Polyfunctional benzylic zinc chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of LiCl and $ZnCl_2$†

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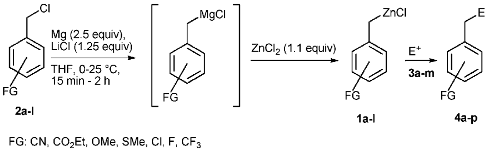
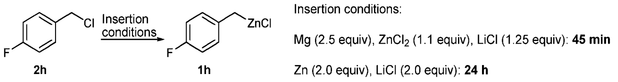
Benzylic zinc chlorides bearing various functional groups are smoothly prepared by the direct insertion of magnesium into benzylic chlorides in the presence of LiCl and $ZnCl_2$.

Polyfunctional organometallics are key intermediates for synthetic organic chemistry.[1] Organozinc compounds play an especially important role since they combine high reactivity with excellent functional group tolerance.[2] Benzylic zinc reagents are of particular interest since, in contrast to benzylic lithium[3] and magnesium[4] reagents, they tolerate numerous functional groups.[5] Recently, we have reported that LiCl considerably facilitates the insertion of metals (zinc,[6] magnesium,[7] indium[8]) into organic halides. Herein, we report the preparation of polyfunctional benzylic zinc chlorides of type **1** by the direct insertion of magnesium turnings into benzylic chlorides of type **2** in the presence of LiCl and $ZnCl_2$ under mild and convenient conditions,[9] and their subsequent reactions with various electrophiles (Scheme 1). In contrast to the previously reported zinc insertion,[5,6] magnesium insertion in the presence of zinc chloride is much faster and proceeds at a lower temperature (see below and Scheme 2). Also, by using 0.5 equivalents of $ZnCl_2$, this method allows the preparation of dibenzylic zinc reagents such as $(PhCH_2)_2Zn$.



Scheme 1



Scheme 2

In a typical experiment, the addition of 3-ethoxycarbonylbenzyl chloride (**2a**) to magnesium turnings (2.5 equiv.), LiCl (1.25 equiv.) and $ZnCl_2$ (1.1 equiv.) in THF leads to the benzylic zinc chloride **1a** within 2 h at 25 °C as indicated by iodometric titration. Prior activation of the magnesium turnings is not required.[10] The intermediate benzylic magnesium reagent is transmetalated *in situ* to the corresponding zinc organometallic. In the absence of $ZnCl_2$ the resulting magnesium reagent decomposes rapidly and a considerable amount of homo-coupling product is observed. Interestingly, *in the presence of* $ZnCl_2$ the amount of homo-coupling formed is below 5%. The benzylic zinc reagent **1a** is transmetalated using CuCN·2LiCl[11] (1.0 equiv.) and reacted with 4-chlorobenzoyl chloride (**3a**) giving the ketone **4a** in 82% yield. (Table 1, entry 1). Additionally, the zinc reagent **1a** also smoothly reacts with the thiosulfonate **3b** yielding the benzylic thio-derivative **4b** in 67% yield (entry 2). Analogously, a cyano function is tolerated as well. 3-Cyanobenzyl chloride (**2b**) is converted to the organozinc compound **1b** within 2 h at 0 °C. After subsequent reactions with benzaldehyde **3c** or Cu(I)-mediated 1,4-addition to 3-iodocyclohex-2-enone (**3d**) the expected products **4c** and **4d** are isolated in 77–83% yield (entries 3 and 4). Also, electron-rich benzylic chlorides are converted to the corresponding zinc reagents without the formation of homo-coupling products. The methoxy-substituted benzylzinc chlorides **1c** and **1d** are obtained after 1 h of stirring at 25 °C. After Cu(I)-mediated treatment with 3,3-dimethylbutanoyl chloride (**3e**) or reaction with 3-chlorobenzaldehyde (**3f**) the products **4e** and **4f** are isolated in 82–92% yield (entries 5 and 6). Similarly, the thio-substituted benzylic zinc chloride **1e** is obtained after 1.5 h reaction time at 25 °C. Its addition to 4-bromobenzaldehyde, provides the alcohol **4g** in 82% yield (entry 7). Other halogen atoms on the aromatic ring are readily tolerated. The chloro-substituted benzylic chlorides **2f** and **2g** react smoothly with magnesium turnings in the presence of LiCl and $ZnCl_2$ (15–45 min, 25 °C) and the resulting zinc reagents are treated with various electrophiles giving the products **4h–j** in 76–89% yield (entries 8–10). As mentioned above, the formation of the benzylic zinc reagent **1h** by the Mg/$ZnCl_2$/LiCl-method is much faster. Thus, using Mg (2.5 equiv.), $ZnCl_2$ (1.1 equiv.) and LiCl (1.25 equiv.) the insertion proceeds in 45 min at 25 °C (Scheme 2 and Table 1, entry 11), whereas with Zn (2.0 equiv.) and LiCl (2.0 equiv.) the formation of **1h** requires 24 h at 25 °C.

A Negishi-catalyzed cross-coupling reaction[12] of 4-fluorobenzylzinc chloride (**1h**) with 4-bromobenzonitrile (**3k**) using $Pd(OAc)_2$·(1 mol%) and S-Phos[13] (2 mol%) as the catalytic system gives the diarylmethane **4k** in 75% yield (entry 11). 3-Trifluoromethylbenzyl chloride (**2i**) is converted to the benzylic zinc organometallic **1i** within 30 min at 25 °C. Reaction with 4-chlorobenzoyl chloride (**3a**) (after transmetalation with CuCN·2LiCl) or 2-chlorobenzaldehyde (**3l**) gives the desired products **4l** and **4m** in 85–91% yield (entries 12 and 13).

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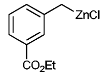
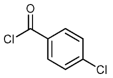
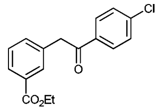
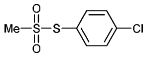
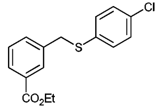
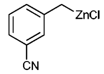
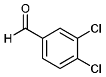
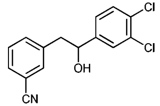
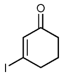
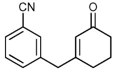
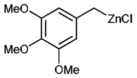
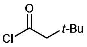
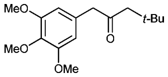
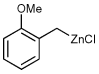
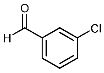
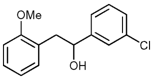
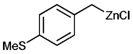
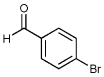
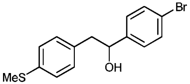
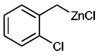
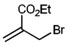
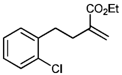
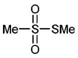
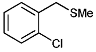
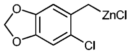
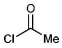
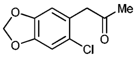
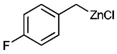
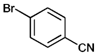
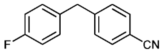
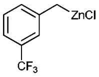
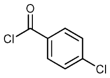
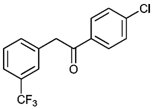
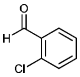
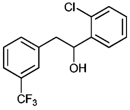
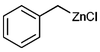
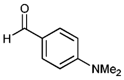
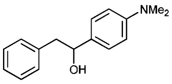
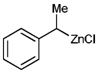
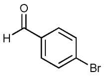
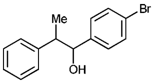
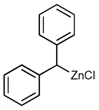
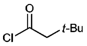
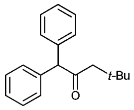
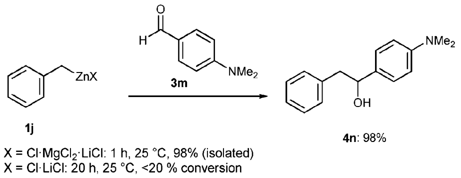
Table 1 Direct insertion of magnesium into benzylic chlorides in the presence of LiCl and $ZnCl_2$ and subsequent reactions with various electrophiles

Entry	Benzylic zinc chloride (**1**)		Electrophile (**3**)[a]		Time/h (insertion/reaction with electrophile)	Product (**4**)		Yield (%)[b]
1		**1a**		**3a**	4 (2/2)		**4a**[c]	82
2		**1a**		**3b**	4 (2/2)		**4b**	67
3		**1b**		**3c**	4 (2/2)		**4c**	83
4		**1b**		**3d**	20 (2/18)		**4d**[c]	77
5		**1c**		**3e**	2 (1/1)		**4e**[c]	82
6		**1d**		**3f**	5 (1/4)		**4f**	92
7		**1e**		**3g**	3.5 (1.5 /2)		**4g**	82
8		**1f**		**3h**	1.5 (0.75/0.75)		**4h**[d]	77
9		**1f**		**3i**	16.75 (0.75/16)		**4i**	89
10		**1g**		**3j**	3.25 (0.25/3)		**4j**[c]	76
11		**1h**		**3k**	1.75 (0.75/1)		**4k**[e]	75
12		**1i**		**3a**	1.5 (0.5/1)		**4l**[c]	91
13		**1i**		**3l**	1.5 (0.5/1)		**4m**	85
14		**1j**		**3m**	3 (2/1)		**4n**	98
14		**1k**		**3g**	3 (1/2)		**4o**	70
15		**1l**		**3e**	1.5 (0.5/1)		**4p**[c]	81

[a] 0.7 equiv. of electrophile is used. [b] Isolated yield of analytically pure product. [c] Stoichiometric amount of CuCN·2LiCl (1.0 M in THF) is used. [d] 0.5 mol% of CuCN·2LiCl (1.0 M in THF) is used. [e] $Pd(OAc)_2$ (1 mol%) and S-Phos (2 mol%) are used.



Scheme 3

Benzyl chloride (**2j**) itself is converted to the corresponding zinc reagent **1j** within 2 h. Reaction with 4-(dimethylamino)benzaldehyde (**3m**) furnishes **4n** in 98% yield (Scheme 3, Table 1, entry 14). In contrast, the reaction of benzylic zinc chloride prepared by the Zn/LiCl-method with the electron-rich benzaldehyde **3m** does not provide the expected product **4n** in any appreciable amount (Scheme 3).

Secondary benzylic chlorides react as well. Thus, 1-phenylethyl chloride[14] (**2k**) or 1,1-diphenylchloromethane (**2l**) are smoothly converted to the corresponding secondary benzylic zinc reagents within 30 min to 1 h at 0–25 °C. Subsequent reaction with 4-bromobenzaldehyde (**3g**) or Cu(I)-mediated acylation with 3,3-dimethylbutanoyl chloride (**3e**) yields the adducts **4o** and **4p** in 70–81% yield (entries 15 and 16).

In summary, we have reported a new and convenient method for the preparation of functionalized benzylic zinc chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of LiCl and $ZnCl_2$. These benzylic zinc organometallics react with a variety of electrophiles, such as aldehydes, acid chlorides and enones or undergo Pd-catalyzed cross-coupling reactions. Additionally, these new benzylic zinc reagents display an exceptional reactivity compared to benzylic zinc compounds prepared by the Zn/LiCl-method. Further extensions of the new method are currently underway in our laboratories.

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