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Highly Functionalized Benzene Syntheses by Directed Mono or Multiple Magnesiations with TMPMgCl·LiCl

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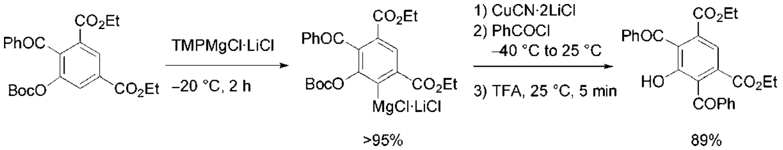
ABSTRACT



The direct magnesiation of highly functionalized aromatics bearing an ester, a nitrile, or a ketone can be readily performed by using an OBoc as a directing group and TMPMgCl·LiCl as a base. It allows, for example, the preparation of a meta-magnesiated benzophenone in >95%. After quenching, highly functionalized and substituted benzenes are obtained.

The preparation of aryl organometallics by a directed lithiation with use of a lithium base (such as *sec*-BuLi or lithium tetramethylpiperidide (LiTMP)) has found broad applications.[1] However, the resulting aryllithiums have a high reactivity, which precludes the presence of sensitive functional groups like an ester or a ketone.[2] Also, the nature of the directing group is limited to functional groups which do not react with strong lithium bases.[3] Due to their moderate solubility and low kinetic basicity, magnesium bases have found fewer applications.[4] However, there is a renewed interest for these bases,[5] since it has been shown that arylmagnesium species are compatible with electrophilic functional groups such as an ester, a nitrile, or even a ketone.[6] Recently, we have developed a new class of magnesium bases of type $R_2NMgCl{\cdot}LiCl$ that, due to the presence of

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(1) (a) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376. (b) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. (c) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059. (d) Schlosser, M. *Eur. J. Org. Chem.* **2001**, *21*, 3975. (e) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *Org. Lett.* **2005**, *7*, 2305. (f) Plaquevent, J.-C.; Perrard, T.; Cahard, D. *Chem. Eur. J.* **2002**, *8*, 3300. (g) Chang, C.-C.; Ameerunisha, M. S. *Coord. Chem. Rev.* **1999**, *189*, 199. (h) Leroux, F.; Schlosser, M.; Zohar, E.; Marek, I. *Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: New York, 2004; Chapter 1, p 435. (i) Henderson, K. W.; Kerr, W. J. *Chem. Eur. J.* **2001**, *7*, 3430. (j) Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Tetrahedron* **2002**, *58*, 4573. (k) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (l) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187. (m) Veith, M.; Wieczorek, S.; Fries, K.; Huch, V. *Z. Anorg. Allg. Chem.* **2000**, *626*, 1237. (n) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (o) Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1575. (p) Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1578. (q) Plé, N.; Turck, A.; Couture, K.; Quéguiner, G. *J. Org. Chem.* **1995**, *60*, 3781. (r) Metallinos, C.; Snieckus, V. *Org. Lett.* **2002**, *4*, 1935. (s) Clegg, W.; Dale, S. H.; Harrington, R. W.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2374. (t) Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2371. (u) Hodgson, D. M.; Miles, S. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 935.

(2) Yus, M.; Foubelo, F. *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1, p 7.

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(4) (a) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *J. Org. Chem.* **2005**, *70*, 5190. (b) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron* **2005**, *61*, 4779. (c) Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E.; Sherrington, D. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 68. (d) Widhalm, M.; Mereiter, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1233.

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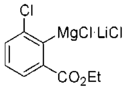
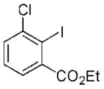
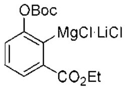
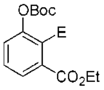
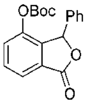
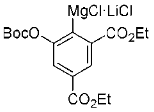
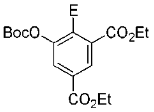
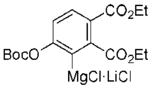
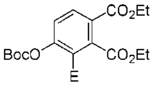
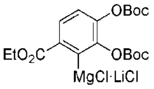
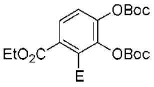
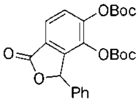
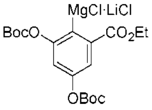
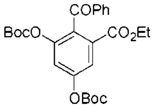
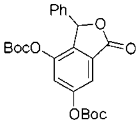
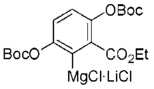
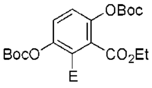
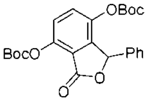
10.1021/ol0625536 CCC: $33.50

Table 1. Generation of Magnesiated Polyfunctionalized Aryl Derivatives of Type **2** and Their Trapping with Electrophiles Leading to Products of Type **3**

entry	Grignard reagent **2**[a]	electrophile	product of type **3**	yield (%)[b]
				
1	**2a** (6 h)	I_2	**3a**	76
				
2	**2d** (3 h)	PhCOCl[c]	**3e:** E=COPh	90
3	**2d**	EtOCOCN	**3f:** $E=CO_2Et$	80
				
4	**2d**	PhCHO	**3g**	83
				
5	**2e** (1 h)	PhCOCl[c]	**3h:** E=COPh	91
6	**2e**	EtOCOCN	**3i:** $E=CO_2Et$	85
7	**2e**	TsCN	**3j:** E=CN	90
8	**2e**	$BrCl_2CCCl_2Br$	**3k:** E=Br	92
				
9	**2f** (1 h)	PhCOCl[c]	**3l:** E=COPh	82
10	**2f**	EtOCOCN	**3m:** $E=CO_2Et$	78
				
11	**2g** (3 h)	PhCOCl[c]	**3n:** E=COPh	90
12	**2g**	EtOCOCN	**3o:** $E=CO_2Et$	88
				
13	**2g**	PhCHO	**3p**	91
				
14	**2h** (3 h)	PhCOCl[c]	**3q**	93
				
15	**2h**	PhCHO	**3r**	90
				
16	**2i** (3 h)	PhCOCl[c]	**3s:** E=COPh	91
17	**2i**	$PhSO_2Cl$	**3t:** E=Cl	78
				
18	**2i**	PhCHO	**3u**	77

[a] Reaction time for the deprotonation with TMPMgCl•LiCl (1.1 equiv) at 0 °C. [b] Isolated yield of analytically pure product. [c] The reaction was performed by using CuCN•2LiCl (0.2 equiv).

LiCl, display an excellent solubility in THF (up to 1.2 M for TMPMgCl•LiCl) as well as an enhanced kinetic basicity that has allowed a selective magnesiation of a broad range of functionalized heterocycles.[7] Herein, we wish to report the use of these bases in combination with the appropriate directing group for the preparation of highly functionalized benzenes. Although the *ortho*-magnesiation of ethyl benzoate with stoichiometric amounts of TMPMgCl•LiCl proved to be sluggish indicating that an ester group is only a moderately active directing group,[8] in the presence of a *meta*-chlorine atom,[1a] a smooth magnesiation of ethyl 3-chlorobenzoate (**1a**) took place at 0 °C within 6 h with TMPMgCl•LiCl (1.2 equiv) as a base. The desired arylmagnesium species **2a** was obtained and furnished after iodolysis the expected aryl iodide **3a** in 76% yield (Table 1, entry 1). This experiment indicates that the electron density of aromatic rings is also of importance and that electron-poor benzenes are more prone to magnesiation. Therefore, we have directed our attention toward various derivatives of ethyl 3-hydroxyben-

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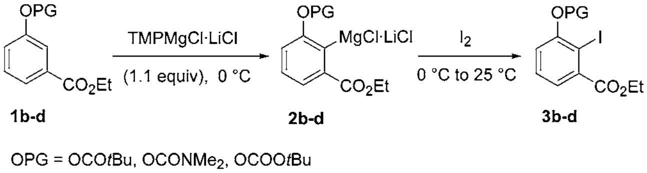
(6) (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (b) Knochel, P.; Krasovskiy, A.; Sapountzis, I. *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1, p 109.

(7) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.

(8) (a) The conversion of the starting material is very slow even at 25 °C and no desired magnesiated product is observed. (b) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (c) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155. (d) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054.

zoate such as the corresponding pivalate **1b**, the *N*,*N*-dimethylcarbamate **1c**, and the Boc-derivative **1d**. We have submitted these aromatics to a magnesiation using TMPMgCl·LiCl (1.1 equiv) at 0 °C. The formation of the intermediate arylmagnesium reagents **2b−d** was monitored by GC analysis of reaction aliquots. We have observed that the pivalate **1b** was only slowly metalated and led to the formation of significant amounts of side products. After iodine quenching, the expected aryl iodide **3b** was detected in only about 20% yield by GC analysis (Table 2, entry 1).

Table 2. Optimization of the Nature of the Protecting Group for the Generation of Grignard Reagents **2b−d**



entry	protecting group	reaction time (h)	product **3** (yield %)[a]
1	*t*BuCO **1b**	20	**3b**, (20)[b]
2	Me_2NCO **1c**	3	**3c**, 50 (52)[c]
3	Boc **1d**	3	**3d**, 86

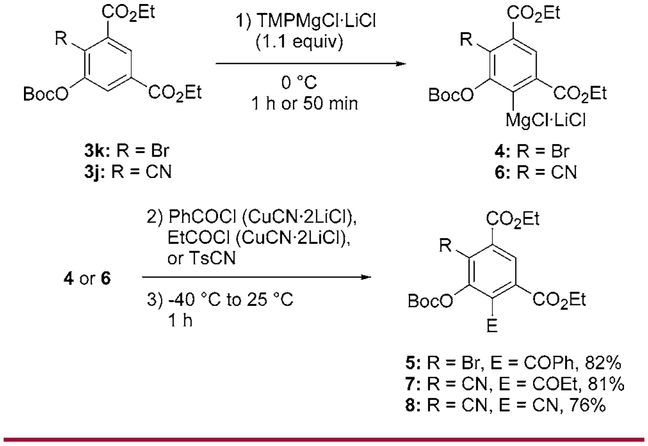
[a] Isolated yield of analytically pure compounds. [b] TMPMgCl·LiCl (1.2 equiv) was used; there was less than 40% conversion and the desired product was detected in ca. 20% by GC-analysis. [c] TMPMgCl·LiCl (1.1 equiv) was used; there was 52% conversion by GC analysis; the conversion did not increase after 1 day reaction time and side products occurred by GC analysis.

The carbamate **1c** was magnesiated much more readily, but never led to a complete conversion. After iodolysis, the aryl iodide **3c** was obtained in 50% yield (entry 2). However, by using the Boc-protected hydroxybenzoate **1d**, a complete magnesiation was obtained at 0 °C within 3 h and led cleanly to the magnesium reagent **2d**. After iodolysis, the aryl iodide **3d** was isolated in 86% yield (entry 3). This preliminary study indicates that a Boc-group is potentially an excellent directing group for the magnesiation of benzenes with TMPMgCl·LiCl.[9] Competitive studies show that the magnesiation rate is also ca. 3 times faster with a Boc-directed group as with Me_2NCO.[10]

The excellent directing ability of the Boc-group was confirmed by further studies summarized in Table 1 and showed that various Boc-protected phenols can be magnesiated leading to the polyfunctional arylmagnesium derivatives **2d−i** (Table 1, entries 2−18). In all cases, the metalations were complete within a few hours at 0 °C with TMPMgCl·LiCl (1.1 equiv). The quenching with various electrophiles proceeded with good yields. Thus, the benzoylation of the copper derivatives of **2d−i** (obtained by the reaction with CuCN·2LiCl)[11] provided the corresponding ketones **3e**, **3h**, **3l**, **3n**, **3q**, and **3s** in 82−93% yield (Table 1, entries 2, 5, 9, 11, 14, and 16). An ethyl carboxylation could be readily realized by the reaction with EtOCOCN (−40 to 25 °C, 0.5 h)[12] leading to the di- and triester derivatives **3f**, **3i**, **3m**, and **3o** in 78−88% yield (entries 3, 6, 10, and 12). The cyanation of the arylmagnesium species **2e** with TsCN[13] led to the aromatic nitrile **3j** in 90% yield (entry 7). A bromination was best performed by the reaction with $BrCl_2CCCl_2Br$. With this method, the magnesium derivative **2e** was smoothly converted to the brominated ester **3k** in 92% yield (entry 8). The reaction of Grignard reagents **2d**, **2g**, **2h**, and **2i** with benzaldehyde provided, after spontaneous cyclization, the lactones **3g**, **3p**, **3r**, and **3u** in 77−91% yield (entries 4, 13, 15, and 18). A chlorination could also be achieved by a reaction with $PhSO_2Cl$.[14] By this method, the Grignard reagent **2i** afforded the ester **3t** in 78% yield (entry 17).

We have found that products of type **3** can be magnesiated again. Thus, the reaction of Boc-protected bromophenol **3k** with TMPMgCl·LiCl (1.1 equiv, 0 °C, 1 h) provided the Grignard reagent **4**, which underwent a smooth benzoylation with PhCOCl (2.0 equiv) in the presence of CuCN·2LiCl (0.2 equiv) affording the ketone **5** in 82% yield. Similarly, the cyano-substituted diester **3j** was converted to the corresponding arylmagnesium derivative **6** with TMPMgCl·LiCl (1.1 equiv, 0 °C, 50 min). Its reaction with EtCOCl in the presence of CuCN·2LiCl provided the ketone **7** in 81% yield (Scheme 1). The reaction of the Grignard reagent **6** with TsCN led to the dinitrile **8** in 76% yield.

Scheme 1. Boc-Directed Magnesiation of Polyfunctional Bromoarene **3k** and Benzonitrile **3j** Followed by Trapping with Electrophiles



Interestingly, the functionalized benzophenone **3h** was readily magnesiated (−20 °C, 2 h) by using TMPMgCl·LiCl (1.1 equiv) leading to the keto-substituted arylmagnesium reagent **9**. This remarkable functional group compatibility

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[9] Interestingly, a OBoc-group cannot be used to direct lithiation due to its sensitivity toward organolithium reagents and various lithium bases.

[10] See the Supporting Information.

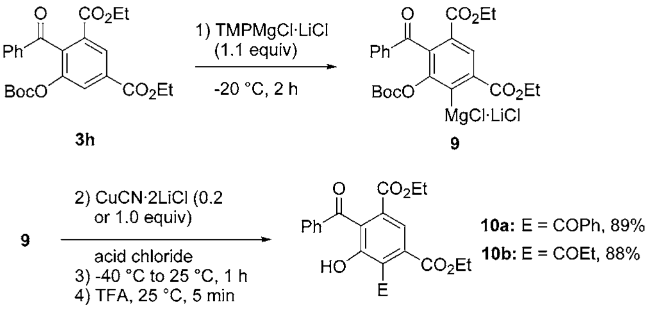
[11] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

[12] Rho, T.; Abuh, Y. F. *Synth. Commun.* **1994**, *24*, 253.

[13] (a) Cox, J. M.; Ghosh, R. *Tetrahedron Lett.* **1969**, *10*, 3351. (b) Kahne, D.; Collum, D. B. *Tetrahedron Lett.* **1981**, *22*, 5011. (c) Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623. (d) Rutan, K. J.; Heldrich, F. J.; Bogers, L. F. *J. Org. Chem.* **1995**, *60*, 2948.

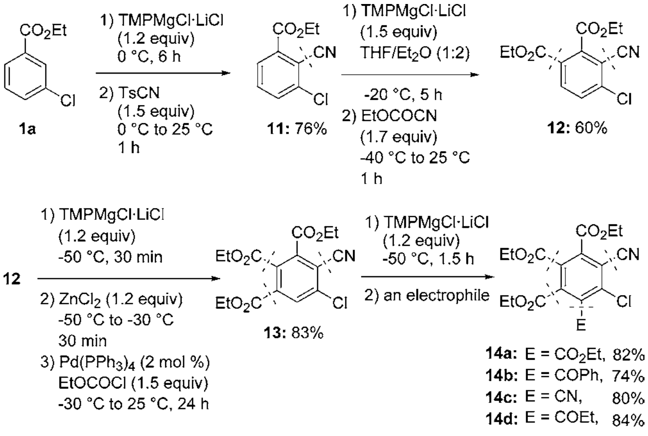
should be general and this magnesiation procedure may give access to various arylketo-substituted arylmagnesium species. After the Cu-catalyzed acylation of **9** with acid chlorides followed by Boc-deprotection (TFA, 25 °C, 5 min), the polyfunctional pentasubstituted phenols **10a**,**b** were obtained in 88−89% yield (Scheme 2).

Scheme 2. Boc-Directed Magnesiation of a Polyfunctional Benzophenone **3h** Followed by Cu-Catalyzed Acylation and Deprotection



Finally, a multiple functionalization of ethyl 3-chlorobenzoate (**1a**) can be achieved by successive magnesiations with TMPMgCl·LiCl and quenching with an electrophile leading to a hexasubstituted benzene (Scheme 3). Thus, the metalation of the ethyl ester **1a** with TMPMgCl·LiCl followed by an electrophilic cyanation with TsCN provided the nitrile **11**, which by a further regioselective magnesiation at the α-position to the carboethoxy group afforded, after reaction with EtOCOCN (1.7 equiv), the diester **12** in 60% yield. The use of a solvent mixture THF/Et_2O (1:2) was essential for controlling the regioselectivity of the magnesiation (>95% regioselectivity). By using only THF, a competitive metalation at the α-position to the chlorine substituent of **11** was also observed (ca. 10% relative to **12** by GC analysis). The treatment of **12** with TMPMgCl·LiCl (1.2 equiv, −50 °C, 30 min) followed by a transmetalation with $ZnCl_2$ and Pd(0)-catalyzed acylation with EtOCOCl[15] gave rise to the triester **13** in 83% yield. The magnesiation of **13** with TMPMgCl·LiCl (1.2 equiv, −50 °C, 1.5 h) followed by the addition of various acylating agents (EtOCOCN, PhCOCl, TsCN, or EtCOCl) furnished the hexasubstituted benzenes **14a−d** in 74−84% yield (Scheme 3).

Scheme 3. Successive Magnesiations of Ethyl 3-Chlorobenzoate (**1a**) Followed by Trapping with Electrophiles Leading to Hexasubstituted Benzenes of Type **14**



In summary, we have shown that the magnesiation of various Boc-substituted aromatics with TMPMgCl·LiCl allows the preparation of new highly functionalized arylmagnesium reagents of which some bear even a keto-function. The easy introduction and removal of a Boc-group make this functionalization method of aromatics a useful complement to the well-known directed lithiation reaction.[1k,r,3b,c] Further applications of this methodology in the synthesis of polyfunctional unsaturated systems is currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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