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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.¹ 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.² 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.³ 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.⁴ The addition of LiCl to *i*-PrMgCl gives an ate-character to the mixed organometallic $(i-\Pr MgCl_2^-Li^+)$. 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.⁵ 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^o 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 transmetallation to the zinc species, the Grignard reagent 2c can also be successfully used in a palladium-catalyzed cross-coupling reaction⁷ with ethyl 4-iodobenzoate to give the functionalized biaryl 3h in 71% yield (entry 8). Interestingly, our method allows us to functionalize selectively 2,6diiodophenols 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 2,6difunctionalized 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 MeSSO₂Me 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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Table 1Preparation and reactions of hydroxy-substituted arylmag-
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 Table 1
 Preparation and reactions of hydroxy-substituted arylmagnesium reagents of type 2 (Continued)



^{*a*} LiCl has been omitted in the formula for the sake of simplicity. ^{*b*} Yield of analytically pure products. ^{*c*} Yield obtained by adding 0.5 equiv. of LiCl. ^{*d*} Yield obtained in the absence of LiCl. ^{*e*} After transmetallation to copper using 1.1 equiv. CuCN·2LiCl. ^{*f*} Carried out in presence of 5 mol% CuCN·2LiCl. ^{*g*} Obtained by palladiumcatalyzed cross-coupling after transmetallation with ZnCl₂.



Scheme 2 ^aConditions for the exchange reaction using 1.1 equiv. of *i*-PrMgCl. ^bCarried out in presence of 1 mol% CuCN·2LiCl.

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