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

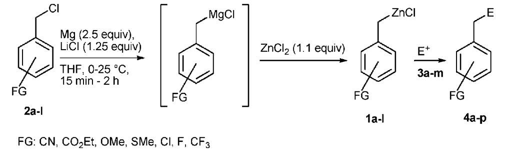
Albrecht Metzger, Fabian M. Piller and Paul Knochel*

Received (in Cambridge, UK) 18th July 2008, Accepted 26th August 2008
First published as an Advance Article on the web 1st October 2008
DOI: 10.1039/b812396a

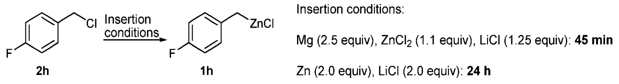
Benzylic zinc chlorides bearing various functional groups are smoothly prepared by the direct insertion of magnesium into benzylic chlorides in the presence of LiCl and $ZnCl_2$.

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 $(PhCH_2)_2Zn$.

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.



Scheme 1



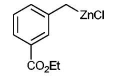
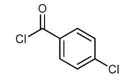
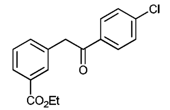
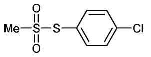
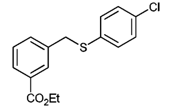
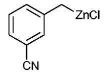
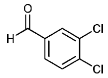
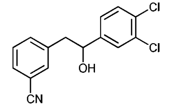
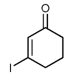
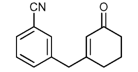
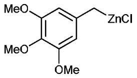
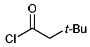
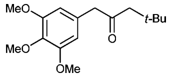
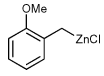
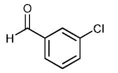
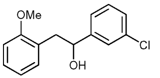
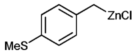
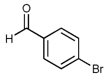
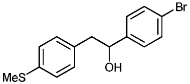
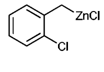
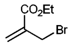
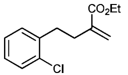
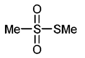
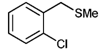
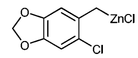
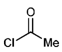
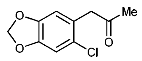
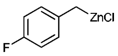
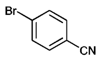
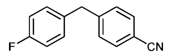
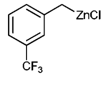
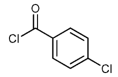
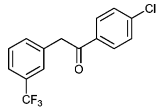
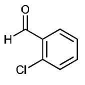
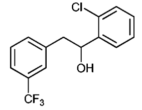
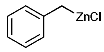
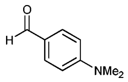
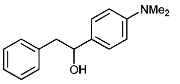
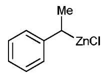
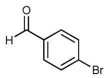
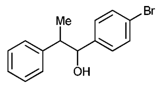
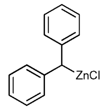
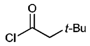
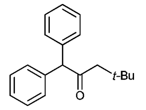
Scheme 2

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).

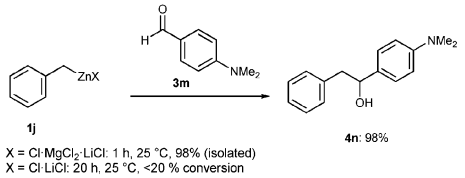
Department Chemie und Biochemie, Ludwig-Maximilians-Universität, München Butenandtstr. 5-13, D-81377 München, Germany.
E-mail: knoch@cup.uni-muenchen.de; Fax: +49-89-2180-77680;
Tel: +49-89-2180-77681

† Electronic supplementary information (ESI) available: Experimental procedures and NMR spectra. See DOI: 10.1039/b812396a

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.

We thank the DFG for financial support. We thank Chemetall GmbH (Frankfurt), Evonik Industries AG (Hanau) and BASF AG (Ludwigshafen) for generous gifts of chemicals.

Notes and references

1 P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone and F. F. Kneisel, in *Handbook of Functionalized Organometallics*, ed. P. Knochel, Wiley-VCH, Weinheim, 2005.
2 P. Knochel, N. Millot, A. Rodriguez and C. E. Tucker, in *Organic Reactions*, ed. L. E. Overman, Wiley & Sons Inc., New York, 2001; P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93**, 2117.
3 J. N. Reed, *Sci. Synth.*, 2006, **8a**, 329.
4 A. H. Stoll, A. Krasovskiy and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 606.
5 A. Metzger, M. A. Schade and P. Knochel, *Org. Lett.*, 2008, **10**, 1107; M. A. Schade, A. Metzger, S. Hug and P. Knochel, *Chem. Commun.*, 2008, 3046; G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr and P. Knochel, *Org. Lett.*, 2008, **10**, 2765; M. M. Yugushi, M. Tokuda and K. Orito, *J. Org. Chem.*, 2004, **69**, 908; C. Piazza, N. Millot and P. Knochel, *J. Organomet. Chem.*, 2001, **624**, 88; J. X. Wang, Y. Fu and Y. L. Hu, *Chin. Chem. Lett.*, 2002, **5**, 405; S. C. Berk, M. C. P. Yeh, N. Jeong and P. Knochel, *Organometallics*, 1990, **9**, 3053; T. Harada, T. Kaneko, T. Fujiwara and A. Oku, *J. Org. Chem.*, 1997, **62**, 8966; M. Gaudemar, *Bull. Soc. Chim. Fr.*, 1962, **5**, 974.
6 A. Krasovskiy, V. Malakhov, A. Gavryushin and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 6040; N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy and P. Knochel, *J. Am. Chem. Soc.*, 2007, **129**, 12358.
7 F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm and P. Knochel, *Angew. Chem., Int. Ed.*, 2008, **47**, 6802.
8 Y.-H. Chen and P. Knochel, *Angew. Chem., Int. Ed.*, 2008, **47**, 7648.
9 For the preparation of benzylic boron compounds see also: H. C. Brown and U. S. Racherla, *J. Org. Chem.*, 1986, **51**, 427.
10 R. D. Rieke, *Science*, 1989, **246**, 1260; R. D. Rieke and M. V. Hanson, *Tetrahedron*, 1997, **53**, 1925.
11 P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390.
12 E. Negishi, *Acc. Chem. Res.*, 1982, **15**, 340.
13 T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 468.
14 In contrast, by using the direct zinc insertion (Zn (1.5 equiv.), LiCl (1.5 equiv.)) a reaction time of 11 h at 25 °C is observed.