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Manganese-Catalyzed Hydrogenation of Esters to Alcohols

Noel Angel Espinosa-Jalapa, Alexander Nerush, Linda J. W. Shimon, Gregory Leitus, Liat Avram, Yehoshoa Ben-David and David Milstein.[*]

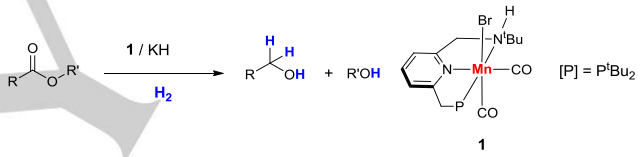
Abstract: *Homogeneous catalytic hydrogenation of esters to alcohols is an industrially important, environmentally benign reaction. While precious metal-based catalysts for this reaction are now well known, only very few catalysts based on first-row metal complexes were reported. Here we present the hydrogenation of esters catalyzed by a complex of earth-abundant manganese. The reaction proceeds under mild conditions and insight into the mechanism is provided based on an NMR study and the synthesis of novel Mn complexes postulated as intermediates.*

Ester hydrogenation represents one of the most important industrial processes for the production alcohols, with applications in cosmetics, pharmaceuticals and in the production of biodiesel.[1] Traditional reduction of esters generally involves the use of stoichiometric amounts of hydride reagents, generating large amounts of hazardous waste.[2] Industrial hydrogenation of esters involves high pressure and temperature.[3] In recent years, several homogeneous catalysts based on precious-metals, such as ruthenium[4] and osmium[5] were developed for ester hydrogenation, mostly under mild conditions.

The development of earth-abundant first-row transition metal-based catalysts for chemical transformations is of much current interest.[6] In this context, very few examples of ester hydrogenation based on earth-abundant metals were reported. Pincer-type complexes, which operate by metal-ligand cooperation (MLC)[7] are particularly attractive for this purpose, since bond activation in such systems proceeds without formal change in the metal oxidation state, obviating the tendency of first row metal to undergo one electron processes, as opposed to two-electron processes common for second- and third-row metals. In 2014 we reported hydrogenation of trifluoroacetic esters, by a PNP iron pincer complex *trans*-[Fe(PNP)$(H)_2$(CO)] (PNP = 2,6-bis(di-*tert*-butylphosphinomethyl)pyridine).[8a] As demonstrated, the reaction proceeds by an outer-sphere mechanism through nucleophilic attack of a hydride ligand on the ester carbonyl group.[7d, 8a] Shortly after, Beller[8b] and Guan[8c] independently reported broad-scope hydrogenation of non-activated esters catalyzed by an iron aliphatic pincer complex [Fe(PNHP)(H)(CO)(BH_4)] with no added base. We have reported recently hydrogenation of esters by a PNNH cobalt pincer complex [Co(PNNH)$(Cl)_2$] (PNNH = N-((6-((di-tert-butylphosphanyl)methyl)pyridine-2-yl)methyl)propan-2-amine) in the presence of $NaHBEt_3$.[8d] In this case, a mechanism involving C=C hydrogenation of an ester enolate intermediate was shown to take place. Co-catalyzed hydrogenation of carboxylic acids and esters was recently reported by Elsevier, de Bruin and co-workers.[8e]

Although manganese is third only to Fe and Ti in earth abundance, catalytic reactions based on manganese complexes are less exploited.[6a, 9] Particularly, hydrogenation and dehydrogenation reactions catalyzed by well defined manganese complexes are very rare. We recently reported the first example of a catalytic Michael addition reaction of nitriles to carbonyl compounds[9a] and the first dehydrogenative coupling of alcohols and amines to form imines and H_2 catalyzed by a PNP pincer manganese complex [Mn(PNP*)$(CO)_2$] (the asterisk denotes the dearomatized ligand).[9b] Recently Kirchner reported the coupling of alcohols and amines to form imines catalyzed by a series of manganese pincer complexes, which are stabilized by a PNP ligand based on the 2,6-diaminopyridine scaffold[9c] and Beller reported the hydrogenation of nitriles, ketones and aldehydes with an aliphatic PNHP-type hydride manganese pincer complex [Mn(PNHP)(H)(Br)$(CO)_2$][9d,e]

Herein, we report the hydrogenation of esters catalyzed by a manganese complex (Scheme 1).



Scheme 1. Ester hydrogenation reported in this study.

Complex **1** is readily obtained upon stirring of a solution of the PNNH ligand and [Mn$(CO)_5$Br] in THF for 60 hours at room temperature. Subsequent concentration of the reaction mixture and precipitation from THF by addition of diethyl ether yields complex **1** as an orange powder. The IR spectrum of **1** exhibits two strong absorption bands at 1828 (ν_{asym}) and 1909 cm^{-1} (ν_{sym}) in 1:1 ratio in agreement with two carbonyls in *cis* position. The $^{31}P\{^1H\}$ NMR spectrum shows a singlet at 118.7 ppm. Single crystals suitable for X-ray analysis were obtained by slow diffusion of pentane into a concentrated solution of complex **1** in CH_2Cl_2.[10] The PNNH pincer ligand binds to the metal center in a meridional fashion with the two carbonyl ligands located *cis* to each other (C – Mn – C = 86.25°), and the bromide in an axial position, completing a distorted octahedral coordination sphere (see Supporting Information (SI)).

Recently our group reported the synthesis and reactivity of a series of analogous [Ru(PNNH)(CO)(H)(Cl)] pincer complexes, which showed exceptional reactivity in hydrogenation and dehydrogenation processes.[4a] Exploring the catalytic activity of the PNNH complex **1**, attempted hydrogenation of hexyl hexanoate under 20 bar of H_2 and catalyst loading of 1 mol% in toluene was not successful (Table 1, Entry 1). However, addition of a base (2 mol%), under the same conditions did result in hexanol formation. Using of *t*BuOK or potassium bis(trimethylsilyl)amide, hexanol was obtained in 31% and 54% yields, respectively (Entries 2, 3). When KH was used as a base, full conversion to hexanol was observed under the same conditions (Entry 4). We have observed that, when preparing the reaction mixture at room temperature,

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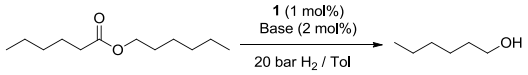
addition of *t*BuOK or KHMDS resulted in a dark green color, in line with ligand deprotonation, as previously observed with the analogous PNNH ruthenium complexes upon deprotonation.[4a] In contrast, no color change was observed at room temperature upon addition of KH, due to its insolubility under these conditions. The lack of immediate reaction with the precatalyst at ambient temperature, can be a practical advantage, avoiding handling the more sensitive active catalyst. Moreover, using KH does not generate a conjugate base in solution, avoiding potential side reactions.

Table 1. Base optimization for manganese-catalyzed hydrogenation of hexyl hexanoate.

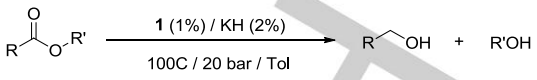


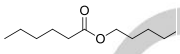
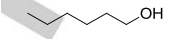
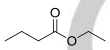
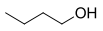
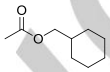
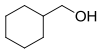
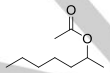
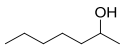
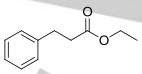
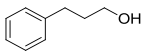
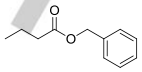
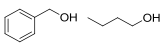
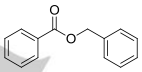
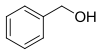
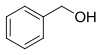
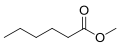
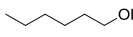
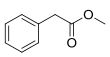
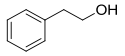
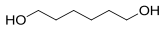
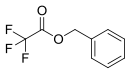
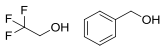
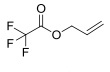
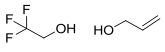
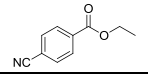
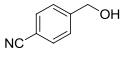
Entry	Base	Time (h)	Conv (%)[a]	Yield (%)[a]
1	-	22	-	-
2	*t*BuOK	22	39	31
3	KHMDS	23	55	54
4	KH	23	99	99

Reaction conditions: substrate (1.0 mmol), toluene (1.0 mL), internal standard (xylene, 1 mmol), 100°C. [a] Products confirmed by GC-MS. Conversions and Yields were determined by ^{1}H NMR with an internal standard (xylene).

Next, the scope of the reaction was examined with various esters using the precatalyst [Mn(PNNH)(CO)$_2$(Br)] (**1**) (1 mol%) and KH (2 mol%) (Table 2). Thus, hydrogenation of 1 mmol of hexyl hexanoate under 20 bar H_2 at 100°C in toluene, resulted in 99% yield of hexanol (Entry 1). Under the same conditions ethyl butyrate was hydrogenated to give 98% yield of butanol and 91% yield of ethanol after 50 hours (Entry 2). Since no other compounds than butanol and ethanol were detected by GC-MS and ^{1}H-NMR, the lower yield of ethanol is attribute to losses due to its volatility.. When the reaction was performed at shorter reaction time (22 hours, Table S3, Entry 2*bis*, see SI), small amounts of ethyl acetate and butyl butanoate were also formed, attributed to a transesterification reaction with the formed ethanol and butanol. Cyclohexylmethyl acetate gave 99% yield of cyclohexylmethanol (Entry 3), and no transesterification products were observed. Hydrogenation of the secondary aliphatic ester heptan-2-yl acetate resulted in 98% yield of heptane-2-ol (Entry 4). Ethyl 3-phenylpropanoate was smoothly hydrogenated, rendering 99% yield of 3-phenylpropan-1-ol after 21 hours (Entry 5). Similarly, ethyl 3-phenylpropanoate gave 99% yield of phenylmethanol and 90% yield of butanol after 22 hours (Entry 6). In order to get full hydrogenation of benzyl benzoate longer reaction time was needed (43 hours, 99% yield benzyl alcohol, Entry 7). Methyl esters were also hydrogenated. Methyl benzoate gave 96% yield of benzyl alcohol after 50 hours (Entry 8). Similarly, methyl hexanoate gave 94% yield of hexanol after 28 hours (Entry 9) and 1% of hexyl hexanoate, attributed to a transesterification reaction with the formed hexanol (Table S3, Entry 9, see SI). Methyl phenylpropanoate gave 99% of phenethyl alcohol after 28 hours (Entry 10)

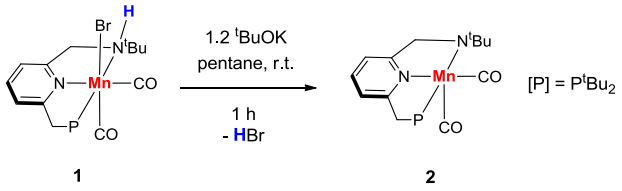
Table 2. Catalytic hydrogenation of esters using the manganese precatalyst **1**.



Entry	Ester	*t* [h]	Conv (%)[a]	Alcohol	Yield [%][b]
1		23	99		99
2[b]		50	99		98
3[b]		43	99		99
4[b]		43	99		98
5[b]		21	99		99
6		22	99		99 / 9
7		43	99		99
8[b]		50	99		98
9[b]		28	95		94
10[b]		28	99		99
11		36	99		98[c]
12		28	99		78 / 9
13[d]		60	99		97 / 9
14[b, e]		60	75		60

Reaction conditions: substrate (1.0 mmol), toluene (1.0 mL), internal standard (xylene, 1 mmol), 100°C. [a] Conversions and Yields were determined by ^{1}H NMR with an internal standard (xylene). Products confirmed by GC-MS. [b] Yields of methanol and ethanol are not reported (see SI). [c] The diol is insoluble in the reaction mixture. Isolated yield. [d] No hydrogenation of the vinyl group was observed. [e] **1** (3%)/KH (6%). No hydrogenation of the nitrile group was detected.

. ε-Caprolactone was smoothly and quantitatively hydrogenated to 1,6-hexanediol (98% yield, Entry 11). The activated benzyl trifluoroacetate gave 99% yield of benzyl alcohol and 78% of 2,2,2-trifluoroethanol (Entry 12), and no secondary products where observed. Gratifyingly, allyl trifluoroacetate gave 97% yield of 2,2,2-trifluoroethanol and 96% of allyl alcohol (Entry 13), showing high chemoselectivity to ester hydrogenation over C=C hydrogenation. Hydrogenation of ethyl 4-isocyano-benzoate required an increase of precatalyst loading to 3%, probably due to competing nitrile coordination, and resulted in 61% yield of (4-isocyanophenyl)methanol, with no hydrogenation of the nitrile group detected **(**Entry 14).



1 **2**

Scheme 2. Synthesis of the amido [Mn(PNN)(CO)$_2$] pincer complex **2**.

Mechanistically, the fact that benzyl benzoate and methyl benzoate undergo hydrogenation indicate that ester enolate intermediates are not involved in the catalysis, unlike the case of cobalt-catalyzed hydrogenation of esters.[8d] Aiming at gaining insight regarding the nature of the active catalyst, deprotonation of **1** was performed. In principle, both deprotonation of the benzylic position, leading to dearomatization of the pyridine ring, as well as deprotonation of the N-H bond, are possible.[4a] Upon addition of 1.2 equivalents of *t*BuOK to a suspension of **1** in pentane the solution became dark blue, yielding the novel amido [Mn(PNN)(CO)$_2$] complex **2** (Scheme 2). After filtration, the pentane solution was stored at -18 °C, forming dark crystals of pure complex **2**. The IR spectrum of **2** (NaCl plates) shows two strong bands at 1797 (ν_{asym}) and 1874 cm-1 (ν_{sym}) in 1:1 ratio, indicating a 90° C-Mn-C angle. The $^{31}P\{^1H\}$ NMR spectrum shows a singlet at 135.0 ppm, downfield shifted by ~ 16 ppm in comparison with **1**. The ^1H NMR spectrum of **2** exhibits only two distinct resonances in the aromatic regime. Two resonances are observed in ^1H NMR for the protons at the two benzylic positions; a singlet at 4.53 ppm and a doublet at 3.08 ppm in 1:1 ratio (Figure S5, see SI). This unexpected behavior is attributed to a dynamic exchange process as confirmed by a VT-NMR experiment. As described previously, a solution of complex **2** in [D$_8$]Tol exhibits two resonances in ^1H NMR for the protons at the two benzylic positions at 298K. At 248K the peaks coalesced and at 222K there is slow exchange, rendering two broad doublet at 4.42 and 2.79 ppm (Figure S7, see SI) due to the diasterotopicity of the protons at the benzylic positions. No resonance due to the N–H proton was observed, indicating deprotonation of the amine group. Two resonances are observed for the carbonyl ligands in the $^{13}C\{^1H\}$ NMR spectrum at 212.9 ppm and 207.8 ppm. X-ray diffraction of single crystal of **2** (Figure 1) show meridional coordination of the deprotonated PNNH pincer ligand.[10] Both carbonyl ligands are located mutually *cis* (C20–Mn–C21 = 87.22°), completing a distorted square pyramidal coordination sphere. The C – C bond lengths of the pyridine ring are almost equal, confirming that no de-aromatization of the pyridine ring occurred, in line with no deprotonation of the benzylic position. The Mn-N amido bond (1.889 Å) is significantly shorter from Mn-amine bond (2.171 Å) in **1,** confirming the amine – amide conversion upon deprotonation.

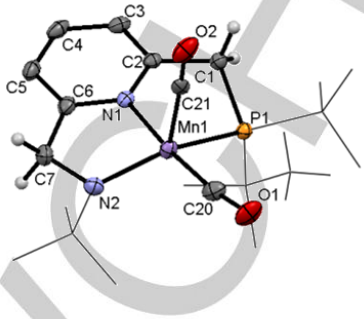
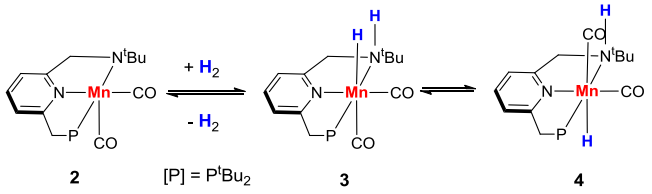


Figure 1. ORTEP diagram of [Mn(PNN)(CO)$_2$] (**2**) with thermal ellipsoids at 30% probability. The P(^{t}Bu)$_2$ and N^{t}Bu groups are drawn as wire frames, and the hydrogen atoms are partially omitted for clarity. Selected bond lengths (Å): Mn1 – C20 = 1.775(2), Mn1 – C21 = 1.822(2), Mn1 – N1 = 2.018(2), Mn1 – N2 = 1.889(2), Mn1 – P1 = 2.2622(6), C1 – C2 = 1.501(3), C6 – C7 = 1.492(3), C1 – P1 = 1.850(2), C7 – N2= 1.464(3). Selected bond angles (°): P1 – Mn1 – N1 = 80.64(5), P1 – Mn1 – N2 = 141.76(6), N1 – Mn1 – C20 = 173.08(8), N1 – Mn1 – C21 = 92.65(7), N2 – Mn1 – C20 = 104.86(8), N2 – Mn1 – C21 = 117.02(8), C20 – Mn1 – C21 = 87.22(9).[10]

Exploring the catalytic activity of the novel amido complex **2** (1 mol%), hydrogenation of hexyl hexanoate under 20 bar H_2 at 100 °C in toluene *in the absence of base* gave 96% yield of hexanol after 22 hours, showing comparable catalytic activity as with the catalyst prepared *in situ* from the PNNH complex **1** and catalytic base (Table 1, Entry 1), indicating that **2** is the catalytically active complex.

To gain more mechanistic insight, NMR investigations were carried out using complex **2**. Under H_2 atmosphere (1 bar) at room temperature, in an NMR Young tube, complex **2** in C_6D_6 reversibly adds H_2 to yield, after 10 min, a mixture of the hydride complex **3** and complex **2** in a ratio of **2** : **3**, 1.0 : 0.6, as determined by $^{31}P\{^1H\}$ NMR (see SI). The hydride resonance appears at -1.71 ppm (d, $^2J_{PH}$ = 52.7 Hz) in ^1H NMR and it shows a singlet at 143.4 ppm in the $^{31}P\{^1H\}$ NMR spectrum, 7.6 ppm downfield shifted in comparison with complex **2.** Complex **3** slowly isomerizes to yield the hydride complex **4**. Complex **4** exhibit a hydride resonance at -1.34 ppm (d, $^2J_{PH}$ = 55.2 Hz) in ^1H NMR spectrum and a singlet at 143.8 ppm in $^{31}P\{^1H\}$ NMR spectrum. After 16 hours no changes in the proportion of **2**, **3** and **4** complexes were observed (**2** : **3** : **4**; 1.0 : 1.1 :1.2, determined by $^{31}P\{^1H\}$ NMR). Complex **3** was independently prepared by treatment of complex **1** with NaHBEt$_3$ under H_2 atmosphere (1 bar) in [D$_8$]Tol at -10°C and characterized by low temperature NMR (0°C). In line with the proposed geometry of **3**, two resonances are observed in the carbonyl region in the $^{13}C\{^1H\}$ NMR spectrum at 219.3 ppm ($^2J_{PC}$ = 12.6 Hz) and 230.4 ppm ($^2J_{PC}$ = 20.7 Hz). When this cold solution containing complex **3** reaches room temperature it slowly forms a mixture of **2**, **3** and **4** complexes (after 12 hours, proportion **2** : **3** : **4**; 1.0 : 0.8 : 0.9, was determined by $^{31}P\{^1H\}$ NMR spectroscopy). The $^{13}C\{^1H\}$ NMR of complex **4** is similar to that of **3**; the carbonyl ligands exhibit two resonances, at 218.4 ppm ($^2J_{PC}$ = 12.5 Hz) and 229.8 ppm ($^2J_{PC}$ = 19.7 Hz), slightly different chemical shifts compared to **3** (see SI).



Scheme 3. Reversible activation of H_2 by **2** at room temperature (1 bar H_2) through metal-ligand cooperation.

The *syn* orientation of the N-H and Mn-H bonds in **3** is determined by a NOE study. Upon selective irradiation of the hydride resonance at -1.71 ppm, the NOE difference spectrum gives NOE enhancement for the resonance at 3.09 ppm (s), which corresponds to the NH group and also for the resonance at 1.42 ppm (d, $^3J_{HP}$ = 12 Hz), due to the ^{t}BuP group which points in the same direction as the Mn-H (Figure 2, see SI). Upon selective irradiation of the hydride resonance at -1.34 ppm, the NOE difference spectrum only shows NOE enhancement for the resonances at 1.37 ppm (d, $^3J_{HP}$ = 12 Hz) and 0.94 ppm (s), which correspond to the ^{t}BuP and ^{t}BuN groups, in agreement with the proposed *anti* orientation of the N-H and Mn-H bonds for **4** (Figure 2).

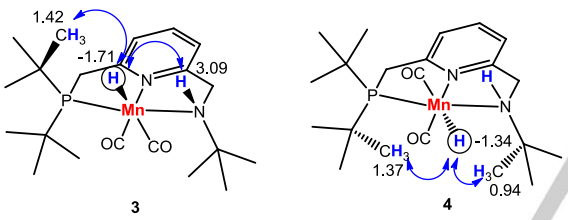


Figure 2. ^{1}H NMR chemical shifts of the NOE correlations observed under selective irradiation of the hydride resonance for **3** and **4**.

We believe that complex **2**, and the coordinatively *saturated syn*-[Mn(PNN*H*)(*H*)(CO)$_2$] complex **3,** formed *in situ* under the catalytic reaction conditions, are actual intermediates in the ester hydrogenation process. Hence it is quite likely that an outer-sphere mechanism, involving hydride and proton transfer from the Mn-H and M-N-H moieties, is operative.

In summary, the first example of ester hydrogenation catalyzed by a complex based on earth-abundant manganese is reported. This environmentally benign reaction proceeds under mild conditions (100 ^{o}C, 20 bar) and is of broad scope. In the reported examples the reaction was selective for ester groups, C=C and CN groups not being affected. The actual catalytically active complex, the amido complex **2**, was prepared by deprotonation of **1** and shown to efficiently catalyze the reaction in absence of added base. No deprotonation of the benzylic position was observed. H_2 activation takes place by metal-ligand cooperation (MLC), in which the manganese metal center and the pincer ligand participate in H_2 activation via Mn-NR_2 *H*Mn-N*H*R_2 equilibrium, leading to coordinatively saturated *syn* and *anti* isomers. Further experimental and theoretical mechanistic studies are underway.

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Keywords: homogeneous catalysis · pincer complexes · manganese · ester · alcohol

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[10] CCDC 1503968 (**1**) and CCDC 1503969 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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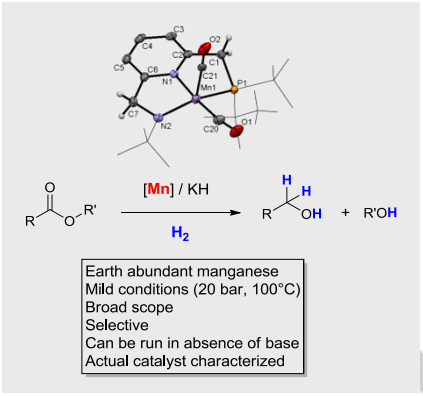
Ester hydrogenation catalyzed by a complex based on earth-abundant manganese is reported. This environmentally benign reaction proceeds under mild conditions and is of broad scope. The catalytically active species can be formed *in situ* by adding base to the reaction mixture. It shows selectivity for ester groups, C=C and CN groups not being affected. The likely actual catalytically active complex was also prepared and shown to efficiently catalyze the reaction in absence of added base.



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Manganese-Catalyzed Hydrogenation of Esters to Alcohols