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A Facile Synthetic Method for the Preparation of Benzylic Manganese Halides Using Highly Active Manganese and Their Coupling Reactions

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Most benzylic lithium reagents have been prepared via bond cleavage reactions[1] and/or transmetalation reactions.[2,3] Unfortunately, these methods are often accompanied by the formation of complex mixtures and homo-coupling products even at low temperature.[1]

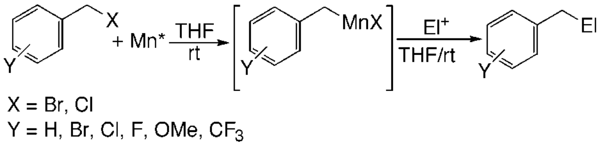
Other metals which undergo oxidative addition to benzylic halides are zinc[4] and cadmium.[5] Recently, an interesting new synthetic method for benzylic zinc reagent has been reported using triorganozincate.[6]

We, herein, report an alternative synthetic route for the direct formation of nonfunctionalized and functionalized benzylic manganese halides from highly reactive manganese and benzylic halides.[7]

Treatment of the highly active manganese (Mn*)[7,8] with benzyl halides (bromide and chloride) gave high yields of the corresponding benzylic manganese halides. The resulting benzylic manganese halides reacted readily with an appropriate electrophile to give the corresponding cross-coupled product. Significantly, the majority of these reactions were carried out without a transition metal catalyst. The environmental advantages are obvious.[9]

The oxidative addition of Mn* to benzyl halides was completed at room temperature in 20 min in THF (Scheme 1). Small amounts (3−9%) of homo-coupling product of benzyl halide were observed. This problem was improved by using more highly active manganese[10] prepared from manganese iodide. Trace amounts (less than 1%) of homocoupling product was formed in this case.

Scheme 1. Preparation and Coupling Reaction of Benzylic Manganese Halides



The cross-coupling reaction of the benzylic manganese halides with acid chlorides was carried out at room temperature in 2 h in THF. It is worthy to note that the coupling reaction was performed in the absence of any transition metal catalyst (except entry 14, Table 1). An excess of acid chloride was employed in this reaction to avoid the further reaction of the remaining benzylic manganese halides with the ketone formed. Both aryl and alkyl acid chlorides gave excellent yields (Table 1). As shown in Table 1, some functionalized benzylic manganese halides (entries 4−9, and 14, Table 1) have been obtained as well as nonfunctionalized ones (entries 1 and 2, Table 1). From these results, it can be inferred that the present conditions tolerate a wide range of functional groups attached to the benzyl halides. Of special interest is entry 8 in Table 1. Preparing organometallics with molecules containing a trifluoromethyl group can be problematic. However, **1g** was readily converted to the corresponding organomanganese reagent, and subsequent cross-coupling proceeded in excellent yield. The oxidative addition will tolerate an electron-withdrawing group such as a carbomethoxy group. In contrast to all the rest of the entries in Table 1, the manganese derivative of **1k** does not undergo cross-coupling in the absence of a catalyst. However, in the presence of CuI, product **2m** readily forms. The reason for this is not clear but may be the reduced nucleophilicity caused by the carbomethoxy group (entry 14, Table 1). The *p*-cyano derivative only leads to homocoupling under a wide variety of solvents and reaction conditions. Interestingly, treatment of Mn* with α,α′-dichloro-*m*-xylene and the consecutive coupling reaction with benzoyl chloride gave a symmetrical biaryl compound in 79% yield (entry 10, Table 1). The reason is not clear at this moment. Presumably, a competitive reaction occurred during the following cross-coupling reaction with benzoyl chloride. Unfortunately, in the reaction of **1j**, homo-coupling product **2l** was obtained during the oxidative addition. The benzylic manganese halides were found to add to several other electrophiles including aldehydes, ketones, and di-*tert*-butyl azodicarboxylate (DBAD). The results are summarized in Table 2. Addition to aldehydes (entries 1−4 and 7, Table 2) gave the corresponding secondary alcohols in good yields (78−93%) even with a bulky aldehyde (entry 8, Table 2). The reaction tolerated halides or a nitrile group in the aldehyde but not a nitro group (entry 10, Table 2). The addition to an alkyl ketone yielded the corresponding tertiary alcohol in good yield (entry 5, Table 2). Coupling with acetophenone was successful. However, yield was uncharacteristically low. Di-*tert*-butyl azodicarboxylate (DBAD) was also employed as an electrophile, and the corresponding coupling product **3i** was obtained in excellent yield (80%).

Benzylic manganese halides were also found to undergo palladium-catalyzed cross-coupling reactions with aryl iodides.[4a] As shown in Scheme 2, the corresponding coupling

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[1] (a) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (c) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1976**, *41*, 1184. (d) Gilman, H.; McNinch, H. A. *J. Org. Chem.* **1961**, *26*, 3723.

[2] (a) Clarembeau, M.; Krief, A. *Tetrahedron Lett.* **1985**, *26*, 1093. (b) Seyferth, D.; Suzuki, R.; Murphy, C. J.; Sabet, C. R. *J. Organomet. Chem.* **1964**, 431. (c) Gilman, H.; Rosenberg, S. D. *J. Org. Chem.* **1959**, *24*, 3.

[3] (a) van den Anker, T. R.; Harvey, S.; Raston, C. L. *J. Organomet. Chem.* **1995**, *502*, 35. (b) Bernardon, C. *J. Organomet. Chem.* **1989**, *367*, 11. (c) Harvey, S.; Junk, P. C.; Raston, C. L.; Salem, G. *J. Org. Chem.* **1988**, *53*, 3, 3134. (d) Gallagher, M. J.; Harvey, S.; Raston, C. L.; Sue, R. E. *J. Chem. Soc., Chem. Commun.* **1988**, 289. (e) Harvey, S.; Raston, C. L. *J. Chem. Soc., Chem. Commun.* **1988**, 652. (f) Itsuno, S.; Darling, G. D.; Stöver, H. D. H.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4644. (g) Raston, C. L.; Salem, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1702.

[4] (a) Betzemeier, B.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2623. (b) Rottländer, M.; Knochel, P. *Synlett*, **1997**, 1084. (c) Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623. (d) Chia, W.-L.; Shiao, M.-J. *Tetrahedron Lett.* **1991**, *32*, 2033. (e) Shing, T.-L.; Chia, W.-L.; Shiao, M.-J. Chau, T.-Y. *Synthesis* **1991**, 849. (f) Chen, H. G.; Hoechstetter, C.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4795. (g) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789.

[5] Burkhardt, E. R.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 416.

[6] Harada, T.; Kaneko, T.; Fujiwara, T.; Oku, A. *J. Org. Chem.* **1997**, *62*, 8966.

[7] (a) An attempt for the preparation of benzylic manganese reagent has been carried out using manganese powder, resulting in the formation of homocoupling product (89%), see: Hiyama, T.; Sawahata, M.; Obayashi, M. *Chem. Lett.* **1983**, 1237. (b) Use of manganese for the preparation of allylic manganese reagent, see: Hiyama, T.; Obayashi, M.; Nakamura, A. *Organometallics* **1982**, *1*, 1249.

[8] Typical procedure for the preparation of Mn*, see: Rieke, R. D.; Kim, S.-H.; Wu. X. *J. Org. Chem.* **1997**, *62*, 6921.

[9] For use of nontoxic manganese in chromium-catalyzed reaction, see: (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349.

[10] Different reactivity of Mn* depending on manganese halide, see: Kim, S.-H.; Rieke, R. D. *Synth. Commun.* **1998**, *28*, 1065.

[11] Goswami, S.; Mahapatra, A. K. *Tetrahedron Lett.* **1998**, *39*, 1981.

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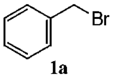
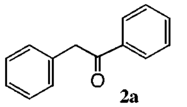
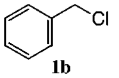
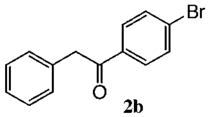
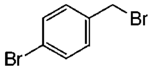
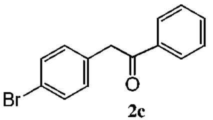
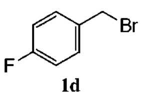
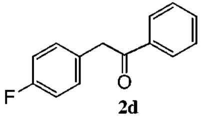
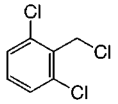
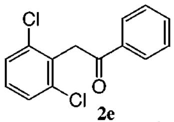
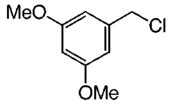
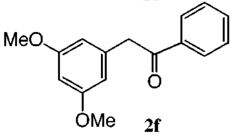
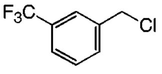
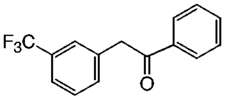
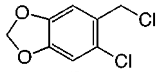
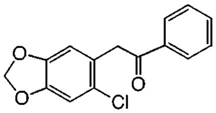
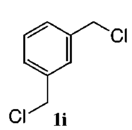
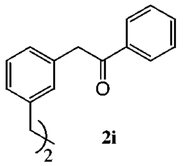
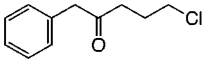
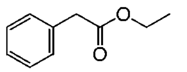
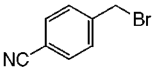
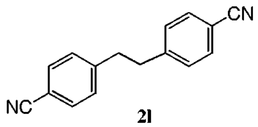
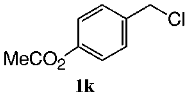
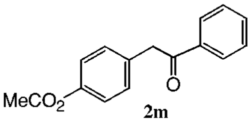
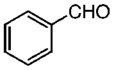
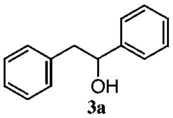
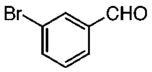
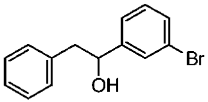
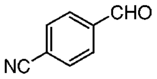
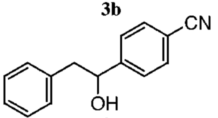
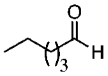
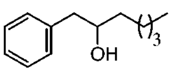
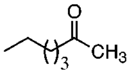
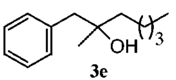
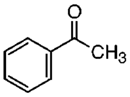
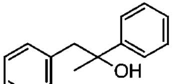
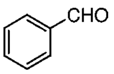
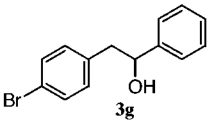
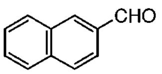
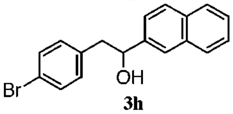
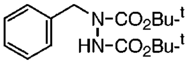
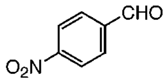
Table 1. Coupling Reaction with Acid Chlorides[a]

Entry	Halide	Electrophile[b]	Product[c]	Yield(%)[d]
1	 **1a**	**I**	 **2a**	82
2	 **1b**	**I**	**2a**	91
3	**1b**	**II**	 **2b**	85
4	 **1c**	**I**	 **2c**	84
5	 **1d**	**I**	 **2d**	74
6	 **1e**	**I**	 **2e**	75
7	 **1f**	**I**	 **2f**	86
8	 **1g**	**I**	 **2g**	71
9	 **1h**	**I**	 **2h**	89
10	 **1i**	**I**	 **2i**	79
11	**1a**	**III**	 **2j**	78
12	**1b**	**IV**	 **2k**	69
13	 **1j**	-	 **2l**	82[e]
14	 **1k**	**I**	 **2m**	75[f]

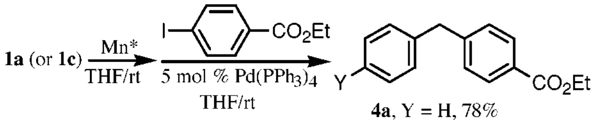
[a] Oxidative addition reaction and coupling reaction were carried out at room temperature in THF. [b] Electrophile: **I** = benzoyl chloride, **II** = *p*-bromobenzoyl chloride, **III** = 4-chlorobutyryl chloride, **IV** = ethyl chloroformate. [c] All products were fully characterized by ^{1}H and ^{13}C NMR and HRMS (or EIMS). [d] Isolated yield (based on benzyl halides). [e] For recent example of homocoupling product, see ref 11. [f] 5 mol % CuI was used as a catalyst.

Table 2. Cross-Coupling Reaction of Benzylic Manganese Halides[a]

Entry	Halide	Electrophile	Product[b]	Yield(%)[c]
1	**1a**		 **3a**	93
2	**1a**		 **3b**	95
3	**1a**		 **3c**	87
4	**1a**		 **3d**	78
5	**1a**		 **3e**	72
6	**1a**		 **3f**	46
7	**1c**		 **3g**	80
8	**1c**		 **3h**	89
9	**1a**	$(t\text{-BuO}_2\text{C}{-}\text{N}{=})_2$	 **3i**	80
10	**1a**		–	0[d]

[a] Oxidative addition reaction and coupling reaction were carried out at room temperature in THF. [b] All products were fully characterized by ^{1}H and ^{13}C NMR and HRMS (or EIMS). [c] Isolated yield (based on electrophile). [d] According to TLC analysis, no coupling reaction occurred.

Scheme 2. Palladium-Catalyzed Coupling Reaction



4a, Y = H, 78%
4b, Y = Br, 56%

compounds **4a** and **4b** were achieved in moderate to good yields (56% and 78%, respectively) using 5 mol % palladium catalyst (Pd(PPh$_3$)$_4$) in THF at room temperature.

In summary, a facile route to benzylic manganese reagents has been developed. The starting benzylic halide can contain a wide variety of substituents, and the subsequent cross-coupling proceeds with good to excellent yields with several electrophiles.

Acknowledgment. We are grateful to the National Science Foundation for support of this work.

Supporting Information Available: Experimental details and characterization of **2a**–**m** and **3a**–**i** (6 pages).

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