C–H Activation

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Manganese-Catalyzed Insertion of Aldehydes into a C–H Bond**

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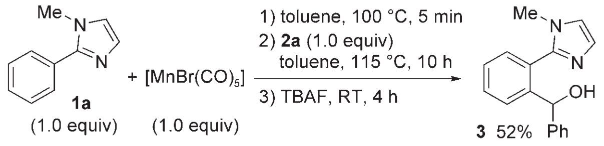
Transition metals of the fourth row are abundant and cheap compared to those of the fifth and sixth rows. Therefore, by introducing new reactivities with fourth-row metal complexes, it might be possible to replace fifth- and sixth-row metals in some fundamental and important reactions. Catalytic Grignard-type addition of nucleophiles to aldehydes is one such reaction. Grignard reagents are usually prepared from organic halides and magnesium metal,[1] but this procedure results in the unwanted formation of stoichiometric amounts of metal salts. One way to solve this problem is to generate the nucleophiles by C–H bond activation;[2] however, it has been difficult to promote nucleophilic addition after the C–H activation step. Although nucleophilic addition of species generated by C–H activation has been reported using ruthenium,[3] rhodium,[4] palladium,[5] and rhenium[6] catalysts, it has been difficult to catalyze such reactions using fourth-row transition-metal complexes.[7] We report herein that 1) complexes of manganese, a fourth-row transition metal, can be employed for C–H bond activation of aromatic compounds; 2) insertion of aldehydes into C–H bonds occurs to give benzyl alcohols; and 3) catalytic transformation is achieved with the manganese complex by the addition of Et_3SiH.

We initially investigated stoichiometric C–H bond activation and insertion of aldehydes with the manganese complex $[MnBr(CO)_5]$. A mixture of 1-methyl-2-phenyl-1*H*-imidazole (**1a**) and $[MnBr(CO)_5]$ in toluene was heated at 100°C for 5 min, at which point a solution of benzaldehyde (**2a**) was added. The mixture was heated at reflux for 10 h to give alcohol **3** in 52% yield (Scheme 1). Although stoichiometric C–H bond activation and insertion of the aldehyde occured with $[MnBr(CO)_5]$, only a trace amount of **3** was produced with a catalytic amount of the manganese complex.

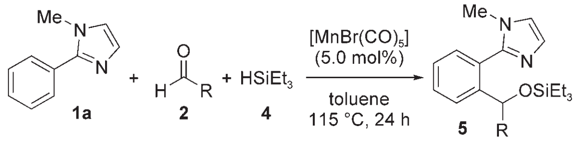


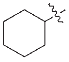
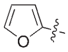
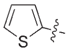
Scheme 1. Stoichiometric insertion of aldehyde into a C–H bond. TBAF = tetra-*n*-butylammonium fluoride

To recycle the manganese complex, 2.0 equiv of triethylsilane (**4**) was added to the reaction mixture from the beginning. As a result, silyl ether **5a** was obtained in 93% yield with 5 mol% $[MnBr(CO)_5]$.[8,9] We examined the catalytic activity of several metal complexes using the reaction between **1a**, **2a**, and **4** as a probe. A different manganese complex, $[Mn_2(CO)_{10}]$, showed similar catalytic activities (82% yield of **5a**). However, the reaction did not proceed at all with the following metal complexes: $[MnCl_2]$, $[Mn(acac)_3]$ (acac = acetylacetonate), $[\{ReBr(CO)_3(thf)\}_2]$,[6] $[ReBr(CO)_5]$, $[Ru_3(CO)_{12}]$, $[RuH_2(CO)(PPh_3)_3]$, $[RhCl(PPh_3)_3]$, and $[Ir_4(CO)_{12}]$.[10]

At the next stage, we investigated several aldehydes (Table 1). Aromatic aldehydes with an electron-donating or an electron-withdrawing group at the *para* position (**2b** and **2c**) gave the corresponding silyl ethers in 87% yield (Table 1, entries 1 and 2). Using an aldehyde with a methyl group at the *ortho* position (**2d**), the yield of the silyl ether slightly decreased, probably because of the steric hindrance (Table 1, entry 3). By the reactions of alkyl aldehydes **2e** and **2f**, the corresponding silyl ethers **5e** and **5f** were formed in 75% and

Table 1: Reactions between **1a** and several aldehydes.[a]



Entry	Substrate	R	Product	Yield [%][b]
1	**2b**	p-(MeO)C_6H_4	**5b**	87 (89)
2	**2c**	p-$(CF_3)C_6H_4$	**5c**	87 (89)
3	**2d**	o-MeC_6H_4	**5d**	59 (60)
4[c]	**2e**	nC_8H_{17}	**5e**	75 (79)
5[c]	**2f**		**5f**	56 (57)
6[d]	**2g**		**5g**	66 (67)
7	**2h**		**5h**	48 (50)

[a] **2** (2.0 equiv); **4** (2.0 equiv). [b] Yield of isolated product. The yield determined by ^1H NMR spectroscopy is reported in parentheses. [c] 135°C. [d] 48 h.

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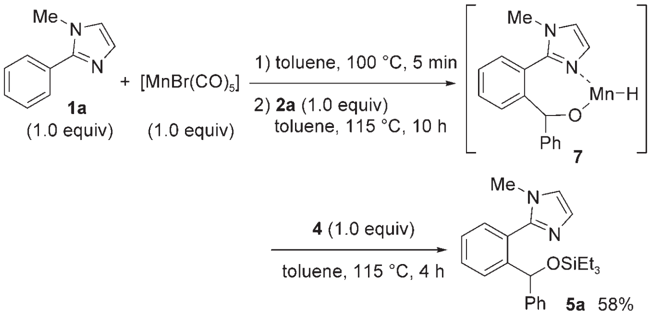
56 % yields, respectively (Table 1, entries 4 and 5). Heteroaromatic aldehydes **2g** and **2h** also provided the corresponding silyl ethers **5g** and **5h** in moderate yields (Table 1, entries 6 and 7).

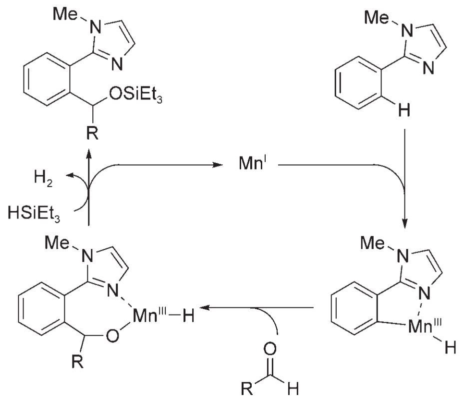
To determine the reaction mechanism, we examined the sequential transformation via intermediate **7** (Scheme 2).



Scheme 2. Manganese-mediated insertion of aldehyde into a C–H bond.

Treatment of **1a** with a stoichiometric amount of the manganese complex in toluene at 100 °C for five minutes, followed by addition of benzaldehyde (**2a**) and heating to reflux for ten hours gave the possible intermediate **7**. Then hydrosilane **4** was added to the reaction mixture and further heating resulted in the formation of silyl ether **5a** in 58 % yield. This result indicates that hydrosilane **4** promotes reductive elimination of manganese by silylation of an alkoxy moiety.

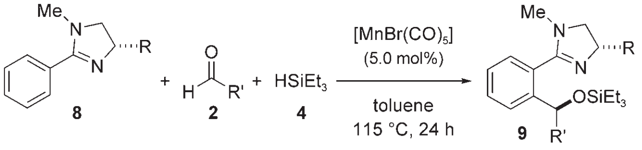
The proposed mechanism is as follows (Scheme 3): 1) oxidative addition of an aromatic compound to a manganese center (C–H bond activation);[11] 2) insertion of an aldehyde into the manganese–carbon (aryl) bond. In this step, the polarity of the manganese–carbon bond is an important factor affecting the insertion of the aldehyde (a polar molecule) into the C–MnH bond; 3) silyl protection via the formation of dihydrogen.



Scheme 3. Proposed mechanism for the formation of silyl ethers.

This reaction could also be applied to asymmetric transformation.[12] By the reaction of chiral imidazolines **8a** and **8b** and benzaldehyde (**2a**) with triethylsilane (**4**) in the presence of manganese catalyst [MnBr(CO)$_5$], an asymmetric reaction proceeded, and a mixture of diastereomers of silyl ethers **9a** and **9b**, respectively, was obtained in moderate diastereomeric excess (Table 2, entries 1 and 2). When we used imidazoline **8c** bearing an isopropyl group at the stereogenic center, the corresponding silyl ether **9c** was provided in high yield and diastereomeric excess (Table 2, entry 3). Using alkyl aldehyde **2e**, the diastereomeric excess of silyl ether **9d** decreased to 38 % (Table 2, entry 4).

Table 2: Asymmetric reactions of chiral imidazoline **8** with **2** and **4**.[a]



Entry	R	R′	Yield of product [%][b]		*de* [%]
1	Ph (**8a**)	Ph (**2a**)	**9a**	60	60
2	PhCH$_2$ (**8b**)	Ph (**2a**)	**9b**	72	30
3	*i*Pr (**8c**)	Ph (**2a**)	**9c**	80	95
4	*i*Pr (**8c**)	*n*C$_8$H$_{17}$ (**2e**)	**9d**	68	38

[a] **2** (2.0 equiv); **4** (2.0 equiv). [b] Yield of isolated product.

In summary, we have succeeded in the insertion of an aldehyde into a C–H bond of an aromatic compound using a manganese catalyst, [MnBr(CO)$_5$]. In this reaction, the polarity of the manganese–carbon bond in the intermediate manganese complex is an important factor for promoting the insertion of aldehydes (polar molecules) into the C–H bond. This reaction could be applied to asymmetric transformation using an aromatic compound with a chiral substituent. Further insertion reactions, promoted by manganese complexes, of polar molecules into a C–H bond are currently being investigated.

Experimental Section

A mixture of aromatic compound **1** or **8** (0.250 mmol), aldehyde **2** (0.500 mmol), hydrosilane **4** (0.500 mmol), [MnBr(CO)$_5$] (3.4 mg, 0.0125 mmol), and toluene (1.0 mL) was stirred at 115 °C for 24 h. The product was isolated by column chromatography on silica gel, using hexane/ethyl acetate 3:1 as eluent, to give **5** or **9**.

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Keywords: aldehydes · asymmetric synthesis · C–H activation · manganese · silyl ethers

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[1] For a book of Grignard reactions, see: *Grignard Reagents: New Developments* (Ed.: H. G. Richey), Wiley, New York, **2000**; *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**.

[2] For a review, see: a) F. Kakiuchi, S. Murai, *Top. Organomet. Chem.* **1999**, *3*, 47–79; b) Y. Guari, S. Sabo-Etiienne, B. Chaudret, *Eur. J. Inorg. Chem.* **1999**, 1047–1055; c) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.*

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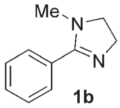
[6] a) Y. Kuninobu, Y. Tokunaga, A. Kawata, K. Takai, *J. Am. Chem. Soc.* **2006**, *128*, 202 – 209; b) Y. Kuninobu, Y. Nishina, M. Shouho, K. Takai, *Angew. Chem.* **2006**, *118*, 2832 – 2834; *Angew. Chem. Int. Ed.* **2006**, *45*, 2766 – 2768; c) Y. Kuninobu, Y. Nishina, C. Nakagawa, K. Takai, *J. Am. Chem. Soc.* **2006**, *128*, 12376 – 12377.

[7] Nucleophilic addition with fourth-row metal complexes by catalytic C–H activation is still rare. However, there are several examples of the insertion of nonpolar unsaturated molecules initiated by C–H fission with complexes of fourth-row metals, see: a) Co: G. Halbritter, F. Knoch, H. Kisch, *J. Organomet. Chem.* **1995**, *492*, 87 – 98; b) Ni: Y. Nakao, K. S. Kanyiva, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 8146 – 8147.

[8] Investigation of hydrosilanes: triethylsilane 93 %; diethylmethylsilane 59 %, dimethylphenylsilane 53 %; triphenylsilane 77 %. This reaction did not proceed using the following silanes: diphenylsilane, tris(trimethylsilyl)silane, hexamethyldisilane, hexamethyldisilazane.

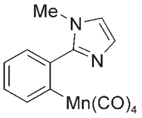
[9] 4,5-Dihydro-1-methyl-2-phenyl-1*H*-imidazole **1b** also afforded the corresponding silyl ether **6** in 72 % yield.



1b

[10] For iridium-catalyzed coupling of imidazoles with aldehydes in the presence of a hydrosilane, see: Y. Fukumoto, K. Sawada, M. Hagihara, N. Chatani, S. Murai, *Angew. Chem.* **2002**, *114*, 2903 – 2905; *Angew. Chem. Int. Ed.* **2002**, *41*, 2779 – 2781.

[11] Another possibility is that the reaction is catalyzed by only a manganese(I) species. There has been a report on the formation of manganese(I) complex **10** by treatment of **1a** with [Mn$(CH_3)(CO)_5$], see: A. Suárez, J. M. Vila, M. T. Pereira, E. Gayoso, M. Gayoso, *J. Organomet. Chem.* **1987**, *335*, 359 – 363. We examined the reaction between **1a**, **2a**, and **4** using [Mn$(CH_3)(CO)_5$] as a catalyst. We found that the reaction proceeded, and **5a** was obtained in 85 % yield. This result indicates that the active species of the reaction would be Mn^I. However, in the reaction reported herein, the active species derived from [$MnBr(CO)_5$] will not be the same as that derived from [$Mn(CH_3)(CO)_5$]. Therefore, it is still not clear whether the real active species is Mn(I) or Mn(III), and further investigation is required.



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[12] For an example of transition-metal-catalyzed enantioselective functionalization via C–H bond activation, see: S. J. O'Malley, K. L. Tan, A. Watzke, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2005**, *127*, 13496 – 13497.