Halogen–magnesium exchange on unprotected aromatic and heteroaromatic carboxylic acids†

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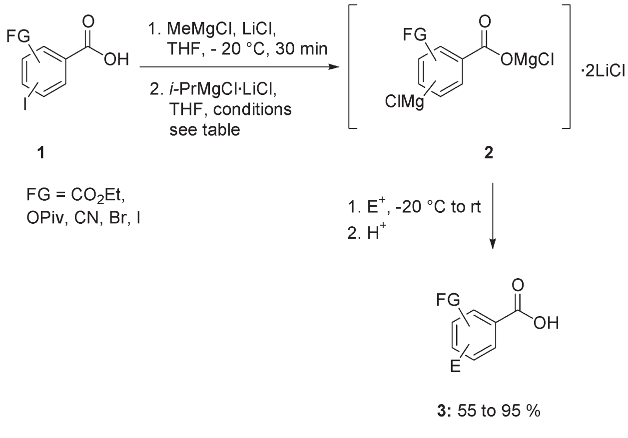
The magnesiation of halogenated aromatic and heteroaromatic carboxylic acids is accomplished by their treatment with MeMgCl in the presence of LiCl and subsequent reaction with *i*-PrMgCl·LiCl; the resulting double-magnesiated species react with a variety of electrophiles in up to 97% yield.

The preparation of functionalized Grignard reagents is an important goal, since these organometallics represent unique tools for the construction of complex molecules.[1] The halogen–magnesium exchange is a broadly applicable and convenient method for the generation of polyfunctional Grignard reagents, recently being extended by the use of LiCl as an additive.[2] Besides increasing the reactivity of Grignard reagents,[3] we have found that LiCl dramatically improves the solubility of organometallics.[4] A double-magnesiation strategy[5] allows the generation of Grignard reagents derived from iodophenols without the need of a protecting group. A similar approach would be very useful for the functionalization of carboxylic acid derivatives.[6] The use of mixed Li/Mg-reagents, as investigated by Mase is not applicable to a broad range of functionalized substrates. Indeed, the high reactivity of lithium reagents precludes the presence of many functional groups.[7]

Thus, 4-iodobenzoic acid was reacted with MeMgCl (1.0 equiv.) in the presence of LiCl (1.0 equiv.) at −20 °C, and subsequently *i*-PrMgCl·LiCl (1.1 equiv.) was added to perform the iodine–magnesium exchange. The reaction mixture was allowed to warm up to room temperature. After 0.5 h, a full conversion to the desired magnesium reagent was observed. The reactions with typical electrophiles like benzaldehyde or benzoyl chloride afforded the desired products **3a** and **3b** in 95 and 71% isolated yield (Table 1, entries 1, 2). By applying a mild acidic workup using citric acid, even a sensitive boronic ester can be installed by a sequential reaction with B(O*i*-Pr)$_3$ and 2,2-dimethylpropane-1,3-diol, yielding the desired boronic ester (**3c**) in 50% yield (entry 3).

Also *meta-* and *ortho-* positions can be easily functionalized using this protocol. Using ethyl 2-(bromomethyl)acrylate,[8] the expected allylated product **3d** is produced in 78% yield (entry 4). The lactone **3e** is obtained by the reaction with cyclohexane carbaldehyde in 87% yield (entry 5). Several functionalized substrates can be used. Halides like a bromide (**1d**) or an additional iodide (**1e**) are tolerated and the corresponding Grignard reagents show a good reactivity towards electrophiles like cyclohexane carbaldehyde, 4-bromobenzaldehyde or allyl bromide. The desired products **3f–h** have been isolated in 69–91% yield (entries 6, 7, 8). The reaction of the organomagnesium reagent **2e** with TsCN gives rise to the benzonitrile **3i** in 55% (entry 9). Also, an ethyl ester (**1f**) or a sensitive pivalate like **1g** are appropriate substrates. The desired products from the reactions with pivaldehyde and anthraldehyde, **3j** and **3k**, are isolated in 70 and 67%, respectively (entries 10 and 11). Finally, a sterically hindered substrate like **1h** reacts smoothly under the usual reaction conditions; subsequent treatment with *p*-bromobenzoyl chloride affords the ketoacid **3l** in 81% yield (entry 12).

Highly activated heteroaromatic acids like 5-bromo-2-furoic acid (**4**), 5-bromothiophene-2-carboxylic acid (**5**), or 4,5-dibromothiophene-2-carboxylic acid (**6**) react rapidly (−20 °C to rt) (Scheme 2). Thus, 5-bromo-2-furoic acid (**4**) is magnesiated in only 30 min and its reactions with allyl bromide and 4-(trifluoromethyl)benzaldehyde lead to the expected products **7a** and **7b** in 92 and 88% yield. Analogously, the corresponding thiophene carboxylic acid **5** was metallated and reacted with MeSSO$_2$Me to give the thioether **8a** in 93% yield. Transmetallation of the same Grignard reagent with ZnCl$_2$ followed by a Pd-catalyzed cross-coupling[9] with 4-iodo-*N*,*N*-dimethylaniline employing Pd(dba)$_2$ (5.0 mol%) and tri-2-furylphosphine (10 mol%) as a catalyst system, affords the functionalized 2-arylated thiophene **8b** in 95% yield. 4,5-Dibromothiophene-2-carboxylic acid (**6**) can be selectively magnesiated in the 5-position (−20 °C, 1 h).[10] The resulting Grignard reagent was reacted with allyl bromide providing the desired product **9a** in 97% yield. The reaction with ethyl chloroformate gives, after recrystallization, the 5-carbethoxythiophene derivative **9b** (56%).



Scheme 1

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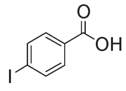
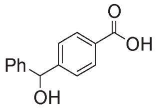
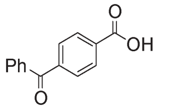
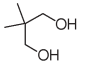
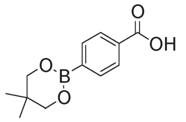
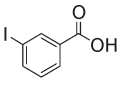
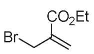
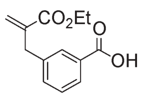
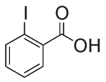
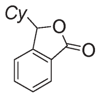
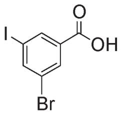
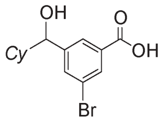
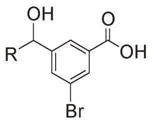
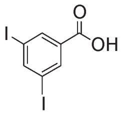
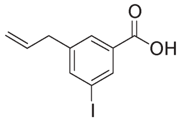
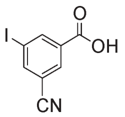
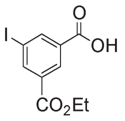
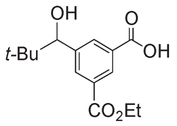
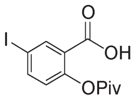
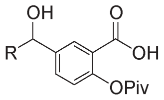
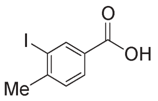
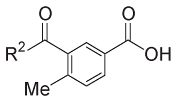
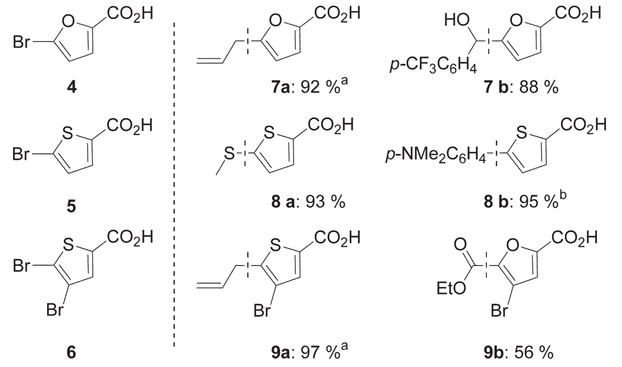
† Electronic supplementary information (ESI) available: experimental procedures for the starting materials and products as well as the characterization of all compounds. See DOI: 10.1039/b618923g

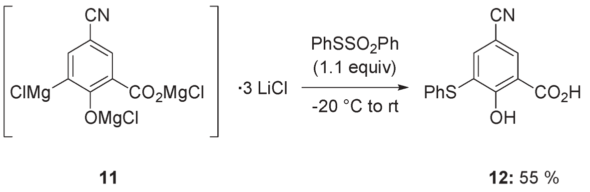
Table 1 Preparation of magnesiated aromatic carboxylates of type **2** and their reactions with various electrophiles

Entry	Substrate of type **1**/exchange conditions		Electrophile	Product of type **3**		Yield (%)[a]
1	 −20 °C to rt, 45 min	**1a**	PhCHO		**3a**	95
2	**1a** −20 °C to rt, 45 min		PhCOCl		**3b**	71[b]
3	**1a** −20 °C to rt, 45 min		1. $B(Oi\text{-}Pr)_3$ 2. 		**3c**	50
4	 −20 °C to rt, 45 min	**1b**			**3d**	78[c]
5	 −20 °C to rt, 45 min	**1c**	*Cy*CHO		**3e**	87
6	 −20 °C, 60 min	**1d**	*Cy*CHO		**3f**	91
7	**1d** −20 °C, 60 min		4-Br-C_6H_4CHO	 R = *p*-BrC_6H_4	**3g**	69
8	 −50 °C, 60 min	**1e**	AllBr		**3h**	70[d]
9	**1e** −50 °C, 60 min		TsCN		**3i**	55
10	 −20 °C, 60 min	**1f**	*t*-BuCHO		**3j**	70
11	 −20 °C, 40 min	**1g**	anthraldehyde	 R = 9-anthranyl	**3k**	67
12	 −20 °C to rt, 45 min	**1h**	4-Br-C_6H_4COCl	 R^2 = *p*-BrC_6H_4	**3l**	81[b]

[a] Yield of analytically pure products. [b] The reaction was carried out in the presence of 20 mol% CuCN·2LiCl. [c] A transmetallation using 1.1 equiv. CuCN·2LiCl was performed. [d] The reaction was carried out in the presence of CuCN·2LiCl (1 mol%).



Scheme 2 [a] The reaction was carried out in the presence of CuCN·2LiCl (1 mol%). [b] Obtained by palladium-catalyzed cross-coupling after transmetallation with $ZnCl_2$.



Scheme 3

Finally, we have also applied this protocol to a substrate bearing two acidic protons. Thus, we have treated 5-cyano-2-hydroxy-3-iodobenzoic acid (**10**) first at −20 °C with two equivalents of MeMgCl (in the presence of an equimolar amount of LiCl), then with *i*-PrMgCl·LiCl (1.05 equiv., −20 °C, 2 h) to get the triple-magnesiated benzonitrile **11**, which reacted with $PhSSO_2Ph$ furnishing the highly functionalized product **12** in 55% yield (Scheme 3).

In conclusion, we have reported a convenient and easy protocol for the functionalization of unprotected aromatic and heteroaromatic carboxylic acids that tolerates a broad variety of functional groups. The resulting organometallics react smoothly with a broad range of electrophiles, giving the desired products in good yields.

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10 Quenching the Grignard reagent with MeOH affords quantitatively 4-bromo-2-furoic acid, which is known in the literature; see also supporting information†.