Grignard Reactions

DOI: 10.1002/anie.200703382

A General Method for *meta* and *para* Functionalization of Arenes Using $TMP_2Mg{\cdot}2\,LiCl$**

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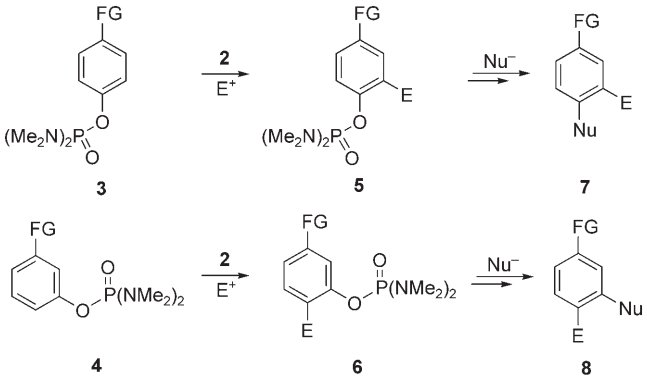
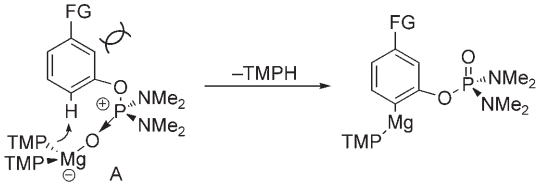
ortho-Directed metalation is an important method for the functionalization of various arenes and heterocycles. Various directed-metalation groups (DMGs) have been used for achieving efficient lithiations.[1] DMGs mediate fast and *ortho*-selective metalation mainly by chelation (entropic effect). Polar DMGs may furthermore transfer electron density to the metal base and increase their metalating power.[2] Recently, magnesiate bases have proven to be of great structural and synthetic interest for the functionalization of arenes.[3] Alternatively, we have shown that the mixed Li/Mg bases TMPMgCl·LiCl (**1**)[4] and $TMP_2Mg{\cdot}2\,LiCl$ (**2**; TMP = 2,2,6,6-tetramethylpiperamidyl)[5] are highly active and soluble magnesium bases that allow smooth metalation of various arenes and heterocycles with an excellent functional-group compatibility.[4–6]

In the course of these studies we observed that the DMG *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate ($(Me_2N)_2P(O)$-O-)[7] is a very strong directing group for magnesiation and that it may overrule the effects of other substituents present on the aromatic substrate. In contrast to directed lithiations, which are usually performed at −105 °C to avoid Fries-type rearrangements,[7] the magnesiation with $TMP_2Mg{\cdot}2\,LiCl$ occurs (even at 0 °C) without anionic migration of the tetramethylphosphorodiamidate group. This would allow new types of functionalization such as formal *meta*[8] or *para* functionalization (Scheme 1). Thus, we have found that a range of aromatic phosphorodiamidates bearing a functional group (FG) either in the *para* position (type **3**) or in the *meta* position (type **4**) undergo efficient magnesiation with $TMP_2Mg{\cdot}2\,LiCl$ (**2**) leading to products of type **5** and **6**, respectively, after the addition of an electrophile. Substitution of the $OP(O)(NMe_2)_2$ group with a nucleophile (Nu) gives *meta*,*para*- and *para*,*meta*-difunctionalized molecules of types **7** and **8** as described below (Scheme 1 and Table 1). The magnesiation of substrates **3** and **4** using $TMP_2Mg{\cdot}2\,LiCl$ (**2**) proceeds smoothly within a few hours at 0 °C for cyano- and ester-substituted phosphorodiamidates **3a** and **4a** (entries 1–3 and 10–13, Table 1). For halogen-substituted starting materials (**3b–d**; entries 4–9. Table 1) as well as for the trifluoromethyl-substituted phosphorodiamidate **4b** (entry 14), lower temperatures (−40 to −50 °C) led to optimum results.



Scheme 1. *meta*,*para* and *para*,*meta* functionalization using $TMP_2Mg{\cdot}2\,LiCl$.

In general, the regioselectivity of arene metalation is governed by a combination of electronic and/or steric effects.[1,2] The tetramethylphosphorodiamidate group, one of the strongest donors in organic synthesis,[9] activates the Mg–N bond giving the base ate character (Scheme 2).[3,10]



Scheme 2. The ate character of $TMP_2Mg{\cdot}2\,LiCl$ (**2**) induces efficient *para* metalation. (LiCl has been omitted for clarity.)

This electronic effect increases the metalation power of the base, and no additional chelation or inductive effects are necessary for achieving the magnesiation. Normally, this phosphorodiamidate-triggered magnesiation occurs preferentially at the sterically less hindered position of the arene ring, promoting formally *meta* metalation. However, in the case of *meta*-substituted substrates bearing bromo, chloro, and fluoro functional groups, we observed that the regioselectivity of the metalation is affected[11] by the competitive directing effects of these halogens.

Various electrophiles such as acid chlorides, TsCN, allylic halides, aldehydes, and aryl iodides react with the organomagnesium intermediates providing the desired products in

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[**] We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG) for financial support. G.C. thanks the Humboldt Foundation for a fellowship. We also thank Chemetall GmbH (Frankfurt), Evonik Industries AG (Essen), and BASF AG (Ludwigshafen) for generous gifts of chemicals.

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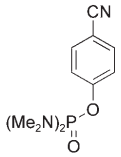
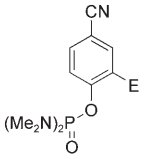
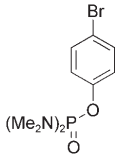
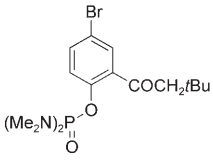
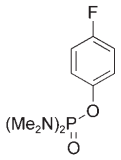
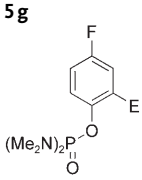
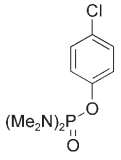
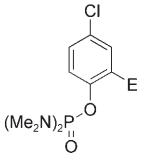
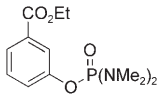
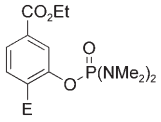
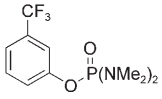
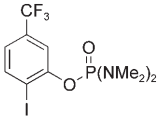
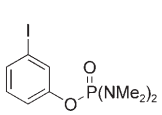
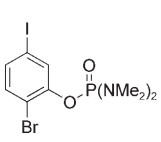
Table 1: Products of types **5** and **6** obtained by direct magnesiation of phosphoroamidates **3** and **4** with $(TMP)_2Mg{\cdot}2\,LiCl$ (**2**) followed by the reaction with electrophiles.

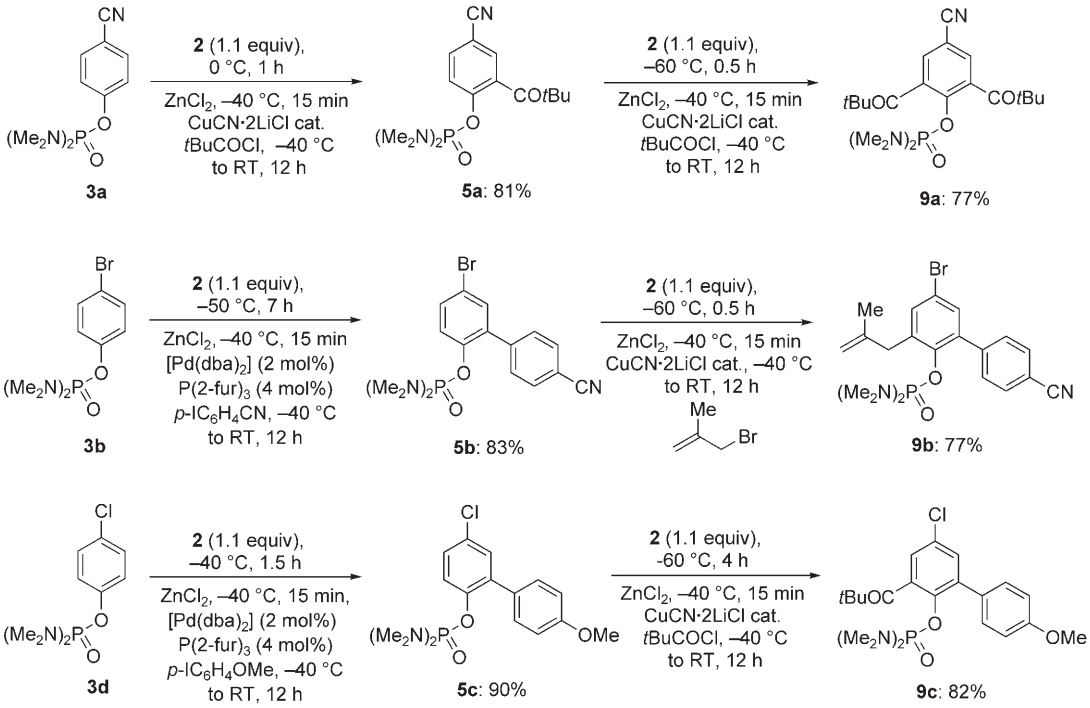
Entry	Substrate	T [°C], t [h]	EX[a]	Product	Yield [%][b]
					
1	**3a**	0, 1	*p*-IC_6H_4OTIPS	**5d**: E = *p*-C_6H_4OTIPS	83[c]
2	**3a**	0, 1	TsCN	**5e**: E = CN	77[d]
3	**3a**	0, 1	$CH_2{=}C(CH_3)CH_2Br$	**5f**: E = $CH_2{=}C(CH_3)CH_2$	84[d]
					
4	**3b**	−50, 7	*t*$BuCH_2COCl$	**5g**	72[d]
					
5	**3c**	−40, 4	*p*-$IC_6H_4CO_2Et$	**5h**: E = *p*-$C_6H_4CO_2Et$	78[c]
6	**3c**	−40, 4	*m*-$CH_3C_6H_4I$	**5i**: E = *m*-$CH_3C_6H_4$	75[c]
7	**3c**	−40, 4	*c*-C_6H_9Br	**5j**: E = *c*-C_6H_9	85[d]
					
8	**3d**	−40, 1.5	PhCOCl	**5k**: E = COPh	85[d]
9	**3d**	−40, 1.5	*t*BuCHO	**5l**: E = *t*BuC(OH)	79
					
10	**4a**	0, 1	$(BrCl_2C)_2$	**6a**: E = Br	80
12	**4a**	0, 1	PhCOCl	**6b**: E = COPh	73[d]
13	**4a**	0, 1	*p*-$IC_6H_4CO_2Et$	**6c**: E = *p*-$C_6H_4CO_2Et$	78[c]
					
14	**4b**	−40, 2	I_2	**6d**	88
					
15	**4c**	0, 0.5	$(BrCl_2C)_2$	**6e**	76

[a] TIPS = triisopropylsilyl; Ts = *p*-toluenesulfonyl. [b] Yield of isolated, analytically pure product. [c] Obtained by palladium-catalyzed cross-coupling after transmetalation with $ZnCl_2$ (1.2 equiv). [d] A transmetalation with $ZnCl_2$ (1.2 equiv) and $CuCN{\cdot}2\,LiCl$ (0.5–1.3 equiv) was performed.

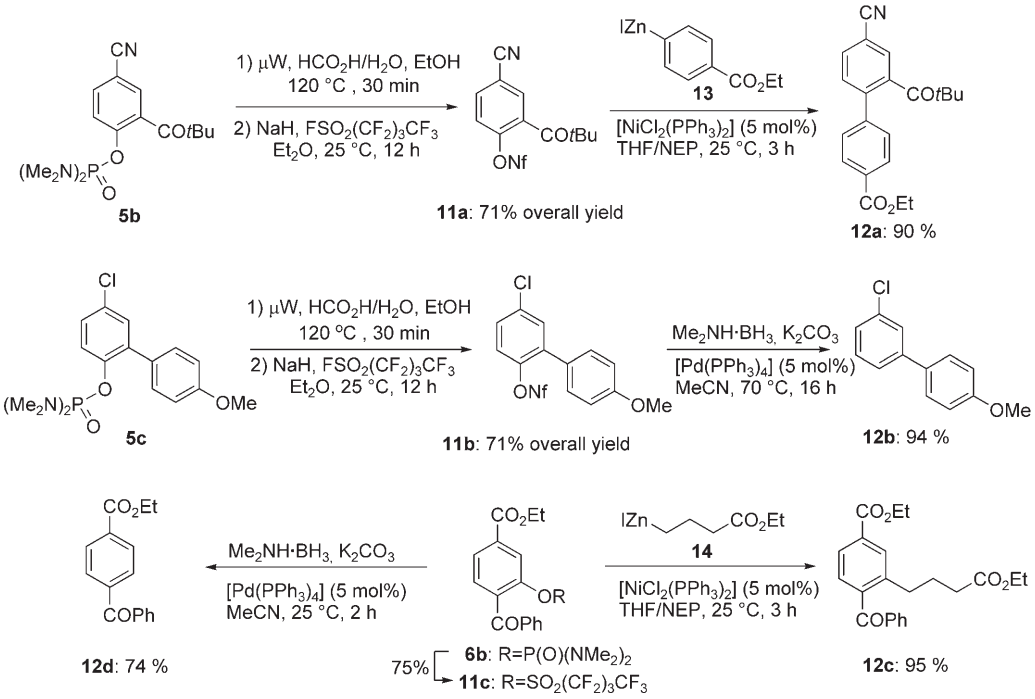
72–90% yields (Table 1). In the case of allylation and acylation reactions, the best results were obtained when the aryl magnesium species were transmetalated with $ZnCl_2$ (1.2 equiv) and $CuCN{\cdot}2\,LiCl$ (0.5–1.3 equiv)[12] prior to the addition of the acid chloride, TsCN, or the allylic halide (entries 2–4, 7, 8, and 12, Table 1). Similarly, Negishi cross-couplings[13] with aryl iodides in the presence of $[Pd(dba)_2]$ (2 mol%; dba = dibenzylideneacetone) and P(2-fur)$_3$ (4 mol%; fur = furfuryl)[14] were successfully performed after transmetalation of the Grignard reagents with $ZnCl_2$ (entries 1, 5, 6, and 13, Table 1).

Double functionalization in the *meta*,*meta*′ positions has also been achieved. Thus, the treatment of the nitrile **3a** with $TMP_2Mg{\cdot}2\,LiCl$ (1.1 equiv, 0 °C, 1 h) followed by a copper(I)-catalyzed reaction with *t*BuCOCl provides the ketone **5a** in 81% yield (Scheme 3). Application of the same reaction sequence (metalation at −60 °C for 0.5 h) converted ketone **5a** into the diketone **9a** in 77% yield. Furthermore, the double functionalization of the bromo- and chloro-substituted phosphorodiamidates **3b** and **3d** led to the preparation of the highly functionalized phosphorodiamidates **9b** and **9c**, respectively, in good overall yields (Scheme 3). This demonstrates the high directing power of the $OP(O)(NMe_2)_2$ group.

Further manipulation of the functionalized aryl phosphorodiamidates of types **5** and **6** was best achieved by converting these intermediates into nonaflates[15] or triflates. Thus, microwave-assisted deprotection of aryl phosphorodiamidates **5b** and **5c** with formic acid in aqueous ethanol (120 °C, 30 min) provided polyfunctional phenols, which after the reaction with $C_4F_9SO_2F$ (NaH, Et_2O, 25 °C, 12 h) provided the corresponding nonaflates **11a** and **11b** in 71% yield (Scheme 4). A nickel-catalyzed cross-coupling of nonaflate **11a** with the arylzinc reagent **13** afforded the biphenyl **12a** in 90% yield. On the other hand, reaction



Scheme 3. Double functionalization of phosphorodiamidates **3a**, **3b**, and **3d**, leading to *meta*,*meta*′-substituted products **9a**–**c**.



Scheme 4. Microwave-assisted deprotection of the aryl phosphorodiamidates for further functionalization or DMG removal. NEP = *N*-ethylpyrrolidone.

of **11b** with dimethylamine–borane complex in the presence of a catalytic amount of $[Pd(PPh_3)_4]$[16] gave the reduced derivative **12b** in 94% yield. Similarly, the aryl phosphorodiamidate **6b** was successfully converted to the diester **12c** and to the keto ester **12d** in 95% and 74% yield, respectively, showing that this reaction sequence allows efficient functionalization as well as removal of the directing metalation group (Scheme 4).

In summary, we have reported a method that leads to arenes with new functionalization patterns through magnesiations with the powerful $TMP_2Mg{\cdot}2\,LiCl$ base (**2**) combined with the phosphorodiamidate ($OP(O)(NMe_2)_2$) as a strong

metalation-directing group. This methodology allows the general preparation of various *meta*,*para*- and *meta*,*meta*′-polyfunctionalized arenes, which are not easily accessible by conventional synthetic strategies. Applications toward the synthesis of biologically active molecules are currently being investigated in our laboratories.

Experimental Section

Synthesis of **2**: In a dry argon-flushed Schlenk tube, 2,2,6,6-tetramethylpiperidine (TMPH; 5.07 mL, 30 mmol) was dissolved in THF (30 mL). This solution was cooled to −40 °C, and *n*BuLi (2.4 M in hexane, 12.5 mL, 30 mmol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Freshly titrated TMPMgCl·LiCl (**1**)[4] (1 M in THF, 30 mL, 30 mmol) was then added dropwise to the LiTMP solution, and the reaction mixture was stirred at 0 °C for 30 min, warmed to 25 °C, and stirred for 1 h. The solvents were then removed in vacuo without heating, affording a yellowish solid. Freshly distilled THF was slowly added with vigorous stirring, until the salts had completely dissolved. The fresh $TMP_2Mg{\cdot}2\,LiCl$ solution was titrated[17] prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.6 M in THF was obtained.

Synthesis of **5c**: In a dry argon-flushed Schlenk tube the aryl phosphorodiamidate **3d** (2.62 g, 8.00 mmol) was dissolved in THF (8 mL) and cooled to −40 °C, and $TMP_2Mg{\cdot}2\,LiCl$ (0.6 M in THF, 14.7 mL, 8.8 mmol) was added dropwise. The mixture was stirred at −40 °C for 1.5 h. Complete metalation was detected by GC analysis of reaction aliquots, which were quenched with I_2 in anhydrous THF. A solution of $ZnCl_2$ (1 M in THF, 9.6 mL, 9.6 mmol) was added dropwise, and the resulting mixture was stirred for 15 min. First a solution of $[Pd(dba)_2]$ (88 mg, 2 mol %) and $P(2\text{-fur})_3$ (72 mg, 4 mol %) in THF (8 mL) then 4-iodoanisole (2.06 g, 8.8 mmol) was added, and the reaction mixture was allowed to warm to room temperature. After stirring for 12 h, the reaction mixture was quenched with aq. sat. NH_4Cl solution (20 mL) and extracted with diethyl ether (3 × 50 mL) then the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (ethyl acetate) furnished **5c** (2.78 g, 90 % yield) as an orange oil.

Received: July 27, 2007
Revised: October 30, 2007
Published online: January 18, 2008

Keywords: arenes · directed metalation · Grignard reagents · magnesium bisamides · phosphorodiamidates

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