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Directed Manganation of Functionalized Arenes and Heterocycles Using $tmp_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$**

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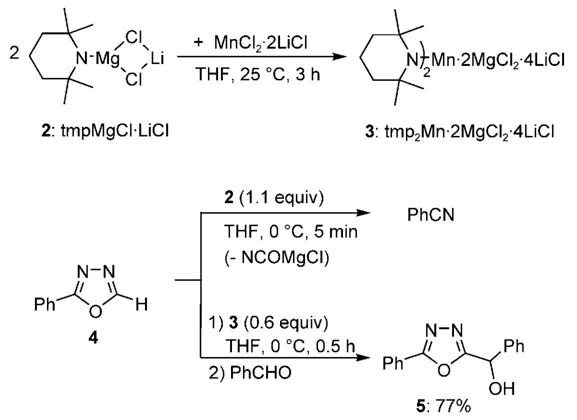
The metalation of arenes and heterocycles is of considerable interest, since it allows direct functionalization of an unactivated C–H bond by the stoichiometric formation of an organometallic intermediate. Whereas the lithiation of unsaturated organic substrates has been extensively used,[1] the search for metalation procedures that are compatible with more functional groups and proceed at close to room temperature has been the subject of considerable efforts. In this regard, the development of various "ate" bases has been very promising.[2,3] Also, the use of sterically hindered metallic amides complexed by LiCl of the type $tmp_nM^1{\cdot}x\,M^2X_m{\cdot}y\,LiCl$ (tmp = 2,2,6,6-tetramethylpiperidyl; $M^1 = Mg$,[4] Zn,[5] Al;[6] $M^2 = Mg$) has led to highly chemo- and regioselective metalations. The presence of LiCl was essential since it increases the solubility of these metallic bases and enhances their kinetic basicity by lowering their aggregation states.[7]

The preparation of transition-metal amides has been envisioned, as transition metals display reactivity patterns not accessible for main-group elements.[8] Especially manganese, owing to its low price, moderate toxicity, and versatile reactivity, is of synthetic interest.[9] Herein, we report a new manganese base[10] that shows a unique chemoselectivity and reactivity, allowing the efficient formation of C–C and C–N bonds. Furthermore, the convenient metalation conditions make it a very practical base for synthetic applications. Thus, the addition of commercially available tmmpMgCl·LiCl (**2**; 2.0 equiv) to $MnCl_2{\cdot}2\,LiCl$[11] (1 equiv) at 0°C with subsequent stirring at 25°C for 3 h provides the manganese amide **3** as a 0.5 M solution in THF (Scheme 1). The base **3** has an excellent thermal stability and can be stored at 25°C for more than eight weeks without appreciable decomposition. Preliminary experiments show immediately that the new Mn base has a very different reactivity than the Mg base **2**. Thus, whereas the reaction of **2** with 2-phenyl-1,3,4-oxadiazole (**4**) provides only ring fragmentation products (PhCN and NCOMgCl), its metalation with **3** furnishes cleanly the corresponding diheteroaryl manganese reagent, which smoothly adds to benzaldehyde, thus providing the alcohol **5** in 77% yield (Scheme 1).



Scheme 1. Preparation and reactivity of **3** compared to **2**.

Remarkably, we found that a range of functionalized aromatic substrates are readily manganated under convenient reaction conditions (0–25°C). Thus, methyl 4-bromobenzoate (**6a**) reacts with **3** (0.6 equiv) within 3.5 h at 25°C, furnishing the diaryl manganese reagent **7a** without cleavage of the sensitive methyl ester function. Copper(I)-catalyzed acylation using $CuCN{\cdot}2\,LiCl$[12] (20 mol%) and 2-thienoyl chloride (1.2 equiv) provides the ketone **8a** in 77% yield. The highly functionalized benzophenone derivative **6b** is converted to the corresponding manganese species **7b** by the reaction with **3** (0.6 equiv, 25°C, 2 h). Cu^I-catalyzed allylation with 3-bromocyclohexene (1.2 equiv) provides the polyfunctional benzophenone **8b** in 74% yield (Scheme 2).

Subsequent palladium-catalyzed arylations are also readily accomplished. The reaction of methyl 3-chlorobenzoate (**6c**) with **3** (0.6 equiv, 25°C, 2 h) provides a diaryl manganese intermediate that undergoes a Pd-catalyzed cross-coupling[13] ($[Pd(PPh_3)_4]$) (2.5 mol%), 25°C, 12 h) with 1-iodo-3-trifluoromethylbenzene (1.1 equiv) to give the *ortho*,*ortho'*-disubstituted biphenyl **8c** in 77% yield (Table 1, entry 1). Similarly, the manganation of methyl 4-chlorobenzoate (**6d**) and cross-coupling with 3-iodotoluene furnishes the biphenyl **8d** in 80% yield (Table 1, entry 2).

The diaryl manganese intermediates also react well with aldehydes.[14] Thus, the manganation of methyl 3-bromobenzoate **6e** with **3** (0.6 equiv, 25°C, 2 h) provides a manganese reagent that adds to 4-methoxybenzaldehyde (1.2 equiv), leading to the lactone **8e** in 81% yield (Table 1, entry 3).[15] A range of substituted benzene derivatives bearing an ester or

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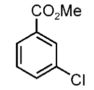
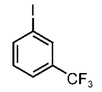
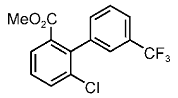
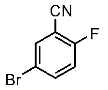
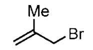
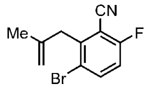
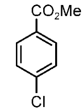
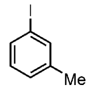
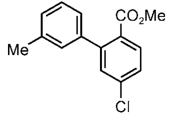
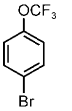
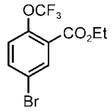
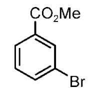
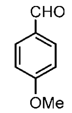
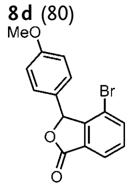
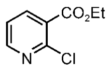
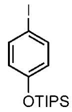
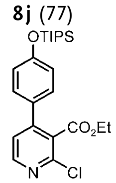
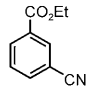
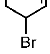
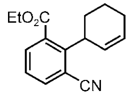
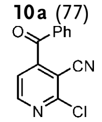
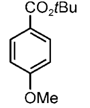
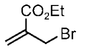
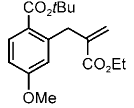
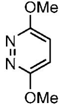
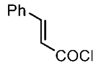
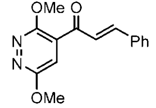
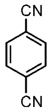
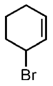
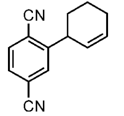
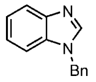
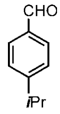
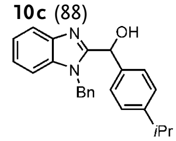
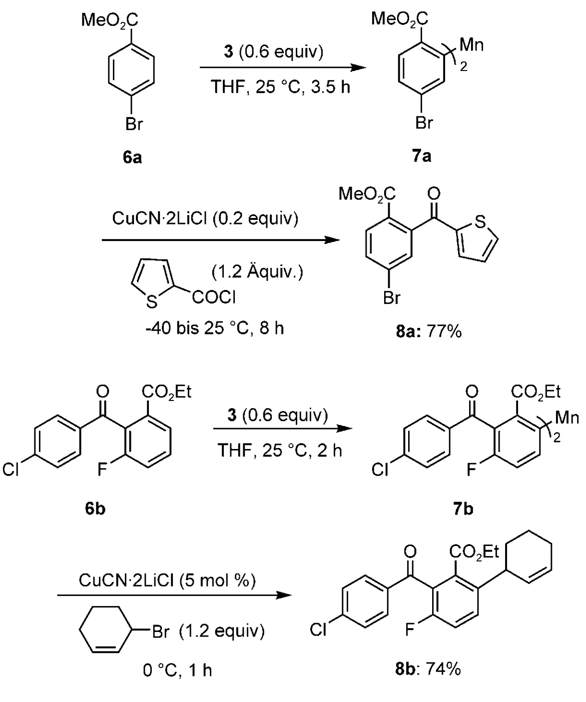
Table 1: Manganation of aromatic substrates (**6c**–**j**) and heterocyclic rings (**9a**–**d**) with **3** and reactions with electrophiles.

No.	Substrate[a]	Electrophile	Product[b]	No.	Substrate[a]	Electrophile	Product[b]
1	 **6c** (25, 2)		 **8c** (77)	7	 **6i** (0, 0.5)		 **8i** (83)
2	 **6d** (25, 3)		 **8d** (80)	8	 **6j** (25, 10)	NC–CO$_2$Et	 **8j** (77)
3	 **6e** (25, 2)		 **8e** (81)	9	 **9a** (0, 0.5)		 **10a** (77)
4	 **6f** (0, 0.75)		 **8f** (88)	10	 **9b** (0, 0.75)	PhCOCl	 **10b** (71)
5	 **6g** (25, 30)		 **8g** (73)	11	 **9c** (0, 0.5)		 **10c** (88)
6	 **6h** (0, 3.5)		 **8h** (78)	12	 **9d** (0, 0.5)		 **10d** (84)

[a] The reaction conditions for the metalation with **3** are given in parentheses (*T* [°C], *t* [h]). [b] Yield [%] of isolated analytically pure product is given in parentheses.

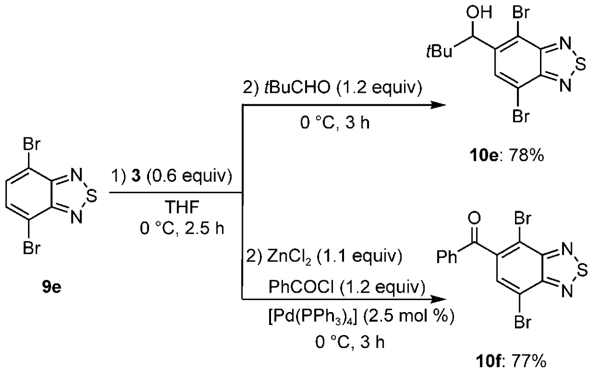


Scheme 2. Manganation of functionalized arenes with **3** and subsequent acylation or allylation.

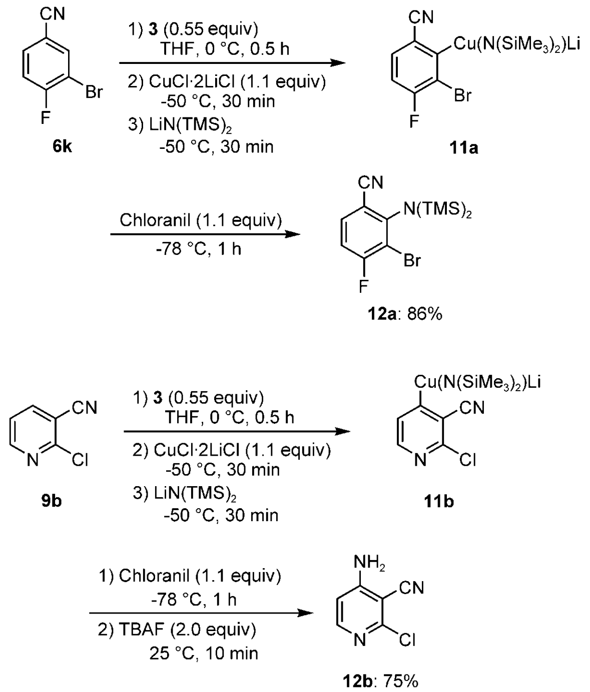
nitrile (**6f**–**i**) are converted with the base **3** to the corresponding diaryl manganese compounds and undergo smooth Cu-catalyzed allylations with various allylic bromides in 73–88% yield (Table 1, entries 4–7). 4-Trifluoromethoxy-substituted bromobenzene (**6j**) was also manganated with **3** (0.6 equiv; 25°C, 10 h) at the *ortho*-position to the CF_3O group. A subsequent acylation with NC–CO$_2$Et provides the disubstituted ethyl benzoate **8j** in 77% yield (Table 1, entry 8).

A range of functionalized heterocycles have been manganated as well. Thus, the nicotinic ester **9a** undergoes a complete manganation with **3** (0.6 equiv; 0°C, 0.5 h), providing the expected manganese reagent, which undergoes a Pd^0-catalyzed cross-coupling ([Pd(PPh$_3$)$_4$] (2.5 mol%); 0°C, 5 h) with *p*-TIPSOC$_6$H$_4$I (1.1 equiv; TIPS = triisopropylsilyl), leading to the polyfunctional pyridine **10a** in 77% yield (Table 1, entry 9). Similarly, the cyano-substituted pyridine **9b** and pyrazine **9c** undergo a complete metalation with **3** (0.6 equiv) at 0°C (30–45 min). After Cu^I-catalyzed acylation, the ketones **10b** and **10c** are obtained in 71 and 88% yield, respectively (Table 1, entries 10 and 11). The electron-rich heterocycle *N*-benzylbenzimidazole **9d** smoothly reacts with **3** (0°C, 30 min). Addition to 4-*i*PrC$_6$H$_4$CHO furnishes the expected alcohol **10d** in 84% yield (Table 1, entry 12).

The functionalization of the benzothiadiazole scaffold is especially important because of potential applications in the preparation of new materials.[16] A novel functionalization of 3,6-dibromobenzothiadiazole (**9e**) in the 4-position is readily achieved by treating **9e** with **3** (0.6 equiv; 0 °C, 2.5 h). The resulting diheteroaryl manganese reagent is quenched with pivaldehyde to give the alcohol **10e** in 78 % yield. Alternatively, a Pd-catalyzed benzoylation gives the ketone **10f** in 77 % yield (Scheme 3).[17]



Scheme 3. Manganation of 3,6-dibromobenzothiadiazole (**9e**) with **3** and reactions with electrophiles.



Scheme 4. Oxidative aminations of a manganated arene or heterocycle leading to polyfunctional amines **12a,b**. TMS = trimethylsilyl. TBAF = tetrabutylammonium fluoride.

Recently, we reported an oxidative amination of organomagnesium reagents[18] using chloranil and copper amides.[19] We have found that aryl copper reagents prepared from diaryl manganese reagents obtained by directed manganation with **3** give superior yields in this amination procedure compared with those prepared from aryl magnesium reagents obtained by metalation with **2**. Thus, the reaction of 3-bromo-4-fluorobenzonitrile (**6k**) with **3** (0.55 equiv, 0 °C, 30 min) and subsequent reaction with CuCl·2 LiCl (1.1 equiv, −50 °C, 30 min) and addition of LiN(SiMe$_3$)$_2$ (2.0 equiv, −50 °C, 1 h) provides the lithium amidocuprate **11a**, which by reaction with chloranil (1.1 equiv, −78 °C, 1 h) furnishes the trimethylsilyl-protected aniline **12a** in 86 % yield (Scheme 4). Performance of the same sequence with the corresponding aryl magnesium reagents provides a 10 % lower yield of the aniline **12a**.[20] A similar amination was performed starting with the functionalized pyridine **9b**. The same sequence leads to the lithium amidocuprate **11b**, which undergoes an oxidative amination mediated by chloranil and, after deprotection with TBAF (2.0 equiv, 25 °C, 10 min), furnishes the deprotected 4-aminopyridine **12b** in 75 % yield (Scheme 4).

This reaction sequence proved to be general, and various aminated arenes and pyridines have been prepared (Table 2). Thus, the treatment of the benzonitrile **6k** with several lithium amides affords after oxidative amination the aryl amines **12c–f** in 66–73 % yields (Table 2, entries 1–4). The related functional benzonitrile **6l** and the nicotinate **9a** are oxidatively aminated, leading to the aniline **12g** (75 %, Table 2, entry 5) and to the amines **12h** and **12i** in 65 and 81 % yield (Table 2, entries 6–7).

In summary, we have reported a convenient directed manganation of various polyfunctional arenes and heterocycles. This metalation procedure tolerates several functional groups (methyl ester, ketone, nitrile) and proceeds at convenient temperatures (0–25 °C), in contrast to tmpMgCl·LiCl (**2**), which requires lower metalation temperatures. The resulting new functionalized diaryl manganese intermediates react with various electrophiles using Pd or Cu catalysis. Finally, these diaryl manganese reagents proved to be especially well-suited for oxidative aminations, thus allowing the preparation of polyfunctional amines. Extensions of these manganations to more complex unsaturated substrates are currently underway in our laboratories.

Experimental Section

5: An argon-flushed 25 mL Schlenk tube equipped with a magnetic stirring bar and septum was charged with a solution of **4** (290 mg, 2 mmol) in dry THF (1 mL) and cooled to 0 °C. A solution of **3** (0.5 M in THF, 2.4 mL, 2.4 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min. Then, PhCHO (254 mg. 2.4 mmol) was added at 0 °C and the mixture was stirred for another 1 h at 0 °C. After standard workup (addition of sat. NH$_4$Cl solution followed by extraction with diethyl ether), the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane/diethyl ether 1:1) to give **5** (390 mg, 77 %) as a colorless solid.

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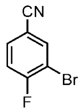
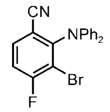
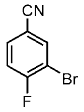
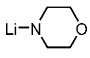
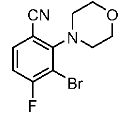
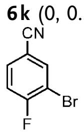
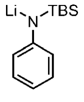
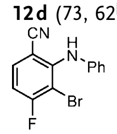
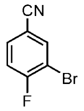
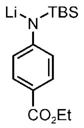
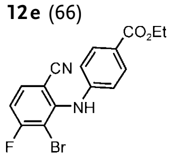
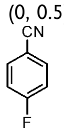
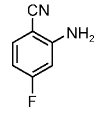
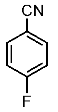
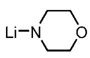
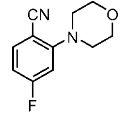
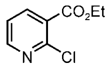
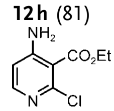
Keywords: amide bases · cross-coupling · directed metalation · manganese · oxidative amination

Table 2: Polyfunctional amines of type **12** obtained by the oxidative amination of diaryl manganese reagents with lithium amides mediated by chloranil.

No.	Substrate[a]	Lithium amide	Product[b]
1	 **6k** (0, 0.5)	LiNPh$_2$	 **12c** (66, 59[c])
2	 **6k** (0, 0.5)		 **12d** (73, 62[c])
3	 **6k** (0, 0.5)		 **12e** (66)
4	 **6k** (0, 0.5)		 **12f** (66[d])
5	 **6l** (25, 2)	LiN(SiMe$_3$)$_2$	 **12g** (75[e])
6	 **6l** (25, 2)		 **12h** (81)
7	 **9a** (0, 0.5)	LiN(SiMe$_3$)$_2$	 **12i** (65[e])

[a] The reaction conditions for the metalation with **3** are given in parantheses (T [°C], t [h]). [b] Yield [%] of isolated analytically pure product is given in parentheses. [c] Yield for the reaction with the corresponding Mg reagents (metalation with **2**). [d] Deprotection was performed using TBAF (1 equiv). [e] Deprotection was performed using TBAF (2 equiv).

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[20] See the Supporting Information for full experimental details.