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Preparation of Functionalized Organomanganese(II) Reagents by Direct Insertion of Manganese to Aromatic and Benzylic Halides

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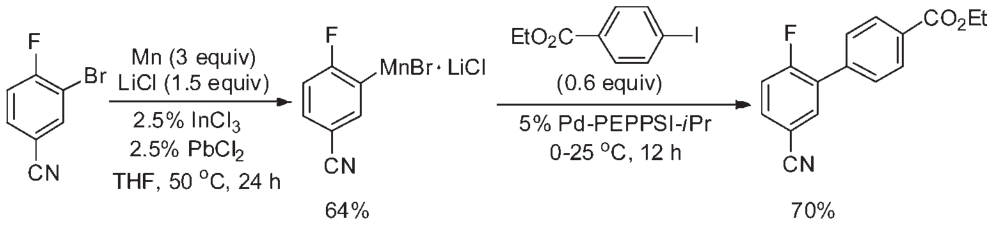
ABSTRACT



Functionalized arylmanganese compounds were prepared using commercial manganese powder in the presence of LiCl and catalytic amounts of both 2.5% $InCl_3$ and 2.5% $PbCl_2$ (THF, 0−50 °C). In addition, benzylic manganese reagents are obtained at 25 °C in ca. 70−80% yield (in the absence of LiCl) using commercial manganese powder and catalytic amounts of 2.5% $InCl_3$ and 2.5% $PbCl_2$. The resulting organomanganese reagents undergo smooth 1,2-addition, acylation, allylic substitution, Pd-catalyzed cross-coupling, and copper-catalyzed conjugate addition, affording the desired products in good yields.

Functionalized organometallics are versatile reagents for forming carbon−carbon bonds reactions in organic synthesis.[1] Organomanganese reagents,[2] because of their excellent chemoselectivity, low toxicity, and good availability, have found widespread applications for performing chemoselective 1,2-additions,[3] acylations,[4] cross-coupling reactions,[5] as well as copper-catalyzed conjugate additions.[6] Despite these advantages, the preparation methods of organomanganese(II) reagents are limited. Most organomanganese(II) reagents are prepared by transmetalation from the corresponding organolithium or organomagnesium reagents with manganese halides.[7] Recently, a directed manganation using $TMP_2Mn \cdot 2LiCl$ allowed the generation of the functionalized arylmanganese compounds by a directed deprotonation.[8] Moreover,

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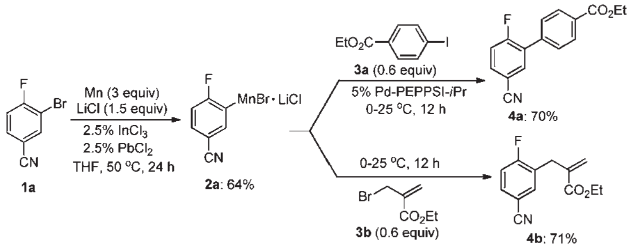
10.1021/ol201109g

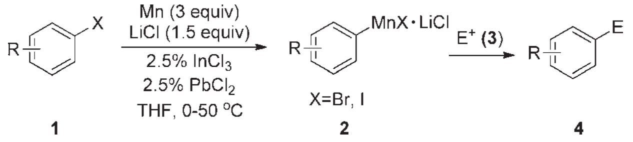
Scheme 1. Preparation of (5-Cyano-2-fluorophenyl)manganese(II) Bromide (**2a**) and Subsequent Reaction with Electrophiles

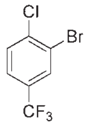
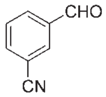
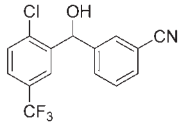
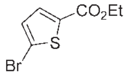
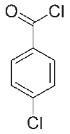
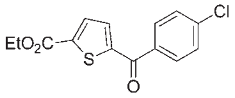
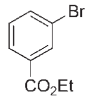
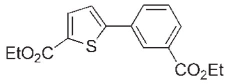
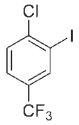
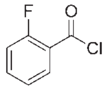
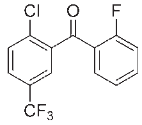
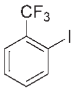
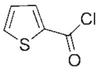
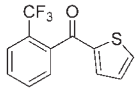
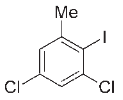
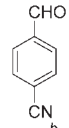
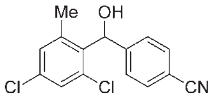
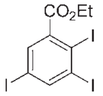
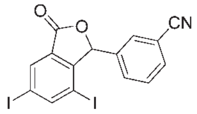
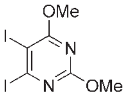
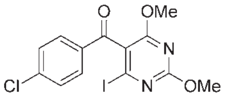
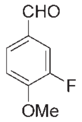
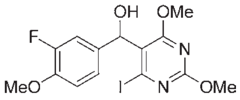


organomanganese(II) reagents are difficult to generate by an oxidative addition to organic halides using commercial manganese powder because of the passivation exhibited by commercial Mn. To date, commercial manganese powder inserts only into reactive organic halides such as allylic halides or α-halogenoesters.[9,10] By using highly activated Mn (Rieke-Mn), the insertion to aromatic and benzylic halides can be achieved.[11] Recently, we have reported that LiCl facilitates the insertion of various metals (Zn,[12] Mg,[13] In[14]). By adding small amounts of a metallic salt like $InCl_3$ and $PbCl_2$ as pioneered by Takai,[15] we were able to prepare functionalized aromatic, benzylic, and allylic aluminum reagents under mild conditions.[16]

Herein, we report a new preparation of aromatic and benzylic manganese reagents by a direct insertion of commercial manganese powder (99+%, ~325 mesh)[17] into organic halides in the presence of $PbCl_2$ (99.999%, 2.5 mol %)[17] and $InCl_3$ (anhydrous, 99.99%, 2.5 mol %).[17] Thus, the reaction of 3-bromo-4-fluorobenzonitrile (**1a**) in THF with manganese powder (3 equiv) in the presence of LiCl (99%, 1.5 equiv), 2.5% $InCl_3$, and 2.5% $PbCl_2$ at 50 °C was complete within 24 h and led to the corresponding arylmanganese reagent (**2a**) in 64% yield. Subsequent Negishi cross-coupling[18] with ethyl 4-iodobenzoate

Table 1. Functionalized Arylmanganese(II) Halides Obtained by Direct Insertion of Commercial Manganese Powder into Aromatic Halides and Subsequent Quenching with Electrophiles



entry	substrate	electrophile	product, yield[a]
1	 **1b**	 **3c**[b]	 **4c**: 73%
2	 **1c**	 **3d**[c]	 **4d**: 68%
3	**1c**	 **3e**[c]	 **4e**: 77%[d]
4	 **1d**	 **3f**[b]	 **4f**: 85%
5	 **1e**	 **3g**[b]	 **4g**: 74%
6	 **1f**	 **3h**[b]	 **4h**: 72%
7	 **1g**	**3c**[c]	 **4i**: 68%
8	 **1h**	**3d**[c]	 **4j**: 71%
9	**1h**	 **3i**[c]	 **4k**: 78%

[a] Isolated yield of analytically pure product. [b] 0.7 equiv of electrophile was used. [c] 0.6 equiv of electrophile was used. [d] Obtained after cross-coupling[18] with ethyl 3-bromobenzoate (**3e**) in the presence of Pd-PEPPSI-*i*-Pr[19] (5 mol %).

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(10) (a) Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373. (b) Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett.* **1996**, *37*, 7049.

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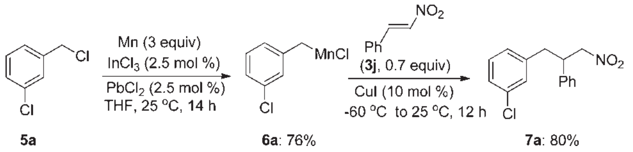
(17) The commercial suppliers are indicated in the Supporting Information.

Scheme 2. Preparation of (3-Chlorobenzyl)manganese(II) Chloride (**6a**) and Its 1,4-Addition with Nitrostyrene (**3j**)

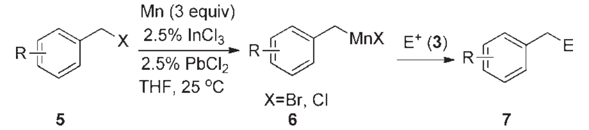


5a **6a**: 76% **7a**: 80%

(**3a**, 0.6 equiv) in the presence of Pd-PEPPSI-*i*-Pr[19] (5 mol %) afforded the biphenyl derivative **4a** in 70% yield. Additionally, a smooth allylic substitution of **2a** with ethyl (2-bromomethyl)acrylate (**3b**, 0.6 equiv) furnished the acrylate **4b** in 71% yield (Scheme 1). Both catalytic amounts of $InCl_3$ and $PbCl_2$ and a stoichiometric amount of LiCl are required for an efficient insertion reaction. By using only $InCl_3$ or only $PbCl_2$, only a trace of the arylmanganese species is formed. This salt combination allows a unique activation of the Mn surface.

Similarly, 2-bromo-1-chloro-4-(trifluoromethyl)benzene (**1b**) was converted to the corresponding organomanganese reagent **2b** (50 °C, 24 h, 72% yield). It readily underwent a 1,2-addition to 3-formylbenzonitrile (**3c**), providing the functionalized alcohol **4c** in 73% yield (entry 1, Table 1). Manganese powder inserted into the functionalized thiophene (**1c**) in the presence of LiCl (1.5 equiv), 2.5% $InCl_3$ and 2.5% $PbCl_2$ between 0 and 25 °C within 12 h, giving the arylmanganese reagent **2c** (70% yield). It was converted to the functionalized ketone derivative **4d** (68% yield) and the biaryl derivative **4e** (77% yield), respectively, by an acylation reaction with 4-chlorobenzoyl chloride (**3d**, 0.6 equiv) and a Pd-catalyzed cross-coupling[18] reaction with ethyl 3-bromobenzoate (**3e**, 0.6 equiv) (entries 2–3). In the same manner, various substituted aryl iodides such as **1d–f**, bearing substituents such as chloride or a trifluoromethyl group, were readily converted to the corresponding arylmanganese reagents at 25 °C within 12–24 h. Subsequent acylation and 1,2-addition afforded the expected polyfunctionalized adducts **4f–h** in 72–85% yield (entries 4–6). Remarkably, manganese powder chemoselectively inserted into ethyl 2,3,5-triiodobenzoate (**1g**), yielding (2-(ethoxycarbonyl)-4,6-diiodophenyl)manganese(II) iodide (**2g**). Its treatment with aldehyde **3c** (0.6 equiv) afforded the desired lactone **4i** in 68% yield

Table 2. Functionalized Benzylmanganese(II) Halides Obtained by Direct Insertion of Commercial Manganese Powder into Benzylic Halides and Subsequent Reaction with Electrophiles



5 **6** **7**

entry	substrate	electrophile	product, yield[a]
1	**5a**	**3h**[b]	**7b**: 73%
2	**5a**	**3d**[b]	**7c**: 75%
3	**5b**	**3k**[b]	**7d**: 88%
4	**5b**	**3l**[b]	**7e**: 74%
5	**5b**	**3m**[b]	**7f**: 84%[c]
6	**5c**	**3h**[b]	**7g**: 75%
7	**5c**	**3a**[b]	**7h**: 80%[d]
8	**5d**	**3d**[b]	**7i**: 67%
9	**5e**	**3c**[b]	**7j**: 66%
10	**5f**	**3b**[b]	**7k**: 70%
11	**5g**	**3m**[e]	**7l**: 71%[f]
12	**5g**	**3a**[e]	**7m**: 67%[g]
13	**5h**	**3b**[e]	**7n**: 45%

[a] Isolated yield of analytically pure product. [b] 0.7 equiv of electrophile was used. [c] Obtained after cross-coupling[18] with 4-bromobenzonitrile (**3m**) in the presence of $Pd(PPh_3)_4$ (10 mol %). [d] Obtained after cross-coupling[18] with ethyl 4-iodobenzoate (**3a**) in the presence of $Pd(PPh_3)_4$ (10 mol %). [e] 0.6 equiv of electrophile was used. [f] Obtained after cross-coupling[18] with ethyl 4-bromobenzonitrile (**3m**) in the presence of Pd-PEPPSI-*i*Pr[19] (5 mol %). [g] Obtained after cross-coupling[18] with ethyl 4-iodobenzoate (**3a**) in the presence of Pd-PEPPSI-*i*Pr[19] (5 mol %).

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(entry 7). Moreover, heterocyclic 4,5-diiodo-2,6-dimethoxypyrimidine[20] (**1h**) was converted selectively to the organomanganese reagent (**2h**) which underwent acylation and 1,2-addition, giving the functionalized benzophenone derivative **4j** and alcohol derivative **4k** in 71–78% yield (entries 8–9). This selective insertion of Mn powder was triggered by a chelation to the neighboring functional group.[21]

In the case of benzylic chlorides or bromides, a smooth manganese insertion proceeds at 25 °C in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$. These insertions proceed best in the absence of LiCl since this salt favors extensive homocoupling reactions. Thus, the reaction of 1-chloro-3-(chloromethyl)benzene (**5a**) with Mn powder (3 equiv) in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$ afforded the benzylic manganese reagent **6a** within 14 h at 25 °C. A Cu-catalyzed 1,4-addition reaction with nitrostyrene (**3j**, 0.7 equiv) provided the nitro derivative (**7a**) in 80% yield (Scheme 2).

A smooth addition of the benzylic manganese reagent **6a** to the benzaldehyde **3h** (0.7 equiv) generated the functionalized alcohol derivative **7b** in 73% yield (entry 1, Table 2). In addition, the treatment of the benzylic manganese reagent **6a** with 4-chlorobenzoyl chloride (**3d**, 0.7 equiv) produced the ketone derivative **7c** in 75% yield (entry 2). Several functionalized benzylic substrates (**5b–f**) readily underwent a manganese insertion in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$ as catalysts, followed by quenching with various electrophiles, affording the desired products **7d–k** in 66–88% yield (entries 3–10). However, the manganese insertion into benzylic chlorides bearing an ester and a cyano group led to unsatisfactory yields. In comparison, by using benzylic bromides, a smooth insertion proceeds at 25 °C, allowing the direct preparation of ester- or cyano-functionalized benzylmanganese bromides. For instance, the reaction of butyl 3-(bromomethyl) benzoate (**5g**) with Mn powder (3 equiv) in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$ furnished the benzylic manganese bromide **6g** within 17 h at 25 °C. A Pd-catalyzed cross-coupling[18] with 4-bromobenzonitrile (**3m**, 0.6 equiv) or ethyl 4-iodobenzoate (**3a**, 0.6 equiv) generated the expected products **7l–m** in 67–71% yield (entries 11–12). Similarly, 3-(bromomethyl)benzonitrile (**5h**) was converted to the corresponding benzylic manganese reagent **6h**, followed by an allylic substitution with ethyl (2-bromomethyl)acrylate (**3b**, 0.6 equiv), producing the allylated product **7n** in 45% yield (entry 13).

In summary, we have developed a convenient method for the preparation of functionalized arylmanganese halides and benzylic manganese halides by direct insertion of commercial manganese powder into aromatic and benzylic halides in the presence of 2.5% $InCl_3$ and 2.5% $PbCl_2$. These organomanganese reagents smoothly undergo 1,2-addition, acylation, allylic substitution, Pd-catalyzed cross-coupling, and copper-catalyzed conjugate addition with various electrophiles affording the desired products in good yields. Further studies of the substrate scope and on the role of LiCl, $InCl_3$, and $PbCl_2$ are currently underway in our laboratories.

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

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[21] For *ortho*-directed metalation, see: (a) Boudet, N.; Sase, S.; Sinha, P.; Liu, C.-Y.; Krasovskiy, A.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 12358. (b) See also ref 20.