Hydrogenation Catalysts

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Non-Pincer-Type Manganese Complexes as Efficient Catalysts for the Hydrogenation of Esters

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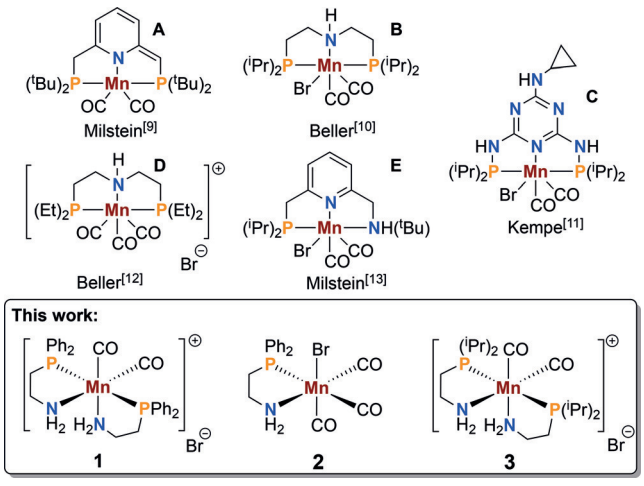
Abstract: *Catalytic hydrogenation of carboxylic acid esters is essential for the green production of pharmaceuticals, fragrances, and fine chemicals. Herein, we report the efficient hydrogenation of esters with manganese catalysts based on simple bidentate aminophosphine ligands. Monoligated Mn PN complexes are particularly active for the conversion of esters into the corresponding alcohols at Mn concentrations as low as 0.2 mol% in the presence of sub-stoichiometric amounts of KO^{t}Bu base.*

The reduction of polar carbonyl moieties is a fundamental organic transformation important for the production of a wide variety of bulk- and fine chemicals, such as biofuels, fragrances, and pharmaceuticals. Catalytic processes employing H_2 as the reductant represent an atom-efficient and sustainable alternative to conventional stoichiometric approaches.[1] To date a wide range of versatile and highly active homogeneous ester hydrogenation catalysts based on Ru,[2] Os,[3] and Ir[4] have been described. Driven by economic and environmental considerations, recent efforts have focused on the replacement of the noble-metal component in such catalysts by cheaper, more abundant, and non-toxic metals.[5] Among these, manganese can be regarded as one of the most desirable candidates in view of its low price, rich chemistry, and exceptional biocompatibility.[6] Yet, most examples of non-noble metal homogeneous hydrogenation catalysts are based on Fe[7] and Co,[8] while the respective catalytic chemistry of Mn was not known until very recently. In early 2016 Milstein and co-workers described the first Mn^I-based catalyst **A** for the dehydrogenative coupling of alcohols and amines (Scheme 1).[9a] Later, Kirchner and co-workers showed that this reaction can also be catalyzed by a related Mn^I PNP pincer complex.[9b] Shortly afterwards, the groups of Beller[10] and Kempe[11] independently reported the hydrogenation of ketones with pincer catalysts **B** and **C**. Complex **B** is also active in the reduction of nitriles and aldehydes. Reduction of less-reactive ester substrates remains a challenge for Mn catalysts with only two examples reported to date. Beller and co-workers described aliphatic Mn^I PNP-pincer catalyst **D** that converts esters into alcohols under basic conditions at 2 mol% catalyst loading (110 °C/30 bar H_2/24 h).[12] Milstein and co-workers reported that lutidine-derived Mn^I PNN-pincer catalyst **E** is active at 1 mol%, but requires addition of KH as the base (100 °C/20 bar H_2/50 h).[13] Despite the impressive progress witnessed in recent years in catalytic hydrogenations with non-noble-metal complexes, even the most active examples are efficient only at relatively high catalyst loading of 1–3 mol%, significantly limiting their utility as practical alternatives to the more active Ru-based systems.[14] Herein we report the catalytic hydrogenation of esters with three novel non-pincer-type Mn PN complexes,



Scheme 1. Mn-based (de)hydrogenation catalysts.

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based on simple and easily accessible bidentate aminophosphine ligands. They show good performance at an unprecedented loading of only 0.2 mol%, bringing Mn-catalyzed hydrogenation a step closer to practical implementation.

The use of P,N ligands for Ru-catalyzed ester hydrogenation was first reported by Saudan et al.[15] We prepared complexes **1** to **3** by reaction of $Mn(CO)_5Br$ with 1 or 2 equivalents of the corresponding P,N ligand in toluene at 100 °C for 24 h. The isolated complexes were fully characterized by $^1H/^{31}P$-NMR, ESI-MS, FTIR, elemental analysis, and single-crystal X-ray structure analysis (see Supporting Information). Single-crystal X-ray structure determination revealed the *cis*-coordination of the N-donor groups of the P,N ligands and CO ligands in **1**, with the two phosphine moieties bound *trans* to each other (Figure 1). Their chemical

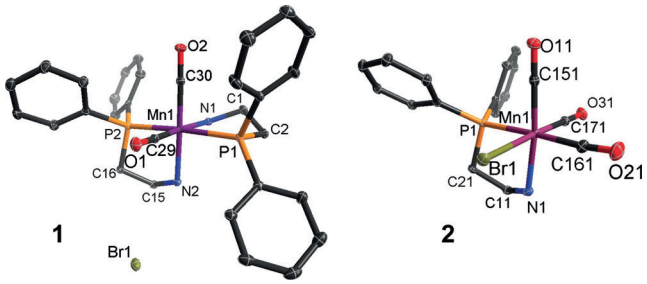
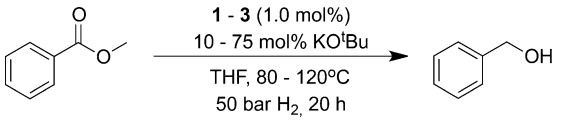


Figure 1. ORTEP diagrams of **1** (left) and **2** (right). Thermal ellipsoids are set at 30% probability. Hydrogen atoms have been omitted for clarity.

equivalence was also detected in solution by ^{31}P NMR, revealing a single resonance for **1** at $\delta = 79.3$ ppm. Complex **2** contains a single P,N ligand. The amine and Br^- in **2** are bound in a *cis* fashion, providing a favorable environment for heterolytic H_2 activation across the Mn–N moiety.[16]

Complexes **1–3** are active catalysts for ester hydrogenation. Table 1 summarizes the results of the initial catalytic tests using methyl benzoate as a model substrate. Monoligated complex **2** was found to be considerably more active than **1** and **3** (Table 1, entries 1–3). This is remarkable as the related Ru-PN catalyst is biligated.[15] Reaction at 80–100 °C gave similar benzyl alcohol (BnOH) yields, while the yield decreased substantially at higher temperatures owing to formation of methyl benzyl ether (Table 1, entries 2,4,5). Increasing the amount of KO^{t}Bu led to improved yields (Table 1, entries 6–8). Ultimately, quantitative BnOH yield was obtained with 0.75 equivalents of KO^{t}Bu relative to the substrate (Table 1, entry 8).

Table 1: Hydrogenation of methyl benzoate with **1–3**.[a]

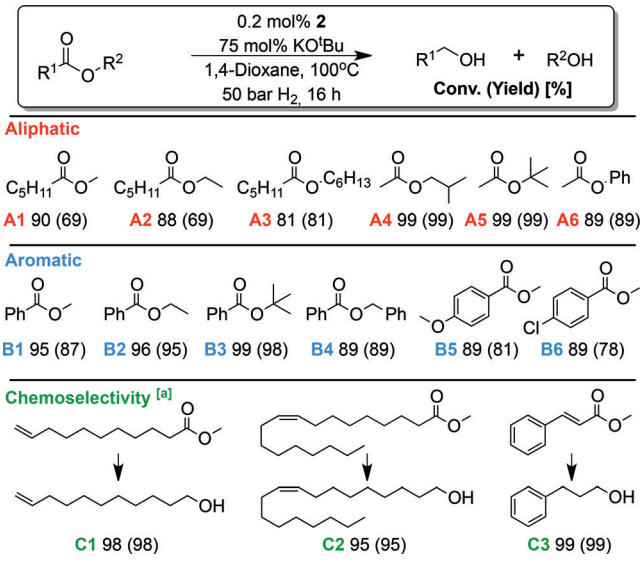


Entry	Catalyst	KO^{t}Bu [mol%]	T [°C]	Conv. [%]	Y_{BnOH} [%][17]
1	**1**	10	100	43	24
2	**2**	10	100	75	66
3	**3**	10	100	13	3
4	**2**	10	80	74	65
5	**2**	10	120	57	43
6	**2**	25	100	86	80
7	**2**	50	100	96	91
8	**2**	75	100	99	98

[a] Conditions: 1 mmol methyl benzoate, 10–75 mol% KO^{t}Bu, 1.0 mol% **Mn**, 2 mL THF, 80–120 °C, 50 bar H_2, 20 h. Yield determined by GC.

After full conversion was achieved, we sought to optimize crucial process parameters such as solvents, bases, reaction temperature and H_2 pressure to enable use of **2** at reduced catalyst loading. With 0.5 mol% of **2** in THF a BnOH yield of 87% could be achieved in just 3 h. Importantly, **2** could also be formed in situ without significant loss of activity, thus eliminating the need for catalyst isolation (Table S1 in the Supporting Information). Mercury poisoning did not evidence inhibition, suggesting the homogeneous nature of catalysis with **2** (Table S1).[18] Replacement of THF for 1,4-dioxane resulted in a higher product yield, while the use of 2-methyl-THF and MTBE led to inferior performance (Table S2). KO^{t}Bu was found to be the superior base for the current catalytic system (Table S3). An increase in temperature and reduction in H_2 pressure resulted in lower BnOH yields (Table S4).

Next, we expanded the scope of the substrates and further decreased the catalyst loading to 0.2 mol%. Under the optimized conditions, **2** was able to convert aromatic and aliphatic esters into their corresponding alcohols in good to excellent yields (Scheme 2). Reduction of hexanoate esters **A1–A3** led to good yields of 1-hexanol with hexyl hexanoate as the only by-product. Interestingly, more sterically hindered esters (**A4–A6**) were almost quantitatively hydrogenated, whereas these are typically more difficult to reduce than their methyl and ethyl analogues.[1] Aromatic benzoate esters with varied steric bulk or electronic properties were all hydrogenated to benzyl alcohol in high yield (**B1–B4**). Similar to aliphatic esters, the reduction of bulky *tert*-butyl benzoate was more efficient than the less-sterically hindered substrates.



Scheme 2. Hydrogenation of various esters with **2**. Conditions: 1 mmol substrate, 75 mol% KO^{t}Bu, 0.2 mol% **2**, 2 mL 1,4-dioxane, 100 °C, 50 bar H_2, 16 h. [a] 0.5 mol% **2**, 6 h.

Hydrogenation of functionalized esters **B5** and **B6** gave high yields of the corresponding alcohols with the functional group being preserved and only trace amount of the methyl ether side products detected by GC-MS. Hydrogenation of unsaturated esters with **2** was fully chemoselective for substrates with the C=C bond distant from the ester moiety, such as fatty acid methyl esters **C1** and **C2**. Methyl cinnamate (**C3**), however, was fully converted into hydrocinnamyl alcohol. No products associated with the Claisen condensation were observed for the enolizable substrates.

To get better insight into the effect of the base in catalysis with **2** we carried out additional catalytic tests using four different benzoate substrates at varied base concentration (Figure 2). For all substrates, the elevated base loading

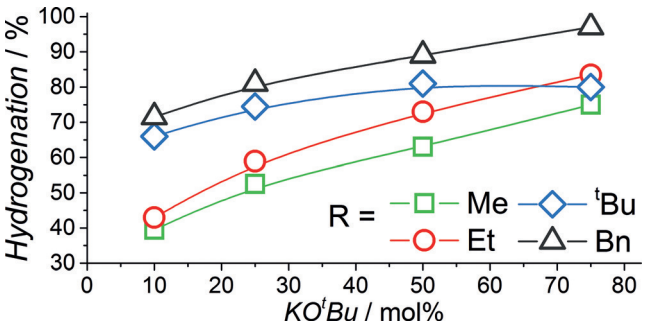


Figure 2. Effect of ester alkoxy group and KO^{t}Bu amount on the degree of hydrogenation (equal to sum of benzyl alcohol, methyl benzyl ether, and $^1/_2$ benzyl benzoate yields).

resulted in a higher product yield. The hydrogenation of methyl- and ethyl benzoates was more sensitive to changes in the base concentration than for the *tert*-butyl- and benzyl benzoate substrates. We attribute this to catalyst inhibition by the short-chain alcohols produced in the reaction. This effect is in line with the lower activity achieved with KOMe and KOEt bases (Table S3). Product inhibition via metal-alkoxide formation is well-known for P,N-type complex catalysts and is consistent with both the lower observed rates for methyl- and ethyl esters as well as the increased TON at reduced catalyst loading.[19]

Dedicated kinetic experiments were next carried out to further study the role of the base (Figure 3).[21] Near-complete hydrogenation was achieved with 0.75 equiv. KO^{t}Bu, while in the presence of 0.1 equiv. base the reaction progress was limited to around 20%. Remarkably, catalytic activity could be instantaneously restored upon addition of 0.65 equiv. KO^{t}Bu. Regardless of the base loading sequence, nearly identical initial rates of about 1100 h^{-1} were observed (see Figure S14). This is consistent with our hypothesis on Mn-alkoxide inhibition, which upon reaction with KO^{t}Bu convert into the catalytically active manganese amide. A similar mechanism of in situ catalyst regeneration has been proposed previously for related Ru-based catalysts.[20]

Next, the reaction mechanism with **2** was studied by density functional theory (DFT) calculations at the PBE0/6-311G(d)//6-31G(d) level (Gaussian 09 D.01).[22] Methyl acetate (MeOAc) was chosen as the model substrate. The proposed mechanism, along with the reaction and activation

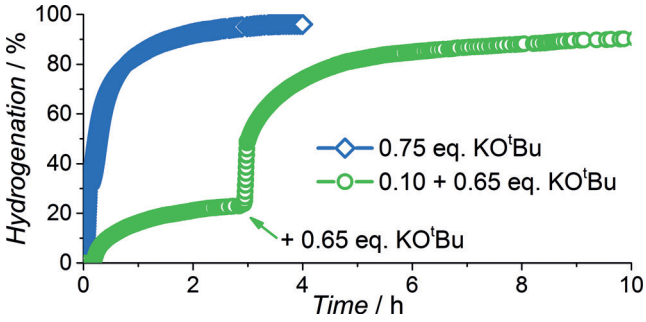


Figure 3. Kinetic traces of methyl benzoate hydrogenation with **2**. Conditions: 15 mmol methyl benzoate, 10–75 mol% KO^{t}Bu, 0.5 mol% **2**, 28 mL THF, 100 °C, 50 bar H_2.

Gibbs free energies for elementary steps, $\Delta G°373K_{solv}$, are summarized in Figure 4. Prior to the catalytic reaction, **2** is activated via a base-assisted hydrogenolysis to produce hydrido complex **I** (see Supporting Information). The cycle starts with an exergonic complexation of MeOAc with **I** to give H-bonded intermediate **II**, which then converts into an activated gem-acetal **III** via a hydride attack with a free energy barrier of 97 kJ mol^{-1}. The addition of H_2 to **III** yields σ-complex **IV**, which after hydrogenolysis produces CH_3OH and CH_3CHO. Methanol elimination gives **VI**, from which the final stage of the catalytic cycle, that is, aldehyde hydrogenation, proceeds. This step is significantly more favorable than the initial ester activation. The first hydride transfer is exergonic by −8 kJ mol^{-1} and shows a free energy barrier of only 29 kJ mol^{-1} (**VI**→**VII**). The resulting alkoxy anion is stabilized by a partial deprotonation of the NH_2-moiety of the ligand, thereby resulting in a trigonal bipyramidal configuration of Mn in **VII**. The interaction with the basic ethoxide facilitates complexation with H_2 to form **VIII** that is followed

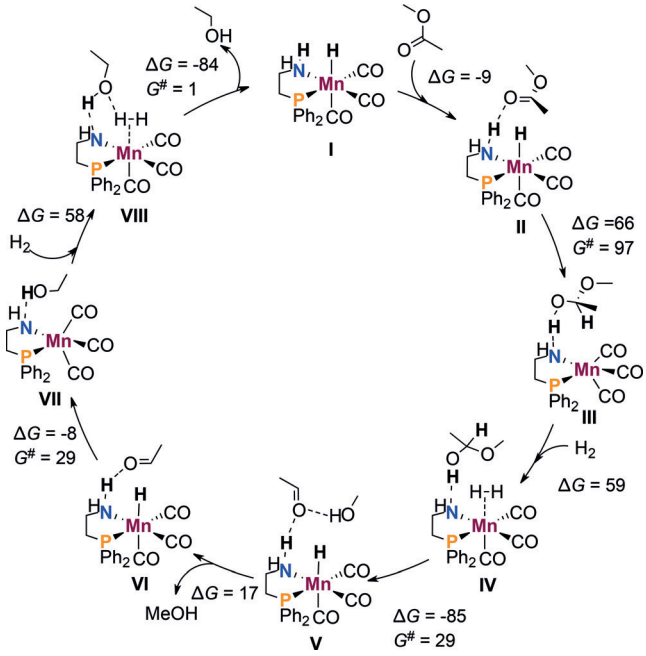


Figure 4. Proposed catalytic cycle for methyl acetate hydrogenation by H_2 and **2** (Δ*G* and *G*‡ stand for the reaction and activation Gibbs free energy changes in kJ mol^{-1} at 373 K).

by a barrierless and highly exergonic heterolytic dissociation to produce **I**. The overall free energy barrier for this alkoxide-assisted catalyst regeneration is 59 kJ mol^{-1}, in which the major energy losses originate from the structural distortions upon the formation of σ-H_2 complex **VIII**. The alternative path via ethanol elimination from **VII** followed by the metal–ligand cooperative H_2 activation shows a free energy barrier of about 100 kJ mol^{-1}.

DFT calculations also reveal a competing side-path for the decomposition of **III**, resulting in CH_3CHO elimination and the formation of a stable Mn-alkoxide complex (see Supporting Information). From this point, the formation of **I** requires a base-assisted hydrogenolysis similar to that proposed for the activation of pre-catalyst **2**. This provides additional support for our proposal on catalyst inhibition by stable Mn-alkoxide resting states. In line with the experimental results, the hydrogenolysis of the bulkier Mn-O^{t}Bu adduct shows a much lower energy barrier than Mn-OMe (89 vs. 106 kJ mol^{-1}, respectively).

In summary, we have synthesized and fully characterized three novel Mn P,N ligand complexes, of which monoligated complex **2** is a highly active catalyst for the hydrogenation of aliphatic and aromatic esters. Considering the high catalytic performance and the simple and straightforward preparation, complex **2** holds a great promise as a cheap and practical non-noble metal-based ester hydrogenation catalyst. Based on the complementary experimental and computational results, we provide a mechanistic proposal that points to a potential for further improvement of the Mn-based catalysts under study.

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Conflict of interest

The authors declare no conflict of interest.

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