yield (entry 1 of Table 1). By adding only 0.5 equiv. of LiCl, the exchange reaction was longer (35 min) and the yield of **3a** was only 79%. In the absence of LiCl, the I/Mg-exchange was sluggish, required 1 h for completion and the yield of **3a** was 69%. The allylation of **2a** with ethyl 2-(bromomethyl)acrylate<sup>6</sup> furnished the unsaturated ester **3b** in 62% yield (entry 2). A range of functional groups like trifluoromethyl (entries 3 and 4), cyano (entries 5–10) and ester (entries 11–14) are perfectly tolerated. In the cases where diiodophenol derivatives were used, a mono-exchange was always observed. This can be expected since the exchange rate is inversely proportional to the electron density of the aromatic ring. After the first exchange, the formed C–Mg bond increases the ring electron-density and therefore the second exchange is disfavoured. Both aliphatic and aromatic aldehydes react with similar yields (entries 3 and 4). Sterically hindered aldehydes like

pivaldehyde furnish the corresponding alcohols in good yields (entries 6 and 10). After transmetalation to the zinc species, the Grignard reagent **2c** can also be successfully used in a palladium-catalyzed cross-coupling reaction<sup>7</sup> with ethyl 4-iodobenzoate to give the functionalized biaryl **3h** in 71% yield (entry 8). Interestingly, our method allows us to functionalize selectively 2,6-diiodophenols with two different electrophiles in the 2- and 6-positions. Thus, the phenol **1c** was first converted to **3g** (entry 7). Subsequent conversion of **3g** to the corresponding Grignard reagent **2e** and reaction with pivaldehyde provided the 2,6-difunctionalized phenol derivative **3j** (entry 10). Acylation reactions can be problematic due to competitive acylation of the phenolate. Thus, the acylation of the Grignard reagent **2c** with benzoyl chloride in presence of substoichiometric amounts of CuCN·2LiCl (0.3 equiv.) affords the desired product only in 27% yield. The product of *O*-acylation, benzoic acid 4-cyano-2-iodo-phenyl ester is also isolated in 25% yield. Our method can be successfully extended to several heterocyclic systems. Thus, 3-hydroxy-2-iodopyridine was converted under similar conditions to the corresponding dimagnesiated species **4**. The reaction with benzaldehyde and butyraldehyde gave the expected secondary pyridyl alcohols **5a–b** in 70% yield. Allylation with allyl bromide provided the product **5c** in 74% yield (Scheme 2). Similarly, 5,7-diiodo-8-hydroxy-quinoline was regioselectively converted to the 5-magnesiated species **6**. It afforded after allylation only the 5-allylated product whereas the reaction with MeSSO<sub>2</sub>Me led to the 5-thiomethyl-quinoline **7b** (Scheme 2).

In summary, we have shown that the *in situ* protection of the hydroxy function of aryl and heteroaryl iodides with MeMgCl in presence of LiCl produces soluble magnesium phenolates which undergo rapidly an I/Mg-exchange with *i*-PrMgCl. Further applications of this procedure are currently underway in our laboratories.

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Scheme 1

† Electronic supplementary information (ESI) available: experimental section. See <http://www.rsc.org/suppdata/cc/b4/b409664a/>

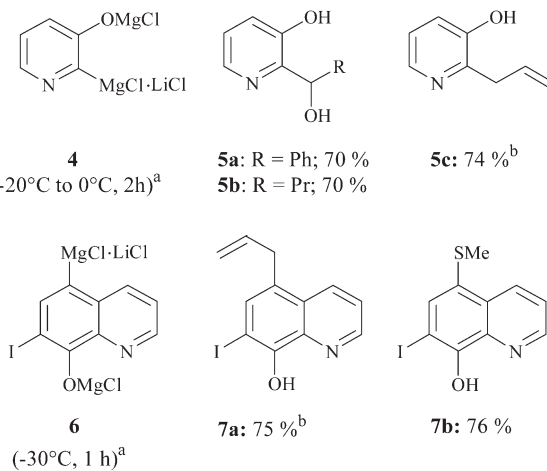
**Table 1** Preparation and reactions of hydroxy-substituted arylmagnesium reagents of type **2**

Entry	Grignard reagent <sup>a</sup>	Electrophile	Product of type 3	Yield (%) <sup>b</sup>
1		PhCHO		84 (79) <sup>c</sup> (69) <sup>d</sup>
2	<b>2a</b>			62 <sup>e</sup>
3		PhCHO		72
4	<b>2b</b>	<i>c</i> -HexCHO	<b>3c: R = Ph</b>	74
5		PhCHO		80
6	<b>2c</b>	<i>t</i> -BuCHO	<b>3e: R = Ph</b>	71
7	<b>2c</b>		<b>3f: R = t-Bu</b>	82 <sup>f</sup>
8	<b>2c</b>			71 <sup>g</sup>
9		PhCHO		75
10		<i>t</i> -BuCHO		70
11		PhCHO		73
	<b>2f</b>		<b>3k</b>	

**Table 1** Preparation and reactions of hydroxy-substituted arylmagnesium reagents of type **2** (Continued)

Entry	Grignard reagent <sup>a</sup>	Electrophile	Product of type 3	Yield (%) <sup>b</sup>
12	<b>2f</b>			74 <sup>f</sup>
13		PhCHO		62
14				70 <sup>f</sup>
	<b>2h</b>		<b>3n</b>	

<sup>a</sup> LiCl has been omitted in the formula for the sake of simplicity.  
<sup>b</sup> Yield of analytically pure products. <sup>c</sup> Yield obtained by adding 0.5 equiv. of LiCl. <sup>d</sup> Yield obtained in the absence of LiCl. <sup>e</sup> After transmetalation to copper using 1.1 equiv. CuCN·2LiCl. <sup>f</sup> Carried out in presence of 5 mol% CuCN·2LiCl. <sup>g</sup> Obtained by palladium-catalyzed cross-coupling after transmetalation with ZnCl<sub>2</sub>.



**Scheme 2** <sup>a</sup>Conditions for the exchange reaction using 1.1 equiv. of *i*-PrMgCl. <sup>b</sup>Carried out in presence of 1 mol% CuCN·2LiCl.

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