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VIP *Very Important Paper*

# Molecularly Defined Manganese Pincer Complexes for Selective Transfer Hydrogenation of Ketones

Marc Perez, Saravanakumar Elangovan, Anke Spannenberg, Kathrin Junge, and Matthias Beller*[a]

For the first time an easily accessible and well-defined manganese *N*,*N*,*N*-pincer complex catalyzes the transfer hydrogenation of a broad range of ketones with good to excellent yields. This cheap earth abundant-metal based catalyst provides access to useful secondary alcohols without the need of hydrogen gas. Preliminary investigations to explore the mechanism of this transformation are also reported.

The development of benign catalytic transformations that are in accordance with the principles of green chemistry is ongoing goal for both academic and industrial researchers.[1] As an example, the reduction of C=O bonds evolved from the use of stoichiometric reducing agents, such as metal hydrides to the application of catalysts. In this field, mainly two reactions are commonly employed, namely hydrogenation[2] and transfer hydrogenation.[3] The latter one is operationally simple and intrinsically safe, avoiding pressurized hydrogen. Until today, transfer hydrogenation of carbonyl compounds mainly relies on precious metal-based catalysts, such as Ru,[4] Rh,[5] Os,[6] or Ir,[7] which are expensive and raise toxicity concerns. To circumvent these problems, base metal complexes have been developed using either Fe[8] or Co.[9] Among the different first-row transition metals, currently also Mn-based catalysts are emerging, but their applications are still limited.[10] For example, the reduction of polar double bonds by Mn-based catalysts is limited to reductive amination of ketones with Eco-Mn®[11] and the hydrosilylation of carbonyl compounds.[12]

Very recently, we established the first hydrogenation of ketones, aldehydes, nitriles, and esters as well as the hydrogen-borrowing alkylation of amines with alcohols in the presence of Mn.[13] Based on these works, we became interested in the development of more operator-friendly Mn-based transfer hydrogenations. Here, we present our findings using well-defined Mn pre-catalysts **1**–**5** (Figure 1) in combination with inexpensive isopropanol as the hydrogen source.

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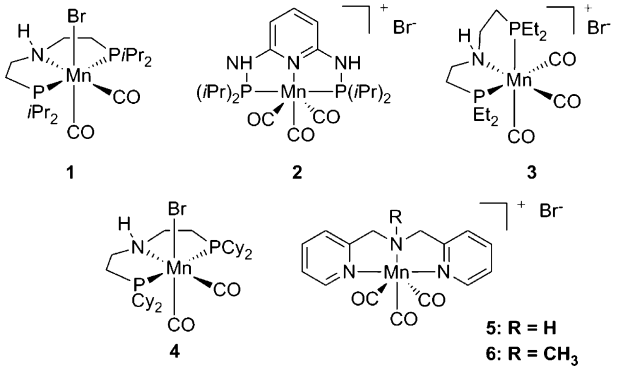
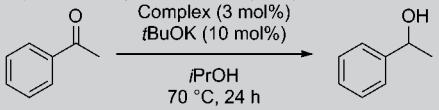



**Figure 1.** Structure of the complexes used in our investigations.

In preliminary experiments, transfer hydrogenation of acetophenone was investigated as a benchmark test system using 3 mol% of complexes **1**–**5** in the presence of *t*BuOK and *i*PrOH (Table 1). To exclude well known base-catalyzed transfer hydrogenation of ketones[14] a control experiment was performed with 10 mol% *t*BuOK yielding only 10% conversion after 24 h at 70 °C (Entry 1). Under the same conditions, the addition of complex **1** led to an encouraging yield of 70% of the corresponding alcohol (Entry 2). Using complex **2** bearing a central pyridine backbone had a detrimental effect on reactivity (Entry 3). In the presence of other PNP pincer-type complexes,

**Table 1.** Manganese-catalyzed transfer hydrogenation of acetophenone.[a]




| Entry | Complex [mol%] | *t*BuOK [mol%] | Conv.[b] [%] | Yield[c] [%] |
|---|---|---|---|---|
| 1 | none | 10 | 10 | n.d. |
| 2 | **1** (3) | 10 | 74 | 70 |
| 3 | **2** (3) | 10 | 8 | n.d. |
| 4 | **3** (3) | 10 | 95 | 90 |
| 5 | **4** (3) | 10 | 96 | 91 |
| 6 | **5** (3) | 10 | 96 | 91 |
| 7 | **4** (1) | 10 | 24 | n.d. |
| 8 | **5** (1) | 10 | 96 | 90 |
| 9 | **5** (1) | 10 | 0[d] | n.d. |
| 10 | **5** (1) | 2 | 96 | 96 |
| 11 | **6** (1) | 2 | 96 | 96 |

[a] Reaction conditions: acetophenone (0.5 mmol), *i*PrOH (2.5 mL), 70 °C, 24 h. [b] Conversion was determined by GC. [c] GC yield. [d] Reaction run at r.t.




**These are not the final page numbers! ↗↗**

such as **3** and **4**, phenylethanol was obtained in up to 91% yield (Entries 4 and 5). Finally, using the phosphine-free complex **5**[15] excellent yields were reached as obtained with the best PNP-based complex **4** (Entry 6).

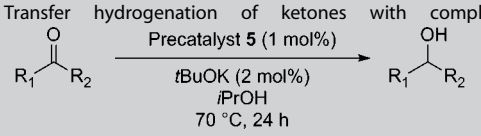
To evaluate the most efficient precatalyst, experiments were conducted at a lower catalyst loading of **4** and **5**. Interestingly, in the presence of 1 mol% of **4** the catalytic activity completely dropped down, while complex **5** still afforded 96% conversion and 90% yield (Entries 7 and 8). However, attempts to conduct the reaction at room temperature left the starting material untouched (Entry 9). Noteworthy, the base concentration could be reduced to 2 mol% without affecting the catalytic activity and affording the product with almost quantitative conversion in 96% yield (Entry 10).

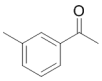
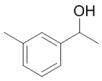
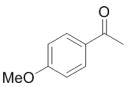
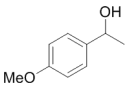
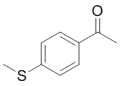
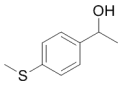
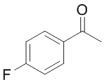
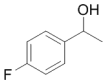
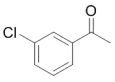
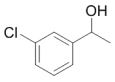
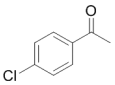
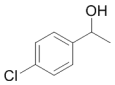
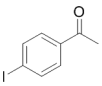
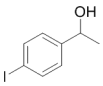
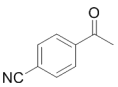
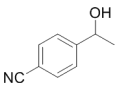
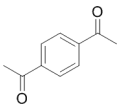
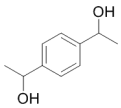
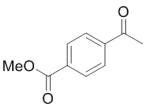
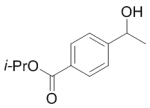
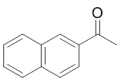
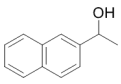
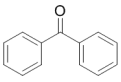
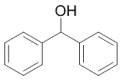
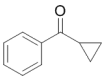
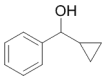
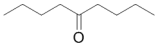
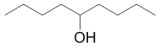
After establishing optimal conditions, we investigated the substrate scope of this first Mn-catalyzed transfer hydrogenation reaction. As shown in Table 2, **5** is an efficient precatalyst for the reduction of a variety of (hetero)aromatic and aliphatic ketones. Acetophenone derivatives bearing electron-donating substituents were effectively converted to the corresponding alcohols with yields ranging from 84% to 91% (Entries 2–5). Various halogen containing substrates produced the desired alcohols with yields up to 99% (Entries 6–9). Other electron-poor aromatic ketones were also tested in the reaction to investigate the chemoselectivity of the catalyst (Entries 10–12). Gratifyingly, nitrile and ester functionalities are not reduced and led to the 1-phenylethanol analogues with excellent yields although transesterification is being observed (Entries 10 and 12). 1,4-Diacetylbenzene was reduced to the corresponding diol in 72% yield (Entry 11) next to the monoalcohol (18% yield). Using longer reaction times (48 h) led to an increased ratio of diol/alcohol of 95:5. Other aromatics ketones such as 2-acetonaphthone and benzophenone were suitable for this reaction delivering the reduced products with yields reaching 98% (Entries 13 and 14). Furthermore, a number of aliphatic ketones were investigated (Entries 16–19).

5-Nonanone was reduced to the corresponding alcohol in moderate yield (64%; Entry 16). On the other hand, cyclic ketones, such as cyclohexanone or 1-ethyl-4-piperidone, could be transformed to the corresponding alcohols in high to excellent yields of 90% and 85%, respectively (Entries 17 and 18). The synthesis of the later product is of relevance as it serves as a key intermediate in the production of Genentech 's GDC-0425 an inhibitor of ChK1 (Checkpoint Kinase 1) that is being currently investigated in clinical phase I for the treatment of cancer.[16] Noteworthy, dihydro-β-ionone, an aliphatic ketone containing an alkene function, was reduced to the corresponding alcohol in 97% without affecting the alkene moiety (Entry 19). Finally, the catalytic system also promoted the reduction of heteroaromatic ketones (Entries 20–23), although a higher metal loading was required to achieve high conversions and excellent yields. Surprisingly, aldehydes were found to be unreactive under our reaction conditions.[17]

After studying the scope and limitation of the reaction, we explored the mechanism of this novel Mn-catalyzed transfer hydrogenation process. To distinguish between the possible monohydride and dihydride pathways,[18] the reaction was per-

**Table 2.** Transfer hydrogenation of ketones with complex **5**.[a]




| Entry | Substrate | Product | Conv.[b] [%] | Yield [%] |
|---|---|---|---|---|
| 1 |  |  | 96 | 96[e] |
| 2 |  |  | 96 | 91 |
| 3 |  |  | 97 | 90 |
| 4 |  |  | 86 | 84 |
| 5 |  |  | 97[c] | 84 |
| 6 |  |  | 97 | 79 |
| 7 |  |  | >99 | 95 |
| 8 |  |  | >99 | 99 |
| 9 |  |  | >99[c] | 91 |
| 10 |  |  | >99[c] | 99 |
| 11 |  |  | >99[c] | 72 |
| 12 |  |  | >99[c] | 96 |
| 13 |  |  | 95 | 95 |
| 14 |  |  | >99 | 98 |
| 15 |  |  | 77[c] | 73 |
| 16 |  |  | 96[c] | 64 |
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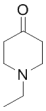
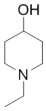
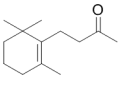
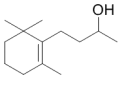
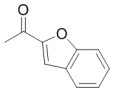
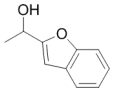
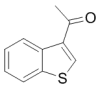
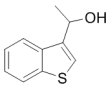
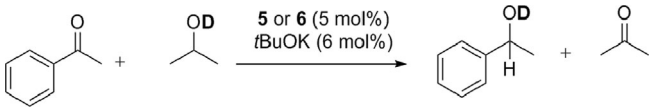
| 18 |  |  | >99 | 90[d] |
| 19 |  |  | >99[c] | 97 |

**Table 2.** (Continued)

| Entry | Substrate | Product | Conv.[b] [%] | Yield [%] |
|---|---|---|---|---|
| 20 |  |  | 97[c] | 96[e] |
| 21 |  |  | >99[c] | 93 |
| 22 |  |  | >99[c] | 97 |
| 23 |  |  | >99[c] | 96 |

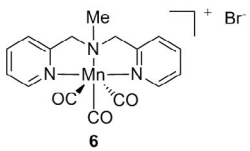
[a] Reaction conditions: substrate (0.5 mmol), complex **5** (0.005 mmol), *t*BuOK (0.01 mmol), *i*PrOH (2.5 mL), 70 °C, 24 h. [b] Conversion was determined by GC. Isolated yield is given. [c] Reaction conditions: substrate (0.50 mmol), complex (0.025 mmol), *t*BuOK (0.030 mmol), *i*PrOH (2.5 mL), 70 °C, 24 h. [d] Isolated as the HCl salt. [e] GC yield.

formed using deuterated isopropanol as the hydride source. The corresponding deuterated 1-phenylethanol was formed in 85% isolated yield with no noticeable D incorporation in the α-position as judged by $^1$H and $^2$H NMR (Scheme 1).[9,19] This result indicates that the reaction does not proceed through the formation of Mn-dihydride species, but through a monohydride mechanism.




**Scheme 1.** Deuterium labelling experiments.

In this monohydride mechanism the hydrogen transfer can proceed through an inner or an outer sphere pathway. For the later one, metal ligand bifunctional catalysis is discussed, where the hydrogen is transferred in a concerted or stepwise manner.[20] To elucidate a possible participation of the central N–H moiety of the ligand in catalyst **5**, this position was blocked by methylation. The introduction of an alkyl group in this position is expected to shut down the catalytic activity in case of an outer sphere mechanism involving the N–H group. To confirm this hypothesis, the methyl substituted complex **6** was tested in the catalytic reaction (Figure 2, see the Supporting Information for details). Surprisingly, also complex **6** was active in the transfer hydrogenation of acetophenone yielding comparable results to **5** (Table 1, Entries 10 and 11). Nevertheless, when **6** was engaged in the same deuterium labelling experiment as **5**, a strong kinetic isotope effect was observed with the corresponding alcohol being isolated in only 49% yield also with no noticeable D incorporation in the α-position (Scheme 1). Obviously, cooperation of the NH moiety with the metal center is not mandatory for the Mn-catalyzed transfer hydrogenation of ketones and activation of the benzylic hydrogen atoms might take place similar to other pyridine-type PNP complexes.[21]



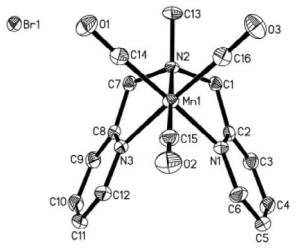




**Figure 2.** Structure of complex **6**.

In conclusion, we have developed the first transfer hydrogenation of ketones using an earth abundant Mn-based complex. Notably, no phosphine ligands are required to stabilize this catalyst, instead a commercially available tridentate amine provides sufficient stability and activity. The mild reaction conditions are tolerant towards various functional groups and offer an efficient route towards valuable secondary alcohols, which make it a promising alternative to previously reported procedures. More detailed explorations on mechanism are in progress.

## Experimental Section

**General procedure for the catalytic transfer hydrogenation**: Mn complex **5** (0.005 mmol) was placed in a Schlenk tube (25 mL) under Ar. Then, dry isopropanol (2.5 mL) was added by syringe. After addition of potassium *tert*-butoxide (0.01 mmol), the mixture was stirred for 5 min at room temperature. The ketone (0.5 mmol) was added in one portion and the reaction vessel was placed at 70 °C for 24 h in a preheated alloy block. After this period of time, the reaction was left to cool at room temperature. An aliquot was taken for determination of conversion by GC analysis, the mixture was concentrated using a rotary evaporator. Purification by silica gel column chromatography afforded the corresponding alcohol.

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**Keywords:** homogeneous catalysis · ketones · manganese complex · pincer ligands · transfer hydrogenation

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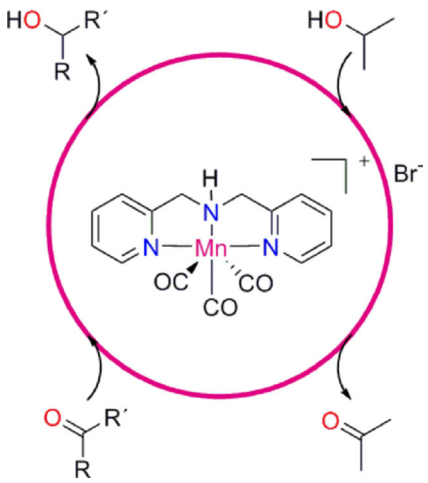
**Broad application:** A manganese complex is applied for the first time in the transfer hydrogenation of a broad variety of ketones with 2-propanol in good to excellent yields and excellent chemoselectivity. The mild reaction conditions are tolerant towards various functional groups and offer an efficient route towards valuable secondary alcohols, which make it a promising alternative to previously reported procedures.




*M. Perez, S. Elangovan, A. Spannenberg, K. Junge, M. Beller**

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**Molecularly Defined Manganese Pincer Complexes for Selective Transfer Hydrogenation of Ketones**

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